308 New lead compounds for treating cancers involving Ras mutations

Asset Overview

Product Type	Small molecule
Indication	Oncology
Current Stage	Hit
Target(MoA)	Ras inhibitor
Brief Description	University of Oxford researchers have developed small molecule inhibitors of Ras proteins, important therapeutic targets in a large number of cancers.
Organization	University of Oxford

Differentiation

□ **Ras**

- Cancer is a major global disease burden, costing the NHS approximately £5bn a year. Around 97% of pancreatic cancer and 45% of colorectal cancer are the result of Ras family gene mutations, and a number of other cancers are linked to Ras mutations, making it a key drug target for cancer therapy

□ **Methods for treating cancer**

- Attempts to develop drugs that target mutant Ras have so far been unsuccessful, meaning tumours bearing this mutation remain the hardest to treat. Small molecules are able to readily penetrate cells, however, were not initially thought to be able to interfere with protein protein interactions
- Such small molecules have been discovered by identifying antibody fragments capable of binding to Ras and using their structure to derive smaller compounds that mimic their properties. The antibody fragments are therapeutically ineffective without intracellular delivery, as they are unable to penetrate the cell membrane to reach their targets

□ **Development of Ras inhibitors**

- Researchers from the University of Oxford have found numerous small molecule Ras inhibitors, the most potent of which has been shown to effectively block proteinprotein interactions between Ras and effector molecules in cell-based assays. These unique small molecules offer a potential therapy for those suffering from mutated Ras related cancers where there is currently no treatment available

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Key Data

Small Molecule that mimic Ab against RAS

Nat Commun. 2018 Aug 9;9(1):3169.

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ARTICLE

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Small molecule inhibitors of RAS-effector protein interactions derived using an intracellular antibody fragment

Camilo E. Quevedo[1], Abimael Cruz-Migoni[1,2], Nicolas Bery[1], Ami Miller[1], Tomoyuki Tanaka[3,8], Donna Petch[3], Carole J.R. Bataille[4], Lydia Y.W. Lee[5], Phillip S. Fallon[5], Hanna Tulmin[1,9], Matthias T. Ehebauer[1,10], Narcis Fernandez-Fuentes[2,6], Angela J. Russell[4], Stephen B. Carr[2,7], Simon E.V. Phillips[2,7] & Terence H. Rabbitts[1]

Proc Natl Acad Sci U S A. 2019 Feb 12;116(7):2545-2550.

PNAS

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Structure-based development of new RAS-effector inhibitors from a combination of active and inactive RAS-binding compounds

Abimael Cruz-Migoni[a,b,1], Peter Canning[a,1,2], Camilo E. Quevedo[a,1], Carole J. R. Bataille[c], Nicolas Bery[a], Ami Miller[a], Angela J. Russell[c], Simon E. V. Phillips[b,d], Stephen B. Carr[b,d], and Terence H. Rabbitts[a,3]

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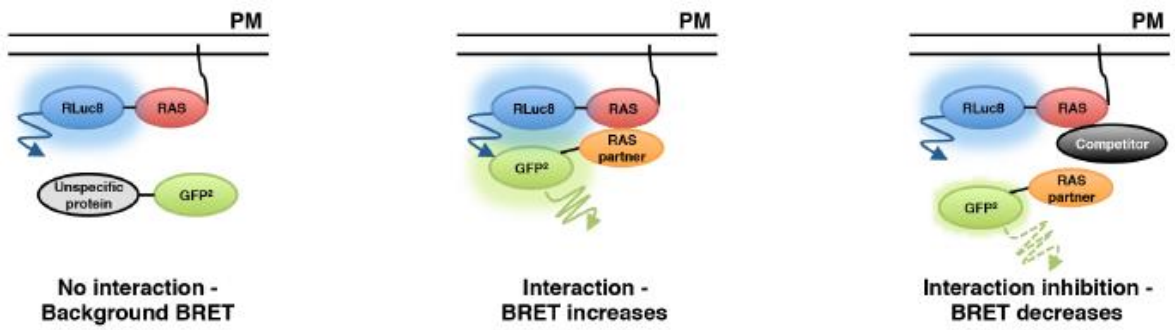
BRET-based RAS biosensors



