Review Article

NY-ESO-1: a promising cancer testis antigen for sarcoma immunotherapy and diagnosis

Stephen M. Smith, O. Hans Iwenofu

Department of Pathology & Laboratory Medicine, The Ohio State University Wexner Medical Center, Columbus, OH, USA

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Correspondence to: O. Hans Iwenofu, MD. Department of Pathology & Laboratory Medicine, Wexner Medical Center at The Ohio State University, 410 West 10th Avenue, Columbus, OH 43210, USA. Email: Hans.Iwenofu@osumc.edu.

Abstract: Sarcomas are heterogenous malignant mesenchymal neoplasms. These are often notoriously difficult to treat particularly in the metastatic setting. There is therefore an urgent need for development of better and more efficacious targeted therapies. Cancer testis antigens (CTAs) are a family of proteins in which aberrant gene-activation and subsequent high level mRNA expression, are restricted to testicular germ cells and are seen in certain malignancies. Importantly, the restriction of this class of antigens to testicular germ cells and malignancies and not somatic tissue, makes them an excellent choice for targeted immunotherapy. The NY-ESO-1is the most immunogenic of CTA and has, of late, become well-studied for its diagnosis and potential treatment implications in sarcomas. This paper reviews both the role of NY-ESO-1 in the diagnosis of sarcomas, as well as the implications of this CTA in vaccine development and treatment of sarcomas.

Keywords: NY-ESO-1; sarcoma

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Introduction

The 1908 Nobel Prize in Medicine and Physiology was, in part, awarded to a German immunologist names Paul Ehrlich for his "work on immunity". Within the next year, he would develop an idea: could carcinogenesis be specifically targeted utilizing an immunologic approach (1). The idea drifted in and out of vogue until the 1950s when tumor-specific immunity peaked interest again (2). From then, vast knowledge has been gained in the immunologic basis of neoplasia, including not only mechanisms by which the immune system combats cancer cells, but also how those same cancer cells may morph to evade the same system. Recent advances in the past several decades have led to immunologic targeting of cancer, the basis of this discussion.

Although external antigens could be readily identified by autologous and allogeneic serologic methods, until the late 1990's, the serum titers were generally too low to permit the molecular identification of the detected antigens. The use of serological identification of antigens by recombinant expression cloning (SEREX) by Chen *et al.* in 1997 lead to the discovery of intracellular antigens in a set of esophageal tumors (3). Among these were primitive antigens aberrantly expressed after the cell's return to a primordial state, including the NY-ESO-1 protein.

The role of NY-ESO-1 cancer testis antigen (CTA) in development

CTAs are a family of proteins which share three common characteristics: (I) predominant normal expression of the pre-cursor mRNA is found in testicular tissue and typically not in other normal tissues; (II) aberrant gene-activation

and subsequent high level mRNA expression in certain malignancies; and (III) lineage-nonspecific expression when arising in a malignant setting (4).

Given the innate immunologic barriers within the testis which prevent immune response to genetically "foreign" material, re-expression of a primitive embryologic protein by tumor cells generates the potential for T-cell recognition of these antigens. Early genes identified included the *MAGE* and *GAGE* families of proteins, first found due to their expression within tumoral cells which were recognized by cytotoxic T-cells (5-7).

The implication of NY-ESO-1 as a tumor antigen was first described by Chen *et al.* in 1997, using prokaryotic-transfected cDNA from an esophageal squamous cell carcinoma patient as an antigenic target within that patient's serum. The humoral response was measured and the corresponding antibodies identified, identifying tumoral targets which generated a clear cell-mediated response. After identifying NY-ESO-1, humoral response to this antigen within various tumors was sought; many melanomas, breast carcinomas and bladder carcinomas (among others) showed a positive response. Of note, two leiomyosarcomas and two other sarcomas were negative for NY-ESO-1-induced humoral response in that study (4).

