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