

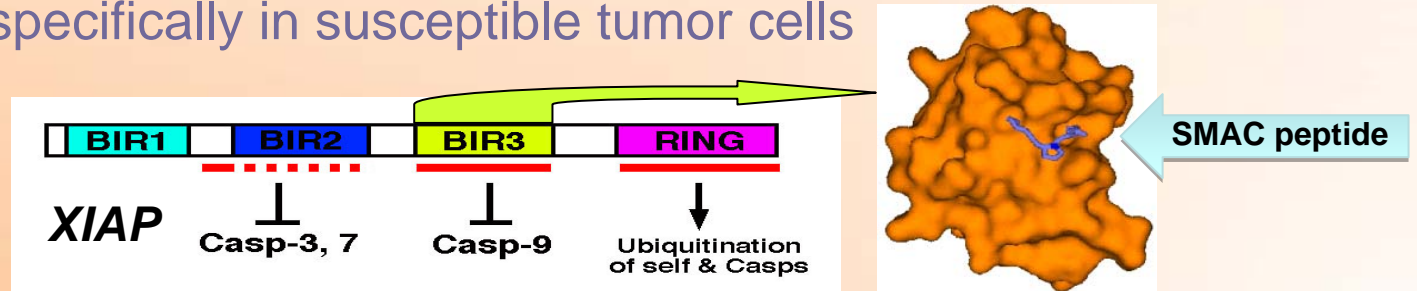
# TL32711- SMAC Mimetic

*Synergizes with the Tumor  
Microenvironment*

October 28, 2010

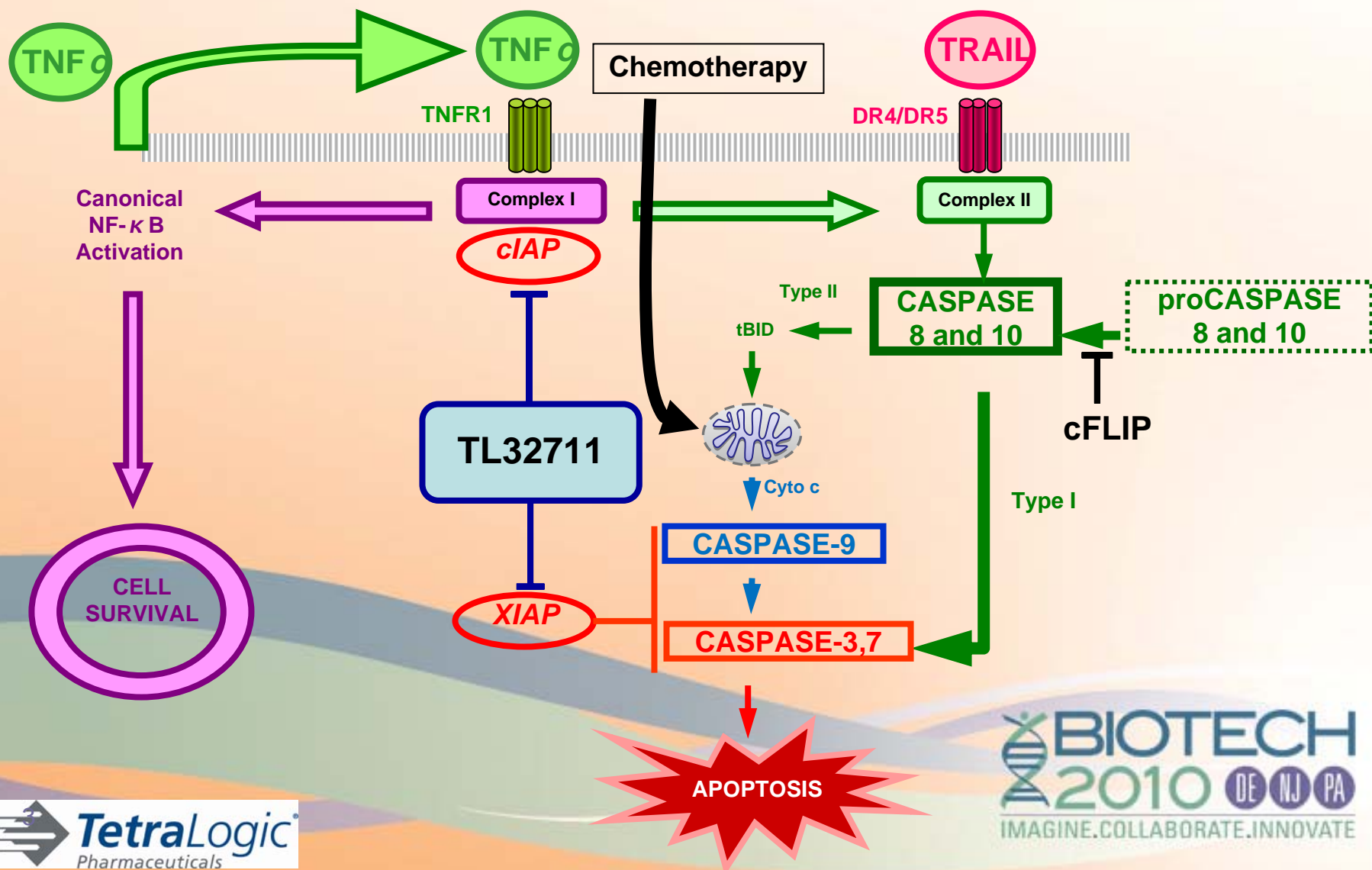
# TL32711 Biology Summary

- Apoptosis is dysregulated in tumor cells
- Inhibitors of Apoptotic proteins (IAPs) are key regulators of apoptosis
