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Summary of the Scientific Session on Personalised Medicine
Paris, 12 November 2008

In introducing the session, Hubert Blum (University of Freiburg) observed that the goal for personalised medicine – the better targeting of interventions to well-defined subgroups of patients, to reduce uncertainty in outcomes – is relevant to much of biomedical R&D, covering pathogenesis, prognosis, diagnosis, therapy and prevention. The basic concepts to be exemplified by clinical applications in this session were: (i) Molecular genetics – the study of disease-related genes; (ii) Molecular imaging – combining metabolic imaging with anatomical information; and (iii) Pharmacogenetics – the study of genes related to drug disposition and response.

Much of the session focused on malignancies, a continuing major health issue worldwide. Despite recent advances in the understanding of molecular oncogenesis and in diagnosis, patient survival is still unsatisfactory in many areas. Prognosis is often poor because of the advances stage of the disease at the time of diagnosis and the limited efficacy and specificity of the available therapeutic strategies – these are the challenges for personalised medicine.

Luigi Frati ("Sapienza" University of Rome, for Isabella Screpanti) described molecular approaches to haematological malignancies, drawing on three case studies to illustrate the concept of genomic instability (the accumulation of genomic errors) in carcinogenesis:

(i) Chronic Myeloid Leukaemia – where the defect is primarily ascribed to BCL-ABL (tyrosine kinase), an ATP binding site abnormality. CML usually progresses to acute leukaemia within 3-5 years but survival (and quality of life) has been significantly improved by the introduction of Gleevec, the first molecular-targeted drug for cancer. The response to Gleevec is predicted by molecular identification of the mutation site and therapy is now routinely accompanied by testing for the mutation.

(ii) Acute Myeloid Leukaemia – is caused by two classes of cooperating mutation, BCR-ABL, treated by Gleevec, plus AML1/ETO or related mutation , treated by all-trans retinoic acid.

(iii) T-Cell Acute Leukaemia (T-ALL) – associated with defects in the Notch Receptor family involved in T-Cell development, possibly together with other mutations. There is no current treatment but development of personalised therapy might include gamma-secretase inhibition plus NK-KB inhibition plus Notch 3 regulation.

In considering the obstacles to wider adoption of molecular therapy, apart from the challenges for drug and diagnostic discovery and development, one current problem is the cost of testing. This cost is chargeable to the hospital budget whereas the economic gains (for example, return of patient to employment) accrue outside the health system. In discussion, it was noted that while there are methodological challenges in conducting more detailed health economic assessment to characterise cost-benefit, the bigger, political, challenge lies in convincing decision-makers to take a longer-term view of cost-benefit. Furthermore, while the described case studies provided convincing evidence of the potential benefits of targeted therapy, for many of the common epithelial tumours a single genetic defect is unlikely and the existence of multiple targets complicates the targeted approach.

Hubert Blum reviewed the prospects for targeted therapy for non-haematological malignancies. Proof of principle, that molecular diagnosis has clinical impact – the concept of molecular tumour staging – was provided by studies on squamous cell carcinoma where tissue samples demonstrating the p53 tumour gene signature, even though histologically negative, were found to be associated with a higher incidence of tumour recurrence.

More recently, studies of colorectal cancer have assessed markers indicative of the clinical progression from normal epithelium to carcinoma, an accumulation of genetic alterations that may take up to 15 years. For example, the gene signature MSI (microsatellite instability) has been found useful to identify poor prognosis in individual patients and the response to adjuvant chemotherapy. In addition to identifying those who can benefit, the inclusion of molecular information in clinical care to determine the use of chemotherapy helps to save costs and spare side effects for those who will not benefit. Other examples of personalised medicine, where there is increasing evidence that defined gene signatures of the individual enable prediction of the response to targeted as well as less selective chemotherapy, include:

(i) CRC therapy, where individual patient over-expression of Topoisomerase 1 enzyme predicts the response to Irinotecan (alone or in combination with 5-FU).

(ii) Breast cancer "186 Gene Invasiveness Gene Signature" – survival is better if the signature is negative.

(iii) NSCLC "5 gene signature" – also a good marker for survival and response to treatment.

Further examples can be drawn from the tyrosine kinase signalling pathways involved in cancer biology in multiple ways (tumour angiogenesis, proliferation, invasion and metastases). These pathways can be inhibited by blocking growth factor extra-cellular receptor binding (by monoclonal antibodies, mabs) or by inhibiting tyrosine kinase, the intracellular step in signal transduction (by small molecule inhibitors, nibs). However, many of these therapeutic agents are expensive and it is important to ascertain clinical

benefit as well as biochemical effect. One recent study using the targeted agent Cetuximab in advanced colorectal cancer found that survival was improved only in the subgroup with wild-type K-ras (whereas there was no difference in survival on standard care whether or not the tumour had the K-ras mutation).

In summary, molecular information has proved useful in diagnostic accuracy (improved staging) and in optimising, targeting, therapeutic efficacy. In developing the field further, much can be learnt from best practice in standardising the process of application from genomic signature to personalised therapy; a process that encompasses initial identification and validation of the signature, expansion of pre-clinical and clinical studies with algorithms to cover clinical characterisation, molecular imaging and proteomics in addition to genomics. Professor Blum emphasised that it is also very important not to focus exclusively on the genetic determinants. For example, clinical experience shows that the level of physical activity has major impact on disease-free survival.

