OMB No. 3145-0279 (Expiration Date 10/31/2026)

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: CAMPBELL, Judith L.

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0001-8291-5551

Position Title: Professor of Chemistry and Biology

Organization and Location: California Institute of Technology, Pasadena, CA, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
Harvard University, Cambridge, MA, USA	DOCTOR OF PHILOSOPHY	09/1969	02/1974	Biological Chemistry
Wellesley College, Wellesley, MA, USA	BACHELOR OF ARTS	09/1961	06/1965	Chemistry

Appointments and Positions

1989 - present	Professor of Chemistry and Biology, California Institute of Technology, Pasadena, CA, United States
1989 - present	Professor, Divisions of Biology and Chemistry, California Institute of Technology, Pasadena, CA, USA
1983 - 1989	Associate Professor, Divisions of Biology and Chemistry, California Institute of Technology, Pasadena, CA, USA
1977 - 1983	Assistant Professor, Divisions of Biology and Chemistry, California Institute of Technology, Pasadena, CA, USA
1974 - 1977	Postdoctoral Fellow and Senior Research Associate, Department of Biological Chemistry, Harvard Medical School, Boston, MA, USA
1969 - 1974	Graduate Student, Department of Biological Chmeistry , Harvard Medical School, Boston, MA, USA

Products

Products Closely Related to the Proposed Project

1. Budd ME, Campbell JL. A yeast gene required for DNA replication encodes a protein with homology to DNA helicases. Proc Natl Acad Sci U S A. 1995 Aug 15;92(17):7642-6. PubMed Central PMCID: PMC41201.
2. Cejka P, Cannavo E, Polaczek P, Masuda-Sasa T, Pokharel S, Campbell JL, Kowalczykowski SC. DNA end resection by Dna2-Sgs1-RPA and its stimulation by Top3-Rmi1 and Mre11-Rad50-Xrs2. Nature. 2010 Sep 2;467(7311):112-6. PubMed Central PMCID: PMC3089589.
3. Duxin JP, Moore HR, Sidorova J, Karanja K, Honaker Y, Dao B, Piwnica-Worms H, Campbell JL, Monnat RJ Jr, Stewart SA. Okazaki fragment processing-independent role for human Dna2 enzyme during DNA replication. J Biol Chem. 2012 Jun 22;287(26):21980-91. PubMed Central PMCID: PMC3381158.
4. Karanja KK, Cox SW, Duxin JP, Stewart SA, Campbell JL. DNA2 and EXO1 in replication-coupled, homology-directed repair and in the interplay between HDR and the FA/BRCA network. Cell Cycle. 2012 Nov 1;11(21):3983-96. PubMed Central PMCID: PMC3507494.
5. Liu W, Zhou M, Li Z, Li H, Polaczek P, Dai H, Wu Q, Liu C, Karanja KK, Popuri V, Shan SO, Schlacher K, Zheng L, Campbell JL, Shen B. A Selective Small Molecule DNA2 Inhibitor for Sensitization of Human Cancer Cells to Chemotherapy. EBioMedicine. 2016 Apr;6:73-86. PubMed Central PMCID: PMC4856754.

Other Significant Products Highlighting Contributions to Science

1. Johnson LM, Snyder M, Chang LM, Davis RW, Campbell JL. Isolation of the gene encoding yeast DNA polymerase I. Cell. 1985 Nov;43(1):369-77. PubMed PMID: 3907855.
2. Sitney KC, Budd ME, Campbell JL. Yeast DNA polymerases. Ann N Y Acad Sci. 1992 Oct 13;665:52-8. PubMed PMID: 1329600.
3. Lou H, Komata M, Katou Y, Guan Z, Reis CC, Budd M, Shirahige K, Campbell JL. Mrc1 and DNA polymerase epsilon function together in linking DNA replication and the S phase checkpoint. Mol Cell. 2008 Oct 10;32(1):106-17. PubMed Central PMCID: PMC2699584.
4. Wawrousek KE, Fortini BK, Polaczek P, Chen L, Liu Q, Dunphy WG, Campbell JL. Xenopus DNA2 is a helicase/nuclease

that is found in complexes with replication proteins And-1/Ctf4 and Mcm10 and DSB response proteins Nbs1 and ATM. Cell Cycle. 2010 Mar 15;9(6):1156-66. PubMed Central PMCID: PMC3059328.

