University of Colorado
TECHNOLOGY TRANSFER OFFICE

# Biomarker for Selection/Modulation of TRAIL and other Cancer Therapies


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**IP Status:**

Patents pending; available for exclusive or non-exclusive licensing.

**Case Manager:**


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Ref # CU1674H

**Background**

Through recent discoveries in cancer biology, it has become increasingly evident that tumor growth and normal development share many properties. Both processes involve alterations in cell proliferation and differentiation, alterations in cell death, neovascularization, cell motility, and invasion of surrounding tissue. Genes involved in normal developmental processes may therefore contribute to tumorigenesis if mis-expressed. Dr. Heide Ford of the University of Colorado Cancer Center has done intensive research on the homeobox superfamily of genes, which encode transcription factors that are essential during normal development and are often dysregulated in cancer. In elucidating the molecular mechanisms by which homeobox genes influence cancer, Dr. Ford has developed methods to treat carcinomas, detect carcinomas and screen for compounds effective against carcinomas.

**Technology**

Dr. Ford has demonstrated that the developmental regulator Six1 is overexpressed in a variety of carcinoma cell lines as compared to normal cell surface epithelium. Six1 overexpression leads to increased A-type cyclin expression and increased proliferation. In addition, Six1 overexpression renders tumors resistant to TNF-related apoptosis inducing ligand (TRAIL)-mediated apoptosis, and Six1 knockdown in the TRAIL-resistant SKOV3 ovarian carcinoma line dramatically sensitizes the cells to TRAIL. Because inactivation of the TRAIL response has been linked to metastasis, and antibodies and recombinant ligands that activate the TRAIL pathway are currently in clinical trials against solid malignancies, Dr. Ford's team screened normal a variety of tumor specimens for Six1 mRNA. Six1 was overexpressed in 50% of the early (stage I) and 63% of the late (stages II, III, IV) ovarian carcinomas examined, and was expressed at an even higher percentage in breast cancers examined, with late stage carcinomas expressing approximately 3-fold higher Six1 mRNA levels on average compared to early stage tumors. Importantly, in patients with late stage disease, high Six1 expression was associated with significantly shortened survival ($p = 0.0015$). These data suggest that Six1 may contribute to carcinogenesis by simultaneously increasing proliferation and decreasing TRAIL-mediated apoptosis, and imply that Six1 may be an important determinant of TRAIL-therapy response that should be considered in patient selection for TRAIL-related clinical trials.

**Applications**

There are currently clinical trials with TRAIL ongoing at CU. Dr. Ford's technology would allow for:

- Accurate identification of patients who will most likely benefit from TRAIL so that these companies can tailor their clinical trials for success
- Potential use as a marker for tailoring patient therapy once these therapies are approved by the FDA (perhaps in conjunction with the FDA label for TRAIL).

**Data Update**

Dr. Ford's earlier results (available upon request) are focused on elucidating the mechanism through which Six1 confers resistance to TRAIL ligands and receptor antagonists. In particular, expression of Six1 seems to be linked with upregulation of certain decoy receptors for those molecules. More recently, Dr. Ford and her collaborators have found that expression of Six1 is linked to resistance to other classes of cancer therapeutics, including VEGF therapeutics (link). For a summary of some of Dr. Ford's earlier data, continue to next page.

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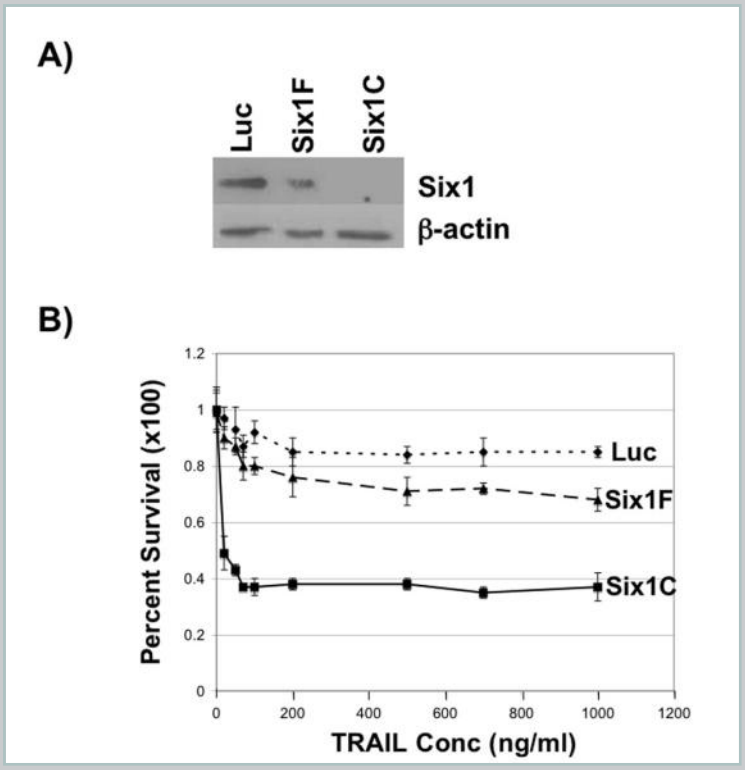


Figure: Six1 knockdown sensitizes OCC to TRAIL-mediated apoptosis. SKOV3 cells were transiently transfected with plasmids expressing siRNA sequences against Six1 and luciferase (Luc).

(A) Six1 Western blot analysis demonstrating efficiency of knock-down with siRNA constructs; in the experiment shown, the Six1C construct completely knocked down Sis1 expression, whereas the Six1F construct only partially knocked down Six1. Confirmatory Western blots were performed for each experiment (3 experiments performed) and showed similar results, with the Six1C construct always giving a near complete knockdown, and the Six1F construct resulting in partial knockdown.

(B) Effect of TRAIL on cells transfected with a control (Luc, dotted line) construct, an efficient Six1-targeting construct Six1C (solid black line) and a less efficient (see Western Blot) Six1-targeting construct Six1F (dashed line). Experiment was performed three times (each condition in sextuplet), and the level of Six1 knockdown correlated with TRAIL sensitivity in each experiment.

**Key Documents**


SIX1 induces lymphangiogenesis and metastasis via upregulation of VEGF-C in mouse models of breast cancer. J Clin Invest. 2012 Apr 2. doi: 10.1172/JCI59858.

Six1 overexpression in ovarian carcinoma causes resistance to TRAIL-mediated apoptosis and is associated with poor survival. Cancer Res. 2007 Apr 1;67(7):3036-42.

Methods for Determining Prognoses and Therapeutic Interventions for Ovarian Carcinomas. PCT filed Dec. 11, 2007 (nationalized to EU and US).