phosphorylation of downstream targets Akt and ERK MAP kinase at a concentration of approximately 100nM and blocked the kinase activity of an EGFR mutant, T790M, which confers resistance to front-line EGFR inhibitors such as Tarceva. Compound LL001 induced full remission of subcutaneous tumors using the human NSCLC cell line H1975 (T790M/L858R+). Most notably, pharmacokinetic studies showed that LL001, when administered at a concentration of 150mg/kg in mice, showed no signs of toxicity and accumulated in the brain at concentrations ranging from 12-171 times higher than the GI50 for inhibition of EGFR+ NSCLC cell line proliferation in vitro.

In order to determine whether LL001 could effectively treat NSCLC brain metastases, we developed an intracranial injection orthotopic xenograft model for the study of NSCLC brain lesions. We found that LL001 could induce complete remission of brain tumors in 67% of mice injected with the human NSCLC cell line HCC827-luciferase, which expresses an exon 19 deletion mutant of EGFR. Compound LL001 (75mg/kg/day) reduced tumor burden in the brain to undetectable levels by in vitro imaging (IVIS) and performed significantly better than Tarceva, a reference compound. We conclude that compound LL001 crosses the blood brain barrier at levels sufficient to block the growth of EGFR+ NSCLC brain metastases and therefore may be therapeutically useful for a critically underserved patient population.

Gold nanorod immunoassay to quantify C-Met expression in NSCLC patients selected for anti-EGFR therapy

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Non-small cell lung cancer (NSCLC) is a subtype of lung cancer that is the leading cause of cancer-related mortality. The average 5-year relative survival rate for NSCLC patients is estimated to be 15.7% depending on the stage of diagnosis. 224,210 new cases of lung cancer, and 159,260 deaths were reported in the year 2014. Out of these reported numbers, NSCLC makes up almost 80% of cases. More importantly the patients are often found in late stages due to ineffective diagnosis and relative insensitivity to chemotherapy. NSCLC is a complex disease due to presence of large number of genomic alterations, such as EGFR overexpression that has been reported to be overexpressed anywhere from 43-89% depending on factors such as stage, ethnicity, and diagnostic method used. EGFR-expressing lung cancers are treated with anti-EGFR drugs such as monoclonal antibodies or small molecule tyrosine kinase inhibitors. Upon treatment with tyrosine kinase inhibitors (TKIs), NSCLC tumors have shown to acquire resistance to TKIs through mutations that circumvent the EGFR pathways targeted. One marker that has been shown to arise in tumors treated with anti-EGFR therapies is the c-Met (HGF) receptor. Once a patient has undergone several months of EGFR targeted therapy, often times a subsequent biopsy will show that the tumor now expresses a large amount of c-Met protein instead of the previously diagnosed EGFR expression. We will thus explore the notion that for a substantial amount of EGFR-expressing NSCLC tissues, there will be a population of cells which overexpress the c-Met receptor at the stage of initial diagnosis which are allowed to continue growth since EGFR is the only therapeutic target utilized for the patient treatment. As a result, a better recommendation for patient treatment would include therapies targeted both at c-Met and EGFR. For this study, we have acquired NSCLC tissues from patients who have been treated with anti-EGFR therapy. To assess levels of EGFR and c-Met in the tissues, we use our platform IHC nanotechnology consisting of gold nanorods (GNR) targeted to either receptor by means of surface modification. By adding a modified peptide specific for EGFR or c-Met to the surface of the gold nanorod, we assess levels of both EGFR and c-Met in the tissues through imaging. GNR stained tissue images can be analyzed quantitatively through specific image processing algorithms, allowing for a precise, accurate method of diagnosis compared to conventional IHC. Tissue levels of c-Met present and the patient response to anti-EGFR treatment will then be compared to determine if the patient would likely benefit from initial treatment targeted at both c-Met and EGFR.

Quantitative mass spectrometry-based proteomics identifies FRAalpha and GARFT as predictive biomarkers in tissues of non-squamous NSCLC patients treated with pemetrexed

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Lung cancer remains the leading cause of cancer mortality in United States and globally. Pemetrexed