

Advances and challenges in cancer immunoprevention and immune interception

Sasha E Stanton ¹, Philip E Castle,^{2,3} Olivera J Finn,⁴ Shizuko Sei ²,
Leisha A Emens ⁵

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¹Cancer Immunoprevention Laboratory, Earle A Chiles Research Institute, Providence Cancer Institute, Portland, Oregon, USA

²Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Rockville, Maryland, USA

³Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, Maryland, USA

⁴Department of Immunology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

⁵Ankyra Therapeutics, Boston, Massachusetts, USA

Correspondence to

Dr Sasha E Stanton;
Sasha.Stanton@providence.org

ABSTRACT

Invasive cancers typically evade immune surveillance through profound local and systemic immunosuppression, preventing their elimination or control. Targeting immune interventions to prevent or intercept premalignant lesions, before significant immune dysregulation has occurred, may be a more successful strategy. The field of cancer immune interception and prevention is nascent, and the scientific community has been slow to embrace this potentially most rational approach to reducing the global burden of cancer. This may change due to recent promising advances in cancer immunoprevention including the use of vaccines for the prevention of viral cancers, the use of cancer-associated antigen vaccines in the setting of precancers, and the development of cancer-preventative vaccines for high-risk individuals who are healthy but carry cancer-associated heritable genetic mutations. Furthermore, there is increasing recognition of the importance of cancer prevention and interception by national cancer organizations. The National Cancer Institute (NCI) recently released the National Cancer Plan, which includes cancer prevention among the top priorities of the institute. The NCI's Division of Cancer Prevention has been introducing new funding opportunities for scientists with an interest in the field of cancer prevention: The Cancer Prevention-Interception Targeted Agent Discovery Program and The Cancer Immunoprevention Network. Moreover, the Human Tumor Atlas Network is spearheading the development of a precancer atlas to better understand the biology of pre-invasive changes, including the tissue microenvironment and the underlying genetics that drive carcinogenesis. These data will inform the development of novel immunoprevention/immuno-interception strategies. International cancer foundations have also started recognizing immunoprevention and immune interception with the American Association for Cancer Research, Cancer Research UK and the Society for Immunotherapy of Cancer each implementing programming focused on this area. This review will present recent advances, opportunities, and challenges in the emerging field of cancer immune prevention and immune interception.

BACKGROUND AND CHALLENGES OF IMMUNOPREVENTION

The immune system eliminates premalignancies through adaptive immune responses. Therefore detectable premalignant changes

represent lesions that have escaped the immune system.¹ The question, therefore, is what immunity is required to suppress or eliminate emerging tumors (protective immunity). One example of protective immunity includes T cell and antibody responses to the oncogene cyclin B1 seen in healthy individuals. Preclinically, cyclin B1 immune responses following vaccination with cyclin B1 peptides in p53^{-/-} mice protect mice from developing spontaneous cancers.² Prophylactic vaccines for virally mediated cancers, like human papillomavirus (HPV) vaccines, induce sterilizing immunity where neutralizing antibodies prevent viral pathogen-induced premalignancies and invasive cancer by preventing primary viral infection.³ Immune interception and prevention strategies would harness the immune system to prevent the development of invasive cancer at a stage when antitumor immunity is most effective and there is the optimal impact on public health (figure 1). This will require identifying individuals at high risk of developing cancer through optimized screening and early detection methods, understanding the features of antitumor immunity required for the elimination of evolving premalignant disease, establishing immune memory to prevent invasive disease, and developing immune-based interventions that effectively achieve these goals.

Cancer was the second most common cause of death worldwide with approximately 8.97 million deaths in 2019. Projections by the WHO and the American Cancer Society estimate ~18.63 million cancer deaths per year by 2060, bringing it to the leading cause of mortality.⁴ Currently, there are four areas of focus in clinical immunoprevention: cancer vaccines (targeting tumor-associated antigens, cancer testis antigens, and tumor-specific antigens, for example from oncogene mutations or gene fusions), non-specific

