NY-ESO-1 is a cancer-testis antigen that is (physiologically) expressed in the testis as well as (aberrantly) in a growing yet limited subset of malignancies including esophageal squamous cell carcinomas.1–3 Immunotherapeutic strategies to target NY-ESO-1-expressing lesions have been suggested since the early discovery of the outstanding immunogenicity of NY-ESO-1, demonstrated by the presence of autologous antibodies as well as T-cell receptors (TCRs) directed against NY-ESO-1 in patients.5–7 Indeed, a recent clinical trial at the National Cancer Institute has demonstrated that NY-ESO-1-targeted immunotherapy with genetically modified T cells exerts promising anticancer effect in malignant melanoma and synovial sarcoma patients.2 Using T cells engineered to express a recombinant TCR that specifically targets NY-ESO-1 in 17 patients with stage 4 synovial sarcoma or malignant melanoma, objective clinical responses were observed in four out of six (4/6) synovial sarcoma and five out of 11 (5/11) melanoma patients. In two of the four melanoma responders, complete regressions persisted for as long as 1 year after therapy and a partial response lasting 18 months was observed in one patient with synovial sarcoma.2

We and others have reported that NY-ESO-1 is expressed in approximately 80% of patients with synovial sarcoma (Fig. 1A), and approximately 25% of patients with malignant melanoma (Fig. 1B). Hence, NY-ESO-1 may be useful both for distinguishing synovial sarcoma from other mesenchymal tumors and as a target for immune-based therapies.2–4 To address the diagnostic utility of NY-ESO-1, we examined NY-ESO-1 expression by immunohistochemistry in cohorts of mesenchymal neoplasms including 50 SS18/SSX1/2 fusion positive synovial sarcomas, 155 gastrointestinal stromal tumors (GISTs), 135 spindle cell sarcomas as well as 77 diverse sarcomas (chondrosarcoma, osteosarcoma, dedifferentiated liposarcoma, alveolar soft part sarcoma, rhabdomyosarcoma, angiosarcoma, malignant mesothelioma, and Ewing’s sarcoma). We found that 76% of synovial sarcomas expressed NY-ESO-1 in a strong and diffuse pattern (2–3+, > 50–70% of tumor cells). In contrast, only rare cases of other spindle cell mesenchymal tumor expressed NY-ESO-1: GIST (2/155), malignant peripheral nerve sheath tumors (1/34) and dermatofibrosarcoma protuberans (2/20). Individual cases of other sarcomas (angiosarcoma, malignant mesothelioma, chondrosarcoma, osteosarcoma, dedifferentiated liposarcoma, alveolar soft part sarcoma, and Ewing’s sarcoma) were positive for NY-ESO-1. However, no positive cases were identified among our cohort of leiomyosarcomas (0/24), hemangiopericytoma/solitary fibrous tumors (0/40) and cellular schwannomas (0/17). Thus, NY-ESO-1 is most consistently expressed in synovial sarcomas with rare exceptions in other sarcomas.4 As it can be difficult to distinguish the monophasic subtype of synovial sarcomas from other spindle cell tumors on histological grounds alone (particularly in small biopsy specimens), and since to date there is a limited number of distinctive markers that help the differential diagnosis of these tumors, the emergence of NY-ESO may be useful.

Recently, an additional lesion in which NY-ESO-1 is robustly differentially expressed has been reported. Pollack et al. reported NY-ESO-1 expression in 25 out of 25 cases of myxoid/round cell liposarcomas. They also demonstrated the in vitro sensitivity of myxoid/round liposarcoma cell lines to antigen-specific lysis by using NY-ESO-1 specific, CD8+ T cells.8 In a cohort of myxoid/round cell liposarcomas, we have also found strong and diffuse NY-ESO-1 staining (Fig. 1C). Though generally with good long-term outcomes, recurrent/metastatic (particularly with extrapulmonary metastases) myxoid/round cell liposarcoma is associated with a high mortality, especially in patients who have been previously treated with conventional therapy.9 Thus, myxoid/round cell liposarcoma constitutes another tumor type that may benefit from NY-ESO-1-targeted therapies.
In conclusion, immunohistochemistry for the detection of NY-ESO-1 (based on a readily available commercial antibody) may have an important role in the selection of patients that would benefit from NY-ESO-1-targeted therapies, but also may be useful in distinguishing synovial sarcomas from other spindle cell neoplasms, such as leiomyosarcoma, cellular schwannoma, metastatic GISTs (Fig. 1).

**Figure 1.** Immunohistochemical detection of NY-ESO-1 in human sarcomas and in metastatic malignant melanoma. (A) Synovial sarcoma (400×). (B) Metastatic malignant melanoma (400×). (C) Myxoid/round cell liposarcoma (400×). (D) Metastatic gastrointestinal stromal tumor with epithelial and spindle cell features (400×).

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