Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Cancer Cell

CellPress

Voices

Cancer vaccines

Given the renewed interest in vaccine development sparked by the COVID-19 pandemic, we are revisiting the current state of vaccine development for cancer prevention and treatment. Experts discuss different vaccine types, their antigens and modes of action, and where we stand on their clinical development, plus the challenges we need to overcome for their broad implementation.

John T. Schiller and Douglas R. Lowy
National Cancer Institute

HPV vaccines: Exceeding expectations

Human papilloma virus (HPV) prophylactic vaccines are based on the simple and compelling concept that antibody-mediated prevention of oncogenic HPV infections will prevent the cancers they cause. Given our involvement since their inception, it has been gratifying to observe that the HPV vaccines have exceeded expectations throughout their development and deployment. Immunologically, the consistently high and durable virion-neutralizing antibody responses they induce far exceed predictions for a protein subunit vaccine. Clinically, they provide almost complete and long-lasting protection against incident persistent infection and premalignant disease caused by the multiple HPV serotypes specifically targeted by the vaccines. Surprisingly, these immunologic and clinical outcomes are observed even after even a single dose. Multidose regimens have also demonstrated herd protection when only ~50% of female birth cohorts were vaccinated and, most importantly, >85% reduction in cervical cancer after adolescent vaccination.

Several factors contribute to these remarkable findings. First, the vaccine immunogens are virus-like particles, whose dense repetitive array of surface epitopes generates exceptionally strong activation and survival signals in cognate B cells. Second, the mechanism of epithelial HPV infection is a remarkably slow process, which makes the virus exceptionally susceptible to inhibition by low levels of antibodies. Third, the surface epitopes encoded by HPV DNA genomes do not rapidly evolve to escape vaccine-induced antibodies. Of note, current COVID-19 vaccines lack these attributes.

HPV vaccines have the potential to annually prevent >500,000 cervical, anogenital, and oral cancers worldwide. However, only 13% of the world's adolescent girls have been fully vaccinated with the recommended two-dose schedule. In our opinion, a dramatic increase in vaccine uptake, especially in low-resource settings, where the majority of HPV cancers occur, could be accomplished by switching to single-dose vaccination programs, as recently recommended by vaccine advisory bodies of the United Kingdom and the WHO.

Ian H. Frazer
The University of Queensland

HPV—Leading the way

Prophylactic vaccines that can prevent infection with cancer-associated HPV genotypes are envisaged to enable eradication of HPV-associated cervical cancer globally by the end of this century, through mass immunization combined with screening and treatment. This goal may be facilitated by the recent observation that a single dose of HPV vaccine seems effective in preventing HPV infection in young people, enabling mass immunization campaigns targeting early adolescents and avoiding the need for follow-up immunization programs.

As HPV-associated cancers continue to express viral proteins and to present these to the host immune system, there is an expectation that immunotherapy targeting the cancer-associated viral early proteins (HPV16 E6 and HPV16 E7) might become the basis of cancer-specific immunotherapy. Unfortunately, clinical trials to date have shown little efficacy for HPV-targeted immunotherapy in patients with HPV-associated cancer and have also proven ineffective for HPV-associated cervical pre-malignancy (CIN 2/3), either when delivered as single immunogens or when combined with

checkpoint inhibitors. Studies of the impact of skin-directed expression of HPV E7 protein on local immunity in animals have suggested that HPV-induced hyperproliferative epithelium impairs local T cells' immune effector cell function and dendritic cell-mediated antigen presentation, which may partly explain these findings. They may also be contributed to by a demonstrated MHC linkage to risk of developing cervical cancer, suggesting that the 1% of HPV infections that progress to cancer may fail to invoke effective immunity to the primary HPV infection and also to subsequent immunotherapy. Further research is required to resolve this issue.

Olivera J. Finn
University of Pittsburgh School of Medicine

MUC1 vaccines: Path to prevention

When starting my laboratory in 1982, my goal was to use important advances in our understanding of the mechanisms of antigen processing, presentation, and recognition by T and B cells to search for ever-elusive tumor antigens. I focused on pancreatic, breast, and colon cancers and what patients' immune systems recognized on those tumors. All patients showed immunity against their tumors and a shared reactivity against epithelial mucin MUC1.

In 1993 we started a clinical trial testing a MUC1 vaccine in breast, colon, and pancreatic cancers. Our goal was to boost pre-existing immunity and/or generate new immunity to destroy tumors and prevent recurrence. After 15 years and seven clinical trials, we failed to reach this goal. The same fate met all other therapeutic vaccines as they came face to face with a newly recognized problem: strong immunosuppression present in cancer patients, which limited vaccine immunogenicity.

