

Stanford



Karlene Cimprich

Professor of Chemical and Systems Biology

Bio

ACADEMIC APPOINTMENTS

- Professor, Chemical and Systems Biology
- Member, Bio-X
- Member, Stanford Cancer Institute

HONORS AND AWARDS

- Kimmel Scholar Award, Kimmel Foundation (1998)
- Burroughs Wellcome New Investigator Award in Toxicology, Burroughs Wellcome Foundation (1999)
- Beckman Scholar Award, Arnold and Mabel Beckman Foundation (2000)
- Leukemia and Lymphoma Scholar Award, Leukemia and Lymphoma Society (2004)
- Ellison Senior Scholar Award, Ellison Foundation (2009)
- AAAS Elected Fellow, AAAS (2015)
- American Cancer Society Research Professor, American Cancer Society (2019-)

PROFESSIONAL EDUCATION

- B.S., University of Notre Dame , Chemistry (1989)
- Ph.D., Harvard University , Chemistry (1994)

LINKS

- My Lab Site: <http://cimprich.stanford.edu/>
- Chemical and Systems Biology Website: <http://molepharm.stanford.edu/faculty/homepages/cimprich.html>

Research & Scholarship

CURRENT RESEARCH AND SCHOLARLY INTERESTS

Genomic instability contributes to many diseases, such as cancer, neurodegenerative disease, and developmental disorders, but it also underlies many natural processes including aging, evolution, and antibody diversification. The Cimprich lab is focused on understanding how cells maintain genomic stability, with an emphasis on the DNA damage response (DDR). This is a complex, multi-faceted response that requires cells to sense the presence of DNA damage within the genome, as well as to “choose” and coordinate a range of downstream events and outcomes. These include effects on DNA repair, transcription, and DNA replication, as well as cell cycle arrest, apoptosis, and senescence.

We are particularly interested in understanding how DNA damage is identified and resolved during DNA replication, when the genome is particularly vulnerable due to stalling of the replication fork at naturally arising and induced DNA lesions, structures or protein-DNA complexes. Stalled replication forks are unstable and can be processed in aberrant ways, leading to double-strand break formation, which is known to drive chromosomal translocation and rearrangements in cancer cells. Indeed, replication stress, a result of slowing replication fork progression, is commonly observed in cancer cells due to loss of the DDR or oncogene activation.

The lab studies the DDR using cultured mammalian cells, as well as cell-free extracts derived from the eggs of the frog *Xenopus laevis* together with a variety of techniques. Our goal is to understand how the DDR is initiated, how this pathway is integrated with the processes of DNA replication and transcription, and how cells recover from DNA damage.

Specific areas of current interest are:

Checkpoint Activation and Signaling. We are interested in understanding how the DDR is initiated, and how it regulates DNA replication and DNA repair. In particular, we are interested in how stalled replication forks are stabilized, so as to prevent further DNA damage, and how replication resumes when forks stall frequently as in cancer cells. We have identified new factors involved in these processes and ongoing projects relate to studying the roles of these factors and other known DDR proteins in these processes.

DNA Damage Tolerance. DNA damage tolerance (DDT) pathways promote the completion of replication when a fork stalls by allowing bypass of the lesion, an event that leaves repair to a more convenient time. Although DDT pathways suppress fork collapse, thereby avoiding deleterious DNA breaks, bypass can be mutagenic. We are interested in understanding the mechanisms involved in DDT, and how the cell balances mutagenic and non-mutagenic DDT pathways.

New Pathways for Genome Stability/Human Disease: Recently, we performed a genome-wide siRNA screen to define the processes and proteins that protect cells from DNA damage, particularly during DNA replication. We are currently characterizing proteins identified in this screen with interesting ties to genome maintenance and human disease. One such protein is Nek8/NPHP9, a protein kinase we have shown to prevent DNA damage at stalled forks by regulating CDK activity. Our findings have provided exciting molecular insight into a novel link between the replication stress response and kidney diseases, including renal ciliopathies.

Transcription, RNA, and DNA Damage. Results from our genome-wide screen indicate that RNA is a prominent and underexplored source of genome instability in cell. Specifically, we found that defects in some RNA processing genes lead to DNA damage through the formation of toxic RNA-DNA hybrids and R-loops. We are interested in studying how these structures arise, how they lead to DNA damage, and their physiological function. We are also interested in understanding how cells deal with transcription complexes during DNA replication, as these can act as replication fork barriers and promote fork arrest.

