BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Gilbert Chu

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

POSITION TITLE: Professor of Medicine and Biochemistry

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
Princeton University, Princeton, NJ	A.B.	06/1967	Physics
M.I.T. (with Francis Low)	Ph.D.	01/1973	Physics
Lawrence Berkeley Laboratory	Postdoctoral	06/1975	Theoretical Physics
Stanford Linear Accelerator Center	Postdoctoral	06/1976	Theoretical Physics
Harvard Medical School	M.D.	06/1980	Medicine
Massachusetts General Hospital	Residency	06/1982	Internal Medicine
Stanford School of Medicine	Fellowship	06/1985	Medical Oncology
Stanford School of Medicine (with Paul Berg)	Postdoctoral	12/1986	Biochemistry

A. Personal Statement

In studying the repair of DNA damaged by ultraviolet radiation, we discovered that XP complementation group E cells lack UV-damaged DNA binding protein (UV-DDB). We showed that a subunit of UV-DDB (p48) is mutated in XP group E cells, and that UV-DDB initiates nucleotide excision repair across the genome.

In studying the repair of DNA double-strand breaks, we discovered that Ku initiates repair by non-homologous end joining, which repairs breaks induced by ionizing radiation and V(D)J recombination, the pathway that generates immunological diversity. We showed that XLF forms a protein-DNA filament with XRCC4 to promote the ligation of DNA ends, including ends with mismatched non-cohesive DNA overhangs.

In studying cognitive impairment from chemotherapy, we discovered that 5-fluorouracil induces hyperammonemia in patients with otherwise occult urea cycle dysfunction. To permit point-of-care diagnosis, we invented a device that measures blood ammonia from a finger, earlobe, or heel stick.

B. Positions and Honors

Positions

1987-94 Assistant Professor of Medicine, Stanford University, Stanford, CA
1994-02 Associate Professor, Departments of Medicine & Biochemistry, Stanford University, Stanford, CA
2002- Professor, Departments of Medicine & Biochemistry, Stanford University, Stanford, CA

Honors and Achievements

1967 Phi Beta Kappa, Princeton; Magna cum laude, Princeton Physics Department
1967-68 Woodrow Wilson Fellow
1973 Giulio Racah Prize, International School of Subnuclear Physics, Erice, Italy
1980 Magna cum laude, Henry Asbury Christian Award, Harvard Medical School

1983 American Board of Internal Medicine, board certification
1984-86 Jane Coffin Childs Fellow, Department of Biochemistry, Stanford University
1988-93 Rita Allen Foundation Scholar
1998-03 Burroughs-Wellcome Clinical Scientist Award for Translational Research
2003 Kaiser Award for Excellence in Preclinical Teaching, Stanford School of Medicine
2007 Kaiser Award for Excellence in Preclinical Teaching, Stanford School of Medicine
2014 Lawrence H. Mathers Award for Exceptional Commitment to Teaching and Active Involvement in Medical Student Education, Stanford School of Medicine
2015 Kaiser Award for Excellence in Preclinical Teaching, Stanford School of Medicine
2018 Stanford Asian American Community Faculty Award
2018 Fellow of the American Physical Society (election from Division of Biological Physics) for contributions at the intersection of physics and life sciences

Federal Government Service

1996-97 U.S. Army Breast Cancer Research Program Molecular Biology Review Panel
1997-06 Lawrence Livermore Laboratory, Biology and Biotechnology Advisory Committee
2000 National Cancer Institute site visit committee to Laboratory of Molecular Pharmacology
2007 Lawrence Livermore Laboratory, Chemical, Material & Life Sciences Directorate Review Committee

C. Contributions to Science

1. Invention of a pulsed field electrophoresis device for resolving very large DNA molecules

Pulsed field electrophoresis extended the resolution limit for DNA molecules 1000-fold, from 10 kilobases to 10 megabases. However, early devices suffered from two problems: they either generated curved trajectories for the DNA molecules; or produced co-migration of the largest and smallest DNA molecules. To solve both problems, I invented a device by generating a contour-clamped homogeneous electric field (CHEF) that resolved DNA according to size in recti-linear trajectories. CHEF was used for mapping and cloning many genes of medical importance, as evidenced by 1500 literature citations.

a. **Chu G,** Vollrath D, Davis RW: Separation of large DNA molecules by contour-clamped homogeneous electric fields. Science 234: 1582-1585, l986.
b. Gunderson K, **Chu G**: Pulsed-field electrophoresis of megabase-sized DNA. Mol Cell Biol 11: 3348-3354, 1991.
c. **Chu G**: Bag model for DNA migrating in a pulsed electric field. Proc Natl Acad Sci USA 88: 11071-11075, 1991.
d. PATENT: Electrophoresis using contour-clamped electric fields (Pat. No. 5,165,898) **G Chu**, D Vollrath, R Davis, 1992.

