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REVIEW ARTICLE

TARGET ONCOGENIC RECEPTORS IN TUMOURS, FROM ITS INITIAL CLINICAL BREAKTHROUGHS TO CURRENT CLINICAL STANDARD THERAPY

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Abstract

Epidermal growth factor (EGF) which originally isolated from mouse submaxillary gland had its key role in the proliferation, differentiation, and survival of neural and glial precursor cells. The physiological effects of EGF are through an EGF receptor (EGFR) with tyrosine kinase activity. The traditionally accepted view is that normal EGFR is no tumorigenic, whereas mutated EGFR such as an oncogenic receptor EGFRvIII is oncogenic. Recently, EGF was found to be beneficial for wound healing, burn and diabetic foot ulcer, and show an attractive perspective in future. Moreover, cosmetic containing EGF play the control role of the amount of erythema and sebum in the skin, anti-aging and whitening, and improving the plasticity of skin. Based on these data, our team has successfully prepared a series of 350 bottles of Shampoo liquid containing EGF and 26 bottles of recombinant human EGF spray, and 4 bottles of EGF-Silvadence ointment. The initial results showed that prepared rhEGF is safe and available in clinical use. On the other hand, progress on the interaction of EGF coupled with its altered oncogenic receptor signaling via its downstream molecules such as Ras/Raf/MAPK and/or PI3k/akt in growth and progression of some cancers such as brain glioblastoma, lung cancers, breast, pancreas and A431 human epidermoid carcinoma cells. In addition to a series of target drugs gefitinib, erlotinib, osimertinib and the CIMAvax-EGF vaccine, an antioncogenic receptor antibody based fusion protein [e.g. Cetuximab-based IL-10 fusion protein, CmAb-(IL10)2] could improve cancer immunotherapy.

Keywords: EGF, EGFR, oncogenic receptor EGFR VIII, Target therapy.

INTRODUCTION

The biological activity of EGF and its normal EGF receptor (EGFR)

In earlier 1989-91, the discovery of oncogenic receptor and its earliest described Ras/Raf/MAPK pathway in cell signaling in concise figure from George Zhu's research work that oncogenic pml/RARa fusion in a specific APL and androgen/androgen receptor oncogenic signaling in hormonal tumorigenesis, this is a new area and its novel etiology of hormonally driven cancers even growth factors involved in this event (process)[1-5]. In the pharmacology textbook, the most notably, Dopamine which was synthesized in 1910, an old clinical drug, was mediated through its D2 dopamine receptor (DRD2) in inducing role of VEGFR2/KDR/FIk-1 endocytosis and angiogenesis. ONC201 is the first clinical bitopic antagonist of classical DRD2, an oncogenic receptor in brain and neuroendocrine tumors[6]. DRD2 activation has been found to promote self-renewal in breast cancer cells by activating STAT3 and IL-6[7]. Here, DRD2 is not an oncogene, and it represents the mechanism of dopamine drug action. Now many studies in this field are dedicated on their clinical targeting therapy. There are presently thousands of publications and over 200 ~ 400 global journals which are focused on this area targeting oncogenic receptor or oncogenic receptor (tyrosine) kinase in tumours. p38 MAPK family are found many subtypes, which are included p38α (MAPK14), p38β (MAPK11), p38γ (MAPK12), and p38δ (MAPK13). The traditionally accepted view is that normal epidermal growth factor receptor (EGFR) is no tumorigenic[8], this is importance in distinguishing normal epidermal growth factor receptor from oncogenic receptor EGFR. Epidermal growth factor (EGF) contains 53 amino acids residues with intra-molecular disulfide bonds that are required for its biological activity.

Table 1: The Comparative data of wound healing rate at 2-10 µg doses of rhEGF spray (Days) (healing per cent).

Group	Exp. No.	Days												
		1	2	3	4	5	6	7	8	9	10	11	13	15
Control	3	23.8	33.9	39.6	42.8	52.1 n=2	53.2 n=2	56.4	62.6	67.2	72.4	84.9 n=1	90.4	94.4
2 µg	1	44.0	55.0	61.9	65.3			68.0	78.8		90.7		96.0	98.4
5 µg	1	43.8 n=2	52.3	59.7	63.3	63.3	66.7	70.0	76.0	77.8	84.0	92.0	96.0	97.0
10 µg	3	39.3	57.5*	64.9	69.7**	73.4 n=2	74.1 n=2	75.0***	83.5	84.5	89.5*	92.3 n=1	96.0$^{\Delta}$	97.6
50 µg	1	39.3	43.7	48.0	56.0			67.0	77.5		86.7		95.0	97.3
100 µg	2	45.4	55.7	61.9	66.1	69.4	72.3	75.9	79.6	84.4	86.0	91.1	94.7	96.7

Note: *A t-test represents significant difference between means of 10 µg rhEGF group and the control.

*p<0.02, **p < 0.002***p<0.05, Δp>0.1. Source: From Zhu G, *et al*. Universal Journal of Pharmaceutical Research. 2020;5(1): 12-20[11].

Such as stimulating or inhibiting proliferation, differentiation and angiogenesis in various of cells, e.g. fibroblasts, keratocytes, myofibroblasts, epidermal cells, corneal epithelial cells[9-11]. EGF also play a role in every tissue in the body during development and in the adult, the exact nature of this role is not clear. EGF interacts with its specific EGF receptor which located at the cell surface[12].

The cell surface EGFR, i.e.,170,000 dalton, tyrosine kinase transmembrane receptor along with a member of the human EGFR (HER) family which constitutes four transmembrane receptors that interact with each other, i.e., EGFR/HER1, HER2/neu, HER3, and HER4. EGFR consist of a 621- amino acids extracelluar EGF binding, a single transmembrane region of 23 amino acids and a 542-amino acids cytoplasmic domain[13]. In epidermal keratinocytes, the binding numbers of normal EGFR was 1.5x10^5 binding sites/cell[14]. EGF bind to EGFR complex induced EGFR autophosphory-lation and the activation of two of the major EGFR downstream- signaling transduction pathways, extracellular signal-regulated kinase (Ras/Raf/ MAPK (MEK)/ERK)[5,15-31] (Figure 1) and phospho-lipase C(PLC)-r, which regulate transcription factors leading to proliferation of skin and other epithelial tissue. EGFR regulates important process including cell survival, cell cycle progression, tumor development, invasion and angiogenesis, and metastasis etc. biological action.

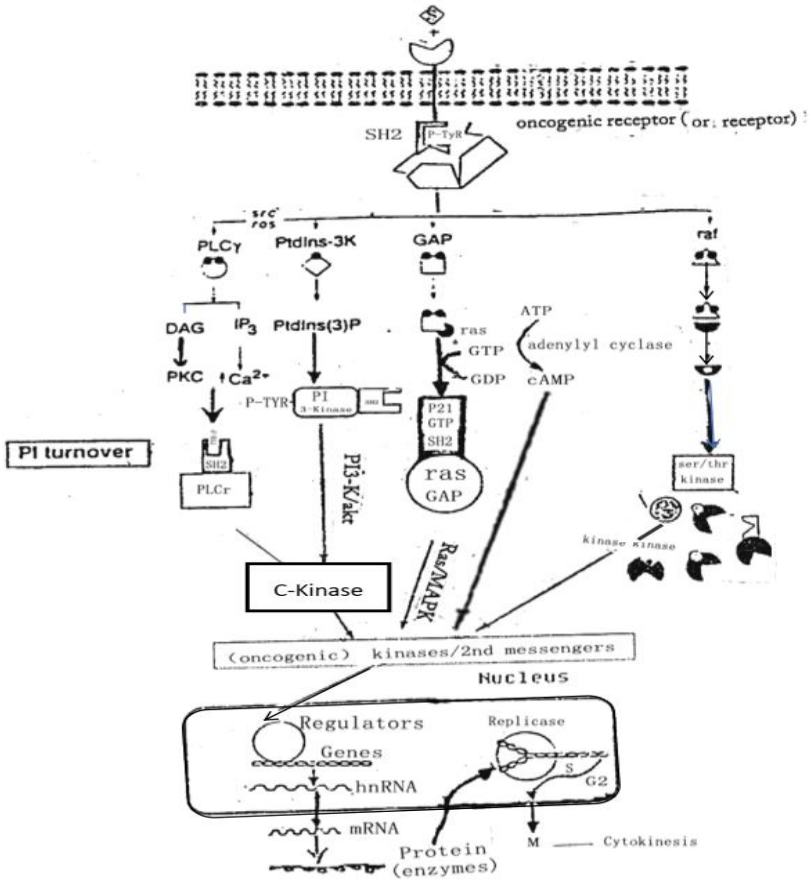

Figure 1: A Scheme of oncogenic receptor (or receptor) mediated multiple signal transductions.

(Here, nuclear regulators include transcriptional factors such as Jun/AP-1: Fos, NF-KB, myc, p53 and RB so on)[Data from George Zhu[4,5], 1991; Science, 2002 (unpublished data)

Table 2: Major clinical trials (completed and/or are ongoing) and their main efficacy results with each drug category.

