BIOGRAPHICAL SKETCH

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NAME: Der, Channing Joseph

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

Since my initial discovery of oncogenic HRAS and KRAS genes in human cancer in 1982, my research has focused on defining the molecular properties essential for RAS oncogenic function, to then guide development of anti-RAS therapies for KRAS-mutant cancers. Our studies have centered on the cancers with the highest frequency of KRAS mutations, pancreatic, colorectal and lung cancers. Our studies take a multi-faceted approach that includes the application of protein crystallography, transcriptome analyses, kinome profiling and proteomics/phosphoproteomics, chemical and genetic screenings, and the use of genetically-engineered mouse or patient-derived organoid models of 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. Our studies have provided the rationale for the initiation of multiple clinical trials evaluating combination drug strategies targeting the key KRAS effector signaling network, the RAF-MEK-ERK mitogen-activated protein kinase (MAPK) protein kinase cascade.

Ongoing projects that I would like to highlight include:

R35 CA232113 (NIH/NCI)
Der (PI)
09/01/2018 - 08/31/25
Targeting undruggable RAS for cancer treatment

T32 CA071341
Der (PI)/Cox (Co-PI)
07/01/2023 – 06/30/2028
Cancer Cell Biology Training Program

P50 CA257911 (NIH/NCI)
Yeh (PI)/Der (Project PI)
07/01/2022 – 06/30/27
Selective Targeting of Pancreatic Cancer SPORE

22-WG-DERB (Pancreatic Cancer Action Network)
Der (PI)/Bryant (PI)
07/01/2022 – 06/30/25
Determination of novel RAF/MEK and/or FAK inhibitor combinations in KRAS-mutant PDAC

Citations:

1. **Der CJ**, Krontiris TG, Cooper GM. (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 U S A*. 79:3637-40.
2. Buss JE, Solski PA, Schaeffer JP, MacDonald MJ, **Der CJ**. (1989). Activation of the cellular proto-oncogene product p21Ras by addition of a myristylation signal. *Science*. 243:1600-3.
3. Bryant KL, Stalnecker CA, Zeitouni D, Klomp JE, Peng S, Tikunov AP, Gunda V, Pierobon M, Waters AM, George SD, Tomar G, Papke B, Hobbs GA, Yan L, Hayes TK, Diehl JN, Goode GD, Chaika NV, Wang Y, Zhang GF, Witkiewicz AK, Knudsen ES, Petricoin EF, 3rd, Singh PK, Macdonald JM, Tran NL, Lyssiotis CA, Ying H, Kimmelman AC, Cox AD, **Der CJ**. (2019). Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer. *Nat Med*. 25:628-40.
4. Hobbs GA, Baker NM, Miermont AM, Thurman RD, Pierobon M, Tran TH, Anderson AO, Waters AM, Diehl JN, Papke B, Hodge RG, Klomp JE, Goodwin CM, DeLiberty JM, Wang J, Ng RWS, Gautam P, Bryant KL, Esposito D, Campbell SL, Petricoin EF, 3rd, Simanshu DK, Aguirre AJ, Wolpin BM, Wennerberg K, Rudloff U, Cox AD, **Der CJ**. (2020). Atypical KRAS(G12R) mutant is impaired in PI3K signaling and macropinocytosis in pancreatic cancer. *Cancer Discov*. 10:104-23.

B. Positions, Scientific Appointments, and Honors

Positions

2019 - 2024	Einstein BIH Visiting Fellow, Charité – Universitätsmedizin Berlin, Berlin, Germany
2015 - 2022	Director, NCI Integrated Training in Cancer Model Systems
1998 - 2015, 2022 - present	Director, NCI Cancer Cell Biology Training Program
1995 - present	Professor, Dept. of Pharmacology, University of North Carolina, Chapel Hill, NC
1992 -1995	Associate Professor, University of North Carolina, Chapel Hill, NC.
1985 -1992	Staff Scientist, La Jolla Cancer Research Foundation, La Jolla, CA
1981 -1985	Postdoctoral Fellow, Harvard Medical School, Department of Pathology, and the Dana-Farber Cancer Institute
1976 -1981	Graduate Student, University of California, Irvine, Irvine, CA

