Shiva Malek, Ph.D.

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Education

Ph.D., Biochemistry, University of California, San Diego, 2000
M.S., Chemistry, University of California, Irvine, 1995
B.S., Biochemistry, University of California, Los Angeles, 1993

Professional Experience

Genentech, South San Francisco, CA

Director and Department Head of Discovery Oncology (2016-present)
Principal Scientist, Discovery Oncology (2015-present)
Associate Director, Discovery Oncology (2014-2016)
Associate Director, Biochemical and Cellular Pharmacology (2012-2014)
Senior Scientist, Biochemical and Cellular Pharmacology (2010-2014)
Scientist, Biochemical and Cellular Pharmacology (2006-2010)

Exelixis, South San Francisco, CA

Senior Scientist (2004-2006)
Research Scientist II (2003-2004)
New Lead Discovery

Vertex Pharmaceuticals, San Diego (Aurora Biosciences)

Senior Scientist (2002-2003)
Scientist (2000-2002)

Oral Presentations and Selected Communications

2017 Sanford Burnham Prebys Medical Discovery Institute's 2016/2017 Cancer Center Seminar Series, invited speaker

2017 Gordon Research Conference: "Cell Growth & Proliferation", invited speaker

2017 Keynote Lecture at the Gordon Research Seminar (GRS) for Cell Growth and Proliferation

2017 FASEB Protein Kinases and Protein Phosphorylation meeting, invited speaker

2017 Keystone Kinases: Next-Generation Insights and Approaches, invited speaker

2016 FASEB conference on Kinase Signaling Network Regulation, July 2016, invited speaker

40th UNC Lineberger Cancer Center Symposium, April 2016, invited speaker

ASBMB Annual Meeting, April 2016. Chair of Targeted Therapeutics Session and invited speaker

ASBMB Pseudokinase Meeting, San Diego CA, December 2015; invited speaker

The BRAF-MEK Complex in KRAS Mutant Cells: a New Strategy for Inhibition of MAPK Signaling. NCI CTEP Early Drug Development Meeting, October 20 – 21, 2014, Bethesda, MD; Invited speaker.

The Molecular Mechanism of RAS-Driven Signaling Through the MAPK Pathway. Frederick's National Laboratories RAS Retreat, November 7, 2014, Frederick MD. Invited Keynote Speaker

Drugging the BRAF/MEK Pathway. Stanford University, March 2014. Invited guest lecturer for oncology course.

A BRAF/MEK Complex Reveals a Kinase-Independent Role for BRAF in MAPK Signaling. Department of Chemistry and Biochemistry, University of California, San Diego, 2013. Invited speaker.

Kinase Independent Roles of BRAF. 2013 FASEB Research Conference: Protein Kinases and Phosphorylation, Invited speaker.

The B-RAF-MEK complex reveals a kinase-independent role for BRAF in MAPK pathway suppression. AACR Annual Conference 2013, Invited speaker.

The Dual Nature of RAF Inhibitors. CHI 5th Annual Protein Kinases in Drug Discovery Conference. Boston, MA May 27, 2010, invited speaker.

Discovering therapeutics for Huntington's Disease. HD2002: Changes, Advances and Good News Biennial Meeting on Huntington's Disease. Cambridge, Massachusetts, August 2002, Invited speaker

Investigation of expanded polyglutamine repeat conformation: A study of glutamine peptides and the huntingtin protein. The Gordon Conference on Triplet Repeat Disorders, Mt. Holyoke, Massachusetts, July 2001; poster presenter, workshop chair, and session moderator.

Selected Publications and Patents

Foster SA, Klijn C, Malek S. (2016) Tissue-Specific Mutations in BRAF and EGFR Necessitate Unique Therapeutic Approaches. *Trends in Cancer*. 2016 Published online: November 21, 2016

Foster SA, Malek S. (2016) The RAS/MAPK axis gets stressed out. *Molecular Cell*, 2016, Published online December 1, 2016.

