AACR Annual meeting 2022

Intra-carotid artery brain metastasis models for the evaluation of lung and breast cancer drugs

No.5988

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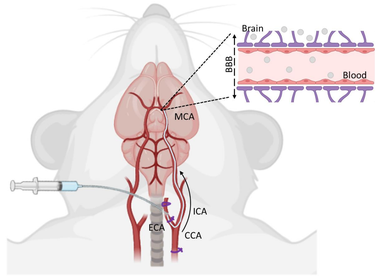
Background

Non-CNS metastatic brain cancer is about 10 times more common than CNS cancer. Lung cancer and breast cancer account for most brain metastasis. KRAS-mutant NSCLC compose a third lung adenocarcinoma, among which 17% to 55% will develop brain metastases. Likewise, more than a third HER2-positive breast cancer will develop brain metastasis. Among existing animal models, the ectopic injection in brain cannot reflect the mechanism of tumor invasion and metastasis, while tail vein and intra-cardiac injection usually produces extra-cerebral metastatic disease and the animals have to be sacrificed before brain metastases appeared.

Method

Luciferase-labeled cells	• Cell line with hot targets (e.g.: EGFR, KRAS, HER2 and BRAF)
Intra-carotid artery model development	• Optimization of tumor location, survival and stability
Intra-carotid artery Model validation	• Bioluminescence intensity curve, animal health status and pathology of brain
Drug evaluation	• Multiple modalities including TKI Inhibitors, antibody, drug conjugate etc.



Results

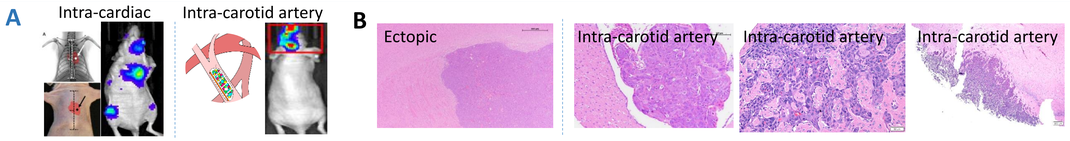


Fig 1 Advantages of the intra-carotid artery Model

A) Bioluminescent imaging of intra-cardiac artery mouse and intra-carotid artery mouse. Tumors were detected in the lung, bone, brain and other parts of body by intra-cardiac artery injection, while only detected in the brain by intra-carotid artery injection.

B) H&E staining images of typical ectopic model and intro-carotid artery models. Ectopic model showed single metastases with clear border between brain and tumor mass, while intra-carotid artery model can replicate single large lesions, multiple metastases and meningeal metastasis which mimic clinic.

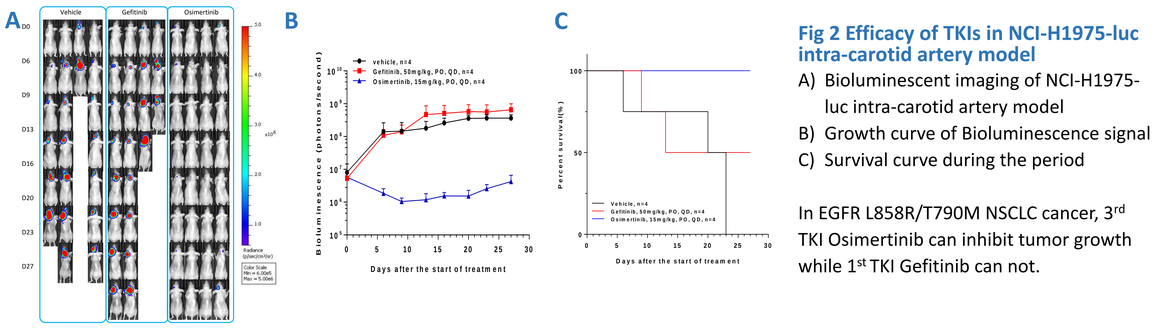


Fig 2 Efficacy of TKIs in NCI-H1975-luc intra-carotid artery model

A) Bioluminescent imaging of NCI-H1975-luc intra-carotid artery model

B) Growth curve of Bioluminescence signal

C) Survival curve during the period

In EGFR L858R/T790M NSCLC cancer, 3rd TKI Osimertinib can inhibit tumor growth while 1st TKI Gefitinib can not.

