Cancer-Testis Antigens: A Novel Group of Tumor Biomarkers in Ovarian Cancers

Zahra Taherian-Esfahani,1 Atieh Abedin-Do,1 Elahe Nikpayam,1 Behnoosh Tasharofi,1 Akram Gahghaei Nezamabadi,2 and Soudeh Ghafouri-Fard1,∗

1Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2Vali-e-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran

∗Corresponding author: Soudeh Ghafouri-Fard, Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel: +98-2123872572, E-mail: s.ghafouriard@sbmu.ac.ir

Received 2015 December 08; Revised 2016 January 11; Accepted 2016 December 03.

Abstract

Context: Ovarian cancer is the most fatal gynecological malignancy with no effective screening strategy for early detection. As most cases are being detected in advanced stages, conventional therapies are not beneficial for the majority of patients. Cancer-testis antigens (CTAs) are a group of tumor associated antigens with specific expression pattern in cancers which potentiate them for application as cancer biomarkers and targets for immunotherapy.

Evidence Acquisition: We performed a computerized search of the MEDLINE/PUBMED databases with key words: ovarian cancer, cancer-testis antigen, biomarker and immunotherapy.

Results: Thirty five CTAs have been shown to be expressed in ovarian cancer. At least 13 of them have been shown to elicit immune responses in different studies. The pattern of expression for some of them may facilitate molecular classification of different histologic classes of ovarian cancer. In addition, some CTAs such as NY-ESO-1 and MAGE have been used as targets for immunotherapeutic approaches with promising results.

Conclusions: The expression pattern of CTAs in ovarian cancer and the preliminary results of clinical trials indicate that CTAs can be used as targets for immunotherapy of ovarian cancer patients.

Keywords: Cancer-Testis Antigen, Ovarian Cancer, Biomarker, Immunotherapy

1. Context

Ovarian cancer as the most fatal gynecological malignancy has been a subject of screening programs for decades (1, 2). Yet no effective screening strategy has been identified so far. Epithelial, stromal and germ cell tumors are the three main types of ovarian cancer with the first one being the most prevalent. Currently, only about one third of women with early-stage disease can be diagnosed by bimanual examination, CA-125 and transvaginal ultrasoundography (3). According to histopathology, immuno-histochemistry, and molecular genetic studies, malignant epithelial tumors have been sub-classified to high-grade serous carcinoma, endometrioid carcinoma, clear-cell carcinoma, mucinous carcinoma and low-grade serous carcinoma (4). Numerous genetic and environmental factors have been shown to be implicated in its development including estrogen hormones which have been shown to contribute in tumor progression by enhancing cell proliferation, invasion or cell mobility (5). Even with novel combinatorial chemotherapy regimens and the introduction of intraperitoneal chemotherapy administration, no significant improvement has occurred in the survival of patients. Consequently, novel treatment strategies, such as immunotherapy, are being evaluated for treating ovarian tumors (6). Cancer-testis antigens (CTAs), as a new group of tumor-associated antigens (TAAs) have special characteristics which make them suitable for immunotherapeutic approaches as well as early detection of cancer (7). They are usually absent from normal adult tissues except for the testis but aberrantly upregulated in cancer tissues. Their expression has been evaluated in various cancers of different origins as well as their normal counterparts so far (8-13). Notably, ovarian tissue has an especial situation in this regard. Based on the similarity in biology between testicular and female germ cells, the most outstanding CTA expression has been assumed to occur in the developing ovary. However, various independent studies have shown that adult ovarian tissue is CTA negative (14). As one of the most important characteristics of a putative cancer biomarker is its absence or low level of expression in normal tissue counterpart, we evaluated the data regarding CTA expression in ovarian cancer as well as normal ovary.
2. Evidence Acquisition

In order to gather data about expression of CTAs in ovarian cancer, we performed a computerized search of the MEDLINE/PUBMED databases with key words: ovarian cancer, cancer-testis antigen, biomarker and immunotherapy.

3. Results

3.1. Immunotherapy in Ovarian Cancer

The role of immune system in recognition and elimination of ovarian tumor cells has been highlighted by the observations indicating that high numbers of tumor-infiltrating lymphocytes are associated with better progression free and overall survival, whereas the existence of regulatory T cells and expression of T cell inhibitory molecules is linked with a poor prognosis (15). Further evidence for such deduction has been provided by identification of a 126-gene expression signature for predicting overall survival in patients with ovarian cancer. Notably according to this gene signature high-risk ovarian cancer patients are recognized by a significant decrease in expression of immune response related genes, in particular those in the antigen presentation pathway (16). Based on the identification of TILs as important antitumor effectors as well as recognition of potentially immunogenic TAAs in ovarian cancer, immunotherapeutic treatment strategy has been suggested for these patients. The discovery of TAA has been an important step in active immunization of cancer patients using peptide vaccines. The first report describing the cloning of a TAA encoding gene has been published in 1991 and the corresponding gene was subsequently attributed to CTA family and named the melanoma antigen-1 (MAGE-1) (17). In addition to the members of the CTA family (e.g. MAGE-A4 and NY-ESO-1), aberrant upregulation of HER2/neu, folate receptor alpha (FRα), mutated p53 and CA125 has been demonstrated in tumor tissue and ascite fluid of ovarian cancer patients. These markers have been suggested as putative targets for induction of immune response and subsequent immune-mediated tumor rejection. Therefore, various immunotherapeutic approaches for ovarian cancer including antibodies, immune checkpoint inhibitors, vaccines, and adoptive cell therapy have recently entered clinical testing (6). Bevacizumab and cetuximab are among monoclonal antibodies which showed promising results in clinical trials (18, 19). Immune checkpoints are specific molecules with the ability to inhibit powerful immunologic effector cells. These checkpoints can be used by cancer cells to circumvent immune control and rejection. Consequently, inhibition of these inhibitory pathways with antibodies against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) has shown promising results in cancer patients (20). In addition, simultaneous blockade of PD-land lymphocyte-activation gene 3 (LAG-3) has a synergistic effect on tumor elimination and has been suggested as a combinatorial immunotherapeutic approach (21). Such dual inhibition during T-cell priming has significantly enhanced proliferation and cytokine production by NY-ESO-1-specific CD8+ T-cells in ovarian cancer patients (22). Furthermore, up to now, various peptide vaccines have been designed which can bind to major histocompatibility complex (MHC) molecules and be recognized by T cells. HER2 and MUC1 are among the most studied TAAs in ovarian cancer patients. On the whole, the most promising results of immunotherapy in ovarian cancer have emerged from dendritic cell (DC)-based vaccines. DCs are responsible for processing and presenting antigens and subsequent induction of specific effector and memory T cells. They have been shown to recognize TAAs and have been applied in a small number of clinical trials in ovarian cancer (23). For instance, subcutaneous vaccination with mature DCs pulsed with HLA-A2-restricted HER2 or MUC1 peptides has been shown to result in development of tumor-specific cytotoxic T cells (CTLs) with the ability to restrain HER2 overexpressing cancer cell lines in vitro (24). Another vaccine formulation includes autologous antigen presenting cells (APCs) loaded with HER2 antigen linked to GM-CSF domain and has been administered in metastatic ovarian cancer patients (25). Early clinical results from these studies have indicated a potential to improve the survival of ovarian cancer patients (6). Adoptive T cell therapy is another approach which relies on the presence of adequate numbers of antitumor lymphocytes with proper effector functions to recognize and destroy cancer cells. Such approach would become more successful by appropriate modifications of patients’ lymphocytes to generate more tumor specific lymphocytes. T cell receptors (TCRs) are among candidate genes for such modifications. Considering the role of TCRs in recognition of human leukocyte antigen-A2 restricted epitopes from known TAAs including NY-ESO-1, this strategy represent a novel promising modality in ovarian cancer immunotherapy (26).

3.2. Expression of CTAs in Ovarian Cancer

Various studies have aimed at expression analysis of CTAs in ovarian cancer tissues by means of reverse-transcriptase polymerase chain reaction (RT-PCR), western blotting as well as microarray. A recent study has suggested global hypomethylation, and not loss of X chromosome inactivation as the principal mechanism of overexpression of CTAs in ovarian cancer (27).
Table 1 provides a summary of CTAs expression in ovarian cancer as well as their genomic location and biological function. As listed in the table 35, CTAs have been shown to be expressed in ovarian cancer samples. According to patterns of expression, they have been divided to testis-restricted (exclusively expressed in the testis) and testis-selective (expressed in few tissues beside the testis). Spontaneous immune responses have been detected for at least 13 of them in patients.

