OMB No. 3145-0279 (Expiration Date 10/31/2026)

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: CHEN, JAMES KENNETH

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0002-9220-8436

Position Title: Professor and Chair

Organization and Location: Department of Chemical and Systems Biology, Stanford University, Stanford, California, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
Johns Hopkins School of Medicine, Baltimore, Maryland, United States	Postdoctoral Fellow	01/1999	05/2003	Developmental Biology
Marine Biological Laboratory, Woods Hole, Massachusetts, United States	Other training	05/1998	07/1998	Embryology
Harvard College, Cambridge, Massachusetts, United States	Doctor of Philosophy (PHD)	09/1991	12/1998	Chemistry and Chemical Biology
Harvard College, Cambridge, Massachusetts, United States	Bachelor of Arts (AB)	09/1987	06/1991	Chemistry

Appointments and Positions

2016 - present	Professor and Chair, Department of Chemical and Systems Biology, Stanford University, Stanford, California, United States
2025 - present	Advisor, Anther Therapeutics, Albany, New York, United States
2022 - present	Faculty Director, ChEM-H/CSB High-Throughput Screening Knowledge Center, Stanford University, Stanford, California, United States
2021 - present	Co-Director, Molecular Pharmacology Training Program, Stanford School of Medicine (T32 GM136631), Stanford, California, United States
2021 - present	Faculty Lead, High-Throughput Screening/Stanford Innovative Medicines Accelerator, Stanford, California, United States
2020 - 2021	Chair of the Basic Science Chairs, Stanford School of Medicine, Stanford, California, United States
2019 - present	Professor, Department of Chemistry, Stanford University, Stanford, California, United States
2016 - present	Professor, Department of Developmental Biology, Stanford University, Stanford, California, United States
2016 - present	Member, International Zebrafish Society, Milwaukee, Wisconsin, United States
2016 - 2019	Professor (by courtesy), Department of Chemistry, Stanford University, Stanford, California, United States
2014 - 2016	Executive Committee Member, School of Medicine Faculty Senate, Stanford, California, United States
2013 - present	Executive Committee Member, Sarafan ChEM-H Institute, Stanford University, Stanford, California, United States
2012 - 2016	Associate Professor, Department of Developmental Biology, Stanford, California, United States
2011 - present	Director, Molecular Basis and Medicine Scholarly Concentration, Stanford School of Medicine, Stanford, California, United States
2010 - 2016	Associate Professor (by courtesy), Department of Chemistry, Stanford University, Stanford, California, United States
2010 - 2016	Associate Professor, Department of Chemical and Systems Biology, Stanford University, Stanford, California, United States
2009 - present	Member, Society for Developmental Biology, Rockville, Maryland, United States
2009 - present	Editorial Board Member, Cell Chemical Biology, Cambridge, Massachusetts, United States
2008 - present	Editorial Board Member, Zebrafish, New Rochelle, New York, United States

2003 - 2022	Faculty Director, High-Throughput Bioscience Center, Stanford School of Medicine, Stanford, California, United States
2003 - 2010	Assistant Professor, Department of Chemical and Systems Biology, Stanford University, Stanford, California, United States
2003 - 2010	Assistant Professor (by courtesy), Department of Chemistry, Stanford University, Stanford, California, United States
1989 - present	Member, American Chemical Society, Washington, District of Columbia, United States