Other notes of caution were introduced during discussion. Many of the gene association studies were done retrospectively using relatively small subgroups and it is necessary to replicate in prospective studies, randomised according to the mutation. Furthermore, it is conceivable that survival benefits may be wrongly interpreted to be proof of causal involvement of a particular biomarker when that marker is actually a surrogate for some other aspect of tumour biology.

Roland Hustinx (University of Liege) described the capability of PET imaging, non-invasively and reproducibly, to evaluate molecular processes that characterise malignant tumour cells. Hybrid PET/CT devices now provide metabolic and anatomic information from a single imaging session.

The criteria for response to therapy using conventional tumour imaging methods are based on lesion size, that is morphological parameters. By contrast, molecular imaging, most commonly using FDG (18F-fluoro-2-deoxyglucose) provides a measure of the volume of viable tumour cells. Metabolic changes precede morphological changes, for example as demonstrated by the pivotal study on GI stroma tumour treated with Gleevec. There are now many studies of tumour response assessment using FDG PET; two examples illustrate the increasing value that can be obtained:

(i) Oesophageal cancer – an initial observational study, demonstrating that an early PET assessment of response to chemotherapy predicted clinical response, was used to inform an interventional study guiding treatment, where further chemotherapy or surgery was used according to the PET measure of the initial response to chemotherapy.

(ii) High-grade lymphomas and Hodgkin's disease – where imaging has become central in the evaluation of treatment and response criteria were recently revised based on metabolic findings, compatible with the clinically-derived Independent Prognostic Index.

Other PET ligands are being investigated to develop the potential of imaging. There is a growing body of pre-clinical and clinical evidence to support the value of 3-deoxy-3-18F-fluorothymidine as a measure of thymidine kinase activity and, hence, tumour cell proliferation. Other processes potentially amenable to PET imaging include membrane synthesis (with choline analogues), amino acid transport (fluorotyrosine), angiogenesis, hypoxia and bone turnover. In summary FDG is likely to remain the most common tracer in the clinical setting but other tracers offer specific applications, supporting targeted clinical care. The current use of PET imaging is largely empirical and it is vital to progress large, multi-centre assessment protocols to codify and standardise practice.
In discussion, it was agreed that FDG PET has many additional applications outside oncology, for example in evaluating inflammation and infection. But the cost and reimbursement status of imaging may limit wider implementation.

Variation in drug disposition and response in patients is a major concern for many drugs and many disease areas. Matthias Schwab (Stuttgart) considered the promise and future perspectives for pharmacogenomics in the context of an increasing number of reported severe adverse drug reactions, the imperative to select responders to drug therapy (where, currently, perhaps half of patients do not respond in many disease areas) and the concomitant need to improve success rates in pharmaceutical R&D pipelines.

Significant progress has been made in elucidating the genomic determinants of drug efficacy and toxicity; regulatory authorities have approved a number of companion tests to optimise therapy, for efficacy, for example Herceptin (HER 2) and Gleevec (BCR-ABL) and for safety, for example warfarin (CyP 450 2C9) and Abacavir (HLA B*5701). The particular promise of pharmacogenomics for drugs with a relatively narrow therapeutic window is exemplified by several recent case studies:

(i) Haemotoxicity of 6-mercaptopurine (6 MP) with thiopurine methyltransferase (TPMT) deficiency in children with acute lymphoblastic leukaemia. Treatment can now be individualised according to measured TPMT polymorphism with the 6 MP dose titrated to deliver the required systemic exposure, minimising toxicity.

(ii) The dose of Efavirenz in HIV type 1-infected individuals can be reduced according to CyP 450 2B6 polymorphism to achieve consistent pharmacokinetics and thereby reduce CNS symptoms.

(iii) Screening for HLA B*5701 before Abacavir treatment of HIV can avoid the hypersensitivity response – further research is needed to understand the mechanism.

Advances in mass spectrometry-based assays are providing new, fast and economic, options for genotyping in clinical practice. But it will often be necessary to take a more comprehensive approach, considering genetic polymorphisms in entire pathways, rather than assuming a single genetic defect and also taking account of the impact of epigenetics (in particular, DNA methylation). Genome Wide Association Studies (GWAS) have recently become important in detecting new genetic determinants. Although much of the work, for example by the Wellcome Trust Case Control Consortium, has focused on

genetic association with disease rather than with drug responsiveness, there are recent examples of the latter. For instance, the GWAS identification of the role of SLC01B1 (liver active uptake transporter) in determining circulating statin level and, hence, the induction of myopathy, is a key observation in understanding and managing this comparatively common clinical problem.

However, in many cases of gene association, whether with disease or drug response, there is a significant gap in knowledge between the observed association and the necessary biological insight that will underpin clinical application. Thus, there is likely to be complementary value in other 'omics approaches, in particular transcriptomics and proteomics, to assess the contribution of putative genes for predicting drug response. Furthermore, development of systems biology networks may be expected to increase understanding of pharmacogenomics.

Discussion reiterated the importance of other issues that may be rate-limiting for the further implementation of pharmacogenomics. For example, the concern about the cost of tests for health systems is compounded if the test has uncertain clinical utility. In this fast-moving area, what level of clinical validation should test manufacturers be obliged to provide?

Robin Fears, 18.11.2008