125 INVITED

If you do not have a laboratory, then turn your clinic into one!

J. Denham. *University of Newcastle, Radiation Oncology, New South Wales, Australia*

In an ideal world all cancer treatment centres would be co-located with research laboratories. Clinicians and laboratory scientists would meet regularly and collaborative translational research projects would be commonplace.
In this presentation examples are provided of detailed sets of clinical observations (made in isolation from the laboratory) that have contributed to the understanding of the mechanisms of radiation injury to normal tissues and tumours.
There remains much to observe and learn in the clinic. Do not be discouraged from doing this just because there is no laboratory next door!

126 INVITED

New drug treatment for cancer in 2007 – real progress at last?

S. Kaye, J. de Bono, I. Judson, M. Scurr, U. Banerji. *Royal Marsden Hospital, Drug Development Unit, Sutton Surrey, United Kingdom*

We have become accustomed in recent years to hearing about major progress in cancer treatment as a result of rational drug development providing molecular targeted therapy linked to specific signalling pathways in certain cancers. How does this translate into the daily practice of one of Europe's largest Phase I clinical trials units?
The Drug Development Unit at the Royal Marsden Hospital sees over 500 patients per year for consideration of experimental treatment, and at least half will enter one of over 20 Phase I trials. These include both single agent and combination approaches with all forms of solid tumours treated.
Is there a changing trend in expectation of efficacy?
Over the past 2 years, our trials have indeed been marked by an increasing number of patients showing major benefit. Two key examples which are set to change clinical practice and illustrate different points are (a) AZD 2281 which is an inhibitor of Poly(ADP-Ribose) Polymerase1 (PARP1). We have recently completed the first oral continuous Phase I trial of this agent. This showed it to be well tolerated, and we demonstrated significant activity in patients with BRCA-associated (ovarian) cancer, precisely bearing out preclinical data indicating the exquisite sensitivity of these repair-deficient cancer cells. (b) Abiraterone, which is an inhibitor of the enzyme CYP 450 C17. This results in complete inhibition of androgen synthesis in prostate cancer cells and adrenal cortex while preserving other adrenal hormone biosynthesis. Our Phase I trial (continuous oral administration) showed it to be well tolerated and the drug has shown major activity in patients with so-called 'hormone-refractory' prostate cancer.
Other instructive examples where clear radiological regression has been seen include patients with refractory cancer treated with AZD 2171 (VEGFR inhibitor), BIBW 2992 (ErbB family inhibitor), PXD101 (HDAC inhibitor) and a Combrestatin A-4P/Bevacizumab combination approach to anti-angiogenesis.
The potential for significant future benefit is considerable. However, it is important to emphasize that advances in molecular diagnostics, through which the careful selection of patients most likely to benefit can be made, will be essential in order that expensive new therapies can be brought into general clinical utility.

127 INVITED

Translational reseach is key in clinical trials: MD/PhDs in the driving seat . . .

A.M.M. Eggermont. *The Netherlands*

Abstract not received.

128 INVITED

Experimental evaluation of anti-angiogenic strategies to improve outcome after fractionated radiotherapy

