BSCI-18. IDENTIFYING NOVEL DRIVERS OF LUNG-TO-BRAIN METASTASIS THROUGH *IN VIVO* FUNCTIONAL GENOMICS

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INTRODUCTION: Brain metastases, the most common tumors of the central nervous system, occur in approximately 20% of primary adult cancers. In particular, 40% of patients with non-small cell lung cancer develop brain metastasis. As systemic therapies for the treatment of non-small cell lung cancer become increasingly effective at controlling primary disease, patients are ironically succumbing to their brain metastases. This highlights a large unmet need to develop novel targeted therapies for the treatment of lung-to-brain metastases (LBM). We hypothesize that an *in vivo* functional genomic screen can identify novel genes that drive LBM. METHODS: To do this, we developed a patient-derived xenograft (PDX) mouse model of LBM using patient lung cancer cell lines. This PDX model of LBM enables the use of fluorescent and bioluminescent *in vivo* imaging to track the progression of lung tumor and brain metastases. RESULTS: We have performed an *in vivo* genome-wide CRISPR activation screening to identify novel drivers of LBM. We will derive candidate genes through mouse brain and lung tissue sequencing after mice reach endpoint. EXPECTED AREA OF FINDINGS: This platform will lead to potential therapeutic targets to prevent the formation of LBM and prolong the survival of patients with non-small cell lung cancer. LIMITATIONS: There may be limitations in getting candidate hits that overlap in all mice in our first replicate. This can be remedied by conducting the *in vivo* screen in at least three biological replicates. CONCLUSION: To the best of our knowledge, this is the first genome-wide *in vivo* CRISPR activation screen searching for drivers of LBM using a PDX animal model. This study can provide a framework to gain a deeper understanding of the regulators of BM formation which will hopefully lead to targeted drug discovery.

BSCI-19. THERAPEUTIC INTERVENTION OF LUNG-, BREAST-, AND MELANOMA-BRAIN METASTASIS

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BACKGROUND: The incidence of brain metastases (BM) is tenfold higher than that of primary brain tumours. BM predominantly originate from primary lung, breast, and melanoma tumours with a 90% mortality rate within one year of diagnosis, posing a large unmet clinical need to identify novel therapies against BM. METHODS: Using a large in-house biobank of patient-derived BM cell lines, the Singh Lab has generated murine orthotopic patient-derived xenograft models of BM and captured a "premetastatic" population of BM cells that have just seeded the brains of mice before forming clinically detectable tumours: a cell population that is impossible to detect in human patients but represents a therapeutic window wherein metastasizing cells can be targeted and eradicated before establishing clinically detectable tumours. RESULTS: RNA sequencing of pre-metastatic BM cells from all three primary tumour models with subsequent Connectivity Map analysis identified a lead compound that exhibits selective anti-BM activity *in vitro*. Preliminary *in vivo* work has shown that this lead compound reduces the tumor burden of treated mice compared to vehicle control while providing a significant survival advantage. Ongoing mechanistic investigations aim to delineate the protein target of this compound in the context of the observed selective anti-BM phenotype. CONCLUSION: Therapeutic targeting of premetastatic BM cells could prevent the formation of BM and dramatically improve the prognosis of at-risk cancer patients.

CLINICAL TRIALS

TRLS-01. TRIAL IN PROGRESS: A PROSPECTIVE, MULTICENTER PHASE 2B STUDY TO ESTABLISH IMAGE INTERPRETATION CRITERIA FOR ^{18}F-FLUCICLOVINE PET IN DETECTING RECURRENT BRAIN METASTASES AFTER RADIATION THERAPY (PURSUE)

