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Emerging Role and Future Directions of Immunotherapy in Advanced Ovarian Cancer

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Introduction

Development of therapeutic strategies for immune-mediated tumor destruction, previously an elusive goal, has been accelerated by understanding the molecular basis of immune recognition and regulation of cancer cells. It is now well known that the immune system plays a pivotal role in monitoring cancer development (1–4). This concept of “cancer immunoediting” (2, 5, 6) holds that the immune system not only protects the host against primary cancer development, but also sculpts tumor immunogenicity (6). Cancer immunoediting is a dynamic process composed of three phases: elimination, equilibrium, and escape (6). Elimination represents the classical concept of cancer immunosurveillance (7, 8), equilibrium is the period of immune-mediated latency after incomplete tumor destruction (9), and escape refers to the final outgrowth of tumors that have outstripped immunological restraints (10). In support of this concept, presence of tumor-infiltrating lymphocytes (TILs) is associated with improved clinical outcome in epithelial ovarian cancer (EOC) (11–14).

Significant progress has been made in the development of antitumor immunity by initiating *de-novo* or boosting pre-existing immune responses; some have gained regulatory approval (Table 1). These interventions include vaccines, cell-based therapy, checkpoint blockade, and oncolytic virotherapy. Dramatic clinical responses in certain solid cancers treated with monoclonal antibodies targeting checkpoint pathways have spurred the popularity of utilizing the immune system to control unchecked tumor growth. FDA approval of

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checkpoint inhibitors, anti-cytotoxic T lymphocyte antigen-4 (anti-CTLA-4) and anti-programmed death-1 (anti-PD-1) for several solid tumors and sipuleucel-T for metastatic prostate cancer (15, 16) suggest these promising results may be expanded to EOC.

EOC tumor antigens and vaccine therapy

The development of approaches to analyze humoral (17) and cellular (18) immune reactivity to cancer led to the molecular characterization of tumor antigens recognized by autologous $CD8^+$ T-cells (19) and/or antibodies (20) including serological analysis of recombinant cDNA expression libraries (SEREX) (21), differential gene expression analysis, T-cell epitope cloning (TEPIC) (22, 23), and bioinformatics (24, 25). As a consequence, human tumor antigens (TA) can be broadly classified into one or more of the following categories:

- **i.** differentiation antigens [e.g. tyrosinase (26), Melan-A/MART-1 (27), gp100 (28)];
- **ii.** mutational antigens [e.g. CDK4 (29), β-catenin (30), caspase-8 (31), P53 (32)];
- **iii.** amplification antigens [e.g. Her2/neu (33), P53 (34)];
- **iv.** splice variant antigens [e.g. NY-CO-37/PDZ-45 (32), ING1 (35)];
- **v.** glycolipid antigens;
- **vi.** viral antigens [e.g. HPV, (36), EBV (37)]; and
- **vii.** cancer-testis antigens (CTA) [e.g. MAGE (22), NY-ESO-1 (21), LAGE-1 (38)].

These TAs give rise to epitopes presented on tumor cells in the context of major histocompatibility complex (MHC) molecules, thereby stimulating $CD8^+$ or $CD4^+$ T-cells.

Although there are several options in deciding which antigen to target, fundamental requirements of ideal TA include:

- **i.** limited or no expression in normal tissues, but aberrant expression at high frequencies in tumor;
- **ii.** immunogenicity; and
- **iii.** a role in tumor progression.

Self-antigens

While no current self-TA completely meets all criteria, the CTA family is closest. Criteria for placing antigens in this category are (39, 40):

- **i.** predominant expression in testis germ cells and generally not in other normal tissues;
- **ii.** expression in malignant tumors of different histological types;
- **iii.** expression in malignancies in a lineage non-specific fashion;
- **iv.** often mapping on the X-chromosome;
- **v.** often members of multigene families.

Despite their poorly characterized biologic function, their expression is known to be restricted in immune privileged sites such as testes, placenta, and fetal ovary, but not in other normal tissues. Abnormal expression of these germ-line genes in malignant tumors may reflect activation of a silenced “gametogenic program,” which ultimately leads to tumor progression and broad immunogenicity (41). CTA immunogenicity has led to development of cancer vaccines targeting these antigens in many solid tumors.

