outcome of two different combination schedules. Our results were then compared against experimental data, in a single-blind test, showing our Virtual Tumour technology was able to accurately predict the experimental results.
Using the Virtual Tumour, thousands of simulations can be performed if necessary to find the best treatment regime. This allows our partners to prioritise the most effective drug combinations and the best schedules for validation *in vivo*.

566 POSTER

Frequent overexpression of Hbo1 in non-small cell lung carcinoma and its potential oncogenic role

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Background: Various histone modifying enzymes have been focused in cancer research because of their chromatin modification function by changes in acetylation or methylation status of the amino-termini of histones, which is intimately correlated to regulation of gene expression. Hbo1 is a member of MYST histone acetyltransferase family having dual functions of H4 acetylation and DNA replication licensing.
Material and Methods: To screen expression status of Hbo1, RT-PCR using fresh frozen lung cancer tissues and immunohistochemistry using tissue microarray of paraffin embedded tissue blocks were performed. Copy number profiling using array CGH and FISH were performed to identify aberration of the gene in genomic level. Using siRNA, knockdown effect of the gene in lung cancer cell line was studied.
Results: In this studies, we show that Hbo1 mRNA is frequently overexpressed in lung cancer tissues comparing normal lung tissues (9/19, 47.4%). The tendency of overexpression in cancer tissues is confirmed by immunohistochemistry (293/495, 51.2%). Its expression was correlated with histone acetylation status. Array comparative genomic hybridization assay showed frequent copy number gain at 17q21.3 region containing HBO1 gene (4/12, 33%). Knockdown of HBO1 mRNA using siRNA significantly inhibited the growth rate of Calu6 cell, in contrast to scrambled siRNA.
Conclusion: In conclusion, the histone acetyltransferase Hbo1 is frequency overexpressed in non-small cell lung cancer not only at mRNA but also protein levels. Its overexpression is supported by genomic copy number gain. Growth inhibition of tumor cell is induced by knock down of the gene. The results suggest that Hbo1 overexpression plays an oncogenic role in NSCLC and can be a potential therapeutic target.

567 POSTER

A rationale for anti-angiogenic therapy in head and neck cancer

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The clinical behavior of head and neck squamous cell carcinoma (HNSCC) is marked by a high degree of lymphatic and distant metastasis, which result in decremental decreases in overall and disease-free survival. VEGF has been demonstrated to be an important mediator of tumor angiogenesis and metastasis in HNSCC, and while anti-angiogenic therapies have been effective in other solid tumors, their role in HNSCC has not been clarified to date. Polymorphisms in the *VEGF* gene have been shown to be predictive of the clinical behaviors, treatment responses, and disease outcomes for tumors of the lung and breast. However, the impact of these mutations have not been extensively explored in HNSCC. The aims of this study were to explore the feasibility of high-throughput VEGF polymorphism analysis and to study the association between these polymorphisms and disease outcomes among patients with HNSCC.
Methods: DNA was extracted from prospectively-collected surgically-resected HNSCC tumors after IRB approval was obtained. High-throughput mutational analysis with the Sequenom® platform was performed for the following polymorphisms: *VEGF-1154G>A, VEGF-1498C>T, VEGF-634C>G, VEGF-2573C>A*. Clinical and pathological data were collected and evaluated for associations between disease outcome and tumor genotype.
Results: Genetic polymorphisms for VEGF were studied in 75 surgically-resected tumors or metastatic lymph nodes, and 58 samples (77%) were found to harbor mutations in one of the tested polymorphisms. Of these, *VEGF-634C>G* were most common, with 36/75 (48%) harboring this genotype. The *VEGF-1154G>A* and *VEGF-1498C>T* genotypes were commonly seen as well (44% and 29.3%, respectively), while the *VEGF-2573C>A* was observed in only 4 tumors. Correlation with clinical outcomes was performed, and while the presence of any polymorphism was significantly associated with death from disease ($p < 0.05$), there was no association with the presence of lymphatic or distant metastasis. When each polymorphism was analyzed independently, only the *VEGF-634C>G* genotype was associated with local-regional recurrence ($p < 0.05$) and death from disease ($p < 0.05$). Kaplan–Meier analysis revealed adverse survival among patients with any *VEGF* polymorphism ($p < 0.05$), with only 45% survival at 5 years, compared with 75% among the WT group.
Conclusions: We identified a significant percentage of patients with *VEGF* polymorphisms among surgically-resected HNSCC patients. Further, the presence of tumoral *VEGF* polymorphisms were predictive of adverse outcomes among patient with HNSCC. These data suggest that anti-angiogenic therapy may be a rational modality for selected patient with HNSCC and provide support for personalized targeted therapy in this disease. Further analysis is necessary to identify which specific polymorphisms are most predictive for both disease outcomes and treatment response.

568 POSTER

A permutation-based confidence interval for treatment effect in the identified subset of sensitive patients in biomarker-adaptive threshold design

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Background: Difficulty in prediction of clinical outcome, efficacy and toxicity, is hallmarks of most anticancer drug. In the era of molecular and individualized medicine, molecular predictive biomarker is playing an increasingly important role. However, reliable predictive biomarkers are rarely available in designing phase of a trial, and then regulatory authorities recently encourage the co-development of drug and biomarker. Jiang et al. proposed the biomarker-adaptive threshold design for situations where a candidate biomarker, which is originally measured on a continuous or ordered categorical scale, e.g. expression levels of HER2 or epidermal growth factor receptor, is available at the start of the trial but a cutoff value is not established for converting the biomarker to a binary classifier to separate sensitive from insensitive patients. This design incorporates both the identification and the internal validation procedures of a cutoff value, with protection of type I error and only a minor increase in sample size. However, estimation method for treatment effect in the identified subset of sensitive patients has not been proposed, although it is especially valuable to aid the interpretation of trial results, and the CONSORT statement requires confidence intervals for treatment effect.
Material and Methods: We develop a permutation-based confidence interval for the parameter representing treatment effect in the identified subset of sensitive patients in the framework of the biomarker-adaptive threshold design. Simulation based on models conforming to several practical situations was performed.
Results: A permutation-based confidence interval was derived, and it is consistent to the design and statistical analysis formulated by Jiang et al. Simulation results showed favorable tendency that proposed method can produce the correct confidence interval, *i.e.* it can reduce bias in parameter estimation and maintain nominal level.
Conclusions: We can construct the permutation-based confidence interval for a co-development design of drug and biomarker, and it can provide us with the valuable information about subset treatment effect.

569 POSTER

Whole-genome sequencing and analysis of an ovarian cancer patient

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Background: Ovarian cancer is the fifth leading cause of cancer death for women in the U.S. and the seventh most fatal worldwide. Although ovarian cancer is notable for its initial sensitivity to platinum-based therapies, the vast majority of women eventually recurs and succumbs to increasingly platinum-resistant disease. To elucidate somatic genetic changes of an individual tumor, we recently completed the sequencing of the tumor genome from an ovarian cancer patient as well as her germline genome using the Illumina Genome Analyzer IIx®.
Material and Methods: Genomic DNA was sheared into segments approximately 400bp long and we generated 180 bp paired-end reads. When mapped back to the genome, this provided an average coverage greater than 15-fold for both cancer and germline genomes. In order to identify single nucleotide variations (SNV) between germline and cancer,