Jungbluth *et al.* first documented normal expression of the NY-ESO-1 antigen in normal human testis (8). NY-ESO-1 can be identified at 18 weeks gestation in testicular gonocytes, similar to MAGE-A4 CTA (9). Within developing spermatogonia, *NY-ESO-1* was identified as one of nine genes upregulated during differentiation, suggesting a role in spermatogonial clonal expansion (10). Little is known, however, about the physiology of NY-ESO-1 within spermatogonia. Expression beyond meiosis I of spermatogenesis has not been shown; this CTA is also not expressed in Sertoli cells (9). Chen *et al.* have shown the NY-ESO-1 protein to arise from a gene region on chromosome Xq28, within the region where other CTA (*MAGE* family members) are encoded (3).

CTA, NY-ESO-1 and cancer pathobiology

The *NY-ESO-1* gene on chromosome Xp28 has approximately 679 bp (3) and encodes a 22 kDa protein derived from three exons within the gene. Of the protein domains studied, perhaps the most intriguing was derived from the *S. cerevisiae* homologue, Pcc1p (11). Alpen *et al.* provided data supporting the evolutionary conservation of the *NY-ESO-1* gene family [though later work by Dobrynin *et al.* found that most CTA are novel or primitive (12)] suggesting significance in cell survival and/or replication (13). Working from that data, Kisseleva-Romanova *et al.* sought to identify the necessity of the Pcc1p protein, showing that this NY-ESO-1 homologue functions as a transcription factor for several major proteins needed during cell cycle regulation and produces cell death when absent (11). Within mammalian cells, other avenues have been pursued to identify the pathobiology of NY-ESO-1. In melanoma cell lines, Cho *et al.* demonstrated that the interactions of NY-ESO-1 with a members of the melanoma antigen family (MAGE family), MAGE-C1, which is another protein family expressed during spermatogenesis (14-16). Co-localization of both proteins was observed via indirect immunofluorescence studies in the same cell population. However, while melanoma cells appear to express NY-ESO-1 in both the nucleus and cytoplasm of the cell; normal mesenchymal stem cells (MSCs) appear to show exclusive nuclear NY-ESO-1 immunoreactivity (17). Although the direct physiologic functions of MAGE are equally as poorly-understood as those of NY-ESO-1, this association is significant as MAGE proteins have documented cell division activity with therapeutically targetable stages. In non-small cell lung carcinoma, breast carcinoma and hepatocellular carcinoma cell lines, Cappell *et al.* showed that the MAGE family was among a cohort of gametogenic proteins required for chromosome segregation and microtubule formation during tumor formation and development (18). Other CTA have been implicated in microtubule formation and development, with increased expression being associated with microtubule-inhibitor anti-neoplastic therapy resistance (e.g., paclitaxel) (19).

Cellular and humoral T-cell responses to NY-ESO-1

NY-ESO-1 became of prime interest after it was determined that this protein represented a prime epitope and, therein, a target for vaccine development. As noted previously, the immunogenic barrier of the testis should, theoretically prevent the presence of anti-NY-ESO-1 (a-NE1) antibody development in a normal human individual. Studies in the general population identified a frequency of anti-NY-ESO-1 T-cells as having a frequency between 0.5 and 5 precursors per one million CD4+ T-cells, with the vast majority of these T-cells exhibiting reactivity to the previously described "hotspots" of overlapping sequences exhibiting higher binding capacity for multiple frequently expressed MHC class II alleles (20,21). Liu *et al.* demonstrated in mice that NY-

ESO-1 binding to immature dendritic cells was dependent on its polymeric structure, requiring Toll-like receptor-4 (TLR4) activation (22). Analysis of a melanoma patient exhibiting high titers of a-NE1 revealed that simultaneous cellular and humoral responses were occurring within the same patient (23). The strong binding interaction of the polymeric structure with TLR4 promotes T_H-cell interactions with B-cells promote a-NE1 production (22). And, as expected, a strong cytotoxic T-cell response is elicited from the activated humoral immunity system—so much so that enzyme-linked immunospot (ELISPOT) assays show strong concordance and are useful in monitoring NY-ESO-1 vaccine efficacy (24).

