Method and Purpose: A census of the specialist nursing workforce from England, Wales, and Northern Ireland was conducted in November 2008 in an attempt to establish baseline data.
Results: Census response rates ranged from 66% to 100% across the three countries. There were inconsistent numbers of nurse specialists compared to published cancer incidence figures. It did not appear that workforce intelligence had driven staff recruitment. There was also a marked variation in the the number of specialist titles used (England recorded 17 different titles).
Conclusions: The large number of specialist titles could undermine the consistent development of specialist nursing practice; it may be useful to standardise titles. England and Northern Ireland have already used this data to commission additional specialist posts. This census has been an extremely powerful management tool and the information gathered has been used in education, policy development, and workforce design. Other European countries may benefit from conducting their own census activity.

Scientific Symposium (Wed, 23 Sep, 09:00−11:00)
Current avenues in clinical trials for melanoma treatment

203 INVITED

Melanoma vaccines – quo vadis?

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Background: Metastatic melanoma is a disease for which no effective therapy is available with the possible exception of IFN-α in stage III patients. The immunotherapy approach to such a tumor was started on more convincing scientific basis 15 years ago thanks to the molecular characterization of melanoma antigens (Ags) recognized by T cells (e.g. MAGE, Melan-A/MART1, etc.). In fact, no therapeutic activity was previously obtained after immunotherapy with anti-melanoma and anti-idiotypes antibodies or with vaccine based on autologous/allogeneic melanoma cells.
Results: Approximately 10 years of clinical studies of immunotherapy, while generating important immuno-biological information on the patient immune functions and a remarkable frequency of anti-vaccine immune responses in patients treated with the self (differentiation or cancer/testis) Ags, failed to induce a significant clinical outcome both as tumor response and survival. However, the new generation of immunotherapy studies of the last 3−5 years based on the wealth of new information obtained both in the laboratory and in the clinic and by the application of the genome and post-genome analysis, has provided a more detailed picture of the relationship between tumor and host (including the role of tumor microenvironment). These data have suggested how to obtain not only an increased frequency and strength of the immune response to the different vaccination approaches but how to improve the clinical outcome.
Emerging principles for a successful vaccination of metastatic melanoma include, a) vaccination with multiple Ags (particularly under the form of peptides, perhaps long peptides) to avoid tumor escape caused by immune selection, including Ags belonging to different subgroups (e.g. differentiation, cancer/testis, universal, mutated) and recognized both by CD8 and CD4 T cells; b) new TLR-binding immune adjuvants; c) combination with immunomodulating antibodies (e.g. anti-CTLA4) or cytokines (IFN-α, IL-2, IL-12); d) administration of reagents that can counteract the immunosuppressive environment (anti-Treg, anti-TGFβ antibodies, etc.).
Recent studies also show a relevant increase of clinical response in metastatic melanoma patients receiving adoptive immunotherapy with Ag-specific T cells after immune depletion including pharmacological treatment and total body irradiation. Finally, a clinical phase III study of peptide-based immunotherapy combined with IL-2 has been presented at ASCO 2009 that showed significant increase of frequency of tumor regression in patients receiving such a biological combination therapy compared to patients arm given IL-2 only.
Conclusion: Therefore, though we are still waiting for a large, perspective, phase III study that may unequivocally document the clinical success of vaccination strategy in metastatic melanoma, the future remains promising for this area of investigation even taking into account the recent results of clinical studies of vaccination in other dreadful tumors like non-small cell lung cancer and prostate cancer.

204 INVITED

Angiogenesis in melanoma

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Angiogenesis is essential if metastatic melanoma is to grow beyond a size of 2−3 mm^3. This 'angiogenic shift' occurs when melanoma cells start to produce several growth factors, including vascular endothelium growth factor (VEGF). The process of angiogenesis depends on an interaction between tumour cells, stromal cells, endothelial cells and bone marrow-derived cells. The vascular endothelial growth factor family of growth factors, their receptors, and a number of cofactors, are key components of angiogenesis. There is evidence for expression of angiogenic factors being both prognostic and predictive. However, not all melanomas express VEGF and other angiogenic factors are also important. Considerable evidence has emerged for the central role of bone marrow-derived endothelial and myeloid cells in tumour related angiogenesis. Tumor-associated macrophages (TAM) are major infiltrates of human solid malignancies and release a number of potent proangiogenic factors. Dendritic cells produce a wide range of angiogenic and angiostatic factors, and are inhibited by VEGF.
A number of drugs have been developed to specifically target the components of these pathways. How these drugs result in inhibition of angiogenesis is unclear, but effects are likely to include inhibition of new growth, induction of endothelial cells apoptosis, and effects on vascular including vascular constriction and vascular normalisation, and effects on cell-cell and cell-matrix interactions. Early phase studies with bevacizumab, afibercept and axitinib have shown evidence of activity, though the addition of sorafenib to carboplatin and paclitaxel chemotherapy in both the first and second line metastitic settings showed no impact on survival. This is at odds with the outcome seen for this regimen in lung cancer, and other combinations in breast and colerectal cancer. Since angiogenesis is critical for invasion and metastasis, adjuvant therapy is an important area to explore. The AVAST-M study is a large randomised study comparing bevacizumab with routine follow-up in patients with resected high risk stage II and stage III disease. Targeting angiogenesis has been successful in a number of common cancers. Whether this will also be the case for melanoma remains to be seen.