Expression of 162 CTA across 53 normal samples from GTeX and 31 tumor samples from TCGA revealed a strikingly contrasting profile. Tumor samples had heterogeneous expression of CTA, while normal tissues (beside testis) had minimal or absent CTA expression (Figure 1). These results strongly suggest CTA can be exquisite candidates for immune targeting in EOC. Furthermore, as their transcription is epigenetically regulated (42–44), there are opportunities to reinstate CTA expression with DNA methyltransferase inhibitors.

The identification and characterization of peptide epitopes from TAs, along with the relative ease of cGMP-grade peptide production, led to a large number of vaccine studies utilizing these peptide epitopes in EOC (Table 2). The most common cancer vaccine strategy is to administer full-length recombinant protein or peptides, most often via intramuscular, subcutaneous, or intradermal route, together with one or more immunostimulatory adjuvants. While short peptides (8–12 a.a.) directly bind to surface MHC, synthetic long peptides (25–30 a.a.) are endocytosed, processed, and presented to elicit an immune response (45). Several reports indicate therapeutic activity of synthetic long peptides is superior to that of their shorter counterparts, especially when they include epitopes recognized by both cytotoxic and helper T-cells or when conjugated to adjuvants (45, 46).

Several NY-ESO-1 vaccine clinical trials have demonstrated clinical activity, but these studies were small and not definitive (47, 48). At present, no peptide- or DNA-based anticancer vaccine is currently FDA approved. Nevertheless, a recent retrospective analysis of EOC patients with NY-ESO-1 positive tumors indicated that vaccination targeting the antigen led to improvement in overall survival (OS) by >2 years (49).

Several forms of DC-based vaccine approaches have been developed, most involving isolation of circulating monocytes and their differentiation *ex-vivo*, in the presence of agents that promote DC maturation. The autologous DCs are injected into patients upon exposure to tumor antigen and thus elicit tumor-specific immune responses *in-vivo*. Another strategy is fusion of TA with mAbs that bind endocytosis receptors (e.g., CD206, DEC-205) on the surface of DCs (50).

Non-self neoantigens

Advances in next-generation sequencing (NGS) and epitope prediction now permit rapid identification of mutational neoantigens. This has led to efforts in utilizing neoantigens for personalized cancer immunotherapies. Indirect support for this approach comes from studies demonstrating:

i. infusion of autologous *ex-vivo* expanded TILs can induce objective clinical responses in melanoma (51), and

ii. the relationship between pretherapy $CD8^+$ T-cell infiltrates and response to checkpoint blockade in melanoma (52).

NGS permit identification of mutations present within the tumor exome allowing for neoantigen prediction. Several pre-clinical and clinical studies have now confirmed the possibility of identifying neoantigens on this basis (53–57). Although there are limitations of probing the mutational profile of tumor in a single biopsy (58, 59), it is evident the vast majority of neoantigens occur within exonic sequence and do not lead to formation of neoantigens recognized by autologous T-cells (59, 60). Consequently, a robust pipeline for filtering cancer exome data is essential. Stimulation of neoantigen-specific T-cell responses in cancer patients can be accomplished using two possible approaches. The first is to synthesize long peptide vaccines that encode a set of predicted neoantigens. The second approach is to identify and expand pre-existing neoantigen-specific T-cell populations to create either bulk neoantigen-specific T-cell products or TCR-engineered T-cells for adoptive therapy. This latter approach was recently tested in a pilot clinical trial of autologous DCs pulsed with oxidized autologous whole-tumor cell lysate (OCDC), which was injected intranodally in platinum-treated, recurrent EOC patients (61).

Immune inhibitory network and immune checkpoint inhibitors in EOC

A major barrier to successful cancer immunotherapy is an immunosuppressive TME. Even if large numbers of tumor-specific T-cells are generated in patients by active immunization or adoptive transfer, these T-cells may not readily destroy tumor targets. In EOC, some of the major mechanisms that subvert anti-tumor immunity in the TME include Tregs (11, 62), MDSC (63–65), inhibitory cytokines such as transforming growth factor-β (TGFβ) (66), immune checkpoint receptors (67–70), and indoleamine-2,3-dioxygenase (IDO) (71–73). This redundant immunosuppressive network may pose an impediment to immunotherapy, thus facilitating tumor progression.