Target	Agent (Phase of trial)	Results	Reference
EGFR	Gefitinib (II)	Rec GBM;PFS-6; 13-14.3%, Mos; 24.6-39.4 weeks	16, 17
	Erlotinib + TMZ (I)	Rec GBM; mOS: 55 weeks	19, 20
	Cetuximab (II)	Ongoing	-
PDGFR	Imatinib±hydr/rea (II)	Rec GBM; PF-6; 3%, mPFS: 14.4 weeks, mOS: 48.9 weeks. Rec AAs; PF-6: 10%	25, 26
VEGFR	Bevacizumab+IRI (II)	Rec GBM; RR: 63% PF-6: 38-46%, PR: 57%	29, 30
	Vatalanib (I/II)	Rec GBM; PR: 4%, stable disease: 56%	32
mTOR	Temsirolimus (II)	Rec GBM; PF6-6: 7.8%, mOS: 44 months	37
	Terms. + erlotinib (I/II)	Ongoing; PF-6: 33%	-
Ras	Tipifarnib (II)	Rec GBM; PF6-6: 33%	40
	Tipifarnib + TMZ (I)	Rec GBM; PF6-6: 12%	41
PKC-b	Enzastaurin vs lomustine (III)	Terminated because of equal efficacy results	45
RAF	Sorafenib (I/II)	Ongoing	-
EGFR/HER-2	Lapatinib (II)	Ongoing	-
HER-1/EGFR	^{125}I-MAb 425 (I/II)	Rec GBM/AAs; OS range: 4-150/4-270 months	47
Tenascin-C	^{131}I-81C6 (II)	Rec GBM; mOS: 78 weeks	49
Integrins	Cilengitide (I/II)	Rec MGs; CR: 4%, PR: 6%, stable disease: 8%	55
	Cilengitide + RT (II)	Ongoing	-

[o]EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor; Mtor. Mammalian target of rapamycin; Her, human epidermal growth factor receptor; TMZ, temozolamide; hydr/rea, hydroxyurea; IRI, irinotecan; Tems, temsirolimus; RT, radiation; Rec; GBM, Glioblastoma muliforme; AAs, anaplastic astrocytomas; MGs, malignant gliomas; PFS-6, 6-month progression-free survival; mPFS, median progression-free survival; mOS, median overall survival; RR, response rate; PR, partial response; C, complete response. Data from Argyriou AA and Kalofonos HP. Mol Med, 2009,15:115-122[64]

EGF accelerate wound healing

Advances in the knowledge of pathway, it has been suggested that EGF could be beneficial for burn, wound healing, diabetic foot ulcer, and provide an attractive perspective[11,32-35]. In mice wound experiments (Table 1)[11], it has been observed that a dose-dependent stimulatory effect of EGF on wound healing was consistent with increased hEGF concentration. Treatment with rhEGF significantly decreased the length of time to over 59% healing by approximately 4-5 days, and that to 90% healing by 3 days, respectively. The initial results showed that prepared rhEGF may assist in clinical wound healing time, and is safe and available. Moreover, cosmetic containing EGF could be effective to show whitening, to remove wrinkle, and anti-aging, and control of erythem amount and sebum amount on the human skin care. In this regard, George Zhu and Zhi QW have successfully prepared a series of 350 bottles of Shampo liquid (New Washing) and 26 bottles of recombinant human EGF spray, and 4 bottles of EGF-Silvadence ointment into market[11]. The responder rate with perfect satisfied and satisfied was over 95 per cent. For instance the detail investigation as to me, aged 60 years. In my own hair for many years, after using Lux soap, there was the phenomenon of dry hair on the forehead. A small white patch on the head. When changing to this Shampoo, no more dry and dandruff on the forehead was seen. This fact indicates that the head skin showed satisfied effects of moisture retention. The author in this paper has used this hair shampoo for 5 years. The second case, aged 73 years, the wound did not heal for over a year after minor surgery. He wipes the wound of flowing water with tissue every day. After using EGF-Silvadence ointment, surprisingly, there was no fluid flowing out of the wound for 24 hrs. Later, the wound was relapsed once again. After using Shampoo containing EGF for 2 years, the recurred wound achieved cure once again. The results implicate EGF in the possible role of wound healing. Another a 42- year-old police officer here has multiple black naevus cutaneus on his right face. After a period of 2 years of Shampoo, the black naevus had obviously fade and/or even disappearance of 2 tiny naevus around right eye, indicating the role of rhEGF in whitening on the human skin care. Now, epidermal growth factor (EGF) was included as an additive ingredient in cosmetics, including hair Shampoo. Actually, EGF is the secreted protein by skin epithelial cells in epidermis. The detail preparation of rhEGF agents has been described in other elsewhere[11].

Oncogenic receptor EGFRvIII in malignant cells and its targeting immunotherapy

On the other hand, malignant cells share oncogenic receptors[11,36-58]. The most common primary brain tumors are malignant gliomas including glioblastomas (GBM) and anaplastic astrocytomas. Aggressive human glioma often express a truncated and oncogenic form of the epidermal growth factor receptor, known as oncogenic receptor EGFRvIII[5,11,36-40,42-58].

Table 3: Baseline characteristics of patients to objective detail response to EGFR- TKIs treatment in different practical trials.

EGFR-TKIs	No of patients	Targets of EGFR (No)	Outcome (No, %)	Median PFS (months)*	Median OS (months)**	References
Gefitinib 250 mg/day	9	Ex19del(4), L858R(2), L861Q(1), G719C(1)	PR:5, MaR:3, MiR:1		12.9, 17.9, 18.8, >4.3,>7.8>14.0, >14.7, >21.4, >33.3	Lynch[97]
	26		CR1(3.8%), PR11(42.3%), SD9(34.6%), ORR:46.2%	8.2	10.4 OS-12:31.6%	Zheng[103]
	597		ORR:43.0%	5.7 PFS-12:24.9%	18.6	Mok[104]
	114	Ex19del(58), L858R(49)	CR5(44%), PR79(69.3%), SD18(15.8%), ORR:73.7%	10.8	30.5	Maemondo[105]
	86		ORR:62.1%	9.2		Mitsudomi[106]
	159	Ex19del(93), L858R(65), L858R+Ex19del(1)	CR1(1%), PR88(55%), ORR:56%	11.0	10.9	Park[107]
	45	Ex19del(19), L858R(26)	CR1(2.2%), PR27(60%), SD15(33.3%), ORR:62.3%	11.5 19del:13.2, L858:9.8	21.7 19del:27.6 L858:20.4	Xue[108]
	44	Ex19del(27); L858R(12); Exon18(5:G719A:1,G719C:2,E709A+G719S:1)	Del19(26:A1, E19,G3):CR1, PR21, SD1;L858R(12:A1, E7):PR8;Exon18(5:A1, E4):PR4, SD1	16.9	EGFR(+):39.6 EGFR(-):19.4 E709A+G719S:9 9.2	Faehling[90]
	55	Ex19del(30), L858R(25)	PR42(76.4%),ORR:76.4%	13.8	OS-12:94.2% OS-18:83.7%	Ohe[109]
	277 (G;183, E:94)	Ex19del, L858R			31.8(26.6-36.0) OS-12:83% OS-24:59% OS-36:44%	Ramalingam[110]
Erlotinib 150 mg/day	427	Ex19del, L858R	ORR: 38(8.9%)	2.2	6.7	Shepherd[111]
	82			13.1		Zhou[112]
	86			9.7 9.3-13.1	19.3-31.8	Rosell[113] Ramalingam[110] Fu[114]
Icotinib 125 mg, 3 times/day	199	Ex19del, L858R		4.6-11.2	30.5	Shi[115] Fu[114]
Afatinib 40 mg/day	242 (Lux-lung6	Ex19del, L858R		11.0		Wu[116]
	345 (Lux - lng 3) 364 (Lux-lung 6)				33.3(del19) 31.4(del19)	Yang[117]
	160	Ex19del(93) L858R(67)	CR1(1%), PR111(69%), SD34(21%), ORR:70%	11.0 Del19:12.7 L858:10.9		Park[107]
	230	Ex19del(113), L858R(91)		11.1(n=230); 13.6(n=204) 11.0-13.6	30.7-31.3*** 19.6-27.6***	Sequist[118] Fu[114]
Osimertinib 80 mg/day	279 144(CNS lesions)	Ex19del(191), L858R (83), T790M(275)	ORR:71%	10.1 8.5		Mok[119]
	30 (80 mg) 30 (160 mg)	Ex19del(11), L858R(15) Ex19del(15), L858R(14)	PR20(67%), SD8(27%), ORR:67% CR2(7%), PR24(80%), SD4(13%), ORR:87%	22.1 19.3	OS-12:72%(n,60) OS-18:56%(n,60)	Ramalingam[93]
	279	Ex19del, L858R			38.6	Ramalingam[110]
	65	Ex19del(33), L858R(32)	CR2(3.1%), PR47(72.3%), ORR:75.4%	19.1	OS-12:96.8% OS-18:90.1%	Ohe[109]
	203(>75yr); 335(<75yr)			16.9 22.1		Sakata[120]

Note: No: Number; G: gefitinib; E: erlotinib; A: afatinib; Yr: year; EGFR-TKIs: human epidermal growth factor receptor tyrosine kinase inhibitors; MaR: major response; MiR: minor response; CR: complete response or complete remission; PR: Partial response; SD: stable disease; ORR: objective or overall response rate; * Median PFS: median progression-free survival, median PFS in chemotherapy:4.2-6.9 months; **Median OS: median overall survival; PFS-12: PFS at 12 months; OS-12,OS-18, OS-24,OS-36: Os at 12 moths, at 18 months,at 24 moths, at 36 months; *** The upper data was derived from patients with Ex19del and the lower data from patients with L858R; LUX-lung3:pemetrexed-cisplatin; LUX-lung6: gemcitabine- cisplatin.

EGFRvIII is the deletion of cDNA nucleotids 275-1075 (exons 2-7) within the extracellular domain of the EGFR, which encode amino acids 6-276 in the EGFR protein. This deletion of 801 bp in the EGFR results in an in-frame trunction of the normal EGFR protein, a 145-kda receptor[8]. This EGFRvIII occurs in up to 30% of high-grade gliomas especially glioblastoma multiforme (GBM). Amplification and high expression

(as high as 6- to 60-fold) of EGFR in GBM may drive tumor growth and proliferation to a significant degree[59]. In the 2021 WHO classification of central nervous system tumors, EGFR amplification, but not EGFRvIII expression, is a diagnostic criterion for GBM, IDH- wild type, when histopathological criteria do not allow for definitive diagnosis. The oncogenic receptor EGFRvIII and platelet derived growth factor receptor (PDGFR) induced Src-mediated tyrosine phosphorylation of DOCK1 (dedicator of cytokinesis) to activate Rac1 and promote cell migration and invasion, suggesting a potential targeted therapeutic window. Recent genetic studies in medulloblastoma (MB) metastasis also revealed that G protein-coupled receptor kinases (GRKs) can regulate EGFR and PDGFR activity at the mRNA and protein level by altered oncogenic receptor signaling, and involved in cancer metastasis through their regulation of G-protein coupled receptors (GPCRs) in growth factor (GF)-mediated cell migration[60].