Products

Products Closely Related to the Proposed Project

1. Feng Z, Hom ME, Bearrood TE, Rosenthal ZC, Fernández D, Ondrus AE, Gu Y, McCormick AK, Tomaske MG, Marshall CR, Kline T, Chen CH, Mochly-Rosen D, Kuo CJ, Chen JK. Targeting colorectal cancer with small-molecule inhibitors of ALDH1B1. Nat Chem Biol. 2022 Oct;18(10):1065-1075. PubMed Central PMCID: PMC9529790.
2. Crapster JA, Rack PG, Hellmann ZJ, Le AD, Adams CM, Leib RD, Elias JE, Perrino J, Behr B, Li Y, Lin J, Zeng H, Chen JK. HIPK4 is essential for murine spermiogenesis. Elife. 2020 Mar 12;9 PubMed Central PMCID: PMC7067585.
3. Payumo AY, McQuade LE, Walker WJ, Yamazoe S, Chen JK. Tbx16 regulates hox gene activation in mesodermal progenitor cells. Nat Chem Biol. 2016 Sep;12(9):694-701. PubMed Central PMCID: PMC4990471.
4. Rack PG, Ni J, Payumo AY, Nguyen V, Crapster JA, Hovestadt V, Kool M, Jones DT, Mich JK, Firestone AJ, Pfister SM, Cho YJ, Chen JK. Arhgap36-dependent activation of Gli transcription factors. Proc Natl Acad Sci U S A. 2014 Jul 29;111(30):11061-6. PubMed Central PMCID: PMC4121843.
5. Shestopalov IA, Pitt CL, Chen JK. Spatiotemporal resolution of the Ntla transcriptome in axial mesoderm development. Nat Chem Biol. 2012 Jan 29;8(3):270-6. PubMed Central PMCID: PMC3288381.

Other Significant Products Highlighting Contributions to Science

1. Zerva A, Raig ND, Zhuang Z, Krämer A, Dopfer J, Togashi R, Schwalm MP, Elson L, Frischkorn JM, Berger BT, Müller S, Chen JK, Knapp S, Hanke T. Macrocyclization of Broad-Spectrum Kinase Inhibitor Bosutinib leads to Potent and Selective Quinoline-based HIPK4 Inhibitor AZ137. bioRxiv. 2026 Apr 24; PubMed Central PMCID: PMC13131581.
2. Zhuang Z, Togashi R, Kearney P, Pass I, Swick S, Zeng F, Bobkov A, Fujimoto L, Dutta S, Zerva A, Raig N, Saha D, Emami A, Schwalm M, Moon B, Howard S, Knapp S, Hanke T, Chung T, Chen J. Small-molecule modulators of HIPK4 activity and proteostasis. 2026 January 01; :2026.05.12.724395. Available from: http://biorxiv.org/content/early/2026/05/14/2026.05.12.724395.abstract DOI: 10.64898/2026.05.12.724395
3. Tarhan A, Feng Z, Fernandez D, Kim A, Bearrood T, Hinman A, White N, Chen J, Tarhan K. Development of next-generation ALDH1B1 inhibitors with enhanced pharmacological and functional properties. ChemRxiv. ; 2026(0515). Available from: https://doi.org/10.26434/chemrxiv-2025-9cq5c/v4 DOI: 10.26434/chemrxiv-2025-9cq5c/v4

Certification:

I certify that the information provided is current, accurate, and complete. This includes, but is not limited to, information related to current, pending, and other support (both foreign and domestic) as defined in 42 U.S.C. § 6605.

In accordance with Section 10632 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19232), each individual identified as a senior/key person must certify that they are not a party to a malign foreign talent recruitment program.

Research Security Training Requirement for Federal Award Personnel: In accordance with Section 10634 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19234), each individual identified as a senior/key person must certify that they have completed the requisite research security training that meets the requirements specified in Item 2 of Important Notice No. 149 within 12 months prior to proposal submission.

Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§287, 1001, 1031 and 31 U.S.C. §§3729-3733 and 3802.

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NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: CHEN, JAMES KENNETH

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0002-9220-8436

Position Title: Professor and Chair

Organization and Location: Department of Chemical and Systems Biology, Stanford University, Stanford, California, United States

Personal Statement

My laboratory has used chemical tools and systems-level approaches to elucidate the molecular mechanisms that underlie developmental biology. We have discovered and characterized several small-molecule modulators of the Hedgehog pathway, including Smoothened antagonists, cytoplasmic dynein inhibitors, and compounds that block Gli transcription factor function. Most recently, we developed the first specific inhibitors of aldehyde dehydrogenase 1B1 (ALDH1B1), a mitochondrial enzyme that is expressed in adult intestinal and pancreatic stem/progenitor cells and plays important roles in colorectal and pancreatic cancer. We have also conducted genetic screens to discover non-canonical regulators of Gli activity, such as the atypical Rho GTPase-activating protein ARHGAP36 and primary cilium components. We subsequently used a deep sequencing-based mutagenesis screen and mass spectrometry-based proteomics to map the structure-activity landscape of ARHGAP36 and identify ARHGAP36-interacting proteins.