5. Liu W, Polaczek P, Roubal I, Meng Y, Choe WC, Caron MC, Sedgeman CA, Xi Y, Liu C, Wu Q, Zheng L, Masson JY, Shen B, Campbell JL. FANCD2 and RAD51 recombinase directly inhibit DNA2 nuclease at stalled replication forks and FANCD2 acts as a novel RAD51 mediator in strand exchange to promote genome stability. Nucleic Acids Res. 2023 Sep 22;51(17):9144-9165. PubMed Central PMCID: PMC10516637.

Certification:

I certify that the information provided is current, accurate, and complete. This includes, but is not limited to, information related to current, pending, and other support (both foreign and domestic) as defined in 42 U.S.C. § 6605.

In accordance with Section 10632 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19232), each individual identified as a senior/key person must certify that they are not a party to a malign foreign talent recruitment program.

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Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§287, 1001, 1031 and 31 U.S.C. §§3729-3733 and 3802.

Certified by CAMPBELL, Judith L. in SciENcv on 2026-07-27 17:36:12

NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: CAMPBELL, Judith L.

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0001-8291-5551

Position Title: Professor of Chemistry and Biology

Organization and Location: California Institute of Technology, Pasadena, CA, United States

Personal Statement

Our lab has made many contributions to the field of DNA replication in both prokaryotes and eukaryotes. In bacteria, we identified and characterized the first antisense regulatory RNA. In 1979 we chose yeast as a system to simultaneously exploit biochemistry and genetics for the study eukaryotic chromosomal DNA replication. We defined the essential cis-acting sequences in origins of replication (ARSs). We exploited reverse genetics to define protein functions, developed plasmid shuffling to make conditional mutants, and incorporated the use of functional genomics to define whole pathways. We co-discovered the first ARS-specific binding protein, Abf1, and DNA polymerase IV, involved in NHEJ; showed that DNA polymerase α, pol δ, and pol ε were essential; discovered elements of the conserved pathway for S phase specific expression of replication genes; defined the enzymatic functions of Cdc7 and Cdc8; defined the role of the essential C-terminus of Pol2, the catalytic subunit of pol ε, in holoenzyme assembly; showed that the Mrc1 checkpoint mediator interacted with the Pol2 C terminus; showed that Cdc6 was regulated by the cell cycle kinase, Cdk1. In 1983, we discovered the archael/eukaryotic specific helicase/nuclease, Dna2, in a genetic screen. In characterizing Dna2, we emphasized biochemical experiments in addition to molecular genetic studies and showed that there are at least two essential pathways for Okazaki fragment processing in yeast. We showed how Dna2 and the conserved RecQ helicase Sgs1 form a RecBCD-like machine for resecting breaks that initiate recombination. More recently, we extended our studies of DNA2 to Xenopus and to human cells, human disease.

In 2014, I embarked on a new and exciting trajectory, the development of repair inhibitors for cancer treatment. I joined a collaboration with the goal of isolating DNA2 inhibitors with a City of Hope colleague. Using a novel homology-based structure of DNA2 and a virtual high throughput screen combined with biochemistry, we identified a potent and specific inhibitor of DNA2, called C5, compound 5. My student, Wenpeng Liu, demonstrated that the inhibitor was on-target in vivo and collaborated with Katharina Schlacher at MD Anderson to demonstrate that C5 inhibited over-resection in BRCA2 fork protection defective tumors, and showed that C5 synergizes with PARPi (Liu et al., 2016). Both the composition of matter and use in cancer treatment were patented. We carried out a screen of NCI 60 cancers and found that C5 was specific for colon, breast, and melanoma. The same cancers were shown to be DNA2 dependent in massively parallel shRNA screens. I entered into a collaboration with Prof. Brian Stoltz, also at Caltech, and have isolated second-generation inhibitors with increased potency. We also carried out mouse xenograft studies and showed that C5 both inhibited tumor induction and reduced tumor growth at 25 mg/kg with high tolerability in human colorectal PDX experiments . In this project, I will serve as Pl of the overall award and oversee designing and interpreting the biological experiments to validate our inhibitors and collaborate with Dr. Stoltz in developing assays and with Dr. Heinz-Joseph Lenz for interpreting organoid work.