Analysis of amino acid sequences within NY-ESO-1 has further characterized these highly antigenic regions. Neumann *et al.* identified a pentadecameric region (p134–148) which stimulated T-cell responses restricted to the HLA-DRB1 subtypes *0101, *0301, *0401, and *0701 (25). This sequence induced responses in four of 38 cancer patients tested, apparently independent of serum a-NE1 titers. The p157–165 peptide sequence was found to be efficaciously recognized by cytotoxic T-cells in melanoma patients (26). The same study also showed that p157–167 and p155–163 peptides were less efficient, despite increased binding affinity to HLA-A*201. Other studies have shown that the p157–167 is likely the dominant peptide recognized by T-cells, targeting HLA-A2 T-cells specifically (23). Fonteneau and colleagues sought to determine the method by which the NE1 p157–167 highly antigenic sequence was processed by antigen-presenting cells for interactions with T-cells (27). Interestingly, in lieu of more common proteosome or autophagy-dependent endogenous processing pathways, a combination of intercellular antigen transfer amongst tumor cells and macroautophagy was found to be utilized in this interaction.

Sommermeyer *et al.* identified three types of T-cells with *in vitro*-designed T-cell receptors exhibiting a-NE1 potential; the most promising of which displayed moderate efficiency in antigen binding but a precise peptide-specific performance in the functional assays assessed (28). Capitalizing on these studies, Rosati *et al.* recently developed a novel murine T-cell receptor which recognized human NY-ESO-1 (29). This receptor was created in part from HLA-A*201 transgenic mice harboring a human a-NE1 sequence which was then injected into a viral vector and transduced to a patient's peripheral blood lymphocytes. These "educated" lymphocytes exhibited a marked (90%) efficiency *in vitro*. At present, this treatment strategy is being tested in advanced-stage melanoma patients (NCT01350401), advanced-stage NY-ESO-1+ solid tumors (NCT01967823, NCT01697527), and in combination with other targeted therapies (NCT02070406).

NY-ESO-1 expression in sarcomas

Cronwright *et al.* documented normal expression of the NY-ESO-1 CTA in *ex vivo* cultured postnatal bone marrow and fetal liver MSCs of first-trimester fetuses (17). NY-ESO-1 expression is down-regulated as MSC differentiate, eventually to undetectable levels in mature mesenchymal tissues.

In their examination of tissues from 36 patients, Ayyoub *et al.* demonstrated NY-ESO-1 expression in gastrointestinal stromal tumor (GIST), synovial sarcoma (SS), angiosarcoma, malignant fibrous histiosarcoma, liposarcoma and chondrosarcoma; with no activity in leiomyosarcoma or osteosarcoma (30). Testing cell lines in the same study, *in vitro* expression of NY-ESO-1 was found in osteosarcoma and fibrosarcoma. Endo *et al.*'s survey of CTA expression in various sarcomas identified high levels of NY-ESO-1 [by immunohistochemistry (IHC)] in myxoid liposarcoma (85%), SS (47%), myxofibrosarcoma (35%), and conventional chondrosarcoma (6–33%) (31).

Methods of detection

Ayyoub *et al.* compared NY-ESO-1 monoclonal antibody (ES121) IHC to polymerase chain reaction (PCR) in their study of 36 sarcoma patients, finding excellent correlation between those these two tests amongst tumors with strong expression of the CTA, with only a few weakly positive PCR samples showing rare positivity or negative IHC results (30).

NY-ESO-1 and SS

Given the fact that the tumor-defining *SSX* gene—also considered a CTA by definition—is found in SS, it is unsurprising that other CTA are involved in this tumor's pathogenesis. Yet the reason for the increased frequency of expression remains unknown. Immunohistochemical detection of NY-ESO-1 in SS has ranged from 47–80% in the literature (31,32). It appears that there is no predilection for CTA expression between monophasic or biphasic histology (32).

