Vaccination is among the most effective therapeutic modalities that modern medicine has been able to provide. Through amplifying existing antigen-specific memory responses and expanding the immune repertoire by inducing de novo ones, vaccines coordinate and direct humoral and T-cell immunity toward eradication of cells bearing the immunizing antigen, generating immunologic memory that confers long-term protection. Over the past century, preventive vaccines have saved countless lives from smallpox, poliomyelitis, and multiple other infectious diseases. Current intense efforts are seeking to achieve this same success in the fight against COVID-19. Cancer immunologists have always looked to viral immunology for insights into how we can extend this type of benefit to our patients with cancer while recognizing the unique biological challenges posed by cancer as a disease. In reviewing our cumulative experience with cancer vaccines over the past decade, we can readily identify similarities and differences with challenges involved in vaccination against viruses. In this review, we take the opportunity to appraise our recent progress and the pitfalls we have encountered on the road to vaccine development for cancers including hematologic malignancies, and reflect on the relevance of these experiences for COVID-19 vaccination.

CHALLENGES FACING THE DEVELOPMENT OF CANCER VACCINES

Cancer vaccines and antiviral vaccines share the goals of eliciting potent antigen-specific immunity. However, the usual focus with antiviral vaccines is the generation of neutralizing antibodies against exposed virion proteins, whereas antitumor immunity is dependent upon T-cell reactivity against HLA-restricted tumor antigens, making their identification particularly important. Other formidable barriers that challenge the ability to generate effective cancer vaccines include the genomic and phenotypic heterogeneity of cancer, along with the immune-dampening effects of cancer cells (Fig. 1A).

Antigenic Specificity and Immunogenicity

The discrimination between self and nonself underpins the foundation of immunity. Although viruses are recognized by the host immune system as incontrovertibly nonself, tumors arise from the transformation of normal cells and retain many of those properties, posing a unique challenge for cancer vaccine development. How can we best select optimal antigenic targets? Historically, cancer vaccines have predominantly targeted tumor-associated antigens (TAA) that are self-antigens disproportionately overexpressed by tumor cells. These vaccines have generally suffered from poor efficacy, in part because T- and B-cell clones of the highest avidity for these broadly expressed antigens are subject to thymic deletion as a consequence of central immune tolerance. Neoantigens, having arisen from somatic tumor-specific mutations, display exquisite tumor-restricted expression and are not subject to central immune tolerance. They are therefore regarded as optimal tumor antigen targets but are more challenging to identify. In addition, only a fraction of mutant proteins are processed and presented on the tumor cell surface as HLA-bound peptides, posing an intrinsic barrier for target selection in lower mutation rate tumors such as hematologic malignancies. How the most immunogenic targets are identified and their immunogenicity further enhanced to achieve optimal vaccine efficacy is a challenge shared between cancer and viral vaccinology.

Tumor Heterogeneity and Clonal Evolution

A major obstacle to the successful eradication of viral infections through vaccination is the ability of viruses to diversify their antigenic composition through antigenic drift and shift, rendering existing vaccines ineffective. In an analogous fashion, cancers exhibit profound intertumoral and intratumoral heterogeneity, providing the fuel for clonal evolution and a basis for therapeutic resistance. This plasticity imposes a major challenge to the impact of individual cancer therapies. For this reason, cancer vaccines that target single rather than multiple epitopes are thought to have lower probability of effectiveness. Although the fundamental genomic
heterogeneity of cancer provides a strong rationale for the generation of individualized vaccines, for example by targeting personal tumor neoantigens, the considerable challenges to this approach include the expense and time required for achieving this high degree of personalization. Moreover, the genetic profile of any cancer can evolve continually through space and time. Thus, information from a single biopsy may underestimate the neoantigen landscape as a result of the spatial and temporal intratumoral diversification that arises under clonal evolution. Indeed, neoantigen heterogeneity, in addition to low neoantigen burden, has been recognized as a predictor of treatment failure with immunotherapy (1). Multiple sampling at different tumor sites and time points to reconstruct clonal architecture, or the use of cell-free DNA sequencing methods in which circulating DNA potentially provides genetic information across multiple distant tumor sites, may aid vaccine design but requires further validation and remains costly. How we can best achieve effective polyepitopic response through vaccination is a shared challenge for oncologists and virologists.