The prognosis for malignant gliomas remains poor. Begin in 2004, concomitant temozolomide (TMZ) with fractionated brain irradiation (gamma knife radiosurgery, or whole brain radiotherapy WBRT) were known the standard of care at most neurooncology centres in Europe and the USA[61]. In 2010, McGirt[62] treated with combined modalities Carmustine (Gliadel) plus concomitant TMZ in 37 GBM patients, and the median survival (OS) was 20.7 months, with a 36% of 2-year survival rate. Targeted toxins (immunotoxins) represent a new class of anticancer agents with high specificity for tumor cells selectively overexpressing surface proteins such as EGFR[63]. At present, various single agent targeted therapies, such as EGFR inhibitor gefitinib and imatinib have failed to successfully improve survival benefits. In recurrent GBM with gefitinib treatment, the 6 months progression-free survival (PFS-6) was 13-14.3% and a median overall survival (OS) time from initial treatment was 24.6-39.4 weeks. Erlotinib treatment was equally as effective as the standard regimen (median OS 58 weeks, median PFS 6.9 months, 11.3% CR (n=7) and 27.4% (n=17) partial response (Table 2)[61,64]. In the EORT randomized phase II trial, 54 recurrent GBM treated with erlotinib and 56 with TMZ or BCNU (bis-chloethylnitrosourea), showing that PFS at 6 months was 12% for erlotinib and 24% for the control, and a similar OS in both arm[65]. In overall, the median OS in gliomas varies in different trials, but is generally to be 18-20 months for anaplastic astrocytomas and 8-14 months for GBM [63]. Otherwise, Vredenburgh *et al*.,[66] conducted a phase II trial of bevacizumab (10 mg/kg) and irinotecan in 23 patients with recurrent grade III-IV glioma. The median PFS was 23 weeks for all patients. The PFS-6 and the 6-month OS were 38% and 72%, respectively. The drug action is through binding to VEGFR-2. The combination of anti-human VEGF bevacizumab and irinotecan is therefore an active regimen and benefits for recurrent III-IV glioma.

Many studies were in recent focused on brain and leptomeningeal metastases in patients with non- small cell lung cancer (NSCLC), and breast cancer brain metastases (BCBM). The leptomeningeal metastases (LM) from lung cancer account for 5-29% of LM from solid tumors. The patients with LM from lung cancer had a median survival of only 1-1.8 months without treatment[67] and 2 to 5 months with whole brain radiation therapy[68], and median survivals of 4 to 6.5 months with chemotherapy[69]. In clinical trials, when compared with chemotherapy, the first-line treatment with reversible EGFR-TKIs, such as gefitinib or erlotinib may improve progression-free survival (PFS). Gefitinib or erlotinib for NSCLC harboring EGFR mutation had unexpected activity against brain and leptomeningeal metastases. The ability of high dose (500-1250 mg/day) gefitinib or erlotinib to cross the blood brain barrier render their use of multiple intracranial lesions, which was in particular reported. The median PFS and median OS on first-line EGFR-TKIs were 19.0-12.68 months and 27.69-28.0 months, respectively. In a cohort of 23 patients with lung adenocarcinoma and asymptomatic brain metastasis[70], treatment concluded oral gefitinib 250 mg or erlotinib 150 mg once daily. 65.2% (13/23) of available patients obtained partial response (PR), 13% (3/23) had stable disease (SD), and a disease control rate of 79.3%. Median PFS and OS were 6.4 months and 18.6 months, respectively. First-line afatinib is also effective in NSCLC with CNS metastases. Total 42% (13/31) of the evaluable patients experienced a PR on afatinib, 39% (12/31) had SD. The overall rate of cerebral response to treatment with afatinib was 35%. The overall survival (OS) was 9.8 months[71].

Among those isolated case reports, there were at least more 20 cases to bring about our clinical practice efficacy. Sakai *et al*.,[72] presented a 40-year-old Japanse case of carcinomatous meningitis from NSCLC. The patient obtained an over 4 months of complete response after the initiation of a dose of 250mg/day gefitinib, and was able to work. Jackman *et al*.,[73] presented a 53-year-old white man with stage IV adenocarcinoma (2 cm tumor) of the lung harboring an exon 19 deletion (2239-2247del TTAAGAGAA) of the EGFR. The patient achieved a partial response to treatment with carboplatin, paclitaxel and 250 mg/day gefitinib. After September 2004, because of his adenocarcinoma cells in the CSF, gefitinib dose was escalated from 500 mg/day to 750 mg/day and then to 1000 mg/day over a period of 10 weeks. At the highest gefitinib CSF concentration (42 nmol/l), the cytologic CSF showed no evidence of malignant cells. As the marked improvement of his carcinomatous meningitis and related symptoms, he was able to return to work. He obtained a near one year of overall survival at initiation of EGFR-TKI therapy. Muller[74] presented a six weeks of CR in a 43-year-old German woman with NSCLC with cerebral metastases following initiation of a dose of 250mg/day gefitinib. Hata *et al*.,[75] reported a 56-year-old woman with metastatic NSCLC harboring an EGFR mutation (exon 18 G719N) on analysis of the malignant effusion. Gefitinib was then given following chest tube drainage, and a partial response was achieved for approximately 1 year. After disease progression on gefitinib, she carried out WBRT due to her brain lesions, subsequently, changed to

erlotinib in 2009, and with a disease stable for 4 months. Moreover, a high dose of 300 mg/day erlotinib was given due to her deteriorated brain lesions.

Two weeks later, both her clinical symptoms and findings of MRI imaging improved, and in further remained stable for 6 months. Yuan reported a 52-year- old Chinese man with stage IIIA lung adenocarcinoma harboring an exon 19 deletion (L747-S752del5) and a point mutation (K754I) in exon19 of EGFR who developed multiple brain metastases one year after operation[76]. After an oral 250 mg/day gefitinib with concomitant WBRT as first-line therapy, the patient achieved a 50 months of PFS. Subsequently, a dosage of 500 mg/day gefitinib combined with pemetrexed were used as the second-line treatment due to new brain lesions and leptomeningeal metastases. The patient obtained a total overall survival of 59 months.

Another attention was focused on the efficacy of erlotinib for the treatment of brain and leptomeningeal metastases instead of high dose gefitinib failure. Katayama *et al*.,[77] used erlotinib administration in treatment of 7 lung adenocarcinoma with EGFR mutation who had shown an initial good response to gefitinib (2CR, 2PR, 2SD; initial PFS 310 days, range: 113-1211 days). 3 patients obtained PR, 3 had SD. The overall survival (OS) from the initiation of erlotinib ranged from 15 to 530 days.

The Spanish Lung Cancer Group[78] monitored a group of chemotherapy- naive, EGFR-mutated NSCLC patients with intracranial lesions who were treated with erlotinib: 4 CR and 3 PR were reported. Lai and Boshoff[79] presented a 55-year-old case of recurrent NSCLC harboring EGFR L858R mutation had complete remission in brain disease after using 150 mg/day erlotinib. Fekrazad *et al*.,[80] reported a 60-year-old case of a non-smoking native American woman who had a complete resolution of brain metastases from a lung adenoarcinoma after 8 months of using oral 150 mg/day erlotinib. Clarke *et al*.,[81] also successfully controlled LM from a 54-year- old woman with stage IV lung adenocarcinoma harboring EGFR mutation using intermittent high dose erlotinib (1000-1500 mg/week), with concurrent high CSF concentration. She survived 14 months following the diagnosis of CNS disease. Bendetti (2009)[82] reported in Italy that 2 cases of NSCLC harboring EGFRexon19 deletion mutation had complete response following a dose of 150 mg/day erlotinib. A 44-year-old case of multiple intracranial metastases (MIMs) from lung adenocarcinoma with L747-P753 deletion of EGFR exon19. He had complete remission of MIMs after 8 months of 150 mg/day erlotinib treatment. Another a 48-year-old woman with lung cancer had the disappearance of MIMs completely after 4 months of 150 mg/day erlotinib. Molecular analysis of a lung neoplasm found an EGFRexon19 deletion (K745-E749del). The disease remained stable after 24 months of erlotinib treatment. These case reports are encouraging.

EGFR mutation is an oncogenic driver in advanced lung cancer that is clinically responsive to EGFR-TKIs

The major of lung cancer is diagnosed at an advanced stage with 5-year survival with conventional chemotherapy regimens of about 5%. A rising incidence of NSCLC subtype harbors a particular activating EGFR mutation. EGFR mutation (Exon19 deletion, Leu858Arg, Exon20 insertion, EGFR-KDD, EGFR–RAD51 fusion) act as an oncogenic driver of NSCLC in non-smokers and light-smokers[83-96]. Targeting for EGFR specific tyrosine kinase inhibitor (EGFR-TKI) therapy was considered, since targeted therapies results in superior outcomes compared with chemotherapy.

To date, four major mutation of EGFR in human lung adenocarcinoma has been described[97]: substitutions for L858 in exon 21 and for G719 in exon 18, in-frame deletions within exon 19, and in-frame insertions within exon 20. In the area of advanced NSCLCs target therapy, two pivotal studies in earlier 2004[97] showed that in lung cancer activating EGFR mutations strongly correlates with its clinical response to gefitinib. Since then, three generations EGFR-TKIs entered as the first line treatment in NSCLC patients with mutated EGFR. Gefitinib (Iressa), the first EGFR-TK inhibitor (gefitinib in 2002, erlotinib in 2003) was through competitively binding to the ATP binding site at EGFR intracellular domain, which inhibits the phosphorylation of EGFR tyrosine kinase, and blocks downstream signaling and EGF-dependent prolife-ration. Gefitinib and erlotinib have a higher binding affinity for EGFR exon 19 deletion and exon 21 substitution mutations than for wild-type EGFR.

Drugs half-life of gefitinib was 48 hours and erlotinib 36.0 hours respectively. Erlotinib is about 60% absorbed after oral administration and its bioavailability is significantly increased by food to almost 100%. Second generation EGFR TKI, afatinib is an orally available, irreversible HER family blocker. As a third generation EGFR TKI, Osimertinib binds to certain mutant forms of EGFR (T790M, L858R and exon 19 deletion) that predominate in NSCLC tumours who have progressed on or after first-line EGFR-TKI therapy[98,99]. Osimertinib is about 200-fold more potent against the T790M mutation than its wild-type counterpart, which irreversibly binds to the cysteine in a covalent manner at C797 in EGFR kinase domain. Therefore, approximately 10% of patients with NSCLC harboring activating EGFR mutation are beneficial to dramatic response to EGFR-TKIs.

Emerging clinical trials in the comparison of three generation EGFR-TKIs clearly showed that there were significantly longer median progression free survival (PFS) and median overall survival (OS) in EGFR-TKIs compared with standard chemotherapy. Notably, Osimertinib was indicated in NSCLC patients with CNS metastases. In these personalized management for an individual with lung cancer, Balk *et al*.,[100] in 2015 presented a case of metastatic lung cancer harboring TKD-EGFR mutation who had a greater than 10 years response to EGFR-TKI therapy (gefitinib in 2003 to 2009, and then erlotinib in late 2009 until late 2014). The patient with overall survival (OS) was approximately 20 years later. At the same year, Gallant *et al*.,[86] also identified a 33-yer-old metastatic lung

adenocarcinoma harboring oncogenic EGFR kinase domain duplication (EGFR- KDD) that is clinically responsive to afatinib (-50% tumor shrinkage) for 7 cycles of therapy. Hirokawa *et al*.,[87] also presented a 45-year-old Japanese woman with NSCLC positive for EGFR- KDD who developed carcinomatous meningitis and showed a marked response to erlotinib and osimertinib.