Importantly, Robbins *et al.* have provided compelling evidence of tumor regression in metastatic melanomas and SS, using anti-NY-ESO-1 therapy (33). After transducing

patient T-cells with a modified T-cell receptor against NY-ESO-1, patients harboring NY-ESO-1-positive metastatic tumors were given these trained T-lymphocytes and the tumoral responses recorded. Four of the six patients with SS exhibited an objective tumor response with partial tumor regression—the longest documented at 18 months. More recently, D'Angelo *et al.* have functionally shown that circulating CD8+ T-cells developed against NY-ESO-1 are continuously maintained for months post-infusion and promote anti-tumor activity in metastatic SS (34).

NY-ESO-1 and adipocytic tumors

After gene profiling identified NY-ESO-1 as a potential analytical target in liposarcomas (35), analysis of NY-ESO-1 expression amongst liposarcomas was undertaken. The utility of NY-ESO-1 as a diagnostic marker for identification of myxoid liposarcomas was established by Hemminger *et al.* (36). Eighty-nine percent (89%) of myxoid/round cell liposarcomas exhibited immunohistochemical expression of NY-ESO-1, with the majority of cases showing strong, diffuse staining (36). In a follow-up study, Hemminger and Iwenofu showed that not only was this CTA frequently expressed in myxoid/round cell liposarcomas, but indeed it was rarely expressed in other forms of liposarcoma, leading to the conclusion that NY-ESO-1 IHC is a highly sensitive and specific marker of myxoid/round cell liposarcomas (37). Endo *et al.* showed similar results in pre-treatment cases, but showed markedly decreased immunohistochemical expression of NY-ESO-1 in post-treatment myxoid/round cell liposarcomas—supporting the argument that as tumor cells are forced to mature through radiation or chemotherapy, the expression of this CTA decreases (31).

From a prognostic point-of-view, univariate analysis has shown that high-level expression of NY-ESO-1 correlates with poorer prognosis. Increased immunohistochemical expression of NY-ESO-1 was significantly correlated with tumor size, the presence of tumoral necrosis, pleomorphism and an increased round-cell component, as well advanced stage at diagnosis and poor overall prognosis (38).

Finally, from a therapeutic perspective, NY-ESO-1 appears to be a strong candidate for treatment in sarcomas, in view of the strong and homogenous nature of expression. After finding expression in 100% of 25 tumors examined, researchers at the University of Washington demonstrated *in vitro* destruction of myxoid liposarcoma cell lines using stimulated antigen-specific CD8+ T-cells (39). Multiple studies using NY-ESO-1-specific T cells are pending for patients with sarcoma (NCT03462316, NCT01343043, NCT03250325, NCT03159585) or mixed population of sarcomas concurrently with LV305 or CMB305 (NCT03450122).

NY-ESO-1 and other sarcomas

NY-ESO-1 has been shown to be at least focally expressed in malignant peripheral nerve sheath tumors, uterine (40,41). Expression has not been seen in non-uterine leiomyosarcomas (41). Intriguingly, though the molecular underpinnings of GISTs have recently expanded to include novel subgrouping based on cKIT, SDH and PDGFRA/B mutations (42), it appears that there is some involvement with CTA expression as well. At least 40% of GIST were positive for at least one CTA in a study by Perez *et al.*, with NY-ESO-1 (E978 clone) reacting in 20% of tumors tested (43). Patients expressing at least one CTA showed poorer prognosis than those which were CTA-pan-negative. Moreover, follow-up studies showed that CTA-positive tumors demonstrated a worse response to conventional tyrosine kinase inhibitors in these tumors, with a shorter recurrence-free period for the same subset (44).

NY-ESO-1 expression in non-sarcomatous tumors

The expression of NY-ESO-1 in primitive tumor cells has led to investigations in multiple tumor subtypes over the past decade, considering the immunogenic nature of this antigen. To date, NY-ESO-1 has been implicated in breast (45-47), lung (48), thyroid (49), colorectal (46), ovarian (50) and genitourinary (51) adenocarcinomas; squamous cell carcinomas of various origins (3,48,52); and unusual tumoral types including hepatic carcinomas (53), ovarian and testicular primitive tumors (9,54) and melanomas (55). These studies have improved the overall understanding of NY-ESO-1 pathobiology.