**Immunosuppressive Tumor Microenvironment**

The transformational nature of immune checkpoint inhibitors (e.g., anti–PD-1, anti–CTLA-4) as an immunotherapy across cancers is a testament to the important role of negative immunoregulation in creating an immunosuppressive tumor microenvironment. Indeed, a distinct challenge in the control of cancer through vaccination is the difficulty of facilitating an adequately strong immune response in the context of an immunosuppressive tumor microenvironment, resulting both from the immune-dampening properties of the tumor and from highly myelosuppressive or lymphodepleting cancer treatments. For many cancers, immune effector cells such as T cells display features of
functional exhaustion, whereas immune suppressor cells such as myeloid-derived suppressor cells (MDSC) and regulatory T cells (Treg) are often in abundance. Although most individuals battling viral infections have a reasonably intact immune system, the insights we gain from dealing with this challenge in patients with cancer could find relevance with immunosuppressive viruses and with antiviral prophylaxis in individuals who are immunosuppressed by virtue of their comorbid conditions or the treatment of these conditions thereof.

OVERCOMING CHALLENGES WITH NEOANTIGEN VACCINES: EXPERIENCE FROM THE PAST 5 YEARS

A recent study demonstrated that under modern adjuvant and delivery approaches, even targeting TAAs can provide effective antigen-specific responses (2). However, much of the recent excitement in the field of cancer vaccinology has been spurred by our newfound ability, utilizing novel technology platforms, to identify neoantigens. Targeting of neoantigens has been shown to lead to tumor regression in preclinical models and in human cells, and the generation of personal neoantigen-targeting vaccines directly addresses the challenges of cancer clonal heterogeneity (Fig. 1B).

Generation of Personalized Multivalent Neoantigen Vaccines for Patients with Cancer

The advent of next-generation sequencing has made it feasible to accurately predict candidate immunogenic epitopes for each tumor through computational integration of mutational and gene expression data obtained from whole-exome and transcriptome sequencing, respectively, taking into consideration the HLA haplotype of the patient, and facilitated by increasingly improved prediction algorithms (3). These breakthroughs have allowed the personalized selection of neoantigens as vaccine targets for each patient that are predicted to bind HLA with high affinity and hence likely to be the most immunogenic. In parallel with advances in personalized neoantigen selection, an expanding portfolio of vaccine delivery platforms has been evaluated. Among the most advanced of these are multiantigenic vaccines delivered as synthetic long peptides, RNA, or dendritic cell vaccines, which induced therapeutically active T-cell responses to predicted immunogenic neoantigens within murine tumor models, with subsequent translation into early-phase clinical trials in the settings of melanoma and glioblastoma (4–7).

Despite differences in these approaches, these early clinical studies have consistently shown neoantigen-targeting vaccines to be immunogenic, safe, feasible, and amenable to combined use with immune checkpoint blockade. Robust polyepitopic neoantigen-specific CD8+ and CD4+ T-cell responses were uniformly observed. Moreover, a recent study by Hu and colleagues revealed neoantigen-specific T-cell responses persisting for more than 4 years following vaccination, consistent with the generation of enduring memory responses, in patients with melanoma who were previously immunized with a synthetic long peptide vaccine consisting of up to 20 personal neoantigen targets together with the adjuvant polyICLC (7). Furthermore, vaccination was accompanied by the diversification of neoantigen-specific clonotypes with emergence of new clonotypes over time. Across a number of studies, regardless of delivery platform, these neoantigen-targeting vaccines generated demonstrable capacity for driving T-cell populations of neoantigen specificity into the tumor site, thus providing infiltration of tumors with a “standing army” of T cells ready to engage and destroy the tumor (4–7).

