Predictive biomarker discovery through the parallel integration of clinical trial and functional genomics datasets

The EU multi-disciplinary personalised RNA interference to enhance the delivery of individualised chemotherapeutics and targeted therapies (PREDICT) consortium has recently initiated a framework to accelerate the development of predictive biomarkers of individual patient response to anti-cancer agents. The consortium focuses on the identification of reliable predictive biomarkers to approved agents with anti-angiogenic activity for which no reliable predictive biomarkers exist: sunitinib, a multi-targeted tyrosine kinase inhibitor and everolimus, a mammalian target of rapamycin (mTOR) pathway inhibitor. Through the analysis of tumour tissue derived from pre-operative renal cell carcinoma (RCC) clinical trials, the PREDICT consortium will use established and novel methods to integrate comprehensive tumour-derived genomic data with personalised tumour-derived shRNA and high throughput siRNA screens to identify and validate functionally important genomic or transcriptomic predictive biomarkers of individual drug response in patients. PREDICT’s approach to predictive biomarker discovery differs from conventional associative learning approaches, which can be susceptible to the detection of chance associations that lead to overestimation of true clinical accuracy. These methods will identify molecular pathways important for survival and growth of RCC cells and particular targets suitable for therapeutic development. Importantly, our results may enable individualised treatment of RCC, reducing ineffective therapy in drug resistant disease, leading to improved quality of life and higher cost efficiency, which in turn should broaden patient access to beneficial therapeutics, thereby enhancing clinical outcome and cancer survival. The consortium will also establish and consolidate a European network providing the technological and clinical platform for large-scale functional genomic biomarker discovery. Here we review our current understanding of molecular mechanisms driving resistance to anti-angiogenesis agents, the current limitations of laboratory and clinical trial strategies and how the PREDICT consortium will endeavour to identify a new generation of predictive biomarkers.

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