BIOGRAPHICAL SKETCH

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NAME: Channing Joseph Der

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

POSITION TITLE: Sarah Graham Kenan Distinguished Professor

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, kinome profiling and proteomics, chemical and genetic screenings, 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 and postdoctoral training and mentoring. I was the Director of the T32 predoctoral Cancer Cell Biology Program from 1998-2015, and I am now the Associate Director of the Lineberger T32 Integrated Training in Cancer Model Systems (ITCMS) postdoctoral training grant. I have an extensive history of training, with the past/present mentorship of 15 undergraduate students in the Carolina Summer Fellow (CSF) or Summer Undergraduate Research Experience (SURE) programs, 53 postdoctoral and 32 predoctoral fellows, 2 medical scholars and 2 clinical faculty. My other experiences in pre- and postdoctoral mentoring include being 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 Rutgers. 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. Finally, I serve on the External Advisory Board of the NCI COBRE grants at Oklahoma University Health Sciences Center and North Dakota University. In summary, I have extensive experience and track records in cancer biology research and pre/postdoctoral mentorship.

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 myristoylation 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 - 2015	Director, NCI Cancer Cell Biology Training Program
2015 - present	Director, NCI Integrated Training in Cancer Model Systems

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
1999 - 2002	Associate Editor, Cancer Research
2000 - 2004	Editorial Board, Cancer Letters
2001 - present	Member, Faculty of 1000
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
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 - 2017	Board of Reviewing Editors, Science Signaling
2014 - 2019	Member, NCI Board of Scientific Counsellors
2015 - present	Consultant, Astex Therapeutics Limited
2015 - present	Scientific Advisory Board, Warp Drive Bio, LLC
2015 - present	Member, Frederick National Laboratory Advisory Committee
2015 - present	Consultant, Astex Pharmaceuticals
2015 - present	Member, Frederick National Laboratory RAS Working Group Committee
2015 - 2021	Member, Pancreatic Cancer Action Network Scientific & Medical Advisory Board
2015	Scientific Advisory Board, Kyras Therapeutics
2018 - present	Scientific Advisory Board, Mechnikoff Therapeutics
2018	Consultant, Kymera Therapeutics
2018	Consultant, SpringWorks Therapeutics
2018	Scientific Advisory Board, Mirati Therapeutics
2018	Consultant, Ribometrix

Honors and Awards

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

Co-Organizer, Lustgarten/AACR Pancreatic Cancer Meeting, Chapel Hill, NC (2006)
Keynote Speaker, Annual Meeting of the Pharmaceutical Society of Korea, Jeju Island, Korea (2008)
Organizer, Cold Spring Harbor/Banbury Lustgarten KRAS Think Tank, Cold Spring Harbor, NY (2008)
Keynote Speaker, International Symposium on RASSF Family of Tumor Suppressor Proteins, Calgary, Canada (2009)
Keynote Speaker, 16th International AEK Cancer Congress, Düsseldorf, Germany (2011)
Recipient, Hyman L. Battle Distinguished Cancer Research Award (2011)
Keynote Speaker, Ras-Like GTPases and Tumor Suppressors,Tel Aviv, Israel (2012)
Recipient, Lauds & Laurels, Distinguished Alumni Award, University of California, Irvine (2012)
The Monroe Schlessinger Lecture, BIDMC/Harvard Medical School, Boston, MA (2013)
Co-organizer, AACR Special Conference on "Ras oncogenes: from basics to therapy", Orlando, FL (2014)
Co-organizer, CSH-Asia Conference on GTPases, Suzhou, China (2014)
Keynote Speaker, FASEB Summer Research Conference on Regulation and Function of Small GTPases, Palm Beach, FL (2015)
Keynote Speaker, 19th Joint Meeting "Signal Transduction, Weimar, Germany (2015)
Inaugural Emmanuel Farber Distinguished Visiting Lectureship, Toronto, Canada (2016)
Keynote Speaker, Duke-NUS Annual Symposium, Singapore (2017)
Keynote Speaker, VCU Massey Cancer Center Annual Research Retreat, Richmond, VA (2018)
Einstein Berlin Institute of Health Visiting Fellow, Berlin, Germany (2019-2022)

C. Contributions 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. 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
   c. 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
   d. Justilien, V. Ali, S.A., Lee Jamieson, L., Cox, A.D., Der, C.J., Nicole R. Murray, N.R., and Fields, A.R. (2016). Ect2 drives lung tumorigenesis by regulating rRNA synthesis. *Cancer Cell*, 31:256

