



OPEN ACCESS

EDITED BY



\*CORRESPONDENCE

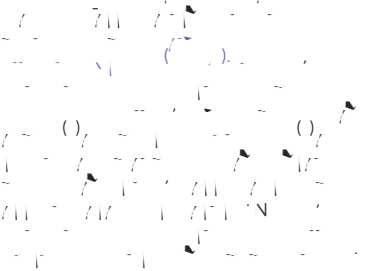


RECEIVED 04 May 2022  
ACCEPTED 30 July 2023  
PUBLISHED 03 June 2023

CITATION

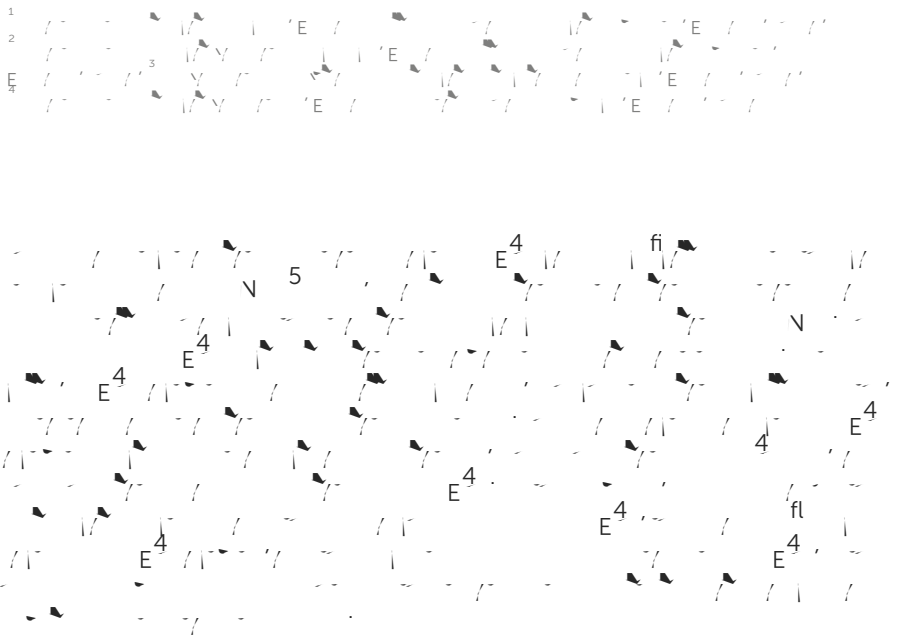
(2023) Chen X, An Y, Tan M, Xie D, Liu L and Xu B. Biological functions and research progress of eIF4E. *Front. Oncol.* 13:10655. doi:10.3389/fonc.2023.10655

COPYRIGHT © 2023



# Biological functions and research progress of eIF4E

Xiacong Chen<sup>1†</sup>, Yang An<sup>1†</sup>, Mengsi Tan<sup>1†</sup>, Dongrui Xie<sup>1</sup>, Ling Liu<sup>2,3,4\*</sup> and Benjin Xu<sup>2,3,4\*</sup>