The capacity of vaccines to “warm” the tumor environment with T cells of antitumor specificity provides a strong rationale for the combined use of neoantigen vaccines with agents capable of “releasing the brakes,” such as immune checkpoint inhibitors, to enhance vaccine efficacy. Indeed, in another recent study that evaluated the PD-1 inhibitor nivolumab in combination with neoantigen vaccination in multiple patients with three types of metastatic solid tumors, sustained tumor regression was observed, with the detection of enhanced epitope spreading wherein tumor destruction resulted in the release of neoantigens triggering further tumor-directed immunity, and the propagation and amplification of neoantigen-specific immune responses (8). Combinations with PD-L1 or CTLA-4 inhibitors also hold great promise and are currently being investigated within clinical studies. The relative timing of cancer vaccines and immune checkpoint inhibitors is an important consideration given the critical role of PD-1 expression in memory T-cell generation (9).

Novel Strategies to Further Enhance Neoantigen Vaccines

Despite the potential immunogenicity of personalized cancer vaccines, clinical efficacy has yet to be ascertained in large-scale studies, with anecdotal reports within the adjuvant setting showing variable long-term outcomes in patients displaying initial robust immune response. It remains a question whether neoantigen vaccination is currently capable of delivering long-lasting protection against tumor recurrence. This could differ depending on the therapeutic setting, as well as the level of immunosuppression and the development of tumor evasion mechanisms. For example, a patient who received an RNA-based melanoma vaccine developed outgrowth of β2-microglobulin–deficient melanoma clones resulting in a loss of neoantigen presentation (5). LOH at the HLA locus represents another tumor evasion mechanism. Furthermore, the lack of sufficient actionable neoantigens could preclude neoantigen vaccination as a therapeutic option (6).

Improvement strategies are currently under active exploration in the preclinical setting to circumvent some of these limitations and enhance vaccine immunogenicity. These include novel formulations that seek to improve vaccine delivery and uptake by antigen-presenting cells, such as through liposomal nanoparticulate carriers, and others that augment immunogenicity by conjugating with proinflammatory adjuvants. Finally, there remain opportunities for experimenting with neoantigen quantity and composition targeted by each vaccine, including the balance between clonal and subclonal neoantigens, and the inclusion of alternate sources of tumor-specific neoantigens more difficult to identify than...
single-nucleotide variants, such as those arising from insertions and deletions, splicing variants, and unannotated open reading frames.

**CAN WE DELIVER CANCER VACCINES FOR HEMATOLOGIC MALIGNANCIES?**

Hematologic malignancies are generally of low mutational burden. Moreover, as cancers of hematopoietic cells that constitute the immune system, immunosuppression in these malignancies tends to be more profound than solid tumors. Notwithstanding these features that impose additional challenges for cancer vaccine development, there are many indications that therapeutic vaccination is feasible in hematologic cancers, as discussed below.

**Current Landscape of Cancer Vaccine Development for Blood Cancers**

Although clinical investigations of personalized neoantigen vaccines in hematologic malignancies have lagged behind solid tumors, it has been known that disease drivers such as BCR–ABL in chronic myeloid leukemia and mutant NPM1 in acute myeloid leukemia (AML) can give rise to neoantigens. Moreover, recent studies have shown, in a broad range of blood cancers including mantle cell lymphoma (MCL), pediatric acute lymphoblastic leukemia (ALL), and myeloma, that predicted neoantigens based on exome and transcriptome analyses could induce effective autologous T-cell response despite their low mutational burden. For example, neoantigens in MCL were derived from the immunoglobulin heavy- or light-chain variable regions, likely arising from V(D)J recombination or somatic hypermutation (10). In ALL, neoantigens within the ETV6–RUNX1 fusion protein were overrepresented and displayed strong immunodominance characteristics where immune responses were directed against a very small subset of the most immunogenic neoantigens (11). These promising data have paved the way for clinical studies of neoantigen vaccines in blood cancers (NCT03219450 and NCT03361852), although these studies are still in their infancy.