Elife. 2018 Jul 10;7. pii: e37122

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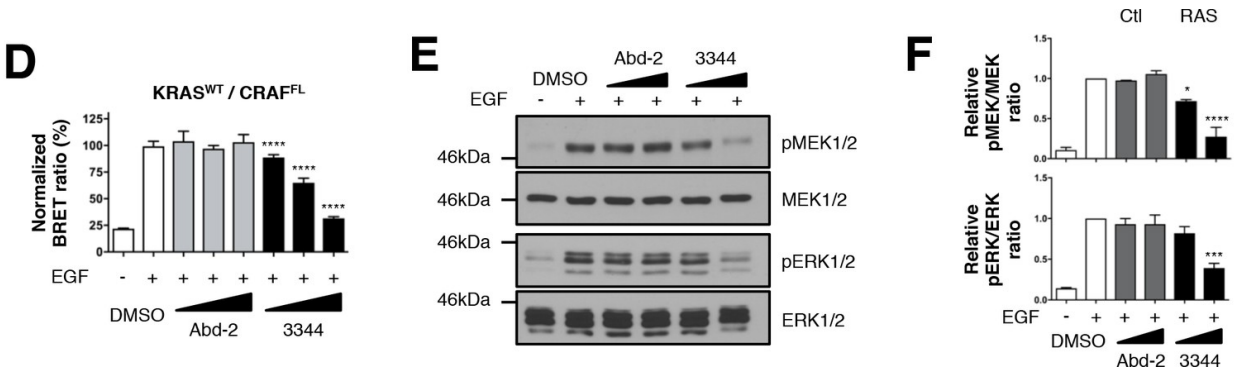
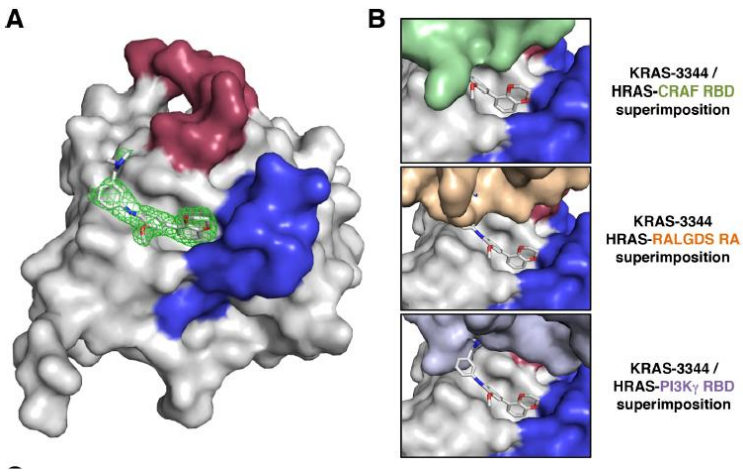
3344 is an inhibitor of KRAS-effector interactions



The BRET KRASWT/CRAFFL pair was tested for interaction after EGF stimulation of HEK293T cells in presence of competitors.

Compound 3344 interacts in a pocket close to the switch regions of KRAS



The interaction of mutant KRAS with compound 3344 was analyzed by X-ray crystallography. (A) KRASQ61H crystals were soaked with 3344 compound and crystal structures obtained from X-ray diffraction. The compound is shown binding in the hydrophobic pocket near switch I (shown in red) and switch II (shown in blue). The electron density map of the compound (2Fo-Fc) is shown as green mesh, and contoured at 1.0 rms.

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Intellectual Property

Patent No.	PCT-GB2019-050198 PCT-GB2019-050200
Application Date	2019.01.23 2019.01.23
Status	Application Pending
Country	

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