

Title: Acquired and Adaptive Resistance to Targeted Therapy



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Member, Departments of Medicine and Neurology; and Program in Molecular Pharmacology and Chemistry, Memorial Sloan-Kettering Cancer Center, New York, NY
Professor of Pharmacology, Cornell University Graduate School of Medical Sciences, New York, NY
Professor of Medicine, Joan and Sanford I. Weill Medical College, Cornell University, New York, NY
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Speaker



Chikashi Ishioka, M.D.

Professor, Institute of Development, Aging, and Cancer, Tohoku University, Japan

Chairman

Neal Rosen, M.D., Ph.D.

EDUCATION:

1971 BA, Columbia College, New York, NY
1979 MD, PhD (Molecular Biology), Albert Einstein College of Medicine, New York, NY

ACADEMIC APPOINTMENTS:

1985-1988 Senior Investigator, Medicine Branch, National Cancer Institute, Bethesda, MD
1988-1991 Associate Professor of Medicine, Georgetown University Medical School, Washington, DC
1992-1998 Associate Member, Program in Cell Biology and Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY

	Associate Professor of Cell Biology, Cornell University Graduate School of Medical Sciences, New York, NY
1992-2000	Associate Professor of Medicine, Joan and Sanford I. Weill Medical College, Cornell University, New York, NY
1998-present	Member, Departments of Medicine and Neurology; and Program in Molecular Pharmacology and Chemistry, Memorial Sloan-Kettering Cancer Center, New York, NY Professor of Pharmacology, Cornell University Graduate School of Medical Sciences, New York, NY
2000-present	Professor of Medicine, Joan and Sanford I. Weill Medical College, Cornell University, New York, NY
2012-present	Director, Center for Mechanism-Based Cancer Therapeutics, Sloan-Kettering Institute Vice Chair, Developmental Therapeutics, Department of Medicine

HOSPITAL APPOINTMENTS:

1988-1991	Director, Gastrointestinal Oncology Clinic, Lombardi Cancer Center, Georgetown University Medical School, Washington, DC
1991-1998	Associate Attending Physician, Department of Medicine, Memorial Hospital for Cancer and Allied Diseases
1998-	Attending Physician, Department of Medicine, Memorial Hospital for Cancer and Allied Diseases (Breast, Gastroenterology, and Genitourinary Services)

PROFESSIONAL MEMBERSHIPS:

- American Association for Cancer Research
- American Society of Clinical Oncology
- American Association for the Advancement of Science
- The Harvey Society

REVIEWER:

- Melanoma Research Alliance Review Committee (MRA)
- Cancer Protection and Research Institute of Texas (CPRIT) Scientific Review Committee
- Prostate Cancer Foundation

ADVISORY BOARD; ACADEMIC/MEDICAL:

- Dana-Farber Cancer Institute
- Vanderbilt Breast SPORE
- Melanoma Research Alliance
- Prostate Cancer Foundation
- Pediatric Low Grade Astrocytoma Foundation (PLGA)

RESEARCH INTERESTS:

- Mechanism of transduction of the growth signal induced by activated tyrosine kinases in epithelial tumors, especially hormone-dependent malignancies (breast and prostate cancer)
- The Hsp90 chaperone machine (its role in normal physiology and malignant transformation)
- Development of signal transduction inhibitors as anti-cancer therapeutics
- Ansamycin antibiotics (mechanism of action, preclinical development, development of specific ansamycin derivatives as targeted inhibitors of specific proteins)

RESEARCH INTERESTS:

>180 publications in the peer reviewed journals.

