OMB No. 0925-0001 and 0925-0002 (Rev. 11/16 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

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NAME: Philip C. Hanawalt

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

POSITION TITLE: The Dr. Morris Herzstein Professor of Biology Emeritus

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 |
| --- | --- | --- | --- |
| Deep Springs College, CA | --- | 06/1950 | Liberal Arts |
| Oberlin College, OH | B.A. | 06/1954 | Physics |
| Yale University, CT  Yale University, CT | M.S., Ph.D. | 06/1955  06/1959 | Physics  Biophysics |
| University of Copenhagen, Denmark | Postdoc | 07/1960 | Bacterial Physiology |
| California Institute of Technology, CA | Postdoc | 09/1961 | Molecular Biology |

**A. Personal Statement**

My experience includes 6 decades of research and leadership in the broad field of genomic maintenance, since completion of my Ph.D. thesis: “*Macromolecular synthesis in E. coli during conditions of unbalanced growth*”. I co-discovered the paradigm-shifting, ubiquitous process of DNA excision repair in 1963-1964. Several decades later my students and I discovered the specialized pathway of transcription-coupled repair (TCR) in mammalian cells, yeast and bacteria. My more recent interest has focused upon mechanisms and genetic control of TCR. We study the behavior of RNA polymerases encountering DNA lesions, guanine-rich DNA sequences and non-canonical DNA structures to learn precise signals that initiate TCR to overcome transcription blockage. We are developing an approach, utilizing peptide nucleic acid (PNA) targeted to the non-template DNA strand in unique expressed genes, to generate stable R-loops (RNA-DNA hybrids) in order to render transcription toxic for selected cells. The current proposal builds logically upon our previous work, to learn more about the mechanism of R-loop formation, to optimize the PNA approach and to validate it in cultured human cells. I have documented expertise in essentially all of the methods to be employed to successfully complete the proposed study.

1. Hanawalt PC & Spivak G (2008) “Transcription-coupled DNA Repair: Two decades of progress and surprises” *Nature Reviews: Molecular Cell Biology* 9:958-970. PMID: 19023283
2. Belotserkovskii BP, Mirkin SM & Hanawalt PC, (2013) “DNA sequences that interfere with transcription: Implications for genome function and stability” *Chemical Reviews,* thematic issue on Gene Expression, 113:8620-8637. PMID: 23972098
3. Hanawalt PC (2015) Invited Perspective. “Historical perspective on the DNA damage response. ”*DNA Repair* 36: 2-7. PMCID: PMC4688148
4. Ganesan A & Hanawalt PC (2016) Invited Review. “Photobiological origins of the field of genomic maintenance.” *Photochem. Photobiol.* 92:52-60. PMCID: PMC4720547

**B. Positions and Honors**

**Positions, all at Stanford University, Stanford, California**

1961-65 Research Biophysicist and Lecturer

1965-70 Tenured Associate Professor of Biology

1968-85 Director, Biophysics Graduate Program

1970- Professor of Biology

1979- Professor of Dermatology (Joint appointment in Stanford Medical School)

1982-89 Chair, Department of Biological Sciences, School of Humanities and Sciences

1997-02 The Howard H. and Jessie T. Watkins University Professorship at Stanford

2009-17 The Dr. Morris Herzstein Professorship in Biology

**Other Relevant Experience and Professional Memberships (partial list)**

1957- Charter Member, Biophysical Society

1966-70 Member, Physiological Chemistry Study Section, National Institutes of Health (NIH)

1969-71 Executive Board Member, Biophysical Society

1971 Program Chair, Biophysical Society Annual Meeting, New Orleans

1974 Chair/Organizer, First Int. Conf. on “Molecular Mechanisms for Repair of DNA”, Squaw Valley, CA

1975 Co-Chair, ICN-UCLA Conf. on “DNA Replication and its Regulation”, Squaw Valley, CA

1981- Member, American Association for Cancer Research (AACR)

1981-84 Member, Chemical Pathology Study Section, NIH

1982-93 Co-Founding Editor, *DNA Repair* (*Mutation Research*); Now *DNA Repair*

1985 Member, Pre-doctoral Fellowship Review Panel, National Science Foundation (NSF)

1987-90 Member, Board of Scientific Counselors, Division of Biometry and Risk Assessment, NIEHS, NIH