Teaching

COURSES

2019-20

- Cancer Biology Journal Club: CBIO 280 (Win)
- Research Seminar: CSB 270 (Aut, Win, Spr)

2018-19

- The Biology of Chromatin Templated Processes: CSB 250 (Spr)

2017-18

- Cancer Biology Journal Club: CBIO 280 (Win)

STANFORD ADVISEES

Doctoral Dissertation Reader (AC)

Nalin Ratnayeke, Owen Smith

Postdoctoral Faculty Sponsor

Gongshi Bai, Josh Brickner, Madzia Crossley, Chames KERMI, Chenlin Song, Tricia Windgassen

GRADUATE AND FELLOWSHIP PROGRAM AFFILIATIONS

- Cancer Biology (Phd Program)
- Chemical and Systems Biology (Phd Program)

Publications

PUBLICATIONS

- **R-Loops as Cellular Regulators and Genomic Threats.** *Molecular cell*
Crossley, M. P., Bocek, M., Cimprich, K. A.
2019; 73 (3): 398–411
- **An intrinsic S/G2 checkpoint enforced by ATR.** *Science (New York, N.Y.)*
Saldivar, J. C., Hamperl, S., Bocek, M. J., Chung, M., Bass, T. E., Cisneros-Soberanis, F., Samejima, K., Xie, L., Paulson, J. R., Earnshaw, W. C., Cortez, D., Meyer, T., Cimprich, et al
2018; 361 (6404): 806–10
- **Stochastic Endogenous Replication Stress Causes ATR-Triggered Fluctuations in CDK2 Activity that Dynamically Adjust Global DNA Synthesis Rates.** *Cell systems*
Daigh, L. H., Liu, C., Chung, M., Cimprich, K. A., Meyer, T.
2018
- **Transcription-Replication Conflict Orientation Modulates R-Loop Levels and Activates Distinct DNA Damage Responses** *CELL*
Hamperl, S., Bocek, M. J., Saldivar, J. C., Swigut, T., Cimprich, K. A.
2017; 170 (4): 774+
- **The essential kinase ATR: ensuring faithful duplication of a challenging genome.** *Nature reviews. Molecular cell biology*
Saldivar, J. C., Cortez, D., Cimprich, K. A.
2017; 18 (10): 622–36
- **Conflict Resolution in the Genome: How Transcription and Replication Make It Work** *CELL*
Hamperl, S., Cimprich, K. A.
2016; 167 (6): 1455-1467
- **Directed evolution using dCas9-targeted somatic hypermutation in mammalian cells.** *Nature methods*
Hess, G. T., Frésard, L., Han, K., Lee, C. H., Li, A., Cimprich, K. A., Montgomery, S. B., Bassik, M. C.
2016
- **Co-transcriptional R-loops are the main cause of estrogen-induced DNA damage.** *eLife*
Stork, C. T., Bocek, M., Crossley, M. P., Sollier, J., Sanz, L. A., Chédin, F., Swigut, T., Cimprich, K. A.
2016; 5
- **Breaking bad: R-loops and genome integrity.** *Trends in cell biology*
Sollier, J., Cimprich, K. A.
2015; 25 (9): 514-522
- **HLTF's Ancient HIRAN Domain Binds 3' DNA Ends to Drive Replication Fork Reversal.** *Molecular cell*
Kile, A. C., Chavez, D. A., Bacal, J., Eldirany, S., Korzhnev, D. M., Bezsonova, I., Eichman, B. F., Cimprich, K. A.
2015; 58 (6): 1090-1100

