BIOGRAPHICAL SKETCH

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NAME: Channing Joseph Der

POSITION TITLE: Sarah Graham Kenan Distinguished Professor

eRA COMMONS USER NAME (credential, e.g., agency login): CHANNING_DER

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California, Los Angeles	BS	06/1975	Biology
University of California, Irvine	Ph.D.	06/1981	Microbiology
Harvard Medical School & Dana-Farber Cancer Institute	Postdoc.	08/1985	Pathology

A. Personal Statement

My research has focused on the Ras oncoprotein and its role in human oncogenesis. Overall, our studies take a multi-faceted approach that includes the application of protein crystallography, gene array analyses, proteomics, genetic analyses of C. elegans, and the use of genetically-engineered mouse models of pancreatic and colon cancer. Our studies address basic mechanisms of signal transduction and we work closely with the biotech and pharmaceutical industry to help transition novel targeted therapies for cancer into the clinic. In addition to my research activities, I am also very active and committed to graduate student training and mentoring. I have been Director of the T32 predoctoral Cancer Cell Biology Program since 1998. I have an extensive history of training, with the past/present mentorship of 47 postdoctoral and 29 predoctoral fellows, 2 medical scholars and 2 clinical faculty. My other experiences in pre- and postdoctoral mentoring include being a member of the Training Advisory Committee for the T32 Lineberger Comprehensive Cancer Center Postdoctoral Training Program. I am also on the External Advisor Boards of current T32 grants at University of Arizona, University of Massachusetts Medical School, University of Minnesota Twin Cities, Vanderbilt University, University of Michigan at Ann Arbor, Duke, University of California, Irvine, Wake Forest School of Medicine and the New Jersey Medical School. I also serve on the Board of Directors for CABTRAC (past President), an organization established to facilitate the exchange of ideas between individuals and institutions dedicated to the mission of training the next generation of cancer researchers. In summary, I have extensive experience and track records in predoctoral and postdoctoral fellow mentorship and training.

1. Der, C.J., Krontiris, T.G. and Cooper, G.M. (1982). Transforming genes of human bladder and lung carcinoma cell lines are homologous to the *ras* genes of Harvey and Kirsten sarcoma viruses. *Proc. Natl. Acad. Sci. USA*, 79, 3637-3640. PMCID: PMC346478
2. Buss, J.E., Solski, P.A., Schaeffer, J.P., MacDonald, M.J., and Der, C.J. (1989). Activation of the cellular proto-oncogene product $p21^{c\text{-}ras}$ by addition of a myristylation signal. *Science*, 243, 1600-1603. PMID: 2648572
3. Lambert, J.M., Lambert, Q.T., Siderovski, D., Sondek, J. and Der, C.J. (2002). Tiam1 is an effector for Ras activation of Rac. *Nat Cell Biol*, 4, 621-625
4. Martin, T.D., Reiner, D.J., Chen, X.-W., Saltiel, A.R., Walter, C.L. and Der, C.J. (2014). Ral and Rheb GAPs integrate mTOR and GTPase signaling in ageing, autophagy, and tumor cell invasion. *Mol Cell*, 53:209-220. PMCID: PMC3955741

B. Positions and Honors

Positions and Employment

1976 -1981	Graduate Student, University of California, Irvine
1981 -1985	Postdoctoral Fellow, Harvard Medical School, Department of Pathology, and the Dana-Farber Cancer Institute
1985 -1992	Staff Scientist, La Jolla Cancer Research Foundation, La Jolla, CA

1992 -1995	Associate Professor, University of North Carolina, Chapel Hill, NC.
1995 - present	Professor, Dept. of Pharmacology, University of North Carolina, Chapel Hill, NC
1998 - present	Director, NIH Cancer Cell Biology Training Grant