D. Zips. *TU Dresden, Radiation OncologyUK Carl Gustav Carus, Dresden, Germany*

Tumour development and growth depends on angiogenesis, i.e. the formation of new blood vessels. Numerous molecules have been identified to control tumour angiogenesis and therefore represent promising targets for cancer therapy. Expression levels of these molecules as well as other parameters related to tumour vasculature are important prognostic factors for radiotherapy suggesting that angiogenesis significantly contributes to radiation resistance of tumours. Molecular compounds targeting tumour angiogenesis have been demonstrated to reduce tumour growth but are not curative in themselves. Yet, radiotherapy is highly effective in sterilizing clonogenic tumour cells. Furthermore, recurrences after high radiation doses arise from a few surviving clonogenic tumour cells. Thus, even if anti-angiogenic compounds have no curative potential in themselves they may interfere with mechanisms of radiation resistance in tumours and thereby may result in important improvement of local tumour control after radiotherapy. However, impaired tumour vascularisation after anti-angiogenic intervention might be harmful because of increased hypoxia. Therefore, a thorough experimental as well as clinical validation of the combination of anti-angiogenic compounds and fractionated radiotherapy is essential.
Experimental data indicate that inhibition of angiogenesis can improve efficacy of irradiation. In the vast majority of experiments, tumour growth delay was used as endpoint and simultaneous combination schedules of irradiation and inhibitors of angiogenesis were tested. The increased efficacy of a simultaneous combination observed in most experiments has been attributed to a direct radiosensitizing effect of anti-angiogenic compounds on endothelial cells. A potential hazard of this combination is the possible increase in tumour hypoxia and thereby radioresistance. Experiments exploring the impact of anti-angiogenic interventions on tumour hypoxia gave controversial results. We have demonstrated that inhibition of multiple angiokinases was effective to reduce tumour angiogenesis but had no effect on the radiobiological fraction of clonogenic tumour cells.
In experimental tumours adjuvant administration of inhibitors of angiogenesis, i.e. after the end of fractionated irradiation, resulted in a prolonged tumour growth delay even in tumour models where the inhibitors alone or given simultaneously to irradiation were not effective. Enhanced sensitivity of radiation-damaged blood vessels against inhibitors of angiogenesis due to up-regulation of target receptors expressed on endothelial cells seems to be the underlying mechanism. These experiments clearly indicate that the schedule of the combination importantly determines treatment efficacy. Despite clear-cut effects on tumour growth delay observed in most experiments, data on local tumour control after fractionated irradiation are inconsistent. Thus, further investigations into the underlying mechanisms are essential to define and exploit the potential of anti-angiogenic strategies to improve outcome after radiotherapy.
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Symposium (Wed, 26 Sep, 09:00−11:00)
Congenital paediatric disorders: What do we learn from nature?

129 INVITED

Cancer-associated congenital disorders along the Ras-pathway: from genetics to novel therapeutic strategies

Abstract not received.

130 INVITED

Novel insight into the pathogenesis of dyskeratosis congenita: how defective ribosome activity can cause cancer and disease

D. Ruggero[1], A. Yoon[1], G. Peng[1], O. Zollo[1], R. Adamo[1], N. Haynes[1], W. Xu[1], E. Rego[2]. *[1]Fox Chase Cancer Center, Human Genetics Programme, Philadelphia, USA; [2]Faculdade de Medicina de Ribeirao Preto, Laboratorio de Hematologia, Ribeirao Preto, Brazil*

X-linked Dyskeratosis Congenita (X-DC) is an inherited disorder characterized by bone marrow failure, skin abnormalities, and cancer susceptibility caused by point mutations in the DKC1 gene. The DKC1 gene encodes for an enzyme that modifies ribosomal RNA (rRNA) through the site-specific conversion of uridine to pseudouridine, guided by small nucleolar RNAs. The molecular mechanisms by which impairments in rRNA modifications contribute to X-DC pathogenesis remain unknown. We utilized an unbiased proteomics strategy to identify mRNAs that were translationally impaired as a result of reductions in rRNA modifications in hypomorphic Dkc1 mutant mice, which recapitulate the clinical features of X-DC. While general protein synthesis was found to be unaffected, subsets of cellular mRNAs containing an internal ribosome entry site (IRES) element within their 5′UTRs were translationally impaired. These genes included the tumor suppressor p27 and the anti-apoptotic factors XIAP and Bcl-xL, which were specifically impaired at the level of IRES-dependent translation in Dkc1 mutant mice as well as X-DC patient cells. Moreover, we provide genetic evidence that impairments in IRES-mediated translation of p27 may contribute to the cancer susceptibility phenotype of X-DC. In order to understand the molecular mechanisms by which Dkc1m ribosomes are defective in IRES-mediated translation, we tested whether viral IRES elements that directly

recruit the ribosome would be translationally impaired in Dkc1m cells. These experiments suggest that the defect in IRES mediated translation present in Dkc1m cells resides from an intrinsic defect in Dkc1m ribosomes to engage IRES-elements. In addition, to extend our understanding of the physiological role of IRES-dependent translation in vivo we are monitoring IRES dependent translation in animal models utilizing a live imaging approach. These findings uncover a novel paradigm for how specific defects in gene expression at the translational level can arise from impairments in ribosome modification and can lead to disease and cancer susceptibility.

