

Comparative Effects of Synthesized BACE1 and EGFR Antagonists on Lung Cancer Metastasis

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Abstract. Non-small cell lung cancer (NSCLC) remains a leading cause of cancer mortality, largely due to high rates of multi-organ metastasis and emerging drug resistance to conventional therapies. Recent findings implicate beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) in driving NSCLC brain metastasis by cleaving the extracellular domain of epidermal growth factor receptor (EGFR) and activating downstream Ras-Raf-MEK-ERK signaling. To address metastatic spread and overcome resistance, this study evaluates two newly synthesized antagonists targeting BACE1 and EGFR. The BACE1 inhibitor has reduced toxicity in the brain and-specific metastasis; the EGFR inhibitor prevents dimerization and induces lysosomal degradation to overcome resistance. Using an orthotopic immunocompromised mouse xenograft model inoculated with bioluminescent human NSCLC cells (CRUK0748-XCL-GLD), we evaluated prevention (pre-inoculation) and therapeutic (post-inoculation) regimens across brain, liver, and bone metastatic sites. BACE1 shows the most prominent early brain effects; EGFR has broader, prolonged inhibition in the liver and bone. Overall, these findings highlight dual-target inhibition of the BACE1-EGFR axis as a novel, potent, and resistance-evading strategy for comprehensive control of metastatic NSCLC.

Keywords: Synthesized BACE1 Antagonists, Synthesized EGFR Antagonists, Lung Cancer Metastasis

1. Introduction

By 2025, there will be more than 2 million deaths from lung cancer around the world, and it remains the top cause of cancer deaths [1]. Although there have been some achievements in cancer treatment recently, many of the current problems of drug resistance and metastasis remain unsolved. Based on the above, this paper aims to propose a potential therapeutic strategy through the design of antagonists targeting epidermal growth factor receptor (EGFR) and beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), and to investigate and compare their effectiveness in inhibiting the metastasis and proliferation of non-small cell lung cancer (NSCLC).

Lung cancer has many kinds, such as squamous cell carcinoma, adenocarcinoma, small cell carcinoma and large cell carcinoma, etc. [2]. Non-small cell lung cancer (NSCLC) includes adenocarcinoma and squamous cell carcinoma, and about 85 per cent of all diagnosed cases are

NSCLC. Subtypes have also been identified among these groups, such as lepidic-predominant adenocarcinoma and basaloid large cell carcinoma, and there are various molecular and pathological alterations in the disease.

To investigate the molecular reasons for metastasis in non-small cell lung cancer (NSCLC), we have selected two representative target genes involved in cell signalling and tumour development as the subjects of study: EGFR and BACE1. EGFR is a kind of transmembrane receptor that regulates the pathways of cell division, survival and migration by RAS/RAF/MEK/ERK. EGFR is frequently mutated or overexpressed in NSCLC, and thus unregulated signalling and tumour proliferation occur [3, 4]. EGFR inhibitors are now the first-line targeted treatments, but due to resistance mechanisms such as secondary mutations, altered signalling pathways or changes in the tumour microenvironment, many patients do not respond. BACE1 (beta-site APP cleaving enzyme 1) is an aspartic protease that generally increases the production of β -amyloid peptides in Alzheimer's disease. BACE1 inhibitors have good safety and crossed the blood-brain barrier in clinical trials for neurodegeneration. Recently, scholars have also found that BACE1 is related to the spread of cancer in the brain [4]. Cleavage of EGFR can promote the migration of cancer cells and regulate the downstream signalling.

We propose to synthesize antagonists of both EGFR and BACE1 in this paper and examine their inhibitory effects on NSCLC metastasis. Based on in vitro and in vivo studies, we will investigate the effect of these inhibitors on the metastasis of tumours to the three primary sites for metastasis: the brain, liver and bone. The two targets may be new ways to address resistance and enhance the results for non-small cell lung cancer patients.

To guide the development of our inhibitors and experimental design, we have studied the three relevant research papers on EGFR resistance, new extracellular EGFR inhibitors and the new role of BACE1 in lung cancer brain metastasis.