Scientific Symposium (Wed, 23 Sep, 09:00−11:00)
Molecular imaging of cancer

206 INVITED

Reporter gene imaging in cancer: from mouse to man

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Molecular-genetic imaging in living organisms has experienced exceptional growth over the past 10 years, and can be defined as "the macroscopic visualization of cellular processes in space and time at the molecular level of function". It has its roots in molecular and cell biology as well as in imaging technology, chemistry and radiochemistry. Three imaging strategies: based on "direct" and "indirect" assessments of molecular-genetic processes, as well as "bio-marker" or "surrogate" imaging have been combined with three imaging technologies: radionuclide-, magnetic resonance- and optical-based imaging systems.
The "direct" imaging motif builds on established relationships between chemistry/radiochemistry and imaging. Bioconjugate chemistry linking specific binding motifs and bioactive molecules to paramagnetic particles for MR imaging or to radionuclides for PET and gamma camera imaging. This interactive relationship has existed for many years and continues to expand through the development of new relationships and focused interactions between molecular/cellular biologists, chemists, radiochemists, imagers and clinicians. The next generation of direct molecular imaging probes will come from better interactions between pharmaceutical companies, academia and hospitals. Such interactions are now being pursued with the objective to develop and evaluate new compounds for imaging; compounds that target specific molecules (e.g., DNA, mRNA, proteins) or activated enzyme systems in specific signal transduction pathways. However, a constraint limiting direct imaging strategies is the necessity to develop a specific probe for each molecular target, and then to validate the sensitivity, specificity and safety of each probe for specific applications prior to their introduction into the clinic.
Biomarker or surrogate imaging that reflects endogenous molecular/genetic processes is particularly attractive for expansion and translation into clinical studies in the near-term. This is because existing radiopharmaceuticals and imaging paradigms may be useful for monitoring down-stream changes

of specific molecular/genetic pathways in diseases such as cancer (e.g., FDG PET). Biomarker imaging is very likely to be less specific and more limited with respect to the number of molecular-genetic processes that can be imaged. Nevertheless, it benefits from the use of radiopharmaceuticals that have already been developed and are currently being used in human subjects. This application strategy is most dramatically illustrated by the use of [18F]FDG PET to image the response, recurrence and progression of particular tumors (e.g., Gleevac treatment of GIST). The translation and application of biomarker imaging paradigms into patient studies, using clinically-approved radiopharmaceuticals or contrast agents, will be far easier than either the direct imaging or reporter transgene imaging paradigms.

Reporter gene imaging studies will be more limited in patients compared to that in animals, due to the necessity of transducing the target tissue or cells with specific reporter constructs, or the production of transgenic animals bearing the reporter constructs. Ideal vectors for targeting specific organs or tissue (tumors) do not exist at this time, although this is a very active area of human gene therapy research. Each new vector requires extensive and time-consuming safety testing prior to regulatory approval for human administration. Nevertheless, reporter gene imaging, particularly the genetic labeling of cells with reporter constructs, has several advantages. There are now three well-defined human genes (*hNIS, hNET and hSSTR2*) with complimentary, clinically approved, radiopharmaceuticals for PET or gamma camera imaging in patients. These complimentary pairs (gene + probe) are excellent candidates for future reporter gene imaging in patients. Importantly, these human genes are less likely to be immunogenic compared to the reporter genes currently used in animals (e.g., viral thymidine kinases, luciferases, fluorescent proteins). It should also be noted that a single reporter gene – reporter probe pair can be used in different reporter constructs to image many different biological and molecular-genetic processes. Once a complimentary reporter-pair (gene + probe) has been approved for human studies, regulatory issues will focus will shift to the particular backbone and regulatory sequence of the reporter construct.