1987-92 Member, Advisory Committee, Biology Department, Brookhaven National Laboratory, (Chair, 1992)

1993-94 Program Chair/President, Environmental Mutagen Society (EMS)

1994-97 Member, Board of Directors, AACR

1995-99 Scientific Advisory Board, Office of Environmental Health Hazard Assessment, California EPA

1995-01 Board of Reviewing Editors, *Science*

1995-01 Toxicology Advisory Committee, The Burroughs - Wellcome Fund (Chair, 1997-2000)

1995-99 Member, Scientific Advisory Board, Fogarty International Center, NIH

1995-98 Member, Board on Radiation Effects Research, NAS/NRC Commission on Life Sciences

1996 External Review Comm. for MRC Molecular/Cell Medicine, Cell Mutation Unit, Brighton, U.K.

1996-98 External Review Working Group, NIEHS, NIH

1996 Chair, Gordon Research Conference on “Mutagenesis”

1998-01 Member, Council for Extramural Grants, American Cancer Society

1999 Chair, Gordon Research Conference on “Mammalian DNA Repair”

2000- Member, American Chemical Society

2001 Member, Genetics Study Section Boundaries Team, CSR, NIH

2001 Member, Intramural site visiting committee, NICHD, NIH

2003-10 Senior Editor, *Cancer Research*

2003- Editorial Board, *Proceedings of the National Academy of Sciences U.S.A.*

2005- Editorial Board, *Genes and Environment,* (Journal of the Japanese EMS)

2005-08 Member, Special Conference Committee, AACR (also 1991-94)

2006 Member, Working Group on Integrated Translational Research on DNA Repair, NIEHS, NIH

2009 Member, Intramural site visiting committee, NCI, NIH

2010-13 External Examiner, Biotechnology Program, Universiti Tunku Abdul Rahman, Kampar, Malaysia

2010 External Reviewer for Cancer Research UK (Quinquennial Review)

2013- Associate Editor, *DNA Repair*, to organize annual special issues on “Cutting-Edge Perspectives”

