Stanford

Paul Salomon Mischel

Fortinet Founders Professor and Professor, by courtesy, of Neurosurgery

Pathology

NIH Biosketch available Online

CONTACT INFORMATION

- **Alternate Contact**

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Bio

BIO

I am a physician scientist trained in pathology and cancer biology. My lab has made a series of discoveries published in Nature, Science, and Nature Genetics, that have identified a central role for ecDNA (extrachromosomal DNA) in cancer development, progression, accelerated tumor evolution and drug resistance. These findings have provided a new understanding of the fundamental mechanisms of oncogene amplification and the spatial organization of altered tumor genomes, launching a new area of cancer research that links circular architecture with tumor pathogenesis. I lead Team eDyNAmiC, which was awarded one of the $25M Cancer Grand Challenges Awards from CRUK and the National Cancer Institute, to tackle the extrachromosomal DNA grand challenge. My lab has also uncovered metabolic co-dependencies that are downstream consequences of oncogene amplification. These include a central role for altered biochemical mechanisms that regulate oncogene copy number and function. These discoveries have resulted in new understandings of some of the fundamental processes by which oncogene amplification drives cancer progression and drug resistance and pointed that way towards new treatments that are being developed.

ACADEMIC APPOINTMENTS

- Professor, Pathology
- Professor (By courtesy), Neurosurgery
- Institute Scholar, Sarafan ChEM-H
- Member, Stanford Cancer Institute

ADMINISTRATIVE APPOINTMENTS

- Professor of Pathology, Stanford University School of Medicine, (2021- present)
- Vice Chair for Research, Department of Pathology, Stanford University School of Medicine, (2021- present)
- Institute Scholar and Deputy Director, Translational Science, Sarafan ChEM-H, Stanford University, (2021- present)

HONORS AND AWARDS

- Fellow, AACR Academy (2025)
- Ernst W. Bertner Memorial Award for Distinguished Contributions to Cancer Research, MD Anderson (2023)

- Member, National Academy of Medicine (2022)
- Elected Fellow, American Association for the Advancement of Science (2015)
- Elected Member, American Association of Physicians (2012-present)
- President, American Society for Clinical Investigation (2010-2011)
- Elected Member, American Society for Clinical Investigation (2007-present)
- American's Top Doctors for Cancer, Castle & Connelly (2006-2021)
- Americas Top Doctors for Pathology, Castle & Connelly (2006-2021)
- Farber Award for Brain Cancer Research, American Association of Neurological Surgeons and the Society for Neuro-Oncology (2004)
- Pfizer New Faculty Scholar, Pfizer (1996)
- Alpha Omega Alpha, AOA (1991)

BOARDS, ADVISORY COMMITTEES, PROFESSIONAL ORGANIZATIONS

- Co-Founder and Chair of Scientific Advisory Board, Boundless Bio, Inc. (2018 - present)

PROFESSIONAL EDUCATION

- Post-Doctoral Fellowship, HHMI-UCSF (mentored by Dr. Louis Reichardt) , Molecular Neuroscience (1998)
- Residency, UCLA , Pathology and Neuropathology (1996)
- M.D., Cornell University Medical College (Weill Cornell) , Medicine (1991)
- B.A., University of Pennsylvania , Philosphy (1984)

LINKS

- My lab website: https://med.stanford.edu/paulmischellab.html
- My wikipedia page: https://en.wikipedia.org/wiki/Paul_Mischel
- My google scholar profile: https://scholar.google.com/citations?user=IvSY4O8AAAAJ&hl=en
- https://chemh.stanford.edu/person/paul-mischel: My ChEM-H page
- My pubmed link: https://pubmed.ncbi.nlm.nih.gov/?term=mischel+p&sort=date