KEYWORDS

eIF4E, eIF4G, eIF4A, eIF4B, eIF4D, eIF4E, eIF4F, eIF4H, eIF4I, eIF4J, eIF4K, eIF4L, eIF4M, eIF4N, eIF4O, eIF4P, eIF4Q, eIF4R, eIF4S, eIF4T, eIF4U, eIF4V, eIF4W, eIF4X, eIF4Y, eIF4Z, eIF4AA, eIF4AB, eIF4AC, eIF4AD, eIF4AE, eIF4AF, eIF4AG, eIF4AH, eIF4AI, eIF4AJ, eIF4AK, eIF4AL, eIF4AM, eIF4AN, eIF4AO, eIF4AP, eIF4AQ, eIF4AR, eIF4AS, eIF4AT, eIF4AU, eIF4AV, eIF4AW, eIF4AX, eIF4AY, eIF4AZ, eIF4BA, eIF4BB, eIF4BC, eIF4BD, eIF4BE, eIF4BF, eIF4BG, eIF4BH, eIF4BI, eIF4BJ, eIF4BK, eIF4BL, eIF4BM, eIF4BN, eIF4BO, eIF4BP, eIF4BQ, eIF4BR, eIF4BS, eIF4BT, eIF4BU, eIF4BV, eIF4BW, eIF4BX, eIF4BY, eIF4BZ, eIF4CA, eIF4CB, eIF4CC, eIF4CD, eIF4CE, eIF4CF, eIF4CG, eIF4CH, eIF4CI, eIF4CJ, eIF4CK, eIF4CL, eIF4CM, eIF4CN, eIF4CO, eIF4CP, eIF4CQ, eIF4CR, eIF4CS, eIF4CT, eIF4CU, eIF4CV, eIF4CW, eIF4CX, eIF4CY, eIF4CZ, eIF4DA, eIF4DB, eIF4DC, eIF4DD, eIF4DE, eIF4DF, eIF4DG, eIF4DH, eIF4DI, eIF4DJ, eIF4DK, eIF4DL, eIF4DM, eIF4DN, eIF4DO, eIF4DP, eIF4DQ, eIF4DR, eIF4DS, eIF4DT, eIF4DU, eIF4DV, eIF4DW, eIF4DX, eIF4DY, eIF4DZ, eIF4EA, eIF4EB, eIF4EC, eIF4ED, eIF4EE, eIF4EF, eIF4EG, eIF4EH, eIF4EI, eIF4EJ, eIF4EK, eIF4EL, eIF4EM, eIF4EN, eIF4EO, eIF4EP, eIF4EQ, eIF4ER, eIF4ES, eIF4ET, eIF4EU, eIF4EV, eIF4EW, eIF4EX, eIF4EY, eIF4EZ, eIF4FA, eIF4FB, eIF4FC, eIF4FD, eIF4FE, eIF4FF, eIF4FG, eIF4FH, eIF4FI, eIF4FJ, eIF4FK, eIF4FL, eIF4FM, eIF4FN, eIF4FO, eIF4FP, eIF4FQ, eIF4FR, eIF4FS, eIF4FT, eIF4FU, eIF4FV, eIF4FW, eIF4FX, eIF4FY, eIF4FZ, eIF4GA, eIF4GB, eIF4GC, eIF4GD, eIF4GE, eIF4GF, eIF4GG, eIF4GH, eIF4GI, eIF4GJ, eIF4GK, eIF4GL, eIF4GM, eIF4GN, eIF4GO, eIF4GP, eIF4GQ, eIF4GR, eIF4GS, eIF4GT, eIF4GU, eIF4GV, eIF4GW, eIF4GX, eIF4GY, eIF4GZ, eIF4HA, eIF4HB, eIF4HC, eIF4HD, eIF4HE, eIF4HF, eIF4HG, eIF4HH, eIF4HI, eIF4HJ, eIF4HK, eIF4HL, eIF4HM, eIF4HN, eIF4HO, eIF4HP, eIF4HQ, eIF4HR, eIF4HS, eIF4HT, eIF4HU, eIF4HV, eIF4HW, eIF4HX, eIF4HY, eIF4HZ, eIF4IA, eIF4IB, eIF4IC, eIF4ID, eIF4IE, eIF4IF, eIF4IG, eIF4IH, eIF4II, eIF4IJ, eIF4IK, eIF4IL, eIF4IM, eIF4IN, eIF4IO, eIF4IP, eIF4IQ, eIF4IR, eIF4IS, eIF4IT, eIF4IU, eIF4IV, eIF4IW, eIF4IX, eIF4IY, eIF4IZ, eIF4JA, eIF4JB, eIF4JC, eIF4JD, eIF4JE, eIF4JF, eIF4JG, eIF4JH, eIF4JI, eIF4JJ, eIF4JK, eIF4JL, eIF4JM, eIF4JN, eIF4JO, eIF4JP, eIF4JQ, eIF4JR, eIF4JS, eIF4JT, eIF4JU, eIF4JV, eIF4JW, eIF4JX, eIF4JY, eIF4JZ, eIF4KA, eIF4KB, eIF4KC, eIF4KD, eIF4KE, eIF4KF, eIF4KG, eIF4KH, eIF4KI, eIF4KJ, eIF4KK, eIF4KL, eIF4KM, eIF4KN, eIF4KO, eIF4KP, eIF4KQ, eIF4KR, eIF4KS, eIF4KT, eIF4KU, eIF4KV, eIF4KW, eIF4KX, eIF4KY, eIF4KZ, eIF4LA, eIF4LB, eIF4LC, eIF4LD, eIF4LE, eIF4LF, eIF4LG, eIF4LH, eIF4LI, eIF4LJ, eIF4LK, eIF4LL, eIF4LM, eIF4LN, eIF4LO, eIF4LP, eIF4LQ, eIF4LR, eIF4LS, eIF4LT, eIF4LU, eIF4LV, eIF4LW, eIF4LX, eIF4LY, eIF4LZ, eIF4MA, eIF4MB, eIF4MC, eIF4MD, eIF4ME, eIF4MF, eIF4MG, eIF4MH, eIF4MI, eIF4MJ, eIF4MK, eIF4ML, eIF4MN, eIF4MO, eIF4MP, eIF4MQ, eIF4MR, eIF4MS, eIF4MT, eIF4MU, eIF4MV, eIF4MW, eIF4MX, eIF4MY, eIF4MZ, eIF4NA, eIF4NB, eIF4NC, eIF4ND, eIF4NE, eIF4NF, eIF4NG, eIF4NH, eIF4NI, eIF4NJ, eIF4NK, eIF4NL, eIF4NM, eIF4NN, eIF4NO, eIF4NP, eIF4NQ, eIF4NR, eIF4NS, eIF4NT, eIF4NU, eIF4NV, eIF4NW, eIF4NX, eIF4NY, eIF4NZ, eIF4OA, eIF4OB, eIF4OC, eIF4OD, eIF4OE, eIF4OF, eIF4OG, eIF4OH, eIF4OI, eIF4OJ, eIF4OK, eIF4OL, eIF4OM, eIF4ON, eIF4OO, eIF4OP, eIF4OQ, eIF4OR, eIF4OS, eIF4OT, eIF4OU, eIF4OV, eIF4OW, eIF4OX, eIF4OY, eIF4OZ, eIF4PA, eIF4PB, eIF4PC, eIF4PD, eIF4PE, eIF4PF, eIF4PG, eIF4PH, eIF4PI, eIF4PJ, eIF4PK, eIF4PL, eIF4PM, eIF4PN, eIF4PO, eIF4PP, eIF4PQ, eIF4PR, eIF4PS, eIF4PT, eIF4PU, eIF4PV, eIF4PW, eIF4PX, eIF4PY, eIF4PZ, eIF4QA, eIF4QB, eIF4QC, eIF4QD, eIF4QE, eIF4QF, eIF4QG, eIF4QH, eIF4QI, eIF4QJ, eIF4QK, eIF4QL, eIF4QM, eIF4QN, eIF4QO, eIF4QP, eIF4QQ, eIF4QR, eIF4QS, eIF4QT, eIF4QU, eIF4QV, eIF4QW, eIF4QX, eIF4QY, eIF4QZ, eIF4RA, eIF4RB, eIF4RC, eIF4RD, eIF4RE, eIF4RF, eIF4RG, eIF4RH, eIF4RI, eIF4RJ, eIF4RK, eIF4RL, eIF4RM, eIF4RN, eIF4RO, eIF4RP, eIF4RQ, eIF4RR, eIF4RS, eIF4RT, eIF4RU, eIF4RV, eIF4RW, eIF4RX, eIF4RY, eIF4RZ, eIF4SA, eIF4SB, eIF4SC, eIF4SD, eIF4SE, eIF4SF, eIF4SG, eIF4SH, eIF4SI, eIF4SJ, eIF4SK, eIF4SL, eIF4SM, eIF4SN, eIF4SO, eIF4SP, eIF4SQ, eIF4SR, eIF4SS, eIF4ST, eIF4SU, eIF4SV, eIF4SW, eIF4SX, eIF4SY, eIF4SZ, eIF4TA, eIF4TB, eIF4TC, eIF4TD, eIF4TE, eIF4TF, eIF4TG, eIF4TH, eIF4TI, eIF4TJ, eIF4TK, eIF4TL, eIF4TM, eIF4TN, eIF4TO, eIF4TP, eIF4TQ, eIF4TR, eIF4TS, eIF4TT, eIF4TU, eIF4TV, eIF4TW, eIF4TX, eIF4TY, eIF4TZ, eIF4UA, eIF4UB, eIF4UC, eIF4UD, eIF4UE, eIF4UF, eIF4UG, eIF4UH, eIF4UI, eIF4UJ, eIF4UK, eIF4UL, eIF4UM, eIF4UN, eIF4UO, eIF4UP, eIF4UQ, eIF4UR, eIF4US, eIF4UT, eIF4UU, eIF4UV, eIF4UW, eIF4UX, eIF4UY, eIF4UZ, eIF4VA, eIF4VB, eIF4VC, eIF4VD, eIF4VE, eIF4VF, eIF4VG, eIF4VH, eIF4VI, eIF4VJ, eIF4VK, eIF4VL, eIF4VM, eIF4VN, eIF4VO, eIF4VP, eIF4VQ, eIF4VR, eIF4VS, eIF4VT, eIF4VU, eIF4VV, eIF4VW, eIF4VX, eIF4VY, eIF4VZ, eIF4WA, eIF4WB, eIF4WC, eIF4WD, eIF4WE, eIF4WF, eIF4WG, eIF4WH, eIF4WI, eIF4WJ, eIF4WK, eIF4WL, eIF4WM, eIF4WN, eIF4WO, eIF4WP, eIF4WQ, eIF4WR, eIF4WS, eIF4WT, eIF4WU, eIF4WV, eIF4WW, eIF4WX, eIF4WY, eIF4WZ, eIF4XA, eIF4XB, eIF4XC, eIF4XD, eIF4XE, eIF4XF, eIF4XG, eIF4XH, eIF4XI, eIF4XJ, eIF4XK, eIF4XL, eIF4XM, eIF4XN, eIF4XO, eIF4XP, eIF4XQ, eIF4XR, eIF4XS, eIF4XT, eIF4XU, eIF4XV, eIF4XW, eIF4XX, eIF4XY, eIF4XZ, eIF4YA, eIF4YB, eIF4YC, eIF4YD, eIF4YE, eIF4YF, eIF4YG, eIF4YH, eIF4YI, eIF4YJ, eIF4YK, eIF4YL, eIF4YM, eIF4YN, eIF4YO, eIF4YP, eIF4YQ, eIF4YR, eIF4YS, eIF4YT, eIF4YU, eIF4YV, eIF4YW, eIF4YX, eIF4YY, eIF4YZ, eIF4ZA, eIF4ZB, eIF4ZC, eIF4ZD, eIF4ZE, eIF4ZF, eIF4ZG, eIF4ZH, eIF4ZI, eIF4ZJ, eIF4ZK, eIF4ZL, eIF4ZM, eIF4ZN, eIF4ZO, eIF4ZP, eIF4ZQ, eIF4ZR, eIF4ZS, eIF4ZT, eIF4ZU, eIF4ZV, eIF4ZW, eIF4ZX, eIF4ZY, eIF4ZZ

