Meeting Report

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Emerging Trends in Cancer Prevention Agent Development

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Advances in omics and immunology over the past 20 years have revolutionized the approach to cancer prevention, with the goal now focused on identifying populations at higher risk for developing cancer in their lifetime as a result of either extensive exposure to environmental carcinogens or harboring precancer lesions or inherited genetic mutations that predispose them to specific types of cancer(s). Thus, the naïve idea that cancer could be "prevented" in the general population has evolved to a more practical approach based on the understanding that the target population for preventive agents will be individuals who already have alterations, in gene pathways, whether inherited or environmentally caused, and the goal will be to "intercept" these lesions at the earliest stages in the path from an initial genetic lesion to full-blown cancer. The Division of Cancer Prevention of the National Cancer Institute and the Office of Disease Prevention at the National Institutes of Health recently sponsored the second biennial "Translational Advances in Cancer Preventive Agent Development Meeting," held virtually from September 7–9th. In this Meeting Report, we highlight the scientific sessions of this meeting that covered the most recent advances in preventive agent development that also highlighted these rapidly emerging trends in this research area.

Key Words Chemoprevention, Immunoprevention, Interception, Prevention

The field of cancer prevention has evolved tremendously since the early studies conducted in the mid-1970s through the mid-1990s. During this time, prevention research was mainly focused on altering the levels of drug metabolic enzymes such as cytochrome P450s and glutathione transferases. The focus was on inhibiting the metabolic activation of environmental carcinogens to mutagenic metabolites while enhancing their metabolism and elimination through enhanced detoxification [1-5] It was thought that the incidence of cancer could be significantly reduced by administering relatively non-toxic chemopreventive agents, such as natural compounds derived from fruits and vegetables, to the healthy population at large. The introduction of molecular biology techniques in the late 1980s led to a paradigm shift in our understanding of the role of mutated genes and aberrant gene regulatory networks in driving tumorigenesis, which has resulted in the identification of druggable targets for the design of more tumor-specific therapeutic agents [6,7]. Simultaneously with these advances in drug treatment and parallel advances in our understanding of how the body's natural immune systems could be harnessed to enhance standard drug therapy [8,9], the adoption of these advances in omics and immunology over the past 20 years have similarly begun to revolutionize our approach to cancer prevention, with the goal now focused on identifying populations at higher risk for potentially developing cancer in their lifetime as a result of either extensive exposure to environmental carcinogens (e.g., current and former smokers, asbestos-exposed individuals) or individuals with precancers or those harboring inherited genetic mutations that predispose them to specific types of cancer(s) (e.g., Li-Fraumeni syndrome, BRCA-1 carriers, Lynch syndrome) [10-14]. Thus, the naïve idea that cancer could be "prevented" in the general population has evolved to a more practical approach based on the understanding that the target population for preventive agents will be individuals who already have alterations, whether inherited or environmentally caused, and the goal will be to "intercept" these lesions at the earliest stages in the path from an initial genetic lesion to full-blown cancer.

These interception strategies will need to be tumor-specific, and should take advantage of the tremendous amount of omics data on tumor progression that has identified the

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most common tumor-specific alterations prevalent in many cancers. Since it is unlikely, at these earliest stages of tumor development, that the clinician will be able to determine the types of driver mutations that may be driving tumor progression, preventive agents will need to be identified that target the most common lesions. Agent combination strategies that either target individual pathways or synergize to provide a more robust immune response will be needed to make headway toward reducing cancer mortality.

The Division of Cancer Prevention of the National Cancer Institute and the Office of Disease Prevention at the National Institutes of Health recently sponsored the second biennial "Translational Advances in Cancer Preventive Agent Development Meeting", held virtually from September 7–9th. There were four scientific sessions that covered the most recent advances in preventive agent development that also highlighted these rapidly emerging trends in this research area (the meeting agenda has been attached as Supplementary Material).