In melanomas, NY-ESO-1 was associated with tumor progression and with reduced tumor infiltrating lymphocytes (56). Moreover, treatment of melanomas with engineered T-cells against the NY-ESO-1 antigen showed marked reduction in tumor burden in advanced stage patients, with two of eighteen patients showing complete responses at nearly 24 months post-treatment (33). The driving force behind these reductions is the antitumoral activity brought on by both proteasome-dependent and –independent mechanisms, dependent on HLA haplotype (57).

Similar results were seen in both *in vitro* and *in vivo* models of multiple myeloma (58).

NY-ESO-1 immunotherapeutic (vaccine) strategies

Simple peptide-vaccine strategies

Both bacterial-derived peptides (from *E. coli*) and yeast-derived peptides (from *S. cerevisiae*) are presently available. Interestingly, when using these proteins as adjuvants, yeast-derived proteins seem to induce NY-ESO-1 immunoreactivity superior to bacteria (59). In 2000, Jäger *et al.* tested the efficacy of several NY-ESO-1 peptide sequences—against known hotspots, including p157–167, p157–165 and p155–163—in eliciting CD8+ T-cell responses in both a-NE1 seropositive and seronegative patients diagnosed with varied metastatic cancers (60). The 11-mer p157–167 peptide sequence showed quicker immunogenic responses in seronegative patients, with four of seven patients exhibiting strong immunoreactivity. Repeated p157–165 9-mer peptide injections showed a similar response but over a longer period of time. Among the five seropositive patients, both the 11-mer and 9-mer peptides showed strong and quick immunoreactivity. Most interesting in this study was that five of seven vaccinated previously-seronegative patients demonstrated developed stabilization or regression of individual metastases. Three of the vaccinated previously-seropositive patients showed disease stabilization. Notably, several patients who achieved disease stabilization or regression eventually manifested disease progression. The limitations of this study protocol prevented further vaccination of the subjects, leaving the question: would these patients could have benefited from additional supplementation to booster a-NE1 activity. Miyai *et al.* showed a similar robust CD8+ response via T-cell receptor β (TCRβ) rearrangements in a patient treated with the p91–110 fragment (61).

In general, however, vaccination with synthetic peptides has been lackluster in patients, secondary to tolerance or deactivation of T-cells (24). Elevated Fas and programmed death-1 expression was elucidated on CD8+ T-cells when stimulated with NY-ESO-1 p81–88 peptide, in one study (62). Most interesting in this study was finding that combining the peptides with adjuvants—CpG in the referenced study—resulted in a marked decrease of T-cell apoptosis. Thus, it seems that combining the stimulating peptides with an alternative delivery mechanism might prove fruitful in eliciting the optimal anti-tumoral response. Similar results have been seen in seropositive patients with coadministration of adjuvants, including picibanil (OK-432, a TLR4 stimulant) and montanide (ISA-51) (63-67), resiquimod (68), and CpG 7909 (65).

Targeting antigen—presenting cells

Targeting dendritic cells to increase a-NE1 response has been proposed. Tsuji *et al.* demonstrated that creating monoclonal antibodies harboring NY-ESO-1 antigens to target specific receptors on dendritic cells was an efficacious delivery system to increase a-NE1 CD4+ and CD8+ T-cells (69). A phase I study for CDX-1401, a modified human antibody targeting dendritic cells with adherent full-length NY-ESO-1, demonstrated tumor regression in two patients and stabilization of disease in 13 patients for a median of 6.7 months (70). At present, there is a study investigating the use of CDX-1401 in combination therapy for prevention of recurrence in select primary gynecologic tumors in remission (NCT02166905). With respect to treatment, a Phase 1b study in patients with advanced NY-ESO-1+ cancers is investigating the usage of LV305, a dendritic cell-targeting viral vector which expresses the NY-ESO-1 gene, and G305, a recombinant NY-ESO-1 protein with adjuvant (NCT02387125). LV305 was initially developed in mice showing a marked anti-tumoral response against an induced CIN.23 NY-ESO-1 antigen-expressing cell line which had been injected in these mice (71). Safety in humans has since been assessed and remains a potential viable candidate for patients with refractory disease (72,73).