Research & Scholarship

CURRENT RESEARCH AND SCHOLARLY INTERESTS

Human genes are arranged on 23 pairs of chromosomes, but in cancer, tumour-promoting genes can free themselves from chromosomes and relocate to circular, extrachromosomal pieces of DNA (ecDNA). These ecDNA don't follow the normal "rules" of chromosomal inheritance, enabling tumours to achieve far higher levels of cancer-causing oncogenes than would otherwise be possible, and licensing cancers with a way to evolve and change their genomes to evade treatments, at rates that would be unthinkable for human cells. The altered circular architecture of ecDNAs also changes the way that the cancer-causing genes are regulated and expressed, further contributing to aggressive tumor growth. These unique features make ecDNA-containing cancers especially aggressive and difficult to treat and cancer patients whose tumours harbour ecDNA have markedly shorter survival.

Despite being first seen over fifty years, ago, and prescient work on its potential importance, the scale, scope, and impact of ecDNA was not well understood. In fact, it was thought to be a rare event of unknown significance. The application of powerful new, integrative molecular approaches has shown us, that ecDNAs are present in nearly half of all human cancer types and at likely in at least a quarter of all cancer patients and they have taught us that ecDNA is indeed, one of the most urgent problems facing patients with cancer, challenging the success of the targeted therapy approaches, and a problem that is certainly worthy of its nomination as a Cancer Grant Challenge. Currently, the collective current understanding of how ecDNA form,

how they move around the cell, how they evolve to resist treatment, how they impact the immune system, and how they can be effectively targeted, are lacking. Can we identify actionable co-dependency pathways that are generated by ecDNA amplification? These are the areas of research focus of research in my laboratory.

We are very collaborative and interactive, with many colleagues around the world. We work very closely with Professor Howard Chang at Stanford, as well as with many other new Stanford colleagues. I have recently joined the faculty of Stanford University as a Professor and Vice Chair for Research for the Department of Pathology, and as an Institute Scholar in ChEM-H, where my lab is based. I am committed to actively contributing not only to the science and its translation for benefit to patients, but also to mentoring trainees at all levels, and helping colleagues, including junior colleagues, develop the skills necessary to navigate the complex landscape of translating science into medicines that will help patients.

Teaching

STANFORD ADVISEES

Doctoral Dissertation Reader (AC)

Sam Scharenberg

Postdoctoral Faculty Sponsor

Yanbo Wang, Xiaowei Yan, Hyerim Yi, Shu Zhang

Doctoral Dissertation Advisor (AC)

Aditi Gnanasekar, Venkat Sankar

Doctoral Dissertation Co-Advisor (AC)

Vishnu Shankar

Publications

PUBLICATIONS

- **High-depth whole genome sequencing of premalignant breast lesions reveals rearrangement hotspots and personalized management opportunities.** *Nature communications*
  Chmelova, L., Davies, H. R., Degasperi, A., Rinaldi, G., Wils, L., Black, D., Memari, Y., Koh, G. C., Shooter, S., Mulder, L., Kristel, P., Szuhai, K., Prasad, et al
  2026
- **A recipe for chaos: Extrachromosomal DNA and the hallmarks of cancer.** *Cell*
  Wong, I. T., Bailey, C., Wu, S., Henssen, A. G., Cravatt, B. F., Chen, Z. J., Bafna, V., Jamal-Hanjani, M., Swanton, C., Chang, H. Y., Mischel, P. S.
  2026; 189 (8): 2307-2321
- **Accurate prediction of ecDNA in interphase cancer cells using deep neural networks.** *Communications biology*
  Prasad, G., Rajkumar, U., Curtis, E. J., Wong, I. T., Yan, X., Zhang, S., Brückner, L., Turner, K., Wiese, J., Wahl, J., Hemmati, H., Wu, S., Theissen, et al
  2026
- **scAmp analyzes focal gene amplifications at single-cell resolution.** *bioRxiv : the preprint server for biology*
  Jones, M. G., Weiser, N. E., Hung, K. L., Yan, X., Agarwal, S., Luebeck, J., Gnanasekar, A., Howitt, B. E., Curtis, E. J., Yu, K., Rose, J. C., Kraft, K., Amiri, et al
  2026
- **Targeting extrachromosomal DNA in human cancers.** *Nature reviews. Drug discovery*
  Wong, I. T., Yi, H., Melillo, B., Cravatt, B. F., Chang, H. Y., Mischel, P. S.
  2026