2. Discovery of human proteins that recognize DNA lesions for nucleotide excision repair

Xeroderma pigmentosum (XP) is a rare disease with extreme risk for skin cancer due to defective repair of ultraviolet radiation-damaged DNA. To identify the first protein defect in XP, I invented a new electrophoretic mobility shift assay (EMSA) for proteins that bind to DNA *lesions*. (EMSAs were previously used for proteins that bind to specific DNA *sequences*.) I discovered that XP complementation group E cells lacked UV-damaged DNA binding protein (UV-DDB). My lab then showed that a UV-DDB subunit (p48) is mutated in XP group E cells, and that UV-DDB initiates global genomic repair.

a. **Chu G,** Chang E: Xeroderma pigmentosum group E cells lack a nuclear factor that binds to damaged DNA. Science 242: 564-567, 1988.
b. Hwang BJ, Toering S, Francke U, **Chu G**: p48 activates UV-damaged DNA binding factor and is mutated in xeroderma pigmentosum group E. Mol Cell Biol 18: 4391-4399, 1998.
c. Hwang BJ, Ford J, Hanawalt PC, **Chu G**: Expression of the p48 xeroderma pigmentosum gene is p53-dependent and is involved in global genomic repair. Proc Natl Acad Sci USA 96: 424-428, 1999.
d. Tang J, Hwang BJ, Ford JM, Hanawalt PC, **Chu G**: Xeroderma pigmentosum p48 gene enhances global genomic repair and suppresses UV-induced mutagenesis. Molecular Cell 5: 737-744, 2000.

3. Discovery of human proteins that recognize DNA double-strand breaks for non-homologous end joining

   My laboratory extended EMSAs to a search for proteins that bind specifically to DNA ends, and discovered that the Ku protein is missing in mutant cells hypersensitive to ionizing radiation and defective in V(D)J recombination. Significantly, V(D)J recombination is the pathway that generates immunological diversity for T and B cells. We then showed that the Ku-associated protein DNA-dependent protein kinase is facilitates synapsis of DNA ends, and that XLF forms a protein-DNA filament with XRCC4 to promote the ligation of DNA ends, including ends with mismatched non-cohesive DNA overhangs.
   a. Smider V, Rathmell WK, Lieber M, **Chu G**: Restoration of X-ray resistance and V(D)J recombination in mutant cells by Ku cDNA. Science 266: 288-291, 1994.
   b. DeFazio L, Stansel R, Griffith J, **Chu G**: Synapsis of DNA ends by the DNA-dependent protein kinase. EMBO J 21: 3192-3200, 2002.
   c. Tsai C, Kim S, **Chu G**: Cernunnos/XLF promotes ligation of mismatched and non-cohesive DNA ends. Proc Natl Acad Sci USA 104: 7851-7856, 2007.
   d. Tsai C, **Chu G**: Cooperative assembly of a protein-DNA filament for nonhomologous end joining. J Biol Chem 288: 18110-20, 2013.

4. Invention of a method to analyze genomic data

   Technology for measuring gene expression across the entire human genome led to a biomedical revolution. However, analyses of data from early experiments were compromised by the absence of a reliable method for identifying valid differences in gene expression. My laboratory helped pioneer methods for analyzing the data, including Significance Analysis of Microarrays (SAM) and Prediction Analysis of Microarrays (PAM). SAM and PAM have been used by investigators in all fields of biomedical research, as evidenced by 10,700 and 2200 citations, respectively, for the first two papers below.
   a. Tusher V, Tibshirani R, **Chu G**: Significance analysis of microarrays applied to the ionizing radiation response. Proc Natl Acad Sci USA 98: 5116-5121, 2001.
   b. Tibshirani R, Hastie T, Narasimhan B, **Chu G**: Diagnosis of multiple cancer types by shrunken centroids of gene expression. Proc Natl Acad Sci USA 99: 6567-6572, 2002.
   c. Rieger K, **Chu G**: Portrait of transcriptional responses to ultraviolet and ionizing radiation in human cells. Nuc Acids Res 32: 4786-4803, 2004.
   d. Hong WJ, Tibshirani R, **Chu G**: Local false discovery rate facilitates comparison of different microarray experiments. Nuc Acids Res 37: 7483-7497, 2009.

