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Genomics and proteomics in drug development

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Drug discovery and development has always been facilitated by technological advances. Here I will describe how we have used genomic and proteomic technology in tandem with other methodologies such as high throughput screening (HTS), combinatorial chemistry, x-ray crystallography, high throughput ADME/pharmacokinetics and molecularly characterized animal models to accelerate and enlighten the development of new molecular therapeutics in the Centre. Empowered by the completion of the Human Genome Sequence, genomic and proteomic technologies are increasingly important for target discovery and validation. High throughput sequencing has identified mutations in kinases in cancer cells including *BRAF* and the *PI3KCA* gene that encodes the p110α catalytic subunit of PI3 kinase. This has helped to validate both kinases as drug targets and HTS has been used to identify inhibitors of both (eg see Raynaud et al Pharmacological properties and in vitro and in vivo anti-tumour activities of the potent and selective PI3 kinase inhibitor PI103, abstract 414a, this meeting). Gene expression microarray profiling (GEMP) is also widely used to identify potential drug targets, eg histone methyl transferase (HMT) EZH2. HMTs are important potential drug targets and we are now screening for and developing inhibitors of these and other chromatin modifying enzymes. We are also using GEMP extensively to find genes that show altered expression in response to new molecular therapeutics and precursors thereof. This provides a genome-wide view of molecular mechanisms of drug action, including both on-target and off-target effects. Also, we have used GEMP to identify molecular biomarkers to demonstrate proof of concept for the proposed mechanism, as well as optimising drug dose and schedule. Furthermore, GEMP can provide new insights into the mechanism of action of well established drugs, as shown by our demonstration that 5-fluorouracil decreases the expression of c-*myc* regulated genes in tumour tissue of patients with advanced rectal cancer (Clarke et al, Molecular pharmacology of cancer therapy in human colorectal cancer by gene expression profiling, Cancer Research 63 6855–6863 2003). Proteomic profiling provides complementary protein expression data. We have used this approach to identify proteins that show altered expression following treatment with the Hsp90 molecular chaperone inhibitors 17AAG, including increased expression of the Hsp90 ATPase activating protein Aha1 (Paneretou et al Activation of the ATPase activity of Hsp90 by the stress regulated co-chaperone Aha1 Molecular Cell 10 1307–1318 2002). The results of a detailed comparative study of GEMP and proteomic profiling of cancer cells following treatment with 17AAG will be described. This provides new insights into mechanism of action, as well as potential novel molecular biomarkers. *Supported by Cancer Research UK*.

7 INVITED

Mapping and targeting proteins at the endothelial cell surface and its caveolae for improved penetration, imaging and radiodestruction of solid tumors

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The overwhelming molecular complexity of each tissue and the in vivo inaccessibility of most cells within a tissue greatly limit the abilities of global genomic and proteomic analysis to discover and validate key targets for directing tissue-specific delivery of many therapies and imaging agents in vivo. A novel hypothesis-driven systems biology approach is described that reduces data complexity to a small subset of proteins induced at the critical tissue–blood interface inherently accessible to antibodies injected intravenously. We use subcellular fractionation, mass spectrometry, *in silico* subtraction, and bioinformatics to unmask, from >100,000 of tumor proteins, <50 proteins apparently induced in solid tumors at the endothelial cell surface and its caveolae. Expression profiling and γ-scintigraphic imaging with antibodies validates several of these proteins as specifically exposed in vivo to permit selective immunotargeting and imaging of solid tumors in 1 hour. Targeted radio-immunotherapy destroys various solid tumors to increase animal survival and induce complete remissions. These accessible targets are expressed on the blood vessels of not only multiple rodent tumor models but also human solid tumors including primary and metastatic lesions of breast, kidney, liver, prostate, lung, and brain. Many of our new targets were discovered to be concentrated endothelial caveolae which are specialized plasmalemmal invaginations that can transcytose their molecular cargo to theoretically provide a means for transporting imaging agents, drugs, and gene vectors across the normally restrictive endothelial cell barriers to reach underlying tissue cells, the usual desired targets of pharmacotherapies. Compared to antibodies to endothelial cell surface proteins not found in caveolae, antibodies targeting caveolae permit not only more rapid and specific targeting and imaging but also selective transendothelial transport within minutes of intravenous injection. This facilitates much greater penetration into and accumulation throughout solid tumors. This unexpected speed of vascular targeting and caveolae-mediated transcytosis in vivo further encourages utility in tissue-specific drug and gene delivery in vivo. This new integrated, multi-step analytical strategy can map tissue- and disease-modulated expression of proteins at the endothelial cell surface and its caveolae to reveal promising novel intravenously accessible cancer targets useful for imaging and therapy.