- **EcDNA-borne structural variants drive oncogenic fusion transcript amplification.** *Cell*
  Yi, H., Zhang, S., Swinderman, J., Wang, Y., Kanakaveti, V., Hung, K. L., Tsz-Lo Wong, I., Srinivasan, S., Curtis, E. J., Bhargava-Shah, A., Li, R., Jones, M. G., Luebeck, et al
  2026
- **Innate immune sensing via the cGAS-STING pathway restricts extrachromosomal DNA-driven tumorigenesis.** *bioRxiv : the preprint server for biology*
  Li, T., Yang, Q. L., Qiao, K., Zhang, A., Sun, C., Huang, H., Mischel, P. S., Wu, S., Chen, Z. J.
  2026
- **Reconstructing the three-dimensional architecture of extrachromosomal DNA with ec3D.** *Nature communications*
  Chowdhury, B., Zhu, K., Li, C., Alsing, J., Luebeck, J., Stefanova, M. E., Chapman, O. S., Kraft, K., Zhang, S., Lim, J. Y., Xie, Y., Kim, Y. J., Wu, et al
  2025
- **Genetic elements promote retention of extrachromosomal DNA in cancer cells.** *Nature*
  Sankar, V., Hung, K. L., Gnanasekar, A., Wong, I. T., Shi, Q., Kraft, K., Jones, M. G., He, B. J., Yan, X., Belk, J. A., Liu, K. J., Agarwal, S., Wang, et al
  2025
- **Enhancer activation from transposable elements in extrachromosomal DNA.** *Nature cell biology*
  Kraft, K., Murphy, S. E., Jones, M. G., Shi, Q., Bhargava-Shah, A., Luong, C., Hung, K. L., He, B. J., Li, R., Park, S. K., Montgomery, M. T., Weiser, N. E., Wang, et al
  2025
- **Genetic elements promote retention of extrachromosomal DNA in cancer cells.** *bioRxiv : the preprint server for biology*
  Sankar, V., Hung, K. L., Gnanasekar, A., Tsz-Lo Wong, I., Shi, Q., Kraft, K., Jones, M. G., He, B. J., Yan, X., Belk, J. A., Liu, K. J., Agarwal, S., Wang, et al
  2025
- **Extrachromosomal DNA-Driven Oncogene Spatial Heterogeneity and Evolution in Glioblastoma.** *Cancer discovery*
  Noorani, I., Haughey, M., Luebeck, J., Rowan, A., Grönroos, E., Terenzi, F., Wong, I. T., Pradella, D., Lisi, M., Kittel, J., Sharma, N., Bailey, C., Weeden, et al
  2025: OF1-OF18
- **Applying multilevel selection to understand cancer evolution and progression.** *PLoS biology*
  Laplane, L., Lamoureux, A., Richker, H. I., Marquez Alcaraz, G., Fortunato, A., Shaffer, Z., Aktipis, A., Mischel, P. S., Plutynski, A., Townsend, J. P., Maley, C. C.
  2025; 23 (7): e3003290
- **Oxidative stress is a shared characteristic of ME/CFS and Long COVID.** *Proceedings of the National Academy of Sciences of the United States of America*
  Shankar, V., Wilhelmy, J., Curtis, E. J., Michael, B., Cervantes, L., Mallajosyula, V., Davis, R. W., Snyder, M., Younis, S., Robinson, W. H., Shankar, S., Mischel, P. S., Bonilla, et al
  2025; 122 (28): e2426564122
- **Extrachromosomal DNA: shaping the evolutionary dynamics of cancer.** *Trends in cancer*
  Haughey, M., Noorani, I., Swanton, C., Mischel, P. S., Werner, B.
  2025
- **Accurate Prediction of ecDNA in Interphase Cancer Cells using Deep Neural Networks.** *bioRxiv : the preprint server for biology*
  Rajkumar, U., Prasad, G., Curtis, E. J., Wong, I. T., Yan, X., Zhang, S., Brückner, L., Turner, K., Wiese, J., Wahl, J., Wu, S., Theissen, J., Fischer, et al
  2025
- **Spatial-Temporal Diversity of Extrachromosomal DNA Shapes Urothelial Carcinoma Evolution and the Tumor Immune Microenvironment.** *Cancer discovery*
  Lv, W., Zeng, Y., Li, C., Liang, Y., Tao, H., Zhu, Y., Sui, X., Li, Y., Jiang, S., Gao, Q., Rodriguez-Fos, E., Prasad, G., Wang, et al
  2025: OF1-OF22
- **A Guide to Extrachromosomal DNA: Cancer's Dynamic Circular Genome.** *Cancer discovery*
  Weiser, N. E., Watkins, T. B., Chang, H. Y., Mischel, P. S.
  2025: OF1-OF10

