Small molecule drug leads for p53 mutant cancers
Tech ID: 33196 / UC Case 2014-211-0

BRIEF DESCRIPTION

Researchers at UC Irvine have used a computationally powered method to identify small molecule drug leads that exhibited anti-cancer activity in a human-cell-based assay. These small molecules and the approach used to find them will accelerate the research and development of anti-cancer therapeutics.

SUGGESTED USES

- Treatment of cancers that exhibit p53 mutations
- Identification of drug leads for the development of anti-cancer therapeutics

FEATURES/BENEFITS

- Accelerate research and development of cancer-targeting therapies
- Functional assay using human cell culture
- Computational tools for identifying active compounds
- Chemical compounds that restore p53 activity

TECHNOLOGY DESCRIPTION

Cancer is one of the leading causes of death in the United States and over 50% of all human cancers have a genetic mutation to a protein called p53. This protein controls several cellular growth pathways, apoptosis (programmed cell death), and cellular senescence (when cell stop dividing) and has therefore been classified as a tumor suppressor gene. Thus, genetic mutations to this protein leads to uncontrolled cell growth and cancer. A considerable amount of effort has been made to identify and test chemical drug leads that restore p53 activity, with the hopes of developing these drug leads into anti-cancer therapeutics. This has been done using rational drug design followed by blind drug screening, but this method has yielded few known leads and lack mechanisms of action and drug binding sites. Furthermore, there is no current functional assay for the rescue of p53 activity.

Researchers at UC Irvine have used a computationally powered drug design approach to identify small molecules that were shown to restore mutant p53 activity in a human-cell-based functional assay. The computational method (molecular dynamics simulation) allowed them to discover a previously unknown transient p53 binding site and with the use of established computer-aided simulations, they were able to computationally screen and biologically validate rescuers of mutant p53 activity with approximately 90% accuracy. Biological validation was conducted using a newly developed functional assay for p53-dependent cell killing that employs the use of a p53 null cell line (Saos-2) that exhibits uncontrolled growth. Expression of functional p53 in the cell line blocks their proliferation, while expression of p53 mutants has no effect. Identified compounds that reactivate p53 cancer mutants specifically block proliferation of Saos-2 cells expressing cancer mutants but have no effect on the growth of Saos-2 p53 null cells. This suggests that cell killing (or senescence) is mediated solely through p53 reactivation.

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INVENTORS

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OTHER INFORMATION

CATEGORIZED AS

» Medical
» Disease: Cancer
» New Chemical Entities, Drug Leads
» Research Tools
» Research Tools
» Cell Lines
» Screening Assays

RELATED CASES

2014-211-0
STATE OF DEVELOPMENT

In vitro studies

RELATED MATERIALS

» Nature Communications Journal: Computational identification of a transiently open L1/S3 pocket for reactivation of mutant p53
» PubMed Central: Computational identification of a transiently open L1/S3 pocket for reactivation of mutant p53

PATENT STATUS

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