BIOGRAPHICAL SKETCH

NAME: James Kenneth Chen

eRA COMMONS USER NAME: CHEN.JAMES

POSITION TITLE: Herbert and Marguerite Jauch Professor, Professor and Chair of Chemical and Systems Biology, Professor of Developmental Biology, Professor of Chemistry

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard College, Cambridge, MA	A.B.	06/1991	Chemistry
Harvard College, Cambridge, MA	Ph.D.	12/1998	Chemistry and Chemical Biology
Marine Biological Laboratory, Woods Holes, MA	N/A	07/1998	Embryology
Johns Hopkins School of Medicine, Baltimore, MD	Postdoc	05/2003	Developmental Biology

A. Personal Statement

My laboratory uses 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 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 the dual-specificity kinase HIPK4 as an essential regulator of mammalian spermiogenesis and male fertility.

Our current research focuses on optogenetic regulators of developmental pathways, ALDH isoforms required for stem cell maintenance, HIPK4 substrates and inhibitors, and the mechanisms of ARHGAP36-mediated tumorigenesis.

Ongoing and recently completed projects that I would like to highlight include:

R35 GM120730
NIH/NIGMS
Chen (PI)
04/01/2018 – 06/30/2028
Chemical tools for developmental biology

R33 HD099720
NIH/NICHD
Chen (co-PI)
09/01/2021 – 08/31/2024
Development of allosteric HIPK4 inhibitors as non-hormonal male contraceptives

R01 CA244344
NIH/NCI
Chen (PI)
06/01/2021 – 05/31/2026
Targeting colorectal cancer stem cells with ALDH1B1 antagonists

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022 – present	Faculty Director, ChEM-H/CSB High-Throughput Screening Knowledge Center
2021 – present	Co-Director, Molecular Pharmacology Training Program, Stanford School of Medicine (T32 GM136631)
2021 – present	Faculty Lead, High-Throughput Screening/Stanford Innovative Medicines Accelerator
2021	Reviewer, NIH Special Emphasis Panel (ZHD1 DSR-M(56): Contraceptive Development Research Centers Program; P50)
2021	Reviewer, NIH Study Section (SBCB: Synthetic and Biological Chemistry B)
2020 – 2021	Chair of the Basic Science Chairs, Stanford School of Medicine
2019 – present	Professor, Department of Chemistry, Stanford University
2018	Reviewer, NIH Study Section (SBCA: Synthetic and Biological Chemistry A)
2018	Reviewer, NIH Special Emphasis Panel (ZRG1 BCMB-A 51R: NIH Transformative Research Awards)
2017 – 2021	Scientific Advisory Board Member, Vibliome Therapeutics
2017	Co-Organizer, 2017 Society for Developmental Biology West Coast Meeting
2016 – present	Professor, Department of Developmental Biology, Stanford University
2016 – present	Professor and Chair, Department of Chemical and Systems Biology, Stanford University
2016 – present	Member, International Zebrafish Society
2016 – 2019	Professor (by courtesy), Department of Chemistry, Stanford University
2015	Reviewer, NIH Study Section (SBCB: Synthetic and Biological Chemistry B)
2015	Reviewer, NIH Special Emphasis Panel (PA-11-184:T32 NRSA Institutional Research Training Grants and PA-14-044: K01 Mentored Research Scientist Development Award)
2014 – 2016	Executive Committee Member, School of Medicine Faculty Senate
2013 – present	Executive Committee Member, ChEM-H Institute
2013 – 2015	Reviewer, NSF CAREER Award
2012 – 2016	Associate Professor, Department of Developmental Biology, Stanford University
2012 – 2016	Member, Research Committee of the American Heart Association, Western States Affiliate
2012, 2014, 2015	Instructor, Introduction to Chemical Biology Short Course, University of São Paulo, São Paulo, Brazil
2011 – present	Director, Molecular Basis of Medicine Scholarly Concentration
2010 – 2016	Associate Professor (by courtesy), Department of Chemistry, Stanford University
2010 – 2016	Associate Professor, Department of Chemical and Systems Biology, Stanford University
2009 – present	Member, Society for Developmental Biology
2009 – present	Editorial Board Member, *Cell Chemical Biology*
2008 – present	Editorial Board Member, *Zebrafish*
2008 – 2011	Consultant, Fate Therapeutics
2004	Consultant, Infinity Therapeutics
2003 – 2022	Faculty Director, High-Throughput Bioscience Center
2003 – 2010	Assistant Professor, Department of Chemical and Systems Biology, Stanford University
2003 – 2010	Assistant Professor (by courtesy), Department of Chemistry, Stanford University