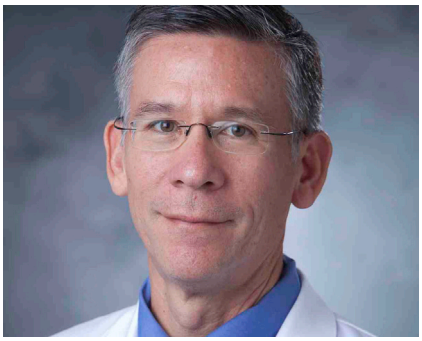
Where do cancer vaccines go from here? Several are being combined with checkpoint inhibitors or adoptively transferred T cells to amplify immunotherapeutic effects. In 2010, we took our MUC1 vaccine down the path to cancer prevention. MUC1 is abnormally expressed on premalignant lesions. In patients with premalignant colonic adenomas, MUC1 vaccine is strongly immunogenic, safe, and shows potential of preventing new adenomas, thus reducing colon cancer risk. We are planning trials in two other premalignancies, ductal carcinoma *in situ* (DCIS) and Barrett's esophagus. Many vaccines that failed as therapy could show efficacy in prevention. Inexpensive, safe, and broadly applicable preventative cancer vaccines could in time stop the cancer pandemic.

Eduardo Vilar
The University of Texas MD Anderson Cancer Center

Cancer interception in Lynch syndrome

Lynch syndrome (LS) affects >1 million Americans, imparting significantly increased risks of several malignancies, especially colorectal and endometrial cancers. LS results from a heterozygous germline mutation in one of four DNA mismatch repair (MMR) genes. When LS cells harboring the germline defect acquire a somatic "second hit" in one of the MMR genes, they lose the ability to maintain genomic integrity, thereby accumulating hundreds to thousands of small insertion/deletions (indels) in microsatellite regions. When these indels occur in coding regions, they result in the expression of mutated neoantigens (frameshift peptides) that are presented on the cell surface via the major histocompatibility complexes (MHC-I/II). Extensive inter-individual variability in both the set of expressed neoantigens and MHC I/II responses has previously challenged the development of a neoantigen-based vaccines for LS patients. However, recent improvements in bioinformatic approaches now allow us to more accurately catalog and identify the most frequently recurring and shared neoantigens in LS-associated tumors. We can now combine sophisticated bioinformatic pipelines with state-of-the art immunology assessments to determine the most immunogenic neoantigens for inclusion in population-based vaccines. Using this approach, the Vilar Lab has worked with Nouscom, s.r.l., and the National Cancer Institute to develop a phase I clinical trial (NCT05078866) using a viral-based vaccine encoding 209 distinct mutated neoantigens present in LS tumors. The primary endpoint is the safety and assessment of immunogenicity. Forty-five participants will be enrolled to receive a prime and boost vaccine, based on a Great Apes and Modified Vaccina Ankara Virus, respectively. Going forward, it will be important to study the ability of NSAIDs to synergize with

a vaccine, as preclinical work in an LS mouse model suggests that the combination of peptide vaccination with either aspirin or naproxen prolongs survival and reduces tumor burden significantly more than vaccination alone. A phase Ib trial in 80 LS patients provides further support for the ability of naproxen to activate different types of immune cells resident in the intestine.



H. Kim Lyerly
Duke University

Self-replicating mRNA vaccines

The potential uses of RNA technology have been increasingly appreciated as SARS-CoV-2 vaccines based on mRNA platforms have been rigorously evaluated and approved for widespread use. First-generation vectors, derived from an RNA alphavirus, are produced by providing the structural proteins in *trans* to create viral replicon particles (VRPs). We have demonstrated that VRP-based vaccines expressing either tumor-associated antigens (such as CEA) or established oncogenes (such as HER2) induce substantial immune responses, despite elevated levels of regulatory T cells in patients with advanced cancers. While mRNA delivery and expression enable target protein production capable of eliciting protective humoral immunity, the relative potency and durability of these responses, as well as the ability to generate robust $CD8^+$ T cell responses, continue to be evaluated.