Emerging evidence suggests that inhibitory receptor expression on TA-specific T-cells is one mechanism by which tumors evade immunosurveillance (74). Although inhibitory receptor blockade has shown significant promise (75–77), recent studies indicate that multiple inhibitory receptors are often co-expressed on TA-specific T-cells (78). In human EOC, TA-specific $CD8^+$ T-cells co-expressing PD-1 and LAG-3 exhibit significantly impaired IFN-γ and TNF-α production compared with single positive cells (70). Simultaneous blockade of both receptors restored effector function of these TA-specific T-cells to a level above single receptor blockade (70). In an EOC mouse model, synergistic blockade of LAG-3 and PD-1 enhanced $CD8^+$ TIL function and promoted tumor control, while single-agent blockade had little or no effect (79).

Immune modulation is designed to reinstate an existing anticancer immune response or elicit novel responses as a result of antigen spreading. This has been achieved through four general strategies:

i. inhibition of immunosuppressive receptors expressed by activated T-cells;

ii. inhibition of the principal ligands of these receptors;

iii. activation of co-stimulatory receptors expressed by effector T-cells; and

iv. neutralization of immunosuppressive mediators in the TME.

The first published data supporting checkpoint blockade as a potentially valuable therapeutic approach in EOC were trials of nivolumab (67), and BMS-93655 (anti-PD-L1) (75). In 20 nivolumab-treated patients in whom responses could be evaluated, the best overall response was 15% and the disease control rate was 45%. Two additional trials using avelumab and pembrolizumab were presented at the annual ASCO meeting in 2015. Of 75 heavily pre-treated avelumab-treated EOC patients, 8 patients experienced partial responses, 33 patients had stable disease, and there were no complete responses, with a disease control rate of 54.7% (80). In another Phase-1b study, 26 heavily pre-treated EOC patients with PD-L1 expression ≥1% on tumor cells were treated with pembrolizumab. The results showed one complete response, two partial responses and six patients with stable disease, corresponding to a disease control rate of 34.6% (81).

While these results are promising, the mechanism(s) of resistance to immune checkpoints in EOC are unclear. It is possible redundant immunosuppressive mechanisms counteract the beneficial effects of checkpoint blockade. Interestingly, a recent study in a murine EOC model showed anti-PD-1 monotherapy resulted in compensatory induction of other checkpoints, a feedback loop further contributing to immunosuppression (82). Additional checkpoint blockade agents are in various phases of clinical development, including anti-LAG-3 and anti-TIM3. Finally, emerging evidence suggests that the clinical efficacy of checkpoint blockade may be profoundly influenced by the mutational burden and “neoantigens” specific to the neoplasm (83), as higher neoantigen load leads to recruitment of a diverse repertoire of neoantigen-specific T-cells, leading to more effective tumor control.

Another critical tolerogenic mechanism in EOC is mediated by IDO, an immunoregulatory enzyme that contributes to profound immunosuppression (72). IDO catalyzes the rate-limiting step of tryptophan degradation. Reduction in local tryptophan levels and the production of tryptophan catabolites both contribute to immunosuppression (84), culminating in negative effects on T-cell proliferation, function, and survival. IDO activity also promotes the differentiation of naïve T-cells to Tregs (85). Since increased Treg activity has been shown to promote tumor growth and Treg depletion has been shown to allow an otherwise ineffectual anti-tumor immune response to occur (62), IDO expansion of Tregs provides an additional immunosuppressive mechanism.

In addition to directly inhibiting IDO enzymatic activity, second-generation IDO1 inhibitors such as epacadostat and navoximod have entered clinical trials due to their favorable pharmacokinetic profile. Phase I clinical trials with these orally available compounds have demonstrated safety and biological efficacy based on reversal of tryptophan depletion (86). A recently completed trial (NCT02042430) sought to determine the magnitude by which epacadostat alters $CD8^+$ TIL frequency when administrated prior to surgery in newly diagnosed stage III-IV EOC patients. Another approach tests whether concomitant IDO inhibition and NY-ESO-1 vaccination will enhance the generation of durable antitumor $CD8^+$ T-cells in EOC patients (NCT02166905).