Some antigens such as SP17 have been previously attributed to CTA family (28). However, recent data demonstrated its expression in a wide array of normal tissues (10). Consequently, it has been omitted from our list of CTAs.

3.2.1. AKAP3 (A-Kinase Anchoring Proteins 3)
AKAP-3 expression has been demonstrated in more than half of the epithelial ovarian cancer specimens at mRNA level. Its expression considerably correlated with increased likelihood of residual tumor and poorer overall survival. Consequently, it has been suggested as an attractive target for antigen-specific immunotherapy in ovarian cancer (29). Another study has indicated a significantly higher frequency of AKAP3 expression in poorly differentiated and advanced stage tumors. In addition, its expression has been shown to be a significant predictor of both overall and progression-free survival in patients with poorly differentiated tumors (30).

3.2.2. AKAP4 (A-Kinase Anchoring Proteins 4)
AKAP4 expression has been shown at both mRNA and protein levels in most of ovarian carcinoma tissue specimens examined in a study. Notably, none of the matched adjacent non-cancerous tissues expressed it. Additionally, more than half of patients have been shown to have circulating antibodies against AKAP4 which maybe of clinical significance in immunotherapeutic approaches (31).

3.2.3. BAGE (B Melanoma Antigen)
BAGE (B melanoma antigen) has been shown to be expressed in both primary and metastatic ovarian cancer lesions with no expression in normal ovary or benign tumors. In addition, a higher expression rate for BAGE has been detected in ovarian cancer patients with ascites as well as patients with serous cystadenocarcinomas. It has been suggested to participate in the occurrence and development of ovarian cancer. The recognition of BAGE antigens by cytotoxic T cells implies that it could have extensive application prospects in cancer immunotherapy (32).

3.2.4. DPPA2 (Developmental Pluripotency Associated-2)
DPPA2 is a non-X-linked pluripotency gene which is expressed in pluripotent embryonic cells and is a putative marker of ‘re-populating’ cells with stem cell-like features. It has been shown to be expressed in about one third of epithelial ovarian cancer patients with detectable spontaneous humoral responses in the minority of them. It has been suggested that it has a shared role in embryogenesis and cancer development especially in emergence and/or maintenance of stem cells. In addition, DPPA2 seropositivity has been demonstrated in healthy female donors and patients whose tumors did not express the antigen which implies previous exposure to DPPA2 for instance in pregnancy. On the whole, such data suggest that this antigen can be used as a target in immunotherapy of ovarian cancer patients (33).

3.2.5. GAGE (G Melanoma Antigen) Family
GAGE expression has been shown in a subset of primary and metastatic ovarian cancer patients excluding mucinous and borderline samples (34). GAGE proteins have been shown to be expressed in a subset of oocytes of resting primordial follicles and in maturing oocytes (35) which limits their potential application as cancer biomarkers as well as antigen specific immunotherapy.

3.2.6. LAGE-1 (L Antigen Family Member 1)
LAGE-1 is a CTA with a highly similar amino acid sequence with NY-ESO-1 (13). LAGE-1 expression has been detected in papillary serous, clear cell and mucinous histologic subtypes of ovarian cancer. In addition, antibody to NY-ESO-1/LAGE-1 was present in about one third of patients whose tumors expressed either NY-ESO-1 or LAGE-1. Such antibodies could be detected up to 3 years after initial diagnosis (36).

3.2.7. MAGE (Melanoma Associated Antigen) Family
In a study of CTA expression in ovarian cancer samples, MAGEC1/CT7 has been the most commonly expressed CTA with positivity in 24.5 % of primary and 35.1 % of recurrent samples. Of note, no mucinous or borderline sample expressed it. Among CTAs expressed in high-grade serous samples, MAGE-C1/CT7 has been the most frequent one. MAGE-C1/CT7 expression has been significantly correlated with grade of endometrioid cancers (34). In the same cohort of patients, MAGE-A4 has been the second most frequently expressed CTA in both primary and recurrent ovarian cancer samples (34). Another study has revealed MAGE-A4 expression in 57% of the serous carcinomas, 9% of the serous tumors of borderline malignancy but not in serous cystadenomas or in the normal ovary. In addition, its expression has been inversely associated with patient survival. Consequently, MAGE-A4 expression has been proposed as a feature of the majority of serous ovarian carcinomas. In addition, a more aggressive regimen
in patients with MAGE-A4 expressing tumors has been suggested (37). MAGE-A3 have also been shown to be expressed in a significant number of ovarian cancer samples in different studies (38). In addition, expression of MAGE-1 and MAGE-3 has been higher in serous cystadenocarcinoma than in other types of ovarian cancer and has been positively associated with tumor differentiation and the clinical stage of the ovarian cancer (32). Furthermore, MAGE3/6 has been among genes which have been detected in exosomes isolated from ovarian cancer patients’ plasma. Interestingly, such exosomes were useful for discrimination of ovarian cancer patients from those with benign tumors and healthy controls (39). Another recent study has indicated that expression of MAGE-A1 or -A10 antigens is associated with poor progression free survival (PFS) while MAGE-C1 expression has been correlated with better PFS (40). MAGE-A9 expression has also been demonstrated as a poor prognosis marker (41). Notably, a recent study has shown that MAGE-A8 is among genes whose expression patterns show specific prognostic effects in ovarian cancer patients. It is also among genes which signify an immunoregulatory pattern in tumors. Such pattern is associated with higher stage, lower treatment response, shorter overall survival, and progression free survival (42).

3.2.8. NY-ESO-1 (New York Esophageal Squamous Cell Carcinoma-1)

NY-ESO-1 is perhaps the most studied CTA and has been regarded as the most immunogenic one (68). However, in one study its expression has been shown in a relatively small subset of both primary and recurrent ovarian cancer samples including serous, endometrioid, clear cell and transitional subtypes with no expression in mucinous samples (34). However, another study has shown its expression in mucinous subtypes (36). An independent study has shown its expression in 19% of the serous carcinomas but not in serous tumors of borderline malignancy and cystadenomas (37). Another study has demonstrated its more frequent expression in ovarian cancer samples with no statement about the expression of NY-ESO-1 in distinct histologic subtypes (43). However, the normal epithelium of the fallopian tube has also shown dispersed weak expression of NY-ESO-1 (34). In an immunological survey in ovarian cancer patients, the presence of autoantibodies to NY-ESO-1 has been correlated with increased tumor-infiltrating CD8+, CD4+ and FoxP3+ cells. Consequently, it has been deduced that autoantibodies may collaborate with tumor-infiltrating T cells to influence clinical outcomes in such patients (44).

3.2.9. OY-TES-1 (Acrosin-Binding Protein; ACRBP)

Expression of OY-TES-1 has been shown in the majority of ovarian cancer patients examined in a study. However, no correlation was found between antigen expression and stage, grade, histology and survival (45). In addition, a recent study has demonstrated its frequent expression in ovarian cancer tissues as well as their adjacent tissues with the higher immunostaining intensity in the former. No statistically significant correlation has been identified between OY-TES-1 expression and any other clinicopathological characteristic. This data indicate that OY-TES-1 can be an attractive target for immunotherapy for ovarian cancer (46).

3.2.10. PASD1 (PAS Domain Containing 1)

In a study of 191 ovarian cancer tissues, which were mostly stage I (n = 164) and stage II (n = 14) disease, only one stage Ic ovarian cancer patient tissue expressed PASD1a and b at noticeable levels. This may principally be due to the stage I ovarian cancer samples assessed (47).

3.2.11. PIWIL2 (Piwi-Like RNA-Mediated Gene Silencing 2)

PIWIL2 is a germline stem cell gene whose ectopic expression is linked with cancer stem cell development. It has been proposed to be a gatekeeper against DNA damage-mediated carcinogenesis. Additionally, its expression has been associated with increased proliferation and apoptosis inhibition (48). PIWIL2 has been shown to be specifically expressed in epithelial cells (cancerous cells) of ovarian cancer samples in addition to the stromal cells adjacent to tumor cells (49). Another study has shown its higher expression in the primary tumor and metastatic tissues compared with the adjacent normal tissues and has suggested it as a diagnostic biomarker for epithelial ovarian cancer (50). However, its expression in normal lymphocytes has limited its application in immunotherapy (48).

