The path to personalized cancer treatment

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In the largest study of its kind, researchers have profiled genetic changes in cancer with drug sensitivity in order to develop a personalised approach to cancer treatments. The study is published in *Nature* on Thursday 29 March 2012.

The team uncovered hundreds of associations between mutations in cancer genes and sensitivity to anticancer drugs. One of the key responses the team found was that cells from a childhood bone cancer, Ewing's sarcoma, respond to a drug that is currently used in the treatment of breast and ovarian cancers. The lowered toxicity of this treatment may mean it is a safer alternative therapy for children and young adults with this aggressive cancer.

There is an intimate relationship between the way a drug works and the genetic changes present in cancers. This study found that sensitivity to most anti-cancer drugs is influenced by mutations in cancer genes and establishes the utility of using large-scale studies to identify these associations and build them into improved patient treatment.

"Our key focus is to find how to use cancer therapeutics in the most effective way by correctly targeting patients that are most likely to respond to a specific therapy," explains Dr Mathew Garnett, first author from the Wellcome Trust Sanger Institute. "We studied how genetic changes in a panel of >600 cancer cell lines effects responses to 130 anti-cancer drugs, making it the largest study of this type to date."

The team identified biological markers of drug sensitivity to a broad

range of cancer drugs. Most of the cancer genes analysed, including those that are not known directs targets of the drugs tested, were associated with either sensitivity or resistance to at least one of the drugs analysed.

"Our research has taken us down unknown paths to find associations that are completely novel," says Dr Cyril Benes, senior author from Massachusetts General Hospital Cancer Centre. "We have identified hundreds of associations, many of which we still don't fully understand. We identified a novel indication for the use of PARP inhibitors, anti-cancer drugs currently used to treat breast and ovarian cancers, for the treatment of Ewing's sarcoma."

Ewing's sarcoma is a cancer of children and young adults with a 15% five-year survival rate in patients where the cancer has spread or they have relapsed after chemotherapy. The use of PARP inhibitors could represent a new treatment option for Ewing's sarcoma patients and these compounds will now be tested in clinical trials to assess their therapeutic benefit.

"Advances in next-generation sequencing technologies are already being translated into the large-scale detection of cancer gene mutations in the clinic," says Dr Ultan McDermott, senior author from the Wellcome Trust Sanger Institute. "There is a compelling need to identify, in a systematic fashion, whether observed mutations affect the likelihood of a patient's response to a given drug treatment. We have therefore developed a unique online open-access resource for the research and medical community that can be used to optimize the clinical application of cancer drugs as well as the design of clinical trials of investigational compounds being developed as treatments."

The team hopes their open-access database will be an important resource for the cancer research community and which will ultimately lead to

improved treatments for patients. This research program is a unique Wellcome Trust funded 5-year collaboration between The Cancer Genome Project at the Wellcome Trust Sanger Institute and the Center for Molecular Therapeutics, Massachusetts General Hospital Cancer Center.

"Our work is helping to move cancer therapeutics away from the conventional tissue-based treatment to a more molecular-based treatment," says Professor Daniel Haber, senior author from Massachusetts General Hospital Cancer Centre. "The next steps for this collaborative project are to evaluate some of the key findings using tumour samples and test new candidate therapeutic strategies in clinical trials so we can hopefully improve the way we treat cancer patients. We are continuing our screening effort, in particular using drug combinations to discover innovative and better therapeutic options."

More information: Garnett et al 'Systematic identification of genomicmarkers of drug sensitivity in cancer cells' Published in *Nature* doi:10.1038/nature11005

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