US009409961B2

(12) **United States Patent**
Danho et al.

(10) **Patent No.: US 9,409,961 B2**
(45) **Date of Patent: Aug. 9, 2016**

(54) **CELL PENETRATING PEPTIDES TO TARGET EIF4E**

(71) Applicant: **Hoffmann-La Roche Inc.**, Nutley, NJ (US)

(72) Inventors: **Waleed Danho**, Del Mar, CA (US); **Nader Fotouhi**, Basking Ridge, NJ (US); **Yi Han**, Morristown, NJ (US); **Wajiha Khan**, Boonton, NJ (US); **Francesca Milletti**, New York, NY (US); **Huifeng Niu**, Scotch Plains, NJ (US)

(73) Assignee: **Hoffmann-La Roche Inc.**, Nutley, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 37 days.

(21) Appl. No.: **14/411,951**

(22) PCT Filed: **Jul. 5, 2013**

(86) PCT No.: **PCT/EP2013/064209**

§ 371 (c)(1),
(2) Date: **Dec. 30, 2014**

(87) PCT Pub. No.: **WO2014/009259**

PCT Pub. Date: **Jan. 16, 2014**

(65) **Prior Publication Data**

US 2015/0166621 A1 Jun. 18, 2015

Related U.S. Application Data

(60) Provisional application No. 61/669,207, filed on Jul. 9, 2012.

(51) **Int. Cl.**
C07K 14/47 (2006.01)

(52) **U.S. Cl.**
CPC ***C07K 14/4702*** (2013.01); *C07K 2319/10* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2012/0172315 A1 7/2012 Cosson et al.

FOREIGN PATENT DOCUMENTS

WO	0078803	12/2000
WO	2006078942	7/2006
WO	2010080248	7/2010
WO	2011136744	11/2011

OTHER PUBLICATIONS

The International Search Report and Written Opinion, mailed on Nov. 14, 2013, in the corresponding PCT Appl. No. PCT/EP2013/064209.

Brown et al., "Stabilizing the eIF4G1 α-Helix Increases Its Binding Affinity with eIF4E: Implications for Peptidomimetic Design Strategies," J. Mol. Biol. (2011) 405, 736-753.

Jia et al., "Cap-Dependent Translation Initiation Factor eIF4E: An Emerging Anticancer Drug Target," Medicinal Research Reviews, 32, No. 4, 786-814, 2012.

Holz et al., "mTOR and S6K1 Mediate Assembly of the Translation Preinitiation Complex through Dynamic Protein Interchange and Ordered Phosphorylation Events," Cell, vol. 123, 569-580, Nov. 18, 2005.

Primary Examiner — Amber D Steele
Assistant Examiner — Schuyler Milton

(57) **ABSTRACT**

The present invention provides compounds to disrupt the eIF4E-eIF4G interaction and pharmaceutically acceptable salts of such compounds. Generally, the compounds are cell-penetrating peptides which bind mammalian initiation factor eIF4E (CPP-eIF4E), wherein the peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 7, 9-11, 12-26, 27-44 and 45-51. More preferably, the amino acid sequence comprises at least 9 to about 40 amino acids and the mammalian initiation factor eIF4E is human initiation factor eIF4E.

14 Claims, 2 Drawing Sheets