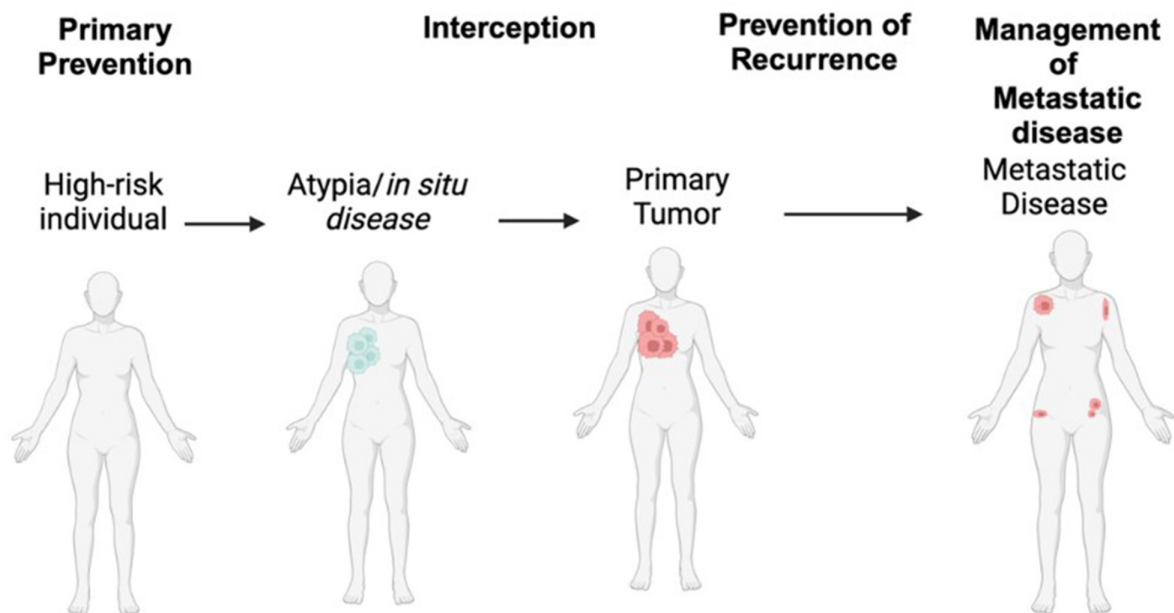


Figure 1 Stages of immunoprevention: primary prevention, interception, and prevention of invasive disease recurrence or management of metastatic disease. The illustration in the figure shows lung disease for the sake of representation of cancer progression and interception. Figure created with BioRender.com.

immunomodulation (including toll-like receptor agonists, retinoids, and rexinoids), immune checkpoint inhibitors, and lifestyle modifications (including weight loss to reduce obesity-related inflammation) (table 1).⁵⁻⁸ The field is small and would benefit from new scientists, improved funding from the National Cancer Institute (NCI) and other funding agencies, increased recognition of immunoprevention research with targeted prizes, engagement of the pharmaceutical industry, and greater patient advocacy and education. Scientific challenges include insufficient knowledge about the immune environment of developing cancers, lack of animal models for preclinical testing of immunoprevention strategies, insufficient biomarkers for early detection of precancer and measuring intervention outcomes, and lack of surrogate endpoints to allow shorter-duration clinical trials. The Society for Immunotherapy of Cancer (SITC) held a virtual summit to convene experts in this field to discuss opportunities and challenges in immunoprevention and immune interception in April 2023 (table 2). Key findings from the summit are presented in this review.

PREVENTION VACCINES FOR VIRALLY INDUCED CANCERS

Immune prevention of virally induced cancers has advanced the most, with approved prophylactic vaccines having a global impact on the incidence of several cancers, including hepatocellular carcinoma (hepatitis B virus (HBV) vaccine) and cervical cancer (HPV vaccines).^{9,10} Where hepatitis B is endemic, the HBV vaccine has significantly reduced the incidence of pediatric hepatocellular carcinoma. In a randomized controlled trial in China with 41,136 participants in the vaccination arm, 41,730 participants in the non-vaccinated control arm, and 37

years follow-up, the incidence of liver cancer was significantly lower in the vaccination arm (HR 0.28; $p=0.007$), reflecting a 70% protection against liver cancer deaths (95% CI 30% to 89%).⁹

HPV infections are the cause of ~5% of all cancers worldwide and virtually all cervical cancers. Current prophylactic HPV vaccines are based on HPV L1 protein recombinantly expressed in cell lines and self-assembled virus-like particles (VLPs). These VLPs resemble native viral capsids but do not cause infection nor are oncogenic because they lack the viral genome necessary for viral replication. Durable, high neutralizing antibody titers are induced as the result of its stable, repetitive structure (72 capsomers each composed of 5 copies of L1 protein) that strongly stimulate CD4 responses through effective receptor-mediated endocytosis.³ The first generation of HPV vaccines targeted HPV types HPV16 and HPV18, responsible for ~70% of HPV-related cancers. The next generation of vaccines include high-risk HPV types HPV31, HPV33, HPV45, HPV52, and HPV58 which, with HPV16 and HPV18, cause 90% of HPV-related cancers. Current HPV vaccines are prophylactic and do not treat pre-existing HPV infections.¹¹

Recent reports from Finland, Denmark, Sweden, and England provide real-world evidence that HPV vaccination significantly reduces the incidence of cervical cancer.¹²⁻¹⁵ Younger age at vaccination correlates with better protection against invasive cervical cancer, especially in those younger than 17 years.^{12,14,15} This is presumably due to fewer young individuals being sexually active and already infected with the targeted HPV types. As more individuals are vaccinated, there will be a reduction of infection in the population by herd immunity