Adoptive Cellular Therapy

Among various immunotherapeutic approaches, adoptive T cell therapy (ACT) has resulted in objective responses in the majority of treated patients (87). ACT approaches involve:

- **i.** the collection of circulating T-cells or TILs (88);
- **ii.** modification and/or expansion *ex-vivo*; and
- **iii.** their re-infusion to patients after lymphodepleting chemotherapy.

Initial studies demonstrating the potential of T-cell immunotherapy to eradicate solid tumors came from the NCI in adoptive transfer studies of TILs (89, 90). Unfortunately, methods of isolating and manufacturing TILs are labor intensive and only successful in a subset of patients (91, 92). In order to improve the therapeutic potential of ACT, peripheral blood lymphocytes can be genetically modified to express: (i) a TA-specific T-cell receptor (TCR) (87), or (ii) “chimeric antigen receptor” (CAR) expressing the TA-binding domain of an immunoglobulin linked to costimulatory molecules (93). In EOC, targets for the TCR approach include NY-ESO-1, MAGE-A4, and WT1. Targets for CAR-T-cells include MUC16, mesothelin, and folate receptor. Several studies are ongoing or completed testing CD8TCR-engineered T-cells in patients. Although spectacular responses have been observed, the majority of clinical responses are short-lived with ultimate tumor relapse. One explanation for this sub-optimal outcome is the relatively limited long-term survival and effector function due to suppression or exhaustion of infused T-cells.

Previous ACT trials have focused on CD8TCR but not CD4TCR. Because $CD4^+$ T-cells maintain $CD8^+$ T-cell responses (94, 95) and rescue exhausted T-cells (96), long-lasting anti-tumor responses are expected by the synergy of CD8TCR− and CD4TCR-engineered T-cells. Recently, two types of TA-specific $CD4^+$ T-cells, tumor-recognizing or non-tumor-recognizing, have been identified that play distinct roles in the TME (97). Though both recognize NY-ESO-1 presented by APCs, only tumor-recognizing CD4 directly recognize cancer cells in an antigen/MHC-restricted manner (97, 98).

Oncolytic Virus-based therapy

Oncolytic viruses (OV) are non-pathogenic viral strains that specifically infect cancer cells, triggering their demise. The anti-neoplastic potential of OV can be innate via a cytopathic effect or by mediating oncolysis due to expression of gene products that are potentially lethal for the host cell. Increasing preclinical and clinical evidence indicate that the therapeutic activity of oncolytic viruses is also related to their ability to elicit immune responses as they (i) reprogram the inflammatory TME to be more immunogenic and (ii) promote the release of TA. OVs can be genetically engineered to endow them with additional attributes, such as antagonism of chemokine receptors (99).

Results from a study testing talimogene laherparepvec (T-VEC), a modified herpes simplex virus type-1, were recently reported (100). Researchers randomized 436 patients with aggressive, inoperable melanoma to receive either T-VEC or a control immunotherapy.

16.3% of the group given T-VEC showed a durable response of >6 months, with some responses extending past three years.

Combination of ACT and OV may have beneficial synergistic effect. In mouse models, it has been shown that T-cells loaded with oncolytic vesicular stomatitis virus efficiently delivered the virus to metastatic lymph nodes leading to tumor clearance (101). The loading of antigen-specific T-cells with vesicular stomatitis virus enhanced the delivery of the virus to lung tumors (102) and the associated pro-inflammatory TME enhanced antigen-specific T-cell proliferation and survival within the tumor.

Conclusions and Future Directions

Cancer immunotherapy is evolving quickly and understanding the dynamics of the antitumor immune response, especially in regards to immunosuppression and counter-regulation, will lead to development of effective personalized targeted approaches. A future direction for EOC is to develop approaches based on shared antigens and the patient's neo-antigenome. This will require a pipeline for rapid and reliable neoantigen identification, consisting of a multidisciplinary team of clinicians and bioinformaticians. Recent examples of "off-the-shelf" tumor antigens and engineered T-cells are limited to the KRAS G12D TCR (103–105). Identifying other pairs of antigen moieties and TCR sequences could offer great benefits for ACT and vaccination strategies in EOC.