131 INVITED

Fanconi anaemia: genomic instability leading to aplastic anaemia and cancer predisposition

J.P. De Winter. *VU Medical Center, Division of Clinical Genetics, Amsterdam, The Netherlands*

Multiple genomic maintenance pathways have evolved to deal with endogenous and exogenous DNA damaging agents and to safeguard the genome's integrity. The inactivation of these pathways leads to genomic instability, which increases the risk to develop cancer. Many of the genes involved in DNA repair and genomic stability are affected in cancer predisposition syndromes such as XPA-G (Xeroderma pigmentosum), NBS1 (Nijmegen Breakage Syndrome), ATM (Ataxia telangectasia), Blm (Bloom syndrome) and Wrn (Werner syndrome). Fanconi anemia (FA) is another genomic instability syndrome that allowed us to identify a novel DNA maintenance network. This network consists of a nuclear protein complex, the FA core complex, essential for the monoubiquitination of one of the FA proteins (FANCD2), and several proteins (FANCD1/BRCA2, FANCJ/BRIP1 and FANCN/PALB2) acting downstream or independent of this modification step. The FA/BRCA DNA damage response network is particularly important for error free replication and a defense against DNA cross-linking agents, specifically in vertebrates. Defects in both copies of a single gene in this network strongly increase the risk for acute myeloid leukemia, squamous cell carcinomas and, in the case of BRCA2 and PALB2, childhood cancer (especially Wilms tumor and medulloblastoma). In addition, single copy defects in the downstream part of the network augment the relative risk for breast cancer. Although many players in the network have been identified the total picture of the process in which they play a role is still incomplete. In this talk, I will give an overview of the FA/BRCA network and focus on the latest developments in the field.

132 INVITED

Acute megakaryoblastic leukaemia in Down syndrome and non-Down syndrome patients – molecular signature of a disease – subtypes with distinct treatment outcomes

P. Vyas[1], A. Norton[1], O. Tunstall-Pedoe[2], I. Roberts[2]. [1] *University of Oxford, The Weatherall Institute of Molecular Medicine, Oxford, United Kingdom;* [2] *Imperial College, Department of Haematology, London, United Kingdom*

Background: 10−20% of neonates with Down Syndrome (DS) develop a myeloid preleukaemic disorder affecting the megakaryocyte lineage, termed transient abnormal myelopoiesis (TAM). In most babies TAM clinically resolves, but 30% later develop acute myeloid leukaemia of the megakaryocyte lineage (AMKL) within 5 years. We and others have previously shown that N-terminal truncating mutations in the key myeloid transcription factor GATA1 are specifically present in all cases of TAM and AMKL and arise in fetal, but not adult, blood cells. GATA1 is encoded on the X chromosome so that in malignant cells only the mutant form of GATA1 is expressed. In cases of TAM that transformed to AMKL, the same GATA1 mutation was present at both stages demonstrating the molecular clonal relationship between the two disorders. Furthermore, we previously showed that in ~30% of DS AMKL samples there were multiple GATA1 mutant leukaemic clones, underscoring the extremely high rate at which mutant GATA1 clones were generated. Given that DS children are not cancer prone in general we proposed that the GATA1 mutation was likely to be positively selected in a trisomy 21 fetal blood cells.
The questions now are:

a. What is the role of the extra gene dosage on chromosome 21? To begin to address this question we have studied fetal myelpoiesis in Down Syndrome.
b. What the role of the N-terminus of GATA1? To begin to address this question we have tried to identify if sequences in the N-terminal of GATA1 are required for normal megakaryocyte differentiation and the proteins that interact with the N-terminus of GATA1.

