Novel Agonists of the Vitamin D Receptor for the Treatment of Cancer and Fibrotic Diseases

INVENTION: Fibrosis is the term used to describe the formation or development of excess fibrous connective tissue in an organ or tissue as a reparative or reactive process, akin to the process involved in wound-healing. Unfortunately, fibrosis can lead to permanent scarring, organ failure, and in certain cancers, create a fibrotic microenvironment to effectively shield a tumor from the immune system and chemotherapeutic agents.

Salk investigators have found that the vitamin D receptor (VDR) is expressed in stroma from human pancreatic tumors and that treatment with the VDR ligand calcipotriol markedly reduces markers of inflammation and fibrosis in pancreatitis and human tumor stroma. They show that activating VDR reprograms the tumor stroma to the quiescent state, resulting in induced stromal remodeling, increased amounts of chemotherapeutic agents inside the tumor, reduced tumor volume, and a 57% increase in survival compared to chemotherapy alone. It is clear that potent agonists of VDR can reduce fibrosis, and when in combination with chemotherapy could be an effective treatment for cancer.

APPLICATIONS:

- Fibrotic diseases, including liver fibrosis, NASH and pancreatitis
- Cancers with fibrotic tumors, including liver and pancreas.

ADVANTAGES:

- Effective combination of the VDR agonist with chemotherapeutic agents to treat cancer
- Fibrotic tissue is restored to normal function instead of being destroyed.

STAGE OF DEVELOPMENT:

- Human pancreatic cancer cell line data.
- In vivo mouse model data.

BACKGROUND: An obstacle in treating certain cancers, including pancreatic cancer, is the fibrotic microenvironment that surrounds the tumor. Tumor cells are able to create this environment by sending out signals that make the nearby environment inflamed and dense, thus creating a “living shield” around the tumor that not only helps the cancer grow but also blocks the access of immune cells and chemotherapeutic drugs. The five-year survival rate (6%) for pancreatic cancer patients has not changed for decades; mainly due to the lethal combination of the tumor stroma fueling the tumor, the protective fibrotic shield, and ineffective treatments that target tumor cells directly. By targeting the vitamin D receptors with the vitamin D-based agonists, the stroma is transcriptionally reprogrammed while simultaneously suppressing inflammatory cytokines and growth factors.

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PATENT STATUS: U.S. Patent 8,318,708 and PCT patent application US 2014/04163 is pending

PUBLICATIONS:

- Ding, et al. (2013) Cell, 153: 601-613
- Sherman, et al. (2014) Cell, 159: 80-93
- https://www.salk.edu/news-release/modified-vitamin-d-shows-promise-as-treatment-for-pancreatic-cancer/

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