## 1 Introduction

The eIF4E protein is a member of the eIF4 family (1), which is a family of proteins that are involved in the regulation of protein synthesis (2). The eIF4E protein is a key component of the eIF4F complex, which is involved in the regulation of protein synthesis (3). The eIF4E protein is a key component of the eIF4F complex, which is involved in the regulation of protein synthesis (4). The eIF4E protein is a key component of the eIF4F complex, which is involved in the regulation of protein synthesis (5). The eIF4E protein is a key component of the eIF4F complex, which is involved in the regulation of protein synthesis (6, 7). The eIF4E protein is a key component of the eIF4F complex, which is involved in the regulation of protein synthesis (8).



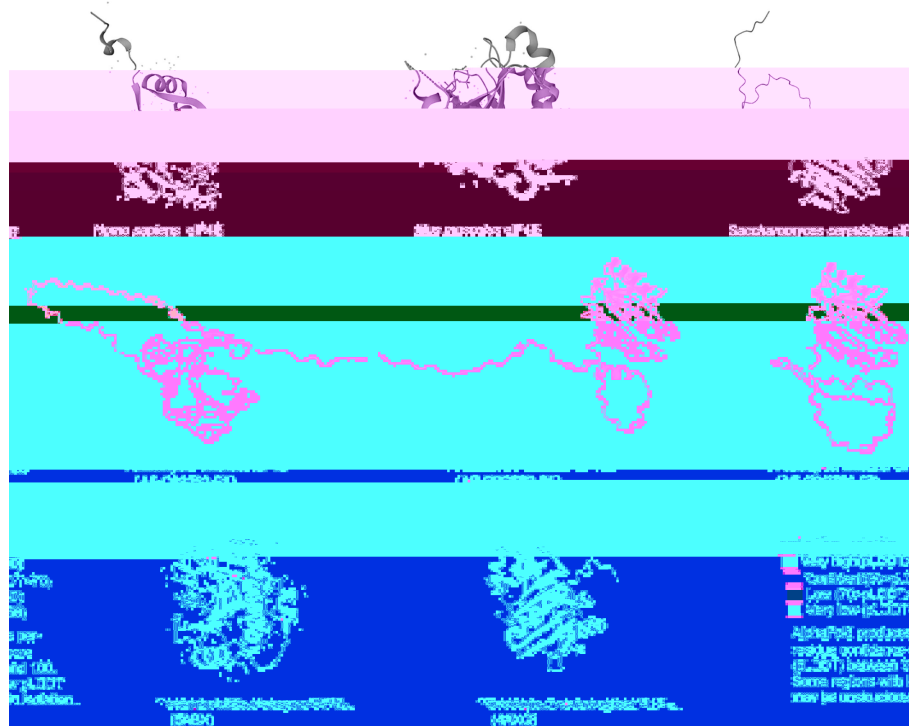


FIGURE 2

Frontiers in Oncology | Volume 13 | Article 1174444 | <https://doi.org/10.3389/fonc.2023.1076855>

CC: D1 (13–16) (T<sub>1</sub>–T<sub>4</sub>), F... (14, 16, 25). F... 3' UTR... RNA... C50... IF4E... (4ESE) (14, 15). F... IF4E... RNA... RNA... C... IF4E... NPC),... IF4E... RNA (26).

F... IF4E... RNA... RNA... C... IF4E... RNA... IF4E... RNA ( IF4E... RNA )... TAP/N F1... REF/A/C (27, 28). C... IF4E... LRPPRC... CRM1 (25). RNP... C... IF4E... IF4E, RNA... 4ESE... LRPPRC, REF/A/C(26).

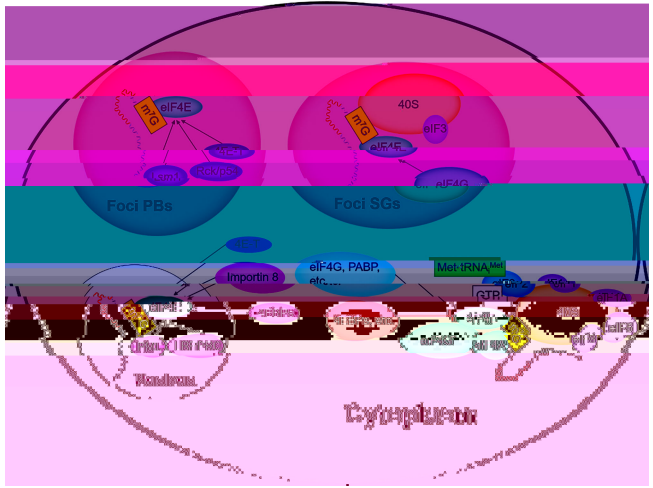


FIGURE 3

Frontiers in Oncology | Volume 13 | Article 1174444 | <https://doi.org/10.3389/fonc.2023.1076855>

CRM1, RNA, IF4E, CRM1, LRPPRC, LRPPRC-IF4E-RNA-CRM1, LRPPRC, IF4E, 4ESE RNA, IF4E, LRPPRC (25, 27).