Microbe-derived recombinant vaccines

Utilizing microorganisms to stimulate immune response has been a strategy utilized by vaccine developers for many years. One study described the use of modified *Lactobacillus plantarum* expressing the cell-wall tumor antigen NY-ESO-1 as an advantageous immunity-inducing agent, showing a marked increase in murine CD8+ T-cells after oral administration (74). Another study involved replacing genes in *Salmonella enterica* with the p155–165 or p157–167 fragments, generating a robust a-NE1 response *in vivo* (75). The generation of novel bacteria-derived adjuvants has also peaked interest recently, including the alum-polysaccharide-HH2 (APH) combination derived from *Escherchia coli*; this vaccine strategy was shown in a mouse model of melanoma to inhibit tumor growth (76). Recombinant vaccines with

fowlpox have also shown promise (77,78).

Whole-cell vaccine strategies

In mice, Xu *et al.* induced renal cancer cells to express NY-ESO-1 (79). When these cells were injected into mice bearing renal cancer cell tumors without NY-ESO-1, a significant reduction in tumor size was noted, compared to controls. The interaction of dendritic cells and T-cells with the whole renal cells bearing NY-ESO-1 was noted to be markedly increased and is thought to be the driving force behind the reduction of these cells. This study strongly suggests that even in NY-ESO-1-deficient tumors, a-NE1 could be used if, if coupled to the proper antigens, to train T-cells to target tumoral epitopes with great immunogenicity.

Modified vaccine strategies

Perhaps the most interesting part of the NY-ESO-1 vaccine story has been the creative—and remarkably effective—way in which immunogenicity has been augmented. Nanoliposomes containing the p87–111 fragment of NY-ESO-1 protein combined with tetanus toxoid were injected into human dendritic cells in one experiment (80). These liposomes were targeted to human dendritic cells which showed a marked immunologic response, representing the early evidence that antigens could be precisely targeted at the molecular level in these constructs. Coupling the peptides to known vaccine-derivatives has proved useful: in another study, binding of the p157–165 domain to tetanus toxin killed tumor cells which endogenously expressed NY-ESO-1 (81).

Other forms of nano-delivery have been attempted. Vaccination with cholesteryl pullulan complexes (CHP) containing NY-ESO-1 protein (CHP-NY-ESO-1) demonstrated no significant response compared to controls in a small sample of NY-ESO-1+ esophageal cancer patients (82). Interestingly, patients receiving higher doses of CHP-NY-ESO-1 survived longer than those receiving lower doses in a trial by Kageyama *et al.*, despite no evidence of tumor shrinkage in these patients (83). These results suggest that CHP-NY-ESO-1 might be useful in arresting tumor growth or spread, explaining the successfulness of coadministration with other therapies (see below).

Administration of CHP-NY-ESO-1 in eight of nine patients demonstrated a heteroclitic response to NY-ESO-1 and at least one other tumor antigen, without response to the CHP/bacterial products used, suggesting that perhaps some degree of homology is shared between known cancer antigens in this interaction (84).

Carbon nanotubes containing NY-ESO-1 peptides utilized in mice were effective delivery systems, showing rapid internalization of the nanotube complex by dendritic cells and a resulting increase in CD8+ T-cells. Mouse survival was accordingly increased and the tumor sizes were decreased (85).

