Docket #: S22-493

Neutrophil activating therapy for the treatment of Cancer

Despite their cytotoxic capacity, neutrophils are often co-opted by cancers to promote immunosuppression, tumor growth, and metastasis. Consequently, these cells have received little attention as potential cancer immunotherapeutic agents.

However, Stanford researchers have demonstrated in mouse models that neutrophils can be harnessed to induce durable eradication of tumors and reduce metastasis through the combined actions of tumor necrosis factor, CD40 agonist, and tumor-binding antibody. The same combination activates human neutrophils *in vitro*, enabling their lysis of human tumor cells. Mechanistically, this therapy induces rapid mobilization and tumor infiltration of neutrophils along with complement activation in tumors. Complement component C5a activates neutrophils to produce leukotriene B4, which stimulates reactive oxygen species production via xanthine oxidase, resulting in oxidative damage and T cell-independent clearance of multiple tumor types. These results establish neutrophils as potent anti-tumor immune mediators and reveal a previously unappreciated inflammatory pathway that can be harnessed to drive neutrophil-mediated eradication of cancer.

Stage of Development

- Proof-of-concept established in mouse models

Applications

- Cancer immunotherapy

Advantages

- **Novel molecular composition** - the lab is unaware of any other cancer therapy based on the activation of tumor-killing neutrophils

- **The Neutrophil Activating Therapy (NAT)**
  - Cures a variety of solid tumor types in mice
  - Works in the absence of T lymphocytes
  - Activates tumor-specific T cells and induces tumor-specific T cell memory
  - Can potentially prevent metastatic cancer

Publications

- Linde, Ian L., Tyler R. Prestwood, Jingtao Qiu, Genay Pilarowski, Miles H. Linde, Xiangyue Zhang, Lei Shen et al. "Neutrophil-activating therapy for the treatment of cancer." *Cancer Cell* 41, no. 2 (2023): 356-372.

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