Table 1 Cancer immunoprevention and immune interception studies

Therapy	Immune prevention	Immune interception	Stage of research	NCT number	Primary institution
Virally-induced cancer prevention	HBV vaccine		FDA approved		
	HPV vaccine		FDA approved		National Institutes of Health
	EBV vaccine		Preclinical		Dana Farber
	<i>Helicobacter pylori</i> vaccine		Preclinical		
Primary prevention vaccines	Kras mutation vaccine in high-risk individuals with pancreatic cysts		Phase I	NCT05013216	Johns Hopkins
	hTERT vaccine BRCA1/2 mutation carriers		Phase I	NCT04367675	University of Pennsylvania
	Lynch syndrome carrier vaccine with 209 conserved Lynch neoantigens		Phase I	NCT05078866	MD Anderson
	CEA/MUC1/brachyury with IL-15 agonist in Lynch syndrome carriers		Phase IIb	NCT05419011	MD Anderson
	MUC1 peptide-poly ICLC vaccine in current and former smokers		Phase I	NCT03300817	University of Pittsburgh Mayo Clinic
Cancer interception vaccines		Kras mutation vaccine in PanIN	Phase I	NCT04117087	Johns Hopkins
		MUC1 peptide-poly ICLC vaccine in colon adenoma	Phase II	NCT00773097	University of Pittsburgh
Immune therapies to enhance cancer interception		Nivolumab in proliferative leukoplakia	Phase I	NCT03692325	Dana Farber
		BCMA CAR T-cell therapy smoldering myeloma	Phase I	NCT05767359	Dana Farber
		BCMA/CD3 bispecific antibody in smoldering myeloma	Phase I	NCT05469893	Dana Farber
		HER2-IGFBP2-IGF1R vaccine with rexinoid agonists in DCIS	Preclinical		University of Washington/ Earle A Chiles Research Institute
		mTOR inhibitors in DCIS	Preclinical		MD Anderson

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; DCIS, ductal carcinoma in situ; EBV, Epstein-Barr virus; FDA, US Food and Drug Administration; HBV, hepatitis B virus; HPV, human papillomavirus; hTERT, human telomerase reverse transcriptase; poly ICLC, polyinosinic-polycytidylic acid and poly-L-lysine; IL, interleukin; mTOR, mammalian target of rapamycin; MUC1, mucin 1; PanIN, pancreatic intraepithelial neoplasia.

even with suboptimal vaccine adoption.^{3 16 17} As sizeable cohorts of HPV-vaccinated populations reach adulthood, there will likely be a significant reduction in other HPV-related cancers, such as oropharyngeal cancer. The Costa

Rica clinical trial showed an estimated vaccine efficiency of 93.3% (95% CI 63% to 100%) in reducing HPV 16/18 infections in the oral mucosa, with 15 infections in the control group and 1 infection in the vaccinated group.

Table 2 Society for Immunotherapy of Cancer immune interception and prevention summit April 3, 2023

Topic	Presentation/panel	Speakers
Welcome		Leisha A. Emens MD PhD
Immunoprevention: opportunities and challenges	Presentation	Olivera J. Finn PhD
Human papillomavirus vaccines: a model for immunoprevention	Presentation	Doug Lowy MD
Immune interception of premalignancy	Presentation	Bernard Fox PhD
Immune targets for interception and prevention	Presentation	Avrum Spira MD PhD
Immune microenvironment of premalignancy	Panel discussion	Moderator: Jerome Galon PhD Steve Dubinett MD Nicolas Jacquelot PhD Kornelia Polyak MD PhD
Immune interception strategies	Panel discussion	Moderator: Bernard Fox PhD Irene Ghobrial MD Glenn Hanna MD Steven Lipkin MD PhD Neeha Zaidi MD
Primary immunoprevention strategies	Panel discussion	Moderator: Powel Brown MD PhD Susan Domchek MD Sasha E. Stanton MD PhD Eduardo Vilar-Sanchez MD PhD Baochun Zhang MD PhD
Clinical trials: participant selection, design, endpoints	Panel discussion	Moderator: Eva Szabo MD Mark Cobbold MRCP, PhD Powel Brown MD PhD Kevin Dodd PhD Steve Dubinett MD Virginia Mason RN, BSN Sasha E. Stanton MD PhD Jeffrey Roberts MD
Resources available	Panel discussion	Moderator: Shizuko Sei MD Altaf Mohammed PhD Mark Miller PhD
Conclusion		Philip E. Castle PhD MPH

An important consideration for promoting compliance in a prevention vaccination regimen is establishing a durable immune response without the need for multiple booster immunizations. Data with the cervical cancer vaccine suggest one dose is effective, with an order-of-magnitude greater antibody titer following a single dose of HPV vaccine than following natural viral infection. In the Costa Rica study, vaccinated volunteers remained seropositive 11 years from vaccination even with one dose of vaccine, whereas responses were only fourfold higher with three doses.¹⁸ Similar results were seen with single-dose vaccine studies in India and Kenya.^{19 20} Although single-dose vaccines are not standard of care, such a regimen may ease disparities in resource-poor countries by minimizing the need to have multiple visits to health-care providers. Accordingly, the WHO Independent Expert Advisory group recommended single-dose HPV vaccination for girls ages 9–14 in April 2022.

HPV and HBV vaccines are good models for cancer prevention strategies: they target a large, healthy

population with a safe intervention, they have good side effect profiles, and they elicit durable immune responses, even with a single vaccination. Additional improvements including improved manufacturing and storage requirements would further facilitate implementation even in resource-poor countries, thus providing the widest benefit.