Alternatives to conventional mRNA-based vaccines include self-replicating RNA (srRNA) capable of amplification up to 100,000-fold after delivery into a cell, but without integration into the host genome. Whether srRNA vaccines provide enhanced cellular and humoral immunity is being tested in a variety of applications, including oncology. Recently, fully synthetic versions of srRNA have been developed, where the viral structural proteins are replaced with a lipid nanoparticle or polymer. Lack of a viral shell allows for repeated dosing due to no or lower anti-vector immunity and a cost-effective, scalable manufacturing process. In addition, the packaging capacity of the viral particle is no longer a limitation, allowing vectors to encode multiple larger genes of interest, including vaccines we are developing to the multiple known activating mutations in proteins encoded by the estrogen receptor or PI3Kα. New cancer vaccine development approaches will optimize these customizable, synthetic srRNA vectors to maximize the chance of clinical success.

Sacha Gnjatic
Icahn School of Medicine at Mount Sinai

Overcoming peripheral tolerance

Cancer vaccines, in particular those eliciting an integrated immune response with coordinated $CD4^+$ T, $CD8^+$ T, and B cell induction, are still a developing arm in the arsenal of tumor immunotherapies. Their aim is to focus immune effectors toward targets expressed in cancer cells, with as much specificity as possible to spare untransformed cells. Many shared tumor antigens, including cancer-testis antigens, were shown to elicit spontaneous immunity in a subset of individuals, which in turn led to a decade of coordinated clinical trials to establish rules of therapeutic vaccine immunogenicity, to induce or boost such responses in cancer patients. While a high frequency of humoral and cellular high-avidity immune responses could be achieved with adjuvanted long peptides or RNA, clinical benefit from vaccines alone has been lacking in clinical trials, without clear mechanisms to explain why. Sequences derived from neoantigens, i.e., arising from aberrations such as mutations unique to tumors, have revived interest in vaccines because of the premise of lack of central immune tolerance, but ultimately, they are proving to face the same unresolved issues as shared tumor antigens: with the best epitopes likely already edited out of the tumor by immune surveillance, how to overcome peripheral tolerance, both intrinsic to immune effectors (low T cell avidity and functionality) and extrinsic once effectors arrive at the local tumor site (suppressive environment, accessibility)? Many challenges still need to be solved, such as timing of vaccine intervention, understanding immunodominance and polyclonality to avoid immune escape, and defining combinations with various immunomodulators both systemic and local. Rising evidence that immune aggregates at the tumor site may represent tumor antigen-specific natural vaccine mini-factories which predict

response to immunotherapy only emphasizes the need to continue research into strategies for exogenous priming or boosting.

Neeha Zaidi
Johns Hopkins School of Medicine

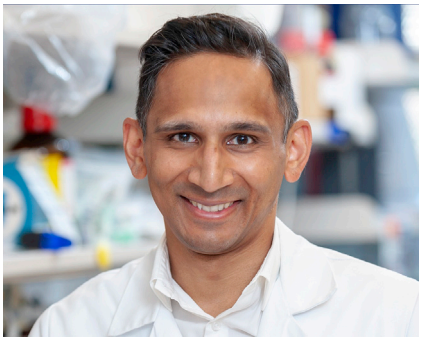
Harnessing the power of DCs

Dendritic cells (DCs) are known for their efficiency in presenting antigens to T cells—a key component of the immune system's fight against cancer. DCs are thus an ideal cell type to harness therapeutically in order to elicit anti-tumor $CD4^+$ and $CD8^+$ T cell responses against specific cancer epitopes. Multiple studies have pulsed DCs *in vitro* with tumor antigens from dying tumor cells, or RNA or peptides corresponding to specific tumor epitopes. Although such studies have shown variable outcomes, the only therapeutic cancer vaccine that has been FDA approved to date is a prostate cancer DC vaccine, Sipuleucel-T, for use against asymptomatic or minimally symptomatic castration-resistant prostate cancer. Methods to generate mature and effective DCs *in vitro*, optimize DC maturation stimuli, and load antigens, as well as algorithms to select immunogenic tumor antigens, will continue to advance DC-based vaccines in the clinic. A second related set of strategies involve coaxing DCs to pick up tumor antigens *in vivo*—for example, GVAX is an irradiated, autologous vaccine consisting of tumor cells modified to secrete GM-CSF. These irradiated tumor cells allow for antigens to be picked up by DCs and then get presented to T cells. GVAX in combination with immune checkpoint blockade has yielded clinical responses in advanced pancreatic cancer, among other immunologically cold cancers. Areas of promise include combining DC vaccines and other immunotherapy strategies, such as immune checkpoint blockade; the use of personalized neoepitopes enabled by the rapidity, efficiency, and low cost of next-generation sequencing; and the deployment of mRNA technology to encode multiple epitopes more rapidly and efficiently in DC-based vaccines as well as for co-encoding of DC maturation stimuli.