- SMAC (second mitochondrial activator of caspases) is the endogenous antagonist of the IAPs (XIAP, cIAP-1 and cIAP-2)
- TL32711 is a peptidomimetic of SMAC that is a potent inducer of apoptosis specifically in susceptible tumor cells

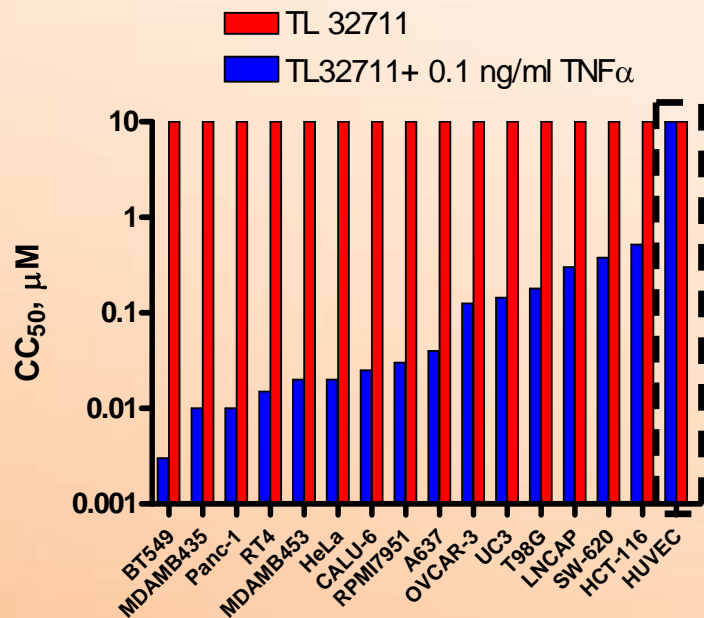


- Tumor cell killing is potently enhanced in the presence of cytokines often found in the tumor microenvironment

