Abstract S101 Table 1

	Low speed walkers (n = 567)	High speed walkers (n = 423)	Between group differences (p value)
Age (years)	70.9 ± 9.7	67.8 ± 9.2	p ≤ 0.001
FEV_1 (L)	1.5 ± 4.9	1.62L ± 3.8	P = 0.7
MRC (IQR)	4 (IQR 3–4)	3(IQR 2–3)	p ≤ 0.001
BMI (kg/m^2)	27.6 ± 9.0	27.1 ± 14.0	P = 0.5
Pre ISWT (m)	128.4 ± 61.6	373.4 ± 103.3	p ≤ 0.001
Post ISWT	191.8 ± 91.1	415.9 ± 115.0	p ≤ 0.001
Change in ISWT	63.4 ± 66.1	42.6 ± 67.7	p ≤ 0.001
Pre ESWT (secs)	166.3 ± 161.5	262.4 ± 147.6	p ≤ 0.001
Post ESWT	510.5 ± 428.4	631.7 ± 388.5	p ≤ 0.001
Change in ESWT	344.2 ± 401.5	369.3 ± 363.9	P = 0.3

All values are mean (±SD) unless otherwise stated. FEV_1, forced expiratory volume in 1 s; MRC, Medical Research Council; IQR, interquartile range; BMI, body mass index; ISWT, Incremental shuttle walk test; m, metres; ESWT, endurance shuttle walk test; sec, seconds.

Conclusion Interestingly, those patients who walk at a faster speed have a greater baseline ESWT performance compared to those patients who walk at a slower endurance speed. However both groups made comparable changes in the ESWT following PR.

Lung cancer biology and biomarkers

S102 SOX2 INITIATES CARCINOGENESIS IN A NOVEL ORGANOTYPIC MODEL OF BRONCHIAL DYSPLASIA

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Introduction and objectives Improving the early detection and chemoprevention of lung cancer are key to improving outcomes. The pathobiology of early squamous lung cancer is poorly understood. We have shown in a previous publication that amplification of SOX2 is an early and consistent event in the pathogenesis of this disease but its functional oncogenic potential remains uncertain. We aimed to test the impact of deregulated SOX2 expression in a novel organotypic system that recreates both the molecular and microenvironmental context in which squamous carcinogenesis occurs.

Our objectives are:

1. To develop a 3D *in vitro* model of bronchial dysplasia that recapitulates key molecular and phenotypic characteristics of the human disease.
2. To test the hypothesis that SOX2 deregulation is a key initiating event in the pathogenesis of bronchial dysplasia.

Methods We use lentiviral transduction to facilitate the inducible activation of SOX2 in immortalised bronchial epithelial cells iBECs. We use lentiviral shRNA and cutting edge CRISPR genome editing technology to introduce specific defects in key tumour suppressor pathways in order to recapitulate the molecular context seen *in vivo*. We incorporate the genetically manipulated iBECs at the air-liquid interface in a 3-dimensional tissue culture system that also comprises a stromal equivalent with embedded pulmonary fibroblasts and carefully defined media to build an organotypic model of bronchial dysplasia.

Results We develop a model that recapitulates human bronchial dysplasia. SOX2 deregulation does not cause an obvious phenotype in standard tissue culture conditions, but can initiate the dysplastic phenotype in 3D culture systems. Loss of TP53 and PTEN are co-operating genetic events that potentiate the dysplastic phenotype. The alterations in cell signalling pathways recapitulate signatures seen in invasive squamous cell lung cancer.

Conclusions In the appropriate molecular and microenvironmental context acute deregulation of SOX2 expression initiates and drives bronchial dysplasia. This confirms it's oncogenic potential in human cells. This model can be used to test the impact of therapeutic agents aimed at chemoprevention and the potential for co-operating genetic lesions to drive disease progression.