HPV and HBV vaccines for cancer prevention are success stories. There are other oncogenic infections against which preventive vaccines would have a huge global impact. Epstein-Barr virus (EBV) infection increases the risk of nasopharyngeal cancer, Burkitt lymphoma, Hodgkin's lymphoma, and stomach cancer. However, there is currently no vaccine for preventing EBV infection.^{21–24} Tumor-associated antigens (TAAs) are shared among EBV-related cancers, and T cells against these antigens kill tumor cells.^{25 26} A vaccine to prevent EBV infection would have a huge global impact, as EBV is associated with ~200,000 new cancer cases per year worldwide.²⁷ Similarly, chronic local inflammation

by the bacterium *Helicobacter pylori* causes 95% of 1.1 million gastric cancers worldwide annually. Antibiotic elimination of *H. pylori* can significantly reduce the risk of gastric cancer.^{28,29} However, with increasing antibiotic resistance,^{30,31} there is a significant risk of recurrent *H. pylori* infection following antibiotic-based eradication. Research is ongoing to develop vaccines against *H. pylori* for both prevention and treatment of infection.³² More research is needed to reduce the high burden of gastric cancer globally.³³

Extending this development strategy to vaccines for cancers unrelated to viral or bacterial infection, vaccines for primary cancer prevention should provide a safe, efficacious, and durable immune response with prompt global deployment to reduce the morbidity and mortality of cancer worldwide.

PREVENTION VACCINES FOR NON-VIRALLY INDUCED CANCERS

Most cancers are not caused by oncogenic infections. Therefore, a priority in the field is to identify appropriate endogenous antigens such as altered self-antigens or neoantigens for immune interception and prevention that both avoid damage to normal tissues that share the antigen and interrupt the process of cancer development. Shared TAAs, such as the transmembrane glycoprotein mucin 1 (MUC1), are commonly expressed in many cancers, and many TAA vaccines are immunogenic and safe in therapeutic trials in patients with advanced cancer. One example is a long MUC1 synthetic peptide vaccine admixed with polyinosinic-polycytidylic acid and poly-L-lysine (poly ICLC) adjuvant given to 39 individuals with a history of high-risk colon adenomas. The vaccine induced durable antigen-specific immunity, defined as ≥ 2 -fold increase in IgG antibody titer, in 43.6% (17/39) of participants. Non-responders to the vaccine had higher levels of circulating myeloid-derived suppressor cells (MDSC) at baseline, demonstrating that a suppressive environment begins very early in cancer development. Adverse events were limited to grade 1 injection site reactions and influenza-like symptoms.³⁴ A follow-up placebo-controlled, double-blind trial enrolled 110 individuals with high-risk adenomatous polyps removed within a year from enrollment. The vaccine was safe and immunogenic, and high levels of MDSC at baseline again correlated with the lack of response to the vaccine. Importantly, in vaccine-induced antibody responders, there was a 38% reduction in polyp recurrence.³⁵

Mouse models can be used to identify antigens of premalignancy. For example, differentially expressed genes identified between normal tissue and hyperplasia, hyperplasia and dysplasia, and dysplasia and invasive disease in patients with head and neck cancer were similar to transcriptomic profiles in the 4-nitroquinoline 1-oxide (4-NQO) carcinogen-induced mouse head and neck cancer model.³⁶ Similarly, autoantibody arrays identified candidate premalignant tumor antigens in the mouse mammary tumor models TgMMTV-neu (similar to

human luminal B breast cancer) and C3(1)Tag (similar to human triple-negative breast cancer) with mammary hyperplasia but no invasive disease; antibodies against these antigens were not found in the FVB mouse parental control. These autoantibodies were also found in serum samples of women who would develop breast cancer, and the autoantibodies could predict which women would develop breast cancer over 150 days prior to tumor detection (area under the curve(AUC) 0.68; $p=0.003$).³⁷ Vaccinating the TgMMTV-neu mice against these premalignant TAAs inhibited tumor growth, suggesting these early TAAs may be effective targets for ductal carcinoma in situ (DCIS) vaccine.³⁸ While therapeutic TAA vaccines in invasive cancer to date have been safe and immunogenic, phase III clinical trials have not shown efficacy.³⁹ Vaccination of individuals with a pre-invasive disease where there is no overt malignancy and the host is less immunosuppressed should allow for greater vaccine efficacy. Additional progress in vaccine development, adjuvant optimization, trial design, and increased clinical translation of vaccines for preventing cancer is essential to advance the immunoprevention field.

One new notable strategy for cancer prevention vaccines is to circumvent immune tolerance by employing TAAs that represent non-mutated “dark matter” proteins that are not expressed in the thymus and are only expressed in cancer. These TAAs are targets of endogenous immunity, epigenetically regulated, and associated with poor outcomes.⁴⁰ These non-canonical peptides are present on ~16% of major histocompatibility complex (MHC) I in cancer cells.⁴¹ One promising strategy is to include both overexpressed proteins and non-canonical peptides in a cancer vaccine to induce a stronger immune response. These antigens can be harnessed by blocking the proteasome in cancer cell lines and using the resulting autophagosomes as a vaccine. In head and neck cancer, this approach was successful in the 4-NQO mouse model⁴² and is currently being tested in a clinical trial (NCT04470024). Non-canonical peptidome expression has not been studied in premalignancies. This is a high-priority area for immunoprevention research.

