Versatile cancer drugs

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Medications that block enzymes belonging to the kinase family are among the most effective pharmaceuticals for targeted cancer therapies. Scientists at the German Cancer Consortium (DKTK) at the Technical University of Munich have examined 243 kinase inhibitors that are either approved drugs or have been tested in clinical trials. According to results published in *Science*, some of these may have more applications than previously thought.

Kinases are key enzymes that control a number of cell functions, including growth and self-destruction. About 500 kinases are encoded in the human genome. In cancer cells, these enzymes are often overactive and the normal regulation mechanisms cease to function. Abnormal cells can multiply uncontrollably and the growing tumor initiates the formation of blood vessels in order to sustain itself.

The use of kinase inhibitors can successfully slow tumor growth in certain types of cancer. More than 350 kinase inhibitors are currently in clinical trials, 37 of which have already been approved for therapeutic use. "In many cases, the precise mode of action of the individual inhibitors is not known," explains Bernhard Küster, the lead researcher on the project, who holds the Chair of Proteomics and Bioanalytics at the Technical University of Munich. "Many inhibitors have different functional targets in cancer cells and therefore could have a much broader spectrum of application than previously thought."

The international team of scientists, physicians, and computer scientists took a unique approach in order to elucidate which kinases and cellular

signaling pathways are specifically targeted by the inhibitors: In over more than 6,000 hours of mass spectrometry, the researchers analyzed the interaction of 243 clinically tested inhibitors with hundreds of kinases. The activity of the inhibitors was examined under near-physiological conditions. Instead of testing them using genetically produced enzymes, the scientists analyzed the entire cell content of leukemia, brain tumors, and colon cancer cells in response to the inhibitors. "In that way, we are much closer to the tumor biology and can systematically map out the spectrum of molecular binding partners."

In this "map" of the entirety of human kinases and their inhibitors, the scientists discovered new target structures that had previously not been linked to the drugs. Among them was the kinase MELK, which has been identified as a biomarker for poor prognosis in certain types of lung cancer. "Surprisingly, some of the tested inhibitors are capable of blocking MELK activity," explains Bernhard Küster. The research team also identified the precise molecular structure of several MELK-inhibitor complexes, forming the basis for the development of optimized MELK inhibitors.

The researchers discovered a new use for the kinase inhibitor cabozantinib, which is currently used to treat thyroid cancer. The results showed that cabozantinib is also effective against a kinase that plays a role in the onset of acute myeloid leukemia (AML). The drug was able to drastically slow the growth of leukemia cells in mice. "Since the agent is already an approved drug, we can take it straight to a new clinical trial," said Bernhard Küster.

Küster coordinates the development of the database ProteomicsDB as well as the DKTK's Cancer Proteome Analysis Platform, which gives the researchers access to the substantial inhibitor data sets.The new data has already generated excitement in the clinical community: "This information is particularly important for patients with unusual genetic

profiles," says Florian Bassermann, a senior physician at Klinikum Rechts der Isar, the university hospital of TU Munich. "Molecular tumor boards now have entirely new options for recommending the most suitable therapy for each individual patient."

More information: Susan Klaeger et al, The target landscape of clinical kinase drugs, *Science* (2017). DOI: 10.1126/science.aan4368

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