She achieved a complete response of CNS metastases, and Osimertinib was effective for 14.5 months. Her overall survival was 44 months from the start of the carboplatin-pemetrexed chemotherapy and first-line EGFR-TKI therapy. Konduri and colleagues[88] reported five patients with metastatic lung cancer whose tumors harbored EGFR fusion, most commonly RAD5, are recurrent in lung cancer. Four of whom were treated with EGFR-TKI erlotinib with documented antitumor response for 5, 6, 8, and 20 months respectively. More data, Zochbauer-Muller and Mullauer *et al*.,[89] described a patient with NSCLC, a multiple adenocarcinoma harboring an EGFR exon 20 insertion mutation who achieved durable stable disease with afatinib (initial 40 mg/day in July 2015, and then dose reductions to 20 mg/day) and remains on treatment after 4.5 years. Faehling *et al*.,[90] reported a longest survivor (99.2 months) who was a male patient with stage IV disease at diagnosis and a complex EGFR exon 18 mutation (E709A and G719S). In our 2 patients with advanced lung cancers, we used oral gefitinib (250 mg/day) in keeping stable disease for 8+ months in a 64-year-old female patient with multiple metastatic adenocarcinoma of the lung, and the overall survival (OS) was over 18 months[101]. Moreover, in my follow up, a 72-year-old woman with advanced lung cancer (a half the size of an egg).

After using oral gefitinib in other hospital, she achieved a 4 years survivor. In a cohort of 114 advanced T790M positive NSCLC with brain metastases, progression free survival in the osimertinib group was 8.5 months, compared to the platinum-based therapy group at 4.2 months[102]. Therefore, three generations EGFR-TKIs can be used as first-line therapy and/or second or third line therapy for stage IIIB/IV NSCLC with oncogenic EGFR mutation that are not suitable for chemotherapy. It is noteworthy that despite higher tumor response rates with first line EGFR- TKIs, disease progresses in a majority of lung cancer after 9 to 13 months of treatment. Acquired resistance to all three generation EGFR-TKIs, especially osimertinib resistance raise new challenges to the long-term effective strategies of those NSCLC patients. Table 3 showed the characteristics of patients to objective detail response to EGFR- TKIs treatment in different practical trials.

In Cuba, the CIMAvax-EGF vaccine trial is another promising strategy for stage IIIB or IV NSCLC with one line of chemotherapy previously. In phase II clinical trial[121], patients received at least four doses of CIMAvax-EGF had a significant effects on survival time. The mean survival was 19.47 months in 20 patients with good antibody responders (GAR),4.97 months in PARs (poor antibody responders) (n=18), and 8.52 months in 37 controls. More data, anti-EGF antibody titers in a phase III trial in 112 patients with advanced III/IV NSCLC[122] was evaluated (89 GAR and 24 patients with super-good responders)[122]. Mean survival time (MST) was 10.83 months in the vaccine arm versus 8.86 months in the controls. Using at least one dose of CIMAvax EGF vaccine[123], the median overall survival (mOS) was 7.0 months, and mOS 9.98 months in a total of 927 patients with at least 4 doses of CIMAvaxEGF compared with only 3.97 months in chemotherapy. Total 44.4% and 23.3% of the patients who completed the induction phase of treatment was still alive at 1 and 2 years, respectively. Two patients with GAR criterion had significant benefits with the longest 7 and 8 years survivor. In recent, a 75-year-old chinese woman with stage IV NSCLC harboring EGFR mutation had 6 years long survivor. The vaccine could induce antibodies against self EGFs that block EGF-EGFR interaction. Thus, CIMAvax-EGF is a very safe drug that could be a feasible intervention for long-term control of those NSCLC patients with tumors depending on the EGF, capable of produce a rapid and durable response.

CONCLUSIONS

In the past thirty years ago, Zhu is the earliest to introduce that target therapy is mainly toward oncogenic receptors (also molecular “missile therapy”) [1,101]. In 1994, edrecolomab (mAb17 -1A) was the first to show its clinical efficacy in increasing disease-free survival in cancer, 3 of 20 patients with metastatic resected colorectal adenocarcinoma had no detectable disease for 10, 13 and 22 months[5,124,125]. Subsequently, more effective anti-EpCAM antibodies engineering (adecatumumab, catumaxomab, NEA125, ING101,and other EpCAM-specific immunotoxin)[144,145] are used in clinical trials. The European Medicines Agency in 2009 approved catumaxomab, which binds to oncogenic receptor EpCAM[5,142,143] and enhances the immunological response against EpCAM- positive cells in malignant ascites.

In 1998, a targeting drug trastuzumab approved by the US FDA was demonstrated to be enough to slow tumor growth and progression[126-139]. In HER2+ metastatic breast cancer, ado-trastuzumab emtansine and trastuzumab enables lysosomal degradation of its cognate oncogenic receptor HER2 or release of prodrugs via antibody- dependent cellular cytotoxicity (ADCC) [126-128,150]. This burgeoning class of targeted chemotherapies in recent called antibody drug conjugates. In 2001, another novel agent called imatinib proved to be effective in chronic myeloid leukemia (CML) and received full approved by the US FDA in 2003[140,141].

As an orally targeting bcr-abl oncogene kinase, Gleevec (imatinib) has been used in breakthrough in treatment of chronic myeloid leukemia. Imatinib is also indicated for GIST patients with oncogenic receptor tyrosine kinase (RTKs) or also oncogenic receptor PDGFR mutants and KIT /or HES, and myeloproliferative neoplasm with oncogenic PDGFR fusion[146-148], and inhibits activation of Ras/raf/MAPK or PI3k/Akt pathway. BMS-354825[149] competes with

ATP for the ATP-binding site in the kinase domain of selected and related oncogenic receptor and non-receptor protein tyrosine kinases (PTKs), including BCR-ABL, c-KIT, and PDGF receptors. During the follow up of May 2023 in my group, a 63-year-old man was diagnosed as his primary hepatocellular carcinoma after biopsy of liver tumor tissue (2.0x2.4 cm tumor in the right anterior lob of his liver in August 23, 2012) on April 26, 2013. He had a past history of viral hepatitis B (HBV) infection.

The patient was therefore performed his hepatectomy in other hospital, with then the combination of oncogenic receptor tyrosine kinase inhibitor Sorafenib Tosylate Tablets (initial dosage 2#/day (2 x 0.2g) x 5 months, and then 1#/day intermittent until to 1.5 years). He was a long survivor now. To date, 34 more drugs have been introduced to clinical trials of various cancer. Down regulating oncogenic receptors, currently the first or third-line setting of targeting therapy might be useful in those hematological malignancies, metastatic and advanced cancers[151-161].

PI turnover: Phospholipase Cr (PLCr) is activated by receptor tyrosine kinase (RTK) through the binding of its SH2 (syc-homology 2) domains to phosphotyrosine (PY) sites of the receptor. Also, the SH2 domain binds specifically to sequences containing a phosphorylated tyrosine motif. After activation, PLCr hydrolyses its substrate ptdins (4, 5) p2 (PIP2) and forms two second messengers, diacyclglycerol (DAG) and Ins (1, 4, 5) p3 (IP3). IP3 bind its receptor that stimulates the release of Ca2+ from intracellular stores. DAG activates members of the protein kinase C (PKC) family. The second messengers generated by PIP2 hydrolysis stimulate a variety of intracellular processes such as cell motility, proliferation, and angio-genesis[15,16].

PI3-K/Akt pathway: The class phosphatidylinositol 3-kinase (PI3-k) is activated by the majority of oncogenic RTKs. Like other SH2 domain-containing proteins, PI3 kinase forms a complex with PY sites on activated receptor. The main function of PI3K activation is the generation of PIP3 (ptdins (3) p), which function as a second messenger to activate downstream tyrosine kinase Btk and Itk, the ser/thr kinase PDK1 (phosphoinositide- dependent protein kinase 1) and Akt (Protein Kinase B, PKB). The major biological functions of Akt activation is involved in cell survival, anti- apoptosis and proliferation and cell growth. Akt is also known to be implicated in several cancers, particularly breast cancer. Proteins encoded by the Syc and ros oncogenes may functions as inositol lipid kinases in convert phosphatidylinositol (PI) into PtdIns (4, 5) P2 process[15,16].

Ras/Raf/MAPK: In Ras/MAPK signal pathway, each of three closely related mammalian ras oncogene (H-ras, K-ras and N-ras) encode a 21-KD protein (p21) of 188 or 189 amino acids which are located at the inner surface of the cell membrane. Ras protein are guanine nucleotide binding proteins with a low intrinsic GTPase activity that can switch from an inactive GDP-bound form to an active GTP-bound. The 120kd cytoplasmic protein (referred as GAP, GTPase activating protein) interacts with normal Ras GTP at p21 effector site and stimulates its intrinsic GTPase activity dramatically to down-regulate Ras GTP. Ras p21 residues thus appear to be required for GAP effector binding. Also, GAP interaction may be essential for Ras p21 biological activity. P21 mutated at codons 12, 13 and 61 abolish the intrinsic GTPase activity, the resulting oncogenic protein can still bound GTP. Thus, in the signal transducing G proteins, they are biologically active when in the guanosine triphosphate (GTP)-bound form and inactive when bound to guanosine diphosphate (GDP)[17-19]. GAP is phosphorylated on tyrosine in response to PDGF or EGF.

After stimulation of cells (in 3T3 cells and in CHO cells) with PDGF, GAP physically associated with PDGF receptor and with PI-3 kinase (Phosphatidylinositol 3-kinase, 85kd), c-raf (a cytoplasmic serine/threonine kinase, 74kd) and PLC-r (140kd). This association occurs via a SH2 domain of the receptor. A 83 amino acids deletion in the mutant PDGF receptor ("kinase insert domain") that blocks PDGF induced mitogenesis, also blocks binding of PI-3 kinase, but not PLC-r or c-raf. This deletion also blocks GAP binding, implying that GAP and PI-3 kinase are essential components of the mitogenic response. EGF also increases the binding of GTP to Ras p21, whereas GTP-binding protein may thus extend in controlling cyclic AMP production. Thus the association of p21 Ras GAP with ligand-activated PDGF receptor may directly link growth factors and Ras signaling transduction from the plasma membrane into the cell[17-22,24].