3.2.12. PLAC1 (Placenta Specific 1)

PLAC1 is a human X-linked gene with placenta-specific expression and a putative marker of ‘repopulating’ cells with stem cell-like features. Its expression has been demonstrated in epithelial ovarian cancer. Such expression has not been correlated with clinicopathological features of patients such as recurrence and survival which may be at least due to selection of advanced stage patients in this study (33).

3.2.13. SCP1 (Synaptonemal Complex Protein 1)

It has been shown to be expressed in a subset of primary ovarian tumors and not in the normal ovarian surface epithelial cell lines. Its expression has been associated
with a higher tumor grade as well as a decrease in survival time. Consequently, it has been suggested as a potential target for vaccine therapy in epithelial ovarian cancer (51).

3.2.14. SGY1 (Soggy-1)

It codes for a secreted protein related to the Dickkopf protein family with inhibitory effects on Wnt pathway during early embryonic development. It is among CTAs whose expressions have been shown to be higher in cancer stem cells than in non-stem cells within cultured cells from lung adenocarcinoma cells, colon adenocarcinoma cells and breast adenocarcinoma cells (52). It has been shown to be expressed in a subset of ovarian cancer samples (53).

3.2.15. SPAG1 (Sperm-Associated Antigen-1)

Its involvement in spermatogenesis has been recognized after the detection of anti-SPAG1 antibodies in the serum of an infertile woman and the consequent sperm agglutination. It has been shown to be expressed in a large proportion of pancreatic ductal adenocarcinomas and promote motility of cancer cells (54). In addition, although it is absent from normal adult ovary, it is expressed in a subset of ovarian cancer samples (54).

3.2.16. SPANX-B (Sperm Protein Associated with the Nucleus on the X Chromosome-B)

SPANX-B has been shown to be expressed in melanoma and carcinomas of lung, ovary, colon and breast. Most importantly, SPANX-B has elicited immune responses in healthy humans. SPANX-B-specific helper CD4+ and cytolytic CD8+ T cells could recognize at least one HLA-DR-restricted Pep-9 epitope and two HLA-A2-restricted Pep-2, and Pep-4 epitopes. The ability of CD8+ T cells to recognize and lyse HLA-A2-expressing tumors has been demonstrated in primary human melanomas (55).

3.2.17. SPANX-N (Sperm Protein Associated with the Nucleus on the X Chromosome-N)

Its protein translation has been shown to occur post-meiotically in human testis. Unexpectedly, a weak expression of SPANX-N has been shown in non gametogenic tissues such as breast, cervix, prostate, lung, ovary, placenta, proximal and distal colon, stomach, and uterus albeit at 50 - 100 times lower levels than that of testis. Although expressed in ovarian cancer, the maximum level of SPANX-N expression similar to that in testis has been only demonstrated in some melanoma cell lines (56).

3.2.18. SSX (Synovial Sarcoma, X) Family

Approximately half of ovarian cancer samples examined in a study have shown the expression of SSX-4 (57). Another study has revealed its expression in a smaller percentage of samples. However, it demonstrated antibodies against SSX4 in a subset of patients which implies that SSX4 could be a potential target for cancer vaccines (58). An independent study has revealed expression of SSX-4, SSX-2, and SSX-4 in a subset of ovarian cancer patients with the latter being the most prevalent. Of note, antibodies against SSX-2 and SSX-4 as well as SSX-4-specific CD4+ T cells have been detected in few patients (59). Historically, the founder member of this family has been identified in a malignant melanoma patient using serological analysis of recombinant tumor cDNA expression libraries (SEREX) (60). Consequently, spontaneous immunological response to this group of CTAs is probable to be seen in cancer patients which facilitates their application in immunotherapy.

3.2.19. TAG Family

The TAG-1, TAG-2a, TAG-2b, and TAG-2c genes have been shown to be expressed in different epithelial cancers including ovarian cancer. Notably, cytotoxic T lymphocytes specific for two HLA-A2-restricted epitopes from these antigens have recognized tumor cells expressing both the corresponding class I MHC encoded molecule and the TAG genes. Consequently, TAG-derived peptides have been suggested as appropriate therapeutic vaccine components against epithelial cell-derived malignancies (61).

3.2.20. TPX1 (Testis-Specific Protein 1)

It codes for an integral protein of the outer dense fibers and the acrosome of spermatids. Its expression has been shown in ovarian cancer. However, a very weak and inconsistent expression of it has been detected in endometrium (53).

3.2.21. TSGA10 (Testis-Specific Gene 10)

The TSGA10 gene has been initially demonstrated by differential mRNA display to be expressed only in adult testis (62). Afterwards, its expression has been shown in various cancers (8, 63, 64), including ovarian cancer (65). Although it has been shown to elicit humoral responses in hepatocellular carcinoma and malignant melanoma patients, there is no evidence for its immunogenicity in ovarian cancer patients (65).

3.2.22. TSPY1 (Testis Specific Protein, Y-Linked 1)

TSPY1 has been reported to participate in the control of cell cycle progression, cell proliferation and tumorigenesis. It is a germ cell specific marker with no expression in fetal ovary. Its protein has been detected in a significant number of dysgerminoma and gonadoblastoma ovarian tumors (66).
3.2.23. TTK (TTK Protein Kinase)

TTK codes for a protein kinase which is a regulator of the mitotic spindle-assembly checkpoint. Its expression has been shown to be associated with cell proliferation. It has been shown to be expressed in ovarian cancer cell lines as well as patients who had malignant ovarian cancer effusions in the peritoneal cavity (67). Although not assessed in ovarian cancer patients yet, specific T-cell responses to epitope peptides originated from TTK were repeatedly induced in patients with esophageal squamous cell carcinoma (68) which implies its suitability for active immunotherapy of other cancer patients.

3.2.24. XAGE1 (X Antigen Family Member 1)

Although attributed to CTA family, it has been shown to be expressed in lung and peripheral blood lymphocytes at mRNA level. In addition to ovarian cancer, it has been shown to be expressed in Ewing’s sarcomas, alveolar rhabdomyosarcomas and breast, lung, and prostate cancers. Western immunoblot analysis has shown its expression in nuclear, cytoplasmic and membrane fractions of cancer cells. In addition, from two identified transcript, XAGE-1b has been shown to be the dominant transcript (69). Although another study has confirmed the predominant expression of the mentioned transcript in the testis and tumors, it failed to detect XAGE-1b protein expression in 8 ovarian cancer samples (70).

3.3. Immunogenicity of CTAs in Ovarian Cancer

As revealed by previous studies, identification of proteins which are involved in the immune response would provide a better recognition of the early stage immune response to cancer in addition to key knowledge about antigens that may be appropriate for immunotherapy (71). Some CTAs have been shown to elicit humoral and/or cellular immune responses in ovarian cancer patients. Possibly the most immunogenic one has been NY-ESO-1 (72). For instance, the NY-ESO-1 epitope 157-170 has been shown to stimulate both Th1 and Th2 type CD4+ T cell responses in epithelial ovarian cancer patients (73). As stated before, its limited expression in some histologic subtypes may limit its potential application in immunotherapy. However, DNA methyltransferase inhibitors have been shown to enhance its expression and increase the presence of circulating antibodies to NY-ESO-1 (74). Other CTAs such as MAGE, BAGE and GAGE have been shown to elicit immune responses as well. Besides, specific SPAG9 antibodies have been detected in majority of epithelial ovarian cancer patients which implies its immunogenicity in these patients as well as its potential for early diagnosis (75). Some other CTAs such as OY-TES-1 have been shown to elicit humoral responses in a smaller percentage of ovarian cancer patients (45).

