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Brain metastasis mouse models for the evaluation of multikinase inhibitors on ROS1-fusion-positive lung cancer

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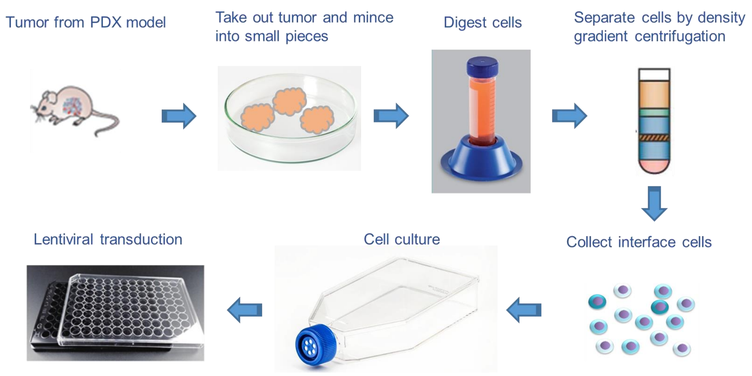
Background

Lung cancer is the leading cause of cancer-related death worldwide. Nearly 80% of lung cancers are non-small cell lung cancer (NSCLC) and 60% of them are diagnosed at the metastatic stage.
Brain metastases affect more than 20% of NSCLC patients with poor prognosis and disabling symptoms. However, few therapies have been approved for the treatment of lung cancer brain metastases. A panel of rapid, predictive and clinically-relevant animal models are urgently needed to study the biology of brain metastases and to identify effective therapeutic approaches.

Method

Here we describe methods for efficient establishment of brain metastases mouse models via different injection route (intracranial or intracarotid). Meanwhile, we established a novel ROS1 positive patient-derived xenograft (PDX) model together with its PDC sub-line, in which the exon 2 of SDC4 was fused to the exon 32 of ROS1 (SDC4ex2-ROS1ex32). The cell has been transduced with firefly luciferase expression vector for in vivo imaging detection. Three ROS1 inhibitors were tested on these brain metastasis models to compare their efficacies.



Schematic diagram procedure to generate LU-01-0414 luc model.

Result

Sample ID	genes5p->genes3p	Reads#	genes5p breakpoint	genes3p breakpoint	5'gene FPKM	3'gene FPKM
LU-01-0414	SDC4-exon2->ROS1-exon32	755	chr20: 43,964,422	chr6: 117650609	271.2	98.2

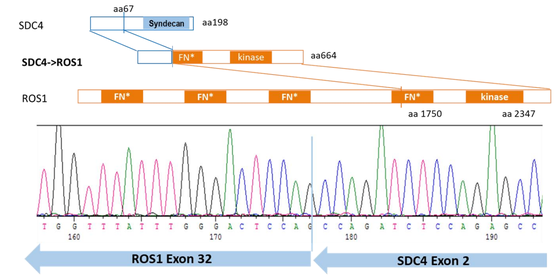


Fig.1 ROS1 fusion identification of LU-01-0414-luc model. ROS1 fusion was identified by RNAseq with 755 reads cover the fusion junction. The fusion was further confirmed by PCR and sanger sequencing.

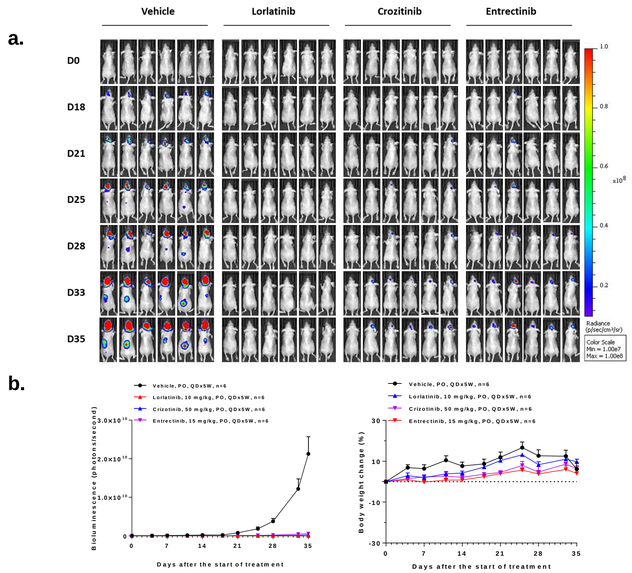


Fig.2 Growth kinetics and drug response in BM model via intracranial injection. a. Bioluminescent imaging of BALB/C nude mice injected with $3x10^5$/3 μL LU-01-0414 luc cells via intracranial injection and treated with either vehicle control or ROS1 inhibitors. n=6 for each group. b. Tumor growth curve as measured by average relative photon intensity (n=6) and body weight change of mice.

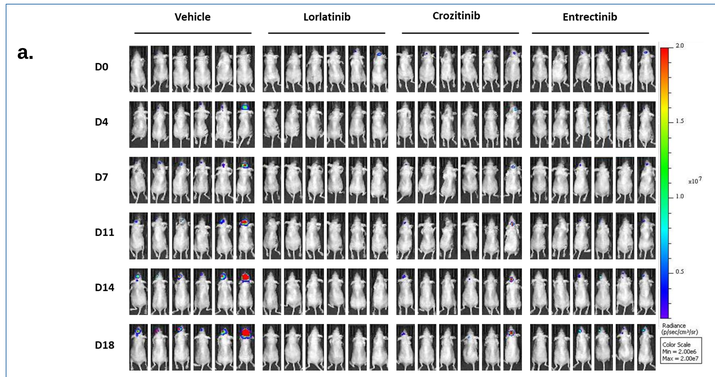


Fig.3 Growth kinetics and drug response in BM model via intracarotid injection. a. Bioluminescent imaging of BALB/C nude mice injected with $1x10^5$/100 μL LU-01-0414 luc cells via intracarotid injection and treated with either vehicle control or ROS1 inhibitors. n=6 for each group. b. Tumor growth curve as measured by average relative photon intensity (n=6) and body weight change of mice.

Summary

- A ROS1 positive patient-derived xenograft model together with its PDC-luc subline for *in-vivo* brain metastasis model was established.
- *In-vivo* brain metastases models were established via intracranial and intracarotid injection to provides a reliable platform for the mechanisms of metastatic development as well as a clinically relevant therapeutic screening. The use of such techniques will increase our knowledge of the metastatic process and help identify new targets of cancer metastasis.

Reference

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