Foster SA, Whalen DM, Özen A, Wongchenko MJ, Yin J, Yen I, Schaefer G, Mayfield JD, Chmielecki J, Stephens PJ, Albacker LA, Yan Y, Song K, Hatzivassiliou G, Eigenbrot C, Yu C, Shaw AS, Manning G, Skelton NJ, Hymowitz SG, **Malek S.** (2016) Activation Mechanism of Oncogenic Deletion Mutations in BRAF, EGFR, and HER2. *Cancer Cell*, 29:477-93.
Scientific Press:

(a) Reviewed in: Freed DM, Park JH, Radhakrishnan R, Lemmon MA. (2016) Deletion Mutations Keep Kinase Inhibitors in the Loop. *Cancer Cell*, 29:423-5.
(b) Research Highlights in Nature Chemical Biology: Miura G. (2016) Kinase regulation: Shortening the loop. *Nat Chem Biol.* 12:305.

Haling J, Sudhamsu J, Sideris S, Yen I, Nguyen L, Sandoval W, Phung W, Bravo B, Giannetti A, Peck A, Masselot A, Morales T, Smith D, Brandhuber B, Hymowitz S*, **Malek S***. (2014) Structure of the BRAF:MEK complex reveals a kinase independent role for BRAF in MAPK Signaling, *Cancer Cell*, 26: 402-413.
Scientific Press:

(c) Highlighted in *Cancer Discovery* "Research Watch"
(d) Highlighted in *SciBX: Science-Business eXchange*
(e) Featured story on gene.com

Xiao Y, Ramiscal J, Kowanetz K, Del Nagro C, **Malek S**, Evangelista M, Blackwood E, Jackson PK, O'Brien T. (2013). Identification of preferred chemotherapeutics for combining with a CHK1 inhibitor. *Mol Cancer Ther.* 12(11):2285-95.

Fauber BP, Dragovich PS, Chen J, Corson LB, Ding CZ, Eigenbrot C, Giannetti AM, Hunsaker T, Labadie S, Liu Y, Liu Y, **Malek S**, Peterson D, Pitts K, Sideris S, Ultsch M, VanderPorten E, Wang J, Wei B, Yen I, Yue Q. (2013). Identification of 2-amino-5-aryl-pyrazines as inhibitors of human lactate dehydrogenase. *Bioorg Med Chem Lett.* 23(20):5533-9.

Hatzivassiliou G, Haling JR, Chen H, Song K, Price S, Heald R, Hewitt JF, Zak M, Peck A, Orr C, Merchant M, Hoeflich KP, Chan J, Luoh SM, Anderson DJ, Ludlam MJ, Wiesmann C, Ultsch M, Friedman LS, **Malek S**, Belvin M. (2013). Mechanism of MEK inhibition determines efficacy in mutant KRAS- versus BRAF-driven cancers. *Nature.* 501(7466):232-6.

Lee W, Ortwine DF, Bergeron P, Lau K, Lin L, **Malek S**, Nonomiya J, Pei Z, Robarge KD, Schmidt S, Sideris S, Lyssikatos JP. (2013). A hit to lead discovery of novel N-methylated imidazolo-, pyrrolo-, and pyrazolo-pyrimidines as potent and selective mTOR inhibitors. *Bioorg Med Chem Lett.* 23(18):5097-104.

Blackwood E*, Epler J, Yen I, Flagella M, O'Brien T, Evangelista M, Schmidt S, Xiao Y, Choi J, Kowanetz K, Ramiscal J, Wong K, Jakubiak D, Yee S, Cain G, Gazzard L, Williams K, Halladay J, Jackson PK, **Malek S.*** (2013). Combination drug scheduling defines a "window of opportunity" for chemopotentiation of gemcitabine by an orally bioavailable, selective ChK1 inhibitor, GNE-900. *Mol Cancer Ther.* 12(10):1968-80.

Dragovich PS, Fauber BP, Corson LB, Ding CZ, Eigenbrot C, Ge H, Giannetti AM, Hunsaker T, Labadie S, Liu Y, **Malek S**, Pan B, Peterson D, Pitts K, Purkey HE, Sideris S, Ultsch M, Vanderporten E, Wei B, Xu Q, Yen I, Yue Q, Zhang H, Zhang X. (2013). Identification of substituted 2-thio-6-oxo-

1,6-dihydropyrimidines as inhibitors of human lactate dehydrogenase. *Bioorg Med Chem Lett.* 23(11):3186-94

Estrada AA, Shore DG, Blackwood E, Chen YH, Deshmukh G, Ding X, Dipasquale AG, Epler JA, Friedman LS, Koehler MF, Liu L, **Malek S**, Nonomiya J, Ortwine DF, Pei Z, Sideris S, St-Jean F, Trinh L, Truong T, Lyssikatos JP. (2013). Pyrimidoaminotropanes as Potent, Selective, and Efficacious Small Molecule Kinase Inhibitors of the Mammalian Target of Rapamycin (mTOR). *J Med Chem.* 56(7):3090-101.