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BACKGROUND: Brain metastases are the most common intracranial tumor in adults, occurring in 10–40% of patients with cancer. Despite multimodal treatment approaches, the prognosis remains poor and post-treatment follow-up with conventional MRI (CE-T1-weighted and FLAIR/T2-weighted) of the brain is recommended to monitor for disease recurrence. However, owing to the similar appearance of treatment-related changes like radiation necrosis with that of true recurrence, conventional MRI has low specificity. Given the high mortality of patients with brain metastases and the considerable treatment-associated morbidity, a need remains for an imaging modality that accurately differentiates recurrence from treatment-related changes. Accurate imaging could help physicians identify patients for whom non-effective or unneeded treatments can be ceased in order to minimize treatment-associated morbidity, and to avoid erroneous premature cessation of potentially effective therapy. ^{18}F-Fluciclovine is a synthetic amino acid-based PET imaging agent that has potential to evaluate primary and metastatic brain cancers owing to its low normal background uptake in the brain and increased uptake in brain tumors. METHODS: NCT04410367 is a prospective, open-label, single-arm, single-dose (185 MBq ± 20%) study with a primary objective to establish visual image interpretation criteria for 18F-fluciclovine PET studies of recurrent brain metastases. Forty subjects with solid tumor brain metastases who have undergone radiation therapy will be enrolled across 8 US sites if they have a reference lesion considered equivocal on MRI for recurrent brain metastasis and are planned for craniotomy. Subjects will undergo 18F-fluciclovine PET <28 days after the equivocal MRI and 2–21 days before planned craniotomy. Outcome measures comprise diagnostic performance of 18F-fluciclovine PET at different thresholds of 18F-fluciclovine uptake compared with histopathology, subject- and lesion-level diagnostic performance based on application of the established image interpretation criteria, and safety evaluations. Enrolment began in August 2020 and the trial is open at the time of submission.

TRLS-02. TRIAL IN PROGRESS: A MULTICENTER PHASE 3 STUDY TO ESTABLISH THE DIAGNOSTIC PERFORMANCE OF ^{18}F-FLUCICLOVINE PET IN DETECTING RECURRENT BRAIN METASTASES AFTER RADIATION THERAPY (REVELATE)

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BACKGROUND: Brain metastases occur in up to 40% of patients with cancer and are associated with poor prognosis and considerable levels of recurrence. Consequently, close follow-up with serial brain MRI is performed post-treatment to monitor for recurrent disease. Although conventional MRI (CE-T1-weighted and FLAIR/T2-weighted) is the recommended follow-up modality, it has poor specificity with limited ability to differentiate between true disease recurrence and treatment-related changes such as radiation necrosis. Therefore, alternative imaging options are sought in order to help physicians confidently diagnose treatment-related changes and thus reliably stratify the risk of continuation of a therapeutic regimen, especially given the morbidity associated with current treatments. Amino acid PET imaging agent, 18F-fluciclovine, has increased uptake in brain tumors relative to normal tissue and may be useful for detecting recurrent brain metastases. METHODS: NCT04410133 is a prospective, open-label, single-arm, single-dose (185 MBq ±20%) study with a primary objective to confirm the diagnostic performance of ^{18}F-fluciclovine PET (read with conventional MRI for anatomical reference) for detection of recurrent brain metastases where MRI is equivocal. Approximately 150 subjects with solid tumor brain metastases who have undergone radiation therapy will be enrolled in this multicenter trial (~18 US sites) if they have a lesion considered equivocal on MRI that requires further confirmatory diagnostic procedures such as biopsy/neurosurgical intervention or clinical follow-up. Subjects will undergo 18F-fluciclovine PET <28 days after the equivocal MRI and 2–21 days pre-biopsy/neurosurgical intervention. Clinical follow-up will occur for 6m post-18F-fluciclovine PET. Secondary objectives include evaluation of subject- and lesion-level 18F-fluciclovine negative and positive percent agreement (equivalent to specificity and sensitivity respectively) for recurrent brain metastases, inter-reader and intra-reader agreement, and safety evaluations. Enrolment began in October 2020 and the trial is open at the time of submission.

TRLS-03. INTRACRANIAL ACTIVITY OF TEPOTINIB IN PATIENTS WITH *MET* EXON 14 (*MET*EX14) SKIPPING NSCLC ENROLLED IN VISION

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