Also, the adaptor protein growth factor receptor-bound protein 2 (Grb2) forms a complex with SOS (son of sevenless) protein by the Grb2 SH3 domain. Grb2 or Grb2/SOS complex is recruited to the membrane by the Grb2 SH2 domain binding to activated PDGFR bound SHP2, thereby allowing interaction with Ras and the exchange of GDP for GTP on Ras via GTPase hydrolysis. Whereas the interaction between Grb2 and activated PDGFR occurs through interaction with the SHP2 protein, Grb2 binds to oncogenic EGFR through Shc, another adaptor protein that forms a complex with many receptors via its phosphotyrosine binding domains (PTB)[17-31]. This Shc-Grb2/EGFR complex activate Ras. After activation, subsequently, Ras interacts with several proteins, namely Raf. Activated Raf stimulates mitogen- activated protein kinase (MAPK) kinase (MAPKK or MEK) by phosphorylating a ser residue in its activation loop. Activated MAPK phosphorylates a variety of cytoplasmic substrates, as well as transcription factors and other kinases, when translocated into nucleus, and thus contribute to the regulation of different cellular processes such as cell survival, apoptosis, proliferation, differentiation, and immune responses.

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AUTHOR'S CONTRIBUTION

Zhu G: Writing original draft, review, methodology, data curation, literature survey, editing.

DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Zhu G. Oncogenic receptor hypothesis (1989-91). VOA (Voice of America) 1992; 12: 31.
2. Zhu G, Musumeci F, Byrne P. Induction of thyroid neoplasm following plant medicine marine algae (sargassum): A rare case and literature. Curr Pharm Biotechnol 2013; 14: 859-863. *https://doi.org/10.2174/13892010156661401131009 46*
3. Zhu G, Mische SE, Seigneres B. Novel treatment of acute promyelocytic leukemia: As_2O_3, retinoic acid and retinoid pharmacology. Curr Pharm Biotechnol 2013; 14: 849-858. *https://doi.org/10.2174/13892010156661401130958 12*
4. Zhu G. EpCAM- An old cancer antigen, turned oncogenic receptor and its targeting immunotherapy. Universal J Pharm Res 2018;3: 41-46. *https://doi.org/10.22270/ujpr.v3i2.140*
5. Zhu G. Treatment of patients with advanced cancer following chemotherapy and traditional medicine- Long term follow up of 75 cases. Universal J Pharm Res 2018; 3: 10-18. *https://doi.org/10.22270/ujpr.v3i3.160*
6. Prabhu V, Kawakibi AR, Madhukar N, *et al*. Exth-71. Ind-enabling characterization of ONC206 as the next bitopic DRD2 antagonist for neuro-oncology. Neuro-Oncol 2019; 21(Supplement 6): vi97.
7. Tegowski M, Fan C, Baldwin AS. Thioridazine inhibits self-renewal in breast cancer cells via DRD2-dependent STAT3 inhibition, but induces a G1 arrest independent of DRD2. J Biol Chem(JBC) 2018;293(41):jbc.RA118. 003719. *https://doi.org/10.1074/jbc.RA118.003719*
8. Tang CK, Gang XQ, Wong AJ, A J Wong, M E Lippman. Epidermal growth factor receptor vIII enhances tumorigenicity in human breast cancer. Cancer Res 2000; 60: 3081-3087. *PMID: 10850460*
9. Cohen S. Isolation of a mouse submaxillary gland protein accelerating incisor eruption and eyelid opening in the new-born animal. J Biol Chem 1962; 237: 1555-1562. *PMID: 13880319*
10. Gregory H. Isolation and structure of urogastrone and its relationship in epidermal growth factor. Nature 1975; 257: 325-327. *https://doi.org/10.1038/257325a0*
11. Zhu G, Xu HL, Zhou XP, Zhi QW. Enhancement of wound healing by topical application of epidermal growth factor in animal model. Universal J Pharm Res 2020; 5: 12-20. *https://doi.org/10.1056/NEJM198907133210203*
12. Stoscheck CM, King LE. Role of epidermal growth factor in carcinogenesis. Cancer Res 1986; 46: 1030-1037. *PMID: 3002608*
13. Ullrich A, Coussens L, Hayflick JS, *et al*. Human epidermal growth factor receptor cDNA sequence and aberrant expression of the amplified gene in A431 epidermoid carcinoma cells. Nature 1984; 309(5967): 418-425. *https://doi.org/10.1038/309418a0*
14. Kamata N, Chida K, Rikimaru K, Horikoshi M, Enomoto S, Kuroki T. Growth-inhibitory effects of epidermal growth factor and over expression of its receptors on human squamous cell carcinomas in culture. Cancer Res 1986; 46 (4_Part_1): 1648–1653. *PMID: 3004701*
15. Berridge MJ, Irvine RF. Inositol triphosphate, a novel second messenger in cellular signal transduction. Nature 1984; 312: 315-320. *https://doi.org/10.1038/312315a0*
16. Berridge MJ, Irvine RF. Inositol phosphates and cell signalling. Nature 1989; 341: 197-205. *https://doi.org/10.1038/341197a0*
17. Gilman AG. GTP-binding protein (G protein). Cell 1984; 36:577-79 Hall A. RAS and GAP-who's controlling whom? Cell 1990; 61: 921-923. *https://doi.org/10.1016/0092-8674(90)90054-I*
18. Calés C, Hancock JF, Marshall CJ, Hall A. The cytoplasmic protein GAP is implicated as the target for regulation by the ras gene product. Nature 1988; 332: 548-551. *https://doi.org/10.1038/332548a0*
19. Adari H, Lowy DR, Wilumsen BM, Der SJ, McCormick F. Guanosine triphosphatase activating protein (GAP) interacts with the p21 RAS effector binding protein. Science 1988; 240: 518-520. *https://doi.org/10.1126/science.2833817*
20. Ray LB, Sturgill TW. Characterization of insulin-stimulated microtubule associated protein kinase. Rapid isolation and stabilization of a novel serine/threonine kinase from 3T3-L1 cells. J Biol Chem 1988; 263: 12721-12727. *PMID: 2842341*
21. Rossomando AJ, Payne DM, Weber MJ, Sturgill TW. Evidence that PP42, a major tyrosine kinase target protein, ia a mitogen-activated serine/threonine protein kinase. PNAS 1989, 86:6940-43. *https://doi.org/10.1073/pnas.86.18.6940*
22. Toksoz D, Farr CJ, Marshall CJ. Ras genes and acute myeloid leukaemia. Br J Haematol 1989; 71: 1-6.
23. Gotoh Y, Nishida E, Yamashita T, *et al*. Microtubule associated-protein (MAP) kinase activated by nerve growth factor and epidermal growth factor in PC12 cells. European J Biochem 1990;193(3). *https://doi.org/10.1111/j.1432-1033.1990.tb19384.x*
24. Kaplan DR, Morrison DK, Wong G, McCormick F, Williams LT. PDGF beta receptor stimulates tyrosine phosphorylation of GAP and association of GAP with a signaling complex. Cell 1990; 61: 125-133. *https://doi.org/10.1016/0092-8674(90)90220-9*
25. Anderson NG, Maller JL, Tonks NK, Sturgill TW. Requirement for integration of signals from two distinct phosphorylation pathways for activation of MAP kinase. Nature 1990; 343: 651-653. *https://doi.org/10.1038/343651a0*
26. Ahn NG, Seger R, Bratlien RL, *et al*. Multiple components in an epidermal growth factor- stimulated protein kinase cascade. *In vitro* activation of a myelin basic protein microtubule- associated protein 2 kinase. JBC 1991; 266:4220-27. *PMID: 1705548*
27. Seger R, Ahn NG, Boulton TG, *et al*. Microtubule-associated protein 2 kinases, ERK1 and ERK2, undergo autophosphorylation on both tyrosine and threonine residues: Implications for their mechanism of activation. PNAS 1991;88(14):6142-46. *https://doi.org/10.1073/pnas.88.14.6142*
28. Rogge RD, Karlovich CA, Banerjee U. Genetic dissection of a neurodevelopmental pathway: Son of sevenless functions downstream of the sevenless and EGF receptor tyrosine kinases. Cell 1991; 64: 48. *https://doi.org/10.1016/0092-8674(91)90207-f*
29. Schlessinger J. SH2/SH3 signaling proteins. Curr Opin Genet Dev 1994; 4: 25-30. *https://doi.org/10.1016/0959-437x(94)90087-6*
30. Cobb MH, Goldsmith EJ. How MAP kinases are regulated. J Biol Chem 1995; 270:14843-846. *https://doi.org/10.1074/jbc.270.25.14843*
31. Molina JR and Adjei AA. The Ras/Raf/MAPK pathway. J Thoracic Oncol 2006; 1:7-9. *https://doi.org/10.1016/S1556-0864(15)31506-9*