IDENTIFICATION OF THE IMMUNE MICROENVIRONMENT IN PREMALIGNANCY

Depending on the cancer type, varied oncogenic stressors can modify the immune environment, causing chronic inflammation and cancer development.⁴³ Current clinical challenges for cancer immunoprevention include reliably identifying individuals with premalignant lesions at risk of progressing to invasive disease, understanding the immune environment of premalignant lesions, and determining the components of the immune environment that can be modified to eliminate the premalignancy and induce immune memory to prevent the future development of invasive disease.⁴⁴

In lung squamous cell carcinoma (SCC), one environmental driver is heavy smoking history. SCC is a good

model for a precancer atlas because it has a dysplastic precursor that is identifiable by low-dose CT screening, and the standard of care is watchful waiting using bronchial biopsy. This allows for profiling biopsied lesions from high-risk smokers over time and following the lesions that progress versus those that regress.⁴⁵ The early immune environment of developing SCC was evaluated in 122 individuals using endobronchial biopsy. The tissues, evaluated by transcriptomic analysis of cancer hallmark genes, were grouped into four main pathologies: normal, low-grade dysplasia, high-grade dysplasia, and SCC. Both adaptive and innate immune evasion was seen in high-grade dysplasia with increased expression of immune checkpoint molecules including T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT) and programmed death-ligand 1 (PD-L1). Low-grade dysplasia predominantly displayed proliferation and DNA repair deficiency profiles. Increased immune sensing and activation of resident immune cells were associated with progression to high-grade dysplasia.⁴⁶

Adenocarcinoma is a subtype of lung cancer that may occur without a smoking history. Progression from normal lung to different degrees of dysplasia and invasive cancer in adenocarcinoma showed a profoundly immune suppressive environment, worsening with disease progression. Laser capture microdissection and whole exome sequencing evaluated normal epithelium, premalignant lesions, and invasive disease in the same individuals. There was an increase in the regulatory T cell (Treg) to total CD4⁺ T-cell ratio with more advanced premalignancy.⁴⁷ While many of the premalignant antigenic epitopes were lost during progression to invasive disease, a subset of progression-associated neoepitopes (PAN) were maintained and were associated with increased CD8 (p=0.0004), CD4 (p=0.05), and PD-L1 (p=0.01) expression in the lung by multicolor immunofluorescence. Those PAN allowed the identification of individuals at high risk of progression to invasive disease.⁴⁸ These studies demonstrate that in lung cancer the immune system senses the progressive premalignant lesions early in tumor development, but full immune evasion does not manifest until later in tumor development. This provides an ideal opportunity for an immune interception strategy.

In order to understand the cellular and molecular changes that occur from normal tissue to invasive disease across the spectrum of tumor development, the National Institutes of Health (NIH) Human Tumor Atlas Network is developing a precancer atlas with several centers across the country focusing on different premalignant tumor types.^{49–51} Bulk RNA sequencing of 150 bronchial biopsies indicated that precancer dysplastic lesions can be grouped into four molecular subtypes: proliferative, inflammatory, secretory, and normal. Notably, similar subtype-specific gene expression patterns were seen in matched distant areas of the lung that were grossly pathologically normal, consistent with a field effect on the entire lung.⁵² The proliferative subtype lacks an immune

signature, has fewer macrophages and CD8⁺ T cells by multicolor immunohistochemistry, and has a worse prognosis. Poor-prognosis squamous cell dysplastic lesions can also be identified by selective evaluation of microRNAs (miRNA) expressed both in invasive cancers and in premalignancy.⁵³ The miRNA miR-145-5 p is increased in progressing dysplastic lesions and downregulates expression of NOD-like receptor family CARD domain containing 5 (NLRC5), which is essential for expressing class I MHC genes. This suggests that as dysplasia worsens, there is a loss of MHC class I, therefore reducing the ability of the immune system to recognize the dysplastic lesion.⁵⁴ The precancer atlas also includes both the oral and gut microbiomes because these further modify the immune environment of developing cancers and may also provide a method to modify the host immune system to prevent cancer.^{55 56}

Similar themes of increased immune suppression and escape with progressive dysplasia are seen in other tumor types. Comprehensive gene expression profiling of normal breast tissue, DCIS, primary invasive breast cancer, and metastatic disease showed that while genetic alterations were predominantly seen in cancer epithelial cells, myoepithelial and myofibroblast cells also impacted the immune system by overexpressing cytokines and chemokines involved in immunosuppression, aiding tumor proliferation and migration.⁵⁷ In DCIS, there is an activated immune environment, including activated CD8⁺ T cells, while in invasive disease there is increased immunosuppression with higher levels of immune checkpoint molecules and Treg.⁵⁸ This suggests that immune escape is one of the key drivers of the progression of DCIS to invasive ductal carcinoma.⁵⁹ As seen in the heterogeneity of invasive breast cancer, the breast precancer atlas demonstrates considerable molecular and immune environment diversity among different DCIS samples.^{60 61} Innate immunity, particularly resident innate lymphoid cells (ILC), also changes during cancer progression. For example, ILC respond rapidly to early premalignancy. They have similar cytotoxic and helper types to those seen in the adaptive immune response: ILC1 releases interferon gamma, tumor necrosis factor alpha, granzymes, and perforin; ILC2 releases interleukin (IL-) 4, IL-5, IL-9, and IL-13; and ILC3 releases IL17, IL22, and granulocyte-macrophage colony-stimulating factor.^{62 63} In breast cancer mouse models, ILC1 infiltrates are important for the immune elimination of the premalignancy while ILC2 and ILC3 infiltrates can induce an immunosuppressive environment that facilitates immune escape.⁵² Understanding the similarities and differences between different premalignant lesions and how the evolving tissue immune environment impacts the development of premalignancy and its progression to invasive disease will be essential for designing appropriate and effective interventions for immune interception and prevention. Studying the immune environment of premalignancy poses unique challenges including the collection and identification of sufficiently sized tissue samples.

