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The performance of a comprehensive CTC anti-body capture cocktail in the detection and phenotypic analysis of CTCs.

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Tumor Biology

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Background: Traditional methods of detecting and classifying circulating tumor cells (CTCs) are complicated by detection limitations and CTC phenotypic heterogeneity. CTCs are generally defined as cytokeratin (CK)-positive, CD45-negative nucleated epithelial cells. However methodologies that rely on single antibody (EPCAM only) capture and detection (CK only) would fail to identify CTCs that are CK-negative. Identification of CK-negative CTCs (cancer stem cells (CSC) or cells undergoing epithelial-mesenchymal transition (EMT)) would be important from a tumor burden perspective and may be more aggressive, drug resistant, prone to metastasis and possibly more clinically relevant. Herein we present a method of both CK+ and CK- CTC capture and identification utilizing a cocktail of antibodies. **Methods:** Studies were conducted to determine the specificity and sensitivity of an antibody cocktail for detecting CTCs in patient samples. CTCs were captured in our microfluidic device by an antibody cocktail targeting a broad spectrum of CTCs (epithelial, EMT and stem cell). Detection was achieved by either cytokeratin or streptavidin targeting the unbound excess biotin present on the surface of the tumor cell thus captured. **Results:** Antibodies of the capture cocktail recognize surface antigens on circulating tumor cells with a high degree of specificity and sensitivity and enable the identification both CK-positive and CK-weak or negative CTCs. Our CTC detection rate on clinical samples in patients with metastatic cancer with our enhanced detection technique has improved our CTC detected rate almost three-fold. **Conclusions:** High specificity and improved sensitivity for isolating and identifying both CK-negative and CK-positive CTCs from

patient blood samples was achieved using an antibody cocktail against tumor-specific antigens in combination with our approach. Compared to traditional methods of CTC isolation and detection, the multiplexed anti-body cocktail method improves the capture and characterization of a broader range of CTC phenotypes resulting in a more thorough screen for predictive and prognostic tumor markers, thereby enabling an informed treatment strategy.

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CtDNA assay to detect EGFR mutations and mechanisms of resistance to EGFR tyrosine kinase inhibitors.

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Background: For lung cancer patients with an EGFR activating mutation, EGFR tyrosine kinase inhibitors (TKI), are standard of care, but resistance to TKIs inevitably develops. Elucidating the mechanisms of resistance typically requires post-progression tissue biopsies, which are associated with complications, and tumor heterogeneity can obscure the true mechanism of resistance. Circulating cell-free tumor DNA (ctDNA) represents an alternative method to detect resistance mutations. **Methods:** Two 8–10 mL tubes of blood were collected from 21 patients with EGFR-mutated Stage IV lung adenocarcinoma, who have progressed on EGFR TKI. Patient samples were tested for the T790M resistance mutation using Target Selector, Biocept's liquid biopsy. Results were compared to data from standard tissue biopsy. **Results:** Of the 21 patients 12/21 (57%) had deletion 19, 8/21 (38%) had the L858R mutation. EGFR status was unknown for 1 patient. CtDNA correctly identified EGFR mutation in 83 % of cases. Median duration of EGFR TKI therapy prior to ctDNA analysis was 17.3 months (range 5.2-64.4). Median time between ctDNA analysis and biopsy was 2.5 months (range 0.3-49.7). 19 patients underwent a post-progression biopsy. Tissue was T790M + in 12/19 (63%); negative in 5/19 (26%); 2/19 pending or not performed. The median mutant allele copy number of T790M in 3mL of plasma was 68 (range 7-20507). 17 patients had paired tissue and blood

samples. Sensitivity of ctDNA to detect T790M mutation was 83%, specificity 40%, PPV 77%, NPV 50%. 13 patients received therapy with 3rd generation EGFR TKI. One ctDNA T790M +, but tissue negative patient was treated with 3rd generation EGFR TKI and has not responded. Two patients with ctDNA T790M negative but tissue T790M + were treated with 3rdgeneration EGFR TKI, one responded, one response TBD. Both of those patients had low systemic burden of the disease, potentially explaining negative liquid biopsy. The analytical validation has a sensitivity of 95% and specificity of 99% at 7 mutant copies against 14,000 copies of wild type EGFR. **Conclusions:** Biocept's blood based assay to detect EGFR mutations and T790M from ctDNA is concordant with mutations present in post-progression tumor tissue biopsies.