# TL32711 Enable Tumor Cell Apoptosis Through Multiple Pathways



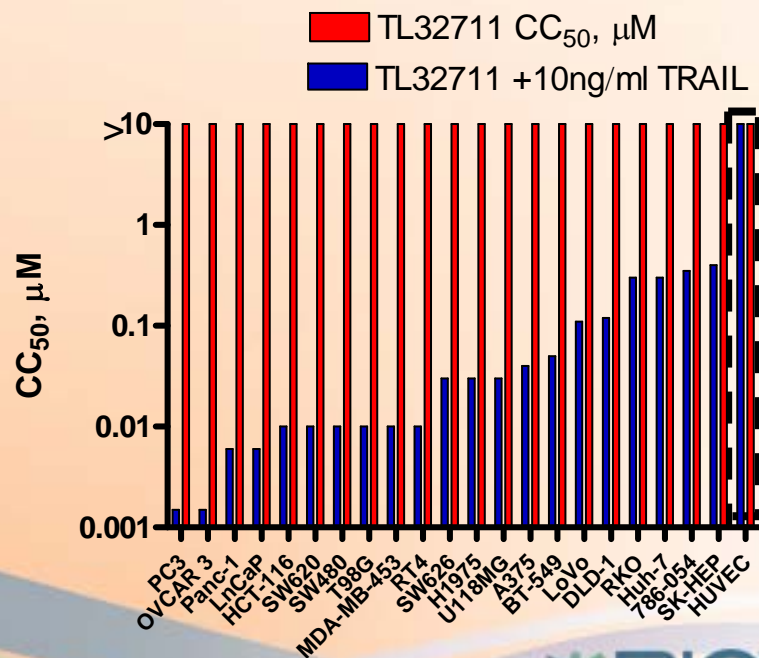
# TNF $\alpha$ and TRAIL Induce Tumor Apoptosis in Combination with TL32711



TL32711 resistant tumor lines were assayed with a non-cytotoxic concentration of **TNF $\alpha$**  in a 72 hour MTT assay

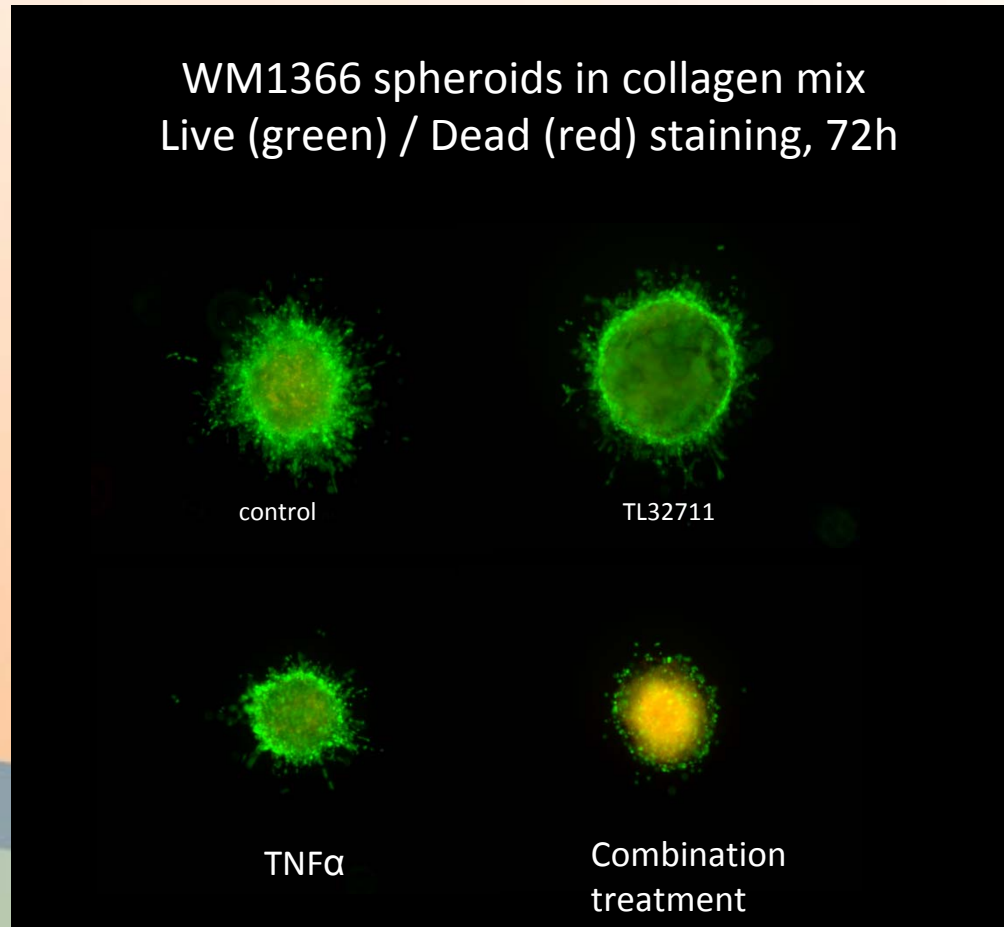
No synergy in HUVEC, HMEC, Simian hepatocytes, Human keratinocytes and dermal fibroblasts at 100 ng/ml TNF $\alpha$