S103 SYNTHESIS OF GOLD-BASED NANOMEDICINES TO TREAT NON-SMALL CELL LUNG CANCER

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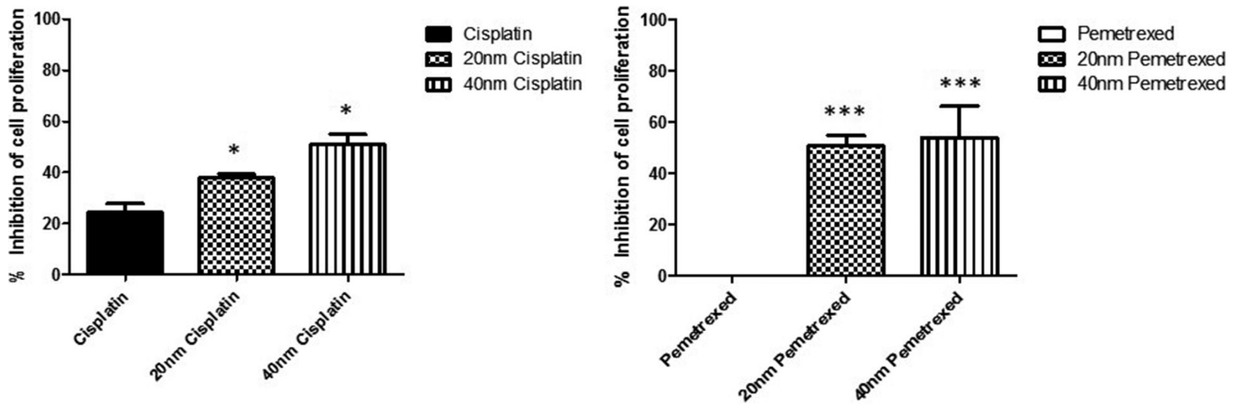
Introduction Lung cancer is the leading cause of cancer death worldwide, with an average 5 yr survival rate of just 9.5% in the UK. The success of current chemotherapy regimens for non-small cell lung cancer (NSCLC), the predominant subtype of lung cancer, is hindered by poor tumour penetration and accumulation, and systemic side effects which significantly affect patient quality of life. The field of cancer nanomedicine seeks to overcome these problems by utilising the unique physicochemical properties of nanoparticles; gold-based nanomedicines (AuNPs) show particular promise as they may be able to offer multimodal therapeutics and diagnostics in a single formulation.

Objectives This study aimed to conjugate cisplatin and pemetrexed, a first line therapy for NSCLC, to AuNPs, and investigate their efficacy on tumour cell proliferation compared to free drug. Furthermore, we investigated whether conjugation to AuNPs abrogated the inflammatory and toxic effects of these drugs on non-cancer human pulmonary epithelial cells.

Methods Cisplatin and pemetrexed were conjugated to AuNPs using heterobifunctional polyethylene glycol (PEG) linkers and were characterised by electron microscopy, ICP-OES, dynamic light scattering and thermogravimetric analysis. The effect of conjugates in *in vitro* cancer (H226 and A549 cells) and non-cancer (human alveolar type I epithelial cells) cell models were measured by electric cell-substrate impedance sensing (ECIS), MTT assay, ELISA and confocal microscopy.

Results Nanoparticle characterisation confirmed successful conjugation of cisplatin and pemetrexed to AuNPs. Confocal microscopy demonstrated that nanoparticles were internalised by cancer cells and distributed throughout the cytoplasm. Further studies showed that conjugates inhibited cancer cell proliferation significantly more than the respective free drug (Figure 1) and abrogated free drug cytotoxicity in non-cancer alveolar type I epithelial cells (0% cell death vs 30% respectively; 10 μM cisplatin; $P < 0.001$). Conjugates also attenuated chemotherapy-induced IL-6 release in both cancer and non-cancer cells; 10 μM cisplatin induced 6.6-fold and 7-fold greater IL-6 release compared to equimolar conjugates in H226 and alveolar type I epithelial cells respectively ($P < 0.001$).



