

Scientific Symposium (Wed, 23 Sep, 14:45–16:45) Targeting tumour cell signalling

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INVITED

BRAF and RAS signalling in human melanoma

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The protein kinase BRAF is mutated in about 50% of human melanomas and its upstream activator, the small G-protein NRAS, is mutated in another 20% of cases. These oncogenes stimulate proliferation and survival, and transform melanocytes, allowing them to grow in an anchorage-independent manner and as tumours in nude mice. We have developed mouse models of melanoma driven by oncogenic BRAF, in which the oncogene is expressed using the endogenous mouse gene. We show that oncogenic BRAF induces melanocyte hyperproliferation, senescence and ultimately progression to melanoma. The tumors display the cardinal features of human melanoma and have metastatic potential. We are also developing new therapeutic agents to target oncogenic BRAF, using structure-based drug design and classical medicinal chemistry approaches to and have developed potent and selective BRAF inhibitors that selectively block the proliferation of melanoma cells expressing mutant BRAF. Importantly, these orally available compounds inhibit the growth of melanoma xenografts in nude mice and now being progressed to clinical development.

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INVITED

The MET oncogene: physiology and pathology of invasive growth

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The tyrosine kinase encoded by the *MET* oncogene is the switch for a genetic program called "invasive growth" that includes cell scattering, invasion, protection from apoptosis and angiogenesis. In a large variety of cancers deregulated activation of *MET*, therefore, is a powerful expedient for cancer dissemination. In fewer instances, *MET* itself can also be the transforming agent genetically selected for the long-term maintenance of the primary transformed phenotype. In this case some tumors appear to be addicted to *MET* continued activity for their relentless growth. Because of its dual role as an adjuvant metastogene for some tumor types and as a necessary oncogene for some others, *MET* is a versatile candidate for targeted therapeutic intervention. Recent progress of the lab in the development of antibodies or drugs that inhibit *MET* function will be reviewed. Their rational application in a subset of human tumors potentially responsive to *MET* targeted therapies will be discussed. For reviews see the references.

References

- Boccaccio C. and Comoglio PM. Invasive growth: a MET-driven genetic programme for cancer and stem cells. *Nature Rev Cancer* 6:637–645, 2006
- Comoglio PM, Giordano S, Trusolino L. Drug development of MET inhibitors: targeting oncogene addiction and expedience. *Nat Rev Drug Discov*. 7:504–516, 2008.

Scientific Symposium (Wed, 23 Sep, 14:45–16:45) Cancer prevention in Europe

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INVITED

The causes of cancer

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It is widely accepted that external factors are responsible for many human cancers; however, precise estimates of the contribution of known carcinogens to the cancer burden in a given European population have been scarce. We estimated the proportion of cancer deaths which occurred in France in 2000 that was attributable to known risk factors. This estimate was based on data on frequency of exposure around 1985, wherever possible from national sources. We have also analyzed temporal changes of the mortality caused by the various types of cancers between 1950 and 2004. Cancer mortality in France has decreased in recent decades in both sexes. Variations are mainly explained in men by mortality from cancers associated with alcohol and tobacco consumption and in women by breast and cervical cancer mortality. In 2000, tobacco smoking was

responsible for 23.9% of cancer deaths (33.4% in men, 9.6% in women), alcohol drinking for 6.9% (9.4% in men, 3.0% in women) and chronic infections for 3.7%. Occupation is responsible for 3.7% of cancer deaths in men; lack of physical activity, overweight/obesity and use of exogenous hormones are responsible for 2 to 3% of cancer deaths in women. Other risk factors, including ultraviolet light, reproductive factors and pollutants, are responsible for less than 1% of cancer deaths. Thus, known risk factors explain 35.0% of cancer deaths, and 15.0% among never-smokers. While cancer mortality is decreasing in France, known risk factors of cancer explain only a minority of cancers, with a predominant role of tobacco smoking. These results provide evidence for priority setting in cancer control, in particular emphasizing the importance of lifestyle factors, underline the limitations of current knowledge of the causes of human cancer and point out the need for further epidemiological and fundamental research. They can be used as benchmarks to estimate the role of known causes of cancer in Europe.

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INVITED

Closing the cancer gap in Europe

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The health transformation that took place after the Second World War in Europe was significantly delayed in the Central and Eastern European (CEE) countries compared to countries of Northern Europe and Great Britain. However, as death rates from cardiovascular disease have begun to fall, cancer has emerged, since the 1990 s, as the most common cause of death among young and middle-aged adult women (20–64 years old) in these countries. In the coming decade it seems likely to be the leading cause of death among young and middle-aged adult men.

It is accepted that behavioural factors play a crucial role in the development of cancer. These include cigarette smoking, alcohol consumption, exposure to occupational and environmental carcinogens, sexual behaviour, obesity, diet, and physical activity. Demographic changes, particularly population ageing, also have impact on cancer incidence. These factors have continued to change in all parts of Europe, often following similar pathways but from different initial levels and at different rates. A consequence each country must confront is different burden of cancer – both in nature and magnitude.

Diversity is also apparent in the control of cancer in Europe. While there is considerable scope for improvement throughout the region, the past decade has brought significant progress. Much of this can be attributed to the introduction of comprehensive approaches to cancer control (including increasingly successful interventions to treat cancer) but fundamentally it stems from achievements in prevention (primary and secondary).

In the CEE countries deficiency of primary prevention is a main reason of poor health awareness (consequences of smoking, fatty diet, low physical activity) and late introduction of secondary prevention responses for worst survival of cancer patient, however tertiary prevention is implemented in similar way as in western part of Europe. Our analysis indicates that the greatest possibilities, but also the greatest unmet needs lie in primary and secondary prevention.

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Scenarios for Cancer prevention in Europe: the Eurocadet project

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It is widely known that, depending on the country, 25 to 50% of cancer in Europe may be avoidable in the long run by adapting various lifestyles based on the European Cancer Code. Usually there is a gradient from the northwest to the southeast, for example with respect to rates of smoking whether initiating or stopping at a larger scale. The various cancer epidemics often come and follow that pattern, related to the forces of industrialisation, mechanisation, prosperity, childbearing and safety. The various lifehabits remain most important, especially with respect to the tendency to get addicted to the use of tobacco, excessive alcohol, (too much) food also in relation to decreasing calory expenditure and lacking variation. Soerjomataram et al. estimated the percentage of avoidable cancer by country for the 10 tumour sites with the highest potential. Central European countries generally exhibited the worst outcomes, especially for males, who generally outperform females. The EU FP6 financed Eurocadet project performed policy research, i.e. providing the data and methodology and software for estimating the impact of cancer prevention on a geographical basis. Started in 2005 it will deliver