

Newly developed inhibitor shows potential for prostate cancer

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Identification of a bi-substrate inhibitor of KMT9. **a** Chemical structure of compound **1a** with predicted binding mode. **b** MST assay to determine the dissociation constant (K_d) of compound **1a** and SAM binding to KMT9. c FTSA



for compound 1a binding to KMT9. d Chemical structure of SAM. e FTSA for SAM binding to KMT9. f Overall structure of the KMT9/compound 1a complex. KMT9 α (yellow) and KMT9 β (green) proteins are represented as ribbons. Arrows indicate the substrate channel (cyan) and the methionine pocket (brown) illustrated by surface view. Compound 1a is shown as sticks (magenta). g Hydrogen bonds between the amino group of compound 1a (magenta) and KMT9 α (yellow) in the substrate branch. KMT9 α is shown as ribbon. Key residues and ligands are depicted as sticks. Contacts are represented by black dashed lines. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-023-44243-6

More than 65,000 men fall ill with prostate cancer each year in Germany. Of these, 12,000 develop a treatment-resistant form that eventually ends in death. Now, a team of researchers from the Medical Faculty at the University of Freiburg has developed an active substance that might represent a future treatment option.

This substance, known as KMI169, targets an enzyme that plays an important role in the development of <u>prostate cancer</u>. The inhibitor displayed massive potential in among others cancer cells that were resistant to conventional treatments.

Researchers from the Department of Urology at the Freiburg University Medical Center as well as the Institut für Pharmazeutische Wissenschaften at the University of Freiburg published <u>their study</u> in *Nature Communications* on 2 January 2024.

"We've had our eye on the enzyme KMT9 as a possible target in prostate cancer for a long time. The development of this specific inhibitor is now a decisive step in combating prostate cancer far more effectively," explains study head Professor Roland Schüle, Academic Director of the Department of Urology at the Freiburg University Medical Center and



Dr. Eric Metzger, group leader in Schüle's department.

The substance's potential use against treatment-resistant forms of cancer makes it especially valuable. "This treatment-resistance means that the classic antihormonal treatment often fails within a few months and the disease then progresses rapidly. The inhibitor we've developed offers us a highly innovative therapeutic approach here," says Schüle.

New approach also relevant to bladder cancer

Using <u>cell cultures</u>, the groups headed by Schüle and co-author Professor Manfred Jung, head of the Chemical Epigenetics group of the Institut für Pharmazeutische Wissenschaften, have shown that the <u>enzyme</u> KMT9, known as a methyltransferase, is a critical factor in the development and progress of certain types of cancer such as prostate or bladder <u>cancer</u>.

"The inhibitor fits snugly like a key in its lock and blocks the functioning of KMT9 and therefore also the growth of both prostate and <u>bladder</u> <u>cancer</u> cells," says Jung. The development of KMI169 was guided by crystal structure analysis of KMT9 and numerous other studies. "We modified the compound many times to increase its potency, selectivity and medicinal properties."

More information: Sheng Wang et al, Structure-guided design of a selective inhibitor of the methyltransferase KMT9 with cellular activity, *Nature Communications* (2024). DOI: 10.1038/s41467-023-44243-6

Provided by Albert Ludwigs University of Freiburg



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