4. CTA-Based Immunotherapy in Ovarian Cancer

The relatively low survival rate and high relapse rate of patients with ovarian cancer necessitate the search for novel treatment modalities such as immunotherapy. With the assumption that most of patients have micrometastases, even after complete response to frontline surgery and chemotherapy, immunotherapy can be considered for patients (36). As ovarian cancer is one of cancers with frequent expression of CTAs, many patients would benefit from CTA-based immunotherapy even after failure of first- and second-line therapies (34). The most widely used CTAs in clinical trials of cancer patients including ovarian cancer is NY-ESO-1 (72). Perhaps the most promising example of NY-ESO-1-based immunotherapy has been a phase II trial of treatment of 22 recurrent ovarian cancer patients with an NY-ESO-1 vaccine containing recombinant vaccinia and fowlpox vectors resulting in improvement of median overall survival to 48 months in patients having immune activation compared to 15 months for patients that lacked immune activation (76). MAGE-A3 is another CTA whose expression pattern and immunogenicity suggest its suitability for immunotherapy. A recent study has shown that co-culture of autologous T lymphocytes with MAGE-A3-expressing DCs would result in production of CTLs with the ability to secret IFN-γ and kill MAGE-A3+ epithelial ovarian cancer cells. Consequently, this form of DC immunotherapy has been suggested for management of epithelial ovarian cancer (77). As revealed by some studies, CTAs tend to be coexpressed in cancer samples (34). This pattern of expression implies the presence of a unique mechanism for aberrant expression and facilitates design of polyvalent vaccines. At present, the most frequent use of MAGE, BAGE and GAGE antigens in the ovarian cancer vaccine is the peptide vaccine and DC vaccine (32). However, the heterogeneity of antigen expression between various histologic tumor types and even between cells of a tumor mass impedes selection of certain antigen for immunotherapy (32). One possible solution for this problem is application of polyvalent vaccines. Such strategy is also regarded as a solution for downregulation of certain CTAs in recurrent tumors due to immune escape (28). Such phenomenon has been observed in a patient who experienced a NY-ESO-1-negative tumor recurrence after complete objective response to NY-ESO-1 peptide vaccine (78). Table 2 provides a list of clinical trials with CTAs-based vaccines conducted in ovarian cancer.
Table 2. Selected Clinical Trials in Ovarian Cancer Patients Expressing Cancer-Testis Antigens

| Reference | Immunological Response/Trial Status | Number of Patients | Phase | Study Year | Vaccine / Adjuvant |
|-----------|------------------------------------|--------------------|-------|------------|--------------------|
| (101)     | Completed                           | 26-56              | I     | July 2000  | MAGE-A2 peptide vaccine/ Montanide ISA-51 |
| (100)     | Completed                           | Not provided       | I     | May 2003 - July 2006 | NY-ESO-1 peptide vaccine/ Montanide ISA-51 |
| (99)      | Completed                           | 9                  | I     | July 2005 - August 2008 | Chimeric-Her2 Fusion Protein (C-Her2)/ Herceptin/ NY-ESO-1 Protein (DSP) /Montanide ISA-51 |
| (98)      | Completed/Thymus and cell mediated immune response | 46 ovarian cancer patients after chemotherapy for primary or recurrent disease with or without residual disease | I     | 2008       | NY-ESO-1 short peptide incomplete Freund’s adjuvant |
| (97)      | Completed/Thymus and cell mediated immune response | 26 with or without residual or recurrent disease after primary therapy | I     | 2008       | Subcutaneous & intrauterine multi peptide vaccine (B7.21.1/2.9 & MAGE-A/1/Montanide ISA-51/ Poly-ICLC) |
| (96)      | Completed/Thymus and cell mediated immune response | 9 ovarian cancer patients with complete clinical response to primary therapy | I     | 2008       | Short NY-ESO-1 peptide/ Montanide ISA-51 |
| (95)      | Completed                           | 6                  | I     | November 2006 - June 2011 |Short NY-ESO-1 peptide/ Montanide ISA-51 |
| (94)      | Completed                           | 22                | I     | March 2012 - December 2015 | NY-ESO-1 short peptide / incomplete Freund’s adjuvant |
| (93)      | Completed                           | 9                 | I     | April 2009 - June 2013 | 5-aza-2’-deoxycytidine (decitabine) in combination with immunization with NY-ESO-1 protein/ Montanide and GM-CSF |
| (92)      | Completed                           | 18                | I     | April 2015 - December 2019 | Combination With INCB024360 |
| (91)      | Completed                           | 12                | I     | January 2015 | Autologous NY-ESO-specific CD8-positive T cells | palliative radiation therapy |
| (90)      | Completed                           | 19                | I     | March 2015 - March 2017 | NY-ESO-1 Specific TCR Gene Transduced T lymphocytes |
| (89)      | Completed                           | 36                | I     | April 2015 - December 2019 | NY-ESO-1 TCR-transduced T cells | Drug: Cyclophosphamide-Tetradecanoic acid |
| (88)      | Completed                           | 17                | I     | August 2012 | Short NY-ESO-1 peptide/ Montanide ISA-51 |
| (87)      | Completed                           | 15                | I     | July 2012 | NY-ESO-1 in Combination With the Adjuvant MPLA of Residual Tissues |
| (86)      | Completed                           | 10                | I     | June 2013 - July 2013 | CYTOTOXIC chemotherapy followed by immunization with NY-ESO-1 (C259) transduced autologous T cells |
| (85)      | Completed                           | 4                 | I     | December 2013 - September 2017 | Recombinant ADVAC(TM)- NYESO-1 (MTRECOM Vaccine) with Poly ICLC and EDO inhibitor R18043660 |
| (84)      | Completed                           | 50                | I     | August 2014 - February 2018 | EIC-265/NY-ESO-1 Fusion Protein CHP-146 (CHP-HER2) and NY-ESO-1 Protein (CHP-HER2) |
| (83)      | Completed                           | 22                | I     | July 2004 - January 2004 | Recombinant Vaccinia NY-ESO-1 (SC- NY-ESO-1) and Recombinant Footpox NY-ESO-1 (PF- NY-ESO-1) |
| (82)      | Completed/Thymus and cell mediated immune response | 4 epithelial ovarian cancer patients after primary debulking surgery | II    | 2006       | NY-ESO-1 short peptide/ incomplete Freund’s adjuvant |
| (81)      | Completed                           | 24 patients undergo primary optimal cytoreductive surgery | II    | April 2006 - August 2016 | MAGE-A3, Her2/neu, BR peptides vaccine / synthetic intranasal hydrogel peptide emulsified in Montanide ISA-51/ Drug: carboplatin – paclitaxel |

5. Conclusions

Ovarian cancer has been regarded as a cancer with frequent and high expression of CTAs. Most studied CTAs have been shown to be absent from adult ovarian tissues. Consequently, expression of CTAs in fetal ovary does not limit application of CTAs as cancer biomarkers or immunotherapy targets. Evaluation of CTA expression in distinct pathologic cancer subtypes may provide clues for molecular classification of ovarian cancers. However, this field is still in its infancy and future researches are needed. Furthermore, these antigens have a potential for specific diagnosis of malignancy both in the tumor specimen and in malignant ascites as revealed for BAGE, GAGE-1/2, MAGE-1, and MAGE-3 (102).

Footnotes

Authors’ Contribution: Zahra Taherian-Esfahani, Atieh Abedin-Do, Elahe Nikpayam, Behnoosh Tasharofi and Akram Gahghaiei Nezamabadi contributed in electronic search and designing tables; Soudeh Ghafori-Fard designed the study and wrote the manuscript; All authors read and approved the final manuscript; Zahra Taherian-Esfahani and Atieh Abedin-Do equally contributed in the study.

Iran J Cancer Prev. 2016; 9(6):e4993.
Financial Disclosure: None Declared.
Conflict of Interests: None Declared.

References

1. Jayson GC, Kohn EC, Kitchener HC, Ledermann JA. Ovarian cancer. Lancet. 2014;384(9951):1376–88. doi: 10.1016/S0140-6736(13)62146-7. [PubMed: 24767708].

2. Rajnar J, Neijolotalli F, Nedaei Ahmadl H, Hafezi H, Saha A. Expression of Vascular Endothelial Growth Factor (VEGF) and Epidermal Growth Factor Receptor (EGFR) in Patients With Serous Ovarian Carcinoma and Their Clinical Significance. Int J Cancer Prev. 2015;9(4):3428. doi: 10.7759/iipc.2015.003428. [PubMed: 26478785].

3. Nguyen T, Cardenas-Goicoechea SJ, Gordon P, Curtis C, Momeni M, Chuang L, et al. Biomarkers for early detection of ovarian cancer. Womens Health (Lond). 2015;9(2):71-85. doi: 10.2217/whe.13.112. [PubMed: 23477323] quiz 186-7.

