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Entirely novel strategy to molecular anticancer therapy tricks malignant cells
Subtitle: New drug prevents tumour growth by inhibiting the nucleotide sanitizing enzyme MTH1
(Vienna, 2 April 2014) A ground-breaking study spearheaded by Scientific Director Giulio Superti-Furga at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences shows that fast-growing cancer cells are sensitive towards imbalances in the metabolism of nucleotides, the building blocks of DNA. This vulnerability can be exploited for a radically novel antitumour therapeutic approach. Not only did the researchers from Vienna, in a joint effort with colleagues from Oxford and Stockholm, identify the enzyme MTH1 as an Achilles heel of malignant tumour cells, but also, in a wonderful twist of fate, they discovered the chemical mirror image of an existing anti-cancer drug called crizotinib to be an efficient inhibitor of MTH1 activity. The study was published in advance online by the renowned scientific journal Nature on 2nd April 2014.

The importance of MTH1 starts at replication forks, where DNA molecules are duplicated by template-guided serial assembly of nucleotide building blocks. It is crucial that these individual building blocks are intact in order to prevent DNA damage and defects such as mutations. MTH1 is a nucleotide sanitizing enzyme that removes damaged nucleotides. Unlike in normal cells where this feature is not required because nucleotides are intact, cancer cells suffer from oxidative stress which leads to the damage of nucleotides and thus, MTH1 is indispensable for preserving genome integrity by preventing the incorporation of damaged DNA building blocks. Clearance of those building blocks damaged by oxidation allows cancer cells to divide and proliferate infinitely. Upon disruption of this protective mechanism by an MTH1 inhibitor, oxidized nucleotides are incorporated into newly synthesized DNA. The damaged DNA strands break and the cancer cell dies.

Selectively toxic anticancer agent identified in model study

In the present study, the researchers at CeMM successfully applied a mass spectrometry-based analytical technique (chemical proteomics) to elucidate the mode of action of a small molecule that was found to selectively target cancer cells. When examining an incidentally impure laboratory-grade batch of the known and approved protein kinase inhibitor and anticancer drug crizotinib, the researchers discovered an interesting activity that could not be explained by the known properties of this compound. Further investigations revealed that the impurity was the chemical mirror image (enantiomer) of crizotinib, which is identical to crizotinib but varies slightly in its three-dimensional structure. Strikingly, this stereoisomer was found to be a highly specific inhibitor of the MTH1 enzyme. This entirely unexpected activity distinguishes the so far unexplored enantiomer completely from the clinically used drug and offers hope for a novel therapeutic strategy:
According to this concept, a specific MTH1 inhibitor should be able to exploit the MTH1 dependency present in cancer cells to induce cell death. While the development of new therapeutic drugs is frequently

associated with complications and years of optimization experiments, which means that it often takes decades before patients can benefit from the initial discovery, this Viennese study could significantly accelerate the drug development process. Giulio Superti-Furga, principal investigator and leader of the study: "It's really a rare stroke of luck that we have not only found a previously unknown sore spot of aggressive cancers, but that by chance we simultaneously identified a chemical substance that is a mirror image of one of the best new anticancer agents in the clinic. Double Jackpot!" Kilian Huber, first author of the study adds: "This very high similarity to an already approved and clinically evaluated drug may open the opportunity to quickly test our findings in the clinic for the benefit of the patients."

In collaboration with Stefan Knapp (University of Oxford), Thomas Helleday (Karolinska Institute, Stockholm) and their teams, and with support of other researchers at CeMM, including Joanna Loizou, Keiryn Bennett and Jacques Colinge, the authors were already able to demonstrate that MTH1-targeting drugs selectively induce DNA damage in cancer cells and impair growth of difficult to treat, aggressive human tumours in model systems. As a target, MTH1 could represent a breakthrough in cancer therapy.

"This paper represents a creative and original application of pharmacology, signal transduction biochemistry, and structural biology employed to make inroads into the therapy of cancers that have to date resisted effective treatment.", commented Robert A. Weinberg, founding member of the Whitehead Institute for Biomedical Research, Professor of Biology at MIT in Cambridge, USA. Professor Weinberg discovered the first human oncogene RAS and the first tumour suppressor gene RB, and in fact, was the first proponent of MTH1 as a potentially novel and attractive target in oncology. This idea is also supported by a study, which was conducted in parallel by Thomas Helleday at the Karolinska Institute in Stockholm and published as an article back-to-back in the same issue of *Nature*.

CeMM is Austria's first independent basic research institute in molecular medicine that was established by the Austrian Academy of Sciences in the 21st century with the specific intent to study innovative diagnostic and therapeutic approaches. CeMM is located amidst the campus of one of the largest university hospitals in Europe. The track record is considerable: Just last December, CeMM researchers published the discovery of a new gene which is responsible for many myeloproliferative neoplasms, in the leading medical journal The New England Journal of Medicine. This discovery is already making a global contribution to a significantly more comprehensive diagnosis of this disease group and thus for the direct benefit of patients.

Giulio Superti-Furga: „The elucidation of the mode of action of drugs is one of the greatest strengths of CeMM, whose expertise and technology assets are world-class in this area. Without the support of public funding for basic research this first breakthrough would not have been possible, and therefore we are grateful to the taxpayers. However, the next challenges will be costly, and it would be a shame if we had to give up at this point in time. Therefore, we depend on a solid funding base and are, in addition, also seeking additional sponsors, philanthropists, organizations, and partners, who share our vision of a fight against diseases through innovative research, and who are interested in a continuation of our research."

Publication:

Kilian V. M. Huber, Eidarus Salah, Branka Radic, Manuela Gridling, Jonathan M. Elkins, Alexey Stukalov, Ann-Sofie Jemth, Camilla Gokturk, Kumar Sanjiv, Kia Strömberg, Therese Pham, Ulrika Warpman Berglund, Jacques Colinge, Keiryn L. Bennett, Joanna I. Loizou, Thomas Helleday, Stefan Knapp & Giulio Superti-

Furga. Stereospecific targeting of MTH1 by (S)-crizotinib as an anticancer strategy. Nature, doi:10.1038/nature13194.

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