Lee HJ, Schaefer G, Heffron TP, Shao L, Ye X, Sideris S, **Malek S**, Chan E, Merchant M, La H, Ubhayakar S, Yauch RL, Pirazzoli V, Politi K, Settleman J. (2013). Noncovalent wild-type-sparing inhibitors of EGFR T790M. Cancer Discov. 3(2):168-81.

Koehler MF, Bergeron P, Blackwood E, Bowman KK, Chen YH, Deshmukh G, Ding X, Epler J, Lau K, Lee L, Liu L, Ly C, **Malek S**, Nonomiya J, Oeh J, Ortwine DF, Sampath D, Sideris S, Trinh L, Truong T, Wu J, Pei Z, Lyssikatos JP. (2012) Potent, selective, and orally bioavailable inhibitors of the mammalian target of rapamycin kinase domain exhibiting single agent antiproliferative activity. *J Med Chem.* 27;55(24):10958-71.

Bussenius J, Blazey CM, Aay N, Anand NK, Arcalas A, Baik T, Bowles OJ, Buhr CA, Costanzo S, Curtis JK, DeFina SC, Dubenko L, Heuer TS, Huang P, Jaeger C, Joshi A, Kennedy AR, Kim AI, Lara K, Lee J, Li J, Lougheed JC, Ma S, **Malek S**, Manalo JC, Martini JF, McGrath G, Nicoll M, Nuss JM, Pack M, Peto CJ, Tsang TH, Wang L, Womble SW, Yakes M, Zhang W, Rice KD. (2012) Discovery of XL888: a novel tropane-derived small molecule inhibitor of HSP90. *Bioorg Med Chem Lett.* 22(17):5396-404.

Maurer T, Garrenton LS, Oh A, Pitts K, Anderson DJ, Skelton NJ, Fauber BP, Pan B, **Malek S**, Stokoe D, Ludlam MJ, Bowman KK, Wu J, Giannetti AM, Starovasnik MA, Mellman I, Jackson PK, Rudolph J, Wang W, Fang G. (2012) Small-molecule ligands bind to a distinct pocket in Ras and inhibit SOS-mediated nucleotide exchange activity. *Proc Natl Acad Sci U S A* 109(14):5299-304.

Cohen F, Bergeron P, Blackwood E, Bowman KK, Chen H, Dipasquale AG, Epler JA, Koehler MF, Lau K, Lewis C, Liu L, Ly CQ**, Malek S**, Nonomiya J, Ortwine DF, Pei Z, Robarge KD, Sideris S, Trinh L, Truong T, Wu J, Zhao X, Lyssikatos JP. (2011) Potent, selective, and orally bioavailable inhibitors of mammalian target of rapamycin (mTOR) kinase based on a quaternary substituted dihydrofuropyrimidine. *J Med Chem.* 54(9):3426-35.

G. Hatzivassiliou*, K. Song, I. Yen, B. J. Brandhuber, D. J. Anderson, R. Alvarado, M. J.C. Ludlam, D. Stokoe, S. L. Gloor, G. Vigers, T. Morales, I. Aliagas, B. Liu, S. Sideris, K. P. Hoeflich, B. S. Jaiswal1, S. Seshagiri, H/ Koeppen, M. Belvin, L. S. Friedman, **S. Malek*** (2010). RAF inhibitors prime wildtype RAF to activate the MAPK pathway and enhance growth. *Nature*, 464:431-435.

Scientific Press:

(a) Selected by *Nature* as one of the most highly cited cancer research articles published in 2010 [*Nature Medicine* 17, 280–282 (2011)] and one of the most important cancer papers published between 2008-2010 [*Nature Medicine* 17, 278–279 (2011)]

(b) Figure 4C featured in Dr. Robert Weinberg's "The Biology of Cancer" textbook revised in 2012.

