جامعة الملك عبدالله
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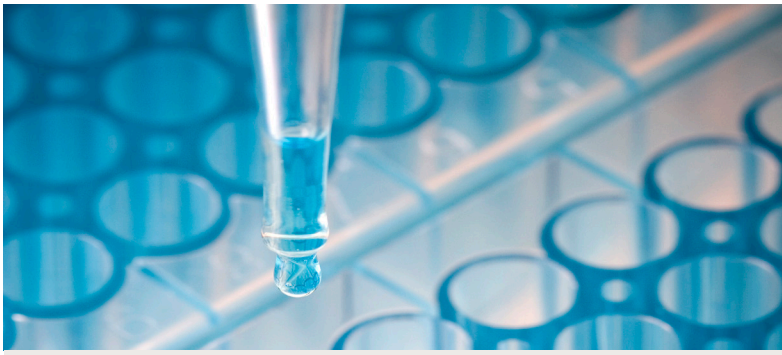
King Abdullah University of
Science and Technology

TECHNOLOGY OPPORTUNITY



A Potential Lead Molecule for Treatment of Estrogen-Positive Breast Cancer

A potential anti-cancer lead molecule

Breast cancer (BC) is the second leading cause of death amongst women (1.7 million new cases diagnosed in 2012), where estrogen receptor (ER)-positive BC accounts for 75% of cases. Approved drugs include selective ER modulators (tamoxifen antagonizes the binding of estrogen to ER and aromatase inhibitors (AIs) directly inhibit the production of estrogen). The adverse side effects of these drugs accentuate the need for new drugs that can provide enhanced efficacy, reduced toxicity, reduced drug resistance and long-term cancer-free survival.

We present acetyl plumbagin (AP), a molecule that selectively inhibits ER-positive BC cell growth in vitro as well as in vivo and induces apoptotic cell death by disrupting cholesterol mechanisms, while showing negligible hepatotoxicity and general toxicity in mice.

Benefits

- **Anti-cancer activity:** Induces apoptosis in cancer cells and inhibits tumor growth
- **No in vivo toxicity:** Molecule causes no liver damage or impairment of liver function
- **Selective action:** Targets ER-positive breast cancer cells and not normal cells

Applications

- Cancer treatment for ER-positive breast cancer
- Cholesterol modulation: Has the potential to be used as a cholesterol modulator in addition to its use for cancer treatment
- Adjuvant therapy: Potential adjuvant drug to reduce the induced toxicity of chemotherapeutic drugs

IP Protection

KAUST has several patents pending for this technology.

Opportunity

This technology is part of KAUST's technology commercialization program that seeks to stimulate development and commercial use of KAUST-developed technologies.

Opportunities exist for joint development, patent licensing, or other mutually beneficial relationships.

For More Information

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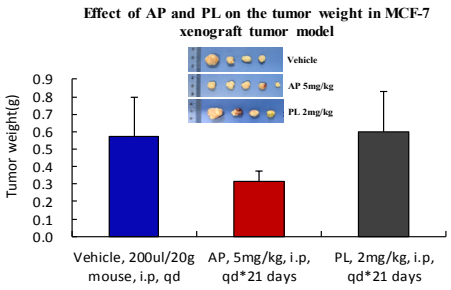
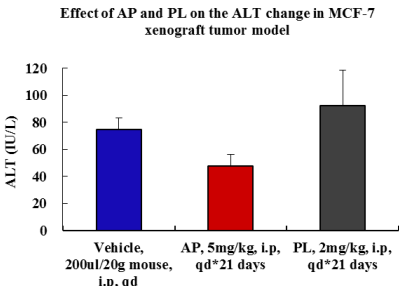
Technology Details

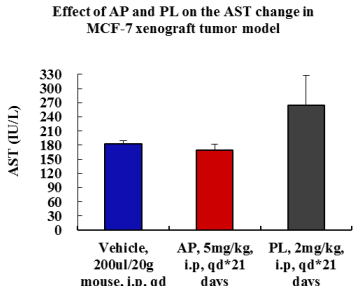
How It Works



Cholesterol has a vital role in the synthesis of new cell membranes and formation of lipid rafts in which receptors are embedded. Because cancer cells divide more rapidly and overexpress membrane receptors compared to normal cells, they have greater demand for cholesterol in order to sustain proliferation and cell membrane integrity. Cholesterol is also used for the biosynthesis of estrogen which further stimulates growth and proliferation of ER-positive BC. Cholesterol lowering drugs such as statins have been shown to reduce cancer growth in vivo. AP acts as a cholesterol modulator as it disrupts lipid rafts and depletes cholesterol from ER-positive BC cells, resulting in tumor growth inhibition and activation of apoptosis (Fig. A). AP reduces cell viability, disrupts mitochondrial function, activates caspases-9 and -7 resulting in PARP-1 cleavage, DNA damage and apoptosis.

Why It Is Better





The natural plant product plumbagin (PL) is known for its promising anti-cancer activity but induces significant toxicity to normal cells. We show that AP, a derivative of PL, exhibits low hepatotoxicity in vivo. AP selectively targets ER-positive BC cells with negligible negative effects on normal cells and liver function (Fig. B, C). The following observations show why AP is better:

1. AP inhibited in vivo tumor growth up to 45% at 5mg/kg dose as compared to PL at 2mg/kg dose. A dose of 5mg/kg of PL was extremely toxic to animals.

2. Toxicity of AP is minimal as compared to PL (no animal died; minimum body weight loss as well as low alanine aminotransferase and aspartate aminotransferase values).

AP acts by depleting cholesterol and inducing apoptosis and has broader application potential as compared to currently used tamoxifen and AIs

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INNOVATION AND ECONOMIC DEVELOPMENT