Abstract S103 Figure 1 Effect of free drug and AuNP conjugates on cancer cell proliferation. A549 cells were exposed to 10 μM cisplatin (A) or pemetrexed (B) and equimolar concentrations of 20 nm and 40 nm conjugates. Proliferation was measured at 48 hours by electrical cell-substrate impedance. Data expressed as mean ± SE (n = 3). *P < 0.05 conjugate vs free cisplatin, ***P < 0.0001 conjugate vs free pemetrexed

Conclusions We have synthesised gold-based nanomedicines that are more efficacious and biocompatible than free drug in *in vitro* cell models, suggesting these formulations could have enhanced therapeutic potency and improve patient quality of life.

S104 FACTORS AFFECTING SENSITISING EGFR MUTATION RATE AND CELL TYPE IN STAGE IIIB/IV LUNG CANCER

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Introduction Treatments for advanced lung cancer in patients with a poor performance status are limited. Such patients (PS 3–4) may not be suitable for chemotherapy for NSCLC, but may benefit from chemotherapy if SCLC is confirmed or treatment with an EGFR-TKI if an EGFR sensitising mutation (EGFR-sm) is detected. Estimates of the likelihood of detecting these two subtypes will enable patients to make informed decisions about undergoing biopsy confirmation.

Aim To analyse patient factors that affect the frequency of sensitising EGFR mutations and cell types in patients with stage IIIB/IV lung cancer.

Method Retrospective review of an electronic database of stage IIIB/IV lung cancer patients with known cell type from 2008-2013 where a quantified smoking history was available. Where EGFR testing was not performed, the estimated prevalence of EGFR-sm was extrapolated from those patients tested according to cell type. Patients with small cell and large cell lung cancer were presumed to be EGFR wild type.

Results 1033 were identified who fulfilled the inclusion criteria. Cell types were as follows: Adenocarcinoma 31.2%, Squamous Cell 23.5%, Small Cell 22.7%, NSCLC NOS 16.2% and Large Cell 6.4%.

Of 348 (33.7%) undergoing genetic testing, EGFR-sm were found in 39 (11.2%) patients. These included 32 of 241 (13.3%) adenocarcinoma, 6 of 80 (7.5%) NOS and 1 of 27 (3.7%) squamous cell. The prevalence of EGFR-sm was estimated for the 384 patients with Adenocaricinoma, NOS and Squamous Cell Carcinoma who were not tested.

Table 1 shows the effect of age and pack year smoking history on EGFR mutation status and cell type. Logistic regression analysis shows increasing pack years ($p < 0.001$) and younger age ($p = 0.004$) are associated with a lower rate of sensitising EGFR mutations. Increasing pack years is associated with a higher frequency of small cell cancers, but this is not affected by age.

Abstract S104 Table 1

		Age (years)	
		<80	80+
Smoking (pack years)	**Never**	29.1% EGFR-sm	31.8% EGFR-sm
		1.9% SCLC	10.0% SCLC
		n = 54	n = 2
	<20	8.4% EGFR-sm	15.3% EGFR-sm
		16.5% SCLC	16.7% SCLC
		n = 91	n = 3
	20+	**3.4% EGFR-sm**	5.4% EGFR-sm
		25.9% SCLC	21.4% SCLC
		n = 726	n = 112

Conclusion Smoking status significantly impacts the likelihood of detecting both EGFR-sm and SCLC, whereas age alters the likelihood of EGFR-sm alone. These data may allow a more informed discussion regarding the likelihood of detecting an actionable result in patients with advanced lung cancer with poor performance when discussing options for biopsy.

S105 MICRODROPLET DIGITAL PCR FOR THE LONGITUDINAL MONITORING OF CIRCULATING TUMOUR DNA BIOMARKERS IN UNSELECTED PATIENTS WITH ADVANCED LUNG CANCER

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Introduction and objectives Circulating cell-free tumour DNA (cfDNA) can be detected in patients with solid organ malignancies and has the potential to be used as a non-invasive biomarker. Specific mutational events can be identified in biopsies using targeted next-generation sequencing and individualised microdroplet digital PCR (mdPCR) assays designed to detect and monitor the individualised biomarker in plasma. This can inform