1989 – present Member, American Chemical Society

Honors

2019	Herbert and Marguerite Jauch Professorship, Stanford University
2019	Rocek Lectureship in Chemical Biology, University of Illinois at Chicago
2013 – 2017	NSF INSPIRE Award
2009	Nature Biotechnology SciCafe Award for Outstanding Research Achievement
2008 – 2013	NIH Director's Pioneer Award
2008 – 2011	American Cancer Society Research Scholar Award
2006 – 2008	Brain Tumor Society Award/Rachel Molly Markoff Research Chair
2005 – 2008	Terman Fellow, Stanford University
2005 – 2007	Basil O'Connor Starter Scholar Research Award, March of Dimes Foundation
2005	Astellas USA Foundation Award
2004 – 2006	Kimmel Scholar Award
2003	W. Barry Wood, Jr. Postdoctoral Award, Johns Hopkins University
2002 – 2003	American Cancer Society Postdoctoral Fellowship
1999 – 2002	Damon Runyon-Walter Winchell Postdoctoral Fellowship
1994 – 1995	American Chemical Society Organic Chemistry Graduate Fellowship
1991 – 1994	National Science Foundation Predoctoral Fellowship

C. 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 that are required for stem cell maintenance, including first-in-class ALDH1B1-specific antagonists. I have authored twelve studies related to the chemical modulation of developmental pathways, including the four listed below.
   a. Hyman, J. M., Firestone, A. J., Heine, V. M., Zhao, Y., Ocasio, C. A., Han, K., Sun, M., Rack, P. G., Sinha, S., Wu, J. J., Solow-Cordero, D. E., Jiang, J., Rowitch, D. H., and **Chen, J. K.** (2009) Small-molecule inhibitors reveal multiple strategies for Hedgehog pathway blockade. *Proc. Natl. Acad. Sci. U. S. A*. 106: 14132-14137. PMCID: PMC2721821
   b. Firestone, A. J., Weinger, J. S., Maldonado, M., Barlan, K., Langston, L. D., O'Donnell, M. D., Gelfand, V. I., Kapoor, T. M.*, and **Chen, J. K.*** (2012) Small-molecule inhibitors of the AAA+ ATPase motor cytoplasmic dynein. *Nature* 484: 125-129. PMCID: PMC3321072
   c. Hom, M. E., Ondrus, A. E., Sakata-Kato, T., Rack, P. G., and **Chen, J. K.** (2020) Bicyclic imidazolium inhibitors of Gli transcription factor activity. *ChemMedChem* 15: 1044-1049. PMCID: PMC7311267
   d. Feng, Z., Hom, M. E., Bearrood, T. E., Rosenthal, Z. C., Fernández, D., Ondrus, A. E., Gu, Y., McCormick, A. K., Tomaske, M. G., Marshall, C. R., Kline, T., Chen, C.-H., Mochly-Rosen, D., Kuo, C. J., and **Chen, J. K.** (2022) Targeting colorectal cancer with small-molecule inhibitors of ALDH1B1. *Nat. Chem. Biol*. 18: 1065-1075.

