BIOGRAPHICAL SKETCH

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NAME: Cheng Keith C.

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

POSITION TITLE: 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
Harvard University, Cambridge, MA	B.A.	06/1976	Biochemical Sciences
New York University School of Medicine, NYC	M.D.	05/1980	Medicine
Brigham & Women's Hospital, Boston, MA	Residency	06/1981	Anatomic Pathology
University of Washington Hospitals, Seattle, WA	Residency	03/1988	Anatomic Pathology
Fred Hutchinson Cancer Research Center & University of Washington, Seattle, WA	Ph.D.	09/1987	Genetic Recombination
University of Washington, Seattle, WA	Sr. Fellow	03/1992	Mechanisms of Mutation

A. Personal Statement

My background in biochemistry, the molecular genetics of recombination and DNA repair, anatomic pathology, virology, and the genetics of cancer led to a desire to understand the molecular and cellular mechanisms that underlie cancer progression and complex traits. My work in pathology led to an understanding of the cellular and tissue architectural characteristics of cancer and other diseases. Among our projects was the application of histopathology to the then semi-quantitative analysis of mutant phenotypes across cell types and organ systems, to inform us about all the functions of each gene – to use histology in forward and reverse genetic screens in zebrafish. What began as a frustration with the impracticality of 2D histopathology for rapid organismal phenotyping led to the exciting realization that we could make histopathology complete for all tissues in whole model organisms if we could image their entire volumes at submicron resolutions across all cell types, as we do in histology today.

Micron-scale computerized tomography (microCT) was a theoretical possibility, but all instances of commercial and synchrotron microCT utilized commercial microscope lenses whose specifications make it impossible to reach the necessary combination of centimeter field of view AND submicron voxel resolution. Breaking this barrier would require the design and creation of large-field, high-NA optics similar to that used in photolithography (used in the manufacture of computer chips) so that we could scan 5-10 mm wide fixed and metal-stained biological samples such as juvenile and adult zebrafish and mammalian tissue samples. The large image files required massive computer power to process, visualize, and analyze, initially using large local workstations, now shifting towards high-performance computing. A Penn State working group has been working towards a computational, distributional phenomics, whose goal is to bring quantitative, and statistical rigor to tissue analysis. As a start, we have now used supervised machine learning and modeling to measure the geometric features of virtually every blood cell in whole zebrafish larvae. Given that cells and nuclei can be considered 3D derivatives of spheres, we are collectively working towards defining all of the finite number of cell types in all of nature in health and disease. We have called this idea, which includes *whole-organism* histopathological phenotyping, *Geometry of Life and Disease.* My present passion is to create a firm foundation for democratizing the use of histotomography globally. The anticipated computational phenomics will facilitate an integrated understanding of how genes, epigenetics, environment and disease define organismal phenotype – leading to greater human and environmental health.

My exploratory, collaborative and interdisciplinary bent is reflected by our: 1) Deciphering of the history of the evolution of human skin color that includes our discovery of a key contributor to the lighter skin color of Europeans (Lamason et al. 2005), 2) a decade's effort to define the key genetic determinants of East Asian and Native American skin color, 3) Conceptualizing, planning, and creating a web-based atlas of microanatomy (bio-

atlas.psu.edu), 4) Organizing and completing a new NIH/Penn State funded Zebrafish Functional Genomics Core, 5) Creating a microCT-based, pan-cellular, 3D, imaging tool for whole, optically opaque vertebrate animals that allows 3D histopathology, X-ray histotomography at Argonne National Laboratory and Lawrence Berkeley National Laboratory, and 6) establishing a Penn State Computational Organismal and Tissue Phenomics initiative, now computational phenomics, or *Geometry of Life and Disease*, being applied across biomedical sciences and science education. Our interdisciplinary research environment, reflected by our recent publications, is well-suited for students learning how to pursue multidisciplinary projects.