2014 Fulbright Specialist Grant to teach course in “Genomic Maintenance”, Santa Fe, Argentina

2014 Chair, Gordon Research Conference on “DNA Damage, Mutation and Cancer”, Ventura, CA

2015 Fulbright Specialist Grant to lecture in Hollaender Course on “Genetic Toxicology”, La Paz, Bolivia

2016 Fulbright Specialist Grant to lecture in Hollaender Course, Buenos Aires, Argentina

**Honors and Professional Recognition**

1981 Elected Fellow, American Association for the Advancement of Science

1987-01 Outstanding Investigator Research Grant, National Cancer Institute, NIH

1989 Elected Member, National Academy of Sciences, U.S.A.

1991 Annual Excellence-in-Teaching Award, Northern California Chapter, Phi Beta Kappa

1992 Annual Award for Excellence in Basic Science, Environmental Mutagen Society (EMS)

1992 Peter and Helen Bing Award for Distinguished Teaching, Stanford University

1993 Elected Fellow, American Academy of Microbiology

1996 Annual Research Award, American Society for Photobiology

1996 Second Severo Ochoa Memorial Honors Lecture, New York University

1997 International *Mutation Research* Award for Excellence in Scientific Achievement

1997 Honorary Doctor of Science, Oberlin College, Ohio

1999 Princess Takamatsu Cancer Foundation Lectureship (Tokyo, Sendai, Kumamoto, Fukuoka), Japan

2000 Inaugural John Abelson Family Lecture, Washington State University, Pullman

2001 Annual Student Mentoring Award, EMS

2001 Elected Foreign Associate, European Molecular Biology Organization (EMBO)

2001-05 Senior Scholar Research Award, Ellison Medical Foundation

2002 Elected Honorary member of the German DNA Repair Network

2002 J.B. Little Award/Lecture in Radiation Sciences, Harvard School of Public Health, Boston

2003 Rothschild-Yvette Mayent Curie Institute Award and Lectureship, Paris, France

2004 Keynote Lecture, ASM International Conference on *DNA Repair and Mutagenesis*, Bermuda

2005 President / Organizer, 9th Int. Conference on Environmental Mutagens, San Francisco

2005 Special Issue, *Mut. Res*. v577, “Molecular Mechanisms of DNA Repair”, dedicated to P. Hanawalt

2006 *Doctor Honoris Causa*, University of Bio Bio, Concepcion, Chile

2007 Centennial Lecture, “Sunrise Session”, 99th AACR Annual Meeting, Los Angeles, CA

2007 Visiting Scholar/Lectureship, Graduate School of Frontier Bio-Sciences, Osaka University, Japan

2008 Elected Fellow, American Academy of Arts and Sciences

2008 *Doctor Honoris Causa*, University of Seville, Spain

2009 Keynote Lecture, 11th Midwest DNA Repair Symposium, Ann Arbor, MI (Also, 1st Symp.1999)

2009 Keynote Lecture, Symp. on DNA Repair and Human Health, Ctr. for Integrative Genetics, Lausanne

2009 Keynote Lecture, 10th Int. Conference on Environmental Mutagens, Florence, Italy

2010 Three publications selected for “Centennial Classics Series” in *J. Biological Chemistry*

2011 AACR - Princess Takamatsu Lectureship Award, presented at AACR Annual Mtg., Orlando, Fl

2012 Keynote Lecture, 3rd Erling Seeberg Symposium on DNA Repair, Trondheim & Ørland, Norway

2012 *Doctor Honoris Causa*, University of Buenos Aires, Argentina

2013 Plenary Lecture, 11th Int. Conference on Environmental Mutagens, Foz do Iguassu, Brazil

2014 Stanford Medal for Faculty Excellence Fostering Undergraduate Research at Stanford University

2014 Keynote lecture, 16th International Congress on Photobiology, Cordoba, Argentina

2014 Appointed to Fulbright Specialist Roster, Council for International Exchange of Scholars (CIES)

2014 *Doctor Honoris Causa*, National University of El Litoral, Santa Fe, Argentina

2015 Wilbur Lucius Cross Medal, Yale University Graduate School Alumni Association

2015 *Doctor Honoris Causa*, Universidad Mayor de San Andreas, La Paz, Bolivia

2016 ALAMCTA Award for discovery of DNA repair pathways and mechanisms, Montevideo, Uruguay

2017 Invited presentation, Cold Spring Harbor Mtg. on “Mechanisms of Eukaryotic Transcription”

2017 Closing Keynote lecture, 6th Europe-U.S. DNA Repair Conference, Udine, Italy

**C. Contributions to Science**

1. In the late 1950’s we knew that ultraviolet light (UV) caused mutations and killed bacteria, but we didn’t know the responsible DNA lesions or how they were processed. My graduate research included studies on recovery of RNA and DNA synthesis in UV-irradiated bacteria and shortening of the lag in recovery by photoreactivation. I suggested in my Ph.D. thesis (1958) that the “visible light facilitates repair of DNA integrity”. That work, followed by the revelation of UV-induced thymine dimerization (by Beukers and Berends) provided underpinning for the subsequent discovery of pyrimidine dimer excision in UV-irradiated *E. coli* by my former mentor, Richard Setlow, along with my discovery of the non-conservative mode of DNA repair replication with my first graduate student, David Pettijohn. Those studies together revealed the “cut and patch” mechanism of nucleotide excision repair. The pathways of base excision repair and mismatch excision repair were discovered by others a decade later.