- **Unified molecular approach for spatial epigenome, transcriptome, and cell lineages.** *Proceedings of the National Academy of Sciences of the United States of America*
  Huang, Y. H., Belk, J. A., Zhang, R., Weiser, N. E., Chiang, Z., Jones, M. G., Mischel, P. S., Buenrostro, J. D., Chang, H. Y.
  2025; 122 (16): e2424070122
- **Oncogene Silencing via ecDNA Micronucleation.** *bioRxiv : the preprint server for biology*
  Brückner, L., Xu, R., Tang, J., Herrmann, A., Wong, I. T., Zhang, S., Tu, F., Pilon, M., Kukalev, A., Pardon, K., Sidorova, O., Atta, J., Yu, et al
  2025
- **Inhibition of human-HPV hybrid ecDNA enhancers reduces oncogene expression and tumor growth in oropharyngeal cancer.** *Nature communications*
  Nakagawa, T., Luebeck, J., Zhu, K., Lange, J. T., Sasik, R., Phillips, C., Sadat, S., Javadzadeh, S., Yang, Q., Monther, A., Fassardi, S., Wang, A., Pestonjamasp, et al
  2025; 16 (1): 2964
- **Breakage fusion bridge cycles drive high oncogene number with moderate intratumoural heterogeneity.** *Nature communications*
  Raeisi Dehkordi, S., Wong, I. T., Ni, J., Luebeck, J., Zhu, K., Prasad, G., Krockenberger, L., Xu, G., Chowdhury, B., Rajkumar, U., Caplin, A., Muliaditan, D., Gnanasekar, et al
  2025; 16 (1): 1497
- **Coupling antigens from multiple subtypes of influenza can broaden antibody and T cell responses.** *Science (New York, N.Y.)*
  Mallajosyula, V., Chakraborty, S., Sola, E., Fong, R. F., Shankar, V., Gao, F., Burrell, A. R., Gupta, N., Wagar, L. E., Mischel, P. S., Capasso, R., Staat, M. A., Chien, et al
  2024; 386 (6728): 1389-1395
- **Engineered extrachromosomal oncogene amplifications promote tumorigenesis.** *Nature*
  Pradella, D., Zhang, M., Gao, R., Yao, M. A., Gluchowska, K. M., Cendon-Florez, Y., Mishra, T., La Rocca, G., Weigl, M., Jiao, Z., Nguyen, H. H., Lisi, M., Ozimek, et al
  2024
- **Enhancing transcription-replication conflict targets ecDNA-positive cancers.** *Nature*
  Tang, J., Weiser, N. E., Wang, G., Chowdhry, S., Curtis, E. J., Zhao, Y., Wong, I. T., Marinov, G. K., Li, R., Hanoian, P., Tse, E., Mojica, S. G., Hansen, et al
  2024; 635 (8037): 210-218
- **Coordinated inheritance of extrachromosomal DNAs in cancer cells.** *Nature*
  Hung, K. L., Jones, M. G., Wong, I. T., Curtis, E. J., Lange, J. T., He, B. J., Luebeck, J., Schmargon, R., Scanu, E., Bruckner, L., Yan, X., Li, R., Gnanasekar, et al
  2024; 635 (8037): 201-209
- **Origins and impact of extrachromosomal DNA.** *Nature*
  Bailey, C., Pich, O., Thol, K., Watkins, T. B., Luebeck, J., Rowan, A., Stavrou, G., Weiser, N. E., Dameracharla, B., Bentham, R., Lu, W., Kittel, J., Yang, et al
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- **Disparate pathways for extrachromosomal DNA biogenesis and genomic DNA repair.** *Cancer discovery*
  Rose, J. C., Belk, J. A., Wong, I. T., Luebeck, J., Horn, H. T., Daniel, B., Jones, M. G., Yost, K. E., Hung, K. L., Kolahi, K. S., Curtis, E. J., Kuo, C. J., Bafna, et al
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- **Contribution of human-viral hybrid ecDNA accumulation to the cancer life cycle and potential for novel targeted therapy**
  Nakagawa, T., Luebeck, J., Lange, J., Zhu, K., Phillips, C., Mischel, P., Bafna, V., Califano, J.
  WILEY.2024: 490
- **Extrachromosomal DNA in cancer.** *Nature reviews. Cancer*
  Yan, X., Mischel, P., Chang, H.
  2024
- **Extrachromosomal DNA: Biogenesis and Functions in Cancer** *ANNUAL REVIEW OF CANCER BIOLOGY*
  Curtis, E. J., Rose, J. C., Mischel, P. S., Chang, H. Y.
  2024; 8: 135-153

