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Therapeutic targeting of genomic mutations in human cancers

Chromosome mutations and rearrangements are some of the hallmarks of human malignancies. Chromosomal rearrangement is frequent in human cancers. One of the consequences of chromosomal rearrangement is gene fusions in the cancer genome. We have identified a panel of fusion genes in aggressive prostate cancers. In the present study, we found that these fusion genes are present in 7 different types of human malignancies with variable frequencies. Among them, CCNH-C5orf30 and TRMT11-GRIK2 gene fusions were found in colon cancer, breast cancer, non-small cell lung cancer, esophageal adenocarcinoma, glioblastoma multiforme, ovarian cancer and liver cancer, with frequencies ranging from 12.9% to 85%. In contrast, four other gene fusions (mTOR-TP53BP1, TMEM135-CCDC67, KDM4-AC011523.2 and LRRC59-FLJ60017) are less frequent. Both TRMT11- GRIK2 and CCNH-C5orf30 are also present in lymph node metastatic cancer samples from the breast, colon and ovary. Thus, detecting these fusion transcripts may have significant biological and clinical implications in cancer patient management. Recently, we developed a genome editing based technology to target at the fusion gene breakpoints in human cancers through insertion of suicide gene into the mutation sites. This approach achieved high specificity in killing the cancer cells and sparing the normal tissues from the collateral damages. The treatment of mice xenografted with cancers that contain the fusion genes achieved partial remission of the cancers. As a result, the mutation targeting of human cancer genome holds promise for the treatment of the disease.

Speaker Biography

Jianhua Luo has been studying molecular mechanisms of human malignancies in the last 32 years. Currently, he is a Professor of Pathology and Director of High Throughput Genome Center at University of Pittsburgh. In the last 20 years, he has been largely focusing on the genetic and molecular mechanism of human prostate and hepatocellular carcinomas. He proposed prostate cancer field effect in 2002. He is one of the pioneers in utilizing high throughput gene expression and genome analyses to analyze field effects in prostate cancer and liver cancer. He is also the first in using methylation array and whole genome methylation sequencing to analyze prostate cancer. Recently, his group discovered several novel fusion transcripts and their association with aggressive prostate cancer. Subsequently, his group discovered that many of these fusion genes are recurrent in many other types of human cancers.

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