Tuesday, 16 November 2010 13:15–14:00

Michel Clavel lecture

1 INVITED

Novel molecular imaging for early drug development

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A major challenge in cancer drug development is early selection of most promising drug candidate(s) for a specific target and to identify the patient (sub)populations most likely to benefit from such a drug. Therefore there is a need for techniques that can rapidly and precisely elucidate the pharmacokinetic and pharmacodynamic profile of new drugs in patients, and for (predictive) biomarkers of antitumor drug efficacy. Molecular imaging can potentially fulfill all these tasks and can be performed with several modalities, including magnetic resonance imaging, optical imaging, and radionuclide imaging with positron emission tomography (PET) or single photon emission computed tomography (SPECT). Most clinical molecular imaging data are gathered on the visualization of general processes, such as glucose metabolism and DNA synthesis with [^{18}F]fluorodeoxyglucose (FDG) and [^{18}F]fluoro-L-thymidine (FLT) PET-imaging, respectively.
Molecular imaging can also visualize tumor cell characteristics that are relevant for treatment, like hormone receptors, growth factors and growth factor receptors. It potentially provides serial non-invasive information about the status of these characteristics within the tumor and across lesions in the entire body. PET imaging of the estrogen receptor (ER) with ^{18}F-fluoro-17-β-estradiol (FES) proved feasible in breast cancer patients, whereas the androgen receptor (AR) was successfully imaged with ^{18}F-fluoro-5α-dihydrotestosterone (FDHT) in prostate cancer patients. FDHT-PET showed that MDV3100, an AR antagonist that blocks androgens from binding to the AR, substantially reduced FDHT binding (Scher et al, Lancet 2010).
We imaged HER2 in metastatic breast cancer patients with ^{111}In-trastuzumab SPECT and ^{89}Zr-trastuzumab PET. ^{89}Zr-trastuzumab showed quantifiable tumor uptake and provided new insights in trastuzumab pharmacokinetics. ^{111}In-bevacizumab SPECT and ^{89}Zr-bevacizumab PET visualized VEGF in lesions of several tumor types. SPECT imaging of the TRAIL-R1 with ^{111}In-mapatumumab showed variable tumor uptake between patients.
HER2 and VEGF-PET proved an excellent read out of downregulation of HER2 and VEGF by HSP90 inhibitors and of VEGF by mTOR inhibitors in xenograft mouse models. Preclinical VEGF imaging provided insights in the heterogeneous vascular tumor responses to sunitinib. These observations are now tested in clinical trials. Preclinical HER2-PET imaging showed decreased tumor tracer uptake after lapatinib treatment, due to inhibition of tracer internalization.
Thus, new molecular imaging can identify the levels of a specific tumor target across the entire body over time, can provide new mechanistic and pharmacological insight and can contribute to development and selection of drug candidates and distinguish patients most likely to benefit from the treatment.

Tuesday, 16 November 2010 14:00–14:45

Keynote lecture

2 INVITED

Resistance to targeted therapy: mechanisms and therapeutic implications

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Kinase inhibitors have emerged as effective clinical therapies for cancer patients. These therapies are most efficacious against cancers that harbor genomic alterations (mutation, translocation or amplification) in the target kinase. Compelling clinical examples to date include ABL kinase inhibitors (imatinib, nilotinib, dasatinib) in chronic myeoloid leukemia and gastrointestinal stromal tumors, EGFR kinase inhibitors (gefitinib & erlotinib) in EGFR mutant lung cancer, ALK inhibitors in ALK translocated cancers and BRAF inhibitors in BRAF V600E mutant melanoma. However, despite initial dramatic clinical responses to these agents, all patients ultimately develop acquired resistance to kinase inhibitors. An understanding of the mechanism(s) that underlie acquired resistance is critical for the development of new and novel treatment strategies.
Two main mechanisms of acquired resistance have been identified to date: secondary mutations in the kinase itself and the activation of bypass signaling pathways. Secondary kinase mutations can result in either steric hindrance (for example in ABL; imatinib resistance) or changes in ATP affinity (gefitinib/erlotinib resistance in EGFR) or both, resulting in clinical drug resistance. In contrast, in other resistance mechanism, the kinase inhibitor is still effective against its target but a bypass signaling pathway becomes activated (for example MET signaling in gefitinib/erlotinib resistance) and independently activates critical pro-survival and proliferative signaling pathways.
The combination of genetic, biochemical and structural studies of acquired resistance mechanisms has resulted in novel therapeutic strategies − many of which are currently under clinical development. For example second and third generation ABL kinase inhibitors, effective against imatinib resistance mutations including T315I, have been developed and are undergoing various stages of clinical evaluation. For gefitinib/erlotinib resistant EGFR mutant NSCLC, covalent (irreversible) EGFR inhibitors (able to overcome increase in ATP affinity) and T790M mutant specific inhibitors are undergoing clinical and pre-clinical evaluation. Analogously combination therapies (such as the combination of EGFR and MET inhibitors) are being developed clinically against drug resistant cancers where a bypass signaling mechanism has become activated.
Several challenges lie ahead in combating drug resistant cancers. As many resistance mechanisms often co-exist, targeting just one may not be clinically sufficient thus prompting the need for combination therapeutic strategies. However, the clinical development of combinations of kinase inhibitors is likely to be more complicated and potentially more toxic. This may thus require the identification of new clinical strategies an approaches on how to best combine two or more kinase inhibitors to effectively combat drug resistant cancers. Finally it will be important to clinically determine whether adding or changing to an agent targeting a specific drug resistance mechanisms should occur at the time of development of clinical drug resistance or prior to its emergence.

Tuesday, 16 November 2010 15:15–17:00

PLENARY SESSION 1

Tumour stem cells: At the crossroads?

3 INVITED

Are cancer stem cells relevant?

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The cellular and molecular basis for the heterogeneity that exists within the individual cells that make up a tumour is not well understood. The cancer stem cell (CSC) model postulates that heterogeneity arises because the tumour is organized as a cellular hierarchy sustained by a CSC at the apex. By employing the principles of stem cell biology, first worked out in hematopoiesis, of clonal assays and prospective cell purification, there is solid evidence that human AML follows a CSC model. We also showed that human colon cancer follows this paradigm.
The CSC in AML and colon cancer possesses distinct properties from non-CSC and some of which render CSC resistant to therapy. In AML we have identified genetic signatures that define the CSC state and found they have more significant prognostic power compared to genetic analysis of the bulk tumor establishing that CSC are relevant not only in experimental xenografts, but clinically as well. Moreover, the CSC from AML and colon cancer are not functionally homogeneous. By clonal tracking we have found that individual CSC possess differing repopulation potential due to variation in their self-renewal capacity. Individual CSC also show variation in response to chemotherapy. Moreover, there was clear evidence for the existence of quiescent or slowly cycling clones in colon cancer that became activated upon in vivo chemotherapy. Thus these data predict that the biological properties of individual CSC are determinants of tumor response providing new avenues for gaining mechanistic insights and new therapeutic directions.