Honors

2009	Ellison Medical Foundation Senior Scholar, Ellison Medical Foundation
1979	Research Career Development Award, National Institutes of Health
1966	Bavarian State Scholarship, University of Munich
1965	Pendleton Scholar, Wellesley College

Contributions to Science

1. In 1979 we, chose yeast as a system to simultaneously exploit biochemistry and genetics for the study eukaryotic chromosomal DNA replication. In a direct lineage from earlier work (cloning of the phage T7 replication origin and demonstration that an origin RNA was an anti-sense regulator of plasmid replication), we defined the essential cis-acting sequences in origins of replication (ARSs). We exploited reverse genetics to define functions of single proteins, developed plasmid shuffling to make conditional mutants, and later incorporated the use of functional genomics to define whole pathways. We co-discovered the first ARS-specific binding protein, Abf1, and DNA polymerase IV, involved in NHEJ; showed that DNA polymerase α, pol δ and pol ε were essential; discovered elements of the conserved pathway for S phase specific expression of replication genes; defined the enzymatic functions of Cdc7 and Cdc8; defined the role of the essential C-terminus of Pol2, the catalytic subunit of pol ε, in holoenzyme assembly; showed that the Mrc1 checkpoint mediator interacted with the Pol2 C terminus; showed that Cdc6 was regulated by the cell cycle kinase, Cdk1.

   a. 389434
   b. 3907855
   c. 2645055
   d. PMC369538

2. Our work on DNA polymerases has been founded on the premise that this machine is central to the organization of the replication fork both at initiation or firing of origins and during elongation. We were the first to clone the gene encoding pol alpha and invented reverse genetics using 5-FOA simultaneously with the Fink lab to show that pol alpha was essential. The mutant was also useful in discovering verifying that pol epsilon and pol delta were distinct polymerases. We focused on the least understood, pol E, and showed that it was a distinct polymerase by identifying the gene, Cdc2, that encoded pol delta and creating mutants that were temperature sensitive for growth and that didn't affect pol delta. Up to that point, pol epsilon was considered not to be required for replication because it was not required in the SV40 in vitro replication system. We went on to show that it was not the polymerase activity that was essential but rather the C terminus, which we and others showed through years of biochemical reconstitution is the major protein/protein interaction domain in the pol epsilon (series of 4 papers by Dua, Edwards, and Reis). Most recently, we showed that the checkpoint regulator Mrc1 interacts with the C terminus of pol epsilon and in that way regulates the slowing of S phase during the S phase checkpoint.

