

## Monday, 21 September 2009

### Opening Session (Mon, 21 Sep, 08:55–10:55)

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INVITED

#### Drug discovery in the p53 pathway

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Small molecules that activate the transcriptional function of wild type p53 have proved active as anti-cancer drugs in preclinical models and are now entering clinical trial. The complexity of the upstream p53 signaling pathway offers many targets for the development of such activators and the action of Mdm2 inhibitors, kinase inhibitors, sirtuin inhibitors and low doses of actinomycin D will be described among other examples. The possibility of using combinations of molecules will also be analyzed as will the issues of toxicity and resistance expected from these types of molecules. One concern is that the activation of p53 might exert some specific harmful effect on normal tissues and another is that treatment with p53 activators will select for tumor cells in the population that have mutant p53. What can be done in those cases where p53 is mutant? One approach is the search for molecules that re-activate mutant p53 proteins, though some have likened this to trying to unscramble eggs, recent discoveries in protein dynamic and protein folding pathways have been very exciting. Recent approaches to developing molecules that will chaperone mutant p53's to fold in the active state will be described with reference to recent crystallographic analysis.

A second conceptual approach to exploiting the frequent loss of p53 function in tumors is that of synthetic lethality. Might p53 mutant tumors be more susceptible to inhibitors of DNA repair as has been seen for BRCA1 mutant tumors for example? Finally the concept of using p53 activating molecules as chemo-protectives has been proposed. In this concept normal cells are arrested temporarily in G1 by p53 activators such as the Mdm2 inhibitor Nutlin. These cells are thus protected from cytotoxic drugs active at G2/M such as taxol. Cells that lack p53 and are not therefore arrested by Nutlin would retain their sensitivity. In this model then the therapeutic index of such cytotoxic drugs for p53 mutant tumors would be enhanced by protection of normal tissues.

#### References

Klein C and Vassilev L T. *B J Cancer* 2004 91:1415.  
Dey A, Verma CS and Lane DP. *BJ Cancer* 2008 98:4.

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INVITED

#### New targeted treatments in oncology: the mammoths and the foxes

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Taxotère was the last cytotoxic molecule of the XXth century closing forty years of research with a simple ambition to inhibit the cellular proliferation. Glivec first targeted molecule of the XXIth century constitutes the model of what it is advisable to call a targeted molecule nowadays. The aimed target is the real cause of the abnormality at the origin of the cancer and neither the effect which results from it. Two radically different technologies were developed targeting these various ways of signalisation: the inhibitors of tyrosine kinase (TKI) "the foxes", mostly small molecules, results of a complicated process of discovery, easy to make and to copy, very often administered by nonstop oral way, their size allow an access to intracellular targets. In this family we find Imatinib, Gefitinib, Erlotinib, Sugen 11258, Sorafenib. Their association in a classic contemporary chemotherapy is often sanctioned by a failure. Most of them are multitargetings (dirty) drugs. In contrast, more voluminous molecules "mammoth", antibodies monoclonaux which are of relatively fast discovery, particularly expensive to manufacture. They are difficult to reproduce. The real generics are then, difficult to introduce they are biosimilar. They are administered by intravenous way with immunogenic risks, they affect only membrane targets of surface and they develop their maximal activity in association with classic antimitotics. They are Rituximab, Trastuzumab, Cetuximab and Bevacizumab. Opposed to the foxes they are sometimes qualified as mammoths. The plan of Hanhan and Weinberg finds these two therapeutic useful tools in six fundamental mechanisms of the oncogénèse:

1. The independence towards the signals of proliferation
2. The metastatic dissemination
3. The loss of the cellular control.
4. The loss of the apoptotic way
5. The immortalisation of the cellular lineages.
6. The neo-angiogénèse.

In those 6 domains were developed at the same moment antibodies and inhibitors of tyrosine kinase either very specific as antibodies, or on the contrary multi-sites as TKI.

As any efficient drugs, those multi-targeted drugs have an efficiency which is dose dependent, but they have particular toxicities dose dependent to as a specific target.