Additionally, serial biopsies are necessary to determine which lesions regress or progress, requiring a committed population of affected individuals.

STRATEGIES USING APPROVED AGENTS TO INTERCEPT CANCER DEVELOPMENT IN PREMALIGNANCY

There are many strategies to use the immune system to intercept cancer development, including immune checkpoint inhibitors, cytokine therapies, tumor-specific adaptive immune therapies such as vaccines, and cellular therapies including chimeric antigen receptor (CAR) T cells. Different levels of toxicities are associated with these distinct approaches, which is an important consideration in the prevention or interception settings. One example of using systemic immune therapies in premalignancy includes treating proliferative leukoplakia with immune checkpoint inhibitors. Proliferative leukoplakia is a premalignant lesion with a 10% annual risk of malignant transformation and a 47% risk of developing head and neck SCC over 5 years.⁶⁴ Proliferative leukoplakia is associated with decreased cancer-free survival as compared with localized leukoplakia in 58 patients, 29 with proliferative leukoplakia and 29 with localized leukoplakia (HR 11.25; $p < 0.01$). Increased CD8⁺ T cells and Treg and a higher expression of PD-L1 were observed in proliferative leukoplakia.⁶⁵ A phase I study in individuals with proliferative leukoplakia tested nivolumab 480 mg monthly for four doses, with biopsies before and after the intervention. 36% of participants responded to nivolumab, including one complete response. Unfortunately, individuals with responses still developed cancer (NCT03692325). Progression-free survival was not different from the control group, and response did not correlate with PD-L1 expression. These findings suggest that further immune modulation, such as a tumor-specific vaccine, may be needed to prevent invasive disease.

Immune interception and prevention are likely where cancer vaccines will have their highest impact. In Lynch syndrome, mismatch repair mutations can lead to recurrent frameshift mutations across multiple cancers. Individuals with this syndrome develop multiple colonic polyps at high risk of progressing to colon cancer.⁶⁶ In a preclinical mouse model of Lynch syndrome, a vaccine targeting recurrent frameshift mutations improved overall survival and reduced tumor burden.⁶⁷ These frameshift mutations may be neoantigens not expressed in normal cells and therefore the vaccine-elicited immune response will target only the premalignancy and cancer. In morphologically normal crypts of patients with Lynch syndrome, similar mismatch repair mutational signatures to neoplastic lesions have been found, suggesting these crypts represent very early stages of pathogenesis that may be targeted.⁶⁸ There is an ongoing effort in the Department of Cancer Prevention (DCP) Cancer Prevention-Interception Targeted Agent Discovery Program (CAP-IT) to incorporate these shared neoantigens into liponanoparticles as RNA-based cancer

prevention vaccines.⁶⁷ Similarly, 90% of high-risk, premalignant pancreatic intraepithelial neoplasia and 80% of pancreatic cancers have conserved KRAS mutations that can be targeted by vaccination for prevention and interception. In advanced metastatic pancreatic cancer, a T-cell receptor-targeted cellular therapy against the KRAS G12D mutation induces a prolonged partial response.⁶⁹ A long peptide vaccine was developed targeting each of the six most common human KRAS mutations found in pancreatic cancer with poly ICLC as an adjuvant. It was effective in a transgenic mouse pancreatic cancer model driven by Kras mutations^{70 71} and was safe and effective in a phase I study of 12 patients with resected pancreatic cancer at high risk of recurrence (NCT04117087). It is being tested in 20 healthy individuals with genetic risks of pancreatic cancer and evidence of pancreatic cysts, evaluating the safety and peripheral T-cell responses (NCT05013216). Intercepting premalignancies with a vaccine therapy that induces tumor-specific T cells is exciting and highly promising for tumors with conserved shared mutations. However, in some cancer types, there are no conserved mutations in premalignancy that correlate with malignant transformation. For these cancers, promising candidate antigens are overexpressed TAA or cancer testis antigens.

Cellular therapy has been a cornerstone for the treatment of advanced B-cell lymphomas and leukemias with the development of CD19 CAR T cells.⁷² Cell therapies are being tested in smoldering myeloma. Progression to multiple myeloma (MM) starts with monoclonal gammopathy of unknown significance (MGUS), with a 1% yearly risk of progression to MM, then to smoldering MM, with a 10% yearly risk of progression to MM. CAR T-cell therapy targeting the B-cell maturation antigen (BCMA) has previously shown benefit in recurrent MM.⁷⁰ Changes in the immune environment start in MGUS, become more immunosuppressive in smoldering myeloma, and are most immunosuppressive in MM.^{73–75} To intercept smoldering myeloma before progression to MM, several immune cell therapies are being evaluated. CAR-PRISM (Precision Intervention in Smoldering Myeloma) uses the BCMA-targeting CAR T-cell ciltacabtagene autoleucel with 41BB and CD3z activation receptors in individuals with high-risk smoldering myeloma (NCT05767359). A second immune interception trial, Immuno-PRISM, tests the bispecific antibody teclistamab specific for BCMA and CD3 and is actively accruing (NCT05469893).