- **Circular extrachromosomal DNA promotes tumor heterogeneity in high-risk medulloblastoma.** *Nature genetics*
  Chapman, O. S., Luebeck, J., Sridhar, S., Wong, I. T., Dixit, D., Wang, S., Prasad, G., Rajkumar, U., Pagadala, M. S., Larson, J. D., He, B. J., Hung, K. L., Lange, et al
  2023
- **Extrachromosomal DNA in the cancerous transformation of Barrett's oesophagus.** *Nature*
  Luebeck, J., Ng, A. W., Galipeau, P. C., Li, X., Sanchez, C. A., Katz-Summercorn, A. C., Kim, H., Jammula, S., He, Y., Lippman, S. M., Verhaak, R. G., Maley, C. C., Alexandrov, et al
  2023
- **Targeted profiling of human extrachromosomal DNA by CRISPR-CATCH.** *Nature genetics*
  Hung, K. L., Luebeck, J., Dehkordi, S. R., Colon, C. I., Li, R., Wong, I. T., Coruh, C., Dharanipragada, P., Lomeli, S. H., Weiser, N. E., Moriceau, G., Zhang, X., Bailey, et al
  2022
- **Deciphering the evolutionary dynamics of extrachromosomal DNA in human cancer** *NATURE GENETICS*
  Lange, J. T., Mischel, P. S.
  2022
- **Leveraging extrachromosomal DNA to fine-tune trials of targeted therapy for glioblastoma: opportunities and challenges.** *Nature reviews. Clinical oncology*
  Noorani, I., Mischel, P. S., Swanton, C.
  2022
- **The evolutionary dynamics of extrachromosomal DNA in human cancers.** *Nature genetics*
  Lange, J. T., Rose, J. C., Chen, C. Y., Pichugin, Y., Xie, L., Tang, J., Hung, K. L., Yost, K. E., Shi, Q., Erb, M. L., Rajkumar, U., Wu, S., Taschner-Mandl, et al
  2022
- **Gene regulation on extrachromosomal DNA.** *Nature structural & molecular biology*
  Hung, K. L., Mischel, P. S., Chang, H. Y.
  2022
- **Mapping clustered mutations in cancer reveals APOBEC3 mutagenesis of ecDNA.** *Nature*
  Bergstrom, E. N., Luebeck, J., Petljak, M., Khandekar, A., Barnes, M., Zhang, T., Steele, C. D., Pillay, N., Landi, M. T., Bafna, V., Mischel, P. S., Harris, R. S., Alexandrov, et al
  2022
- **ecDNA hubs drive cooperative intermolecular oncogene expression.** *Nature*
  Hung, K. L., Yost, K. E., Xie, L., Shi, Q., Helmsauer, K., Luebeck, J., Schopflin, R., Lange, J. T., Chamorro Gonzalez, R., Weiser, N. E., Chen, C., Valieva, M. E., Wong, et al
  2021
- **Extrachromosomal DNA: An Emerging Hallmark in Human Cancer.** *Annual review of pathology*
  Wu, S., Bafna, V., Chang, H. Y., Mischel, P. S.
  2021
- **Targeting glioblastoma signaling and metabolism with a re-purposed brain-penetrant drug.** *Cell reports*
  Bi, J., Khan, A., Tang, J., Armando, A. M., Wu, S., Zhang, W., Gimple, R. C., Reed, A., Jing, H., Koga, T., Wong, I. T., Gu, Y., Miki, et al
  2021; 37 (5): 109957
- **Altered cellular metabolism in gliomas - an emerging landscape of actionable co-dependency targets.** *Nature reviews. Cancer*
  Bi, J., Chowdhry, S., Wu, S., Zhang, W., Masui, K., Mischel, P. S.
  2020; 20 (1): 57-70
- **Circular ecDNA promotes accessible chromatin and high oncogene expression.** *Nature*
  Wu, S., Turner, K. M., Nguyen, N., Raviram, R., Erb, M., Santini, J., Luebeck, J., Rajkumar, U., Diao, Y., Li, B., Zhang, W., Jameson, N., Corces, et al
  2019
- **Oncogene Amplification in Growth Factor Signaling Pathways Renders Cancers Dependent on Membrane Lipid Remodeling.** *Cell metabolism*

