Biomarkers Of Response To Inhibition Of Poly-Adp Ribose Polymerase (PARP) In Human Cancers
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SUMMARY
The Slamon and Finn groups at UCLA have discovered that specific chromosomal gains can serve as biomarkers that predict a cancer patient response to treatments that use poly-ADP ribose polymerase (PARP) inhibitors.

BACKGROUND
Poly-ADP ribose polymerase (PARP) is an enzyme that plays a critical role in DNA repair. Since alterations or changes in DNA repair pathways have been implicated in the pathogenesis of human cancers, PARP inhibition has been put forward as a potential strategy to treat various cancers. Several small molecule inhibitors of PARP have been developed, and show growth inhibitory activity in a small number of human cancers. Specifically, the use of PARP inhibitors has been validated in cancers that lack specific DNA repair mechanisms either through inherited mutations and/or non-inherited silencing of specific genes, such as BRCA1 and BRCA2.

The biomarkers that are most frequently used to identify potential patients with cancers that would be responsive to PARP inhibition are inherited mutations in either the BRCA1 or BRCA2 gene. Therefore, those identified are typically breast or ovarian cancer patients. However, not all BRCA-mutated breast and ovarian cancers respond to PARP inhibition. Additionally, only a minority of patients with breast and ovarian cancer have inherited mutations in the BRCA genes. Therefore, a more robust biomarker for sensitivity to PARP inhibition would increase the patient population that successfully receives PARP inhibition treatment for cancer.

INNOVATION
Researchers at UCLA have discovered specific chromosomal alterations that serve as biomarkers for cancer patient sensitivity to PARP inhibitors. Using over 300 cell lines that include over 15 different cancer types, they found that a genomic gain in chromosome 1q21 and/or chromosome 20q13.3 were robust biomarkers of sensitivity to this type of treatment. Their results showed a number of cancers other than breast and ovarian cancers that are sensitive to this type of treatment, including malignancies of the lung, bladder, stomach, colon, rectal, and liver, as well as cancers in the head and neck regions.

APPLICATIONS
- Increase the population of patients identified as appropriate candidates to receive PARP inhibitors as a cancer treatment.
- Enable clinicians to better select cancer patients with malignancies responsive to PARP inhibitors.

ADVANTAGES
Increased specificity

Easy to implement in the clinic:
- Since these DNA-based chromosomal gains and gene amplification are associated with overexpression of the gene products, the alteration can be measured in cancer cells or tumor tissue using any techniques that will determine copy number increases at the DNA level as well as gene expression at the RNA or protein levels. For example, common techniques such as SNP arrays or comparative genomic hybridization can be used to detect changes at the DNA level, RNA in situ hybridization or northern blot analysis can be used to detect alterations at the RNA level, and protein arrays or western blotting can be used to detect expression differences at the protein level.

STATE OF DEVELOPMENT
The predictive potential of the two independent chromosomal biomarkers of sensitivity to PARP inhibitors has been validated in over 300 human cancer cell lines.
- Panel of cell lines includes 15 separate histologic subtypes, e.g. breast, ovary, lung, colorectal, gastric, melanoma, pancreas, etc.
- Cell lines have been characterized with regards to the individual line's ability to grow in vitro both on plastic and in soft agar as well as in vivo growth both subcutaneously and orthotopically.
- In addition, each line in the panel has been characterized for gene expression by transcript microarray as well as gene copy number variation (CNV).

Future work includes validation of biomarkers in clinical human specimens.

PATENT STATUS
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Additional Patent Pending

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Early Detection of Colon Cancer
- Differentially Expressed Genes Associated with Her-2/Neu Overexpression
- Her-2/Neu Overexpression Abrogates Growth Inhibitory Pathways
- Frozen Tissue Microarray Technology for Analysis of RNA, DNA, and Proteins
- Methods and Materials for Characterizing and Modulating Interaction between Heregulin and HER3
- An Amplified and Overexpressed Gene in Colorectal Cancers
- Predictive Markers for Dasatinib to Treat Solid Tumors
- Biomarkers Of Response To Cyclin D - CDK4/6 Targeted Therapies In Human Cancers
- Biomarkers Of Response And Synergistic Combinations With ERK Targeted Therapies In Human Cancers