STRATEGIES FOR PRIMARY IMMUNOPREVENTION

Intercepting the development of invasive cancer in individuals with known premalignancy can positively impact individuals with premalignant changes found on screening scans but is limited to those for whom early detection screening is available. Currently, research in immunoprevention is focused on individuals that carry cancer-predisposing genetic mutations. Once these proof-of-principal studies are performed, immunoprevention strategies may be more broadly used in individuals at high

risk due to gender, lifestyle, or family history. Over 85% of human cancers overexpress human telomerase reverse transcriptase (hTERT), making hTERT a good candidate tumor antigen for a broad cancer immunoprevention strategy. A phase I trial testing vaccination with human leukocyte antigen (HLA)-A2-restricted hTERT peptide-loaded dendritic cells demonstrated safety and immunogenicity in patients with metastatic breast cancer.⁷⁶ A distinct vaccine incorporating IL-12 into an hTERT DNA plasmid tested in patients with high-risk solid tumors in remission demonstrated safety and immunogenicity, with an antigen-specific CD8⁺ T-cell response associated with survival in patients with pancreatic cancer.⁷⁷ A variant of this vaccine has been moved into primary prevention in BRCA1/2 mutation carriers. The vaccine includes hTERT, WT1, and prostate-specific membrane antigen with or without the IL-12 plasmid (NCT04367675). Another primary prevention trial, NCT05078866, is a phase Ib/II trial testing a vaccine containing 209 recurrent frame-shift peptide neoantigens found in Lynch syndrome-associated colon and other cancers.⁷⁸ It aims to accrue 45 Lynch syndrome carriers with no evidence of active or recurrent invasive cancer to evaluate vaccine safety and immunogenicity. NCT05419011 is a phase IIB trial through the Cancer Prevention Clinical Trials Network (CP-CTNet) of a trivalent adenovirus vaccine composed of three antigens (CEA, MUC1, and brachyury) and an IL-15 superagonist.⁷⁹ The trial will initially accrue 30 individuals to evaluate safety and efficacy using colonic adenoma incidence as the primary endpoint, followed by a randomized controlled trial of 140 Lynch syndrome carriers if the first phase is successful. Similarly, testing primary prevention in 45 current and heavy smokers through CP-CTNet (NCT03300817) using the MUC1 peptide/poly-ICLJ adjuvant vaccine evaluated the safety and immunity of the vaccine. The immune response to the vaccine in this population was only 15%, but heavy smoking correlated with high circulating levels of immunosuppressive MDSC in peripheral blood mononuclear cells. This study suggests that even in primary immunoprevention, the immune status of the recipients will be important in determining response.

Other methods of immunoprevention may repurpose medications that have established roles in cancer therapy but also modulate immunity.⁷ For example, oral retinoids modify the tumor immune environment in breast cancer to enhance the efficacy of a CD4⁺ Th1 plasmid HER2-IGFBP2-IGF1R preventative vaccine with granulocyte-colony stimulating factor adjuvant in the transgenic mouse mammary tumor model TgMMTV-neu. Bexarotene, an agonist for the retinoid X receptor found on ~30% of human peripheral blood mononuclear cells, is a direct activator of type 1 dendritic cells. In TgMMTV-neu mice, the HER2-IGFBP2-IGF1R vaccine alone prevented 60% of mouse tumors and prevented 85% when combined with bexarotene.⁸⁰ Furthermore, bexarotene combined with the vaccine increased both CD4⁺ and CD8⁺ antigen-specific polyfunctional T cells in the

mice.⁸¹ The mammalian target of rapamycin (mTOR), a serine/threonine-specific protein kinase in the phosphatidylinositol-3 kinase-related family, is a frequently dysregulated pathway in multiple cancers. mTOR inhibitors currently treat multiple metastatic cancers, including breast cancer.⁸² When evaluated in the TgMMTV-neu transgenic and p53-null mutant mouse mammary tumor models, mTOR inhibitors delayed tumor development with minimal toxicity.⁸³ For primary prevention trials, genetic mutations or premalignancy carriers are the optimal “high-risk” groups for enrollment. It is critical to recognize that, in primary prevention trials, safety needs to be paramount because the trial participants are healthy individuals.