ISCOMATRIX is an immune-stimulating complex comprised of cholesterol, phospholipid and saponin (similar to chylomicrons) utilized to deliver proteins to stimulate immunogenicity (86). Priming the immune system with ISCOMATRIX-containing compounds has shown mixed reviews: one study demonstrated no significant increase in CD8+ T-cells in patients with NY-ESO-1+ tumors (87); others have shown a robust immune response (88,89). The latter studies, however, did not analyze CD8+ T-cells, but rather CD4+ T_{reg}-cells and—importantly—utilized fragments of immunogenic peptides in lieu of the total NY-ESO-1 protein. Coadministration of this vaccine with cyclophosphamide shows a more robust immunologic response in advanced stage melanoma patients, likely via increased NY-ESO-1-specific CD4+ T_{reg}-cells (90).

Data from the ISCOMATRIX trials have been followed long-term, showing that the adjuvant/delivery mechanism not only dictates the degree of immunogenic response, but also the degree of immunologic memory. Nicholaou *et al.* showed persistent immunity in 10 of 14 vaccine recipients after a median of two years of follow-up (91). Importantly, the degree of relapse of tumor (melanoma) in this study was notably different between those receiving NY-ESO-1 peptide and those receiving ISCOMATRIX complexed NY-ESO-1: 5/19 vaccinated patients relapsed compared to NY-ESO-1 alone or placebo.

Modified human antibody strategies

A fascinating strategy has been to modify existing human IgG DNA to tailor a "ready-made" antibody without requiring an antigen interaction (92). After inserting 16 NY-ESO-1 epitopes (representing over 80% of known HLA phenotypes) into the complementary determining regions (CDR) of human IgG1, authors identified a marked increase in NY-ESO-1 T-cell responses (93). Consistent with *in vitro* results, the p157-165 11-mer peptide encoded in this scheme was the most antigenic. In mice, NY-ESO-1 cells treated with this modified human IgG antibody were controlled and showed increased long-term survival of the hosts.

Use of a-NE1 vaccines as adjuvant to chemotherapeutic intervention

Co-administration of a-NE1 has shown promise. Mice treated with either anti-CD25, anti-CTLA4 (ipilimumab) and anti-PD-1, each co-treated with a-NE1, showed a marked increase in tumor cytotoxicity compared to respective monotherapy (93). Blockade of the CTLA-4 pathway was shown to significantly increase the CD8+ T-cell response in mice receiving *T. cruzi*—expressing NY-ESO-1, indicating that this cell-cycle regulator likely plays a significant role in a-NE1 efficacy (94) (although it has been described that *T. cruzi* specifically stimulated T-cell activity via CpG motifs in TLR4) (95).

In advanced stage melanoma patients, Yuan *et al.* showed that compared to their seronegative counterparts, patients expressing a-NE1 antibody demonstrated a greater likelihood of benefiting from anti-CTLA4 (ipilimumab) treatment (96). Post-vaccine treatment (with subsequent a-NE1 induction) with ipilimumab showed at least partial regression of tumors in four of six (66.7%) advanced-stage melanoma patients (70).

It is known that NY-ESO-1 expression is regulated by DNA methylation, with this process silencing CTA expression in normal cells (97). The hypothesis that augmenting the methylation of DNA to increase NY-ESO-1 expression in tumor cells as a treatment strategy was tested in epithelial ovarian carcinomas by Odunsi *et al.* (98). Co-administering NY-ESO-1 peptide/montanide with decitabine (a hypomethylating agent) resulted in a spontaneous increase in NY-ESO-1 expression and a-NE1 immune recognition. Disease stabilization was seen in a majority of patients tested in the phase I trial, with partial regression identified in one patient.

In summary, we have discussed the current understanding and potential of utilizing the CTA, NY-ESO-1, as a therapeutic target and in some cases can serve as a diagnostic marker. As this molecule represents a super-antigen, with marked potency, and given the unique expression profile on tumors, NY-ESO-1 represents an opportunity for both cancer prevention and cancer treatment. As the results of current immunotherapeutic trials using various forms of NY-ESO-1 unravel, better understanding of the epigenetic control of this highly immunogenic CTA will continue to evolve. This will refine better combinatorial strategies going forward in the treatment of sarcomas.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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