5. Our current focus centers are the identification, validation and clinical advancement of therapeutic approaches for targeting mutant Ras for cancer treatment. We have critically evaluated the past/current approaches and are pursuing (1) direction RAS inhibitors, (2) metabolism, (3) synthetic lethal interactors, and (4) inhibitors of effector signaling.
   a. Hayes, T.K., Neel, N.F., Hu, C., Gautam, P., Chenard, M., Long, B., Aziz, M., Kassner, M., Bryant, K.L., Pierobon, M., Marayati, R., Kher, S., George, S.D., Xu, M., Wang-Gillam, A., Samatar, A.A., Maitra, A., Wennerberg, K., Petricoin, E.F. III, Yin, H.H. Nelkin, B., Cox, A.D., Yeh, J.J., Der, C.J. (2016). Long-term ERK inhibition in KRAS-mutant pancreatic cancer is associated with Myc degradation and senescence-like growth suppression. *Cancer Cell*, 29:75-89.
   b. Anderson, G.R., Winter, P.S., Lin, K.H., Nussbaum, D.P., Cakir, M., Stein, E.M., Soderquist, R.S., Crawford, L., Leeds, J.C., Newcomb, R., Stepp, P., Yip, C., Wardell, S.E., Tingley, J.P., Ali, M., Xu, M., Ryan, M., McCall, S.J., McRee, A.J., Counter, C.M., Der, C.J. and Wood, K.C. (2017). A landscape of therapeutic cooperativity in KRAS mutant cancers reveals principles for controlling tumor evolution. *Cell Rep*, 20:999-1015.
   c. Vaseva, A.V., Devon R. Blake, D.R., Gilbert, T.S.K., Ng, S., Hostetter, G., Azam, S.H., Ozkan-Dagliyan, I., Gautam, P., Bryant, K.L., Pearce, K.H., Herring, L.E., Han, H., Graves, L.M., Witkiewicz, A.K., Knudsen, E.S., Pecot, C.V., Rashid, N., Houghton, P.J., Wennerberg, K., Cox, A.D. and Der, C.J. (2018) KRAS suppression-induced degradation of MYC is antagonized by a MEK5-ERK5 compensatory mechanism. *Cancer Cell*, 34:807–822.
   d. Bryant, K.L., Stalnecker, C.A., Zeitouni, D., Klomp, J.E., Peng, S., Tikunov, A.P., Gunda, V., Pierobon, M., Waters, A.M., George, S.D., Tomar, G., Papke, B., Hobbs, G.A., Yan, L., Hayes, T.K., Diehl, J.N., Goode, G, Chaika, N.V., Wang, Y., Zhang, G.F., Witkiewicz, A.K., Knudsen, E.S., Petricoin III, E.F.,

Singh, P.K., Macdonald, J.M., Tran, N.L., Lyssiotis, C.A., Ying, H., Kimmelman, A.C., Cox, A.D., and Der C.J. (2019). ERK inhibition increases pancreatic cancer dependence on autophagy. *Nat Med*, in press.

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. Additional Information: Research Support
Ongoing Research Support

NIH/NCI T32CA009156 Der (PI) 7/1/1980 - 7/31/2021
Integrated Training in Cancer Model Systems
The goal of this program is to train the next generation of cancer biologists to lead research studies using state-of-the-art models of cancer.
Role: PI

NIH/NCI R01 CA175747 Der/Hahn (MPI) 2/1/2014 - 1/31/2019
Mechanisms of PAK1 Activation, Signaling and Tumor Resistance
The goal of this research is to define the critical role of spatial regulation defining PAK1 substrate utilization and biological output, and to profile the dynamic reprogramming of the kinome in response to PAK1 inhibition.
Role: Lead PI

Pancreatic Cancer Action Network Der (PI) 7/1/2015 - 6/30/2019 (NCE)
Defining Novel Combination KRAS-targeted Therapeutic Strategies
The goal is to identify and validate effector signaling combination inhibitor approaches for the treatment of KRAS-mutant pancreatic cancer.
Role: PI

NIH/NCI U01 CA199235-01 Der/Cox (MPI) 9/1/2015 - 6/30/2019
Identification of Synthetic Lethal Interactors in Pancreatic Cancer
The goal of this research is to determine the mechanism of KRAS-mediated MYC protein stability to target MYC degradation as an anti-KRAS therapeutic approach for pancreatic cancer.
Role: PI

NIH/NCI P01 CA203657-01 Der (PI) 4/1/2016 - 3/31/2021
Defining RAS Isoform- and Mutation-Specific Roles in Oncogenesis
The goal of this program project, comprised of four projects and two cores, is to utilize structural, biochemical and biological analyses to establish RAS isoform and RAS mutation specific functions in cancer.
Roles: Program PI, Project 1 PI, Core A PI

NIH/NCI P50 CA196510 Der (PI) 8/1/2016 - 6/30/2021
Project 3: Combination inhibition of ERK for pancreatic cancer treatment (Wang-Gillam/Der)
The goal of Project 3 is to advance anti-ERK therapeutic combinations for clinical evaluation in pancreatic cancer
Roles: Project 3 PI, Career Enrichment Program Co-Director

NIH/NCI R01 CA223775 Bass/Der/Wang (MPI) 6/08/2018 – 3/31/2023
The Role of RHOA in Diffuse Gastric Cancer
The goal is to determine the mechanism and role of aberrant RHOA signaling in diffuse gastric cancer development and growth
Role: PI

NIH/NCI R35 CA232113 Der (PI) 9/1/2018 - 08/31/25
Targeting Undruggable RAS for Cancer Treatment
The goal is to identify and develop novel therapeutic strategies for KRAS-mutant pancreatic cancer
Role: PI