1. Hanawalt PC & Buehler (1960) “Photoreactivation of Macromolecular Synthesis in E. coli” *Biochim Biophys Acta* 37:141-143. PMID: 14399415
2. Pettijohn D & Hanawalt PC (1963) “Deoxyribonucleic Acid Replication in Bacteria Following Ultraviolet Irradiation” *Biochim Biophys Acta* 72: 127-129. PMID: 13942980
3. Pettijohn D & Hanawalt PC (1964) “Evidence for repair-replication of ultraviolet damaged DNA in bacteria” *J.Mol Biol* 9:395-410. PMID: 14202275
4. Hanawalt PC, Pettijohn DE, Pauling CE, Brunk CF, Smith DW, Kanner LC & Couch JL (1968) “Repair Replication of DNA in vivo” Cold Spring Harbor Symposia on Quantitative Biology XXXIII :187-194. PMID: 4891962

2. In the late 1950’s we knew almost nothing about the regulation of the bacterial cell cycle. During my postdoc at the University of Copenhagen, I discovered that RNA and protein synthesis are required to initiate the DNA replication cycle in *E. coli*, but not to enable its completion, thereby establishing a widely-used approach for synchronizing DNA replication. My results were important to the formulation of the replicon model, and they provided clues to the mechanism of the classic phenomenon of thymineless death (TLD). The insights derived from our understanding of TLD have had translational value for chemotherapies (e.g. methotrexate, trimethoprim & fluorouracil) that depend upon TLD-like responses.

1. Hanawalt PC, Maaløe O, Cummings O, & Schaecter M (1961) “The normal DNA replication cycle II” *J Mol Biol* 3:156-165. PMID: 13711156
2. Hanawalt PC (1963) “Involvement of synthesis of RNA in thymineless death” *Nature* 198:286. PMID: 13952474
3. Morganroth P & Hanawalt PC (2006) “Role of DNA replication and repair in thymineless death in *Escherichia coli*” *J. Bacteriology* 188: 5286-5288. PMCID: PMC1539979
4. Khodurski A, Guzman EC, & Hanawalt PC (2015) “Thymineless death lives on: New insights into a classic phenomenon.” *Annual Review of Microbiology* 69:247-263. PMID: 26253395

3. My postdoc, Hiroaki Nakayama, and I discovered the *recQ* gene, while searching for mutants in *E. coli* that are resistant to TLD. My graduate student, Justin Courcelle, and I characterized the role of the RecQ helicase in processing arrested replication forks. We reported selective degradation of the nascent lagging DNA strand, and we proposed a model in which fork regression revealed the offending lesion for excision repair. Five RecQ homologues have now been reported in human cells, for which the respective mutants result in predisposition to cancer; including Werner’s syndrome, characterized by premature aging, and Bloom’s syndrome, characterized by high levels of sister chromatid exchanges. Lessons learned from our discovery of RecQ underscore the value of basic research in bacterial systems that can have profound implications for human health.

1. Nakayama H, Nakayama K, Nakayama R, Irino N, Nakayama Y & Hanawalt PC (1984) “Isolation and genetic characterization of a thymineless death-resistant mutant of *Escherichia coli* K-12: Identification of a new mutation, *recQ1*, that blocks the RecF recombination pathway” *Mol Gen Genet* 195:474-480. PMID: 6381965
2. Courcelle J, & Hanawalt PC (1999) “RecQ and RecJ process blocked replication forks prior to the resumption of replication in UV-Irradiated Escherichia coli”, *Mol Gen Genet* 262:543-551. PMID: 10589843
3. Hanawalt PC (2015) “A balanced perspective on unbalanced growth and thymineless death*.” Frontiers in Microbiology* 6: Article 504. [Open access, doi:10:3389/fmicb.2015.00504] PMCID: PMC4456962

4. In the early 1980’s little was known about the intra-genomic heterogeneity of DNA repair efficiency. My student, Mimi Zolan, and I reported in 1982 that chemical adducts in centromeric alpha DNA in African green monkey cells were poorly repaired in comparison to those in the bulk DNA. We then discovered in mammalian cells, yeast and bacteria that expressed genes are preferentially repaired by a mechanism of transcription-coupled DNA repair (TCR), targeted to the transcribed DNA strand; we have pioneered this important field for many years. We have established that cells from the sun-sensitive genetic diseases, Cockayne syndrome (CS) and UV-sensitive syndrome, are equally deficient in TCR of UV photoproducts and oxidative DNA damage, although CS patients suffer severe developmental and neurological problems unrelated to TCR. Importantly, humans with deficiencies in TCR have, thus far, presented no cancers of any type! Sequenced genomes from tumors often provide the *mutational signature* for the causal agent and they can additionally indicate the extent to which TCR is operating for repair of the damage due to that agent. Some types of damage are recognized by blockage of transcription, but not by the global genomic excision repair pathway. TCR has now emerged as a very important and popular field of investigation in many laboratories worldwide.