Patrick A. Ott
Dana Farber Cancer Institute

Personalized cancer vaccines

Cancer vaccines aim to eliminate tumor cells by stimulating and broadening T cell responses specific for those cells. The lack of a foreign invader to target against and the diversity and complexity of tumors are key obstacles and explain at least in part why it has been difficult to achieve successes similar to vaccines against infectious pathogens. The availability of powerful genomic sequencing technologies has enabled the targeting of neoantigens encoded by tumor mutations, which is conceptually attractive, as cancer is a disease driven and characterized by mutations. Because most mutations are specific to individual tumors (i.e., not shared) and the restriction of neoantigen epitopes to specific MHC molecules, vaccines directed at neoantigens ideally should be customized for each individual patient. Initial forays in the clinic have demonstrated that such personalized vaccines are feasible and immunogenic in patients with cancer. While signals for vaccine-mediated anti-tumor activity have been detected in these early trials, more definitive efficacy data from ongoing randomized studies are awaited. Key opportunities for further progress lie broadly in three arenas: (1) vaccine technology, (2) neoantigen discovery, and (3) co-therapies. Improved vaccine technology includes the development of optimal vaccine formulations, delivery vehicles, and immune adjuvants including most effective dosing and scheduling, as well as timely and cost-effective manufacturing processes. Innovation in the neoantigen discovery field can be achieved by further optimizing current neoantigen prediction tools including the development of new discovery tools that will allow tapping into new classes of neoantigens. Co-therapies will be critical to maximize priming of vaccine-induced T cells and to counteract immune suppressive circuits in the tumor microenvironment.



Vinod P. Balachandran
Memorial Sloan Kettering Cancer Center

Custom cancer vaccines

It is clear that mutation-derived neoantigens spark the immune system to target and even eliminate cancers. To translate this discovery into new immunotherapies, the simplest medicine to target a neoantigen would be a vaccine. Yet, as most neoantigens arise in cancer-specific passenger mutations, unique challenges emerge.

First—which neoantigens are ideal for vaccines? As cancers can generate hundreds of mutations but only a fraction become immunogenic, custom vaccines will require a universal neoantigen selection strategy. Though current strategies measure how strongly neoantigens bind the MHC, a comprehensive strategy must further quantify how neoantigens activate T cells. As most neoantigens differ from wild proteins by merely single amino acids, understanding which substitutions activate T cells will be critical to rationally select neoantigens for vaccines.

Second—what tumors are suited for vaccines? The lowly mutated immunologically "cold" tumor—that one may presuppose renders them suboptimal for vaccines—may paradoxically be ideal to refine vaccination principles. Their lower mutation burden reduces the selection challenge to a lower dimension. Cold tumors also harbor pools of weak neoantigens that can be boosted by vaccines. Thus, cancers like pancreatic cancer may be ideal target diseases to iteratively improve best vaccination strategies.

Lastly—custom vaccines require a platform to rapidly manufacture the drugs in real time. As the COVID-19 pandemic has abruptly revealed mRNA's potential to create vaccines with startling speed, we are poised to see if this sudden awareness can spur similar efforts to use mRNA to create custom cancer vaccines.

Pierre-Yves Dietrich and Denis Migliorini
University of Geneva and Swiss Cancer Center Léman

Brain tumors: The ultimate challenge

Malignant gliomas remain a devastating disease. In contrast to many cancer types, vaccines and other immunotherapies were initially considered as an unrealistic dream for brain tumors, because of the blood-brain barrier (BBB) properties allowing only partial efflux of immune cells and due to the absence of identified glioma antigens and the astounding ability of the glioma and its microenvironment to cloak itself to any immune cell attack. In the 2000s, however, we started to understand the rules by which the immune system plays within the CNS; to identify the immune roles of the resident brain cells; to dissect the mechanisms underlying homing, transmigration through the BBB, and retention; and to distinguish subpopulations of immunosuppressive cells. Next, glioma antigens were identified, opening the promise of specific targeting of tumor cells while sparing collateral damage, at least theoretically. These discoveries fostered the development of various vaccine strategies, including personalized vaccines. Clinical success was far from expected, partly due to the low mutational burden, the lack of mutated cell surface-presented peptides, and the immune hostile brain microenvironment. But this wave of basic, translational, and clinical research, in addition to amazing advances in biotechnology, bioinformatics, manufacturing, and imaging, is now opening a novel therapeutic dimension combining different approaches: (1) RNA vaccines and derivates encoding for proteins of interest leveraging the innate immune system or other cell-based therapies, (2) engineered immune cells as CAR-T cells (i.e., recent clinical success for patients with H3K27M-mutated diffuse midline glioma with GD2 CAR-T cells), and (3) strategies to reprogram the immunosuppressive microenvironment. The next decade should definitively be the good one to switch from illusion to realistic hope for the treatment of glioma patients.

