Mapping of protein inhibitors facilitates development of tailor-made anticancer agents

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(PhysOrg.com) -- A team of researchers at Karolinska Institutet in Sweden has generated a map over the effects of small drug-like molecules on PARP1 and other similar proteins in the body. This map may explain the mechanism behind putative side effects of the so-called PARP inhibitors, and can play an important role in the development of novel tailor-made cancer drugs. The study is presented in the journal *Nature Biotechnology*, and will hopefully contribute to new cancer therapies with fewer detrimental side effects.

PARP1 is a protein with enzymatic activity that governs repair of DNA damage in our cells. In the past decade, PARP1 has been in the focus for a large number of industrial drug development projects, primarily targeting breast and ovarian cancers. More than 50 clinical studies have been initiated around the world.

In the current study, the researchers at Karolinska Institutet have tested the effects of small drug-like molecules – inhibitors – on PARP1 and other enzymes of the same class. The effects of 180 substances on 13 different human PARP enzymes were studied. Many of the drugs that are currently being tested in clinical studies were part of the survey.

“Our results give us a map over the effects of a number of known but also less well characterized drug-like compounds on different PARP enzymes”, says Herwig Schüler, who headed the study at the Department of Medical Biochemistry and Biophysics. “Studying the crossreactivity of less well characterized compounds on different PARP enzymes is

especially interesting, since it can give clues to the interpretation of clinical side effects."

The chemical interaction map was complemented with high-resolution structural information, showing at atomic detail how inhibitors bind to these PARP enzymes. Together, the results give unique insights into specificity and cross-reactivity of PARP inhibitors. This in turn will be an important hallmark toward development of selective PARP inhibitors – tailor-made substances that can inhibit one PARP enzyme while leaving the others unaffected

This project builds upon a long-standing industry collaboration that Karolinska Institutet has participated in within the Structural Genomics Consortium 2005-2010. The study published in Nature Biotechnology is the result of collaboration between the research group at KI, the University of Perugia (Italy), Actar AB, and GE Healthcare.

More information: "Family-wide chemical profiling and structural analysis of PARP and tankyrase inhibitors," Elisabet Wahlberg, Tobias Karlberg, Ekaterina Kouznetsova, Natalia Markova, Antonio Macchiarulo, Ann-Gerd Thorsell, Ewa Pol, Åsa Frostell, Torun Ekblad, Delal Öncü, Björn Kull, Graeme Michael Robertson, Roberto Pellicciari, Herwig Schüler & Johan Weigelt, *Nature Biotechnology*, Advance Online Publication 19 February 2012, doi: 10.1038/nbt.2121

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