Towards personalized cancer medicine: Molecular therapeutics and biomarkers

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The last several years have seen remarkable progress in our comprehension of the molecular basis of cancer and in the development of targeted therapies designed to exploit this knowledge. Proof of concept for drugging the cancer genome, and especially the kinome, has been established with approved agents like trastuzumab, imatinib, gefitinib, erlotinib, sorafenib and others. However, alongside some real successes and tremendous opportunities there are also considerable challenges. On the one hand, we have increasing knowledge of the genetic and molecular causation of cancer. On the other hand, the attrition rate for cancer drugs in the clinic remains high, failure often occurs very late in development, and survival rates in the major solid tumours have not been extended dramatically. Furthermore, an age-old problem with traditional cancer therapy – that of the development of drug resistance – is still an issue with the new generation of molecular cancer therapeutics. In this presentation I will describe the opportunities and challenges in the discovery of molecularly targeted small molecule cancer drugs. In particular, I will stress the importance of integrating three key themes: targets**,** technologies and treatments. Firstly, the molecular targets of contemporary drug discovery projects now reflect our increasing, though still incomplete, elucidation of the genes and pathways that are responsible for the initiation and malignant progression of cancer. High-throughput technologies, including gene expression profiling and genome resequencing methods, are accelerating the rate of cancer gene discovery, but also revealing a high level of complexity. We now know that there are large numbers of low abundance driver gene mutations in many cancers and that combinations of many mutant genes exist within individual cancers. A method for assessing potential new molecular targets will be presented. Secondly, the integrated application of a range of powerful drug discovery technologies, including genomics, high-throughput, fragment, computational and other compound screening methodologies, together with chemical and structural biology, will be illustrated. Thirdly, the new treatments that have been emerging over the last decade are beginning to reflect the success of the new mechanism-based molecular therapeutics that act on cancer-causing targets and also that have benefited from technological innovations in drug design. In order to develop innovative new drugs effectively and to maximize their success, biomarkers are essential. These can be used to select appropriate patients, to monitor the effects of treatment and to develop the best schedule of administration. Important decisions can be taken based on the use of biomarkers in a 'pharmacologic audit trail.' Future challenges for drugging the cancer genome will be highlighted, including drug resistance and the development of effective drug combinations. Examples will be given from our work on the design and development of inhibitors of the PI3 kinase – AKT pathway and of the molecular chaperone HSP90. The use of invasive molecular biomarkers and of minimally invasive imaging endpoints will be illustrated.