New Class of RAS Inhibitors Could Treat Many Cancers

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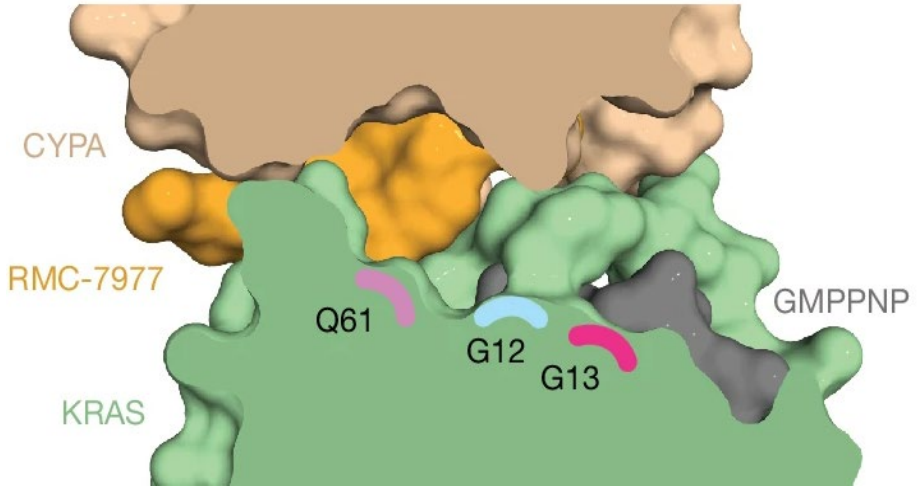
FMX



The tri-complex binding mode of RMC-7977 creates a groove between CYPA, KRAS, and RMC-7977 along the Q61–G12–G13 axis.

M. Holderfield, B.J. Lee, J. Jiang, A. Tomlinson, K.J. Seamon, A. Mira, E. Patrucco, G. Goodhart, J. Dilly, Y. Gindin, N. Dinglasan, Y. Wang, L.P. Lai, S. Cai, L. Jiang, N. Nasholm, N. Shifrin, C. Blaj, H. Shah, J.W. Evans, N. Montazer, O. Lai, J. Shi, E. Ahler, E. Quintana, S. Chang, A. Salvador, A. Marquez, J. Cregg, Y. Liu, A. Milin, A. Chen, T.B. Ziv, D. Parsons, J.E. Knox, J.E. Clomp, J. Roth, M. Rees, M. Ronan, A. Cuevas-Navarro, F. Hu, P. Lito, D. Santamaria, A.J. Aguirre, A.M. Waters, C.J. Der, C. Ambrogio, Z. Wang, A.L Gill, E.S. Koltun, J.A.M. Smith, D. Wildes, M. Singh. *Nature* **629**, 919-926 (2024). DOI: 10.1038/s41586-024-07205-6

Work was performed in part at NSLS-II

Scientific Achievement

Researchers describe the RAS(ON) multi-selective inhibitor RMC-7977, which targets the frequently mutated RAS oncogenes in tumors.

Significance and Impact

This preclinical work supports evaluation of a new therapeutic approach for many "RAS-addicted" cancers.

Research Details

- The RAS genes include KRAS; there are no approved inhibitors for the majority of KRAS mutations in cancers.
- The activity and structure of RMC-7977 was studied with many methods, including x-ray diffraction at the NSLS-II FMX beamline.
- RMC-7977 forms a tri-complex structure that binds to KRAS along with cyclophilin A (CYPA), an abundant protein involved in many cellular functions.

National Synchrotron Light Source II

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