Other Experience and Professional Memberships

1992 -1996	Member, NIH Pathology B Study Section
1993 -1995	Consultant, Bristol-Myers Squibb
1994	Consultant, Pfizer
1996 - 2000	Editorial Board, Journal of Biological Chemistry
1997 -1998	Consultant, Dupont-Merck
1998	Consultant, Schering-Plough
1998 - 2009	Editorial Board, Molecular and Cellular Biology
1998 - 2000	Board of Advisors, Children's Tumor Foundation
1999 - 2003	Susan G. Komen Breast Cancer Review Panel
2000	Consultant, Tularik
1999 - 2002	Associate Editor, Cancer Research
2000 - present	Editorial Board, Cancer Letters
2001 - present	Member, Faculty of 1000
2003 - present	Editorial Board, Cancer Therapy
2004 - present	Editorial Board, Molecular Cancer Therapeutics
2006 - 2009	DOD Neurofibromatosis Research Program Integration Panel
2008 - 2011	Scientific Advisory Board, Lustgarten Foundation for Pancreatic Cancer Research
2009	Consultant, GlaxoSmithKline
2010 – present	Editorial Board, Genes and Cancer
2010 – present	Editorial Board, Small GTPases
2010 – present	Editorial Board, World Journal of Biological Chemistry
2011 - 2014	Board of Directors, Cancer Biology Training Consortium (CABTRAC)
2013	Consultant, Eli Lilly
2013	Consultant, AstraZeneca
2013	Consultant, Merck
2013 - 2014	President, Cancer Biology Training Consortium (CABTRAC)
2013, 2015	Consultant, Novartis
2013 - present	Board of Reviewing Editors, Science Signaling
2014 - present	Editor, Proceedings of the National Academy of Sciences USA
2014 - 2019	Member, NCI Board of Scientific Counsellors
2015	Consultant, Astex Therapeutics Limited
2015	Member, RAS Scientific Advisory Board, Warp Drive Bio, LLC
2015 - present	Member, Frederick National Laboratory Advisory Committee
2015 - 2016	Consultant, Astex Pharmaceuticals
2015 - present	Member, Frederick National Laboratory RAS Working Group Committee
2015 - 2018	Member, Pancreatic Cancer Action Network Scientific and Medical Advisory Board

Honors and Awards

Keynote Speaker, FASEB Summer Research Conference on Regulation and Function of Small GTPases, Palm Beach, FL (2015)
Co-organizer, CSH-Asia Conference on GTPases, Suzhou, China (2014)
Co-organizer, AACR Special Conference on "Ras oncogenes: from basics to therapy", Orlando, FL (2014)
The Monroe Schlessinger Lecture, BIDMC/Harvard Medical School, Boston, MA (2013)
Recipient, Lauds & Laurels, Distinguished Alumni Award, University of California, Irvine (2012)
Keynote Speaker, Ras-Like GTPases and Tumor Suppressors: Are We Ready For Translation? Tel Aviv, Israel (2012)
Recipient, Hyman L. Battle Distinguished Cancer Research Award (2011)
Keynote Speaker, 16th International AEK Cancer Congress, Düsseldorf, Germany (2011)
Keynote Speaker, International Symposium on RASSF Family of Tumor Suppressor Proteins, Calgary, Canada (2009)
Keynote Speaker, Annual Cancer Center Retreat, Wake Forest University (2009)
Organizer, Cold Spring Harbor/Banbury Lustgarten KRAS Think Tank, Cold Spring Harbor, NY (2008)
Keynote Speaker, Annual Meeting of the Pharmaceutical Society of Korea, Jeju Island, Korea (2008)

Co-Organizer, Lustgarten/AACR Pancreatic Cancer Meeting, Chapel Hill, NC (2006)
Sarah Graham Kenan Distinguished Professorship (2006)
Keynote Speaker, FASEB Summer Research Conference, Saxton River, VT (2006)
Co-Chair, CNIO Cancer Conference, Madrid, Spain (2003)
Co-Organizer, Annual Oncogene Meeting, Frederick, MD (2003)
Keynote Speaker, MIT/Neurofibromatosis Foundation Consortium Meeting, Cambridge, MA (1999)
Organizer, NIEHS Symposium on Small GTPases and Cancer, Research Triangle Park, NC (1998)
Co-Organizer, FASEB Summer Research Conference, Saxton River, VT (1991)
Recipient, American Cancer Society Faculty Research Award (1990-1995)
Recipient, NRSA Postdoctoral Fellowship (1985-86)
Recipient, Damon Runyon-Walter Winchell Postdoctoral Fellowship (1983-85)

C. Contribution to Science

1. My initial Ras studies as an independent investigator focused on the role of C-terminal lipid modifications in oncogenic Ras function and the development of farnesyltransferase inhibitors as anti-Ras drugs. This included the initial identification of the farnesyl lipid modification of HRAS and the demonstration of its critical role in oncogenic RAS function. A bitter lesson learned from these studies is that the incorrect assumption that the three RAS isoforms were functionally equivalent was a key contributor to the dismal failure to develop farnesyltransferase inhibitors (FTIs) for cancer treatment. While some researchers still erroneously point to this failure as an argument that RAS is not a good target, the more accurate conclusion is that more effective approaches are needed to block the association of the RAS isoforms refractory to FTI treatment, the more commonly mutated KRAS and NRAS proteins. The unexpected modification of KRAS4B by geranylgeranyltransferase-I then prompted our research to develop inhibitors of this related prenyltransferase as an approach to block the membrane association of the RAS protein most commonly mutated in human cancers, KRAS.

