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

263 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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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

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

267 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.

268 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

J. Coebergh[1], E. de Vries[1], I. Soerjomataram[1], J. Barendregt[1], A. Oenema[1], V.E. Lemmens[1], A. Kunst[2], M. Boniol[3], P.H. Autier[3], K.I. Klepp[4]. [1]*Erasmus MC, dept of Public Health, Rotterdam, The Netherlands;* [2]*Academic Medical Centre, dept of Social Medicine, Amsterdam, The Netherlands;* [3]*IARC, dept of Epidemiology, Lyon, France;* [4]*University of Oslo, dept of Nutrition, Oslo, Norway*

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

by end of 2009. www.eurocadet.org For this purpose IARC collected and synthesised country-specific data on important exposures (smoking, alcohol consumption, level of physical exercise, fruit and vegetables and furthermore the level of physical exercise, where possible by SES. Relative risks were assigned based on most recent research, allowing for estimation of potential impact fraction. Furthermore trends in incidence were collected and extrapolated until 2020, so that extrapolations of these trends after this year could be affected up till 2050 by changes in exposure in the next 10–15 years. Literature overviews of effectiveness of interventions and also of barriers, e.g. legal, fiscal etc. They were explored in order to adjust to the realities in the various countries and also to identify best practices. An existing (since 20 years) computer model, PREVENT that includes latency and lag times was refined and made userfriendly, and finally introduced to epidemiologists across the EU in 5 workshops. The presentation will provide examples of prevention impact in the various countries of comparative strategies, e.g. tax increases and/or free provision of anti-smoking tools, menas to increase fruit & vegetable intake, to tackle obesity etc. Results of this project enable professionals in public health, or working in Cancer Societies to become more precise in their proposals for prevention and sketch impact of both desirable and undesirable alternatives.

References

Soerjomataram I. et al. Int J Cancer 2007;

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Frontiers of cancer prevention research

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In this presentation, cancer prevention research will be reviewed from two perspectives; and include research that is focused on primary and secondary prevention.
Areas of primary prevention research that will be covered include successful areas (example: smoking cessation), and areas that have received massive attention but, however, with moderate success. The latter will include, among others, chemoprevention attempts (example: chemoprevention against prostate and breast cancer). The presentation will also deal with novel biomarkers (both from serum and genetic material) as predictors of different cancers. Such biomarkers (including serum proteins and genetic variants) may have the potential to be attractive targets for cancer prevention, but their test properties in relation to individual risk have been questioned, and their usefulness needs to be discussed.
The second part of the presentation will cover preventive measures of cancer deaths; mainly by early detection of cancer. This part of the presentation will mainly deal with the present status of early detection programs, such as mammography screening with the aim of preventing deaths from breast cancer, and PSA-based screening aiming to prevent prostate cancer deaths. Among several topics, the paradigm of early detection to prevent cancer deaths will be discussed.

Scientific Symposium (Wed, 23 Sep, 14:45−16:45)
Symptom management: from molecular biology to bedside including pain and cachexia

271 INVITED

Genotyping – does it matter in clinical practice for pain and cachexia?

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One of the main challenges in the clinical management of complex symptoms or syndromes such as cancer associated pain or cachexia is the early identification of specific components that are treatable. Put another way, assessment and classification of patients with such symptoms/syndromes aims to identify phenotypes that may respond optimally to available therapy. It is clear, however, that there may be genotypes that underlie such phenotypes (pharmacogenetics). Moreover, there may be genotypes that predispose patients to the symptoms/syndrome per se and which if identified might allow deployment of prophylactic therapy to specific sub-groups. The latter approach is particularly relevant to cachexia where intervention at an advanced stage of wasting may be futile and may simply increase the burden on the patient.
Cachexia is thought to arise as a result of host-tumour interaction activating the pro-inflammatory cytokine network and the neuro-endocrine stress response. Recent work has identified a single nucleotide polymorphism (SNP) in the IL 10 gene that is associated with the development of weight loss in patients with upper GI cancer. These results raise the possibility of identifying groups of patients in the pre-cachectic phase for early multimodal intervention.
With regard to differences in pain sensitivity and response to opioids, recent research has suggested that in cancer patients genetic variation in the catechol-o-methyltransferase enzyme influences the efficacy of morphine. Equally, the prevalent 118A>G polymorphism in the micro-opioid receptor has been linked with variability in the response to opioids.
Unfortunately, current data are only valid at the group level and cannot be used to predict outcome in individuals. The goal of personalised medicine for cancer pain or cachexia requires further large scale studies and more precise phenotyping to improve the quality of genotype association studies.

273 INVITED

Cancer pain treatment. New approaches based upon the WHO pain ladder

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World Health Organization guidelines have provided an important template for cancer pain management. The majority of poorly-controlled cancer pain on a world-wide basis could be improved by following these guidelines. However, individual management often needs a refinement to optimize analgesia and minimize side-effects. In addition, difficult to control pain such as movement-related pains, spontaneous pain at rest and other types of neuropathic pain, can provide a challenge. Imrpoved pain assessment is key. We are developing an improved understanding of both key clinical questions in the oncology setting and also more objective clinical findings using techniques such as quantitive sensory testing. Optimum use of morphine and alternative opioids remains crucial. The recent availability of fast-acting fentanyl preparations will clearly be of use for some types of breakthrough pain. The newer antidepressants, such as duloxetine, provide the opportunity of both using a drug which can be easily titrated to both an antidepressant dose and an effective neuropathic pain dose with a much improved side-effect profile over the older antidepressants. Understanding the role of topical analgesia, eg lidocaine, capsaicin, is of increasing importance as we learn to combine skilfully systemic and topical preparations acting on different receptor profiles. Assessment and management of interventional analgesia (including domicillary), is an important area. Appropriate use of implantable intrathecal pumps can improve both pain and quality of life substantially. A greater understanding of the peripheral and central mechanisms of pain and integration with other factors has been central to the expansion of the analgesic armamentarium. The mechanisms and management of cancer treatment-related pain has attracted more attention as patients live longer and the treatment armamentarium expands further.
The expanded WHO analgesic ladder and its many applications will be discussed in relation to both cancer and cancer-treatment related pain.

274 INVITED

Treatment of cachexia-a preventive or symptomatic approach?

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Cancer cachexia is a very frequent and burdensome complication of advanced cancer, characterized by increased nutritional intake and appetite, an altered metabolism causing a catabolic drive, associated with neuroendocrine alterations. It is a continuum reaching from pre-cachexia to the full anorexia/cachexia syndrome to late irreversible cachexia. In pre-cachexia typical characteristics are present, but weight loss is not obvious. While in the full syndrome weight loss is >5% in 6 months and <2% in 2 months. Treatment of cachexia encompasses pharmacological, nutritional, behavioral and educational interventions. The therapeutic targets are increase of nutritional intake by cognitive control of eating, improvement of dietary habits, oral supplements or enteral or parenteral nutrition, reversal of the catabolism by antiinflammatory agents and/or effective antineoplastic interventions and they include also improvement of muscle function by physical activity training and development of drugs to reverse muscle proteolysis and increase protein synthesis. As a wealth of data documenting that inflammatory weight loss and/or loss of appetite is associated with decreased response to anti-cancer treatment, increase of toxicity and finally survival.
There is good evidence (grad A) that nutritional continuous counseling, including but not limited to supplements increases survival and treatment tolerability in curative rectum and head and neck cancer situations, also