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

DOE ALS-11657
Cheng (PI)
10/15/22 - 9/30/25 (approximate)
Exploring applications of novel, wide-field, submicron resolution lens and camera systems for microCT (towards defining the Geometry of Life)

2R24OD018559
Cheng (PI)
08/15/19 – 07/31/24 (NCE)
Groundwork for a Synchrotron MicroCT Imaging Resource for Biology (SMIRB)

1R01NS108407
Kim (PI)
09/1/18 – 05/31/23
Architecture of the Neurovascular Unit and Its Function in the Whole Mouse Brain

1R01MH116176
Kim (PI)
06/1/18 – 02/28/23
Brain-Wide Input and Output Wiring Diagram of Oxytocin Neurons and Its Function in Claustrum-Endopiriform Complex

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2019-present	Director, Penn State Computational Phenomics and Geometry of Life and Disease (GOLD) Initiatives
2008-2018	Director, Division of Experimental Pathology, Pennsylvania State University College of Medicine
2007-present	Professor, Departments of Pathology and Biochemistry & Molecular Biology, Pennsylvania State University College of Medicine
1998-2007	Associate Professor; Professor, Departments of Pathology and Biochemistry & Molecular Biology, Pennsylvania State University College of Medicine
1992-1998	Assistant Professor; Professor, Departments of Pathology and Biochemistry & Molecular Biology, Pennsylvania State University College of Medicine

Other Experience, Professional Memberships and Honors

2021-2022	Penn State Institute for Computational and Data Science (ICDS) Faculty Scholar Award
2020-2022	Penn State Institute for Computational and Data Science (ICDS) Faculty Advisory Council
2020-2021	Co-Chair, NIH ORIP Validation of Animal Models Workshop Committee
2020	AAAS Fellow, Medical Sciences
2019-present	Member, PSU Research Computing and Cyberinfrastructure (RCCI) executive committee
2018-present	Member, Penn State Research Computing and Cyberinfrastructure (RCCI)/ Group Leader for Cognitive and Immersive Technologies/Emerging and Evolving Technologies
2012-present	Member, Penn State Institute for Personalized Medicine
2010-2012	Member, NCRR Linking Animal Models of Human Disease (LAMHDI) Project Team
2009-present	Research Computing Advisory Group, PSCOM
2005-2015	Founding Co-Director, Penn State IBIOS Intercollege program in Bioinformatics and Genomics
2004-present	Founding Curator of the Zebrafish Atlas of Microanatomy, renamed bio-atlas in 2016 2005 FASEB Symposium Chair: Systems Morphogenetics: Biological Context for the Genome Project

2004-present	Editorial Board, *Zebrafish*
2004-2005	Co-director, Cross-campus Biology of Neoplasia Course at Pennsylvania State University
2003	Penn State Symposium organizer: Genetic and Functional Genomics Approaches in Model Organisms
1998-2000	Chair, Genetics and Functional Genomics Strategic Planning Committee, PSCOM
1992-present	Graduate faculty appointments in Biochemistry & Molecular Biology, Cell & Molecular Biology, and Intercollege Genetics, Biomedical Sciences (BMS) graduate programs
1992-present	Ad hoc reviewer for NSF, *Carcinogenesis*, *Cancer Research, Biotechniques, Genetics, Science, Genes & Development, Nature, Nature Communications, PLoS Genetics, PLoS Biology*

C. Contributions to Science

Hotspots of Homologous Recombination. As a graduate student in the laboratory of Gerald Smith (Fred Hutchinson Cancer Research Institute), I worked on Chi hotspots of recombination defined by the sequence 5'GCTGGTGG3. We were the first to establish a range of genetic hotspot activity associated with sequences similar to Chi in bacteriophage lambda, and to then show that their degree of genetic activity was determined by the degree of single stranded DNA cleavage induced by *E. coli*'s RecBCD enzyme. To test the predictions of models of recombination induced by Chi hotspots, I used a series of clear-plaque mutations to map the distribution of heteroduplex DNA in the region of Chi on phage lambda that were preserved using a mismatch-correction-deficient background.

- **Cheng KC** and Smith GR (1984) Recombinational hotspot activity of Chi-like sequences. *J. Mol. Biol.* 180:371-377. PMID: 6239928.
- **Cheng KC** and Smith GR (1987) Cutting of Chi-like sequences by RecBCD enzyme. *J. Mol. Biol.* 194:747-750. PMID: 2958631.
- **Cheng KC** and Smith GR (1989) Distribution of Chi-stimulated recombinational exchanges and heteroduplex endpoints in phage lambda. *Genetics* 123:5-17 (cover article) PMID: 2530132. PMCID: PMC1203790.