32. Brown GL, Nanney LB, Groffen J, *et al*. Enhancement of wound healing by topical treatment with epidermal growth factor. N Engl J Med 1989; 321: 76-79. *https://doi.org/10.1056/NEJM198907133210203*
33. Wang SL, Guo ZR, Fu XB, *et al*. Effects of recombinant human epidermal growth factor on healing of chronic ulcer wound. Chinese J Traumat (in chinese) 1998; 14: 348-349.
34. Afsbari M, Larijani B, Fadayee M, *et al*. Efficacy of topical epidermal growth factor in healing diabetic foot ulcer. Therapy 2005; 2: 759-765.
35. Wong WKR, Ng KL, Hu XH, *et al*. Authentic human epidermal growth factor: A panacea for wound healing. EC Endocr Metab Res 2018; 3: 138-146.
36. Robinson B. Tumor cells share oncogenic receptors. J Cell Biol 2008; 181: 570. *https://doi.org/10.1083/jcb.1814rr3*
37. O'Connor R. Concealed cargo within the tumor microenvironment: Microvesicles disseminate oncogenic receptors among cancer cells. Cancer Biol Ther 2008;7: 1350-1351. *https://doi.org/10.4161/cbt.7.9.6742*
38. Al-Nedawi K, Meehan B, Micallef J, *et al*. Intracellular transfer of the oncogenic receptor EGFR VIII by microvesicles derived from tumour cells. Nat Cell Biol 2008; 10: 619-624. *https://doi.org/10.1038/ncb1725*
39. Lee JC, Vivanco I, Beroukhim R, Huang JH, *et al*. Epidermal growth factor receptor activation in glioblastoma through novel missense mutations in the extracellular domain. Plos Med 2006; 3(12): e485 *https://doi.org/10.1371/journal.pmed.0030485*
40. Stutz MA, Shattuck DL, Laederich MB, Carraway HI KL, Sweeney C, *et al*. LRIG1 negatively regulates the oncogenic EGF receptor mutant EGFRvIII. Oncogene 2008; 27(43):5741-5752. *https://doi.org/10.1038/onc.2008.185*
41. Malfettone A, Saponaro C, Paradiso A, *et al*. Peritumorial vascular invasion and NHERF1 expression define an immunophenotype of grade 2 invasive breast cancer associated with poor prognosis. BMC Cancer 2012;12:106. *https://doi.org/10.1186/1471-2407-12-106*
42. Huber V, Filipazzi P, Rivoltini L. Chapter 30 - Tumor exosomes and their impact on immunity and cancer progression. Immune suppression and tumor growth. Cancer Immunotherapy (Second Edition) 2013;517-535
43. Yan T, Mizutani A, Chen L, *et al*. Characterization of cancer stem-like cells derived from mouse induced pluripotent stem cells transformed by tumor-derived extra - cellular vesicle. J Cancer 2014; 5: 572-584.
44. Wang LK, Hsiao TH, Hong TM, Chen HY, Kao SH, *et al*. MicroRNA-133a suppresses multiple oncogenic membrane receptors and cell invasion in non-small cell lung carcinomas. Plos One 2014; 9(5):e96765. *https://doi.org/10.1371/journal.pone.0096765*
45. Montermini L, Meehan B, Garnier D, *et al*. Inhibition of oncogenic epidermal growth factor receptor kinase triggers release of exosome-like extracellular vesicle and impacts their phosphoprotein and DNA content. J Biol Chem 2015; 290: 24534-24546. *https://doi.org/10.1074/jbc.M115.679217*
46. Li J, Davidson D, Souza CM, *et al*. Loss of PTPN12 stimulates progression of erbB2-dependent breast cancer by enhancing cell survival, migration, and epithelial-to-mesenchymal transition. Mol Cell Biol 2015;35:4069-82. *https://doi.org/10.1128/MCB.00741-15*
47. Shen Y Jie Li J, Nitta M, Futalan D, Steed T, *et al*. Orthogonal targeting of EGFRvIII expressing glioblastomas through simultaneous EGFR and PLK1 inhibition. Oncotarget 2015; 6:11751-11767. *https://doi.org/10.18632/oncotarget.3996*
48. Keith Sabin, Nobuaki Kikyo. Microvesicles as mediators of tissue regeneration. Translating Regenerative Medicine Clinic 2016; 215-224. *https://doi.org/10.1016/j.trsl.2013.10.005*
49. Ratajczak MZ, Ratajczak J. Horizontal transfer of RNA and proteins between cells by extracellular microvesicles: 14 years later. Clin Translational Medicine (Clin Trans Med) 2016; 5:7. *https://doi.org/10.1186/s40169-016-0087-4*
50. Peciak J, Stec WJ, Treda C, *et al*. Low incidence along with low mRNA levels of EGFRvIII in prostate and colorectal cancers compared to glioblastoma. J Cancer 2017; 8(5):146-151. *https://doi.org/10.7150/jca.16108*
51. Rajagopal C, Harikumar KB. The origin and function of exosomes in cancer. Fronters Oncol (Front Oncol); 2018; 8:66. *https://doi.org/10.3389/fonc.2018.00066*
52. Rutkowska A, Stoczynska Fidelus E, Janik K, Wlodarczyk A, Rieske P. EGFRvIII: An oncogene with ambiguous role. J Oncol (Hindawi) 2019. *https://doi.org/10.1155/2019/1092587*
53. Yekula A, Balaj L, *et al*. Extracellular vesicles in glioblastoma tumor microenvironment. Front Microenv 2020; 10:3137. *https://doi.org/10.3389/fimmu.2019.03137*
54. Nair A, Chung HC, Sun T, Tyagi S, Dobroleck LE. Combinatorial inhibition of PTPN12- regulated receptors leads to a broadly effective therapeutic strategy in triple negative breast cancer. Nat Med 2018; 24 (4): 505- 511. *https://doi.org/10.1038/nm.4507*
55. Cuesta-Mateos C, Alcaraz-sema A, Somovilla-Crespo B, Munoz-Calleja C. Monoclonal antibody therapies for hematological malignancies: Not just lineage-specific targets. Front Immunol 2018; 8:1936. *https://doi.org/10.3389/fimmu.2017.01936*
56. Wei YM, Poon DC, Fei R, *et al*. A platinum-based hybrid drug design approach to circumvent acquired resistance to molecular targeted tyrosine kinase inhibitors. Sci Reports 2016; 6: 25363. *https://doi.org/10.1038/srep25363*
57. Wu SC, Chen YJ, Wang HC, *et al*. Biospecific antibody conjugated manganese-based magnetic engineered iron oxide for imaging of HER2/neu- and EGFR-expressing tumors. Theranostics 2016; 6(1):118-130. *https://doi.org/10.7150/thno.13069*
58. Lauretti L, Cenci T, Montano N, *et al*. Molecular analysis in a glioblastoma cohort – Results of a prospective analysis. J Person Med 2022; 12:685. *https://doi.org/10.3390/jpm12050685*
59. Liberman TA, Nusbaum HR, Razon N, *et al*. Amplification and overexpression of EGF receptor gene in primary human glioblastomas. J Cell Sci 1985(supplement 3):161-172. *https://doi.org/10.1038/313144a0*
60. Yuan L, Zhang HY, Liu JB, *et al*. Growth factor receptor-Src-mediated suppression of GRK6 dysregulates CXCR4 signaling and promotes medulloblastoma migration. Mol Cancer 2013, 12:18. *https://doi.org/10.1186/1476-4598-12-18*
61. Stupp R, Mason WP, Bent MJ, *et al*. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352:987-96. *https://doi.org/10.1056/NEJMoa043330*
62. McGirt MJ, Brem H. Carmustine Wafers (Gliadel) plus concomitant temozolomide therapy after resection of malignant astrocytoma growing evidence for safety and efficacy. Ann Surg Oncol 2010; 17:1729-31. *https://doi.org/10.1245/s10434-010-1092-2*
63. Rainer NG, Heidecke V. Clinical development of experimental therapies for malignant glioma. SQU Med J; 2011; 11(1):5-28. *PMID: 21509204*
64. Argyriou AA, Kalofonos HP. Molecularly targeted therapies for malignant gliomas. Mol Medicine 2009; 11:111-122. *https://doi.org/10.1586/ern.09.116*
65. Van den Bent MT, Brandes AA, Rampling R, *et al*. Randomized phase II trial of erlotinib versus temozolomide or carmustine in recurrent glioblastoma: EORTC brain tumor group study 26034. J Clin Oncol 2009;27(8):1268-74. *https://doi.org/10.1200/JCO.2008.17.5984*
66. Vredenburgh JJ, Desjardins A, Herndonll JE, *et al*. Phase II trial of bevacizumab and irinotecan in recurrent

malignant glioma. Clin Cancer Res 2007; 13(4):1253-1259. *https://doi.org/10.1158/1078-0432.CCR-06-2309*