TL32711 resistant tumor lines were assayed with a non-cytotoxic concentration of **TRAIL** in a 72 hour MTT assay



Cell Line

# TNF $\alpha$ Enables TL32711 Killing of Melanoma Cells



Krepler and Herlyn - Wistar Institute

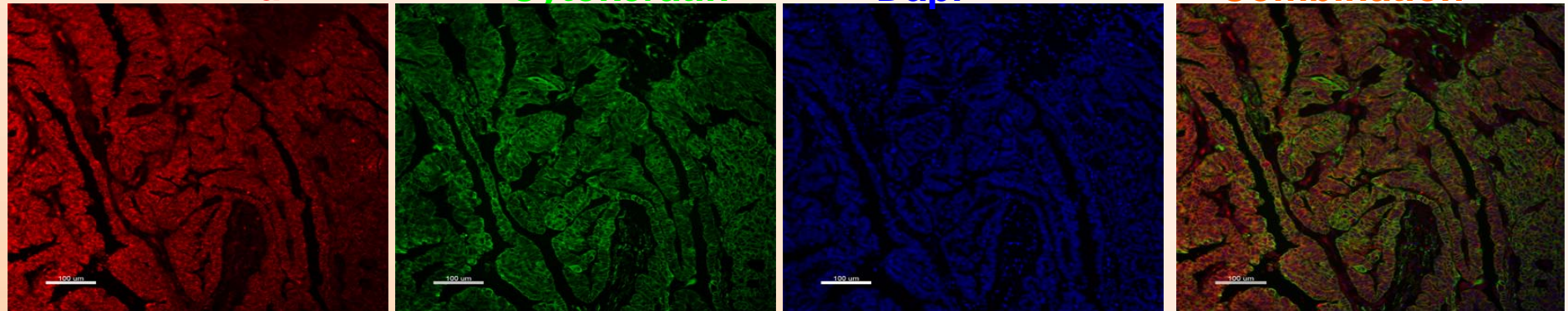
# High Level TNF $\alpha$ Expression in Tumor and Stroma