Dr. Elizabeth Jaffee from Johns Hopkins University delivered the plenary talk, "Intercepting Pancreatic Cancer Development with Oncogene-Targeted Immunotherapy." She highlighted the resistance of pancreatic tumors to immunotherapy treatment and the benefits of intercepting tumors at the early stages of tumor progression before the development of an immuno-suppressive microenvironment. Results of pre-clinical studies demonstrating the feasibility of administration and safety profiles have led to a cancer prevention trial testing a Kirsten rat sarcoma viral oncogene homolog (KRAS) vaccine targeting 6 of the most common mutations in patients at high risk for pancreatic cancer.

The session on "Advances in Small Molecule Agent Development Pipelines: Promising Leads", focused on intercepting tumors at the early stages of development to prevent tumor progression. Dr. Daniel Rosenberg (University of Connecticut) described how the combination of naproxen and a chemically stable eicosapentaenoic acid analogue (TP-252) provided synergistic prevention of colon tumors in PIRC rats, resulting in 95% and 98% decreases in tumor number and volume, respectively. This was accompanied by decreases in the mucosal levels of pro-inflammatory ω-6 eicosanoids and increases in anti-inflammatory ω-3 eicosanoids. Dr. Nouri Neamati (University of Michigan) discussed the development of SC144 as a first-in-class, efficacious, safe, and orally active inhibitor of glycoprotein 130 (GP130) and the las in IL-6/GP130/STAT3 pathway, which showed significant in vivo efficacy but poor solubility and metabolic instability. An extensive medicinal chemistry lead optimization campaign produced analogs with increased solubility and metabolic stability with desirable pharmacokinetic properties. Dr. David Tweardy (MD Anderson Cancer Center) targeted STAT3 with the small oral molecule TT-101 to prevent hepatocellular carcinoma and intestinal cancer. TTI-101 administration in three mouse models of inflammatory bowel disease resulted in a dose-dependent reduction in polyps, adenomas, and/or adenocarcinomas, while administration to the Hep*Pten*-mouse model of nonalcholic steatohepatitis-induced hepatocellular carcinoma (HCC) resulted in a dose-dependent reduction in liver p_STAT3 levels. Dr. Chinthalapally Rao (University of Oklahoma) developed LFA-9, a dual mPGES-1/5-LOX inhibitor, which significantly suppressed colonic adenocarcinoma formation in both rat and mouse models of sporadic and familial adenomatous polyposis colon cancer. Dr. Yujin Hoshida (University of Texas Southwestern Medical Center) described a drug development strategy employing archived biospecimens to identify tumor-specific molecularly dysregulated targets. In this "reverse-engineering" strategy, his laboratory successfully identified HCC chemoprevention targets, involved cell types, and potential agents to facilitate the translation of promising chemoprevention agents to the clinic.

The session on "State of the Science and Advances in Immunomodulatory Agents Development", looked at modulating tumor cells and developing ways to use the immune system to intercept pre-invasive cancer cells. Dr. Jennifer Guerriero (Harvard Medical School) described her research demonstrating that removal or conversion of tumor-associated macrophages (TAMs) to an anti-tumor phenotype enhances chemo- and immuno-therapy in breast cancer, establishing TAMs as targets for anti-cancer therapy. She discussed the complexity of TAMs in solid tumors including characterizing TAM subsets, location, and crosstalk with neighboring cells, as well as novel TAM-modulating strategies and combinations that are likely to enhance current therapies and overcome chemotherapy and immunotherapy resistance. Dr. Yaguang Xi (Louisiana State University) examined the efficacy of sulindac to enhance the response of proficient mismatch repair (pMMR) colorectal cancer (CRC) to anti-programmed death ligand 1 (PD-L1) immunotherapy. He found that mice treated with combination therapy showed a significant reduction in tumor volume, along with increased infiltration of CD8+ T lymphocytes in the tumor tissues and downregulation of PD-L1. These results were validated in humanized patient-derived xenografts (PDX) animal models, suggesting that the combination could be used for the immunoprevention of pMMR CRC. Dr. Jennifer Bailey-Lundberg (University of Texas Health Science Center) described studies testing three small molecule CD73 inhibitors in a syngeneic pancreatic ductal adenocarcinoma mouse model. One of these inhibitors, AB680, significantly reduced tumor volume and intratumoral adenosine levels. CyTOF immune profiling showed that activated CD8+ T cells, dendritic cells, and macrophages were significantly increased in the tumors from AB680 treated mice. Dr. Nasser Altorki (Weill-Cornell College of Medicine) described studies to characterize molecular and cellular alterations in the tumor microenvironment that are associated with the progression of pre-invasive to invasive lung cancer, including differences in gene expression profiles and molecular pathways between normal, non-solid and solid lesions,