1.1. Study 1: ligand-activated EGFR/MAPK signaling, but not PI3K; these are key resistance mechanisms to EGFR-inhibitor therapy in colorectal cancer

Research on the development of resistance to EGFR- and VEGF-targeted therapy in colorectal cancer (CRC) patients is presented here [5]. Only the IMblaze370 trial patients were included; resistance to anti-EGFR drugs is frequently caused by alterations in EGFR/MAPK pathway genes, but not PI3K pathway genes. Mutations in the EGFR extracellular domain (ECD) occur more often in patients with resistance. Patients with higher basal expression of EGFR ligands are more likely to develop resistance through mutations. The paper also puts forward that, in the event of resistance, an EGFR- and KRAS-inhibitor combination may be used.

The research also found that patients treated with anti-EGFR drugs had a relatively high proportion of chromosomal gains, particularly on chromosome 8, which carries the MYC gene, and this may be related to resistance. Therefore, the research indicates that EGFR ligands can be used as prognostic indicators for treatment response, and the development of EGFR-inhibiting agents should be considered. The above data provide support for modifying the treatment plan of metastatic colorectal cancer (mCRC) to target the EGFR/MAPK pathway and adjust drug combinations.

1.2. Study 2: preliminary discovery of small molecule inhibitors of epidermal growth factor receptor (EGFR) that bind to the extracellular domain

This paper reports the discovery of DSF-102, a small-molecule inhibitor of epidermal growth factor receptor (EGFR) that binds directly to the extracellular domain (ECD) of EGFR and thus avoids

inhibition of the intracellular tyrosine kinase domain characteristic of most EGFR inhibitors [6]. EGFR is a receptor tyrosine kinase that is frequently overexpressed in non-small cell lung cancer (NSCLC) and therefore promotes the uncontrolled proliferation and metastasis of cells. DSF-102 is a non-conventional inhibitor that avoids the issue of kinase domain mutation resistance by blocking ligand-induced EGFR dimerization and activation extracellularly.

DSF-102 suppresses the downstream signal via the MAPK and PI3K/AKT pathways, and also promotes the degradation of EGFR by diverting it to the lysosomal degradation pathway from the recycling endosome. DSF-102 reduced EGFR expression in KRAS-mutant A549 cells and inhibited oncogenic signals.

An extracellular targeting strategy is used to develop new therapeutics or synthetic proteins with the same function as DSF-102, and they can also be combined with kinase inhibitors for a synergistic effect. Provide the foundation for the following models of EGFR signalling inhibition at different stages of cancer development, such as metastatic formation and metastasis spread.

1.3. Study 3: a genome-wide in vivo CRISPR activation screen identifies BACE1 as a therapeutic vulnerability in lung cancer brain metastases

This paper investigates the molecular path of brain metastases in non-small cell lung cancer (NSCLC) and identifies BACE1 as an oncogenic factor via genome-wide CRISPR activation screening [4]. Approximately 40% of the patients with non-small cell lung cancer (NSCLC) had developed brain metastases and were in a poor health state. Using patient-derived lung cancer cell lines and xenograft mouse models, the authors have shown that elevated BACE1 promotes brain metastasis; therefore, BACE1 deletion or inhibition (e.g., with MK-8931) effectively inhibits tumour dissemination and extends the life of mice.

A mechanistic study has shown that BACE1 modulates the activity of the EGFR/MEK/ERK signalling pathway by cleaving a specific site in EGFR (L119→A120), thus promoting the migration, invasion and brain metastasis of cancer cells. BACE1 and EGFR are in physical contact, and the catalytic activity of BACE1 is required for it to promote the development of brain metastasis. There is clinical data in the article to support that BACE1 is highly expressed in NSCLC patients with brain metastases and is associated with a shorter lifespan; therefore, it may be used as a new therapeutic target. BACE1 inhibitors have shown a good safety profile and blood-brain barrier permeability in clinical trials for Alzheimer's disease, and are also expected to be developed as drugs for treating brain metastases of lung cancer.