1. Mellon I, Spivak G & Hanawalt PC (1987) “Selective removal of transcription-blocking DNA damage from the transcribed strand of the mammalian DHFR Gene” *Cell* 51:241-249. PMID: 3664636
2. Mellon I & Hanawalt PC (1989) “Induction of the *Escherichia coli* lactose operon selectively increases repair of its transcribed DNA strand” *Nature* 342:95-98. PMID: 2554145
3. Donahue BA, Yin S, Taylor J-S, Reines D & Hanawalt PC (1994) “Transcript cleavage by RNA polymerase II arrested by a cyclobutane pyrimidine dimer in the DNA template” *Proc Natl Acad Sci* *USA* 91:8502-8506. PMCID: PMC44634
4. Guo J, Hanawalt PC & Spivak G (2013), “Comet-FISH with strand-specific probes reveals TCR of 8-oxo-guanine in human cells.” *Nucleic Acids Res.* 41: 7700-7712. PMCID: PMC3763531

5. In addition to damage caused by endogenous and environmental threats to DNA function and stability, some naturally-occurring DNA nucleotide sequences are intrinsically mutagenic and pose hurdles to replication and transcription. We have provided important insights toward an understanding of the behavior of RNA polymerases encountering non-canonical DNA structures and unusual sequences. These studies have culminated in our recent focus upon a potential approach to selectively inactivate tumor cells, by forming toxic R-loops in expressed genes that are not expressed in the population of normal cells.

1. Belotserkovskii BP, Liu R, Tornaletti S, Krasilnikova MM, Mirkin SM & Hanawalt PC, (2010) “Mechanisms and implications of transcription blockage by guanine-rich DNA sequences.” *Proc. Natl. Acad. Sci.* USA 107: 12816-12821. PMCID: PMC2919923
2. Salinas-Rios, V, Belotserkovskii, BP, & Hanawalt, PC, (2011) “DNA slip-outs cause RNA polymerase II arrest in vitro: potential implications for genetic instability.” *Nucleic Acids Res*. 39: 7444-7454. PMCID: PMC3177194

c. Panday S, Ogloblina AM, Belotserkovskii BP, Dolinnaya NG, Yakubovskaya MG, Mirkin SM, & Hanawalt PC, (2015) “Transcription blockage by stable H-DNA analogs in vitro.” *Nucleic Acids Res.* 43:6994-7004. PMCID: PMC4538819

d. Belotserkovskii BP & Hanawalt PC (2015) “PNA binding to the non-template DNA strand interferes with transcription, suggesting a blockage mechanism mediated by R-loop formation.” *Molec. Carcinog*. 54: 1508-1512. PMCID: PMC4345152

**For complete list of Philip Hanawalt’s published work, search Pubmed**

**https://www.ncbi.nlm.nih.gov/pubmed/?term=hanawalt+p**

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

**Ongoing Research Support**

**2RO1-CA77712** Hanawalt (PI) 04/01/09 – 07/31/17

Project extended without additional funds. 08/01/17 - 01/31/18

***Role of Transcription in Genomic Stability***

The goal is to characterize unique features of transcription complexes encountering different impediments; non-canonical DNA structures, guanine-rich sequences, strand breaks and other lesions, to reveal signals for initiating TCR and possible gratuitous repair.

**Completed Research Support**

**1R01-ES018834** Hanawalt (PI) 04/01/10 – 09/30/15

***Oxidative DNA damage processing; role in human pathology and aging***

We developed novel approaches for elucidating effects of oxidative DNA lesions on transcription, and for analysis of DNA repair at physiologically relevant levels in transcriptionally active and silent genomic domains; including an ultrasensitive comet-FISH assay for quantifying 8-oxo-guanine and its repair in an expressed gene, and its application to reveal the DNA repair deficiencies in cells from patients with Cockayne syndrome and UV-sensitive syndrome.