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

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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

targeting for radiation oncology depends critically on the appropriateness of tumor models, experimental design and endpoints.

135 INVITED

Combining molecular targeted agents with radiotherapy

S.R. Wedge[1], K.J. Williams[2], I.J. Stratford[2]. *[1]AstraZeneca, Cancer Bioscience, Cheshire, United Kingdom; [2]University of Manchester, Dept. of Pharmacy, Manchester, United Kingdom*

An increased understanding of the signalling pathways that are implicated in cancer progression has led to the identification of a number of tractable targets for therapeutic intervention. Whilst novel agents that inhibit these molecular targets may provide benefit as monotherapy, their use in combination with established modalities warrants examination in an attempt to augment existing treatment outcome. This includes the opportunity to modulate responses to ionising radiation, either through a direct effect on the repair of DNA lesions or via effects on other responses that are known to influence radiosensitivity, such as the rate of tumour cell repopulation or extent of reoxygenation. These complexities present a need for preclinical studies to examine combinations and potentially gain further mechanistic insight into the precise nature of any positive or negative interaction. There are many experimental variables to consider, including the molecular pathology of a given tumour, the selectivity profile of the novel agent, the respective treatment doses and duration of administration, and the relative sequencing of the drug/radiation combinations.
In this presentation, particular reference will be made to preclinical studies that have examined radiation in combination with inhibitors of vascular endothelial growth factor (VEGF) signalling. These have either utilised strategies that sequester VEGF ligand (using antibody or soluble receptor constructs) or used specific tyrosine kinase inhibitors, such as Vandetanib (ZACTIMA^{TM}, ZD6474) and AZD2171, which prevent VEGF receptor activation and intracellular signalling. Blockade of VEGF signalling can reduce tumour vessel perfusion and density, which could potentially increase the hypoxic tumour fraction and limit the effectiveness of ionising radiation. However, studies have shown that concomitant inhibition of VEGF signalling with fractionated radiotherapy can provide better control of tumour xenograft growth when compared to radiotherapy alone.
Ultimately, the translation of preclinical combination strategies to the clinic will benefit from additional biomarker endpoints, to define better the response of pathways to radiation and novel therapies in man.

136 INVITED

Clinical integration of EGFR inhibitors with radiation

P. Harari. *University of Wisconsin, Dept of Human Oncology, Madison, USA*

Background: Examine the impact and challenges in integrating molecular targeted therapies, particularly EGFR inhibitors, into cancer treatment.
Materials and Methods: The introduction of molecular targeted therapies in oncology is relatively recent, reflecting several decades of modern molecular biology coming to fruition in the form of smart new anti-cancer drugs. The EGFR inhibitors are highly promising agents in this arena. Increasing numbers of cancer patients are now receiving EGFR inhibitors and many clinical trials are incorporating these agents into future trial design.
Results: The scientific rationale and collective enthusiasm for advancing molecular cancer therapies is very strong. In addition to compelling preclinical results, there are now clinical trial successes that support the concept that we are making true progress. Indeed, the first Phase III trial to identify a survival advantage when combining a molecular targeting agent (anti-EGFR) with radiation has recently emerged in H&N cancer (NEJM 354: 567−78, 2006). Broadly speaking however, there are several challenges worthy of acknowledgement with regard to molecular targeting in oncology. First, there are more negative than positive clinical trials to date. There is a tendency for oncologists to illuminate positive trials and downplay or rationalize inadequacies for negative trials. Second, we may inadvertently over dramatize the impact of positive clinical trials with regard to overall benefits and translatability to global cancer populations. Third, although the toxicity profiles for most molecular targeted therapies appear milder than that of conventional cytotoxic agents, the unique toxicities of molecular therapies are not trivial, particularly for the average performance cancer patient who may be underrepresented in controlled clinical trials. Fourth, many of the new molecular targeted therapies are remarkably expensive. This high cost reflects the manner in which new drugs are discovered, developed and promoted in the current era, and this feature carries implications for who will receive these new cancer drugs in the coming years.
Conclusions: As we make stepwise advances in cancer treatment, it is important for oncologists to exercise rigor in describing the benefits achieved with each new therapy, and to remain actively engaged in promoting the rational and judicious application of new cancer treatments and technologies.

Special session (Wed, 26 Sep, 13:30−14:30)
Treatment of localised gastric cancer. Preoperative versus postoperative adjuvant treatment

137 INVITED

Treatment of localized gastric cancer: pre-operative versus post-operative adjuvant treatment

D. Cunningham. *The Royal Marsden Hospital, Medicine, Sutton, United Kingdom*

Gastric cancer is one of the most common cancers globally, and is one of the top causes of cancer related deaths. Around the world, there is significant variation in the incidence of gastric cancer, being higher in the Far East than in the United States or Western Europe. Surgery is the only potentially curative treatment modality in this disease. However only 20−30% of patients have disease which is localized and operable at the time of diagnosis and many of those who have had complete surgical resections will suffer from disease recurrence of their disease, most likely due to local or distal micrometastatic disease which was undetectable at the time of surgery. With surgery alone patients in randomized trials with operable gastric cancer have a median survival of approximately 25 months and a 5-year survival of between 20−30% [1,2]. Whilst surgical trials in Japan in particular have been able to improve on these outcomes with more extensive surgery and lymph node dissections, these results have not been reproduced in Western patients.
Systemic chemotherapy has recently been shown to improve the survival of these patients, with several trials which have used chemotherapy either perioperatively or post-operatively reporting improvements in survival in favour of adjuvant treatment. The most mature trial results are from the UK NCRI MAGIC trial in which patients treated with 3 cycles of ECF (epirubicin, cisplatin and infused 5-flurouracil, 5FU) chemotherapy before and after surgery had an improved overall and progression-free survival compared to patients treated with surgery alone [1]. The preliminary results of a French (FFCD 9703) in which perioperative treatment consisted of 2−3 cycles of 5FU and cisplatin before and after surgery also suggest a benefit for the treatment strategy [3] – updated results for this trial are expected this year. More recently, a Japanese randomized trial has reported a survival benefit from using the oral agent S-1 as post-operative adjuvant chemotherapy in patients treated with D2 gastrectomies, compared to D2 surgery alone [4]. This presentation will review the available data on the use of adjuvant chemotherapy in resectable gastric cancer, whether given as perioperative or post-operative treatment, and discuss the implications of these results on clinical practice.

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138 INVITED

Gastric cancer: multimodal treatment

C.J.H. van de Velde. *Leiden University Medical Centre, Department of Surgery, Leiden, The Netherlands*

Radical surgical dissection of gastric cancer is the basis of cure in this disease. However, because most patients in the Western world present with advanced stages, surgery alone provides long-term survival in only 20−30% of patients. Western series report locoregional failures in about 60% of patients with positive lymph nodes or involvement of the serosa [1,2]. This high relapse rate has initiated a whole spectrum of more aggressive treatments which did not result in favorable survival until the introduction of combined chemoradiation in the adjuvant setting [3].
A few prospective randomized trials, have investigated the role of more extensive lymph node dissection (D2) in comparison with the standard D1 lymph node dissection in which only the perigastric nodes are removed.