Oxidative DNA damage. As a Damon-Runyon fellow in the laboratory of Larry Loeb (U Wash), I established the mutagenic spectrum of the chemical carcinogen vinyl chloride, and of one of the most important mutagenic intermediates of oxidative DNA damage, which is a byproduct of oxidative metabolism and inflammation leading to formation of the 8-hydroxy (aka 8-oxo) derivative of guanine. We performed a comprehensive in vivo assessment of the mutagenic spectrum of this moiety both as template and substrate. We established mechanisms by which 8-hydroxyG can cause either of two types of mutation, (GC -> TA or AT -> CG) by mispairing with A, depending upon its presence in template vs. substrate. This work I believe constitutes the first detailed description of how a single DNA base modification can cause two types of mutation.

- **Cheng KC** et al. 1991, The vinyl chloride DNA derivative, $N^{2,3}$-ethenoguanine, causes G to A transitions in *E. coli*, *Proc. Natl. Acad. Sci., U.S.A.* 88:9974-9978. PMCID: PMC52849.
- **Cheng KC** et al. 1992, 8-Hydroxyguanine, an abundant form of oxidative DNA damage, causes G to T and A to C substitutions, *J Biol Chem.* 267:166-172. PMID: 1730583; *2335 Google Scholar citations*.

Zebrafish as a disease model. My lab's first projects included two of the first genetic screens in zebrafish for cancer phenotypes: a somatic mutator screen (Moore et al.2006), and the first histological screen for genes involved in nuclear atypia, a key histological feature of cancer (Mohideen et al 2003). We also established tools for large-scale histological screening of zebrafish larvae (Tsao-Wu et al 1998; Moore et al 2002) and participated in the Zebrafish Encode Project (Yang et al. 2020).

- Moore JL, Rush LM, Breneman C, Mohideen MA, **Cheng KC** (2006) Zebrafish genomic instability mutants and dominant cancer susceptibility. *Genetics*. 174(2):585-600. PMID: 11848405 PMCID: PMC1602069. cover article.
- Mohideen MA, Beckwith LG, Tsao-Wu GS, Moore JL, Wong AC, Chinoy MR, **Cheng KC** (2003) Histology-based screen for zebrafish mutants with abnormal cell differentiation. *Dev Dyn.* 228(3): 414-23. PMID: 14579380. First genetic screen in a vertebrate based on histology.
- Lin AY, Ding Y, Vanselow DJ, Katz SR, Yakovlev MA, Clark DP, Mandrell D, Copper JE, van Rossum DB, **Cheng KC** (2018). Rigid Embedding of Fixed and Stained, Whole, Millimeter-Scale Specimens for Section-free 3D Histology by Micro-Computed Tomography. *J Vis Exp* Oct 17;(140). PMID: 30394379 PMCID: PMC6235553.
- Yang H, Luan Y, Liu T, Lee HJ, Fang L, Wang Y, Wang X, Zhang B, Jin Q, Ang KC, Xing X, Wang J, Xu J, Song F, Sriranga I, Salameh T , Li D, Choudhary MNK, Topczewski J, Wang K, Gerhard GS, Hardison

RC, Wang T, **Cheng KC**, Yue F (2020) A map of cis-regulatory elements and 3D genome structures in zebrafish. *Nature*, i588:337-343. PMID: 33239788. PMCID: PMC8183574 ["Zebrafish Encode Project"]

Skin color and Personalized Medicine. We discovered what appears to be the central determinant of of the lighter skin phenotype of people of European ancestry: the *A111T* allele of *SLC24A5*. The lighter color of a zebrafish pigment variant was associated with a decrease in the number, size, and pigmentation of the melanosomes. That these features also characterize European skin suggested to me that a polymorphism in the variant gene in zebrafish, *slc24a5*, could play a role in human pigmentation. This suspicion led to the corresponding realization that a coding polymorphism in the orthologous human *SLC24A5* gene is homozygous in every European (CEU) individual in the then-new HapMap database of human polymorphisms. The human gene rescued the zebrafish *golden* phenotype, and African/European admixed individuals are generally lighter in the presence of the mutation (see cover article in *Science* (Lamason et al. 2005). Related work includes the first chapter of scientific considerations of race and skin color, the identification of the zebrafish *albino* gene as *slc45a2*, a known albinism gene in humans, and published in the context of a whole-animal assay for assessing phenotypes caused by human coding polymorphisms (Tsetskhladze ZR et al., 2012 in *PLoS One* 7(10): e47398 10.1371/journal.pone.0047398). Our haplotype analysis of the genomic region surrounding *SLC24A5* in global human populations supports our hypothesis that natural selection for the A111T mutation occurred once in human history in the middle east, potentially around the time of the last glacial maximum about 15,000 years ago (Canfield et al. 2013). We have since been probing the genetic origin of light skin in East Asians and Amerindians.