4. Prat J, Figo Committee on Gynecologic Oncology. FIGO’s staging classification for cancer of the ovary, fallopian tube, and peritoneum: abridged republication. J Gynecol Oncol. 2015;26(2):87-9. doi: 10.1038/jjgo.2015.87. [PubMed: 25872849].

5. Maleki J, Noorbakhsh M, Shabani M, Korani M, Nourazarian SM, Ostadali Dahagh MR, et al. Beta-Estradiol Stimulates Generation of Reactive Species Oxygen and Nitric Oxide in Ovarian Adenocarcinoma Cells (OVCAR 3). Iran J Cancer Prev. 2015;8(4):2332. doi: 10.7795/ijcp2332. [PubMed: 26412522].

6. Chester C, Dorigo O, Berek JS, Kohrt H. Immunotherapeutic approaches to ovarian cancer treatment. J Immunother Cancer. 2015;3:7. doi: 10.1186/s40425-015-0051-7. [PubMed: 25806006].

7. Ghafouri-Fard S, Madarresi MH. Cancer-testis antigens: potential targets for cancer immunotherapy. Arch Iran Med. 2009;12(4):395-404. doi: 10.1900/aim.2009.13459. [PubMed: 19566518].

8. Dianatpour M, Mehdipour P, Nayernia K, Mobasheri MB, Ghafouri-Fard S, Savad S, et al. Expression of Testis Specific Genes TSGA10, B11, B14, B15, B18, B23, B25, B26, B29, B30, B31 and B32 in breast tumors: implications for cancer immunotherapy. Iran J Cancer Prev. 2012;5(1):722-6. doi: 10.5812/ircmj.3611. [PubMed: 23396665].

9. Schmid BC, Oehler MK. New perspectives in ovarian cancer treatment. Maturitas. 2014;77(2):128-36. doi: 10.1016/j.maturitas.2013.11.009. [PubMed: 23830827].

10. Brossart P, Wirths S, Stuhler G, Reichardt VL, Kanz L, Brugger W. Inhibition of cytolytic T lymphocytes on a human melanoma. J Immunother: PD-1 may not be LAG-ing behind any more. Oncoimmunology. 2012;1(7):2172-4. doi: 10.4161/onci.20591. [PubMed: 23659070].

11. Peethambaram PP, Melisio ME, Rizzetti MC, Cavallero N, Taliani D, Luzi P, et al. Tumor-infiltrating NY-ESO-1-specific CD8+ T cells are negatively regulated by LAG-3 and PD-1 in human ovarian cancer. Proc Natl Acad Sci U S A. 2010;107(17):7875-80. doi: 10.1073/pnas.1003450107. [PubMed: 20388500].

12. Schmid BC, Oehler MK. New perspectives in ovarian cancer treatment. Maturitas. 2014;77(2):128-36. doi: 10.1016/j.maturitas.2013.11.009. [PubMed: 23830827].

13. Schmid BC, Oehler MK. New perspectives in ovarian cancer treatment. Maturitas. 2014;77(2):128-36. doi: 10.1016/j.maturitas.2013.11.009. [PubMed: 23830827].

14. Berek JS, Edwards RP, Parker LP, Demars LR, Herzog TJ, Lentz SS, et al. Catumaxomab for the treatment of malignant ascites in patients with chemotherapy-refractory ovarian cancer: a phase II study. Int J Gynecol Cancer. 2014;24(2):358-9. doi: 10.1097/JIGC.0000000000000286. [PubMed: 25254563].

15. De Felice F, Marchetti C, Paliai I, Musio D, Muzii L, Tombolini V. Immunotherapy of ovarian cancer: The role of checkpoint inhibitors. J Immunother Cancer. [PubMed: 23762804].

16. van der Bruggen P, Traversari C, Chomez P, Lorquin C, De Plaen E, Van den Eynde B, et al. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science. 1991;254(5038):364-7. [PubMed: 1840703].

17. Poveda AM, Selle F, Hilpert F, Reuss A, Savarese A, Vergote I, et al. Bevacizumab Combined With Weekly Paclitaxel, Pegylated Liposomal Doxorubicin, or Topotecan in Platinum-Resistant Recurrent Ovarian Cancer: Analysis by Chemotherapy Cohort of the Randomized Phase III AURELIA Trial. J Clin Oncol. 2015;33(32):3836-8. doi: 10.1200/JCO.2015.61.4088. [PubMed: 26282651].

18. Wefers C, Lambert LJ, Torensma R, Hato SV. Cellular immunotherapy: potential for immunotherapy of ovarian serous carcinoma. Oncoimmunology. 2013;2(5):24270. doi: 10.4161/onci.24270. [PubMed: 23762804].
32. Zhang S, Zhou X, Yu H, Yu Y. Expression of tumor-specific antigen MAGE, GAGE and BAGE in ovarian cancer tissues and cell lines. BMC Cancer. 2010;10(1):163. doi:10.1186/1471-2407-10-163. [PubMed: 20423514]

33. Tchabo NE, Mhawech-Fauceglia P, Caballero OL, Villella J, Beck AF, Miliotto AJ. Expression and serum immunoreactivity of developmentally restricted differentiation antigens in epithelial ovarian cancer. Cancer Immunology. 2009;1(1):13.

34. Zimmermann AK, Imig J, Klar A, Renner C, Korol D, Fink D, et al. Expression of MAGE-C1/CT7 and selected cancer/tessis antigens in ovarian borderline tumours and primary and recurrent ovarian carcinomas. Vircows Arch. 2013;462(5):565-74. doi:10.1007/s00428-013-1395-1. [PubMed: 23529156]

35. Gjerstorff MF, Johansen LE, Nielsen O, Kock H, Ditzy HF. Restriction enzyme digestion for DNA amplification in ovarian cancer. Int J Oncol. 2005;26(1):143-7. [PubMed: 15503546]

36. Odunsi K, Jungbluth AA, Stockert E, Qian F, Gnjatic S, Tammela J, et al. Expression and serum immunoreactivity of develop-mental cancer/tessis targets for cancer immunotherapy in epithelial ovarian cancer. Cancer Immunology. 2004;4(4):11.

37. Yamada R, Takahashi A, Torituge T, Morita R, Tamura Y, Tsukahara T, et al. Preferential expression of cancer/tessis genes in stem cells: proposal of a novel sub-category, cancer/tessis/stem gene. Tissue Antigens. 2003;61(6):428-34. doi:10.1111/j.1399-0046.2003.00214.x. [PubMed: 12357462].

38. Kosloski M, Tureci O, Bell C, Krause P, Lehr HA, Brunner J, et al. Multiple splice variants of lactate dehydrogenase C selectively expressed in human cancer. Cancer Res. 2002;62(23):6765-9. [PubMed: 12438276].

39. Esfandiary A, Ghafouri-Fard S. MAGE-A3: an immunogenic target for cancer immunotherapy. Eur J Gynaecol Oncol. 2006;27(3):12104. doi:10.1038/srep12104. [PubMed: 26175056].

40. Xu Y, Wang C, Zhang Y, Jia L, Huang J. Overexpression of MAGE-A9 gets for immunotherapy in epithelial ovarian cancer. PLoS One. 2013;8(9):e77774. doi:10.1371/journal.pone.0077774. [PubMed: 24326379].

41. Tchabo NE, Mhawech-Fauceglia P, et al. OY-TES-1 expression and serum immunoreactivity of synovial sarcoma X (SSX) antigens in epithelial ovarian cancers. Int J Oncol. 2005;27(1):185-8. doi:10.3892/ijol.2005.56. [PubMed: 15606816].

42. Adair SJ, Carr TM, Fink MJ, Slengluff CJ, Hogan KT. The TAG antigen that is expressed in human tumors and readily recognized by human CD4+ and CD8+ T cells. Clin Cancer Res. 2009;15(16):4929-40. [PubMed: 19276289].

43. Koupria N, Noskov NV, Pavlicek A, Collins NK, Schoppee Bzd, Ottolenghi C, et al. Evolutionary diversification of SPANX-N sperm protein gene structure and expression. PLoS One. 2007;2(4):e359. doi:10.1371/journal.pone.0000359. [PubMed: 17406683].

44. Neesse A, Gangeswaran R, Luetjens J, Feakins R, Weeks ME, Lemoine SR, et al. Sperm-associated antigen 1 is expressed early in pancreatogenic tumorigenesis and promotes motility of cancer cells. Oncogene. 2007;26(11):1531-43. doi:10.1038/sjo.2006.348. [PubMed: 17098334].

