levels of both NIS and RARA expression were detected in benign breast tissue (NIS: 1.65±0.25 $\log_{10}$ RQ; RARA: 1.01±0.13 $\log_{10}$ RQ). Analysis based on hormone receptor status, menopausal status, tumour grade or stage revealed no significant differences in NIS or RARA expression. However, when analysed on the basis of epithelial subtype there was a trend towards higher levels of NIS expression in more invasive epithelial subtypes, with the Luminal B group having significantly lower expression than the Her2 group ($p < 0.05$).
Conclusion: This study is an important first step to further understand the presence, regulation and relevance of NIS expression in breast tumour tissue.

1114 POSTER

Pazopanib-induced hyperbilirubinemia is associated with Gilbert's syndrome UGT1A1 polymorphism

C. Xu[1], B. Reck[2], Z. Xue[2], L. Huang[2], K. Baker[2], M. Chen[2], V. Mooser[2], L. Cardon[2], C. Spraggs[2], L. Pandite[2]. *[1]GlaxoSmithKline, Therapy Area Genetics, Essex, United Kingdom; [2]GlaxoSmithKline, Research and Development, Essex, United Kingdom*

Background: Pazopanib, an oral multikinase inhibitor, has demonstrated antitumor activity in several tumour types. Despite an overall acceptable and tolerable safety profile, treatment associated elevations in transaminases and bilirubin have been observed. As pazopanib inhibits UGT1A1 activity, we sought to determine the effect of a *UGT1A1* polymorphism on bilirubin elevation in pazopanib treated patients.
Material and Methods: Association between the *UGT1A1* TA repeat polymorphism and bilirubin levels was examined in 112 Caucasian patients from a Phase II pazopanib monotherapy study (VEG102616) for metastatic renal cell carcinoma (RCC). A replication analysis was carried out in an independent sample of 124 Caucasian patients from a Phase III RCC study (VEG105192). The data were analyzed both as continuous variables (quantitative trait analysis) and as discrete values according to predefined thresholds (case-control analysis).
Results: The *UGT1A1* TA repeat polymorphism was strongly associated with pazopanib-induced hyperbilirubinemia (defined as total bilirubin levels $\geqslant$1.5 upper limit of normal) in patients from the Phase II study ($p = 7.3 \times 10^{-6}$). This association was replicated in patients from the Phase III study ($p = 2.4 \times 10^{-3}$). Of the 38 Caucasian patients with hyperbilirubinemia, 32 (84%) were carriers of one or two TA7 alleles. Overall, when compared to other genotypes, the odds ratio (95% CI) of the TA7/TA7 genotype for developing hyperbilirubinemia was 13.1 (5.3−32.2), with positive and negative predictive values of 0.49 and 0.90. All results were confirmed in analyses treating TBL as a continuous measure.
Conclusions: These data suggest that most cases of pazopanib-induced isolated hyperbilirubinemia are benign manifestations of Gilbert's syndrome, therefore support continuation of pazopanib monotherapy for mild to moderate isolated indirect bilirubin elevation without the need for population-based prospective *UGT1A1* screening. For specific patients of concern, bilirubin fractionation or *UGT1A1* genotyping should be conducted to elucidate the nature of the bilirubin elevation which might enable differentiation of the risk of progression of drug induced liver injury.

1115 POSTER

Development of cancer genetic timeline analysis for identification of cancer founder mutations and driver mutations

D. Dai[1], B. Beck[1], W. Luo[1], S. Kingsmore[2], F. Wu[1]. *[1]University of New Mexico Health Sciences Center, Obstetrics & Gynecology, Albuquerque New Mexico, USA; [2]National Center for Genome Resources, Genome Sequencing Center, Santa Fe New Mexico, USA*