More mature clinical studies of cancer vaccines in hematologic malignancies have focused on vaccines targeting nonmutated individual TAAs such as WT1 or PR1 in AML and myelodysplasia, as well as anti-idiotypic vaccines targeting specific immunoglobulin antigen-binding sites in lymphoma. In myeloma, the tripel peptide vaccine PVX-410 targeting the myeloma-associated proteins XBP1, CD138, and CS1 has recently been tested within a dose-escalation study (12). Although immunologic and clinical response was observed in a proportion of patients, these vaccination strategies are generally associated with variable response quality and durability, and sometimes with equivocal clinical benefit, highlighting the limitations of strategies relying on monoepitopic or oligoepitopic antitumor immune responses and of targeting exclusively TAAs. On the other hand, whole-cell vaccines, in which a broad range of antigen targets are available as immunogens, and which are manufactured through enforced expression of the immunostimulatory cytokine GM-CSF in primary tumor cells (e.g., GVAX vaccines) or through fusion of tumor cells with dendritic cells, have generated encouraging clinical results and continue to be under active investigation.

**Novel Therapeutic Combinations Involving Cancer Vaccines**

The combined use of cancer vaccines with other immunotherapies offers exciting prospects for the treatment of hematologic malignancies (Fig. 1B). In addition to immune checkpoint inhibitors, lenalidomide has been shown to attenuate tumor-specific responses in vaccine-immunized mice through reducing Treg frequency and inhibitory Th2-type cytokine production as well as improving immune synapse formation, thereby enhancing cancer vaccine efficacy when tested in lymphoma and myeloma (12, 13). Another innovative therapeutic combination is that between cancer vaccines and chimeric antigen receptor (CAR)-T cells, the latter being a major immunotherapeutic advance for hematologic malignancies. In a recent preclinical study, the cytotoxic potential of CAR-T cells targeting an HLA-presented WT1 antigen was enhanced by the concurrent administration of a dendritic cell vaccine against the corresponding antigen, which facilitated CAR-T–cell proliferation and activation (14). Although such a combination strategy still requires clinical development, this study raises the tantalizing possibility of future personalized immunotherapy combining multiplexed neoantigen vaccines with CAR-transduced T cells corresponding to neoantigen targets that can be further augmented by immune checkpoint inhibitors.

**Delivery of Cancer Vaccines for Patients with Hematologic Malignancies**

An important consideration for vaccination in patients with hematologic malignancies is the choice of vaccination setting and the optimization of vaccination timing to derive maximal benefit from vaccine therapy. In this regard, cancer vaccines are generally more effective in patients with lower tumor burden that is expected to be accompanied by a lower level of immunosuppression (i.e., early-stage disease, or minimal residual disease or postallograft settings). For patients with more clinically advanced disease, there is compelling rationale for the use of conventional cancer treatments to achieve substantial tumor load reduction prior to administering cancer vaccines.

In patients receiving highly T-cell–depleting treatments such as alemtuzumab and purine analogues, it is likely beneficial to await recovery from lymphopenia before undergoing vaccination, although lymphopenia following conditioning chemotherapy has been shown in preclinical models to create a favorable cytokine milieu for T-cell propagation and expansion. Alternatively, chemotherapy-related myelosuppression may have beneficial effects on immunity that can be exploited to maximize vaccine efficacy. It has been shown, for example, that cyclophosphamide and gemcitabine reduce Treg numbers and proliferation, whereas gemcitabine- and platinum-based chemotherapy increases M1 macrophages and decreases MDCs. Timing vaccinations with chemotherapy could allow these benefits to be reaped. Indeed, a study on cervical cancer showed that timing human papillomavirus vaccines with the second and subsequent cycles of carboplatin/paclitaxel chemotherapy, when MDCs were at their lowest levels, enhanced immune response to vaccination (15). Likewise, in patients receiving...
allogeneic hematopoietic stem cell transplantation, the postransplant period with prevailing low disease burden, fully functional reconstituted immunity, and an inflammatory state that supports antigen presentation provides particularly favorable conditions for vaccination.