45. Almanzar G, Olinkhan BD, Bodogai M, Dell’agnola C, Baatar D, Hewitt SM, et al. Sperm-derived SPANX-B is a clinically relevant tumor antigen that is expressed in human tumors and readily recognized by human CD4+ and CD8+ T cells. Clin Cancer Res. 2009;15(16):6395-40. doi:10.1158/1078-0432.CCR-08-2490. [PubMed: 20302618].

46. Klune K, Barnes RD, Girardin A, Mawer MA, Nesterling NJ, Ng A, et al. Tumor-infiltrating T cells correlate with NY-ESO-1-specific autoantibodies in ovarian cancer. PLoS One. 2008;3(10):e3409. doi:10.1371/journal.pone.0003409. [PubMed: 18923710].

47. Tammela J, Uenaka A, Ono T, Noguchi Y, Jungbluth AA, Mhawech-Fauceglia P, et al. OY-TES-1 expression and serum immunoreactivity in epithelial ovarian cancer. Int J Oncol. 2005;26(3):493-8. [PubMed: 16344486].

48. Fan R, Huang W, Luo B, Zhang GM, Xiao SW, Xie XX. Cancer testsis antigen OY-TES-1: analysis of protein expression in ovarian cancer with tissue microarrays. Eur J Gynaecol Oncol. 2015;36(1):298-305. [PubMed: 26819805].

49. Khan G, Brooks SE, Mills KI, Guinn BA. Infragent Expression of the Cancer-Testsis Antigen, PASHI, in Ovarian Cancer. Biomark Cancer. 2015;7(6):31–8. doi:10.4137/BIC.S28378. [PubMed: 26327782].

50. Chen C, Liu J, Xu G. Overexpression of PIWI proteins in human stage III epithelial ovarian cancer with lymph node metastasis. Cancer Biomark. 2013;13(5):315-21. doi:10.3231/CBM.130160. [PubMed: 24449970].

51. Tammela J, Jungbluth AA, Qian F, Santiago D, Scanlan MJ, Keitz B. SCP-1 cancer testsis antigen is a prognostic indicator and a candidate target for immunotherapy in epithelial ovarian cancer. Cancer Immunology. 2004;4(4):11.

52. Khosravi-Far S, Oehler MK, Tan IM, Russell D, Grutzner F. Overexpression of p1RNA pathway genes in epithelial ovarian cancer. PLoS One. 2014;9(6):e99687. doi:10.1371/journal.pone.0099687. [PubMed: 24932571].

53. Chen C, Liu J, Xu G. Overexpression of PIWI protein in human stage III epithelial ovarian cancer with lymph node metastasis. Cancer Biomark. 2013;13(5):315-21. doi:10.3231/CBM.130160. [PubMed: 24449970].

54. Taherian-Esfahani Z et al. Expression and serum immunoreactivity of develop-mental cancer/tessis targets for cancer immunotherapy in epithelial ovarian cancer. Cancer Immunology. 2004;4(4):11.

55. Gjerstorff MF, Johansen LE, Nielsen O, Kock H, Ditzy HF. Restriction enzyme digestion for DNA amplification in ovarian cancer. Int J Oncol. 2005;26(1):143-7. [PubMed: 15503546].

56. Tchabo NE, Mhawech-Fauceglia P, et al. OY-TES-1 expression and serum immunoreactivity of synovial sarcoma X (SSX) antigens in epithelial ovarian cancers. Int J Oncol. 2005;27(1):185-8. doi:10.3892/ijol.2005.56. [PubMed: 15606816].

57. Adair SJ, Carr TM, Fink MJ, Slengluff CJ, Hogan KT. The TAG family of cancer/t testsis antigens is widely expressed in a variety of malignancies and gives rise to HLA-A2-restricted epitopes. J Immunother. 2008;31(1):7-17. doi:10.1097/CJ.0b013e318159f797. [PubMed: 18175007].

58. Modarresi MH, Cameron J, Taylor KE, Wolfe J. Identification and characterisation of a novel gene, TSGA40, expressed in testsis. Gene. 2001;262(1-2):249-55. [PubMed: 11796900].

59. Modarresi MH, Jahanzad I, Mobaghehi MA, Arabai M, Farzan S, Modarresi MH. Expression of two testsis-specific genes, TSGA40 and SYCP3, in different cancers regarding to their pathological features. Cancer Detect Prev. 2007;31(4):296-302. doi:10.1016/j.cdpp.2007.05.002. [PubMed: 17920210].
64. Mobasher MB, Modarressi MH, Shabani M, Asgarian H, Sharifian FA, Vossough P. Expression of the testis-specific gene, TSGA10, in Iranian patients with acute lymphoblastic leukemia (ALL). Leukemia Res. 2006;30(7):883-9.

65. Tanaka R, Ono T, Sato S, Nakada T, Koizumi F, Hasegawa K, et al. Over-expression of the testis-specific gene TSGA10 in cancers and its immunogenicity. Microbiol Immunol. 2004;48(4):339-45. [PubMed: 1507545].

66. Hoei-Hansen CE, Kraggerud SM, Abeler VM, Kaern J, Raipert-De Meys E, Lothe RA. Ovarian dysgerminomas are characterised by frequent kIT mutations and abundant expression of pluriptomorphism markers. Mol Cancer. 2007;6:12. doi:10.1186/1476-4598-6-12. [PubMed: 17274819].

67. Mills GB, Schmandt R, McGill M, Amendola A, Hill M, Jacobs K, et al. Expression of TTK, a novel human protein kinase, is associated with cell proliferation. J Biol Chem. 1992;267(21):16000-6. [PubMed: 1639825].

68. Mizukami Y, Kono K, Daigo Y, Takano A, Kawaguchi T, et al. Detection of novel cancer-testis antigen-specific T-cell responses in TIL, regional lymph node, and PBL in patients with esophageal squamous cell carcinoma. Cancer Sci. 2008;99(7):1448-54. doi:10.1111/j.1349-7006.2008.00844.x. [PubMed: 18452554].

69. Egland KA, Kumar V, Duray P, Pastor I. Characterization of overlapping XAGE1 transcripts encoding a cancer testis antigen expressed in lung, breast, and other types of cancers. Mol Cancer Ther. 2002;1(7):1441-50. [PubMed: 12479262].

70. Sato S, Noguchi Y, Ohara N, Uenaka A, Shimono M, Nakagawa K, et al. Identification of XAGE-1 isoforms: predominant expression of XAGE-1b in testis and tumors. Cancer Immun. 2007;7;[PubMed: 17315148].

71. Philip R, Murthy S, Krakover J, Sinnamon G, Zerfas J, Keller L, et al. Shared immunoproteome for ovarian cancer diagnostics and immunotherapy: potential therapeutic approach to cancer. J Proteome Res. 2008;7(7):2509-17. doi:10.1021/pr7006877. [PubMed: 17547437].

72. Esfandiary A, Ghaffouri-Fard S. New York esophageal squamous cell carcinoma-1a and cancer immunotherapy. Immunotherapy. 2015;7(4):331-39. doi:10.2217/imt.15.3. [PubMed: 2597631].

73. Qian F, Gnajot S, Jager E, Santiago D, Jungbluth A, Grande C, et al. Th1/Th2 CD4+ T cell responses against NY-ESO-1 in HLA-DPB1*0401/0402 patients with epithelial ovarian cancer. Cancer Immun. 2004;4:12. [PubMed: 15527197].

74. Odunsi K, Matsuzaki J, James SR, Mhawech-Fauceglia P, Tsuji T, Miller A, et al. Epigenetic potentiation of NY-ESO-1 vaccine therapy in human ovarian cancer. Cancer Immunol Immunother. 2012;61(1):37-49. doi:10.1007/s00262-011-1026. [PubMed: 24535917].

75. Garg M, Chaurasia D, Rana R, Jagdish N, Kanojia D, Dudha N, et al. Sperm-associated antigen 9, a novel cancer testis antigen, is a potential target for immunotherapy in epithelial ovarian cancer. Clin Cancer Res. 2007;13(5):1541-8. doi:10.1158/1078-0432.CCR-06-2440. [PubMed: 17332284].

