International Conference on
GASTROINTESTINAL CANCER AND THERAPEUTICS
4th World Congress on &
DIGESTIVE & METABOLIC DISEASES
26th Annual Congress on &
CANCER SCIENCE AND TARGETED THERAPIES
October 29-30, 2018 | San Francisco, USA

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Testing HER2-related therapeutic strategies in GI cancers guided by integrated genomics

Many somatic mutations have been detected in GI cancers, leading to the identification of some key drivers of disease progression, but the involvement of large genomic rearrangements has often been overlooked. Chromosomal rearrangement detection allows coverage of the entire genome as opposed to narrowly focusing on selected genes. It is far less prone to false positives and can potentially identify driving rearrangements/fusions within pathways that may be therapeutically targetable. Due to tumor-specificity of the breakpoint-junctions, it can be used for defining clonal relationships and allows for designing individualized diagnostic tests for monitoring a patient's disease progression. We performed mate-pair sequencing (MPseq) on genomic DNA and RNAseq on mRNA from several patients with pancreatic adenocarcinoma, cholangiocarcinoma and colorectal cancer to identify genome-wide rearrangements. We found a small number of potentially targetable amplifications and fusions including four cases with ERBB2 amplification. 3D micro cancer modeling was performed followed by a drug screen informed by the genomic analysis. Finally, dose-response curves (including IC_{50} values), were generated after measuring cellular ATP. Significant responses were noted for all Her2 targeted therapies. The combined genomic/micro cancer analysis pointed towards the possibility that these patients have a Her2 activated pathway and could benefit from Her2 targeted therapies.

Biography

George Vasmatzis is a Consultant in the Department of Molecular Medicine and a member of the Mayo Clinic Cancer Center, as well as the co-director of the Biomarker Discovery Program, within the Center for Individualized Medicine. His research program consists of bioinformatics specialists, molecular biologists, epidemiologists, and pathologists. His team has demonstrated success in discovery and translation of several biomarkers as well as developing evidence-based models that should help clinicians stratify (cancer) patients in order to provide each individual with the appropriate care. With the recent advances in Next Generation Sequencing (NGS) technologies his laboratory has been engaging in massive sequencing to scan the genome of cancer cells for abnormalities that can be used for clinical purposes such as diagnosis and stratification of patients for optimal treatment. Published papers in the journal of Clinical Oncology, Cancer Research, and BLOOD further demonstrate their discovery, validation, and translation capabilities.

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