(c)"Melanoma Drugs Have Unintended Effects in Some Tumors," by Edward R. Winstead, National Cancer Institute NCI Cancer Bulletin February 9, 2010. (**S. Malek** interviewed)
(d) "BRAF Inhibitors: Research Accelerates in Wake of Positive Findings," by Vicki Brower Journal of the National Cancer Institute Advance Access published online on February 9, 2010. JNCI Journal of the National Cancer Institute, doi:10.1093/jnci/djq037 (**S. Malek** interviewed)
(e) "A Study in RAF: On-Target Effects Can be Surprisingly Fickle" by Mark Ratner. StartUp, Feb 1, 2010 (**S. Malek** interviewed)
(f) "RAF complexities spark caution" by Nicola McCarthy in Nature Reviews Cancer 10: 237, April 2010.
(g) "The Raf inhibitor Paradox: Unexpected Consequences of Targeted Drugs" by A.D. Cox and C.J. Der, in Cancer Cell 17: 221-222, March 16, 2010.
(h) "Drug Discovery: Inhibitors that activate" by K. Cichowski and PA Janne, in Nature 464: 358-359. March 18 2010.
(i) "The Wrath of RAFs: Rogue Behavior of B-RAF Kinase Inhibitors" by F. Kaplan, M.J. Mastrangelo, A.E. Aplin, in Journal of Investigative Dermatology AOP June 24, 2010.

G. Hatzivassiliou and **S. Malek**. Determining Sensitivity of Cells to B-Raf Inhibitor Treatment by Detecting KRas Mutation, Serial No. 61/236,466 (Docket No. PR4358), filed August 24, 2009.

S. Ramaswamy, I. Yen. S. Sideris, **S. Malek,** and C. E. Heise (2010). A plate based assay to measure Cellular ERK substrate phosphorylation: Utility for drug discovery of the MAPK signaling cascade. *ASSAY and Drug Development Technologies*, Assay Drug Dev Technol. 8(4):497-503.

S. Malek, D. Huang, T. Huxford, and G. Ghosh (2003). X-ray crystal structure of the IκBβ/NF-κB p65 homodimer complex: Structural basis for nuclear localization and DNA binding of the complex. *Journal of Biological Chemistry*, 278:23094-23100.

S. Malek, Y. Chen, T. Huxford, and G. Ghosh (2001). IκBβ, but not IκBα, functions as a classic cytoplasmic inhibitor of NF-κB dimers by masking both nuclear localization sequences. *Journal of Biological Chemistry* 276: 45225-45235.

T. Huxford, **S. Malek**, and G. Ghosh (2000). Preparation and crystallization of dynamic NF-κB:IκB complexes. *Journal of Biological Chemistry* 275: 32800-32806.

C. Phelps, L. Sengchanthalangsy, **S. Malek**, and G. Ghosh (2000). Mechanism of κB DNA binding by Rel/NF-κB dimers. *Journal of Biological Chemistry* 275: 24392-24399.

T. Huxford, **S. Malek**, and G. Ghosh (1999). Structure and mechanism of NF-κB/IκB signaling pathway. *Cold Spring Harbor Symposia on Quantitative Biology: Signaling and Gene Expression in the Immune System* 64: 533-540.

T. Huxford, D. Huang, **S. Malek**, and G. Ghosh (1998). The crystal structure of the IκBα/NF-κB complex reveals mechanism of NF-κB inactivation. *Cell* 95: 759-770.

S. Malek, T. Huxford, and G. Ghosh (1998). IκBα functions through direct contacts with the nuclear localization signals and the DNA binding sequences of NF-κB. *Journal of Biological Chemistry* 273: 25427-25435.

E. Wang, **S. Malek**, and J. Feigon (1992). Structure of a G♦T♦A triplet in an intramolecular DNA triplex. *Biochemistry* 31: 4838-4846.

R.F. Macaya, D.E. Gilbert, **S. Malek**, J.S. Sinsheimer, and J. Feigon (1991). Structure and stability of X-G-C mismatches in the third strand of intramolecular triplexes. *Science* 254:270-274.