the difference in immune phenotype using deconvolution of RNAseq data, and differences in mutational burden, copy number variations, and driver mutations. He demonstrated that an immunosuppressive microenvironment occurs early in preinvasive and minimally invasive lung adenomas and is dominantly T-reg driven. Disease progression was associated with progressive alterations in the extracellular matrix, suggesting that fibroblast activation and spatial topography may contribute to immune suppression and disease progression.

The session on "Emerging Vaccines for Cancer Prevention" focused on new vaccine strategies to target high-risk populations for cancer development. Dr. David Largaespada (University of Minnesota) described his efforts toward development of prophylactic vaccine for patients with Neurofibromatosis type 1 syndrome, who have a 15% life-time risk of developing malignant peripheral nerve sheath tumors (MPNSTs). He demonstrated the use of mass spectrometry and RNA sequencing-based discovery of frameshift antigens and cryptic neoantigens from MPNSTs to identify novel tumor neoantigens for vaccine development. Dr. Ming You (Houston Methodist Research Institute) described the immunogenicity and antitumor efficacy of a newly formulated multi-peptide vaccine targeting multiple epitopes of the Top2A protein. The formulated vaccine contained the top three Top2A peptides, which elicited the strongest immunologic response and showed 100% sequence homology between human and mouse. The Top2A peptide vaccine reduced tumor burden by >90% when compared with adjuvant alone in a genetically engineered triple negative breast cancer mouse (C3(1)/Tag) model with no overt toxicities observed. Dr. Nora Disis (UW Medicine Cancer Vaccine Institute) described the development of STEMVAC, a vaccine targeting breast cancer stem cells. STEMVAC targets multiple antigens from different regulatory pathways that are over- or under-expressed and are associated with epithelial to mesenchymal transition, cancer stem cells, and poor prognosis. Preliminary results from a Phase II trial showed immune responses to all of the antigens, increases in the immune responses with booster vaccines, and loss of HER2 expression in 7 of 11 patients, suggesting potential immunoprevention strategies for breast cancer interception. Dr. David Weiner (Vaccine & Immunotherapy Center, Wistar Institute) described efforts to engineering DNA to improve the immune response in multiple cancers. DNA vaccine antigen cassettes can incorporate multiple antigens, be specifically developed for different tumor types with different target antigens, are well tolerated *in vivo*, and can be reproducibly delivered to drive cytotoxic T-cell responses in both precancer and cancer in the presence of tumor cells. Data from clinical trials demonstrated the efficacy against HPV vulvar and head and neck precancerous lesions, as well as potential synergy with co-administration of immune checkpoint inhibitors. Dr. Robert Schoen (University of Pittsburgh) reported on three trials of a Mucin 1 peptide vaccine for cancer prevention. All trials successfully recruited their full complement of participants; the vaccine was well tolerated with no safety concerns. The response rate in the colon adenoma trials was 43% in the pilot study and 25% in the placebo-controlled multicenter trial. Higher levels of circulating myeloid derived suppressor cells were consistently associated with the lack of an immune response, suggesting that even in pre-malignancy immunosuppressive tendencies can impair vaccine immunogenicity and should be considered in patient selection in future trials.