67. Herrlinger D, Forschler H, Kuker W, *et al*. Leptomreningeal metastasis survival and prognostic factors in 155 patients. J Neurol Sci 2004; 223:167-178. *https://doi.org/10.1016/j.jns.2004.05.008*
68. Khuntia D, Brown P, Li J, *et al*. Whole brain radiotherapy in the management of brain metastases. J Clin Oncol 2006; 24:1295-1304. *https://doi.org/10.1200/JCO.2005.04.6185*
69. Postmus PF, Smit EF. Chemotherapy for brain metastasis of lung cancer: A review. Ann Oncol 1999; 10:253-59. *https://doi.org/10.1023/a:1008318515795*
70. Lee DH, Kim SW, Suh C, *et al*. Epidermal growth factor receptor tyrosine kinase inhibitors as a first - Line therapy for never-smokers with adenocarcinoma of lung and asymptomatic synchronous brain metastasis. Clin Lung Cancer 2008; 9(5):296. *https://doi.org/10.7759/cureus.13470*
71. Hoffknecht P, Tufinan A, Wehler T, *et al*. Efficacy of irreversible ErbB family blocker afatinib in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)- pretreated non-small-cell lung cancer patients with brain metastases or leptomeningeal disease. J Thorac Oncol 2015; 10(1):156-163. *https://doi.org/10.1097/JTO.0000000000000380*
72. Sakai M, Ishikawa S, Ito H, *et al*. Carcinomatous meningitis from non-small-cell lung cancer responding to gefitinib. Int J Clin Oncol 2006;11(3):243-5. *https://doi.org/10.1007/s10147-005-0558-x*
73. Jackman DM, Holmes AJ, Lindeman N, *et al*. Response and resistance in a non-small cell lung cancer patient with an epidermal growth factor receptor mutation and leptomenineal metastases treated with high-dose gefitinib. J Clin Oncol 2006; 24:4517-20. *https://doi.org/10.1200/JCO.2006.06.6126*
74. Muller F, Riesenberg H, Hirnle P, *et al*. Complete remission of multiple brain metastases of non- small cell lung cancer induced by gefitinib monotherapy. Strahlenther Onkol 2011; 187(12): 826 -30. *https://doi.org/10.1007/s00066-011-2260-4*
75. Hata A, Kaji R, Fujita S, *et al*. High-dose erlotinib for refractory brain metastases in a patient with relapsed non-small cell lung cancer. J Thorac Oncol 2011; 6:404. *https://doi.org/10.1097/JTO.0b013e3181d899bb*
76. Yuan Y, Tan C, Li M, *et al*. Activity of pemetrexed and high-dose gefitinib in an EGFR-mutated lung adenocarcinoma with brain and leptomeningeal metastasis after response to gefitinib. World J Surgical Oncol 2012, 10:235. *https://doi.org/10.1186/1477-7819-10-235*
77. Katayama T, Shimizu I, Suda K, *et al*. Efficacy of erlotinib for brain and leptomeningeal metastases in patients with lung adenocarcinoma who showed initial good response to gefitinib. J Thorac Oncol 2009, 4:1415-19. *https://doi.org/10.1097/JTO.0b013e3181b62572*
78. Paz-Ares L, Sanchez JM, Garcia-Veloasco A, *et al*. A prospective phase II trial of erlotinib in advanced non-small cell lung cancer (NSCLC) patients (p) with mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR). J Clin Oncol 2006; 24:369s (supple, abstract 9020). *https://doi.org/10.1200/jco.2006.24.18_suppl.7020*
79. Lai CS, Boshoff C, Falzon M, *et al*. Complete response to erlotinib treatment in brain metastases from recurrent NSCLC. Thorax 2006; 61:91. *https://doi.org/10.1136/thx.2005.052233*
80. Fekrazad MH, Ravindranathan M, Jones DV Jr. Response of intracranial metastases to erlotinib therapy. J Clin Oncol 2007; 25:5024-26. *https://doi.org/10.1200/JCO.2007.13.3751*
81. Clarke JL, Pao W, Wu N, *et al*. High dose weekly erlotinib achieves therapeutic concentrations in CSF and is effective in leptomeningeal metastases from epidermal growth factor receptor mutant lung cancer. J Neurooncol 2010; 99(2):283-286. *https://doi.org/10.1007/s11060-010-0128-6*
82. Benedetti G, Latini L, Galetta D, *et al*. Epidermal growth factor receptor exon 19 deletions predict complete regression of multiple intracrnial metastases in two cases of non-small cell lung cancer treated with erlotinib. J Thorac Oncol 2009; 4:936-937. *https://doi.org/10.1097/JTO.0b013e3181a9a0a2*
83. Greulich H, Chen TH, Janne PA, *et al*. Oncogenic transformation by inhibitor-sensitive and -resistant EGFR mutants. PloS Med 2005; 2: 313.
84. Chihara E, Takeda H, Kubo T, *et al*. Chemo preventive effect of gefitinib on non-smoking-related lung tumorigenesis in activating epidermal growth factor receptor transgenic mice. Cancer Res 2009; 69: 7088-7095. *https://doi.org/10.1158/0008-5472.CAN-08-4205*
85. Li H, Pan Y, Li Y, *et al*. Frequency of well-identified oncogenic driver mutations in lung adenocarcinoma of smokers varies with histological subtypes and graduated smoking dose. Lung Cancer 2013; 79(1):8-13. *https://doi.org/10.1016/j.lungcan.2012.09.018*
86. Gallant GN, Sheehan JH, Shaver TM, *et al*. EGFR kinase domain duplication (EGFR-KDD) is a novel oncogenic driver in lung cancer that is clinically responsive to afatinib. Cancer Discov 2015; 5:1155-63. *https://doi.org/10.1158/2159-8290.CD-15-0654*
87. Hirokawa E, Watanabe S, Sakai K, *et al*. Durable response to EGFR tyrosine kinase inhibitors in a patient with non-small cell lung cancer harboring an EGFR kinase domain duplication. Thorac Cancer 2021; 12(16):2283-2287. *https://doi.org/10.1111/1759-7714.14081*
88. Konduri K, Gallant JN, Chae YK, *et al*. EGFR fusions as novel therapeutic targets in lung cancer. Cancer Discov 2016; 6: 601-611. *https://doi.org/10.1158/2159-8290.CD-16-0075*
89. Zochbauer-Muller S, Kaserer B, Mullauer L, *et al*. Case report: Aftatinib treatment in a patient with NSCLC harboring a rare EGFR Exon 20 mutation. Front Oncol 2021; 10:593852. *https://doi.org/10.3389/fonc.2020.593852*
90. Faehling M, Schwenk B, Kramberg S, *et al*. Oncogenic driver mutations, treatment, and EGFR- TKI resistance in a Caucasian population with non-small cell lung cancer: Survival in clinical practice. Onco target 2017;8(44): 77897-77914. *https://doi.org/10.18632/oncotarget.20857*
91. Takeda K, Yamasaki A, Igishi T, *et al*. Frequency of epidermal growth factor receptor mutation in smokers with lung cancer without pulmonary emphysema. Anticancer Res 2017; 37:765- 772. *https://doi.org/10.21873/anticanres.11375*
92. Liu X, Wang P, Ma Z, *et al*. Epidermal growth factor receptor (EGFR): A rising star in the era of precision medicine of lung cancer. Oncotarget 2017; 8(30):50209-50220. *https://doi.org/10.18632/oncotarget.16854*
93. Ramalingam SS, Yang JC, Lee CK, *et al*. Osimertinib as first-line treatment of EGFR mutation- positive advanced non-small-cell lung cancer. J Clin Oncol 2018; 36(9):841-49. *https://doi.org/10.1200/JCO.2017.74.7576*
94. Chen D, Li XL, Wu B, *et al*. A novel oncogenic driver in a lung adenocarcinoma patient harboring an EGFR-KDD and response to afatinib. Front Oncol 2020; 10:16-9. *https://doi.org/10.3389/fonc.2020.00867*
95. Du Z, Brown BP, Kim S, *et al*. Structure-function analysis of oncogenic EGFR kinase domain duplication reveals insight into activation and a potential approach for therapeutic targeting. Nat Commun 2021; 12:1-15. *https://doi.org/10.1038/s41467-021-21613-6*
96. Huang LT, Zhong SL, Han CB, *et al*. Impact of EGFR exon 19 deletion subtypes on clinical outcomes in EGFR-TKI-treated advanced non-small-cell lung cancer. Lung Cancer 2022; 166: 9-16. *https://doi.org/10.1016/j.lungcan.2022.01.014*
97. Lynch TJ, Bell DW, Sordella R, *et al*. Activating mutations in the epidermal growth factor receptor

underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004; 350: 2129-2139. *https://doi.org/10.1056/NEJMoa040938*

98. Cross DA, Ashton SE, Ghiorghiu S, *et al*. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 2014;4: 1046-1061. *https://doi.org/10.1158/2159-8290.CD-14-0337*
99. Finlay MR, Anderton M, Ashton S, *et al*. Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistance mutations that spares the wild type form of the receptor. J Med Chem 2014; 57: 8249-8267. *https://doi.org/10.1021/jm500973a*
100. Balk CS, Wu D, Smith C, *et al*. Durable response to tyrosine kinase inhibitor therapy in a lung cancer patient harboring epidermal growth factor receptor tandem kinase domain duplication. J Thoracic Oncol 2011; 10(10):e97-e99. *https://doi.org/10.1097/JTO.0000000000000586*
101. Zhu G, Musumecci F, Byrne P, Deepti Gupta, Ekta Gupta, Baer J. Clinical trials of lung cancer after chemotherapy and traditional medicine (12 cases). Advance Pharm J 2017; 2 (5):199-203.
102. Mok TS, Wu YL, Ahn MJ, *et al*. Osimertinib or platinum-pemetrexed in EGFR T790M- positive lung cancer. N Engl J Med 2017; 376: 629-640.
103. Zheng H, Wang Zp, Meng QY, *et al*. Target therapy of gefitinib in advanced adenocarcinoma of the lung. Chinese J Lung Canc 2007; 10(3;229. *https://doi.org/10.3779/j.issn.1009-3419.2007.03.16*
104. Mok TS, Wu YL, Thongrasert S, *et al*. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361:947-57. *https://doi.org/10.1056/NEJMoa0810699*
105. Maemondo M, Inoue A, Kobayashi K, *et al*. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010; 362:2385-88. *https://doi.org/10.1056/NEJMoa0909530*
106. Mitsudomi T, Morita S, Yatabe Y, *et al*. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG 3405): An open label, randomised phase 3 trial. Lancet Oncol 2010; 11(2):121-128. *https://doi.org/10.1016/S1470-2045(09)70364-X*
107. Park K, Tan EH, O'Byrne K, *et al*. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-lung 7): A phase 2B, open-label, randomised controled trial. Lancet Oncol 2016; 17(5):577-89. *https://doi.org/10.1016/S1470-2045(16)30033-X*
108. Xue J, Sun H, Wu T, *et al*. Clinical study of gefitinib as first-line treatment for EGFR-mutant advanced lung adenocarcinoma. J Shanxi Med Univ 2017; 48:352.
109. Ohe Y, Imamura F, Nogami N, *et al*. Osimertinib versus standard-of-care EGFR-TKI as first-line treatment for EGFRm advanced NSCLC: FLAURA Japanese subset. Japanese J Clin Oncol 2018; 49(1):29-36. *https://doi.org/10.1016/j.jtho.2018.09.004*
110. Ramalingam SS, Vansteenkiste J, Planchard D, *et al*. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med 2020; 382(1):41-50. *https://doi.org/10.1056/NEJMoa1913662*
111. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, *et al*. Erlotinib in previousl treated non-small- cell lung cancer. N Engl J Med 2005; 353:123-132. *https://doi.org/10.1056/NEJMoa050753*
112. Zhou C, Wu YC, Chen G, *et al*. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer(OPTIMAI,CTONG-0802): A multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011; 12(8):735-42. *https://doi.org/10.1016/S1470-2045(11)70184-X*
113. Rosell R, Carcereny F, Gervais R, *et al*. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012; 13(3): 239- 46. *https://doi.org/10.1016/S1470-2045(11)70393-X*
114. Fu K, Xie F, Fu L, *et al*. Therapeutic strategies for EGFR-mutated non-small cell lung cancer patients with osimertinib resistance. J Hematol Oncol 2022;15:173. *https://doi.org/10.1186/s13045-022-01391-4*
115. Shi Y, Zhang L, Liu X, *et al*. Icotinib versus gefitinib in previously treated advanced non-small- cell lung cancer (ICOGEN): A randomised, double-blind phase 3 non-inferiority trial. Lancet Oncol 2013; 14(10):953-61. *https://doi.org/10.1016/S1470-2045(13)70355-3*
116. Wu YL, Zhou C, Hu CP, *et al*. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-lung 6): An open-label, randomised phase 3 trial. Lancet Oncol 2014; 15:213-22. *https://doi.org/10.1016/S1470-2045(13)70604-1*
117. Yang JC, Wu YL, Schuler M, *et al*. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-lung 3 and LUX-lung 6): Analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015; 16(2):141-51. *https://doi.org/10.1016/S1470-2045(14)71173-8*
118. Sequist LV, Yang JC, Yamamoto N, *et al*. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2023;31(27): 3327-34. *https://doi.org/10.1200/JCO.2012.44.2806*
119. Mok TS, Wu YL, Ahn MJ, *et al*. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 2017; 376(7):629-40. *https://doi.org/10.1056/NEJMoa1612674*
120. Sakata Y, Saito G, Sakata S, *et al*. Osimertinib as first-line treatment for elderly patients with advanced EGFR mutation-positive non-small-cell lung cancer in a real-world setting (OSI- FACT-EP). Lung Cancer 2023; 186:107426. *https://doi.org/10.1016/j.lungcan.2023.107426*
121. Rodriguez PC, Rodrigue G, Gonzalez G, Lage A. Clinical development and perspectives of CIMAvax EGF, Cuban vaccine for non-small-cell lung cancer therapy. MEDICC Rev 2010; 12: 17-23. *https://doi.org/10.37757/MR2010.V12.N1.4*
122. Rodriguez PC, Popa X, Martinez O, *et al*. A phase III clinical trial of the epidermal growth factor vaccine CIMAvax-EGF as switch maintenance therapy in advanced non-small-cell lung cancer patients. Clin Cancer Res 2016; 22: 3782-3790.
123. Hernandez M, Ortiz RA, Salomon E, *et al*. Safety and efficacy of CIMAvax-EGF vaccine for the treament of real-world non-small cell lung cancer patients. Integrative Clin Med 2021;5:1-5. *https://doi.org/10.3389/fonc.2023.1287902*
124. Sears HF, Herlyn D, Steplwski Z. Effects of monoclonal antibody immunotherapy on patients with gastrointestinal adenocarcinoma. J Biol Response Med 1984; 3: 138-150. *PMID: 6374043*
125. Riethmuller G, Holz E, Schlimok G, *et al*. Monoclonal antibody therapy for resected Dukes' colorectal cancer: Seven-year outcome of a multicenter randomized trial. J Clin Oncol 1998; 16: 1788-1794. *https://doi.org/10.1200/JCO.1998.16.5.1788*
126. De Bacco F, *et al*. Receptor tyrosine kinases as targets for cancer therapy. Cancer Ther 2004;2: 317-328.
127. Moody P, Sayers EJ, Magnusson JP, *et al*. Receptor crosslinking: A general method to trigger internalization and lysosomal targeting of therapeutic receptor: Ligand complexes. Molecular Ther 2015; 23: 1888-1898. *https://doi.org/10.1038/mt.2015.178*