In parallel with our interest in cell signaling, my research group has investigated the roles of developmental pathways in vertebrate organisms. For example, we invented caged morpholino oligonucleotides that enable light- or enzyme-triggered gene silencing, and we have applied these tools in zebrafish models to study how T-box transcription factors control notochord, medial floor plate, and somite development. We have developed lanthanide-based methods for ultrasensitive in vivo imaging and optogenetic tools for targeted cell ablation. My laboratory also established homeodomain-interacting protein kinase 4 (HIPK4) as an essential regulator of mammalian spermiogenesis and male fertility.

My current research focuses on: (1) the roles of aldehyde dehydrogenases in stem/progenitor cell maintenance and cancer; (2) the mechanisms by which HIPK4 promotes spermiogenesis; and (3) optogenetic regulators of developmental pathways. We are also developing synthetic ligands for specific aldehyde dehydrogenase family members and HIPK4, which respectively could lead to new anti-cancer therapies and male contraceptives, respectively.

A complete list of my PubMed publications can be accessed at this link (My Bibliography, 92 references):
https://www.ncbi.nlm.nih.gov/myncbi/james.chen.1/bibliography/public/

Since I joined the Stanford faculty in 2003, I have mentored 13 Ph.D. students and 24 postdoctoral fellows. My goal is to rigorously train researchers who can solve major biomedical challenges by transcending conventional scientific boundaries. All my former trainees have continued to pursue science-related careers, including positions in academia (e.g., University of Geneva, University of Illinois at Chicago, University of North Carolina at Chapel Hill, and San Jose State University), research institutes (e.g., Allen Institute for Brain Science), or industry (e.g., Bristol-Myers Squibb and Calico). My most recent Ph.D. graduate will join the Rice University faculty this fall. I am Co-Director of the Molecular Pharmacology Training Grant (T32 GM136631) for Stanford Ph.D. students and Director of the Molecular Basis of Medicine Scholarly Concentration, which enables Stanford M.D. students to gain hands-on research experience in basic science. I regularly teach a Ph.D.-level course in chemical biology. In addition to these graduate-level mentoring and teaching activities, I have served as a research advisor for 27 undergraduates and 11 post-baccalaureate researchers.

Honors

2019	Herbert and Marguerite Jauch Professorship, Stanford University
2019	Rocek Lectureship in Chemical Biology, University of Illinois at Chicago
2013 - 2017	INSPIRE Award, National Science Foundation
2008 - 2013	NIH Director's Pioneer Award, National Institutes of Health
2008 - 2011	Research Scholar Award, American Cancer Society
2006 - 2008	Brain Tumor Society Award, Rachel Molly Markoff Research Chair
2005	Astellas USA Foundation Award, Astellas USA Foundation

2005 - 2008	Terman Fellow, Stanford University
2005 - 2007	Basil O'Connor Starter Scholar Research Award, March of Dimes Foundation
2004 - 2006	Kimmel Scholar Award, Sidney Kimmel Foundation
2003	W. Barry Wood, Jr. Postdoctoral Award, Johns Hopkins University
2002 - 2003	American Cancer Society Postdoctoral Fellowship, American Cancer Society
1999 - 2002	Damon Runyon-Walter Winchell Postdoctoral Fellowship, Damon Runyon Cancer Research Foundation
1994 - 1995	American Chemical Society Organic Chemistry Graduate Fellowship, American Chemical Society
1991 - 1994	National Science Foundation Predoctoral Fellowship, National Science Foundation