EIF1, EIF1A, IF3, IF5, TC, PIC (30, 31), 43S

## 3.2 EIF4E and translation

### 3.2.1 The mechanism of eIF4E in translation

I AUG RNA, 48S, (PIC) RNA, IF2/GTP/M-RNA, IF4F, 48S PIC, S, (E).

F. "avaia...C RNA...C...a...a...C  
 RNA...5 UTR...fi...C...  
 C(36). A...C...RNA  
 RNA...RNA...RNA...5 UTR  
 RNA...C...43S PIC...RNA...  
 5 UTR...W...RNA...RNA...  
 IF4A)...C...fi...C...  
 (37). P...VEGF, FGF2, -MC, ODC, CC...D1, B...2  
 S...RNA (35, 36, 38).  
 W...RNA  
 C IF4E...RNA  
 IF4E... (13)...C...  
 IF4F... (36). F...5 UTR  
 RNA...GC...  
 C...F...β...GAPDH...C...  
 RNA (35, 36)...C...IF4F...  
 EIF4E...C...RNA...  
 C... (15, 16). W...  
 IF4E... (36). W...IF4E...  
 RNA...C...IF4E...  
 RNA...W...IF4E...  
 RNA...RNA...IF4E...  
 (35, 36). N...F...  
 IF4E...C...  
 RNA (35)...

PB...RNP...a...fa...ai...a...C...  
 RNA... (46, 48). PB...RNA...  
 RNA...RNA...RNA...  
 (43, 46). PB...RNA...  
 RNA...C...  
 (48). A...P...L...A...C...C 10%  
 PB...  
 C...R89.80.670...19T 62(

### 3.3 EIF4E and cytoplasmic foci

F...RNA... (39, 40), a...  
 C...fi RNA... (RBP) (39,  
 40). M...CRBP...RNA...RNP (41). A...  
 RNP... (40, 42).  
 N...C...S...G... (SG)  
 (P-B...PB), C...  
 RNP...  
 C...B...C... (40). R...  
 C...RNA...  
 C... (43).  
 PB...SG... (E... 3, 5)  
 (44, 45),...IF4E,  
 RNA...RBP...S...PB...  
 IF4E-T, L...1...R...54...IF4E...  
 PB...H...PB...SG...IF3, PABP...  
 C...IF4G...  
 SG (40, 46, 47). T...  
 RNA...IF4E...  
 PB...SG...IF4E... (46).

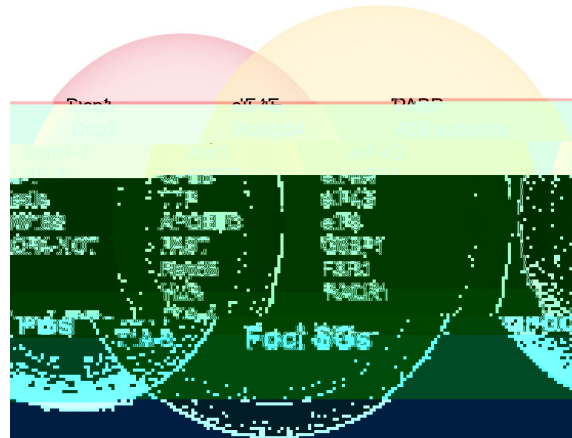


FIGURE 5

... Ca<sup>2+</sup> 4EBP ... D ... 4EBP ... 4EBP ... (4).  
 4E ... (4E-T), IF4E ... (4EBP).  
 PB ... RNA ... DD 6, L 14 ... L 1-7-PAT1 ... (55, 56).

3.4.3 PRH

P ... (PRH) ... N- ... DNA ... (HHEX) ... (57), IF4E ... PRH ... (58), ... (59), PRH ... B ... (60). I ... PRH ... IF4E. P ... N- ... (58). PRH ... IF4E ... RNA ... (61).

3.4.4 PML

F ... C ... PML, IF4E ... F ... C ... PML ... IF4E ... IF4E ... PML (62, 63). PML ... RING ... (B1

B2), ... PML (64). PML ... IF4E, ... T<sup>73</sup> ... RING ... RING ... PML, ... (62, 65). M ... PML ... IF4E ... IF4E”.

3.4.5 EIF4G and eIF4A

EIF4G ... DEAD- ... RNA, IF4E, IF4A, ... (A)- ... (PABP), IF3, IF1, IF5 (2, 3, 5, 6).  
 EIF4A: ... 44 D ... ATP- ... DEAD- ... RNA (4), ... RNA (30, 36, 66).

4 Regulation of EIF4 expression

EIF4E ... IF4E

4.1 Increased gene copy number

S ... H<sub>2</sub>C ... IF4E ... C ... PCR. O ... IF4E ... (67). EIF4E ... IF4E ... IF4E ... IF4E ... (68).

## 4.2 Increased stability of 4 mRNA

IF4E, EIF4E 3'UTR (ARE), H R (69), AUF1, 42, IF4E RNA 3'UTR, IF4E, I, IF4E, H R, IF4E, W, H R, IF4E RNA, H R, IF4E (CC, D1 -MC) (VEGF), T, 42, AUF1, 3'UTR, IF4E RNA, C(70).

## 4.3 Epigenetic modification

### 4.3.1 Methylation

5 (PRMT5) (71), PRMT5, H3, H4, IF4E, IF4E (72-74), I, (CRC), IF4E, PRMT5, PRMT5, IF4E (75), IF4E.

### 4.3.2 MiRNAs regulation

MiRNA, C, C, (76), D, R-141, IF4E, VEGF -MC, H1299, H2009 (77, 78), MiRNA-455-3, IF4E (79), O, RNA, IF4E2, IF4E, RNA, IF4A, RNA, C, RNA (80).

## 5 EIF4E and metabolic reprogramming

I 2011, H, W, (81), IF4E, C, IF4E.

### 5.1 EIF4E and glycolysis

TORC1/IF4E, HIF-1α, HIF-1α, ATP (82, 83).

## 5.2 EIF4E and lipid metabolism

I 2012, 3.9% (544300), C I 2016, I, A, C, R, C, 13, (84), BMI, C, (85), D, IF4E, C, IF4E, IF4E, C(86), S, RNA, IF4E, RNA, K, IF4E, RNA, IF4E, IF4E, IF4E, IF4E (86).