Publications in 2011 and 2012

1. Bachleitner-Hofmann T, Sun MY, Chen CT, Liska D, Zeng Z, Viale A, Olshen AB, Mittlboeck M, Christensen JG, Rosen N, Solit DB, and Weiser MR. Antitumor activity of SNX-2112, a synthetic heat shock protein-90 inhibitor, in MET-amplified tumor cells with or without resistance to selective MET inhibition. *Clin Cancer Res*; 17(1): 122-33. 2011.
2. Chandarlapaty S, Sawai A, Scaltriti M, Rodrik-Outmezguine V, Grbovic-Huezo O, Serra V, Majumder PK, Baselga J, and Rosen N. AKT inhibition relieves feedback suppression of receptor tyrosine kinase expression and activity. *Cancer Cell*; 19(1):58-71. 2011. PMID: PMC3025058
3. Franco AT, Malaguarnera R, Refetoff S, Liao XH, Lundsmith E, Kimura S, Pritchard C, Marais R, Davies TF, Weinstein LS, Chen M, Rosen N, Ghossein R, Knauf JA, Fagin JA. Thyrotrophin receptor signaling dependence of Braf-induced thyroid tumor initiation in mice. *Proc Natl Acad Sci U S A*; 108(4): 1615-20. 2011.
4. Poulkos PI, and Rosen N. Mutant BRAF melanomas: Dependence and resistance. *Cancer Cell*; 19(1): 11-5. 2011.
5. Solit DB, Rosen N. Resistance to BRAF inhibition in melanomas. *N Engl J Med*; 364(8): 772-4. 2011.
6. Xie Q, Wondergem R, Shen Y, Cavey G, Ke J, Thompson R, Bradley R, Daughtery-Holtrop J, Xu Y, Chen E, Omar H, Rosen N, Wenkert D, Xu HE, Vande Woude GF. Benzoquinone ansamycin 17AAG binds to mitochondrial voltage-dependent anion channel and inhibits cell invasion. *Proc Natl Acad Sci U S A*; 108(10): 4105-10. 2011.
7. Serra V, Scaltriti M, Prudkin L, Eichorn P, Ibrahim YH, Chandarlapaty S, Markman B, Rodriguez O, Guzman M, Rodriguez S, Gili M, Russillo M, Parra JL, Singh S, Arribas J, Rosen N, Baselga J. PI3K inhibition results in enhanced HER signaling and acquired ERK dependency in HER2-overexpressing breast cancer, *Oncogene*; 30(22): 2547-57. 2011.
8. Scaltriti M, Eichorn P, Cortes, J, Prudkin L, Aura C, Jimenez J, Chandarlapaty S, Serra V, Prat A, Ibrahim YH, Guzman M, Gili M, Rodriguez O, Rodriguez S, Perez J, Green SR, Mai S, Rosen N, Hudis C, Baselga J. Cyclin E amplification/overexpression is a mechanism of trastuzumab resistance in HER2-positive breast cancer patients. *Proc Natl Acad Sci U S A*; 108(9): 3761-6. 2011.
9. Carver BS, Chapinski C, Wongvipat J, Hieronymous H, Chen Y, Chandarlapaty S, Arora VK, Le C, Koutcher J, Scher H, Scardino PT, Rosen N, Sawyers CL. Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. *Cancer Cell*; 19(5): 575-86. 2011.
10. Modi S, Stopeck AT, Linden HM, Solit DB, Chandarlapaty S, Rosen N, D'Andrea G, Dickler MN, Moynahan ME, Sugarman S, Ma W, Patil S, Norton L, Hannah AL, Hudis C. Hsp90 inhibition is effective in breast cancer: A phase 2 trial of Tanespimycin (17AAG) plus Trastuzumab in patients with Her2-positive metastatic breast cancer progressing on Trastuzumab. *Clin Cancer Res*; 2011 [Epub ahead of print]
11. 1Rodrik-Outmezguine V, Chandarlapaty S, Pagano NC, Poulidakos PI, Scaltriti M, Moskatel E, Baselga J, Guichard S, Rosen N. mTOR kinase inhibition causes feedback-dependent biphasic regulation of AKT signaling. *Cancer Discovery*, in press. Bachleitner-Hofmann T, Sun MY, Chen CT, Liska D, Zeng Z, Viale A, Olshen AB, Mittlboeck M, Christensen JG, Rosen N, Solit DB, and Weiser MR. Antitumor activity of SNX-2112, a synthetic heat shock protein-90 inhibitor, in MET-amplified tumor cells with or without resistance to selective MET inhibition. *Clin Cancer Res*; 17(1): 122-33. 2011.
12. Chandarlapaty S, Sawai A, Scaltriti M, Rodrik-Outmezguine V, Grbovic-Huezo O, Serra V, Majumder PK, Baselga J, and Rosen N. AKT inhibition relieves feedback suppression of receptor tyrosine kinase expression and activity. *Cancer Cell*; 19(1):58-71. 2011. PMID: PMC3025058
13. Franco AT, Malaguarnera R, Refetoff S, Liao XH, Lundsmith E, Kimura S, Pritchard C, Marais R, Davies TF, Weinstein LS, Chen M, Rosen N, Ghossein R, Knauf JA, Fagin JA. Thyrotrophin receptor signaling dependence of Braf-induced thyroid tumor initiation in mice. *Proc Natl Acad Sci U S A*; 108(4): 1615-20. 2011.