    a. Casey, P.J., Solski, P.A., Der, C.J., and Buss, J.E. (1989). p21ras is modified by a farnesyl isoprenoid. *Proc Natl Acad Sci USA*, 86, 8323-8327. PMCID: PMC298273
    b. Buss, J.E., Solski, P.A., Schaeffer, J.P., MacDonald, M.J., and Der, C.J. (1989). Activation of the cellular proto-oncogene product $p21^{c\text{-}ras}$ by addition of a myristylation signal. *Science*, 243, 1600-1603.
    c. Jackson, J.H., Cochrane, C.G., Bourne, J.R., Solski, P.A., Buss, J.E., and Der, C.J. (1990). Farnesol modification of Kirsten-ras exon 4B is essential for transformation. *Proc Natl Acad Sci USA*, 87, 3042-3046. PMCID: PMC53830
    d. Kato, K., Cox, A.D., Hisaka, M.M., Graham, S.M., Buss, J.E. and Der, C.J. (1992). Isoprenoid addition to Ras protein is the critical modification for its membrane. *Proc Natl Acad Sci USA.* 89, 6403-6407. PMCID: PMC49509

2. My Ras studies next turned to the issue of downstream effector signaling. A key discovery was the fact that mutant RAS-mediated oncogenesis could not be ascribed simply to activation of the RAF-MEK-ERK mitogen-activated protein kinase cascade. These studies led us to connect other RAS superfamily small GTPases with Ras, as components of RAS effector signaling critical for oncogenesis. These studies centered on the Tiam1-Rac small GTPase and RalGEF-Ral small GTPase signaling networks.

    a. Khosravi-Far, R., White, M.A., Westwick, J,K, Solski, P.A., Chrzanowska-Wodnicka, M., Wigler, M.H. and Der, C.J. (1996). Oncogenic Ras activation of Raf/MAP kinase-independent pathways is sufficient to cause tumorigenic transformation. *Mol Cell Biol,* 16, 3923-3933. PMCID: PMC231289
    b. Oldham, S.M., Clark, G.J., Gangarosa, L.M., Coffey Jr., R.J. and Der, C.J. (1996). Activation of Raf-1/MAP kinase cascade is not sufficient for Ras transformation of RIE-1 epithelial cells. *Proc Natl Acad Sci USA*, 93, 6924-6928. PMCID: PMC38910
    c. Lambert, J.M., Lambert, Q.T., Siderovski, D., Sondek, J. and Der, C.J. (2002). Tiam1 is an effector for Ras activation of Rac. *Nat Cell Biol*, 4, 621-625.
    d. Lim, K.-H., Baines, A.T., Fiordalisi, J.J., Shipitsin, M., Feig, L.A., Cox, A.D., Der, C.J. and Counter, C.M. (2005). Activation of RalA is critical for Ras-induced tumorigenesis of human cells. *Cancer Cell*, 7, 533-545. PMID: 15950903

3. One component of our research has been the use of model genetic organisms to study RAS effector signaling. In particular, we have utilized C. elegans, where the key human effector components are conserved. However, unlike human cells, these effector components lack the multiple isoforms that complicate evaluation of effector function in mammalian cells. Using genetic functional studies, we identified

a mechanism for how RAS effector utilization is regulated, to toggle between Raf and RalGEF utilization. We also identified effector signaling crosstalk, where the Ral small GTPase links with the PI3K effector pathway at the level of mTOR. These findings emphasize that RAS effector signaling is much more complex than originally believed, and hence, identifies issues that need to be understood if effector inhibition will be an effective anti-Ras approach.

a. Zand, T.P., Reiner, D.J. and Der, C.J. (2011) Ras effector switching promotes divergent cell fates in C. elegans vulva patterning. *Dev Cell*, 20, 84-96. PMCID: PMC3028984.
b. Martin, T.D., Reiner, D.J., Chen, X.-W., Saltiel, A.R., Walter, C.L. and Der, C.J. (2014). Ral and Rheb GAPs integrate mTOR and GTPase signaling in aging, autophagy, and tumor cell invasion. *Mol Cell*, 53:209-20. PMCID: PMC3955741