76. Odunsi K, Matsuzaki J, Karnbach J, Neumann A, Mhawech-Fauceglia P, Miller A, et al. Efficacy of vaccination with recombinant vaccinia and fowlpox vectors expressing NY-ESO-1 antigen in ovarian cancer and melanoma patients. Proc Natl Acad Sci U S A. 2012;109(5):25797-802. doi:10.1073/pnas.112081097. [PubMed: 22454499].

77. Batchu RB, Grudzyn OV, Moreno-Bost AM, Szmiania S, Jayaharan G, Srivistava A, et al. Efficient lysis of epithelial ovarian cancer cells by MAGE-A1-induced cytotoxic T lymphocytes using rAAV6 capsid mutant vector. Vaccine. 2014;32(8):338-43. doi:10.1016/j.vaccine.2013.02.049. [PubMed: 24406396].

78. Odunsi K, Qian F, Matsuzaki J, Mhawech-Fauceglia P, Andrews C, Hoffman EW, et al. Vaccination with an NY-ESO-1 peptide of HLA class II| specificities induces integrated humoral and T cell responses in ovarian cancer. Proc Natl Acad Sci U S A. 2007;104(3):12837-42. doi:10.1073/pnas.0703342104. [PubMed: 17652558].

79. Vaccine therapy in treating patients with metastatic cancer Available from: https://clinicaltrials.gov/ct2/show/NCT00202067?term=MAGE&rank=33.

80. Vaccine therapy in treating patients with ovarian epithelial, primary peritoneal, or fallopian tube cancer Available from: https://clinicaltrials.gov/ct2/show/NCT00667297?term=NY-ESO-1&rank=59.

81. Safety and immunogenicity of chp-her2 and chp-ny-eso-1 protein with ok-432 in antigen-expressing cancer Available from: https://clinicaltrials.gov/ct2/show/NCT02951473?term=NY-ESO-1&rank=26.

82. Nishikawa H, Qian F, Tsuji T, Ritter G, Old Lj, Gnajot S, et al. Influence of CD4+CD25+ regulatory T cells on high/low-avidity CD4+ T cells following peptide vaccination. J Immunol. 2006;176(10):6340-6. [PubMed: 16670346].

83. A phase i study of ny-eso-1 overlapping peptides (olp4) immunoadjuvants montanide and poly-iclc vaccination of epithelial ovarian cancer (esc), fallopian tube, or primary peritoneal cancer patients in second or third remission Available from: https://clinicaltrials.gov/ct2/show/NCT00616941?term=NY-ESO-1&rank=12.

84. Tsuji T, Sabbatini P, Jungbluth AA, Ritter E, Pan L, Ritter G, et al. Effect of Montanide and poly-ICLC adjuvant on human self/tumor antigen-specific CD4+ T cells in phase I overlapping long peptide vaccine trial. Cancer Immunol Res. 2013;1(3):340-50. doi:10.1158/2326-6066.CIR-12-0089. [PubMed: 24777970].

85. Leffers N, Daemen T, Helfrich W, Boozen HM, Cohen B, Meleef et al. Antigen-specific active immunotherapy for ovarian cancer. Cancer Database Syst Rev. 2014;4(9):CD007287. doi:10.1002/iarc.1207287.pub3. [PubMed: 25299900].

86. Chiavese-Bullock KA, Irwin W, Petroni GR, Murphy C, Smolkin M, Olson WC, et al. A multipepptide vaccine is safe and elicits T-cell responses in participants with advanced stage ovarian cancer. J Immunother. 2008;31(4):420-30. doi:10.1097/CJG.0b013e3181d4d10. [PubMed: 18390753].

87. Vaccine therapy in treating patients with stage ii, stage iii, or stage iv ovarian epithelial cancer, fallopian tube cancer, or primary peritoneal cancer cancer Available from: https://clinicaltrials.gov/ct2/show/NCT00803569?term=NY-ESO-1&rank=64.

88. Decitabine, vaccine therapy, and pegylated liposomal doxorubicin hydrochloride in treating patients with recurrent ovarian epithelial cancer, fallopian tube cancer, or peritoneal cancer Available from: https://clinicaltrials.gov/ct2/show/NCT01673217?term=NY-ESO-1&rank=42.

89. Vaccine therapy with or without sirolimus in treating patients with ny-eso-1 expressing solid tumors Available from: https://clinicaltrials.gov/ct2/show/NCT01522820?term=NY-ESO-1&rank=12.

90. Sirolimus and vaccine therapy in treating patients with stage ii-iv ovarian epithelial, fallopian tube, or primary peritoneal cancer cancer Available from: https://clinicaltrials.gov/ct2/show/NCT01536054?term=NY-ESO-1&rank=33.

91. Matsuzaki J, Tsuji T, Luescher I, Old LJ, Shrikant P, Gnjatic S, et al. Non-classical antigen-processing pathways are required for MHC class II-restricted direct tumor recognition by NY-ESO-1-expressing sarcomas receiving palliative radiation therapy Available from: https://clinicaltrials.gov/ct2/show/NCT01536054?term=NY-ESO-1&rank=33.

92. Investigators initiated phase 1 study of tbi-101 Available from: https://clinicaltrials.gov/ct2/show/NCT0231982?term=NY-ESO-1&conds%22Ovarian+Neoplasms%22&rank=5.

93. T cell receptor-transduced t cells targeting ny-eso-1 for treatment
of patients with ny-eso-1 expressing malignancies Available from: https://clinicaltrials.gov/ct2/show/NCT02457650?term=NY-ESO-1&rank=19.

96. Clinical trial of a therapeutic vaccine with ny-eso-1 in combination with the adjuvant monophosphoryl lipid a (mpla) Available from: https://clinicaltrials.gov/ct2/show/NCT01584115?term=NY-ESO-1&rank=3.

97. Ct antigen tcr-redirected t cells for ovarian cancer Available from: https://clinicaltrials.gov/ct2/show/NCT01567891?term=NY-ESO-1&rank=37.

98. Vaccine therapy and idot inhibitor incoh024360 in treating patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in remission Available from: https://clinicaltrials.gov/ct2/show/NCT01982487?term=NY-ESO-1&rank=48.

99. Dec-205/ny-eso-1 fusion protein cdx-1401, poly icalc, and idot inhibitor incoh024360 in treating patients with ovarian, fallopian tube, or primary peritoneal cancer in remission Available from: https://clinicaltrials.gov/ct2/show/NCT02166905?term=NY-ESO-1&rank=18.

100. Vaccine therapy in treating patients with stage ii, stage iii, or stage iv ovarian epithelial, fallopian tube, or peritoneal cancer Available from: https://clinicaltrials.gov/ct2/show/NCT00112957?term=NY-ESO-1&rank=43.

101. Vaccine therapy, paclitaxel, and carboplatin in treating patients who are undergoing surgery for stage iii or stage iv ovarian cancer, primary peritoneal cancer, or fallopian tube cancer Available from: https://clinicaltrials.gov/ct2/show/NCT00373217?term=MAGE&rank=63.

102. Hofmann M, Ruschenburg I. mRNA detection of tumor-rejection genes BAGE, GAGE, and MAGE in peritoneal fluid from patients with ovarian carcinoma as a potential diagnostic tool. Cancer. 2002;96(3):87-93. doi: 10.1002/cncr.10622. [PubMed: 12115308].

103. Chen YF, Scanlan MJ, Sahin U, Iureci O, Gure AO, Tsang S, et al. A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. Proc Natl Acad Sci U S A. 1997;94(5):2904-8. [PubMed: 9050879].

104. Jager E, Karbach J, Gnjatic S, Neumann A, Bender A, Valmori D, et al. Recombinant vaccinia/fowlpox NY-ESO-1 vaccines induce both humoral and cellular NY-ESO-1-specific immune responses in cancer patients. Proc Natl Acad Sci U S A. 2006;103(39):14453-8. doi: 10.1073/pnas.0606512103. [PubMed: 16994998].

105. Tchabo NE, Mhawech-Fauceglia P, Caballero OL, Villella J, Beck AF, Millotto AJ, et al. Expression and serum immunoreactivity of developmentally restricted differentiation antigens in epithelial ovarian cancer. Cancer Immun. 2009;9(6). [PubMed: 19705800].

106. Gillespie AM, Rodgers S, Wilson AP, Tidy J, Rees RC, Coleman RE, et al. MAGE, BAGE and GAGE: tumour antigen expression in benign and malignant ovarian tissue. Br J Cancer. 1998;78(6):816-21. [PubMed: 9743307].

