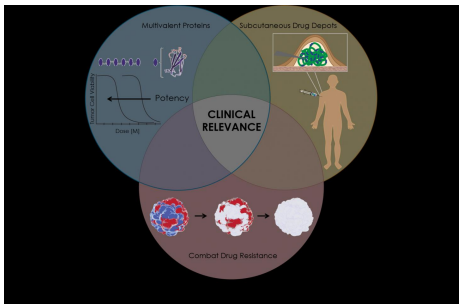
Anti-cancer therapeutic for the induction of apoptosis in solid tumors via TRAIL receptors

Unmet Need

Tumor necrosis factor-**R**elated **A**poptosis-**I**nducing **L**igand (TRAIL, CD253) acts as an activator of apoptosis in many tumor cells, while remaining innocuous to normal cells. Both membrane-bound and soluble forms of TRAIL can trigger apoptosis of target cells through interaction with TRAIL receptors. TRAIL **R**eceptor **2** (TRAIL-R2) is expressed in many human cancers and is exploited in cancer therapy for its ability to trigger caspase-related cell death upon receptor engagement. Several therapies based on purified TRAIL or TRAIL-R agonists have been unsuccessful due to the extremely short half-life (~30 minutes) of TRAIL, inadequate delivery to cancer cells, and weak agonist activity. Thus, there is a need for novel molecules that can bind to TRAIL receptors with improved pharmacokinetic activities and methods for using such molecules in the therapeutic treatment of a wide variety of cancers.

Technology

Duke inventors have developed an anti-cancer therapeutic for tumors that express TRAIL-R2. This is intended to be used as an intratumoral injection for solid tumors before advanced metastatic disease, or in combination with other therapies for advanced metastatic disease. Specifically, this technology implements use of a thermally responsive multivalent therapeutic anti-cancer protein (Tn3-ELP) with inverse phase transition behavior that can be used to create subcutaneous and intratumoral drug depots for controlled release of the therapeutic. This has been demonstrated in an *in vitro* model of cancer cell killing with adenocarcinoma cells, where the thermally responsive fusion protein outperformed TRAIL alone



Duke File (IDF) Number

IDF #:T-004515

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Publication(s)

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External Link(s)

• From the lab of Dr. Ashutosh Chilkoti
• Duke researchers utilize gene editing to improve cancer drugsu2019 performance (Press release, WRAL TechWire, 2019)
• Gene-targeted cancer drugs, slow release overcome resistance (Press release, EurekaAlert!, 2019)
• Poster abstract (pg.154, 2014)

with no decrease in potency compared to standard Tn3 multimers. Using a mouse xenograft model of colorectal adenocarcinoma, the depot-forming Tn3-ELP fusion protein showed greatly improved anti-cancer efficacy compared to soluble Tn3, as measured by reduced tumor size compared to control mice.

Advantages

- The protein can be injected into a tumor as a liquid at room temperature followed by rapid formation of a gel-like depot in the tumor upon reaching body temperature, thus improving the half-life and therapeutic utility of Tn3 multimers
- Outperforms TRAIL without a decrease in potency compared to standard Tn3 multimers
- Greatly improved anti-cancer efficacy compared to soluble Tn3
- The Tn3-ELP fusion protein can be easily purified without complicated affinity-based methods by using a process called “inverse transition cycling”, which makes use of the temperature-dependent phase transition of ELP