A new molecular mechanism for brain metastasis of lung cancer has been proposed in this paper, and a theoretical basis for BACE1-targeted therapy has been provided. In the future, more studies will be carried out on how BACE1 regulates EGFR signalling and its function in the immune microenvironment to advance the clinical application of related drugs and improve the therapeutic effect and prognosis of lung cancer patients with brain metastases.

2. Materials and methods

2.1. Working model

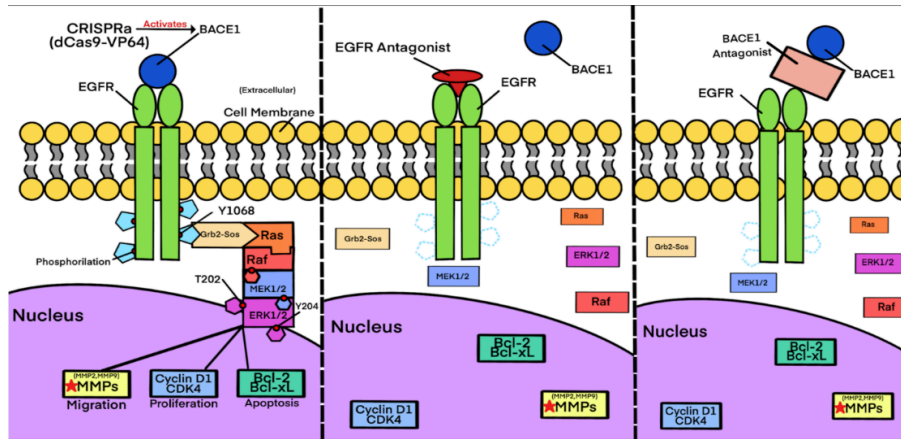


Figure 1. Theoretical mechanism of BACE1-EGFR signaling pathway and EGFR and BACE-1 antagonists

Figure 1 shows the regular pathway of EGFR and BACE-1 binding and the pathway after inhibition of EGFR and BACE-1, respectively. In research on brain metastasis of non-small cell lung cancer (NSCLC), CRISPR activation technology has been employed to specifically enhance the expression of the BACE1 gene; at the same time, a dCas9-VP64 complex is used to bind to the promoter region of BACE1 to increase the level of BACE1 protein, and thus its effect on tumor metastasis in vivo and in vitro has been investigated. BACE1 and EGFR have been found to be in close physical proximity at the cell membrane in a study. BACE1 can specifically cleave the extracellular domain of EGFR, and the primary cleavage site is L119-A120. Cleavage of EGFR results in a change in its shape, and thus it can phosphorylate itself by adding phosphate groups to tyrosine residues and become active. Activated EGFR further recruits the adaptor protein Grb2, which binds to and activates Sos; thus, Ras is activated. Activated Ras binds GTP to activate the downstream Raf kinase, which in turn phosphorylates MEK1/2; MEK1/2 acts as a bispecific kinase and phosphorylates ERK1/2 at T202 and Y204. Phosphorylated ERK1/2 is transported to the nucleus, binds with transcription factors, alters the expression of genes associated with cell migration and invasion, such as matrix metalloproteinases (MMPs), and thereby promotes the migration and invasion of cancer cells by degrading the extracellular matrix. The mechanism of BACE1 expression activation → EGFR cleavage and activation → classical Ras-Raf-MEK-ERK signalling pathway → regulation of migration-related genes is a molecular pathway network that promotes NSCLC brain metastasis.

2.2. Mechanisms of the two antagonists

2.2.1. BACE1—"A"(modified MK-8931)

Mechanism: Some inhibitory MK-8931 derivatives have been modified to achieve "moderate inhibition" of BACE1 enzyme activity and avoid complete inhibition [7]. It still occupies the active site of BACE1 but weakly binds to it or inhibits conformational change; thus, only the cleavage efficiency of the BACE1 substrate is reduced, not completely blocked [7, 8]. Stable interaction with

the key residues of the active site (such as Asp32 and Asp228) was reduced after replacing the groups in the MK-8931 structure that strongly bound to the active pocket of BACE1 (such as the hydrophobic group at the P1 or P2 site) [8]. Therefore, the enzyme has a reduced affinity for the substrate and is unable to process the substrate efficiently.

