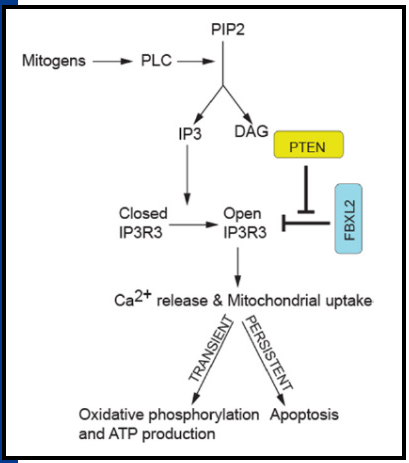
PTEN Mutation as a Novel Biomarker of Response to GGTI-2418 Treatment in Cancer



This technology presents a method of using PTEN mutations in tumors as a biomarker for response to GGTI-2418 treatment. GGTI-2418, a small molecule that inhibits geranylgeranyltransferase I can promote Ca2+-mediated apoptosis limiting tumor growth when PTEN is no longer present in cells. In a mouse xenograft model with a low PTEN expressing cell line, treatment with GGTI-2418 increased apoptosis in the tumors by about 100% and decreased tumor weight by about 25%. These data suggest that tumors with PTEN mutations are likely to benefit from GGTI-2418 treatment. Also, GGTI-2418 was shown to sensitize xenotransplanted tumors to photodynamic therapy.

COMMERCIAL OPPORTUNITY

- PTEN mutations can be found in multiple tumor cell types including glioblastoma (41.9%), endometrial cancer (38%), melanoma (17%), prostate cancer (14%), cervical cancer (13.9%), lung SCC (11.3%), ovarian cancer (8%), breast cancer (7.5%) and colorectal cancer (6.3%).
- PTEN mutations might be used as a diagnostic once GGTI-2418 is approved to determine which patients are most likely to respond to GGT-2418. They could also be used as a companion diagnostic to pick those subsets of patients more likely to respond to GGTI-2418 in clinical trials.
- As shown in the Figure above, FBXL2 that is part of a ubiquitin complex binds the inositol triphosphate receptor (IP3R3) and targets it for degradation. When IP3R3 is degraded, apoptosis is decreased potentially contributing to cancer cell growth. PTEN however can bind IP3R3 and block its degradation by FBXL2 resulting in increased apoptosis and increased cancer cell death. When PTEN is not around, GGTI-2418 can mimic PTEN blocking FBXL2 from binding and degrading IP3R3 by stopping the lipid modification of FBXL2. When FBXL2 is not geranylgeranylated, it cannot bind and degrade IP3R3 leading to increased apoptosis and increased cancer cell death.

TECHNOLOGY

NOD/SCID gamma mice were subcutaneously injected with A549 lung cells with low PTEN expression. Mice were randomly assigned to three groups: untreated, treated with GGTI-2418, and treated with both PDT and GGTI-2418 and PDT (phthalocyanine). GGTI-2418 treatment meant 2 rounds of the drug (50mg/kg) treatment by intra-tumoral injections for 5 consecutive days. Tumor progression was confirmed by either retro-orbital or intravenous injection of fluorescently labelled IR Dye 2-deoxyglucose (2-DG). This dye was detected 24 hours after injection using a Pearl Triology Imaging System. Tumor weights and degree of apoptosis were different between day 32 vs. the end of the experiment. On its own, GGTI-2418 reduced tumor size by 25% compared to controls and increased apoptosis by about 100% relative to controls. In combination with PDT, GGTI-2418 reduced tumor weight by about 62.5% and increased apoptosis by about 300% relative to controls.

PUBLICATION/PATENT

- Provisional patent filed in 2017 for Drs. S. Sebti & M. Pagano
- Publication by Kuchay et al. in Nature (546:554) June 22, 2017 titled “PTEN counteracts FBXL2 to promote IP3R3- and Ca2+-mediated apoptosis limiting tumour growth”

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