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 neuropilins 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.

a. Hillman, R. T., Feng, B. Y., Ni, J., Woo, W.-M., Milenkovic, L., Hayden Gephart, M. G., Teruel, M. N., Oro, A. E., **Chen, J. K.**, and Scott, M. P. (2011) Neuropilins are positive regulators of Hedgehog signal transduction. *Genes Dev*. 25: 2333-2346. PMCID: PMC3222900
b. Rack, P. G., Ni, J., Payumo, A. Y., Nguyen, V., Crapster, J. A., Novestadt, V., Kool, M., Jones, D. T. W., Mich, J. K., Firestone, A. J., Pfister S. M., Cho, Y.-J., and **Chen, J. K.** (2014) Arhgap36-dependent activation of Gli transcription factors. *Proc. Natl. Acad. Sci. U. S. A*. 111: 11061-11066. PMCID: PMC4121834
c. Breslow, D. K.*, Hoogendoorn, S., Kopp, A. R., Morgens, D. W., Vu, B. K., Han, K., Li, A., Hess, G. T., Bassik, M C., **Chen, J. K.***, and Nachury, M. V.* (2018) A CRISPR-based screen for Hedgehog signaling provides insights into ciliary function and ciliopathies. *Nat. Genet*. 50: 460-471. PMCID: PMC5862771.
d. Nano, P. R., Johnson, T. K., Kudo, T., Mooney, N. A., Ni, J., Demeter, J., Jackson, P. K., and **Chen, J.K.** (2021) Structure-activity mapping of ARHGAP36 reveals regulatory roles for its GAP homology and C-terminal domains. *PLoS One* 16: e0251684. PMCID: PMC8128262

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 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 explored how LOV domain-based technologies can be used to control gene expression and cell ablation in zebrafish models. I am the corresponding author for the four papers listed below and six other studies in this area. I also co-authored a study describing light-inducible protein degradation in zebrafish and the development of chemically triggered caged MOs.
   a. Shestopalov, I. A., Sinha, S., and **Chen, J. K.** (2007) Light-controlled gene silencing in zebrafish embryos. *Nat. Chem. Biol*. 3: 650-651. PMCID: PMC3288381
   b. Yamazoe, S., McQuade, L. E., and **Chen, J. K.** (2014) Nitroreductase-activated caged morpholino oligonucleotides for in vivo gene silencing. *ACS Chem. Biol.* 9: 1985-1990. PMCID: PMC4168795
   c. Cho, U., Riordan, D. P., Ciepla, P., Kocherlakota, K. S., **Chen, J. K.***, and Harbury, P. B.* (2018) Ultrasensitive optical imaging with lanthanide lumiphores. *Nat. Chem. Biol.* 14: 15-21. PMCID: PMC5726931
   d. Mruk, K.*, Ciepla, P., Piza, P. A., Alnaqib, M. A., and **Chen, J. K.*** (2020) Targeted cell ablation in zebrafish using optogenetic transcriptional control. *Development* 147:dev183640. PMCID: PMC7328002

4. **Mechanistic studies of vertebrate development 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 No tail-a (Ta; 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 Ta 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 am the corresponding author on the four papers listed below and three additional zebrafish-related research articles. I have also co-authored five other studies of zebrafish development and a clinical report on a novel missense GLI3 variant.

a. Shestopalov, I. A., Pitt, C. L. W., and **Chen, J. K.** (2012) Spatiotemporal resolution of the Ntla transcriptome in axial mesoderm development. *Nat. Chem. Biol.* 8: 270-276. PMCID: PMC3288381
b. Payumo, A. Y., Walker, W. J., McQuade, L. E., Yamazoe, S., and **Chen, J. K.** (2015) Optochemical dissection of T-box gene-dependent medial floor plate development. *ACS Chem. Biol.* 10: 1466-75. PMCID: PMC4672996
c. Payumo, A. Y., McQuade, L. E., Walker, W. J., Yamazoe, S., and **Chen, J. K.** (2016) Tbx16 regulates *hox* gene activation in mesodermal progenitor cells. *Nat. Chem. Biol.* 12: 694-701. PMCID: PMC4990471
d. Crapster, J. A.*, Rack, P. G., Hellmann, Z. J., Behr, B., Li, Y., Lin, J., Zeng, H., and **Chen, J. K.*** (2020) HIPK4 is essential for mammalian spermiogenesis. *eLife* 9:e50209. PMCID: PMC7067585

Complete List of Published Work (78 peer-reviewed and 12 non-peer-reviewed publications):

MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/james.chen.1/bibliography/public/