- **Transcription-coupled nucleotide excision repair factors promote R-loop-induced genome instability.** *Molecular cell*
Sollier, J., Stork, C. T., García-Rubio, M. L., Paulsen, R. D., Aguilera, A., Cimprich, K. A.
2014; 56 (6): 777-785
- **Causes and consequences of replication stress** *NATURE CELL BIOLOGY*
Zeman, M. K., Cimprich, K. A.
2014; 16 (1): 2-9
- **NEK8 Links the ATR-Regulated Replication Stress Response and S Phase CDK Activity to Renal Ciliopathies.** *Molecular cell*
Choi, H. J., Lin, J., Vannier, J., Slaats, G. G., Kile, A. C., Paulsen, R. D., Manning, D. K., Beier, D. R., Giles, R. H., Boulton, S. J., Cimprich, K. A.
2013; 51 (4): 423-439
- **ATR phosphorylates SMARCA1 to prevent replication fork collapse** *GENES & DEVELOPMENT*
Couch, F. B., Bansbach, C. E., Driscoll, R., Luzwick, J. W., Glick, G. G., Betous, R., Carroll, C. M., Jung, S. Y., Qin, J., Cimprich, K. A., Cortez, D.
2013; 27 (14): 1610-1623
- **A Role for the MRN Complex in ATR Activation via TOPBP1 Recruitment** *MOLECULAR CELL*
Duursma, A. M., Driscoll, R., Elias, J. E., Cimprich, K. A.
2013; 50 (1): 116-122
- **SHPRH and HLTF Act in a Damage-Specific Manner to Coordinate Different Forms of Postreplication Repair and Prevent Mutagenesis** *MOLECULAR CELL*
Lin, J., Zeman, M. K., Chen, J., Yee, M., Cimprich, K. A.
2011; 42 (2): 237-249
- **Continued primer synthesis at stalled replication forks contributes to checkpoint activation** *JOURNAL OF CELL BIOLOGY*
Van, C., Yan, S., Michael, W. M., Waga, S., Cimprich, K. A.
2010; 189 (2): 233-246
- **A Genome-wide siRNA Screen Reveals Diverse Cellular Processes and Pathways that Mediate Genome Stability** *MOLECULAR CELL*
Paulsen, R. D., Soni, D. V., Wollman, R., Hahn, A. T., Yee, M., Guan, A., Hesley, J. A., Miller, S. C., Cromwell, E. F., Solow-Cordero, D. E., Meyer, T., Cimprich, K. A.
2009; 35 (2): 228-239
- **The structural determinants of checkpoint activation** *GENES & DEVELOPMENT*
MacDougall, C. A., Byun, T. S., Van, C., Yee, M., Cimprich, K. A.
2007; 21 (8): 898-903
- **Functional uncoupling of MCM helicase and DNA polymerase activities activates the ATR-dependent checkpoint** *GENES & DEVELOPMENT*
Byun, T. S., Patek, M., Yee, M. C., Walter, J. C., Cimprich, K. A.
2005; 19 (9): 1040-1052
- **A novel protein activity mediates DNA binding of an ATR-ATRIP complex** *JOURNAL OF BIOLOGICAL CHEMISTRY*
Bomgardner, R. D., Yean, D., Yee, M. C., Cimprich, K. A.
2004; 279 (14): 13346-13353
- **ATR kinase activity regulates the intranuclear translocation of ATR and RPA following ionizing radiation** *CURRENT BIOLOGY*
Barr, S. M., Leung, C. G., Chang, E. E., Cimprich, K. A.
2003; 13 (12): 1047-1051
- **A requirement for replication in activation of the ATR-dependent DNA damage checkpoint** *GENES & DEVELOPMENT*
Lupardus, P. J., Byun, T., Yee, M. C., Hekmat-Nejad, M., Cimprich, K. A.
2002; 16 (18): 2327-2332
- **PPARgamma Interaction with UBR5/ATMIN Promotes DNA Repair to Maintain Endothelial Homeostasis.** *Cell reports*
Li, C. G., Mahon, C., Sweeney, N. M., Verschuere, E., Kantamani, V., Li, D., Hennings, J. K., Marciano, D. P., Diebold, I., Abu-Halawa, O., Elliott, M., Sa, S., Guo, et al
2019; 26 (5): 1333
- **Faulty replication can sting** *NATURE*