2.2.2. EGFR—"B" (modified TKI)

Mechanism: The original molecular structure of conventional. It was intended to be in line with some parts of the ATP molecule. Thus, it will also be able to enter the ATP-binding pocket. As the TKI has a high affinity for the pocket compared with ATP, it can effectively "occupy the seat" and exclude true ATP [9]. Novel inhibitors do not bind to the ATP pocket but instead bind to the allosteric site; they are stably associated with residues such as Glu762 through non-covalent hydrogen bonds and thus avoid resistance caused by ATP-pocket mutations (e.g., C797S, T790M) [9]. When EGFR is in an inactive state, the allosteric pocket is exposed; at this time, inhibitor "B" quickly binds to it and forms strong hydrogen bonds with residues such as Glu762 [9].

2.3. Experimental approach

In terms of the above hypothesis, the following specific goals have been set:

1. To find new inhibitors of BACE1 and EGFR, and to develop antagonists by identifying deficiencies in the previous inhibitors.
2. The antagonists of EGFR and BACE-1 have been designed and synthesized; now, experiments will be conducted to evaluate their inhibitory effects on tumour metastasis in model organisms. Then we will collect the data and compare the control group, the EGFR antagonist, the BACE-1 antagonist, and the group using both.
3. Both BACE1 and EGFR inhibitors reduce brain metastasis by inhibiting EGFR activation; however, our new extracellular EGFR inhibitor may have other advantages, such as preventing receptor dimerization and promoting lysosomal degradation, and is therefore expected to be more effective in suppressing liver and bone metastases where receptor recycling and local microenvironmental factors frequently limit the effects of BACE1-targeted strategies. In combination, the above mechanisms are expected to achieve more uniform anti-tumour effects in the brain, liver and bone metastatic sites.

Table 1. Experimental grouping based on timing and combination of EGFR and BACE1 inhibitors

	I	II	III	IV	V	VI	VII	VIII
BACE1	-	-	PRE	-	PRE	POST	-	POST
EGFR	-	-	-	PRE	PRE	-	POST	POST
Tumor	-	+	+	+	+	+	+	+

To explore the inhibitory effects of BACE1 and EGFR inhibitors on the initiation and spread of non-small cell lung cancer (NSCLC) in this study, an orthotopic xenograft model will be established in NOD/SCID. NSG mice are immunodeficient and support good engraftment of human cancer cells. CRUK0748 XCL GLD is a human non-small-cell lung cancer cell line that has been modified to stably express GFP and luciferase [4]. We would inject these cells subcutaneously into the mice and create a local solid tumour model. As these cells are light-emitting, they can be used for in vivo imaging to observe the speed of tumour growth and whether the treatment has been effective. The

model can help us understand the progress of cancer and how well it responds to treatment more easily.

In Table 1, the eight experimental groups (I-VIII) of mice will be divided according to the different treatment conditions. A "+" indicates a positive value, a "-" indicates a negative value, "Pre" is before tumour inoculation, and "Post" is after tumour inoculation in the design.

Group I is the negative control, and neither tumour cells nor treatment will be applied here. Group II is a positive control, and no treatment or intervention will be performed on the tumor cells. Groups III to V will be given the treatment before the tumour cell injection to determine how well the BACE1 and EGFR antagonists prevent metastasis and establishment. Groups VI-VIII received the model therapeutic intervention and then injected tumour cells to inhibit further tumour growth.