With an incidence of 12.3 million and a mortality of 7.6 million, cancer increasingly presents as a serious health issue worldwide. Although there is great progress in cancer research, the genetic basis of oncogenesis is still not well understood. Increasingly powerful genomic sequencing technologies have yet to identify the causal mutations for oncogenesis and the driver mutations responsible for cancer progression. We have developed a novel cell-ontology-based strategy, Cancer Genetic Timeline Analysis (CGTA), to determine the mechanistic relevance of genetic mutations in the formation and progression of an individual tumor. RNA from matched normal and tumor specimens from a uterine cancer patient was sequenced by mRNA-seq and bioinformatic filtering identified 246 somatic non-synonymous single-nucleotide variants in the tumor transcriptome. The Sanger method was used to re-sequence these variants in genomic DNA from coisogenic normal and tumor specimens, and 26 were validated to be somatic mutations in the tumor genome. Thirty single cancer cells were acquired through laser-captured micro-dissection from frozen sections of the tumor. The genomic DNA of each cell was extracted and amplified separately. The 26 mutated genes were re-sequenced to investigate their occurrence in single cells and a phylogenetic tree was thus constructed based upon maximum parsimony and statistical partitioning of the distribution of mutations. Five mutations were ubiquitous among all 30 cells and were imputed to be present in the cancer founder cell, and thus are considered to be the oncogenic pathway for tumorigenesis. Additionally, through an analysis by a phylogenetic probability model, two mutations were identified to be driver mutations, potentially responsible for the emergence of a dominant clone. Further analysis of the identified oncogenic pathway in an additional ten uterine tumors suggested that human uterine tumors may have multiple distinct oncogenic pathways, which is consistent with recent reports in breast, colorectal, pancreatic cancer and glioblastoma, and these findings collectively provide strong evidence against the notion of a single oncogenic pathway for any type of human cancer. Without relying on the prevalence of mutations in other tumors, the CGTA method can identify the oncogenic pathway and the driver mutations in individual tumors, which could serve as the etiological and mechanistic basis for novel molecular classification and drug development.

1116 POSTER

Differential expression in inflammatory-related genes after preoperative chemoradiation (CRT) in normal rectal tissue compared with rectal carcinoma

F. Calvo[1], E. Bandrés[2], J.A. Díaz-González[3], E. Alvarez[4], J. García-Foncillas[3]. *[1]Hospital General Gregorio Maranon, Oncology, Madrid, Spain; [2]Center for Applied Medical Research. University of Navarra, Oncology, Pamplona, Spain; [3]University of Navarra, Oncology, Pamplona, Spain; [4]Hospital General Gregorio Maranon, Pathology, Madrid, Spain*

Background: Radiation therapy (RT) initiates molecular and cellular events affecting both the tumor and the tissue microenvironment. Pre-clinical growing evidence suggests that the interaction and balance between those compartment effects rather than a single action of RT over the tumor is responsible of the tumor response and normal tissue tolerance. Novel preoperative CRT strategies in rectal cancer look for improving response without increasing toxicity. Identification of differential profile of radiation-effect in tumor and normal peritumoral tissue may be useful to achieve such goal. The purpose of this study is to compare the expression profile in inflammatory-related genes between tumor and peritumoral normal tissues in a series of rectal cancer patients treated with preoperative RT.
Material and Methods: 92 inflammation-related genes and 4 *housekeeping* genes were studied by Q-RT-PCR by using Taq-Man Low Density Array in tumoral and normal tissue obtained from 15 patients homogeneously treated with oxaliplatin followed by preoperative CRT (45 Gy and oral Tegafur). In order to obtain more reliable results, we assessed the normalization data using three different approaches: global median-normalization (similar to microarray analysis), 18 s rRNA (the most stable housekeeping gene in our CRC samples) and the geometric-mean of 4 *housekeeping* genes analyzed. To identify genes with significantly differential expression between tumoral and normal samples, we performed Class Comparison test, a multivariate permutation test provided in BRB-ArrayTools package.
Results: We identify 8 common genes whose expression were different ($p < 0.01$, FDR < 0.05) with the three different normalization approaches, suggesting that tumoral presence could affect the inflammation process. 4 of them were down-regulated in tumoral tissues: 3 members of secreted serine-protease-endopeptidases kallikreins (KLK) family (KLK3, KLK15 and KLKB1) and the mitogen-activated protein kinase MAPK8. The 4 up-regulated genes included 3 receptors (ADRB1, LTB4R and MC2R) and the adhesion molecule ICAM1.
Conclusions: This study describes a differential expression in inflammatory-related genes after preoperative CRT in normal rectal tissue and rectal tumor. Further studies to confirm whether this pattern of expression may play a role in the tumor response and side effects to RT are warranted.

1117 POSTER

Identifying the challenges in establishing a lung cancer tissue repository for translational research: a single institution experience

O. Belvedere[1], N. Chaudhuri[2], A. Thorpe[2], R. Milton[2], L. Davidson[3], C. McKinley[1], P. Egan[1], C. Daly[1], K. Papagiannopoulos[2], P. Rabbitts[1]. *[1]Leeds Institute of Molecular Medicine, Experimental Therapeutics, Leeds, United Kingdom; [2]St James's University Hospital, Dept of Thoracic Surgery, Leeds, United Kingdom; [3]St James's University Hospital, Dept of Histopathology, Leeds, United Kingdom*

Background: As part of a study of molecular abnormalities associated with the development of lung cancer, we had to establish a tissue repository,