- Crossley, M. P., Cimprich, K. A.
2018; 557 (7703): 34–35
- **A new mitotic activity comes into focus** *SCIENCE*
Saldivar, J. C., Cimprich, K. A.
2018; 359 (6371): 30–31
 - **Co-transcriptional R-loops are the main cause of estrogen-induced DNA damage** *eLIFE*
Stork, C. T., Bocek, M., Crossley, M. P., Sollier, J., Sanz, L. A., Chédin, F., Swigut, T., Cimprich, K. A.
2016
 - **DNA replication stress underlies renal phenotypes in CEP290-associated Joubert syndrome** *JOURNAL OF CLINICAL INVESTIGATION*
Slaats, G. G., Saldivar, J. C., Bacal, J., Zeman, M. K., Kile, A. C., Hynes, A. M., Srivastava, S., Nazmutdinova, J., den Ouden, K., Zagers, M. S., Foletto, V., Verhaar, M. C., Miles, et al
2015; 125 (9): 3657-3666
 - **DNA damage-specific deubiquitination regulates Rad18 functions to suppress mutagenesis.** *journal of cell biology*
Zeman, M. K., Lin, J., Freire, R., Cimprich, K. A.
2014; 206 (2): 183-197
 - **The contribution of co-transcriptional RNA:DNA hybrid structures to DNA damage and genome instability.** *DNA repair*
Hamperl, S., Cimprich, K. A.
2014; 19: 84-94
 - **The contribution of co-transcriptional RNA:DNA hybrid structures to DNA damage and genome instability** *DNA REPAIR*
Hamperl, S., Cimprich, K. A.
2014; 19: 84-94
 - **Whole-Exome Sequencing Reveals TopBP1 as a Novel Gene in Idiopathic Pulmonary Arterial Hypertension** *AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE*
Perez, V. A., Yuan, K., Lyuksyutova, M. A., Dewey, F., Orcholski, M. E., Shuffle, E. M., Mathur, M., Yancy, L., Rojas, V., Li, C. G., Cao, A., Alastalo, T., Khazeni, et al
2014; 189 (10): 1260-1272
 - **Causes and consequences of replication stress.** *Nature cell biology*
Zeman, M. K., Cimprich, K. A.
2013; 16 (1): 2-9
 - **PHD domain from human SHPRH** *JOURNAL OF BIOMOLECULAR NMR*
Machado, L. E., Pustovalova, Y., Kile, A. C., Pozhidaeva, A., Cimprich, K. A., Almeida, F. C., Bezsonova, I., Korzhnev, D. M.
2013; 56 (4): 393-399
 - **Finally, Polyubiquitinated PCNA Gets Recognized** *MOLECULAR CELL*
Zeman, M. K., Cimprich, K. A.
2012; 47 (3): 333-334
 - **A Two-Dimensional ERK-AKT Signaling Code for an NGF-Triggered Cell-Fate Decision** *MOLECULAR CELL*
Chen, J., Lin, J., Cimprich, K. A., Meyer, T.
2012; 45 (2): 196-209
 - **Checkpoint recovery after DNA damage: a rolling stop for CDKs** *EMBO REPORTS*
Duursma, A. M., Cimprich, K. A.
2010; 11 (6): 411-412
 - **HARPing on about the DNA damage response during replication** *GENES & DEVELOPMENT*
Driscoll, R., Cimprich, K. A.
2009; 23 (20): 2359-2365
 - **Proliferating Cell Nuclear Antigen Uses Two Distinct Modes to Move along DNA** *JOURNAL OF BIOLOGICAL CHEMISTRY*
Kochaniak, A. B., Habuchi, S., Loparo, J. J., Chang, D. J., Cimprich, K. A., Walter, J. C., van Oijen, A. M.
2009; 284 (26): 17700-17710