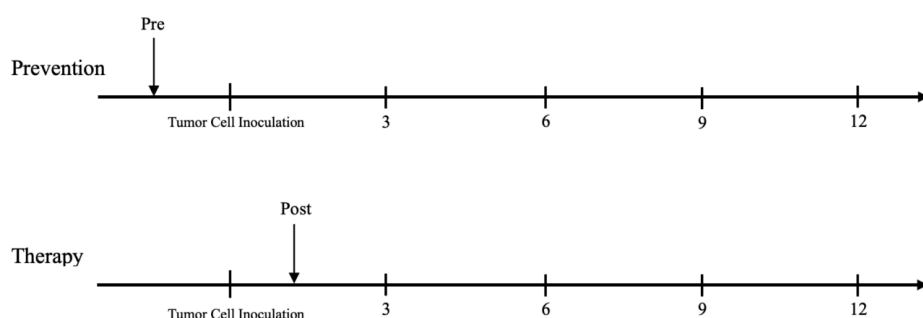


Figure 2. Schematic diagram of antagonist injection time and observation of tumor migration

As shown in Figure 2, to monitor the spread and metastasis of tumors, Bioluminescence Imaging (BLI) will be regularly employed to detect the location, size and growth speed of tumors, and thus assess the effect of inhibitors.

To determine whether BACE1 inhibition and our extracellular EGFR inhibitor have different efficacies in the metastatic sites of the brain, liver and bone, we will conduct the corresponding experiments in these models. These treatments will be used at two different times: in the early stage before widespread metastasis and later on, after metastasis has occurred. The BACE1 inhibitor reduces EGFR cleavage and downstream signalling, and our EGFR inhibitor prevents receptor dimerization and induces lysosomal degradation. As shown in Table 2, we believe that our EGFR inhibitor will consistently show better results, especially in the liver and bone, where a complex tumour microenvironment and receptor recycling may reduce the effectiveness of BACE1-targeted therapy.

Table 2. Comparative effects of BACE1 and extracellular EGFR inhibition in metastatic sites and treatment phases

ORGAN SITE	INTERVENTION TYPE	TREATMENT TIMING	OBSERVED ANTI-TUMOR EFFECT
BRAIN	BACE1 inhibitor	PRE/POST	moderate
	EGFR inhibitor	PRE/POST	high
	Combined	PRE/POST	very high

Table 2. (continued)

LIVER	BACE1 inhibitor	PRE/POST	low
	EGFR inhibitor	PRE/POST	moderate
	Combined	PRE/POST	high
BONE	BACE1 inhibitor	PRE/POST	low
	EGFR inhibitor	PRE/POST	moderate
	Combined	PRE/POST	high

As shown in Table 2, the effect of treatment varies by the site of disease, type of inhibitor used and time elapsed since the start of treatment. Both BACE1 and EGFR inhibitors showed good results when used early for brain metastases, but the extracellular EGFR inhibitor performed better overall and, in combination with BACE1 inhibition, was even better. In liver and bone metastases, BACE1 inhibition was less effective at later stages, but our EGFR inhibitor still performed better. Therefore, although both treatments reduce the activity of EGFR, our inhibitor is also capable of regulating receptor trafficking, and thus may be a more universally effective option in various metastatic sites.

3. Anticipated results

To determine the therapeutic effect of the EGFR and BACE1 inhibitors we have synthesized, we will establish a human non-small cell lung cancer (NSCLC) xenograft model by injecting CRUK0748-XCL-GLD cells into NSG mice. Treatments were given either before (early) or after (late) tumour inoculation, and metastases in the brain, liver and bone were tracked by bioluminescence imaging.

BACE1 inhibitor "A", for example, a modified MK-8931, is proposed to be designed for partial inhibition to avoid neurological side effects such as synaptic dysfunction and cognitive decline. By reducing the interaction of the active site residues Asp32 and Asp228, it is hoped that some enzymatic activity will be retained and EGFR cleavage inhibited [10]. It is effective in inhibiting brain metastases of living organisms, especially after early treatment; however, due to the complex microenvironment of the liver and bone, it is less effective there.

EGFR antagonist "B" is proposed to be engineered to overcome resistance mutations like C797S by targeting an allosteric site rather than the ATP-binding pocket [11]. C797S mutation causes drug resistance to EGFR inhibitors targeting T790M, which is a secondary mutation that initially emerges to resist first- and second-generation Tyrosine Kinase Inhibitors (TKI) [12]. Binding non-covalently to Glu762 and Asp855, it blocked receptor dimerization and promoted lysosomal degradation of EGFR. This dual mechanism is expected to result in strong inhibition across all metastatic sites, even in late-stage interventions.