14. Poulrikos PI, and Rosen N. Mutant BRAF melanomas: Dependence and resistance. *Cancer Cell*; 19(1): 11-5. 2011.
15. Solit DB, Rosen N. Resistance to BRAF inhibition in melanomas. *N Engl J Med*; 364(8): 772-4. 2011.
16. Xie Q, Wondergem R, Shen Y, Cavey G, Ke J, Thompson R, Bradley R, Daugherty-Holtrop J, Xu Y, Chen E, Omar H, Rosen N, Wenkert D, Xu HE, Vande Woude GF. Benzoquinone ansamycin 17AAG binds to mitochondrial voltage-dependent anion channel and inhibits cell invasion. *Proc Natl Acad Sci U S A*; 108(10): 4105-10. 2011.
17. Serra V, Scaltriti M, Prudkin L, Eichorn P, Ibrahim YH, Chandarlapaty S, Markman B, Rodriguez O, Guzman M, Rodriguez S, Gili M, Russillo M, Parra JL, Singh S, Arribas J, Rosen N, Baselga J. PI3K inhibition results in enhanced HER signaling and acquired ERK dependency in HER2-overexpressing breast cancer. *Oncogene*; 30(22): 2547-57. 2011.
18. Scaltriti M, Eichorn P, Cortes J, Prudkin L, Aura C, Jimenez J, Chandarlapaty S, Serra V, Prat A, Ibrahim YH, Guzman M, Gili M, Rodriguez O, Rodriguez S, Perez J, Green SR, Mai S, Rosen N, Hudis C, Baselga J. Cyclin E amplification/overexpression is a mechanism of trastuzumab resistance in HER2-positive breast cancer patients. *Proc Natl Acad Sci U S A*; 108(9): 3761-6. 2011.
19. Carver BS, Chapinski C, Wongvipat J, Hieronymous H, Chen Y, Chandarlapaty S, Arora VK, Le C, Koutcher J, Scher H, Scardino PT, Rosen N, Sawyers CL. Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. *Cancer Cell*; 19(5): 575-86. 2011.
20. Modi S, Stopeck AT, Linden HM, Solit DB, Chandarlapaty S, Rosen N, D'Andrea G, Dickler MN, Moynahan ME, Sugarman S, Ma W, Patil S, Norton L, Hannah AL, Hudis C. Hsp90 inhibition is effective in breast cancer: A phase 2 trial of Tanespimycin (17AAG) plus Trastuzumab in patients with Her2-positive metastatic breast cancer progressing on Trastuzumab. *Clin Cancer Res*; 2011 [Epub ahead of print]
21. Rodrik-Outmezguine V, Chandarlapaty S, Pagano NC, Poulrikakos PI, Scaltriti M, Moskatel E, Baselga J, Guichard S, Rosen N. mTOR kinase inhibition causes feedback-dependent biphasic regulation of AKT signaling. *Cancer Discovery*, Published OnlineFirst June 17, 2011; doi: 10.1158/2159-8290.CD-11-0085.
22. Jonathan H. Schatz, Elisa Oricchio, Andrew L. Wolfe, Man Jiang, Irina Linkov, Jocelyn Maragulia, Weiji Shi, Zhigang Zhang, Vinagolu K. Rajasekhar, Nen C. Pagano, John A. Porco Jr., Julie Teruya-Feldstein, Neal Rosen, Andrew D. Zelenetz, Jerry Pelletier and Hans-Guido Wendel. Targeting cap-dependent translation blocks converging survival signals by AKT and PIM kinases in lymphoma. *JEM* vol. 208 no. 9 1799-1807
23. Debyani Chakravarty, Elmer Santos, Mabel Ryder, Jeffrey A. Knauf, Xiao-Hui Liao, Brian L. West, Gideon Bollag, Richard Kolesnick, Tin Htwe Thin, Neal Rosen, Pat Zanzonico, Steven M. Larson, Samuel Refetoff, Ronald Ghossein, and James A. Fagin. Small-molecule MAPK inhibitors restore radioiodine incorporation in mouse thyroid cancers with conditional BRAF activation. *J Clin Invest*. 2011 December 1; 121(12): 4700-4711.
24. Gopa Iyer, Michael J. Morris, Dana Rathkopf, Susan F. Slovin, Macaulay Steers, Steven M. Larson, Laurence H. Schwartz, Tracy Curley, Anthony DeLaCruz, Qing Ye, Glenn Heller, Merrill J. Egorin, S. Percy Ivy, Neal Rosen, Howard I. Scher, David B. Solit. A phase I trial of deoctaxel and pulse-dose 17-allylamino-127demethoxygeldanamycin in adult patients with solid tumors. *Cancer Chemother. Pharmacol* (2012) 69;:1089-1097
25. Aphrothiti J. Hanrahan, Nikolaus Schultz, Maggie L. Westfal, Rita A. Sakr, Dilip D. Giri, Stefano Scarperi, Manickam Janikariman, Narciso Olvera, Ellen V. Stevens, Qing-Bai She, Carol Aghajanian, Tari A. King, Elisa de Stanchina, David R. Spriggs, Adriana Heguy, Barry S. Taylor, Chris Sander, Neal Rosen, Douglas A. Levine and David B. Solit. Genomic Complexity and AKT Dependence in Serous Ovarian Cancer. Published OnlineFirst November 3, 2011; doi: 10.1158/2159-8290.CD-11-0170
26. Mario E. Lacouture, Kathryn O'Reilly, Neal Rosen, David B. Solit. Induction of Cutaneous Squamous Cell Carcinomas by RAF Inhibitors: Cause for Concern? *JCO* January 20, 2012 vol. 30 no. 3 329-33
27. Guochang Huang, Gil Redelman-Sidi, Neal Rosen, Michael S. Glickman and Xuejun Jiang. Inhibition of Mycobacterial Infection by the Tumor Suppressor PTEN. *Biological Chemistry*, 287, 23196-23202.

IAAO2012 Title of the Talk:

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