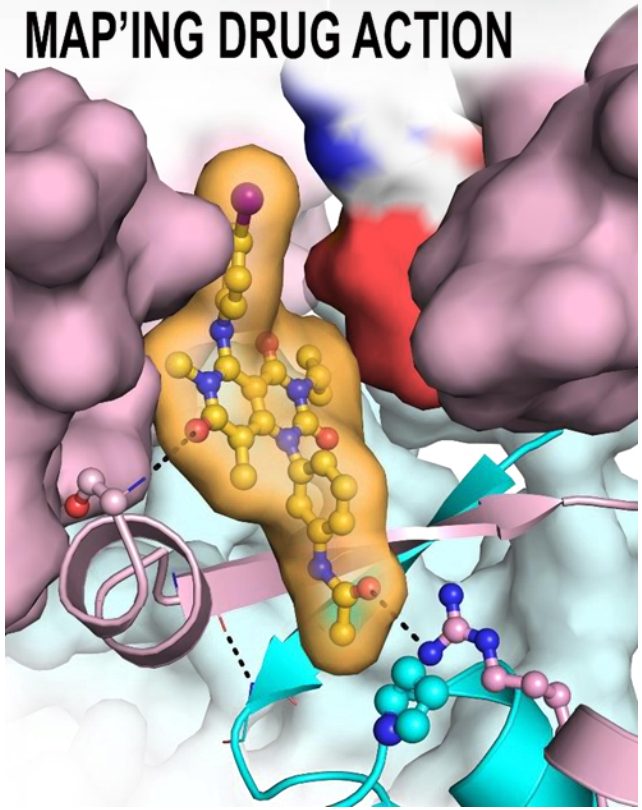
Fine Tuning Drugs to Fight Cancer



The schematic shows the trametinib-binding pocket of MEK (pink) and KSR (cyan).

Scientific Achievement

Scientists revealed the first co-crystal structures of the clinical MEK inhibitor, Trametinib, and find that the drug binds at the interface of MEK and its scaffold protein Kinase Suppressor of RAS (KSR).

Significance and Impact

Although Trametinib is used to treat melanoma, its mechanism of action was not fully understood; this work reveals how the drug binds to its target.

Research Details

- X-ray crystal structures of several clinical MEK inhibitors, including Trametinib, bound to the KSR1:MEK1 and KSR2:MEK1 complexes were solved using AMX and FMX at NSLS-II and at LS-CAT at APS.
- The structures reveal unique aspects of how Trametinib binds MEK, and engages KSR, at an interfacial region to impact efficacy and selectivity.
- A new compound called Trametiglue was created to improve the potency and activity of targeting cancer cells with mutations in the RAS oncogene.
- The findings suggest new opportunities for drugs that may engage multiple proteins.

Zaigham M. Khan, Alexander M. Real, William M. Marsiglia, Arthur Chow, Mary E. Duffy, Jayasudhan R. Yerabolu, Alex P. Scopton, Arvin C. Dar *Nature* (2020).

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