The session on "Cancer Prevention Clinical Trials" focused on vaccine development for cancer prevention. Dr. Robert Keith (University of Colorado) described clinical studies of iloprost that included both oral and inhaled preparations. Oral iloprost improved endobronchial dysplasia, the precursor lesion for invasive squamous cell carcinoma, in former smokers. Investigations on the dysfunction of airway progenitor cells, the most critical cell type for maintaining normal airway epithelium, was predictive of the evolution of bronchial dysplasia. Response of the dysplastic epithelium to iloprost predicted patient responses in vivo. Current studies are focusing on the mechanism of iloprost-associated cancer prevention, (including effects on basal progenitor cells, progenitor multi-potentiality, and differentiation) and biomarkers. Dr. Eduardo Vilar-Sanchez (MD Anderson Cancer Center) described recent advances in next-generation sequencing and associated bioinformatic approaches that are allowing for more accurate profiling of the most frequently recurring and shared mutated neoantigens in Lynch syndrome associated colon tumors. This allows for identification of the most immunogenic neoantigens that can be incorporated into different vaccine platforms to test the development of a population-based vaccine. The mutated neoantigen-based strategies are currently being tested in a Phase I clinical trial (NCT05078866) using a viral-based vaccine including 209 distinct neoantigens. Dr. Scott Waldman (Thomas Jefferson University) described clinical trials of oral Guanylyl cyclase C (GUCY2C) receptor agonists for colon cancer prevention. The expression of guanylin, the endogenous agonist for GUCYC, is the most commonly lost gene in colon tumors. GUCY2C agonists are formulated for duodenal activity, without bioavailability in the colorectum. High doses of linaclotide induced a cGMP response in mucosal biopsies obtained and preclinical models, suggesting that oral GUCY2C agonists stimulate GUCY2C signaling, opposing tumorigenesis. These studies suggest that development of GUCY2C agonists formulated for the colorectum could be an effective chemopreventive strategy. Dr. Silvio Gutkind (University of California, San Diego) described ongoing studies targeting the mTOR pathway for the prevention of oral premalignant lesion (OPL) progression. Unlike many mTOR pathway inhibitors, which have side effects not conducive for use in a prevention setting, the repurposed drug metformin displays good safety, decreases mTOR signaling in head and neck squamous cell carcinoma, and displays potent chemopreventive activity in experimental oral premalignancy

models. Results from a Phase IIa clinical trial demonstrated that metformin inhibited the mTOR signaling pathway and improved the histological severity of 60% of the OPLs, including a subset (17%) of patients that exhibited complete responses.

In summary, themes that emerged from the recent Translational Advances in Cancer Prevention Agent Development meeting identified several new approaches that could be applied to ongoing cancer prevention:

1. A focus on identifying high-risk populations with targetable lesions. These can be the result of genetic inheritance of known susceptibility gene variants (e.g., Lynch Syndrome) or known genetic lesions associated with environmental toxicants (e.g., KRAS mutations in lung adenocarcinomas of smokers) or individuals with existing precancer lesions.

2. Investigate pathways/genes that initiate and/or potentiate the progression from normal to cancer cells and the discovery of ways to modulate the immune system in the early stages to fight cancer development.

3. Develop novel molecularly targeted safer cancer interception-prevention agents applying novel strategies (e.g., reverse engineering).

4. Focus on improving the safety profiles of known (repurposing drugs) and novel agents by designing novel delivery methods or improved formulations and dosing strategies.

5. An increasing focus on utilizing strategies that alter the precancer immunosuppressive microenvironment and promote immune responses against tumor progression.

6. Explore the potential of immune checkpoint inhibitors to minimize toxicities while maintaining efficacy, when used in combination with cancer interception agents, to synergize and enhance immune responses.

7. Development of multi-antigen targeted vaccines that can target a variety of dysfunctional signaling and immune pathways that are associated with specific tumor types; in a prevention setting, the specific lesion(s) may not be identifiable thus targeting multiple pathways offer the chance to provide preventive efficacy to a larger portion of patients. This will necessitate the use of novel antigen discovery platforms to drive multi-antigen vaccine development.

8. Focus on the development of biomarkers predictive of cancer interception-prevention efficacies in clinical trials.

9. Design appropriate clinical trials that target the population(s) most likely to harbor the lesion(s) that the preventive agent is targeted to.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.15430/JCP.2023.28.1.24.

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