## 6 Main factors affecting eIF4E activity

### 6.1 Intracellular regulation of eIF4E

B, C, IF4E, RNA, I, IF4E, C, PRH, PML, (13, 87, 88), PRH, IF4E, IF4E, RNA, (61), IF4E, N, IF4G, 4EBP1 (62), PRH, C, (60, 87), A, PRH, PRH, (60), PRH, IF4E, (AML, CML) (60, 87), I, PRH, IF4E, CC, D1, RNA, (61), T, CC, D1, (87), M, PRH, VEGF, VEGF, IF4E, C, PRH, C, PML, IF4E, RNA, (62, 89), IF4E, IF4E (64), PML, IF4E (13), T, RING, PML, IF4E, C, IF4E, C, (100), IF4E, 5, RNA (64, 88, 90-92), T, IF4E, IF4G, 4EBP,

IF4E, C(65). O<sup>2</sup> PML, AKT, 4EBP1, PML, IF4E, AKT (90). UPR, PRH, PML, IF4E, PRH, IF4E (61), IF4E, RNA, PRH (87).

MAPK, ERK, 38 MAPK, -J N

## 6.2 Phosphorylation of 4EBPs

PI3K-AKT-TOR, RNA, PI3K-AKT-TOR (93). A TOR, 4EBP (94). TOR, TORC1, TORC2, TORC1, RNA, 4EBP, S6K (96). 4EBP, S6K (97). TORC1, 4EBP1, T70, S65, IF4E, IF4F, C(54). A S6K, IF4F, IF4B, IF4A (98). TORC2, AGC, AKT, SGK1, S, 70%, TOR (96). A, 4EBP, (LPS), -1, (IGF-1) (99). LPS, 4EBP1, 4EBP1, IF4E, IGF-1, (100), 4EBP1, IGF-1, (101). I, O, 4EBP1, IF4E, IF4G, O, IF4E, IF4G (102).

## 6.3 Phosphorylation and sumoylation of eIF4E

### 6.3.1 Phosphorylation of eIF4E

IF4E, MNK1, MNK2 (103). IF4E, RNA, (104). RAS-RAF-MEK-ERK-MNK, ASK1-MKK3/6, 38-MNK, (MAPK), MAPK (MAPKK /MEK/MKK), MAPKK (MAPKKK). F







IF4E (140). HNSCC, IF4E (141). HNSCC, IF4E (142). HNSCC (143).

### 7.5 EIF4E and colorectal carcinoma

IF4E (144). CRC (145). CRC (146).

### 7.6 EIF4E and leukemia

IF4E (87). AML (147, 148). CML (149). ALL, RAS-RAF-MEK-ERK PI3K-AKT- TOR, IF4E (150). B (7).

## 8 Targeted therapy of eIF4E

EIF4E (4EASO) (151, 152). 4EASO (153). CRNA (153). ASO (154).

(154). L 2275796 (E-7, T-3). FDA TOR, ATP TOR1, U TORC1, TORC2 (179, 180). ATP TOR (179). MEK MAPK (181). 50% (182).

FT508 (CD, MNK1/2, FT508 (86, 183). RNA (5). AKT, TOR, 4EBP1, IF4E, MEK, ERK, MNK1, IF4E, ERK-MNK1, IF4E, 4EBP1, IF4E, IF4G, R, IF4E (148). F (184).

EIF4E,  $\beta$ -C (185). S209  $\beta$ -C (186). R, IF4E,  $\beta$ -C, IF4E,  $\beta$ -C, IF4E,  $\beta$ -C, IF4E,  $\beta$ -C, EIF4E, BET, JQ1, I-BET151, NSCLC, BRD4, BET, RNA, NSCLC, IF4E, JQ1, IF4E, JQ1, I-BET151, NSCLC



TABLE 3 | ... IF4E ...

Drugs	Targets	Mechanisms	Related diseases	Clinical trials
L 2275796	IF4E	C ... IF4E RNA ... RNA ... IF4E RNA.	C ... ( ... ) ...	Phase I
R ...	TOR	I ... TOR ... FKBP12 ... TOR.	H ...	Phase IV
			S ...	Phase II
			S ...	Phase I
T ... (155)	TORC1	L ... TOR ... TOR	N ...	Phase IV
			H ...	Phase III
			B ...	Phase II
S ...	RAS	L ... RAS ... RAS ... (156, 157)	P ... (158)	Phase II
S ...	RAF	I ... RAF ... MEK/ERK ... (159-161)	H ... (159-161)	Phase IV
			A ...	Phase III
			D ...	Phase II
P ...		T ... VEGFR1, VEGFR2, VEGFR3, PDGFR $\alpha$ , PDGFR $\beta$ A ... RAF ... (162, 163)	M ...	Phase IV
			R ...	Phase III
V ...		A ... BRAF ... BRAF V600E ... (164, 165). V ...	M ... (164, 165)	Phase IV
			B ...	Phase II
E ...		I ... MAP .../ERK ...	S ...	Phase IV
			M ... (166, 167), ...	Phase III
R ...		L ...	M ... (168)	Phase IV
			G ...	Phase III
L ...		L ... RAF ... EGFR ...	A ... (169, 170)	Phase II
T ...	MEK1/2	L ...		



## Author contributions

Conceptualization: C, LL, B. Writing—original draft: C, LL, B. Writing—review and editing: A, MT, D. Writing—review and editing: C, LL, B. All authors read and approved the final manuscript.

## Funding

This work was supported by the National Natural Science Foundation of China (Grant Numbers: 20210302123397; 202203021212351), Shanghai Leading Academic Project (Grant Number: 2020L0749), Key Research and Innovation Project of Shanghai Leading Academic Project (Grant Number: 2020L0749), Key Research and Innovation Project of Shanghai Leading Academic Project (Grant Number: 2020L0749).