TNF $\alpha$

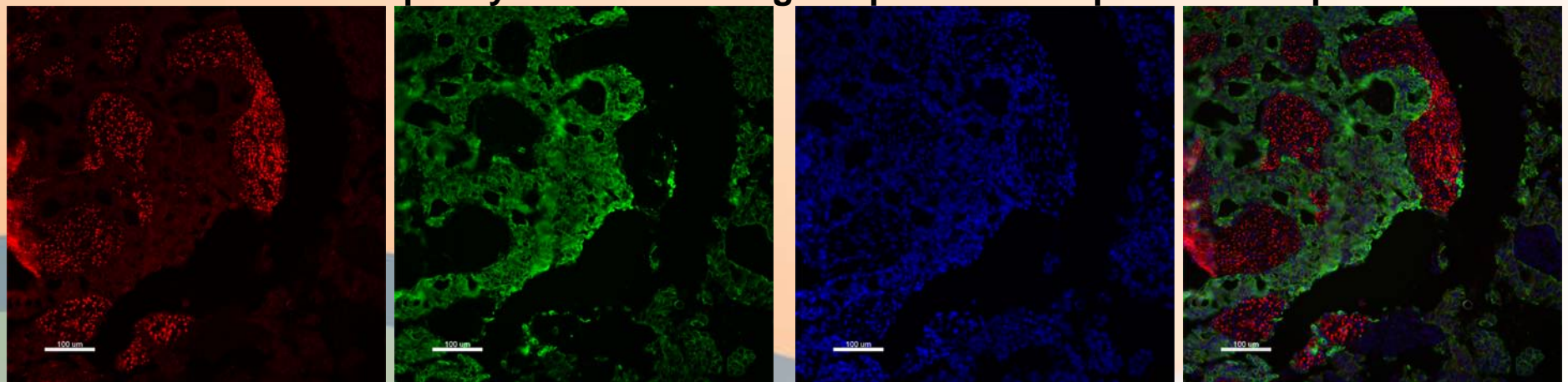
Cytokeratin

Dapi

Combination



Ovarian Papillary serous CA – High Expression in Epithelial component



Ovarian Endometrioid CA – High Expression in Stroma

# High Level Expression of TRAIL in Tumors

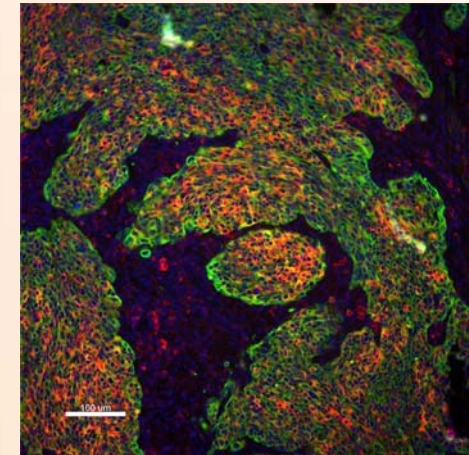
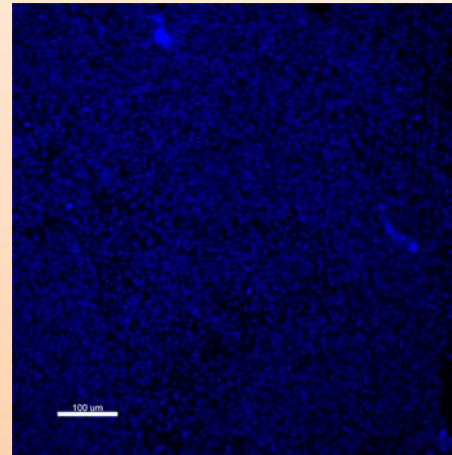
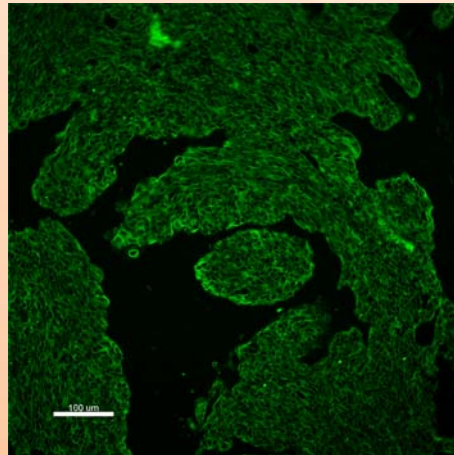
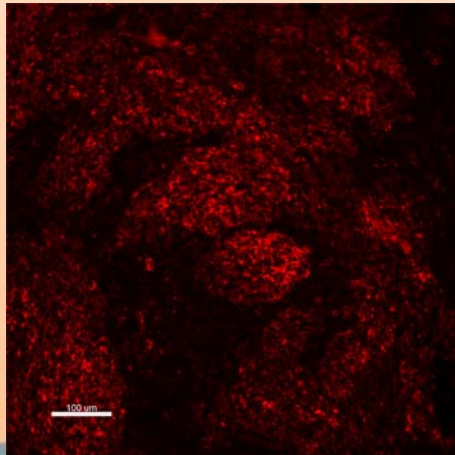
Ovarian TMA 09-17 spot 40 Serous CA 200x; AQUA score: 419.9212