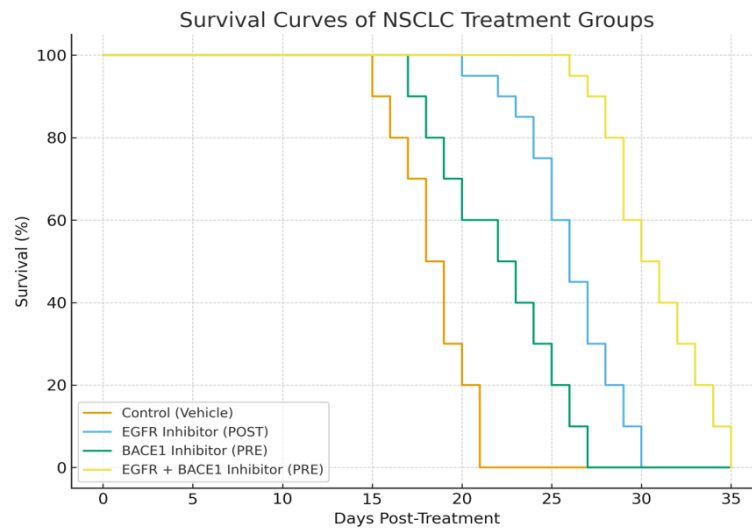


Figure 3. Survival curves of NSCLC treatment groups

Figure 3 is the survival curve of NSCLC xenograft-bearing mice treated with Control (Vehicle), EGFR Inhibitor (POST), BACE1 Inhibitor (PRE), and Combination (EGFR + BACE1, PRE). The combination group had the best survival rate (50% at day 32) compared to BACE1 or EGFR inhibitors alone. Data shown as percentage survival per group ($n = X$ mice per group). A Log-Rank Test was used to compare statistics.

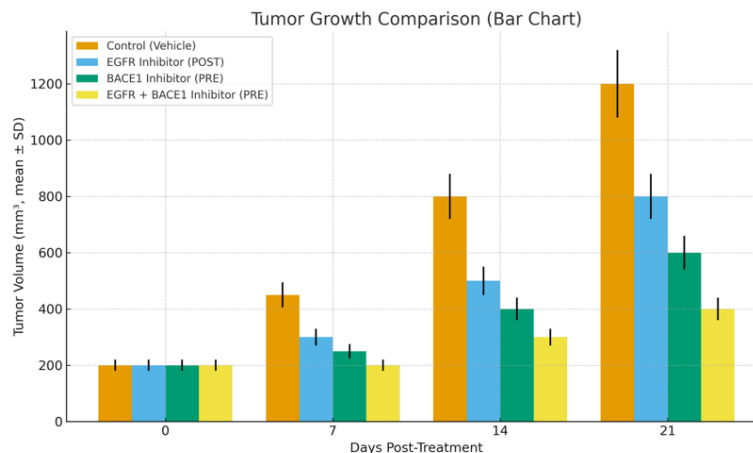


Figure 4. Tumor growth curves of NSCLC treatment groups

Figure 4 shows the tumour growth volumes of NSCLC xenograft-bearing mice after treatment with Control (Vehicle), EGFR Inhibitor (POST), BACE1 Inhibitor (PRE) and Combination (EGFR + BACE1, PRE). Values shown as mean $\pm$ SD ($n = X$ mice per group), in mm^3 . The combination group showed the strongest inhibition of tumour growth among all groups, and individually, EGFR and BACE1 inhibitors were more effective than the control group.

Based on the time of treatment, it is hoped that both inhibitors will be used early to curb the spread of cancer effectively; otherwise, if they are used late, full remission may not be realised. Combination of BACE1 and EGFR inhibitors will be expected to have the strongest anti-metastatic effect in all tissues.