Immunotherapy mediates tumor destruction, but also triggers coordinated induction of counter-regulatory and suppressive pathways. Concomitant blockade of suppressive pathways at the time of vaccination or T-cell transfer will allow inflammation-induced transformation of the TME from a tolerogenic to an immunogenic milieu. Based on promising results of PD-1/PD-L1 pathway blockade, it is important to consider opportunities for combination therapies. These include PD-1/PD-L1 blockade with anti-CTLA-4 or anti-LAG-3, an approach that has demonstrated excellent results in pre-clinical models of ovarian cancer and melanoma (70, 79, 106–110). Additional potential combinations include targeted agents (e.g. BRAF and EGFR targeted agents) (111), blocking IDO, chemotherapies with potential to cause immunogenic cell death, and vaccine combinations.

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Key points:

1. Harnessing the immune system to eradicate established tumors is emerging as a viable and efficacious therapy for advanced ovarian cancer.
2. Shared tumor antigens, such as NY-ESO-1, or patient-specific mutational neoantigens are attractive targets for initiation of T-cell responses.
3. The presence of redundant and compensatory immune checkpoint pathways indicate that combinatorial checkpoint blockade may be required for effective tumor control in ovarian cancer.
4. Addressing the molecular mechanisms governing poor in-vivo persistence of engineered T-cells will enhance the therapeutic potential of adoptive T-cell therapy.

Synopsis

Clinical progress in the field of cancer immunotherapy has been slow for many years but within the last 5 years, breakthrough successes have brought immunotherapy to the forefront in cancer therapy. Promising results have been observed in solid tumors and hematological malignancies with adoptive cell therapy using tumor-infiltrating lymphocytes (TILs), host cells genetically engineered with antitumor T-cell receptors (TCRs) or chimeric antigen receptors (CARs), immune checkpoint inhibitors, and oncolytic virotherapy. However, most treatment modalities have shown limited efficacy when utilized as monotherapy. The complex nature of cancer with intra- and inter-tumor antigen and genomic heterogeneity, coupled with the immunosuppressive microenvironment, emphasizes the potential need to personalize immunotherapy by manipulating the patient's own immune system against cancer. For successful and long-lasting cure of cancer, a multi-modal approach is essential, combining antitumor cell therapy with manipulation of multiple pathways in the tumor microenvironment (TME) to ameliorate tumor-induced immunosuppression.