Scientific Appointments

2023 - present	Scientific Advisory Board, aSKY Therapeutics
2023	Consultant, Sanofi
2022 - present	Scientific Advisory Board, Kestral Therapeutics
2022 - present	Scientific Advisory Board, Verastem Oncology
2021 - present	Scientific Advisory Board, SHY Therapeutics
2021 - present	Scientific Advisory Board, Day One Biopharmaceuticals
2021 - 2023	Scientific Advisory Board, Reactive Biotherapeutics
2021	Consultant, Revolution Medicines
2020 - present	Scientific Advisory Board, Anchiano Therapeutics
2019 - present	Scientific Advisory Board, Deciphera Pharmaceuticals
2018 - present	Consultant, Ribometrix
2018 - 2023	Scientific Advisory Board, Mirati Therapeutics
2018	Consultant, Kymera Therapeutics
2015	Scientific Advisory Board, Kyras Therapeutics
2015 - 2021	Member, Pancreatic Cancer Action Network Scientific & Medical Advisory Board
2015 - present	Member, Frederick National Laboratory RAS Working Group Committee
2015 - 2016	Member, Frederick National Laboratory Advisory Committee
2015 - 2018	Scientific Advisory Board, Warp Drive Bio, LLC
2014 - 2019	Member, NCI Board of Scientific Counsellors
2013 - 2017	Board of Reviewing Editors, Science Signaling
2013, 2015	Consultant, Novartis
2013 - 2014	President, Cancer Biology Training Consortium (CABTRAC)
2013	Consultant, Merck
2013	Consultant, AstraZeneca
2013 - present	Consultant, Eli Lilly
2011 - 2014	Board of Directors, Cancer Biology Training Consortium (CABTRAC)

2008 - 2011	Scientific Advisory Board, Lustgarten Foundation for Pancreatic Cancer Research
2006 - 2009	DOD Neurofibromatosis Research Program Integration Panel
2004 - present	Editorial Board, Molecular Cancer Therapeutics
1999 - 2002	Associate Editor, Cancer Research
1999 - 2003	Susan G. Komen Breast Cancer Review Panel
1998 - 2000	Board of Advisors, Children's Tumor Foundation
1998 - 2009	Editorial Board, Molecular and Cellular Biology
1996 - 2000	Editorial Board, Journal of Biological Chemistry
1992 -1996	Member, NIH Pathology B Study Section

Honors

Keynote Speaker, Challenging the unexplored KRAS gene, May 26, 2023, Kyoto, Japan (2023)
Keynote Speaker, DKTK German Cancer Consortium 7th Cancer Retreat, Berlin, Germany (2022)
Keynote Speaker, FASEB The regulation and function of small GTPases conference, New Orleans, LA (2022)
Keynote Speaker, FASEB Cell signaling in cancer: from mechanisms to therapy, New Orleans, LA (2022)
Fellow, American Association for the Advancement of Science (2019)
Keynote Speaker, Talbot Pancreatic Cancer Awareness Reception, Hollings Cancer Center, Charleston, SC (2019)
Keynote Speaker, Gigi Shaw Arledge Conference on Pancreatic Disease Conference, Columbia University, New York, NY (2019)
Mentorship Award for Lifetime Achievement, University of North Carolina at Chapel Hill (2019)
Keynote Speaker, VCU Massey Cancer Center Annual Research Retreat, Richmond, VA (2018)
Keynote Speaker, Duke-NUS Annual Symposium, Singapore (2017)
Emmanuel Farber Distinguished Visiting Lectureship, Toronto, Canada (2016)
Keynote Speaker, 19th Joint Meeting "Signal Transduction, Weimar, Germany (2015)
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)
Monroe J. Schlesinger 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,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)
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-Organizer, CNIO Cancer Conference, Madrid, Spain (2003)
Co-Organizer, Annual Oncogene Meeting, Frederick, MD (2003)
Keynote Speaker, MIT/Neurofibromatosis Foundation Consortium Meeting, Cambridge, MA (1999)
Co-Organizer, FASEB Summer Research Conference, Saxton River, VT (1991)
Recipient, American Cancer Society Faculty Research Award (1990-1995)
Recipient, Damon Runyon-Walter Winchell Postdoctoral Fellowship (1983-85)

C. Contributions to Science

1. My initial independent research studies centered on determining the role of posttranslational lipid modifications in promoting RAS membrane association and oncogenic function. My group was one of three that independently determined that RAS proteins are modified by a farnesyl isoprenoid lipid. We then demonstrated the critical role of this modification for RAS membrane association and oncogenic function. This finding set the foundation for the development of inhibitors of farnesyltransferase, the enzyme that catalyzed this lipid modification, for the treatment of RAS-mutant cancers. Despite advancing to phase III clinical evaluation, farnesyltransferase inhibitors were not effective against KRAS mutant cancers, due to alternative modification of KRAS by a geranylgeranyl lipid. However, we later determined that FTIs were

effective against another farnesyltransferase substrate, lamin A, now approved for the treatment of the mutant lamin A driven genetic disorder progeria.

