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NEW APPROACH COULD IDENTIFY RAS-BLOCKING SMALL MOLECULES

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With an eye on historically undruggable cancer target Ras, a University of Oxford team and colleagues devised a way to find small molecules that have the same qualities as Ras inhibitors too large to access the intracellular targets.

Ras proteins are particularly attractive as an intracellular target for cancer: nearly a third of all cancers have mutated K-Ras (KRAS), neuroblastoma Ras viral (v-Ras) oncogene (NRAS) and v-Ha-ras Harvey rat sarcoma viral oncogene homolog (HRAS).

Modulating Ras has proven difficult, however. Small molecules that can slip within a cell lack the affinity and surface interactions that larger molecules, such as intracellular antibodies, have to block the protein-protein interactions mediating a given target's function. Delivering intracellular antibodies as a therapy is ineffective as they cannot penetrate cells.

The University of Oxford team previously identified a intracellular antibody fragment that binds to activated forms of KRAS, NRAS and HRAS, and slowed tumor growth in xenograft mouse models of lung cancer in a 2010 *Oncogene* **study**.

In a *Nature Communications* **study**, the researchers led by Oxford Professor of Molecular Biology Terence Rabbitts screened the intracellular antibody fragment against a library of small molecules to identify Ras-binding compounds, then used those hits to optimize a series of compounds that bound to the same site.

The most potent small molecule Ras inhibitor bound to KRAS with an IC50 of 8 μM in a human KRAS-mutant colorectal cancer cell line and to NRAS with an IC50 of 10μM in a NRAS-mutant non-small cell lung cancer (NSCLC) cell line. It also decreased cancer cell viability in both cell lines.

Cell-based assays indicated the compound effectively blocked protein-protein interactions between Ras and its effector molecules.

Rabbitts told BioCentury the approach -- in which intracellular antibody fragments are first used to validate targets, then the antibody binding site is used to guide small molecule development -- could be applied to any target protein in a cell.

The researchers' work contributes to a resurrecting field of Ras inhibition to treat cancer, partially due to emerging therapeutic modalities such as nucleic acids and T cell therapies that circumvent historic challenges (see **"p53 and Ras: Back from the Dead"**).