Washington University in St. Louis
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MESOTHELIN-TR3: TARGETED TRAIL TRIMERS WITH SUPERIOR ANTICANCER ACTIVITY

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Technology Description

Researchers at Washington University in St. Louis have developed a strategy to specifically target the anticancer therapeutic TR3 to cancer cells using the mesothelin/MUC16 interaction. Mesothelin is a GPI linked cell surface protein expressed in mesothelial cells that is involved in tumor adhesion and metastasis. MUC16 (also known as CA125) is a membrane anchored mucin that binds with high affinity to mesothelin. Further, it is a well characterized biomarker in several human cancers including pancreatic, ovarian, and breast cancers. These cancers lack effective therapeutics and are among those with the worst survival rates. Thus, there is a great need for new therapeutics. To help meet the need, the inventors took advantage of the strong mesothelin/MUC16 interaction to target the anticancer therapeutic TR3 to MUC16 expressing cancer cells. The fusion proteins allow targeted tumor cell delivery and increased tumor cell death. This technology provides much needed anticancer therapeutics for pancreatic, ovarian and breast cancers.

The inventors generated several versions of the MUC16-targeted, mesolthelin-TR3 fusion protein including:

- Mesothelin-TR3 (Meso-TR3): full length mesothelin without its GPI anchor fused to TR3
- Meso64-TR3: N-terminal 64 amino acids of mesothelin (the minimal sequence required for MUC16 binding) fused to TR3

Schematic of mesothelin-TR3 fusion proteins.

Left: TR3- non-targeted TRAIL trimer drug platform, *Center:* Meso-TR3, *Right:* Meso64-TR3.

Stage of Research

The inventors have shown that the mesothelin-TR3 fusion proteins target TR3 to MUC16 expressing cancer cells and increase the killing activity in vitro and in xenograft mouse models of cancer.

Applications

- Anticancer therapeutic for:
  - Pancreatic cancer
  - Ovarian cancer

- Breast cancer

Key Advantages

- Solves an unmet need- provides new therapeutics for pancreatic, ovarian and breast cancers
- Selectively targets MUC16 expressing cancer cells- minimizes off target toxicities
- Enhances tumor cell killing capacity of TR3
- May reduce metastatic potential of cancer cells
- Can be used in combination with other anticancer therapeutics

Publications

- Garg G, Gibbs J, Belt B, Powell MA, Mutch DG, Goedegebuure P, Collins L, Piwnica-Worms D, Hawkins WG, Spitzer D. Novel treatment option for MUC16-positive malignancies with the targeted TRAIL-based fusion protein Meso-TR3. BMC Cancer. 2014 Jan 21;14:35. doi: 10.1186/1471-2407-14-35.

- Su Y, Tatzel K, Wang X, Belt B, Binder P, Kuroki L, Powell MA, Mutch DG, Hawkins WG, Spitzer D. Mesothelin's minimal MUC16 binding moiety converts TR3 into a potent cancer therapeutic via hierarchical binding events at the plasma membrane. Oncotarget. 2016 May 24;7(21):31534-49. doi: 10.18632/oncotarget.8925.

Patents

- Issued US Patent 9,127,081
- Issued US Patent 9,815,882
- Issued US Patent 10,072,061

Related Web Links

- Dr. Spitzer profile
- Dr. Hawkins profile