a. Casey PJ, Solski PA, **Der CJ**, Buss JE. (1989). p21ras is modified by a farnesyl isoprenoid. *Proc Natl Acad Sci U S A*. 86:8323-7.
b. Buss JE, Solski PA, Schaeffer JP, MacDonald MJ, **Der CJ**. (1989). Activation of the cellular proto-oncogene product p21Ras by addition of a myristylation signal. *Science*. 243:1600-3.
c. Jackson JH, Cochrane CG, Bourne JR, Solski PA, Buss JE, **Der CJ**. Farnesol modification of Kirsten-ras exon 4B protein is essential for transformation. (1990). *Proc Natl Acad Sci U S A*. 187:3042-6.
d. Kato K, Cox AD, Hisaka MM, Graham SM, Buss JE, **Der CJ**. (1992). Isoprenoid addition to Ras protein is the critical modification for its membrane association and transforming activity. *Proc Natl Acad Sci U S A.* 89:6403-7.

2. My RAS studies next turned to the issue of RAS 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 and RalGEF-RAL small GTPase signaling networks. Finally, we also determined that the atypical KRAS mutant G12R was impaired in activation of the PI3K-RAC effector pathway and defective in driving macropinocytosis. This finding provided critical support for the premise that different RAS mutants are functionally distinct.
   a. Oldham SM, Clark GJ, Gangarosa LM, Coffey RJ, Jr., **Der CJ**. (1996). Activation of the Raf-1/MAP kinase cascade is not sufficient for Ras transformation of RIE-1 epithelial cells. *Proc Natl Acad Sci U S A*. 93:6924-8.
   b. Lambert JM, Lambert QT, Reuther GW, Malliri A, Siderovski DP, Sondek J, Collard JG, **Der CJ**. (2002).Tiam1 mediates Ras activation of Rac by a PI(3)K-independent mechanism. *Nat Cell Biol*. 4:621-5.
   c. Lim KH, Baines AT, Fiordalisi JJ, Shipitsin M, Feig LA, Cox AD, **Der CJ**, Counter CM. (2005). Activation of RalA is critical for Ras-induced tumorigenesis of human cells. *Cancer Cell*. 27:533-45.
   d. Hobbs GA, Baker NM, Miermont AM, Thurman RD, Pierobon M, Tran TH, Anderson AO, Waters AM, Diehl JN, Papke B, Hodge RG, Klomp JE, Goodwin CM, DeLiberty JM, Wang J, Ng RWS, Gautam P, Bryant KL, Esposito D, Campbell SL, Petricoin EF, 3rd, Simanshu DK, Aguirre AJ, Wolpin BM, Wennerberg K, Rudloff U, Cox AD, **Der CJ**. (2020). Atypical KRAS(G12R) mutant is impaired in PI3K signaling and macropinocytosis in pancreatic cancer. *Cancer Discov*. 10:104-23.
3. One component of our research has been the use of model genetic organisms to study RAS effector signaling. In particular, we utilized C. elegans, where the key components of RAS regulation and effector signaling are conserved. 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 demonstrated effector signaling crosstalk, an important basis for adaptive compensatory responses to pharmacologic inhibition of specific effector signaling nodes.
   a. Zand TP, Reiner DJ, **Der CJ** (2011) Ras effector switching promotes divergent cell fates in C. elegans vulva patterning. *Dev Cell*. 20, 84-96.
   b. Martin TD, Reiner DJ, Chen XW, Saltiel AR, Walter CL, **Der CJ.** (2014). Ral and Rheb GAPs integrate mTOR and GTPase signaling in aging, autophagy, and tumor cell invasion. *Mol Cell*. 53:209-20.
4. Another focus of our research has involved determining the involvement of RAS homologous (RHO) proteins, small GTPases that comprise a major branch of the RAS superfamily small GTPases, in cancer. Our studies found that RHO proteins are aberrantly activated in cancer through their deregulation by RHO-selective guanine nucleotide exchange factors (RhoGEFs; Dbl family proteins) and GTPase-activating proteins (RhoGAPs) and by direct mutational activation. An emphasis of these studies was the application protein crystallography to define the mechanisms that cause aberrant RhoGEF activation in cancer. We also determined that RHOA mutants in gastric cancer acted as oncogenes through activation of the YAP-TEAD transcription factor complex. More recently, we determined that RHO activation is a driver of resistance to direct KRAS inhibitors through YAP-TEAD activation.
   a. Karnoub AE, Worthylake DK, Rossman KL, Pruitt WM, Campbell SL, Sondek J, **Der CJ**. (2001). Molecular basis for Rac1 recognition by guanine nucleotide exchange factors. *Nat Struct Biol*. 8:1037-41.