WHAT TYPE OF IMMUNE RESPONSE IS DESIRABLE FOR A COVID-19 VACCINE?

Evaluating Immune Response to COVID-19 Vaccination

Similar to many other infectious agents, the generation of neutralizing antibodies against SARS-CoV-2 is currently the holy grail of immunity against COVID-19, particularly antibodies against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, the molecule that facilitates viral entry into host respiratory epithelial cells through its interaction with the epithelial angiotensin-converting enzyme 2 receptor. In this regard, the titer of antibodies reactive to the RBD/spike protein and neutralization of viral infectivity are the primary measures of response to COVID-19 vaccines.

However, some patients recovering from COVID-19 infection do not have detectable neutralizing antibodies against SARS-CoV-2, and in those who do, their levels are observed to decline rapidly after recovery. On the other hand, in the majority of convalescent patients, a CD4+ and CD8+ memory T-cell response is also seen. The T-cell response can be multispecific, directed toward antigens derived from SARS-CoV-2 viral matrix, envelope, and nucleoprotein as well as the spike protein, and reminiscent of the polyepitopic T-cell responses observed with multivalent neoantigen vaccines. These “natural history” data support the notion that both humoral and cellular immunity, perhaps orchestrated in a coordinated manner, is required for immunity against COVID-19. Although we will have to learn as data emerge from the COVID-19 vaccine experience, we posit that the efficacy of a COVID-19 vaccine will likely not be judged solely by its ability to elicit an antibody response, but also by the potency and breadth of the generated T-cell response upon which vaccine protection indispensably depends.

Optimizing the Immunogenicity of COVID-19 Vaccines

There are currently >100 COVID-19 vaccines under preclinical or clinical development, including several in phase III trials. These vaccines utilize a range of platforms. The most advanced vaccines utilize recombinant viral vectors, attempting to mimic the natural immunogenicity of such viruses [AZD1222 (Oxford/AstraZeneca) and Ad26.COV.2.S (Johnson & Johnson)] or protein-encoding mRNA [BNT162 (BioNTech/Pfizer) and mRNA-1273 (Moderna)]. Other platforms include inactivated whole-virus vaccines [PfCoVacc (Sinovac) and BBIBP-CorV (Sinopharm)] and protein subunit vaccines [NVX-CoV2373 (Novavax)]. No SARS-CoV-2 attenuated strains are currently available. Which platform(s) will generate immune responses of sufficient quantity and quality is to be determined and anxiously awaited.

The engineered viral-vector or mRNA vaccines currently target only the SARS-CoV-2 spike protein. Notably, BNT162 targets exclusively the RBD within the spike protein. Although BNT162 has shown clinical efficacy, vaccines targeting a single SARS-CoV-2 domain potentially risk losing effectiveness in the event of viral mutation or variable antigen presentation, as demonstrated by the limitations of monospecific or oligospecific cancer vaccines. In contrast, vaccines targeting multiple SARS-CoV-2 coding domains, such as inactivated virion vaccines, have similarities to whole-cell vaccines in that they act against polyepitopic targets from the entire SARS-CoV-2 virion. This gives rise to a multitude of antibody and T-cell responses, thus offering additional layers of protection.

An issue intrinsic to the viral platforms is immunogenicity against the viral components, both preexisting immunogenicity in some individuals in the form of antiviral antibodies due to prior virus exposure and vaccine-generated immunogenicity that could abrogate later doses. In this respect, the chimpanzee adenoviral vector ChAd adopted for AZD1222 is less affected by preexisting immunity than the human adenoviral vector Ad26 used for Ad26.COV.2.S. This is because ChAd, being derived from a chimpanzee virus, has lower human seroprevalence than Ad26, whereas preexisting immunity against Ad26 may potentially hamper vaccine response. With respect to other vaccine platforms, peptide, protein subunit, or inactivated COVID-19 vaccines are generally thought to be less immunogenic and elicit weaker CD8+ T-cell response than other vaccine types. However, as peptide and whole-cell cancer vaccine studies demonstrate, robust immune responses are achievable with the use of longer peptides, potent adjuvants, and advanced delivery systems.