Contributions to Science

1. **Small-molecule modulators of developmental signaling pathways.** Since I first learned of the plant-derived teratogen cyclopamine, I have been interested in small-molecule modulators of developmental signaling pathways. As a postdoctoral fellow with Prof. Philip Beachy (then at Johns Hopkins School of Medicine), I discovered that cyclopamine directly inhibits Smoothened (SMO), a transmembrane receptor in the Hedgehog (Hh) pathway. I subsequently identified the first synthetic SMO antagonists (SANTs 1-4) and agonists (SAG and purmorphamine). This work helped advance the development of Hh pathway-targeting therapeutics, some of which are now being used to treat advanced basal cell carcinoma and medulloblastoma. My laboratory has focused on Hh pathway inhibitors that act downstream of SMO (e.g., HPIs 1-4, JK184, etc.). Among these compounds are the first specific chemical antagonists of cytoplasmic dyneins 1 and 2 (ciliobrevins), which we discovered through a high-throughput phenotypic screen and characterized in collaboration with Prof. Tarun Kapoor (Rockefeller University). More recently, we have developed small-molecule inhibitors of aldehyde dehydrogenases (ALDHs) that are required for stem cell maintenance, including first-in-class ALDH1B1-specific antagonists. I have authored 28 studies related to the chemical modulation of developmental pathways. Our ongoing, unpublished work includes inhibitors of ALDH1A3 and homeodomain-interacting protein kinase 4 (HIPK4), a spermatid-specific enzyme that is required for spermiogenesis.

2. **Genetic regulators of developmental signaling pathways.** In addition to the chemistry-driven studies described above, I have pursued the identification of new Hh pathway regulators through genetic screens. My laboratory collaborated with Prof. Matthew Scott (Stanford) to conduct a focused siRNA screen, through which we identified neuropilins as positive regulators of the Hh pathway. Investigations by other laboratories have subsequently implicated neuropiIins in medulloblastoma, the most common pediatric brain tumor. My research group also completed a genome-scale cDNA overexpression screen, leading to our discovery of ARHGAP36 as a potent, non-canonical activator of Gli transcription factors. ARHGAP36 plays important roles in spinal cord development and medulloblastoma, and our studies have established how this atypical member of the Rho GTPase-activating protein family interacts with the Hh/Gli pathway. We subsequently elucidated key functional domains within this proto-oncoprotein and identified ARHGAP36-interacting proteins. Finally, I have collaborated with Profs. Maxence Nachury and Michael Bassik (Stanford) to conduct a genome-wide CRISPR-based screen for Hh signaling modulators. Our study yielded the most comprehensive compendium of pathway regulators to date, including several new ciliopathy genes. I have authored 8 studies related to the genetic regulation of developmental pathways.

3. **Chemical technologies for in vivo biology.** As a scientist deeply interested in both chemistry and developmental biology, I have explored how chemical tools can advance our understanding of tissue formation. My laboratory invented the first caged morpholino oligonucleotides (MOs), which enable light inducible inhibition of RNA splicing and translation in whole organisms. For example, we developed cyclic caged MOs that can be optically or enzymatically activated, enabling tissue-specific gene silencing in transgenic animals that express the triggering enzyme. We also collaborated with Prof. Pehr Harbury (Stanford) to develop new methods for ultrasensitive, autofluorescence-free imaging of lanthanide probes. More recently, we have developed bicyclic cMOs and explored how LOV domain-based technologies can be used to control gene expression and cell ablation in zebrafish models. I have authored 28 studies related to chemical technologies for in vivo studies. Our ongoing, unpublished work includes the development of a transposase-based platform for optogenetic engineering and its application to Hedgehog pathway regulators.

4. **Mechanistic studies of embryonic development, tumorigenesis, and regeneration.** A major strength of our research program is our ability to go beyond proof-of-concept demonstrations for new technologies and conduct in-depth biological investigations. For example, we have used caged MOs and zebrafish models to study how T-box transcription factors such as Tbxta (the zebrafish ortholog of Brachyury) and T-box 16 (Tbx16) drive key aspects of early development. Our unconventional approach has: (1) revealed dynamic changes in Tbxta function during notochord development and identified new regulators of notochord vacuolization; (2) uncovered a role for Tbx16 in collinear hox gene activation, supporting a new model for anterior-posterior somite patterning; and (3) led to our discovery that the two T-box proteins regulate the morphogenetic movements of medial floor plate progenitors (and not their specification as previously believed). Most recently, we have used mouse models to study the roles of homeodomain-interacting protein kinase 4 (HIPK4) in spermiogenesis. I have authored 15 studies related to mechanistic studies of vertebrate development and regeneration. Our ongoing, unpublished work includes studies of aldehyde dehydrogenase 1B1 (ALDH1B1) function in colorectal cancer cells, including its endogenous substrates, and the identification of HIPK4-dependent phosphoproteins in developing sperm.

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