CONSIDERATIONS IN IMMUNOPREVENTION CLINICAL TRIALS: PARTICIPANT SELECTION, DESIGN, AND ENDPOINTS

Most immune prevention and interception strategies are first tested in advanced disease. However, individuals receiving immunoprevention or immune interception for precancer are a very different population than those who are receiving therapy for active disease or secondary prevention after having the invasive disease. Individuals with no or only premalignant diseases have less systemic immunosuppression, and the premalignant immune environment is different from heavily pretreated tumors. Close collaboration with the US Food and Drug Administration (FDA) is needed to find a safe pathway to move immunoprevention into the most appropriate populations in the clinic, following the recommendations of FDA guidelines. The NCI PREVENT Cancer Preclinical Drug Development Program (PREVENT) can provide advice on interpreting the FDA guidance in developing prevention trials. Including the patient advocate community in designing these trials is also critical to understand and incorporate the patient’s perspective on the risks of toxicities and concerns related to delaying established therapies in prevention trials. The pharmaceutical industry has expressed interest in prevention and is likely to become more interested with advances in the science of premalignancy and immunoprevention and immune interception. Finally, major trial design challenges in cancer immunoprevention include the number of participants needed to test the intervention and the most appropriate endpoints to use. Multiple surrogate endpoints must be evaluated because there is likely no complete correlation of any one endpoint with preventing disease. Some of these possible endpoints can include changes in the immune environment with therapies, development of polyfunctional T-cell responses in response to vaccination, or elimination of pre-invasive disease in window of opportunity studies. In invasive cancer vaccine clinical trials, higher antigen-specific T-cell responses have been associated with improved survival. Examples include a glypican-3-peptide vaccine in hepatocellular carcinoma or the PROSTVAC vaccine in prostate cancer where increased antigen-specific T cells were associated with better survival. However, there

is no consensus on the magnitude and type of immune response necessary for efficacy.⁸⁴ Data from the precancer atlas may identify surrogate endpoints based on disease biology, a critical step to identify appropriate prevention surrogate endpoints. It is thus important to use basic and translational science to understand how different cancers develop, to determine which premalignancies will progress and when, to identify appropriate biomarkers for identifying high-risk individuals and those with progressive disease, and to develop a safe intervention with appropriate surrogate endpoints for efficacy.

NEW AND EXISTING NCI RESOURCES FOR IMMUNOPREVENTION RESEARCH

The NCI DCP has been the primary federal agency to fund prevention research, and their portfolio includes a natural product agent discovery program, CAP-IT, and Cancer Immunoprevention Network (CIP-Net). New agents can feed into PREVENT for preclinical translational work. PREVENT provides technical resources, investigational new drug (IND) and regulatory affairs resources, and access to the DCP repository for the final development of clinic-ready agents for clinical trials. The PREVENT program is based on a peer-reviewed contract to move promising new agents from preclinical development into clinical trials. PREVENT supports immunoprevention, chemoprevention including novel agents, drug repurposing and toxicity reduction through alternative dosing regimens, and clinically translatable biomarkers. This program can assist in the confirmation of candidate agents' preventive activity and optimization of regimens, IND-enabling testing, and current good manufacturing practices of clinical-grade vaccines and other immunoprevention agents. CAP-IT is a network of U54 and U24 centers focused on the discovery of novel agents for cancer prevention and interception tailored for clinically identifiable high-risk populations including those with hereditary cancer syndromes and individuals with screen-detected premalignant lesions. CIP-Net includes UG3/UH3 grants with a U24 coordinating center for early research. It supports basic research to discover immune pathways and new immunomodulating targets of immunoprevention and to develop a research pipeline for the basic mechanisms of immunoprevention including fostering the career development of scientists new to the field of immunoprevention. CP-CTNet is the program for early-phase clinical trials while the NCI Community Oncology Research Program (NCORP) is the program for late-phase trials. CP-CTNet designs and conducts early-phase clinical trials to assess the safety, tolerability, and cancer-preventive potential of test agents as well as developing intermediate endpoint biomarkers and testing novel imaging technologies. NCORP is a national network of community providers that conducts clinical trials focused on cancer prevention, screening, surveillance, cancer care delivery, and disparity research. There is also an NIH Adjuvant Development program and

Vaccine Adjuvant Compendium to support the development of adjuvants for vaccines for both infectious disease and cancer prevention and adjuvant discovery, comparison, and mechanistic research.⁸⁵ Additional programs in the early detection research network and precancer atlas feed into the DCP network.

CONCLUSION

The field of cancer immunoprevention and immune interception is still nascent and presents many exciting opportunities to address a current unmet need to prevent invasive cancer rather than to treat established cancer. Work is ongoing to understand the premalignant immune environment of all tumor types and improve early detection with imaging and biomarkers to identify individuals who are candidates for immune-based prevention or interception strategies. Collaborations with the FDA and NIH to bring more prevention agents into clinical trials, particularly for high-risk individuals who are cancer-free, are essential. Vaccines will have an important role in prevention, but the utility of other immune approaches including systemic and cellular therapies are being evaluated in the context of the risk/benefit ratio for different high-risk groups. Finally, it is critical to raise awareness of the field of immunoprevention to recruit new investigators to the field. The NCI DCP has been designing funding and programs particularly focused on young scientists. The importance and potential impact of immune prevention and interception must be increasingly recognized by the NIH and other major cancer funding agencies. The American Association of Cancer Research and SITC now have cancer immunoprevention interest groups and cover the topic at their meetings, which will help increase both the recognition of progress and the need for further work in this exciting field.

Twitter Leisha A Emens @EmensLeisha

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ORCID iDs

Sasha E Stanton <http://orcid.org/0000-0002-4300-551X>

Shizuko Sei <http://orcid.org/0000-0002-4822-6602>

Leisha A Emens <http://orcid.org/0000-0002-7694-0731>

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