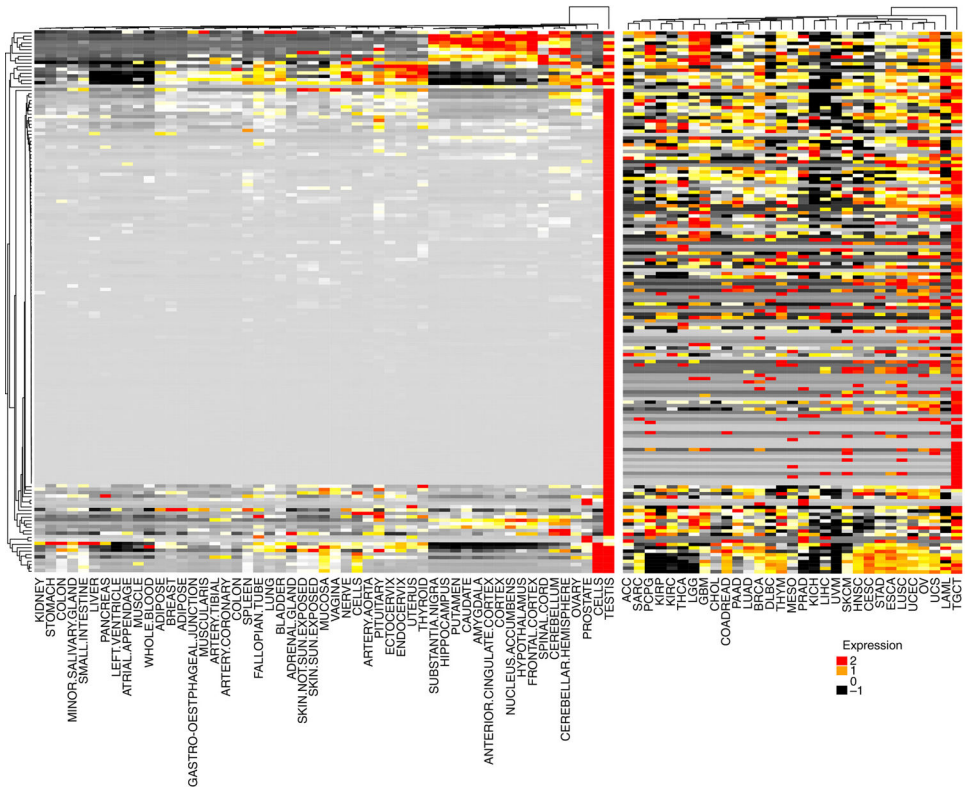

Figure 1.

Expression pattern of 162 CT genes across normal tissues from GTeX and patient tumor samples from TCGA. RNASeq data were obtained from GTeX (normal tissues) or TCGA PANCancer study (tumors). The median expression per each CT gene was calculated across all patients in a specific tissue. Each cell in the heatmap indicates the median expression of a CT gene in the tissue indicated at the bottom of the figure. Red cells indicate high expression and black cells low expression levels.

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Table 1:

Available Anti-cancer Immunotherapies

Approach	Licensed
Tumor targeting antibodies	Yes
DC vaccination	Yes
Peptide vaccines	Yes
Immunostimulatory cytokines	Yes
Immunomodulatory antibodies	Yes
Oncolytic virotherapy	Yes
TLR agonists	Yes
DNA and recombinant viral vaccines	No
Inhibitors of IDO, arginase	No
Adoptive cell therapy	No

Table 2.

Selected cancer vaccine studies

Antigen	Phase	Disease	Technology	Co-therapy	Sponsor	Reference
NY-ESO-1	I	Metastatic cancer	Recombinant protein	GLA -SE	Immune Design	NCT02015416
	I	Ovarian, fallopian tube cancer	DEC-205 Fusion protein	Poly-ICLC, IDO1 inhibitor	Roswell Park Cancer Institute	NCT02166905
	I	NY-ESO-1 expressing solid tumors	DEC-205 Fusion protein/Dendritic ell	Rapamycin	Roswell Park Cancer Institute	NCT01522820
	I/II	NY-ESO-1 expressing tumors	DEC-205 Fusion protein	Resiquimod, Poly-ICLC	Celldex Therapeutics	NCT00948961
	I	NY-ESO-1 expressing tumors	Full length protein	Montanide, Resiquimod	Mount Sinai School of Medicine	NCT00821652
	I	Ovarian, fallopian, primary peritoneal cancer	Peptide	Decitabine, Doxorubicin, Montanide	Roswell Park Cancer Institute	NCT01673217
	I	NY-ESO-1/LAGE-1 expressing tumors	Peptide	CpG7909, Montanide	Ludwig Institute for Cancer Research	NCT00199836
	I	Ovarian, fallopian, primary peritoneal cancer	Peptide	Montanide	Memorial Sloan Kettering Cancer Center	NCT00066729
	I	Prostate cancer	Peptide		Baylor College of Medicine	NCT00616291
	I	Ovarian, fallopian, primary peritoneal cancer	Overlapping Long peptides (OLP4)	Montanide, Poly-ICLC	Ludwig Institute for Cancer Research	NCT00616941
	I	Ovarian, fallopian, primary peritoneal cancer	Vector (ALVAC(2)-NY-ESO-1(M) TRICOM)	GM-CSF, Rapamycin	Roswell Park Cancer Institute	NCT01536054
	I	Ovarian, fallopian, primary peritoneal cancer	Vector (ALVAC(2)-NY-ESO-1(M) TRICOM)	GM-CSF	Ludwig Institute for Cancer Research	NCT00803569
	II	Ovarian, fallopian, primary peritoneal cancer	Vector (Fowlpox-NY-ESO-1)	Recombinant Vaccinia-NY-ESO_1	Ludwig Institute for Cancer Research	NCT00112957