The major factor limiting translation of reporter gene imaging studies to patients is the "transduction requirement"; target tissue or adoptively administered cells must be transduced (usually with viral vectors to achieve high transduction efficiency) with reporter constructs for reporter gene imaging studies. At least *two* different reporter constructs will be required in most future applications of reporter gene imaging. One will be a "constitutive" reporter that will be used to identify the site, extent and duration of vector delivery and tissue transduction or for identifying the distribution/trafficking, homing/targeting and persistence of adoptively administered cells (the "normalizing" or denominator term). The second one will be an "inducible" reporter that is sensitive to endogenous transcription factors, signaling pathways or protein-protein interactions that monitor the biological activity and function of the transduced cells (the "sensor" or numerator term). The initial application of such double-reporter systems in patients will most likely be performed as part of a gene therapy protocol or an adoptive therapy protocol where the patients own cells are harvested (e.g., lymphocytes, T cells or blood-derived progenitor cells), transduced with the reporter systems and expanded *ex vivo*, and then adoptively re-administered to the patient. For example, adoptive T cell therapy could provide a venue for imaging T cell trafficking, targeting, activation, proliferation and persistence. These issues could be addressed in a quantitative manner by repetitive PET imaging of the double-reporter system described above in the same subject over time.

Once in place, Cancer Clinical Trials and Personalized Medicine will be able to benefit from the noninvasive imaging paradigms described above; similar to the benefits of sequential FDG PET scans performed today in order to monitor GIST tumor response and recurrence. The ability to visualize transcriptional and post-transcriptional regulation of endogenous target gene expression, as well as specific intracellular protein-protein interactions in patients will provide the opportunity for new experimental venues in patients. They include the potential to image the malignant phenotype (e.g., signal pathway activity) of an individual patient's tumor at a molecular level and to monitor changes in the phenotype over time. The potential to image a drug's effect on a specific target molecule or signal transduction pathway in an individual patient's tumor provides the opportunity for monitoring treatment response at the molecular level.

207 INVITED

Causes and consequences of glycolysis and acid pH in tumors

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Over the last decade, we have developed and improved MR-based techniques with which to measure the pH of tumors. These have included 31-P MRS and 1-H MRSI approaches and, most recently, pH-dependent relaxometry using pH-dependent contrast agents. This latter approach has been particularly challenging as it required simultaneous and independent quantification of relaxation rates and contrast agent concentration. All of these approaches have shown that the extracellular-interstitial pH (pHe) of tumors is unequivocally acidic, reaching as low as pH 6.7. This low pHe is caused by high glucose metabolism in tumors coupled with poor perfusion. The high glucose metabolism occurs in the presence or absence of oxygen, also known as the Warburg Effect., WE. There is evidence, by us and others, that the WE is hardwired in the most aggressive tumors, and that this can occur through the oncogenic activation of at least 6 different pathways. Darwinian evolution selects for phenotype, not genotype and thus, we have proposed that the glycolytic phenotype is evolutionarily selected early during the in situ stage of carcinogenesis, when it is an avascular disease. This does not explain, however, why this phenotype continues to be selected later in carcinogenesis, when invasive and metastatic cells have access to the vasculature. Examining the sequelae of glucose catabolism yields a finite number of consequences that could lead to further selection, including acid production. Acid production could be selected because it has been shown to induce invasion and exacerbate metastasis. We have proposed that this occurs by induction of cathepsin release and export of H^+ from growing tumors into surrounding parenchyma, thus facilitating their ability to invade host tissue. Notably, tumor acidity can be inhibited with oral buffers, such as bicarbonate, and we have shown that this inhibits spontaneous metastasis in some, but not all, animal tumor models.

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209 INVITED

MR imaging of angiogenesis

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Angiogenesis has been validated as a target in multiple randomized clinical trials that tested the advantage of adding VEGF inhibitors to conventional treatment. There remains a clear need to identify the patients who most benefit from this class of drug as the data demonstrate only a modest improvement in overall survival if all patients in a defined disease population are treated; some pre-clinical and clinical data suggest that maintenance therapy is required; the drugs can be toxic; and because the development of combination regimens that include VEGF inhibitors can only occur once we have learned how to identify the patients who most benefit from this class of drug.

Biomarker science is evolving to address the issue of treatment individualisation. Imaging offers the advantage of allowing serial measurements of tumour vascular pathophysiology and has been implemented throughout the development of anti-angiogenic agents. To date multiple clinical trials have evaluated VEGF inhibitors with Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) and have demonstrated a relationship between drug dose and reductions in DCE-MRI parameters and secondly between the reduction in DCE-MRI parameters and patient benefit. These relationships are confounded by heterogeneity. However, histogram analysis of imaging data, to examine vascular heterogeneity in greater detail demonstrates clinically useful information that is otherwise overlooked.

One of the parameters that evolved from the analysis of heterogeneity was the enhancing fraction, which reflects the vascularity of the tumour. In several clinical trials using MR or CT, in patients treated with anti-vascular agents, cytotoxic drugs or radiotherapy we have demonstrated the clinical value of measuring the vascular enhancing fraction and have shown that this parameter augments traditional prognostic factors. These data led to further clinical trials which demonstrated that VEGF inhibitors reduce the