Material and Methods: We have purified myeloid progenitors (common myeloid progenitor, granulocyte-myeloid progenitor and erythroid-megakaryocyte progenitor) from fetal liver, bone marrow and blood. We have used GATA1 mutants to rescue megakaryopiesis from GATA1-deficient megakaryocyte progenitors. We have used an in vivo biotinylation technique to isolate GATA1-interacting proteins.
Results: We now show that trisomy 21 per se alters human fetal haemopoietic differentiation, causing an expansion of the megakaryocyte progenitor compartment that is further expanded by GATA1 mutation. Furthermore, using a mouse model we show that N-terminal truncation of GATA1 compromises the ability of GATA1 to restrict proliferation of primary megakaryocyte progenitors though permitting some differentiation. Finally, we show that GATA1 is present in a number of transcriptional activating and repressive complexes to help coordinate megakaryocyte gene expression.
Conclusions: We conclude that trisomy 21 and GATA1 synergistically produce a preleukaemic expansion of a proliferative megakaryocyte compartment, which then presumably acquires additional (epi)genetic mutations that fully transform cells to the leukaemic state.

Keynote lecture (Wed, 26 Sep, 11:40−12:30)
Approaches to targeted therapy optimization: The Epidermal Growth Factor Receptor Family as a model system

133 INVITED

Approaches to targeted therapy optimization: The Epidermal Growth Factor Receptor Family as a model system

J. Baselga. *Spain*

Abstract not received.

Special session (Wed, 26 Sep, 13:30−14:30)
Integrating molecular targeted agents into radiation therapy

134 INVITED

Specific requirements for molecular targeted agents in radiotherapy, including specific pre-clinical research designs

M. Baumann, M. Krause, D. Zips. *Universitätsklinikum Carl Gustav Carus, Radiation Oncology and OncoRay Center for Radiation Research in Oncology, Dresden, Germany*

Background: Because of its high efficacy to kill cancer cells, radiotherapy offers a particularly promising environment for integration of molecular targeted drugs into oncology.
Methods: This presentation will review preclinical research methodology and results to address the question of appropriate research strategies.
Results: Interaction of irradiation and drug action requires specific experiments for defining the potential of a new drug for combination with radiotherapy. The perfect drug for molecular targeting in radiotherapy will have little or even no activity on its own but will selectively decrease mechanisms involved in radioresistance of tumor cells. Therefore it is important to involve radiobiologists and radiotherapists, and to test the combination with irradiation at a very early stage of drug development. This is unfortunately not the case in current drug screening, development and preclinical testing. Thus, candidate compounds that are not effective alone, but could be promising for radiosensitising tumour cells have a high chance to be missed. When brought into preclinical studies combined with irradiation, proof-of-principle experiments have shown efficacy of a variety of molecular targeted approaches (e.g. EGFR and VEGFR inhibition, antibody linked chemotherapy). However, different experimental endpoints may reveal different results. Evaluation of tumor regression, tumor volume and growth delay, particularly when performed with low radiation doses and at only one dose level, may significantly overestimate the efficacy of combined treatments. One possible explanation is that these endpoints do not reflect the efficacy of the combined treatment on clonogenic cells or cancer stem cells but on the bulk of non-tumorigenic cells. Local tumor control measures inactivation of tumorigenic cells and therefore is by far more relevant for curative radiotherapy. However, tumor control assays are expensive and slow, which limits their use and calls for supplementation with surrogate markers, e.g. by using biological imaging. As specific radiobiological mechanisms (e.g. repopulation, reoxyenation) may be targeted by combined treatment approaches, it is important to select adequately characterized tumor models and relevant treatment schedules for the experiments.
Conclusions: Molecular targeting combined with radiotherapy has demonstrated effectiveness in preclinical and clinical studies. To prevent that important potential of new drugs for oncology is missed, combination with irradiation should be regularly tested at a very early stage of drug development. The validity of preclinical in vivo experiments on molecular