   a. PMC358929
   b. 9792727
   c. 10428796
   d. PMC2699584

3. Our lab has made many contributions to the understanding of the function of the DNA2 helicase/nuclease. We discovered DNA2, identifying the dna2 mutant in a screen for new eukaryotic DNA replication mutants in yeast. Biochemical characterization demonstrated that it was both a nuclease and helicase and reverse genetics showed that both nuclease and helicase were essential for viability. We discovered that Dna2 copurified with FEN1 nuclease, and used extensive yeast genetics to demonstrate that Dna2 and FEN1 function in the same pathway, Okazaki fragment processing. In collaboration with the laboratory of Robert Bambara, we used biochemical reconstitution assays that indicated that FEN1 was the major Okazaki fragment-processing enzyme and that Dna2 was likely involved only when flaps became long. This presented a paradox because FEN1 is not essential in yeast, but DNA2 is essential. We resolved this paradox later by showing through genetics that deletion of the checkpoint mediator protein, RAD9, suppressed the lethality of deletion of DNA2. (The checkpoint is lethal in dna2 mutants because there is no function that can compensate for its DSB resection/repair function (see Contribution 4), since Rad27 is dedicated to replication). Conversely, DNA2 can repair failures due to Rad27 deficiency if S phase is delayed by the checkpoint, and rad27 rad9 double mutants are dead. This work illustrates our commitment to the combination of genetic and biochemical approaches in our laboratory and to our expertise in both areas. We went on to discover that Dna2 in yeast plays a special role at telomeres, where it is required for telomerase-dependent telomere elongation, recombinational healing of telomeres, and where it associates with telomeres in a cell cycle specific pattern. I recently collaborated with Dr. BH Shen in demonstrating that telomeres are dysfunctional in the mouse Dna2 heterozygous knockout.

   a. PMC41201
   b. 7592912
   c. PMC133873
   d. 12686542

4. In 2004, using dna2 alleles as bait, we carried out a global synthetic lethal screen (SGA) in yeast in collaboration with the Toronto group of C. Boone. 43 genes interacted with Dna2 and further demonstration of the interaction of these 43 genes with each other generated a network of DNA replication and repair genes in yeast. Our analysis of the network revealed two additional critical functions for Dna2: a role in mitochondrial maintenance and a role in DSB repair pathways. In work derived from the network we discovered that deletion of Pif1 helicase overcame the lethality of the dna2 deletion mutant. This had both practical and scientific implications. It allowed us to demonstrate that dna2 nuclease can compensate for loss of Mre11 nuclease in DSB repair, suggesting Dna2 was the nuclease involved in 5' resection at DSBs, which we and others quickly proved using in vivo biochemistry. In further collaboration with the Bambara lab, biochemical experiments proved our hypothesis that Pif1 helicase is a processivity factor for pol delta/PCNA/Pol32 during Okazaki fragment maturation. During this period we also carried out a microarray analysis of young and old yeast cells using dna2 mutants to enrich for prematurely aged cells, and found that the pattern resembled gene expression in cells undergoing telomere attrition, i.e. telomeric senescence in yeast.

   a. PMC363132
   b. PMC1298934
   c. PMC1430326
   d. PMC3089589

5. In 2005 we reported the characterization of human DNA2 protein. We then demonstrated a role in S phase using shRNA knockdowns. We transitioned from an exclusively yeast lab to one with expertise in working with human cells, and we made use of this to show that DNA2, as in yeast, is required for DSB repair in human cells. We reconstituted the Mre11/Sgs1/Dna2 pathway with purified proteins in yeast and the MRN/BLM/DNA2 pathway in humans (collaboration with Stephen Kowalczykowski). A major contribution to the studies was the discovery that RPA inhibits the 3' activity of DNA2, thus preserving the 3' overhang for strand invasion during recombination and for checkpoint activation. Until recently, all laboratories working on Dna2 biochemically used our expression vectors as this protein had proven very difficult to express and purify. In particular, we engineered the clone that overexpresses yeast and human Dna2 in E. coli in amounts suitable for biophysical studies. We showed that human cells, like yeast, deficient in DNA2 are defective repair of DSBs at replication forks by DNA damage and that, as in yeast, DNA2 and EXO1 were redundant. We also found that DNA2 is a component of the FA/BRCA pathway but that, surprisingly, depletion of DNA suppresses the DNA damage sensitivity of FANCD2 deficient patient cells, suggesting that DNA2 inhibitors that we are now developing, may be useful in sensitizing cells to DNA damaging agents and establishing a therapeutic window for use of standard chemotherapies in FA patient cancers, which are currently impossible because of the sensitivity of non-tumor cells. Most recently we showed that FANCD2 stimulates strand exchange by RAD51.

   a. PMC1428797
   b. PMC3042158
   c. PMC3507494
   d. PMC4050159

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