b. Zhang H, Schaefer A, Wang Y, Hodge RG, Blake DR, Diehl JN, Papageorge AG, Stachler MD, Liao J, Zhou J, Wu Z, Akarca FG, de Klerk LK, Derks S, Pierobon M, Hoadley KA, Wang TC, Church G, Wong KK, Petricoin EF, Cox AD, Lowy DR, **Der CJ**, Bass AJ. (2020). Gain-of-function RHOA mutations promote focal adhesion kinase activation and dependency in diffuse gastric cancer. *Cancer Discov*. 10:288-305.
c. Schaefer A, Hodge RG, Zhang H, Hobbs GA, Dilly J, Huynh MV, Goodwin CM, Zhang F, Diehl JN, Pierobon M, Baldelli E, Javaid S, Guthrie K, Rashid NU, Petricoin EF, Cox AD, Hahn WC, Aguirre AJ, Bass AJ, **Der CJ**. (2023). RHOA(L57V) drives the development of diffuse gastric cancer through IGF1R-PAK1-YAP1 signaling. *Sci Signal*. 16:eadg5289.
d. Edwards AC, Stalnecker CA, Jean Morales A, Taylor KE, Klomp JE, Klomp JA, Waters AM, Sudhakar N, Hallin J, Tang TT, Olson P, Post L, Christensen JG, Cox AD, **Der CJ**. (2023). TEAD inhibition overcomes YAP1/TAZ-driven primary and acquired resistance to KRASG12C inhibitors. *Cancer Res*. 83:4112-29.

5. Our recent focus centers on therapeutic approaches targeting the ERK MAPK effector signaling network. Our studies determined that ERK activation alone can near completely phenocopy RAS and drive the RAS-dependent gene transcription and protein phosphorylation. We also determined that the MYC oncoprotein and transcription factor is a key driver of ERK-dependent cancer growth. Finally, we recently applied a multi-omics approach to establish a comprehensive molecular portrait of the ERK-regulated transcriptome, total proteome, phosphoproteome and kinome. From these studies, we identified ERK inhibitor based combination-based therapies that we transitioned to clinical evaluation.
   a. Hayes TK, Neel NF, Hu C, Gautam P, Chenard M, Long B, Aziz M, Kassner M, Bryant KL, Pierobon M, Marayati R, Kher S, George SD, Xu M, Wang-Gillam A, Samatar AA, Maitra A, Wennerberg K, Petricoin EF, 3rd, Yin HH, Nelkin B, Cox AD, Yeh JJ, **Der CJ**. (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. Vaseva AV, Blake DR, Gilbert TSK, Ng S, Hostetter G, Azam SH, Ozkan-Dagliyan I, Gautam P, Bryant KL, Pearce KH, Herring LE, Han H, Graves LM, Witkiewicz AK, Knudsen ES, Pecot CV, Rashid N, Houghton PJ, Wennerberg K, Cox AD, **Der CJ**. (2018). KRAS suppression-induced degradation of MYC is antagonized by a MEK5-ERK5 compensatory mechanism. *Cancer Cell*. 34:807-22.
   c. Klomp JE, Diehl JN, Klomp JA, Edwards AC, Yang R, Morales AJ, Taylor KE, Drizyte-Miller K, Bryant KL, Schaefer A, Johnson J., Huntsman EM, Yaron TM, Pierobon M, Baldell E, Prevatte AW, Barker NK, Herring LE, Petricoin III EF, Graves LM, Cantley LC, Cox AD, **Der CJ,** Stalnecker, CA (2024). Determining the ERK-regulated phosphoproteome driving KRAS-mutant cancer. *Science*. 384:eadk0775.
   d. Klomp JA, Klomp JE, Stalnecker CA, Bryant KL, Edwards AC, Drizyte-Miller K, Hibshman PS, Diehl JN, Lee YS, Morales AJ, Taylor KE, Peng S, Tran NL, Herring LE, Prevatte AW, Barker NK, Hover LD, Hallin J, Chowdhury S, Coker O, Lee HM, Olson P, Christensen JG, Shen JP, Kopetz S, Graves LM, Lim KH, Wang-Gillam A, Cox AD, **Der, CJ**. (2024). Defining the KRAS-and ERK-regulated transcriptome in KRAS-mutant cancers. *Science*. 384:eadk0850.

Complete List of Published Work in MyBibliography
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