Washington University in St. Louis
Office of Technology Management

TUMOR-TARGETED FUSION PROTEIN PLATFORM FOR ENHANCED CANCER IMMUNOTHERAPY

Pachynski, Russell

Zou, Dianxiong

T-015906

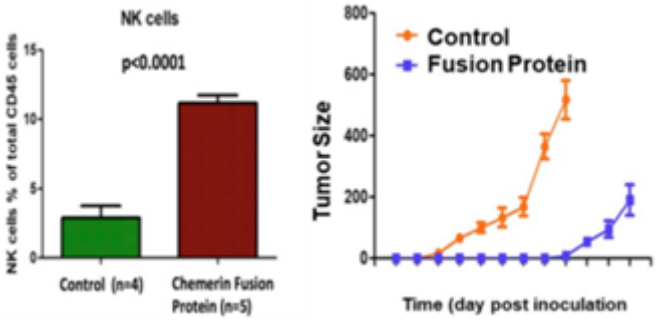
Disease indication – cancer, particularly lung, breast, colon, and prostate cancer or melanoma (cancers where chemerin is down-regulated at the tumor site)

Drug format – engineered fusion protein

Drug class – first in class

Research stage and Preliminary data

- **In vitro validation** – the fusion protein binds the tumor target with high specificity at nanomolar concentrations and efficiently recruits human NK cells
- **In vivo validation** – the fusion protein concentrates specifically in target tumors after systemic administration and significantly reduces tumor growth compared to controls
- **Proof of concept** – the fusion protein redirected immune effector cells (NK cells) to a prostate cancer cell line and increased T-cell mediated cytotoxicity (comparable to a checkpoint inhibitor)



Target – Fusion protein construct includes a flexible targeting motif that can be adapted to bind to specific cell surface antigens to treat different types of cancer. Initial validation studies were designed to target CD20 (for lymphoma and leukemia). With minor modifications, additional targets could include HER2 (for breast cancer), EGFR (for colon cancer), PSMA (for prostate cancer) and others.

Background

Tumor microenvironments promote tumor growth in part by suppressing immune response. Current checkpoint inhibitor immunotherapy drugs are designed to counteract immune evasion (one of the mechanisms of immune suppression). However, these drugs suffer from side effects on healthy cells and they do not work in all patients.

Another mechanism that tumors use to escape immune defenses is downregulating chemerin. Chemerin (also known as RARRES2 and retinoic acid responder-2) is a chemoattractant, tumor suppressor protein

that recruits tumor infiltrating cells ("TILs" such as NK cells) to the tumor microenvironment. Chemerin can modulate tumor growth and increased chemerin levels have been correlated with improved overall survival for a variety of tumor types (breast, melanoma, adrenocortical carcinoma and prostate). Harnessing the effects of chemerin specifically within the tumor microenvironment could provide an alternative immunotherapy approach that has the potential to provide an independent treatment or a synergistic combination therapy with checkpoint inhibitors.

Keywords – immunooncology, immunotherapy, chemerin, tumor microenvironment, chemoattractant, RARRES2

Mode of action

This invention is a chemerin fusion protein with three components: a tumor-targeting motif, the active chemerin protein and a cleavable linker that joins them together. The tumor targeting motif directs the fusion protein to a specific cell-surface antigen expressed by the tumor. The linker is designed to be cleaved at the tumor site, releasing chemerin locally in the tumor microenvironment. The chemerin would then activate the patient's immune defenses, recruiting NK cells and other TILs to the tumor site with the goal of reducing the size of the tumor. This approach offers a flexible platform because the effects of chemerin have been observed in a range of tumor types and the tumor-targeting motif (e.g., scFv) can be adapted for a variety of tumor markers.

Competitive edge:

- **Tumor targeting –** directs therapy to tumor microenvironment with a targeting motif directed to a tumor-specific antigen
  - could enable systemic administration with reduced side effects on healthy cells
  - off-the-shelf molecules could be developed for specific types of cancer without the need for patient-specific customization
- **Versatile platform**
  - chemerin-based therapy could be widely used because immune evasion through reducing levels of chemerin appears to be shared across many tumor types
  - basic fusion protein structure can be adapted for a variety of cancers, with the potential for parallel design, production, and testing of multiple lead candidates in multiple tumor types
- **Potential synergy with checkpoint inhibitors –** for possible combination therapy to improve response rates to checkpoint inhibitors
  - mechanism of chemerin is independent of the effects of checkpoint inhibitors
  - localizes activated immune cells (e.g., NK cells) to the site of a tumor
- **Durable response –** compared with endogenous chemerin, chemerin fusion proteins are more stable and diffuse more slowly

Patent status – Compositions comprising chemerin and methods of use thereof (PCT Application, Publication No. WO2017/120589)

Publications - Shin, W. J., Zabel, B. A., & Pachynski, R. K. (2018). Mechanisms and functions of chemerin in cancer: Potential roles in therapeutic intervention. *Frontiers in immunology*, 9.

Web Links - Pachynski Profile