30. G. L. CS, G. N, L. JR, JR, H. AG. D. IF4A-IF4E RNA. *E* (2020) 9: 58243. [10.7554/1.58243](https://doi.org/10.7554/1.58243)
31. M. RK, D. CA, H. T. RNA. IF4. *B* (2020) 59(1):34-46. [10.1021/acschembio.9c00788](https://doi.org/10.1021/acschembio.9c00788)
32. P. E-H, W. SE, L. JM, R. S, L. JR, H. AG. M. IF4G1 N-IF4G1-PABP RNP. *EMBO J* (2011) 30(2):302-16. [10.1038/emboj.2010.312](https://doi.org/10.1038/emboj.2010.312)
33. H. HP, S. JS, S. H, H. MA, H. JL, B. DS. IF4E. *Ca* *J C S* (2020) 133(6):237990. [10.1242/jcs.237990](https://doi.org/10.1242/jcs.237990)
34. H. O, S. U, T. B. H. A, B. A, U. G. A, W. A. DC. 4G1 (IF4G1) IF4E IF1. *M C B* (2018) 38(18):00139-18. [10.1128/MCB.00139-18](https://doi.org/10.1128/MCB.00139-18)
35. D. B. A, G. JR. IF4E. *O* (2004) 23(18):3189-99. [10.1038/1207545](https://doi.org/10.1038/1207545)
36. G. JR, K. BW, C. JH, M. EG. T. 4E. *Ca* *R* (2008) 68(3):631-4. [10.1158/0008-5472.CAN-07-5635](https://doi.org/10.1158/0008-5472.CAN-07-5635)
37. G. S, G. F. DJ, V. J. H. H. AG. R. RNA. *E* (2021) 10: 64283. [10.7554/1.64283](https://doi.org/10.7554/1.64283)
38. T. B, M. P. C. F. Q, W. L. U. IF4E RNA. *J Ma C B* (2017) 5(2):307-17. [10.1039/6.02360](https://doi.org/10.1039/6.02360)
39. G. NH, W. E, E. U. D. RNP. RNA-*T B S* (2017) 42(5):369-82. [10.1016/j.tbs.2017.02.004](https://doi.org/10.1016/j.tbs.2017.02.004)
40. I. P, K. N, A. P. S. *C S Ha P B* (2019) 11(5):032813. [10.1101/032813](https://doi.org/10.1101/032813)
41. K. B. S, G. MP, K. CV, K. M, S. ML. DC. RNP. *B* (2020) 10(9):1310. [10.3390/10091310](https://doi.org/10.3390/10091310)
42. M. SF, P. R. P. RNP. *M C* (2014) 54(4):547-58. [10.1016/j.mcb.2014.04.033](https://doi.org/10.1016/j.mcb.2014.04.033)
43. A. P. A. RNA. *D C* (2005) 9(3):311-2. [10.1016/j.dcb.2005.08.003](https://doi.org/10.1016/j.dcb.2005.08.003)
44. S. M, M, S. M, A. K. S, T. M. F. H. 90. IF4E IF4E IF4G. *J B C* (2009) 284(51):35597-604. [10.1074/jbc.M109.036285](https://doi.org/10.1074/jbc.M109.036285)
45. B. JR, P. R. E. *M C* (2009) 36(6):932-41. [10.1016/j.mcb.2009.11.020](https://doi.org/10.1016/j.mcb.2009.11.020)
46. F. PV, L. C. C. P. E, G. P, H. G, R. P. RV. C. IF4E. *B B A a* (2012) 1823(7):1217-24. [10.1016/j.bbba.2012.03.013](https://doi.org/10.1016/j.bbba.2012.03.013)
47. A. MA, I. D, H. R, A. T, R. P. R, L. R. A. IF4E IF4E RNP. *RNA* (2005) 11(5):717-27. [10.1261/1.2340405](https://doi.org/10.1261/1.2340405)
48. S. U, P. R. D. RNA. *C* (2003) 300(5620):805-8. [10.1126/science.11082320](https://doi.org/10.1126/science.11082320)
49. C. J, P. R. G. RNA. *C* (2005) 122(6):875-86. [10.1016/j.ccr.2005.07.012](https://doi.org/10.1016/j.ccr.2005.07.012)
50. V. L, C. K. B, O. MJ, R. A, S. Q, N. A. I. 8 7G. IF4E. *P Na A a S USA* (2016) 113(19):5263-8. [10.1073/pnas.1524291113](https://doi.org/10.1073/pnas.1524291113)
51. R. L, L. M, S. R, P. E, G. AC, C. CK. C. IF4E IF4E IF4E-BP. *RNA* (2008) 14(7):1318-27. [10.1261/1.950608](https://doi.org/10.1261/1.950608)
52. I. C, P. D, W. C, I. E. 4E-BP. IF4E. *Na C* (2014) 5:4790. [10.1038/ncom05790](https://doi.org/10.1038/ncom05790)
53. A. S, L. S, M. V, B. D, P. M, P. DM. A. IF4E. *Ca C* (2004) 5(6):553-63. [10.1016/j.ccr.2004.05.024](https://doi.org/10.1016/j.ccr.2004.05.024)
54. G. JM, T. N, K. R, P. N, P. V, K. DA. BAD. C4E-BP1. *Na C* (2021) 12(1):2939. [10.1038/s41467-021-23269-8](https://doi.org/10.1038/s41467-021-23269-8)
55. R. F, W. R, I. E, I. C. 4E-T- RNA. *G D* (2020) 34(11-12):847-60. [10.1101/336073.119](https://doi.org/10.1101/336073.119)
56. N. T, P. F. H, M. S, D. WH, G. AC. F. IF4E 4E-T. RNA. *C R* (2015) 11(9):1425-36. [10.1016/j.ccr.2015.04.065](https://doi.org/10.1016/j.ccr.2015.04.065)
57. G. K, T. MA, W. CK, J. PS. M. (PRH/HHE). *C B* (2016) 6:12. [10.1186/13578-016-0077-7](https://doi.org/10.1186/13578-016-0077-7)
58. S. fi A, G. K, I. C. PS. P. PRH. PRH. DNA. *I J B Ma* (2006) 39(1-3):45-50. [10.1016/j.jmb.2006.01.004](https://doi.org/10.1016/j.jmb.2006.01.004)
59. S. fi A, S. C, C. AR, G. K, I. C. PS. O. (PRH/H). *J M B* (2006) 358(4):943-62. [10.1016/j.jmb.2006.02.020](https://doi.org/10.1016/j.jmb.2006.02.020)
60. P. JE, T. I, P. KW, B. KL, R. A. A. PRH. *M C B* (2009) 332(1-2):173-81. [10.1007/11010-009-0188-0](https://doi.org/10.1007/11010-009-0188-0)
61. T. I, C. B, C. N, P. JM, S. L, B. KLB. F. IF4E. PRH. D1 RNA. *EMBO J* (2003) 22(3):689-703. [10.1093/emboj/ckg069](https://doi.org/10.1093/emboj/ckg069)
62. P. A, C. A, C. S. S. *J G G* (2018) 45(1):13-24. [10.1016/j.jgg.2018.01.003](https://doi.org/10.1016/j.jgg.2018.01.003)
63. H. TG, W. H. B. C. PML. *C D a D* (2003) 10(12):1290-9. [10.1038/14401313](https://doi.org/10.1038/14401313)
64. C. N, S. M, K. A, P. JM, S. S, B. KL. PML RING. IF4E. RNA. *EMBO J* (2001) 20(16):4547-59. [10.1093/emboj/cda164](https://doi.org/10.1093/emboj/cda164)
65. S. S, B. KL. E. PML. APL. *EMBO J* (2001) 20(16):4547-59. [10.1093/emboj/cda164](https://doi.org/10.1093/emboj/cda164)