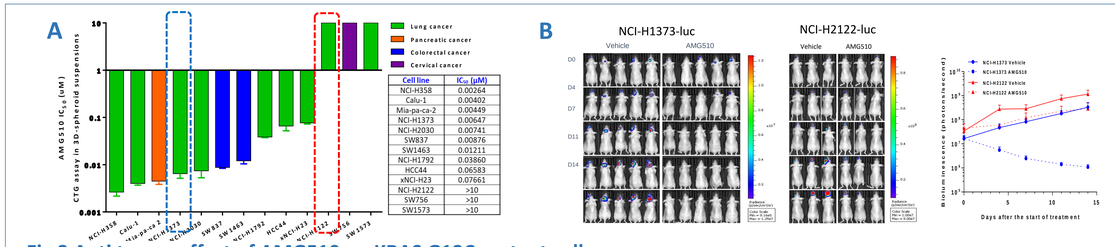


Fig 3 Anti tumor effect of AMG510 on KRAS G12C mutant cells

A) IC50 of AMG510 on KRAS G12C mutant cells. B) Efficacy study of AMG510 in NCI-H1373-luc intra-carotid artery model and NCI-H2122-luc intra-carotid artery model.

NCI-H1373 can achieve better tumor inhibitory effect compared to NCI-H2122 both *in vitro* and *in vivo*.

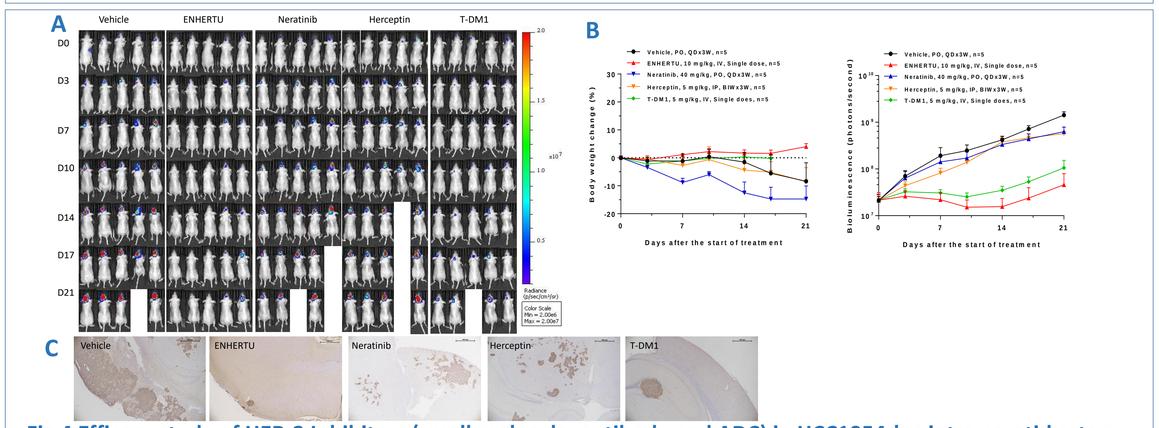


Fig 4 Efficacy study of HER-2 Inhibitors (small molecule, antibody and ADC) in HCC1954-luc intra-carotid artery model

A) Bioluminescent imaging of HCC1954-luc intra-carotid artery model. B) Body weight curve and growth curve of Bioluminescence signal. C) IHC staining of brain tissue.

HER-2 ADC (ENHERTU and T-DM1) can inhibit the tumor growth of HCC1954 intra-carotid artery model, while small molecule Neratinib and antibody Herceptin can't.

Summary

- Intra-carotid artery brain metastasis model can provide a better observation opportunity compared to intra-cardiac model, and well mimic the penetration through Blood brain barrier (BBB) compared to ectopic model.
- Several intra-carotid brain metastasis models from lung cancer have been developed including EGFR and KRAS related models (e.g. 3rd TKI sensitive model, KRAS G12C sensitive and insensitive models). These well-established models can serve for the next generation drug development.
- Several intra-carotid artery brain metastasis models from breast cancer have been developed. HER-2 positive model HCC1954 showed a good discriminative power on anti-HER2 modalities including antibodies, small molecules and ADC.
- In summary, we have developed a panel of intra-carotid artery brain metastatic models for drug evaluation, and demonstrated their superiority in growth kinetics, brain microenvironment and drug. These models can be a promising predictive tool for novel drug/modality discovery to target brain metastasis.

Reference

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