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TR3: A STABILIZED TRAIL TIMER FOR USE AS AN ANTICANCER THERAPEUTIC

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Technology Description

Researchers at Washington University in St. Louis (WUSTL) have developed a novel TRAIL (TNF-related apoptosis inducing ligand)-based anticancer drug platform, designated TR3. TRAIL has potent and specific apoptotic activity against tumor cells. Thus, there is great clinical interest in developing it to be an anticancer therapeutic. TRAIL, however, must form a homotrimer to become biologically active. Attempts to produce bioactive TRAIL from monomers have failed for a variety of reasons thereby limiting its therapeutic potential. To overcome this limitation, the inventors have developed this technology which provides a covalently-linked human TRAIL trimer (TR3). TR3 is comprised of three consecutive extracellular TRAIL domains fused together in a head-to-tail configuration and encoded by a single DNA construct. This design provides improved stability without impacting the killing ability of TRAIL.

Additionally, TR3 can serve as a drug platform for the design of targeted cancer therapeutics under stoichiometric control. TR3 can be modified to include cell targeting moieties that enable cancer cell specific delivery. To this end the inventors have developed additional technologies:

- WUSTL T-011885- Targeted delivery of TR3 using the high affinity mesothelin/MUC16 ligand/receptor interaction.
- WUSTL T-016481- Targeted delivery of TR3 to mesothelin using single chain antibody fragments (scFvs).

This portfolio of technologies provides a more stable TRAIL trimer (TR3) that can be modified for tumor cell specific delivery to provide superior target cell death and thus more successful anticancer therapeutics.

Schematic of the genetically encoded TRAIL trimer, TR3. The bioactive domain of secreted TRAIL (TR) was joined three times to result in TR3.

Stage of Research

The inventors targeted TR3 to mouse RBCs. Then they showed, the TR3-decorated RBCs effectively killed target cells in a model of pancreatic cancer.

Applications

- Anticancer therapeutic

Key Advantages

- Greater stability than native TRAIL
- Effective killing ability
- TR3 has no artificial linker sequences- minimizes immunogenicity
- Can be modified in a stoichiometrically controlled fashion without interfering with TRAIL function
- Allows cell specific targeting to increase drug potency and to reduce off target effects
- Increases amount of active protein produced
- Can be used as a stand-alone therapeutic or in combination with other anticancer therapies

Publications

- Spitzer D, McDunn JE, Plambeck-Suess S, Goedegebuure PS, Hotchkiss RS, Hawkins WG. A genetically encoded multifunctional TRAIL trimer facilitates cell-specific targeting and tumor cell killing. Mol Cancer Ther. 2010 Jul;9(7):2142-51. doi: 10.1158/1535-7163.MCT-10-0225. Epub 2010 Jun 22.

Patents

- Issued US Patent 8,461,311

Related Web Links

- Dr. Spitzer profile
- Dr. Hawkins profile
- Hotchkiss lab