80. G. S. G. M. RNA. IF4E2. RNA. P C (2017) 8(10):750-61. : 10.1007/13238-017-0444-0
81. H. D. W. RA. H. C (2011) 144(5):646-74. : 10.1016/j.2011.02.013
82. L. J. F. L. H. G. J. H. C. L. F. TORC1/IF4E/HIF-1 $\alpha$  E a d a F P (2021) 12:626240. : 10.3389/f.2021.626240
83. G. P. I. H. WR. G. HC. L. J. N. BL. L. HJ. A.  $\sigma$ A- TOC1/IF4E/HIF-1 $\alpha$ . C. C. TCA. C. C. M (2018) 20(12):12946. : 10.1111/12946
84. S. H. S. RL. T. LA. P. S. J. I. F. E. SA. G. CA Ca J C (2019) 69(2):88-112. : 10.3322/21499
85. F. W. J. H. L. J. H. D. A. P. Q. A. M. J. Ca (2018) 143(7):1595-603. : 10.1002/31553
86. C. CS. H. T. HJ. I. K. O. P. JA. V. H. F. IF4E. Na M a (2021) 3(2):244-57. : 10.1038/42255-021-00349
87. T. I. G. ML. M. C. MJ. L. JD. C. B. N. SJ. A. RNA. M C B (2003) 23(24):8992-9002. : 10.1128/MCB.23.24.8992-9002.2003
88. H. T. G. JD. W. G. M. C. F. RNA. IF4E. Na S M B (2004) 11(6):503-11. : 10.1038/779
89. L. HK. B. KL. F. C. (PML). D1. RNA. O (2000) 19(13):1623-34. : 10.1038/1203473
90. C. B. T. K. O. S. A. A. M. S. B. KL. F. IF4E RNA. C J C B (2008) 181(1):51-63. : 10.1083/200707018
91. P. SA. M. O. M. WHJ. D. R. SV. F. MNK1/2-IF4E. J J M S (2020) 21(11):4055. : 10.3390/21114055
92. S. S. B. KLB. F. IF4E. D a (2002) 70(1):10-22. : 10.1046/1432-0436.2002.700102
93. M. P. E. L. B. O. S. N. TOR. O (2006) 25(48):6416-22. : 10.1038/1209888
94. S. S. R. LM. W. P. F. H. A. A. IF4E. Ca R (2005) 65(16):7052-8. : 10.1158/0008-5472.CAN-05-0917
95. T. A. T. F. BD. N. R. S. N. T. TORC1. IF4E-BP3. Na C (2016) 7:11776. : 10.1038/11776
96. A. T. M. F. BD. C. A. S. N. B. M. IF4E/4E-BP. TOR. Ca R (2012) 72(24):6468-76. : 10.1158/0008-5472.CAN-12-2395
97. S. L. L. J. P. M. C. S. W. CG. A. M. F. 4E-BP-IF4E. S S a (2016) 9(430):57. : 10.1126/8463
98. G. S. L. G. P. BF. J. C. P. JH. H. L. TORC1. RNA. M C (2021) 81(10):2064-75. 8. : 10.1016/2021.03.010
99. I. H. K. N. I. M. H. K. H. T. C. fi. TOR. IF4E-BP1. S6K1. L S (2006) 79(8):737-43. : 10.1016/2006.02.037
100. I. CH. F. RA. J. LS. K. SR. V. CTC. E. IF2B. IF4E. IGF-I. A J P E M d (2000) 278(6):E1133-43. : 10.1152/2000.278.6.E1133
101. L. BA. D. A. K. MG. P. MR. J. GD. J. V. BA. 4E-BP1. IGF-I. IF4F. B J Ca (2009) 101(3):424-31. : 10.1038/6605184
102. S. E. S. RV. Q. SB. N. RNA. A R N (2020) 40:51-75. : 10.1146/120919-041411
103. G. C. H. F. W. W. F. ERK-MNK-IF4F. TPDHT. A549. F C (2020) 137:111158. : 10.1016/2020.11.1158
104. F. L. B. CE. T. L. IF4E. MAPK. T a a a (D : S ) (2014). 363-74.
105. S. L. W. L. T. F. N. HF. S. MAPK/ERK. S a T a R (2015) 35(6):600-4. : 10.3109/10799893.2015.1030412
106. R. R. B. A. H. N. C. D. G. CS. R. A. D. R. M. PI3K-AKT-TOR. A -FLIP. 3-AWA. IF4E. S R (2016) 6:18800. : 10.1038/18800
107. G. K. Q. L. W. P. E. RAS. C J H a O (2021) 14(1):116. : 10.1186/13045-021-01127-
108. T. TH. G. AH. LC. B. L. N. C. M. S. KRAS. RAF1 RAS. RAF. Na C (2021) 12(1):1176. : 10.1038/41467-021-21422-96
109. I. H. G. J. F. M. ERK. Na R M C B (2020) 21(10):607-32. : 10.1038/41580-020-0255-7
110. L. L. R. GD. S. Q. LL. R. L. F. R. /R. /MEK/ERK. HCC. O L (2016) 12(5):3045-50. : 10.3892/2016.5110
111. H. CN. M. IF4E. C P Na A a S USA (2010) 107(32):13975-6. : 10.1073/1008908107
112. PC. S. I. H. G. AC. F. R. H. T. S. N. H. 4G (IF4G). IF4E. EMBO J (1999) 18(1):270-9. : 7.8.(3.1)-54.0697

