Des-acyl Ghrelin and Analogs as Cancer Therapies

Technology Summary

This technology describes the use of des-acyl ghrelin and analogs for the treatment of multiple cancer types, including breast and colorectal, that do not carry mutations in BRAF, HRAS, or KRAS.

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Technology Overview

Breast cancer is the most common cancer diagnosed in women and is second only to lung cancer in terms of mortality. Although most breast tumors occur after menopause when ovarian estrogen synthesis has ceased, most of these tumors remain estrogen dependent. The aromatase enzyme catalyzes the conversion of androgens to estrogens and is thus a major driver of estrogen-dependent breast cancer after menopause and a promising therapeutic target. However, currently approved aromatase inhibitors used in first-line therapy are associated with serious side effects due to the global inhibition of estrogen, leading a proportion of patients to discontinue treatment. Additionally, select patients have or develop resistant cancers, or are poor candidates for targeted therapies, such as those with triple-negative breast cancers (TNBCs).

This technology describes the use of the gut-derived peptide hormone des-acyl ghrelin and analogs for the treatment of cancer, including breast and colorectal. This technology is based on the finding that des-acyl ghrelin and the analog AZP-531 suppress the growth of patient-derived breast and colorectal cancer cells at picomolar doses. The inventor demonstrated des-acyl ghrelin acts by a novel mechanism of action via activation of Gαi, suppression of cAMP production, and inhibition of MAPK and Akt signaling. Importantly, the inhibitory effects were demonstrated in 3D cell culture with a biologically relevant extracellular matrix (ECM), as well as *in vivo* preclinical models of breast cancer, suggesting the results may translate to clinical studies. Of note, inhibition was not observed in cells with a BRAF or KRAS mutation, suggesting des-acyl ghrelin acts upstream of these proteins. As such, des-acyl ghrelin and analogs may lead to improved treatment for patients with breast and colorectal cancer.

Potential Applications

- Treatment of breast and colorectal cancer
- Treatment of other cancers that do not carry mutations in BRAF, HRAS or KRAS
- Reduction of chemotherapy-induced side effects such as muscle cell death or cardiotoxicity

Advantages

- Picomolar inhibitor of patient-derived 3D cell cultures
- Tolerability of AZP-531 has been demonstrated in clinical trials for type II diabetes and Prader-Willi syndrome
- Demonstrated activity in select triple-negative breast cancers (TNBCs) and cells resistant to tamoxifen
- Side effects associated with aromatase inhibition are expected to be minimal due to selectivity for breast cancer promoters

Publications

- Au et al. “Three-dimensional growth of breast cancer cells potentiates the anti-tumor effects of unacylated ghrelin and AZP-531.” *Elife.* 2020.
- Au et al. “Des-acyl ghrelin inhibits the capacity of macrophages to stimulate the expression of aromatase in breast adipose stromal cells.” *J Steroid Biochem Mol Biol.* 2017.
- Au et al. “Ghrelin and Breast Cancer: Emerging Role in Obesity, Estrogen Regulation, and Cancer.” *Front Oncol.* 2016.
- Docanto et al. “Ghrelin and des-acyl ghrelin inhibit aromatase expression and activity in human adipose stromal cells: suppression of cAMP as a possible mechanism.” *Breast Cancer Res Treat.* 2014.
- PCT Patent Application: WO/2020/051132. “Des-acyl ghrelin therapies and analogs as cancer therapies.” Published Mar 12, 2020.