128. Del Mar Maldonado M, Medina JI, Velazquez L, *et al*. Targeting Rac and Cdc42 GEFs in metastatic cancer. Frontiers Cell Dev Biol 2020;8: 201. *https://doi.org/10.3389/fcell.2020.00201*
129. Duarte HO, Balmaña M, Mereiter S, *et al*. Gastric cancer cell glycosylation as a modulator of the ErbB2 oncogenic receptor. Int J Mol Sci 2017; 18: 2262. *https://doi.org/10.3390/ijms18112262*
130. Jenke R, Holzhäuser-Rein M, Mueller-Wilke S, *et al*. SATB1-mediated upregulation of the oncogeic receptor tyrosine kinase HER3 antagonizes Met inhibition in gastric cancer cells. Int J Mol Sci 2021; 22: 82. *https://doi.org/10.3390/ijms22010082*
131. Singh RR and Kumar R. Steroid hormone receptor signalling in tumorigenesis. J Cell Biochem 2005; 96: 490-505. *https://doi.org/10.1002/jcb.20566*
132. Marx C, Yau C, Banwait S, *et al*. Proteasome-regulated ERBB2 and estrogen receptor pathways in breast cancer. Molecular Pharmacol 2007; 71(6): 1525-1534. *https://doi.org/10.1124/mol.107.034090*
133. Elangovan S, Ramachandran S, Venkatesan N, *et al*. SIRT1 is essential for oncogenic signaling by estrogen/estrogen receptor α in breast cancer. Cancer Res 2011; 71(21): 6654-6664. *https://doi.org/10.1158/0008-5472.CAN-11-1446*
134. Yue W, Yager JD, Wang JP, *et al*. Estrogen receptor-dependent and independent mechanisms of breast cancer carcinogenesis. Steroids 2013; 78: 161. *https://doi.org/10.1016/j.steroids.2012.11.001*
135. Veeraraghavan J, Tan Y, Cao XX, *et al*. Recurrent ESR1-CCDC170 rearrangements in an aggressive subset of oestrogen receptor-positive breast cancers. Nature Comm 2014; 5: 4577. *https://doi.org/10.1038/ncomms5577*
136. Ludwik KA, McDonald OG, Brenin DR, *et al*. ERα-mediated nuclear sequestration of RSK2 is required for ER+ breast cancer tumorigenesis. Cancer Res 2018; 78(8): 2014-2025. *https://doi.org/10.1158/0008-5472.CAN-17-2063*
137. Hickey TE, Dwyer AR, Tilley WD, *et al*. Arming androgen receptors to oppose oncogenic estrogen receptor activity in breast cancer. British J Canc 2021; 125(12): 1599-1601. *https://doi.org/10.1038/s41416-021-01478-8*
138. Chirieac LR, Dacic S. Targeted therapies in lung cancer. Surgical Pathol 2010; 3:71-82. *https://doi.org/10.1016/j.path.2010.04.001*
139. Domingo G, Perez C, Velez M. EGF receptor in lung cancer: A successful story of targeted therapy. Expert Review Anti-infective Ther 2010; 10(10):1577-87. *https://doi.org/10.1586/era.10.141*
140. Druker BJ, Tamura S, Buchdunger E, *et al*. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of BCR-Abl positive cells. Nat Med 1996;2(5):561-566. *https://doi.org/10.1038/nm0596-561*
141. Druker BJ, Talpaz M, Resta DJ, *et al*. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001; 344(14):1031-37. *https://doi.org/10.1056/NEJM200104053441401*
142. Denzel S, Maetzel D, Mack B, *et al*. Initial activation of EpCAM cleavage viacell-to-cell contact. BMC Cancer 2009;9, 402. *https://doi.org/10.1186/1471-2407-9-402*
143. Mohtar MA, Hernychova L, O'Neill JR, *et al*. The sequence-specific peptide-binding activity of the protein sulfide isomerase AGR2 directs its stable binding to the oncogenic receptor EpCAM. Mol Cell Prot 2018; 17(4):737-763. *https://doi.org/10.1074/mcp.RA118.000573*
144. Baeuerle PA, Gires O. EpCAM(CD326) finding its role in cancer. Br J Cancer 2007; 96: 417-423. *https://doi.org/10.1038/sj.bjc.6603494*
145. Hosseinian SA, Haddad-Mashadrizeh A, Dolatabadi S. Simulation and stability assessment of anti-EpCAM Immunotoxin for cancer therapy. Adv Pharm Bull 2018; 8(3), 447-455. *https://doi.org/10.15171/apb.2018.052*
146. Zhu G. Use of traditional medicine in severe edema amelioration of refractory congestive heart failure - Case report. Blood, Heart and Circulation 2018; 2.1: 1-2.
147. Esposito CL, Cauogno S, Condorelli G, *et al*. Aptamer chimeras for therapeutic delivery: The challenging perspectives. Genes 2018; 9: 529. *https://doi.org/10.3390/genes9110529*
148. Zhu G. Targeting oncogenic receptor: From molecular physiology to currently the standard of target therapy. Advance Pharm J 2017; 2(1): 10-28.
149. FY Lee, L Lombardo, A Camuso, *et al*. BMS-354825 potently inhibits multiple selected oncogenic tyrosine kinases and possesses broad-spectrum antitumor activities *in vitro* and *in vivo*. Cancer Res 2005;65 (9_ Supplement): 159.
150. Pramanik S D, Kumar Halder A, *et al*. Potential of histone deacetylase inhibitors in the control and regulation of prostate, breast and ovarian cancer. Front Chem 2022 (10): 948217. *https://doi.org/10.3389/fchem.2022.948217*
151. Zhu G. Vitamin A and its derivatives- retinoic acid and retinoid pharmacology. Am J Biomed Sci Res 2019; 3: 162-177. *https://doi.org/10.34297/AJBSR.2019.03.000656*
152. Prabhu V, Morro S, Kawakibi AR, *et al*. ONC201 and imipridones: Anti-cancer compounds with clinical efficacy. Neoplasia 2020; 22:725–744. *https://doi.org/10.1016/j.neo.2020.09.005*
153. Jackson H, Granger D, Jones G, *et al*. Novel bispecific domain antibody to LRP6 inhibits Wnt and R-spondin ligand-induced Wnt signaling and tumor growth. Molecular Cancer Res (Mol Cancer Res) 2016; 14(9):859-68. *https://doi.org/10.1158/1541-7786.MCR-16-0088*
154. Shida D, Inoue S, Yoshida Y, Kodaka A, Tsuji T, Tsuji M. Sphingosine kinase 1 is upregulated with lysophosphatidic acid receptor 2 in human colorectal cancer. World J Gastroenterol 2016; 22(8): 2503-2511. *https://doi.org/10.3748/wjg.v22.i8.2503*
155. Yang X, Zhang X, Fu ML, *et al*. Targeting the Tumor Micro- environment with Interferon-B bridges innate and adaptive immune responses. Cancer Cell 2014; 25: 37-48. *https://doi.org/10.1016/j.ccr.2013.12.004*
156. Qiao J, Liu Z, Fu YX, *et al*. Targeting tumors with IL-10 prevents dendritic cell-mediated CD8+ T cell apoptosis. Cancer Cell 2019; 35:901-915. *https://doi.org/10.1016/j.ccell.2019.05.005*
157. Weng S, Stoner SA, Zhang DE. Sex chromosome loss and the pseudoautosomal region genes in hematological malignancies. Oncotarget 2016;7(44):72356-372. *https://doi.org/10.18632/oncotarget.12050*
158. Mansour MR, Reed C, Eisenberg AR, *et al*. Targeting oncogenic interleukin-7 receptor signaling with N-acetylcysteine in T-cell acute lymphoblastic leukemia. Br J Haematol 2015; 168(2):230- 238. *https://doi.org/10.1111/bjh.13115*
159. Huang SC, Wei PC, Hwang-Verslues WW, *et al*. TGF-beta secreted by Tregs in lymph nodes promotes breast cancer malignancy via upregulation of IL-17RB. EMBO Molecular Med 2017; 9: 1660-1680. *https://doi.org/10.15252/emmm.201606914*
160. Poultsidi A, Dimopoulos Y, He TF, *et al*. Lymph node cellular dynamics in cancer and HIV: What can we learn for the follicular CD4(Tfh) cells? Frontiers Immunol 2018; 9: 2233. *https://doi.org/10.3389/fimmu.2018.02233*
161. Wilmes S, Maximillian H, Vuorio Joni, *et al*. Mechanism of homodimeric cytokine receptor activation and dys-regulation by oncogenic mutations. Science 2020; 367(6478): 643-652. *https://doi.org/10.1126/science.aaw3242*