- **DNA damage tolerance: when it's OK to make mistakes** *NATURE CHEMICAL BIOLOGY*
Chang, D. J., Cimprich, K. A.
2009; 5 (2): 82-90
- **ATR: an essential regulator of genome integrity** *NATURE REVIEWS MOLECULAR CELL BIOLOGY*
Cimprich, K. A., Cortez, D.
2008; 9 (8): 616-627
- **Probing ATR activation with model DNA templates** *CELL CYCLE*
Cimprich, K. A.
2007; 6 (19): 2348-2354
- **The ATR pathway: Fine-tuning the fork** *DNA REPAIR*
Paulsen, R. D., Cimprich, K. A.
2007; 6 (7): 953-966
- **Analyzing the ATR-mediated checkpoint using Xenopus egg extracts** *METHODS*
Lupardus, P. J., Van, C., Cimprich, K. A.
2007; 41 (2): 222-231
- **Monoubiquitination of proliferating cell nuclear antigen induced by stalled replication requires uncoupling of DNA polymerase and mini-chromosome maintenance helicase activities** *JOURNAL OF BIOLOGICAL CHEMISTRY*
Chang, D. J., Lupardus, P. J., Cimprich, K. A.
2006; 281 (43): 32081-32088
- **Opposing effects of the UV lesion repair protein XPA and UV bypass polymerase eta on ATR checkpoint signaling** *EMBO JOURNAL*
D Bomgardner, R., Lupardus, P. J., Soni, D. V., Yee, M., Ford, J. M., Cimprich, K. A.
2006; 25 (11): 2605-2614
- **Phosphorylation of Xenopus Rad1 and Hus1 defines a readout for ATR activation that is independent of claspin and the Rad9 carboxy terminus** *MOLECULAR BIOLOGY OF THE CELL*
Lupardus, P. J., Cimprich, K. A.
2006; 17 (4): 1559-1569
- **Characterization of the minimal checkpoint-activating DNA structure**
Cimprich, K. A., Byun, T. S., MacDougall, C.
FEDERATION AMER SOC EXP BIOL.2006: A1360
- **Fanconi anemia proteins are required to prevent accumulation of replication-associated DNA double-strand breaks** *MOLECULAR AND CELLULAR BIOLOGY*
Sobeck, A., Stone, S., Costanzo, V., De Graaf, B., Reuter, T., de Winter, J., Wallisch, M., Akkari, Y., Olson, S., Wang, W. D., Joenje, H., CHRISTIAN, J. L., Lupardus, et al
2006; 26 (2): 425-437
- **A cell-permeable, activity-based probe for protein and lipid kinases** *JOURNAL OF BIOLOGICAL CHEMISTRY*
Yee, M., Fas, S. C., Stohlmeyer, M. M., Wandless, T. J., Cimprich, K. A.
2005; 280 (32): 29053-29059
- **G2 damage checkpoints: what is the turn-on?** *JOURNAL OF CELL SCIENCE*
O'Connell, M. J., Cimprich, K. A.
2005; 118 (1): 1-6
- **Replication-dependent activation of the DNA damage checkpoint.**
Byun, T. S., Yee, M. C., Cimprich, K. A.
AMER CHEMICAL SOC.2004: U180
- **Checkpoint adaptation: Molecular mechanisms uncovered** *CELL*
Lupardus, P. J., Cimprich, K. A.
2004; 117 (5): 555-556

- **Fragile sites: Breaking up over a slowdown** *CURRENT BIOLOGY*
Cimprich, K. A.
2003; 13 (6): R231-R233
- **Enforced proximity in the function of a famous scaffold** *MOLECULAR CELL*
Ferrell, J. E., Cimprich, K. A.
2003; 11 (2): 289-291
- **An ATR- and Cdc7-dependent DNA damage checkpoint that inhibits initiation of DNA replication** *MOLECULAR CELL*
Costanzo, V., Shechter, D., Lupardus, P. J., Cimprich, K. A., Gottesman, M., Gautier, J.
2003; 11 (1): 203-213
- **Phosphorylation of serines 635 and 645 of human Rad17 is cell cycle regulated and is required for G(1)/S checkpoint activation in response to DNA damage** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Post, S., Weng, Y. C., Cimprich, K., Chen, L. B., Xu, Y., Lee, E. Y.
2001; 98 (23): 13102-13107
- **Xenopus ATR is a replication-dependent chromatin-binding protein required for the DNA replication checkpoint** *CURRENT BIOLOGY*
Hekmat-Nejad, M., You, Z. S., Yee, M. C., Newport, J. W., Cimprich, K. A.
2000; 10 (24): 1565-1573
- **Activation of the ATM kinase by ionizing radiation and phosphorylation of p53** *SCIENCE*
Canman, C. E., Lim, D. S., Cimprich, K. A., Taya, Y., Tamai, K., Sakaguchi, K., Appella, E., Kastan, M. B., Siliciano, J. D.
1998; 281 (5383): 1677-1679
- **Overexpression of a kinase-inactive ATR protein causes sensitivity to DNA-damaging agents and defects in cell cycle checkpoints** *EMBO JOURNAL*
Cliby, W. A., Roberts, C. J., Cimprich, K. A., Stringer, C. M., LAMB, J. R., Schreiber, S. L., Friend, S. H.
1998; 17 (1): 159-169
- **cDNA cloning and gene mapping of a candidate human cell cycle checkpoint protein** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Cimprich, K. A., Shin, T. B., Keith, C. T., Schreiber, S. L.
1996; 93 (7): 2850-2855