New technique predicts gene resistance to cancer treatments

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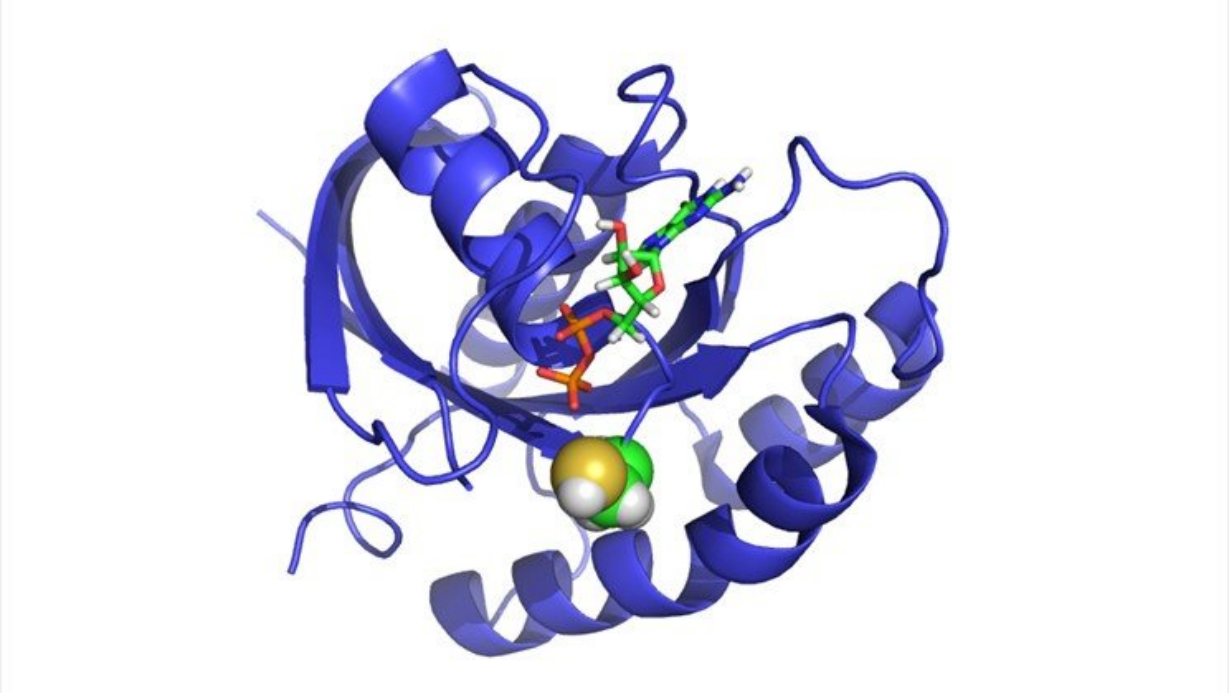

Credit: Yale University

Yale School of Public Health researchers have developed a new method to predict likely resistance paths to cancer therapeutics, and a methodology to apply it to one of the most frequent cancer-causing genes.

That gene, KRAS, is mutated in approximately 20 percent of all human

cancers and has a major presence in pancreatic, colorectal and lung cancers, can continue to mutate and evolve even after successful chemotherapy, radiation or drug treatment.

The study, published in *Oncogene* , follows up on new targeted therapies that show promise in inhibiting the KRAS G12C variant. Researchers collaborated with Gilead Sciences in Foster City, California to perform sequencing of KRAS-positive lung tumors to determine the prevalence of other oncogenic mutations that could lead to treatment resistance. They were also able to assess new mutations in KRAS itself that could present after treatment of specific tumors.

"The treatment initially appears to successfully target a specific mutation in KRAS," said Jeffrey Townsend, Ph.D., the Elihu Associate Professor of Biostatistics at the Yale School of Public Health and associate professor of ecology and evolutionary biology at Yale. "But, other mutations can appear down the road. By assessing the tumor's potential to reinvent itself after therapy, our findings inform us on how to combine therapies to intervene before cancer comes back in full force."

The researchers focused on getting ahead of potential new tumor development by preventing resistance and inhibiting the KRAS G12C mutation. The study findings offer insight into new mutations likely to resist treatments based on the degree that specific mutations drive the growth and evolution of cancer, and the potential of therapeutic that may be able to stop deviant gene function.

"Currently, we treat tumors with medication to target and inhibit the tumor as is, but not to prevent the future evolution of tumors into resistant forms," said Townsend. "We need to develop techniques and drugs that not only target the mutations that we know are there, but that also stop the evolution of the tumor."

Using a national database of tumor sequences along with tumor sequences from previous Yale studies, the researchers created a promising evolutionary framework with potential utility in prediction of pathways to resistance to new targeted therapies as they become available. By judicious combinations of multiple therapies that prevent the emergence of resistant forms, the researchers predict that cancer can eventually be overcome.

More information: Vincent L. Cannataro et al. Heterogeneity and mutation in KRAS and associated oncogenes: evaluating the potential for the evolution of resistance to targeting of KRAS G12C, *Oncogene* (2018). DOI: 10.1038/s41388-017-0105-z

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