5. Invention of methods with clinical applications

   My physics and biochemistry training led to methods with clinical applications. I developed the first mathematical algorithm for reconstructing a 3-dimensional distribution of positron emissions, for what is now known as PET scanning. We developed an algorithm for identifying cancer patients at risk for suffering toxicity from radiation therapy. The 2013 patent application provides a genomic method assessing the risk of 5-fluorouracil-induced hyperammonemia and encephalopathy ("chemobrain"). The 2014 patent describes the detection of ammonia from small blood volumes.
   a. **Chu G**, Tam K: Three-dimensional imaging in the positron camera using Fourier techniques. Phys Med Biol 22: 245-265, l977.
   b. Rieger K, Hong WJ, Tusher VG, Tang J, Tibshirani R, **Chu G**: Toxicity from radiation therapy associated with abnormal transcriptional responses to DNA damage. Proc Natl Acad Sci USA 101: 6635-6640, 2004.
   c. PATENT: Assessing risk for encephalopathy induced by 5-fluorouracil or capecitabine (2013, Provisional application) **G Chu**
   d. PATENT: Rapid small volume detection of blood ammonia (2015, Pat. No. 9,625,443) T Veltman, C Tsai, M Kanan, **G Chu**

Published Work listed in PubMed
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41156663/?sort=date&direction=descending

Additional published work in physics, biophysics and statistics are included in a comprehensive user profile for "Gilbert Chu" in Google Scholar, which reports an h-index of 54 and an i10-index of 76.

D. Additional Information: Research Support and/or Scholastic Performance

Patents

Electrophoresis using contour-clamped electric fields (Pat. No. 5,165,898) **G Chu**, D Vollrath, R Davis
Significance analysis of microarrays (Pat. No. 7,363,165) **G Chu**, R Tibshirani, V Tusher
Cancer prevention and treatment by transcriptional profiling (Pat. No. 7,465,542) **G Chu**, V Tusher, J Tang
Mismatched end DNA ligase (Pat. No. 8,263,332) **G Chu**, C Tsai, S Kim
Assessing risk for encephalopathy induced by 5-fluorouracil or capecitabine (Provisional application) **G Chu**
Rapid small volume detection of blood ammonia (Pat. No. 9,625,443) T Veltman, C Tsai, M Kanan, **G Chu**

Research Support

Targeting HIF-1 Alpha dysfunction in complications of aging
NIH 2R01AG025016-06A2 G. Gurtner (PI) 05/15/11–03/31/16
This proposal aims to precisely define the causative mechanisms underlying HIF-1a dysfunction in hypoxic tissue, determine the role of increased oxidative stress in age-related dysfunctional vasculogenesis, and refine a therapeutic strategy to restore normal neovascularization to aged patients.
Role: Co-investigator

Osteogenic enrichment of adipose derived stromal cells
NIH R01 DE021683 M. Longaker (PI) 10/01/12–09/30/17
This aims to define human adipose stem cell (hASC) heterogeneity by single cell transcriptional analysis; enrich for hASC subpopulations with highly osteogenic transcriptional profiles by cell sorting; and elucidate the cell biology of hASCs sorted on specific cell surface receptors and analyze their osteogenic potential in vivo.
Role: Co-investigator

Rapid small volume detection of blood ammonia
Stanford Innovation Project G. Chu (PI) 11/01/13-07/31/16
This project aims to develop a device for measuring blood ammonia in 100 µL blood samples, and test the device in a clinical trial to show correlation with the standard laboratory test. Funding was insufficient for development of a prototype for measuring blood ammonia from a finger stick.

A device that measures blood ammonia in mice
Sanofi-Genzyme G. Chu (PI) 10/01/15–06/30/16
This sponsored research will provide up to three devices to Sanofi-Genzyme for quantification of ammonia levels in blood samples from mice to support pre-clinical development of new drugs to treat hyperammonemia. The devices for Sanofi-Genzyme require 100 µL blood samples.

Drug to block double-strand break repair in breast cancer
California Breast Cancer Research Program, 20IB-0126 G. Chu (PI) 06/01/14–12/31/15
This proposal aims to use a high-throughput screen to identify a drug that inhibits non-homologous end joining using an in vitro assay with purified proteins. For breast cancers defective in homologous recombination, the drug would inhibit the other major pathway for double-strand break repair, and thus induce synthetic lethality.

Clinical trial for detection of blood ammonia from finger and heel sticks
Stanford-Coulter Translational Research Grant G. Chu (PI) 05/16/16–05/15/18
This proposal aims to build and then perform a clinical trial for a point-of-care device that measures ammonia from 20 µL of blood obtained by finger or heel stick, and to demonstrate correlation with measurements from Stanford Clinical Lab on blood obtained by intravenous phlebotomy.