Robert H. Vonderheide and Susan M. Domchek
University of Pennsylvania

hTERT DNA vaccines

The impact of cancer immunotherapy and the ever-growing biological insights that underpin these advances have prompted us to consider the potential of immune strategies for cancer interception, what we call "immuno-interception." Neither truly prevention nor therapy, cancer interception erases non-invasive neoplastic lesions that would otherwise progress toward cancer and metastasis. Polypectomy of adenomatous polyps during colonoscopy is an example of mechanical cancer interception. Because polypectomy does not reduce the underlying driving factors, whether genetic or lifestyle, patients with polyps are asked to repeat colonoscopy in 3 years—to be intercepted again if needed.

To enable immuno-interception with broad applicability, we have focused on universal tumor antigens and identified the catalytic subunit of telomerase, hTERT, as a surprisingly immunogenic target that is so fundamental to early steps in oncogenesis that loss as a means of immune escape is felt unlikely. Most recently, we vaccinated 93 cancer patients with hTERT plasma DNA and electroporation and reported *de novo* hTERT-specific T cell responses in 96% of participants who had been in remission after standard treatments for high-risk local tumors. Toxicity was minimal. We are now testing hTERT DNA vaccination for immuno-interception in individuals who carry mutations in *BRCA1* or *BRCA2* and are thus at very high lifetime risks of breast, ovarian, pancreas, prostate, and other cancers (NCT04367675). In the first cohort, vaccines are given to *BRCA1/2* mutation carriers in remission after therapy for local tumors. Next, healthy individuals who carry *BRCA1/2* mutations and yet have never been diagnosed with cancer will be enrolled. If hTERT-specific T cells can eliminate early, non-invasive lesions, the clock will be reset. Instead of necessarily relying on persistent hTERT T cell memory, we can intercept again even years later with booster vaccines. Pulses of immuno-interception—akin to repeat polypectomy as mechano-interception—may be a safer and more feasible approach.

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DECLARATION OF INTERESTS

J.T.S. and D.R.L. are co-inventors of U.S. goverment-owned patents related to the HPV vaccine technology that were licensed to Merck and GlaxoSmithKline, but these licensed are now expired. I.H.F. is a named inventor on patents relating to HPV prophylactic and therapeutic vaccines; the University of Queensland as employer of I.H.F. receives royalties from the sale of HPV prophylactic vaccines referred to in the article; I.H.F. is a director of a company (Jingang Medcines Australia Pty LTd) involved in developing thearpeutic vaccines for HPV-associated cancers. E.V. has a consulting or advisory role with Janssen Research and Development and Recursion Pharma and has received research support from Janssen Research and Development; note that these financial relations are not connected to the research reported in this manuscript. E.V. is an author of a patent related to this work (PCT/US2022/023,714). H.K.L. is a member of the board of directors and shareholder of Oncosec; is a co-founder of Replicate, a shareholder, and a member of its scientific advisory board; is a founder of Sonokine, and shareholder; and is a co-founder of Trio, and shareholder. P.A.O. received research funding from and has advised Neon; Therapeutics, Bristol Myers Squibb, Merck, CytomX, Pfizer, Novartis, Celldex, Amgen, Array, AstraZeneca/MedImmune, Armo BioSciences, Xencor, Oncorus, Phio, Evaxion, LG Chem, and Roche/Genentech. V.P. B. is an inventor on patent applications related to work on antigen cross-reactivity and neoantigen quality modeling. P.-Y.D. is an inventor on patents related to CAR T cell therapy and vaccines filed by the University of Geneva and has been a consultant for Amal Therapeutics. D.M. is an inventor on patents related to CAR T cell therapy, filed by the University of Pennsylvania and the University of Geneva, and has been a consultant for Limula Therapeutics and MPC Therapeutics. R.H.V. is an inventor on a licensed patent relating to cancer cellular immunotherapy and cancer vaccines; R.H.V. receives royalties from Children's Hospital Boston for a licensed research-only monoclonal antibody. All other authors declare no competing interests.