Although SARS-CoV-2 may not display genetic heterogeneity to the extent seen in cancer or in viruses like influenza or human immunodeficiency virus, the evolution of SARS-CoV-2 quasi-species is recognized both within individual patients and at a population level, which, in some cases, will inevitably result in immune escape. Future modification and renewal of COVID-19 vaccine targets will undoubtedly be required in light of antigenic evolution. Neoantigen vaccines have spurred the development of enabling technologies that provide us with versatile systems to identify and select immunogenic antigen targets and manufacture multivalent vaccines corresponding to these targets with rapidity. Meanwhile, the field of cancer vaccines continues to be actively engaged in efforts to further enhance vaccine immunogenicity through innovative use of adjuvants and delivery platforms. These systems could be cross-fertilizing and potentially be adapted for future COVID-19 vaccine development.

CONCLUSION AND PERSPECTIVES

In reviewing our cancer vaccine experience, we can clearly identify areas of relevance for COVID-19 vaccine development, particularly around T-cell immunity and the importance of a broad, polyepitopic response. Notwithstanding these important overlaps, because COVID-19 vaccines are designed for prophylactic use, we can hopefully anticipate that some issues encountered with cancer vaccines that are primarily applied in the therapeutic setting, such as local and systemic immunosuppression, will not overlap in the majority of cases. Thus, efforts targeting premalignant lesions (e.g., monoclonal gammopathy) or a genetic
predisposition to cancer (e.g., familial Lynch syndrome) may be more relevant comparators.

In patients with hematologic malignancies where immunosuppression can be profound, immunomodulatory drugs such as immune checkpoint inhibitors and lenalidomide could potentially play a role in reinvigorating functionally exhausted immunity that might impede an effective response to COVID-19 vaccination. In addition, our cancer vaccine experience suggests that these patients might possibly benefit from rational timing of COVID-19 vaccinations in relation to cancer treatments to maximize vaccine efficacy. Admittedly, the nature of immune response to therapeutic cancer vaccines and prophylactic COVID-19 vaccines may have differences, with antibody-dependent enhancement of viral infection being a particularly important consideration for COVID-19 vaccines. It is therefore of paramount importance that any strategy aiming at enhancing vaccination response to COVID-19 in patients with cancer be tested within the context of well-designed clinical trials. Cancer and COVID-19 vaccine development will each benefit from the knowledge, failures, and successes of the other as we forge a path to lasting immune protection against these life-threatening diseases.

Authors’ Disclosures

C.J. Wu reports equity in BioNTech, as well as a patent for compositions and methods for personalized neoplasia vaccines pending, licensed, and with royalties paid from BioNTech, a patent for combination therapy for neoplasia vaccine pending, licensed, and with royalties paid from BioNTech, a patent for methods for profiling the T-cell receptor repertoire issued, licensed, and with royalties paid from BioNTech. E.F. Fritsch reports other from BioNTech (equity holder and consultant) and BioEnte (equity holder) outside the submitted work, as well as a patent for compositions and methods for personalized neoplasia vaccines pending, licensed, and with royalties paid from BioNTech, a patent for formulations for neoplasia vaccines pending, licensed, and with royalties paid from BioNTech, a patent for a nonrandomized clinical trial. Cancer and COVID-19 vaccine development will each benefit from the knowledge, failures, and successes of the other as we forge a path to lasting immune protection against these life-threatening diseases.

Acknowledgments

M. Kwok is supported by a UK National Institute for Health Research clinical lectureship. This work is supported by the NIH (NCI-1R01CA155010).

Published first December 17, 2020.

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## Updated version
Access the most recent version of this article at:
doi: [10.1158/2643-3230.BCD-20-0205](https://doi.org/10.1158/2643-3230.BCD-20-0205)

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