Their utilisation raise different questions: acquired and de novo resistance, dose adjustment, multitargeted drug, versus association of mono-targeted molecules, associations between mammoths and foxes.

**Conclusion:** the XXI<sup>th</sup> century has opened a therapeutic era radically different from the XX<sup>th</sup> century. To the scarcity of medicine cytotoxics opposes today a considerable number of molecules candidates in the course of preclinical evaluation. Clinical skills are critical at the early development period to select between those candidates.

### Scientific Symposium (Mon, 21 Sep, 11:00–13:00) The hypoxia pathway in tumour progression and therapy

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INVITED

#### Oxygen sensing, HIF hydroxylases and new cancer targets

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Most successful drugs are small organic molecules that bind to, and inhibit, a specific protein within the cell (i.e. its target). Enzymes have historically proven to be attractive drug targets as they frequently have catalytic clefts or pockets that can bind to small organic molecules that possess drug-like properties. 2-oxoglutarate-dependent dioxygenases are a recently identified superfamily of oxygen-dependent enzymes that have now been linked to a number of biological processes, including cancer. For example, we and others showed that the alpha subunit of the heterodimeric transcription factor HIF (Hypoxia-inducible Factor) is hydroxylated by members of the PHD (also called EglN) family of prolyl hydroxylases, which are 2-oxoglutarate-dependent dioxygenases. Prolyl hydroxylation of HIFalpha leads to its recognition by the pVHL tumor suppressor protein, which earmarks HIF for proteasomal degradation. Under low oxygen conditions, or in cells lacking pVHL, HIF accumulates in its active form and transcriptionally activates ~200 genes that promote survival in a low oxygen environment, including genes that promote erythropoiesis. There are 3 PHD family members in humans although PHD2 (EglN1) appears to be the primary HIF prolyl hydroxylase under normal conditions and hypomorphic PHD2 mutations have been identified in families with familial polycythemia. Small molecule PHD inhibitors stimulate erythropoiesis in mice, monkeys, and man and have advanced to Phase 2 studies. We have identified HIF-independent roles for PHD1 and PHD3 in the control of cell proliferation and apoptosis, respectively. For example, PHD1 is induced by estrogen and appears to play an important role in the control of ER positive breast cancers as well as other cancers. Recently it was discovered that many histone demethylases are also 2-oxoglutarate-dependent dioxygenases. For example, we showed, with the help of Drs. Robert Klose and Yi Zhang, that RBP2 (JARID1A) is an H3K4 demethylase that belongs to this family. RBP2 binds to the RB tumor suppressor protein and some of RB's actions can be replicated in RB-/- tumor cells by inactivating RBP2. Genetic disruption of RBP2 inhibits tumor cell proliferation and promotes differentiation in vitro. Our preliminary data indicate that loss of RBP2 inhibits tumor formation in two genetically engineered mouse models.

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INVITED

#### Mechanisms of tumour suppression by VHL

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Mutations in the von Hippel-Lindau (VHL) tumor suppressor gene are causally linked to the development of various inherited and sporadically occurring tumors including clear cell renal cell carcinoma. Work over the last years has established key roles of the VHL gene product VHL in the regulation of diverse cellular processes (Frew et al., 2007). Their disruption is believed to endow susceptible cells with attributes to progress towards an aggressive tumorigenic potential. A commonly accepted tumor suppressor function of VHL relates to its role in hypoxia signaling, where it acts as a substrate recognition component of an ubiquitin ligase that targets hypoxia-inducible factor (HIF)α subunits for degradation. We have previously reported on a HIF-independent function of VHL, which is linked to its ability to bind to and stabilize microtubules (MTs) (Hergovich et al., 2003). The MT stabilization function of VHL is compromised by certain naturally-occurring VHL mutations and has been linked to primary cilium maintenance (Thoma et al., 2007) and suppression of renal cyst formation in mouse models (Frew et al., 2008), implying that regulation of MT stability by VHL is a critical aspect of its tumor suppressing activity. More recently, we have investigated whether other cellular processes that depend on