# A method for treating TRAIL-resistant cancers

Duke LICENSING & VENTURES

## Unmet Need

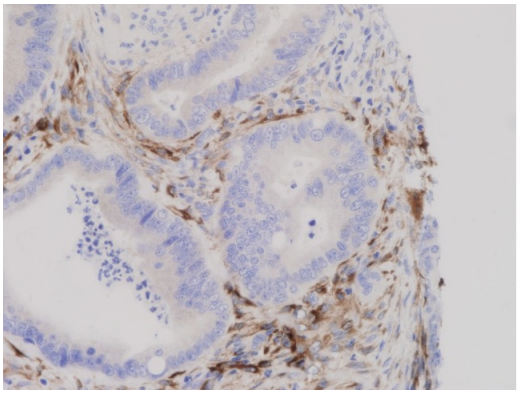
Over the past twenty years, TNF-related apoptosis-inducing ligand (TRAIL) has been shown to kill a variety of human cancer cells in vitro and in vivo while remaining innocuous to healthy cells. Unfortunately, the preclinical promise of TRAIL and other agonists of TRAIL receptors (TRAILR1 and TRAILR2) has not translated to clinical efficacy for patients. The majority of primary cancer cells are TRAIL-resistant, including colorectal cancer. The American Cancer Society's estimates 104,270 new cases of colorectal cancer and 45,230 new cases of rectal cancer in the United States for 2021. There is a need to translate the promising efficacy of TRAIL treatment observed in pre-clinical studies to cancer patients.

## Technology

Duke inventors have developed a drug combination for treating TRAIL-resistant cancer, including colorectal cancer. Specifically, these are highly potent pro-apoptotic drug combinations comprising a TRAIL receptor agonist (TRA) and targeted sensitizing agents. The inventors used a genetic knockout screen in a TRA-resistant human cancer cell line to identify the genetic markers of resistance. They then developed a set of informed, rational drug combinations that inhibited proteins encoded by the resistance genes, and synergistically sensitized the cell lines to TRA. Two such combinations have induced apoptosis at picomolar EC50 in human patient-derived cell lines ranging in TRA sensitivity from completely resistant to highly sensitive. Drug combinations were evaluated for long-term efficacy in human colorectal cell lines. This technology creates a gel-like depot upon subcutaneous injection that abolished tumors in TRA-sensitive Colo205 mouse xenografts. Additionally, tumor growth inhibition and extended survival were observed using TRA-resistant patient-derived xenografts.

## Advantages

- Could better translate the promising pre-clinical efficacy observed for TRAIL treatments to cancer patients
- Has demonstrated long-term efficacy in human colorectal cancer cell lines
- Use with multiple compounds allow co-targeting of three



### Duke File (IDF) #

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- Wood, Kris

### Links

- From the lab of Dr. Ashutosh Chilkoti

### College

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distinct anti-apoptotic pathways and provides broad spectrum of use
- Demonstrated *in vivo* efficacy using patient-derived subcutaneous xenografts and mouse models

**Publications**

- Genomically informed small-molecule drugs overcome resistance to a sustained-release formulation of an engineered death receptor agonist in patient-derived tumor models (Science Advances, 2019)