Both inhibitors are expected to suppress brain metastases by inhibiting the EGFR pathway, but the extracellular EGFR antagonist will likely be more effective overall. Modulation of receptor recycling and degradation will enhance the inhibitory effect of EGFR antagonists in the liver and bone; therefore, BACE1 inhibition alone is likely to be inadequate. As shown in the above expected results, EGFR inhibitor B may be a relatively general treatment option, and dual targeting can enhance this effect further for metastatic NSCLC.

4. Discussion

Determine whether therapeutic strategies based on putative antagonists of EGFR and BACE1 can inhibit metastasis in non-small cell lung cancer (NSCLC). We hope both have some therapeutic effects, but to different extents.

An EGFR antagonist is proposed to bind to an allosteric site rather than the ATP pocket; thus, it may effectively inhibit metastases in the brain, liver and bone, as well as in resistant models. The two reasons for this are that they prevent the formation of dimers and are degraded by lysosomes. MK-8931 has been modified to create a partial BACE1 inhibitor that is expected to be highly effective in suppressing brain metastasis by inhibiting EGFR cleavage and downstream activation of the MEK/ERK pathway.

The time of application for the above treatments will affect the results; therefore, they may be more effective when used before tumour inoculation than after, especially for preventing metastasis.

Off-target effects are also possible at this time. EGFR is required for normal tissue repair, and BACE1 has some functions in the nervous system [13]. Modifications have reduced the toxicity, and in the future, tumour-selective delivery may be employed.

A serious problem is that our proposed way is not specific enough. EGFR and BACE1 are expressed in normal tissues, such as the brain and lungs [14], so the inhibitor may interfere with necessary physiological signals. Off-target binding may interfere with the normal function of cells, such as tissue repair and neural homeostasis, and thus be toxic.

Targeted Therapy for EGFR and its related pathways have shown good results in NSCLC. However, clinical and experimental data show that tumour cells will evade prolonged inhibition by multiple routes of drug resistance and may even lead to disease progression [15]. Known resistance mechanisms to EGFR inhibitors include secondary mutations in the kinase domain of EGFR, activation of other receptor tyrosine kinases, and altered downstream signalling pathways; thus, these drugs cannot bind to EGFR and the tumour continues to be driven by other proliferation and survival pathways [15]. Similarly, the suppression of a single target by molecularly targeted therapy selects for resistant clones in tumor cells, and as a result, there is an initial significant reduction in sensitivity followed by a rapid loss of sensitivity [15]. Given the above therapeutic deficiency, many clinical and research strategies have gradually moved towards combined-treatment regimens [15]. Combined inhibition of EGFR and other signalling molecules has been shown to extend the period of response in some spike [16]. At the same time, a combination of drugs targeting EGFR resistance has shown a trend of improving the tumour control rate in clinical trials [16]. In the future, drug resistance management for BACE1-EGFR signaling axis should also learn from this multi-target combined inhibition strategy to reduce the risk of drug resistance by blocking the main EGFR pathway and possible alternative pathways, thus improving the clinical effect of long-term anti-metastasis therapy [17].

In short, EGFR inhibitors had a broader systemic impact, and BACE1 inhibitors were brain-selective. The two will work together to address the whole problem of metastatic NSCLC.

5. Conclusion

Based on the two target strategies we put forward in this paper, we have developed and examined two new antagonists against BACE1 and EGFR to inhibit metastasis of non-small cell lung cancer (NSCLC). Based on the above results, it is expected that BACE1 inhibition can suppress the development of new brain tumours in early stages, but its impact on other sites in the body will be relatively minor. On the other hand, the extracellular EGFR antagonist we designed is expected to have more extensive and prolonged anti-metastatic effects at all primary and secondary sites of metastasis, such as the brain, liver and bone, even in late-stage disease. Importantly, it is expected that both inhibitors will have an additive therapeutic effect and thus work through different mechanisms.

In the future, the above results will need to be validated in preclinical trials, prolonged toxicity and other adverse effects will be studied, and tumour-targeting delivery systems will be explored to enhance specificity. In short, this paper has helped advance research on how dual-target inhibition of the BACE1-EGFR axis can provide a more durable and effective treatment strategy for patients with metastatic non-small cell lung cancer.

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