Bi, J., Ichu, T., Zanca, C., Yang, H., Zhang, W., Gu, Y., Chowdhry, S., Reed, A., Ikegami, S., Turner, K. M., Zhang, W., Villa, G. R., Wu, et al
2019

- **NAD metabolic dependency in cancer is shaped by gene amplification and enhancer remodelling.** *Nature*
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  2019; 569 (7757): 570-575
- **Extrachromosomal oncogene amplification in tumour pathogenesis and evolution.** *Nature reviews. Cancer*
  Verhaak, R. G., Bafna, V., Mischel, P. S.
  2019; 19 (5): 283-288
- **Extrachromosomal oncogene amplification drives tumour evolution and genetic heterogeneity** *NATURE*
  Turner, K. M., Deshpande, V., Beyter, D., Koga, T., Rusert, J., Lee, C., Li, B., Arden, K., Ren, B., Nathanson, D. A., Kornblum, H. I., Taylor, M. D., Kaushal, et al
  2017; 543 (7643): 122-+
- **Targeted therapy resistance mediated by dynamic regulation of extrachromosomal mutant EGFR DNA.** *Science (New York, N.Y.)*
  Nathanson, D. A., Gini, B., Mottahedeh, J., Visnyei, K., Koga, T., Gomez, G., Eskin, A., Hwang, K., Wang, J., Masui, K., Paucar, A., Yang, H., Ohashi, et al
  2014; 343 (6166): 72-6

PRESENTATIONS

- Location, location, location— the role of extrachromosomal DNA (ecDNA) in cancer - Department of Pathology, Stanford University School of Medicine (April 27, 2021)