

# **Structural biology: Mechanisms of novel anti-cancer drugs elucidated**

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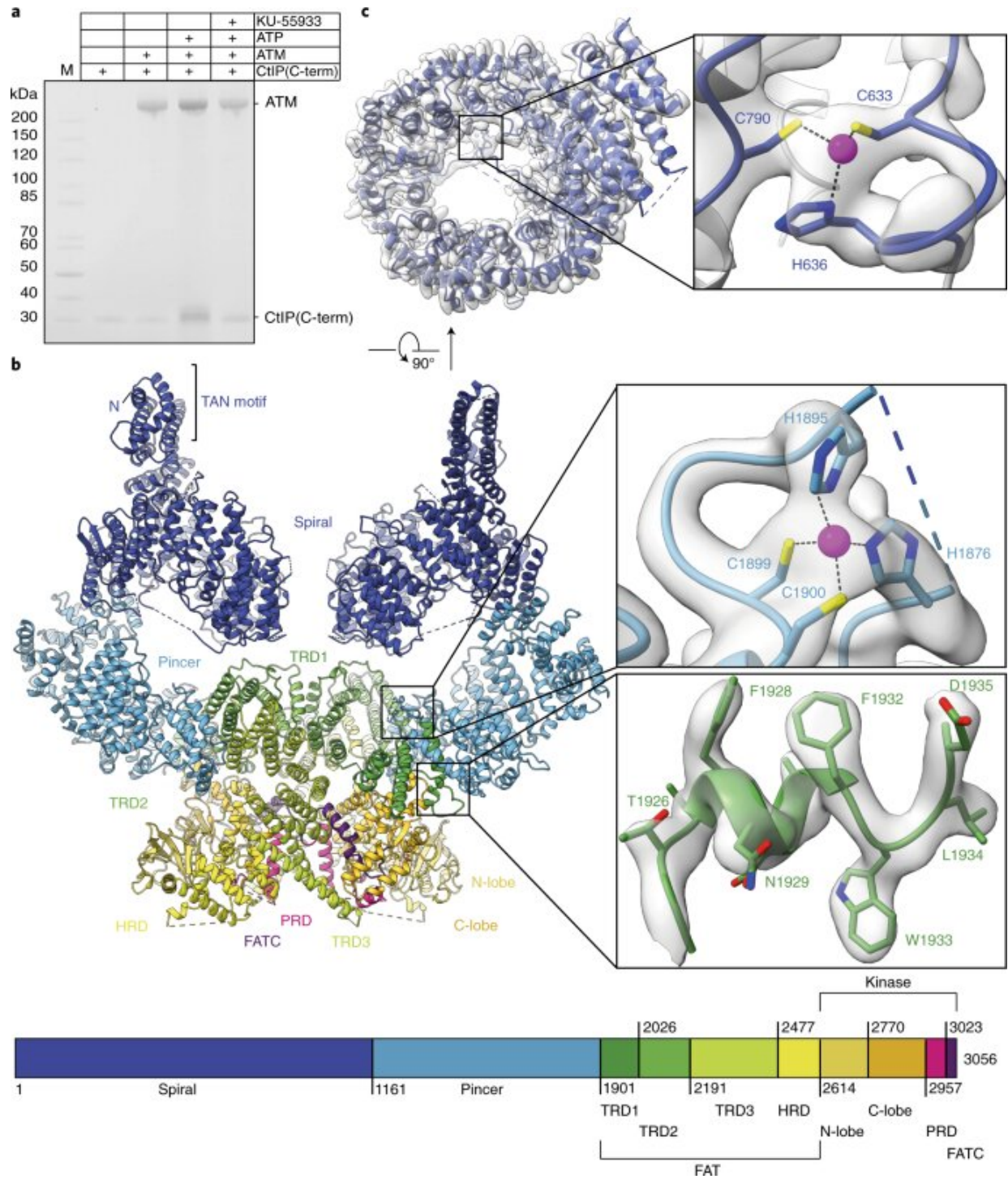


Fig. 1: Cryo-EM structure and activity of dimeric human ATM. Credit: DOI: 10.1038/s41594-021-00654-x

Double-stranded breaks (DSBs) are among the most hazardous forms of DNA damage. The checkpoint protein kinase ATM plays a key role in the repair of DSBs. Many anti-tumor drugs act by inducing DSB formation, so inhibition of ATM should enhance the sensitivity of cancer cells to these agents.

Owing to its [instability](#) and conformational flexibility, ATM—like other members of the family of checkpoint kinases—has been inaccessible to high-resolution structural analysis. However, detailed structural information greatly facilitates for the development of targeted and selective anti-cancer agents.

With the aid of cryo-[electron microscopy](#), Karl-Peter Hopfner's research group, in collaboration with the drug company Merck, has now elucidated the structure of ATM at a resolution that enables a virtually complete atomic model of the protein to be built. Moreover, the model allows the binding modes of novel ATM inhibitors that are currently in [clinical trials](#) to be determined. The structural model can account for the selectivity of two ATM inhibitors, and thus provides the basis for the stereochemical optimization of new therapeutic compounds.

The study is published in *Nature Structural & Molecular Biology*.

**More information:** K. Stakyte et al, Molecular basis of human ATM kinase inhibition, *Nature Structural & Molecular Biology* (2021). [DOI: 10.1038/s41594-021-00654-x](#)

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