- Lamason RL et al and **Cheng KC** (2005) SLC24A5, a putative cation exchanger, affects pigmentation in zebrafish and humans, *Science* 310:1782-1786 PubMed PMID: 16357253. (1201 Google Scholar citations)
- Tsetskhladze ZR, et al, Kawakami K, **Cheng KC** (2012) Functional assessment of human coding mutations affecting skin pigmentation using zebrafish. *PLoS One* 7(10): e47398 10.1371/journal.pone.0047398. PMID: 23071798 PMCID: PMC3468441.
- Canfield VA, et al, Oppenheimer S, **Cheng KC** (2013) Molecular phylogeography of a human autosomal skin color locus under natural selection, *G3* 3(11): 2059-2067. doi: 10.1534/g3.113.007484. PMID: 24048645 PMCID: PMC3815065.
- Ang KC,et al., **Cheng KC** (2023) Native American genetic ancestry and pigmentation allele contributions to skin color in a Caribbean population. *eLife 12*, e77514. PMID: 37294081. PMCID: PMC10371226.

Phenomics. Our contributions to phenomics began with the idea of analyzing histological images (Canada et al. 2006, 2007, 2008a, 2008b, 2011). Histology, while a powerful tool, has significant limitations: two-dimensional assessments of 3D tissue architecture, and limited sampling. Our current dream is to automate whole-body tissue phenotyping for every cell type and tissue to study the function of every protein-encoding gene in the vertebrate genome, and to assess the phenotypic impact of >100,000 chemicals to which we are potentially exposed during the manufacture of drugs and materials. These issues are covered by a new, evolving field, phenomics (see Cheng KC et al., 2011, 2012, 2016). We have used a systems approach towards creating infrastructure for scientists to study every cell of an entire specimen in 3 dimensions, cutting by computer in any direction, allowing analysis of specific cell types, and enabling quantitative volumetric and pattern analysis. This new imaging method is based on microCT, more specifically X-ray tomographic reconstruction of fixed and stained tissues, utilizing both the monochromatic and parallel beam geometry of the x-rays at the Advanced Photon Source at Argonne National Laboratory based on optimizations (Ding et al. 2018, 2019) and Lawrence Berkeley Laboratory. We are beginning to integrate spatial -omic studies into our development of Computational Phenomics (Van Nuffel et al. 2020 PMID: 33112610).

- **Cheng KC**, Xin X, Clark DP, and La Riviere PJ (2011) Whole-animal imaging, gene function, and the Zebrafish Phenome Project. *Current Opinion in Genetics & Development* 2011, 21:620–629. PMID: 21963132 PMCID: PMC3413372.
- **Cheng KC**, Katz SR, Lin AY, Xin X, and Ding Y (2016) Chapter Four, Whole-Organism Cellular Pathology: A Systems Approach to Phenomics. *Advances in Genetics* 95:89-115. PMID 27503355 PMCID 6592046.
- Yakovlev MA, Vanselow DJ, Ngu MS, Zaino CR, Katz SR, Ding Y, Parkinson D, Wang SY, Ang KC, La Riviere P and **Cheng KC** (2022) A wide-field micro-computed tomography detector: Micron resolution at half-centimetre scale. *J. Synchrotron Rad.* 29, doi.org/10.1107/S160057752101287X.
- **Cheng, KC,** Burdine RD, Dickinson ME, Ekker SC, Lin AY, Lloyd KCK, Lutz CM, MacRae CA, Morrison JH, O'Connor DH, Postlethwait JH, Rogers CD, Sanchez S, Simpson JH, Talbot WS, Wallace DC, Weimer JM, Bellen HJ. (2022) Promoting validation and cross-phylogenetic integration in model organism

research. *Dis Model Mech.* Sep 1;15(9): dmm049600. doi: 10.1242/dmm.049600. Epub 2022 Sep 20. PMID: 36125045. Special article.

Other Publications:
http://www.ncbi.nlm.nih.gov/sites/myncbi/keith.cheng.1/bibliography/40809552/public/?sort=date&direction=ascending