4. Another focus of our research has involved protein structure-function studies evaluating how Ras superfamily small GTPases are recognized and regulated. In particular, these studies have focused on members of the Rho branch of the Ras superfamily and their regulation by Rho-selective guanine nucleotide exchange factors (RhoGEFs; Dbl family proteins) and GTPase-activating proteins (RhoGAPs). Overall, these studies emphasize the need to consider the role of regulators in the function of the GTPase.
   a. Karnoub, A., Worthylake, D., Rossman, K.L., Pruitt, W.M., Campbell, S.L. Sondek, J., and Der, C.J. (2001). Molecular basis for Rac1 recognition by guanine nucleotide exchange factors. *Nature Struct Biol*, 8, 1037-1041. PMID: 11685227
   b. Snyder, J.T., Worthylake, D.K., Rossman, K.L., Betts, L., Pruitt, W.M., Siderovski, D.P., Der, C.J. and Sondek, J. (2002). Structural basis for the selective activation of Rho GTPases by Dbl exchange factors. *Nat Struct Biol,* 9, 468-475. PMID: 12006984
   c. Mitin, N., Betts, L., Yohe, M., Sondek, J., Der, C.J. and Rossman, K.L. Release of auto-inhibition of Asef by APC leads to Cdc42 activation and tumor suppression. (2007). *Nature Struct. Mol. Biol.*, 14, 814-823. PMCID: PMC2716141
   d. Kim, T.Y., Jackson, S., Whitsett, T.G., Lobello, J.R., Tran, N.L., Bang, Y.-J. and Der, C.J. (2013). CRL4A-FBXW5-mediated degradation of DLC1 Rho GTPase activating protein tumor suppressor promotes non-small cell lung cancer cell growth. *Proc. Natl. Acad. Sci.*, 110:16868-16873. PMCID: PMC3801067

Complete List of Published Work in MyBibliography
http://www.ncbi.nlm.nih.gov/myncbi/channing.der.1/bibliography/40525359/public/?sort=date&direction=ascending

D. Research Support:

Ongoing Research Support

R01CA42978-29A1 Der (PI) 08/12/2015-07/31/2020
National Cancer Institute
Biological Activity of Ras Oncogenes
The goal is to elucidate the mechanism and role of KRAS inhibition of Myc oncoprotein degradation in pancreatic cancer.
Role: PI

2T32CA071341-17 Der (PI) 09/01/2012-08/31/2017
National Cancer Institute
Cancer Cell Biology Training Grant
The goal of this program to foster the cancer biology and translational research training of predoctoral students.
Role: PI

1R01GM106227-01 Campbell (PI) 04/01/2013-03/31/2017
National Institutes of Health
Regulation of Ras by Monoubiquitination
The goal is to assess the role and relevance of a novel posttranslational modification (ubiquitination) of Ras proteins in normal and neoplastic cell physiology.
Role: Co-Investigator

1R21CA179193-01A1 Der (PI) 01/01/2014-12/31/2015
National Cancer Institute

ERK Inhibitor Resistance and ERK Isoform-Dependent Growth in Pancreatic Cancer
The goal is to identify ERK isoform distinct biological functions and substrate utilization in KRAS mutant pancreatic cancer.
Role: PI

1R01CA175747-01A1 Der, Hahn (MPI) 02/05/2014-01/31/2019
National Institutes of Health
Mechanisms of PAK1 activation, signaling and tumor resistance
The goal is to validate the importance of the RacGEF-Rac small GTPase effector pathway, and its activation of the PAK1 serine/threonine kinase in KRAS-dependent pancreatic cancer growth.
Role: MPI

(no number) Der, Fleming, Wenneberg (MPI) 07/01/2015-06/30/2018
AACR-Pancreatic Cancer Action Network
Defining novel effective combination KRAS-targeted therapeutic strategies
The goal is to identify a combination KRAS effector signaling inhibitor strategy for the treatment of KRAS-mutant pancreatic cancer.
Role: MPI

(no number) Der (PI) 01/01/2015-12/31/2017
Lustgarten Foundation
Identification and validation of Raf inhibitor-based combination KRAS-targeted therapies
The goal is to identify combination inhibitor strategies to target RAF for pancreatic cancer treatment.
Role: PI

CA140731 Der (PI) 07/01/2015-06/30/2017
Department of Defense
Targeting KRAS for pancreatic cancer treatment
The goal is to profile KRAS-dependent DNA methylation, gene expression, protein kinase activation and phospho-protein activation to identify novel targets for anti-KRAS drug discovery.
Role: PI

U01CA199235-01 Der, Cox (MPI) 07/01/2015-06/30/2019
National Cancer Institute
Identification of synthetic lethal interactors in pancreatic cancer
The goal this project is to apply innovative chemical and genetic functional screens to identify modulators of KRAS-dependent pancreatic cancer growth.
Role: MPI

Completed Research Support

(no number) Der (PI) 07/01/2012-06/30/2014
Pancreatic Cancer Action Network (AACR)
Mechanisms of ERK inhibition resistance and ERK-dependent pancreatic cancer
The goal of this research is to delineate the role of ERK1 and ERK2 in pancreatic cancer and to identify combination protein kinase inhibitor approaches for pancreatic cancer treatment.
Role: PI

12-60-25-DER Der (PI) 01/01/2012-06/30/2014
American Association of Cancer Research
Mechanism of ERK Inhibition Resistance and ERK-Dependent Pancreatic Cancer
The goal is to assess mechanisms that allow tumor cells to overcome ERK addiction.
Role: PI