133. D Q, D L, S K, M, W, T. IF4E. *M S M* (2020) 26: 923210. doi: 10.12659/MSM.923210
134. Q S, S G, W L, W C, EGPI-1, IF4E/IF4G. *R /MNK/ERK/IF4E*. *C C B I a* (2022) 352:109773. doi: 10.1016/.2021.109773
135. A F, J S, S K, E T, J H, S M, O. IF4E. *C Ca R* (2010) 16(1):240–8. doi: 10.1158/1078-0432.CCR-09-0986
136. K V, S C, K H, B S, A G, F B, AD. F. IF4E. *I J Ca* (1995) 64(1):27–31. doi: 10.1002/.2910640107
137. M C, CDR, Q, H, D, A, J, LW, M, C, A. 4E (IF4E). *A S* (2005) 242(4):584–90. doi: 10.1097/01.0000184224.55949.90
138. H, L, LW, S, M, W, JH, F, B, I. IF4E. *B B R C* (2012) 423(4):878–83. doi: 10.1016/.2012.06.064
139. H, CI, W, CC, T, TS, H, T, CC, H, CM. IF4E. *C P S O* (2019) 14(11): 0225537. doi: 10.1371/.0225537
140. D F, RJ, N, CA, B, AD. A. RNA. IF4E. *La* (2000) 110(6):928–33. doi: 10.1097/00005537-200006000-00007
141. O, N, K, HJ, L, R, G. RNA. IF4E. *Ca B T* (2005) 4(3):318–23. doi: 10.4161/.4.3.1504
142. S, J, J, R, B, S, M, S, J, D, NK. IF4E. *M C O* (2016) 4(2):166–72. doi: 10.3892/.2015.689
143. S, D, C, G, P, C, S, C, N, CO, A, FW, C. IF4E. *La* (2011) 121(10):2136–41. doi: 10.1002/.G22144
144. N, W, J, M, S, N, W, L, E, P, C, P. IF4E. *C B* (2014) 4:23. doi: 10.1186/2045-3701-4-23
145. G, M, L, D, H, P, T, W, B, E. VEGF-C, E, MMP-2. *O a* (2016) 7(51):85502–14. doi: 10.18632/.13453
146. R, H, L, B, J, T, J, L. IF4E S209. *E* (2020) 9: 60151. doi: 10.7554/.60151
147. R, H, R, G, S, PF, Q, S, T. IF4E. *L a* (2020) 61(5):1084–96. doi: 10.1080/10428194.2017.1390229
148. C, B, B, KL, U. IF4E. *JO* (2009) 2009:981679. doi: 10.1155/2009/981679
149. G, R, H, F, W, Q, M, G, C, C. STAT3. IF4E. *P a B* (2021) 59(1):893–903. doi: 10.1080/13880209.2021.1944224
150. B, D, B, VI, G, SA, T, CDT, T. PI3K/AKT/ TOR. *Pa a D* (2012) 14(5):299–316. doi: 10.2165/11594740-000000000-00000
151. I, BA, F, SC, I, CD, J, P, MR, D, K, K, MG. IF4E. *P S O* (2013) 8(11): 81669. doi: 10.1371/.0081669
152. D, C, AG, M, R, OV, U, SV, R, OE, E, S, W, M, M. IF4E. *I J Ca* (2016) 139(7):1648–57. doi: 10.1002/.30199
153. F, SC, I, BA, P, MR, K, BW, F, MJ, I, CD, J, A. 4E. *Ca G T* (2015) 22(8):396–401. doi: 10.1038/.2015.34
154. G, JR, K, BW, V, TM, I, C, RL, M, D, W, SN, F. IF4E. *C J C I* (2007) 117(9):2638–48. doi: 10.1172/JCI32044
155. P, I, S, M, J, M, B, SE, D, C, T. RNA. *C H a Ma R* (2019) 14(4):219–27. doi: 10.1007/11899-019-00530-C
156. B, L, E, K, R, T, A-M, S. F. *O* (2010) 6(6):885–91. doi: 10.2217/.10.71
157. W, E, S, E, S, C, ST, K, P, K, R. E, FTS (S). *B C* (2015) 107(5):130–43. doi: 10.1111/.201400087
158. R, B, F, M, H, R, K, F, R, C. (S). *M E* (2008) 439:467–89. doi: 10.1016/S0076-6879(07)00432-6
159. L, L, C, C, M, N, A, W, D, S. RAF/MEK/ERK. *Ca R* (2006) 66(24):11851–8. doi: 10.1158/0008-5472.CAN-06-1377
160. M, F, M, S, R, R. *M M M* (2011) 44(4):183–9. doi: 10.1007/00795-011-0558-
161. W, SM, A, L, N, P, V, A, L, JM, I, C, M, P. VEGF, PDGF. *M Ca T* (2008) 7(10):3129–40. doi: 10.1158/1535-7163.MCT-08-0013
162. G, B, P, D, Q, S, D, L, L, DJ, P. B-R. HER2+. *Ca R* (2011) 17(1):142–53. doi: 10.1158/1078-0432.CCR-10-1603
163. G, B, P, D, Q, A, T, L, B, M, T, B-R. *P S O* (2011) 6(10): 25625. doi: 10.1371/.0025625
164. J, E, K, CCM, V. *E O P a a* (2012) 13(17):2533–43. doi: 10.1517/14656566.2012.737780
165. H, E, S, A, AE, R. RAF. *J I D a* (2014) 134(2):319–25. doi: 10.1038/.2013.358
166. D, MH, P, C, D, S, JM, B, M, M, R, D, S, JN, SC, B-R. *ACS O a* (2020) 5(33):20960–6. doi: 10.1021/.02419
167. D, J, W, C, M, E. *J A P a O* (2022) 13(4):450–5. doi: 10.6004/.2022.13.4.7
168. C, DJ, K, MD, W, CM, R. *A P a a* (2013) 47(12):1685–96. doi: 10.1177/1060028013509792
169. T, D, R, S, H, SH, RAF. MEK, K-RAS. *M O* (2020) 14(8):1833–49. doi: 10.1002/1878-0261.12698
170. D, J, G, H, B, C, I, M, A, V, H, C, A, R, I, (BGB-283), RAF. *J C O* (2020) 38(19):2140–50. doi: 10.1200/JCO.19.02654
171. R, C, G, JJ, S, CD, K, B, H, A, L, E, F, C. *J M* (2019) 381(7):626–36. doi: 10.1056/NEJM.1904059
172. U, KA, W, LS, C, K, B, D, JW, P, V, TL, T. EIF4E. *O* (2019) 38(13):2241–62. doi: 10.1038/41388-018-0567-7
173. D, A, I, BA, P, MS, I, CD, J, K, MG, S, AA. 4EGI-1. *I N D* (2018) 36(2):217–29. doi: 10.1007/10637-017-0535-
174. T, K, T, P, E, S, R, K, E, H, S. 4EGI-1, IF4E/IF4G. *E J M C* (2014) 77:361–77. doi: 10.1016/.2014.03.034
175. S, N, S, N, S. IF4E. *B S T a* (2015) 43(5):763–72. doi: 10.1042/BST20150126
176. G, T, R, N, P, S, G, L, P, T, BRD4. NSCLC. IF4E. *Ca B T* (2018) 19(5):407–15. doi: 10.1080/15384047.2018.1423923
177. R, TND, K, K, D, C, BT, S, M, M, S, M, M, I, MNK. IF4E. *M Ca T* (2019) 18(2):235–44. doi: 10.1158/1535-7163.MCT-18-0768
178. H, P, J, W, R, L, H, Q, A, S, E, C, S. *C C C S a* (2020) 18(1):175. doi: 10.1186/12964-020-00607-9
179. N, P, L, J, H, J, S, D, A. TOR. *M M R* (2020) 21(3):1399–407. doi: 10.3892/.2019.10898
180. B, M, K, J, D, A, S, D, M, T, R, C, R, CD44, ATP. INK128. *O a* (2018) 9(40):26032–45. doi: 10.18632/.25430

181. H, L, SQ, D, M, TM, G, HSP90/A L/ IF4E-  
 (2019) 8(9):45. : 10.1038/41389-019-0158-7
182. B, DW, J, N, P, S, A, SR, R, DM, T, (2015) 34  
 (5):2319-24. : 10.3892/2015.4225
183. E, L, G, CA, R, C, V, S, T, RNA, (2021) 21(9):558-77.  
 : 10.1038/41568-021-00380-C
184. S, F, L, G, S, R, N, D, R, TOR/ IF4E, ERK/M 1/ IF4E, B-A, P S O (2015) 10(8): 0136746. : 10.1371/0136746
185. L, J, H, G, W, H, D, W, L, L, A