**TRAIL**

**Cytokeratin**

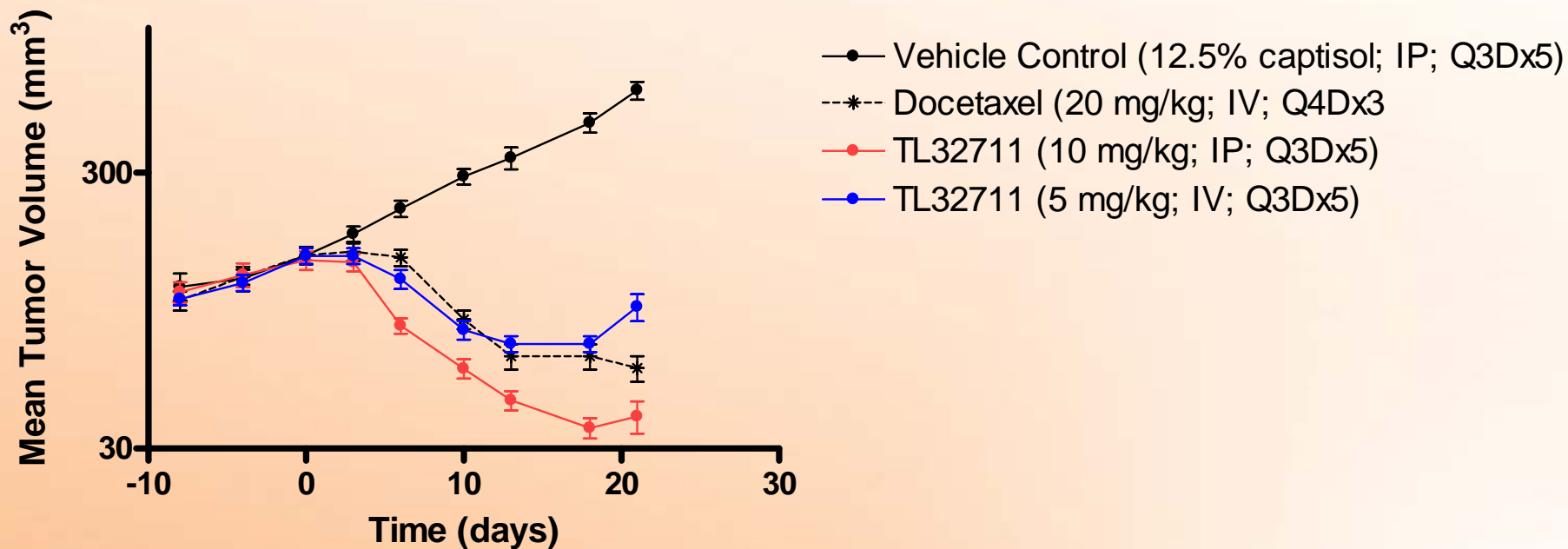
**Dapi**

**Combination**



High level expression in tumor

# TL32711 Causes Tumor Regressions at Well Tolerated Doses in a MDA-MB-231 Xenograft Model



TL32711 ↑ ↑ ↑ ↑ ↑  
Docetaxel ↑ ↑ ↑

# TL32711 Clinical Evaluation

- Phase 1 single agent study ongoing at University of Pennsylvania, Fox Chase and Roswell Park
- Phase 1 5 arm combination study being initiated at same sites

# Summary

- TL32711 potently and selectively induces tumor apoptosis through antagonizing the Inhibitors of Apoptosis proteins (IAPs)
- TNF $\alpha$  and TRAIL are cytokines often present in the tumor microenvironment
- TL32711, when combined with these cytokines, results in cell death in susceptible tumor cells
- TL32711 is presently undergoing clinical evaluation