Meeting Report | Molecular Targeting Probes - Radioactive & Nonradioactive

Synthesis and preclinical evaluation of a molecular probe for imaging lung cancer with L858R/T790M mutation of epidermal growth factor receptor (EGFR)

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Abstract

471

Introduction: Tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor (EGFR) have been widely used for treatment in non-small cell lung carcinoma (NSCLC). Although they have a great clinical effect, patients carrying the dual mutation $EGFR^{L858R/T790M}$ only respond to third-generation EGFR-TKIs. Thus, detecting the mutation status of EGFR is essential before therapy to ensure effectiveness and efficiency. CO-1686 is one of the third-generation EGFR-TKIs, which are selective toward $EGFR^{L858R/T790M}$ and so radiolabeled CO-1686 is expected to work in monitoring $EGFR^{L858R/T790M}$ mutation. In this study, we aim to provide a novel radiolabeled probe, *N*-{3-[(2-{[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]amino}-5-(trifluoromethyl)pyrimidine-4-yl] amino}-5-([^{125}I]iodophenyl)acrylamide ([^{125}I]ICO1686) to determine the $EGFR^{L858R/T790M}$ mutation for selection of sensitive patients to the therapy by imaging.

Methods: The precursor was synthesized by tributylstannylation of cold ICO1686. [^{125}I]ICO1686 was prepared by iododestannylation of a corresponding tributylstannyl precursor with [^{125}I]NaI and NCS. We evaluated the plasma stability and biological potency of [^{125}I]ICO1686 as molecular probes for detecting $EGFR^{L858R/T790M}$ using three human NSCLC cell lines: H1975 (dual mutation $EGFR^{L858R/T790M}$), H3255 ($EGFR^{L858R}$ active mutant), and H441 (wild-type EGFR).**Results:** A reliable [^{125}I]ICO1686 radiosynthesis

In this issue

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Table of Contents
Index by author

Article Alerts
Email Article
Citation Tools
Share
Tweet
Suka 0

Jump to section

Article
Info & Metrics

was established with high radiochemical yield (77%) and purity (>99%). In vitro radioactivity accumulation in H1975 was three and ten-fold higher than those in H3255 and H441, respectively. The cell uptake of [^{125}I]ICO1686 into H1975 was significantly blocked with nonradioactive CO-1686, which indicates that the binding site of [^{125}I]ICO1686 is identical with that of CO-1686. The tracer revealed high stability in plasma with >90% at 60 min. In vivo biodistribution study, the accumulation of the tracer in H1975 tumor (1.8 %ID/g) tended to be higher compared to that in H3255 tumor (1.6 %ID/g) at 60 min postinjection. However, the tumor-to-background ratio needs to optimize.**Conclusion:** This radiotracer holds great potential and can serve as a pioneer to discover new potential radiotracers for EGFR$^{L858R/T790M}$ mutation.

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