107. Yamada A, Kataoka A, Shichijo S, Kamura T, Imai Y, Nishida T, et al. Expression of MAGE-1, MAGE-2, MAGE-3/-6 and MAGE-4a/-4b genes in ovarian tumors. Int J Cancer. 1995;64(6):388-93. [PubMed: 8550240].

108. Lee JH, Schutte D, Wulf G, Fuzesi L, Radzun HJ, Schweyer S, et al. Stem-cell protein Piwil2 is widely expressed in tumors and inhibits apoptosis through activation of Stat3/Bcl-XL pathway. Hum Mol Genet. 2006;15(2):201-11. doi: 10.1093/hmg/ddi430. [PubMed: 16377660].
| Reference | Expression Pattern Among Normal Tissues | Gene Locus | Function | Expression in Histologic Subtypes of Ovarian Cancer | Expression in Ovarian Tumor Cell Line | Expression in Other Cancers | ImmunoLogic Response | Cancer-Testis Antigen |
|-----------|----------------------------------------|------------|----------|--------------------------------------------------|----------------------------------|---------------------------|---------------------|---------------------|
| (45)      | Testis selective                       | 12p13.31   | Binds the acrosome protein proacrosin and is involved in packaging the acrosin zymogen into the acrosomal matrix | Papillary serous, clear cell, endometroid, mucinous, undifferentiated, transitional and mixed carcinosarcoma | SK-OV-3                         | Bladder, colon, prostate, liver | CD8+ T cell response | ACRBP (OV-TEG-1)   |
| (29)      | Testis selective                       | 12p13.3    | Participate in protein-protein interactions with the R-subunit of the protein kinase A as well as sperm-associated proteins | Serous, endometroid, clear cell, mixed | IOSE, HOSE, SVOV3, SKOV3, Ov412 | Breast, lung, cervical cancers | Unknown             | AKAP1               |
| (31)      | Testis selective                       | Xp11.2     | Signal transduction via targeting cyclic adenosine monophosphate-dependent protein kinase-A | Epithelial ovarian cancer, serous adenocarcinoma, serous papillary carcinoma | -                              | Non small lung cancer; breast | Humoral responses    | AKAP4               |
| (32)      | Testis restricted                      | 2p11.1     | Unknown  | Metastatic lesions of ovarian cancer, primary ovarian cancer tissues | Not expressed in SKOV3, COCG, A2780 | Expressed in a wide range of tumors | BAGE                |
| (34, 37, 101, 104) | Testis restricted                      | Xq28       | -        | Serous, clear cell, endometroid | -                              | Expressed in a wide range of tumors | Humoral responses    | CTAGIB (NY-ESO-1)  |
| (53)      | Testis restricted                      | 19q13.33   | Secreted antagonist of Wnt signal transduction, may be involved in acrosome assembly or function | Not mentioned | -                              | Breast, gynecological, lung-melanocyte | -                  | DKK1 (SGY)          |
| (105)     | Testis restricted                      | 3q13.33    | -        | Papillary serous, clear cell, mucinous, undifferentiated | -                              | Expressed in a wide range of tumors | Humoral responses    | GAGE3/6             |
| (34)      | Testis restricted                      | Xp11.23    | Chromatin regulation | Serous, clear cell, endometroid | -                              | Expressed in a wide range of tumors | Some GAGE epitopes are recognized by T cells. | GAGE                |
| (106)     | Testis restricted                      | Xp11.23    | Chromatin regulation | Serous, mucinous | A2780                           | Expressed in a wide range of tumors | GAGE 1/2            |
| (106)     | Testis restricted                      | Xp11.23    | Chromatin regulation | Mucinous | A2780                           | Expressed in a wide range of tumors | -                  | GAGE3/6             |
| (36)      | Testis selective                       | Xq28       | -        | Papillary serous, clear cell, mucinous, undifferentiated | -                              | Expressed in a wide range of tumors | Humoral responses | LAGE (CTAG-2)       |

Table 1. Expression of Cancer-Testis Antigens in Ovarian Cancer
| Reference | Chromosomal Localization | Gene | Tumor Type/Expression Pattern |
|-----------|--------------------------|------|------------------------------|
| (106)     | Testis restricted         | Xq28 | MAGE family proteins bind to and activate RING E3 ubiquitin ligases. MAGE-A proteins interact with p53 and may block the association of p53 with its cognate sites in chromatin. Serous cystadenocarcinomas, mucinous, granulosa cell tumors, of Krukenberg tumors, metastatic. Surface-epithelial-stromal tumors, serous, transitional-cell, yolk-sac tumors, fibrosarcoma. | Expressed in a wide range of tumors | MAGE-A1 |
| (107)     | Testis restricted         | Xq28 | Surface-epithelial-stromal tumors, serous, Yolk-sac tumors. | - | MAGE-A2 |
| (107)     | Testis restricted         | Xq28 | Surface-epithelial-stromal tumors, serous, mucinous, endometrioid. | - | MAGE-A3/A6 |
| (37)      | Testis restricted         | Xq28 | Serous, serous tumors of borderline malignancy. Surface-epithelial-stromal tumors, serous adenocarcinoma, endometrioid. | - | MAGE-A4 |
| (107)     | Testis restricted         | Xq28 | Benign ovarian tumor, borderline ovarian tumor. | - | MAGE-A9 |
| (40)      | Testis restricted         | Xq28 | Not mentioned. | - | MAGE-A10 |
| (34)      | Testis restricted         | Xq26 | Not mentioned. Primary and recurrent ovarian cancer. | - | MAGE-C1 |
| (53)      | Testis selective          | 6p21-qter | May regulate ion channel activity and is relevant for sperm-oocyte interaction. | - | TPX1 (CRISP2) |
| (108)     | Testis restricted         | 8p21.3 | Anti-apoptosis and promote proliferation in tumor cells. | - | PIWIL2 |
| (54)      | Testis restricted         | 8q22.2 | A signal transduction protein during fertilization. | - | SPAG1 |
| (56)      | Testis restricted         | Xq27.1 | Not mentioned. | - | SPANX-A1 |
| (55)      | Testis restricted         | Xq27.1 | Not mentioned. | - | SPANX-B1 |
| (58, 59) | Testis restricted | Xp11.23-p11.22 | Transcriptional regulator | Epithelial ovarian cancers | Various cell lines | Hematologic malignancies, brain, hepato-biliary cancer, lung cancer, melanocytic lesions | Cellular responses | SSX1 |
|----------|-------------------|----------------|---------------------------|--------------------------|------------------|-------------------------------------------------|------------------|-----|
| (58, 59) | Testis restricted | Xp11.23-p11.22 | Acts as a transcriptional regulator | Epithelial ovarian cancers | Various cell lines | Expressed in a wide range of tumors | Humoral and cellular responses | SSX2 |
| (57, 59) | Testis restricted | Xp11.23-p11.22 | Transcriptional regulator | Epithelial ovarian cancers | Various cell lines | Expressed in a wide range of tumors | Humoral immune responses | SSX4 |
| (57) | Unknown | Xp11.23-p11.22 | - | Not mentioned | - | - | unknown | SSX5 |
| (51) | Testis restricted | 3p12-p13 | Interacts with SYCE1 and CESC1 as part of the assembly of the synaptonemal complexes and with RAD51 | Papillary serous | Various cell lines | Expressed in a wide range of tumors | Humoral and cellular responses | SYCP1 (SCP1) |
| (61) | Testis restricted | 5p13 | - | Not mentioned | Various cell lines | Melanocytic cancers | Melanocytic cancers | TAG |
| (65) | Testis restricted | 2q11.2 | Involved in cell division, differentiation and migration. | Not mentioned | - | Expressed in a wide range of tumors | - | TSGA10 |
| (66) | Testis restricted | Yp11.2 | Participates in the control of cell cycle progression, cell proliferation and tumorigenesis | Dygerminoma, dygerminomas with gonadoblastoma, gonadoblastoma | - | Hepatobiliary and testicular cancers | - | TSP11 |
| (67) | Testis restricted | 6q13-q21 | Regulator of the mitotic spindle-assembly checkpoint | Not mentioned | HEY, OCCi, OCC5, ARO, SW5716, NPA | Myeloma, gastric, lung, esophageal | Cellular immune response | TTK |