

## BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Shelley D. Copley	Professor, Department of Molecular, Cellular and Developmental Biology

### EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Harvard-Radcliffe	A.B.	1980	Biochemistry
Harvard Medical School		1980-82	Medicine
Harvard University	Ph. D.	1987	Biophysics
MIT		1987-1988	Molecular Biology
University of Colorado		1988-1990	Bioorganic chemistry

### A. Personal Statement

The Copley laboratory studies the evolution of enzymes and metabolic pathways in the context of the complex metabolic and regulatory networks in cells. At the molecular level, we investigate the evolutionary potential of promiscuous activities. Although promiscuous activities are inefficient, they are often orders of magnitude faster than uncatalyzed reactions. Thus, a promiscuous activity provides an excellent starting place for evolution of a new enzyme if that activity becomes important for growth or survival. We have characterized several promiscuous enzymes that are in the process of evolving a new function so that we can understand the reasons for their relatively poor performance and the reasons for improvements caused by mutations.

The prospects for evolution of a new enzyme depend upon the complement of enzymes expressed in a bacterium under a particular set of environmental conditions. Thus, improvement of a promiscuous activity may be possible only in some microbes, or only under some conditions. We have carried out adaptive evolution of strains in which an inefficient enzyme limits growth rate, and have discovered that fitness can be improved by mutations within the gene encoding the inefficient enzyme, but also elsewhere in the genome.

The presence of hundreds of enzymes, each of which probably has a number of promiscuous activities, within a particular microbe provides the possibility of patching together multiple promiscuous activities to generate a novel metabolic pathway. We are identifying novel pathways that can reconstitute biosynthesis of the cofactor PLP in various bacteria when an essential gene is deleted. This model system allows us to address questions such as 1) how many novel pathways can be assembled from the resources in a given genome, and are some better than others?; 2) how do different bacteria solve this evolutionary challenge, and why do their solutions differ?; and 3) how do mutations enable assembly of a novel pathway?

Finally, we are investigating the importance of synonymous mutations that do not change the sequence of the encoded protein, but alter mRNA sequence and thus have the potential to affect mRNA structure and function. We have identified thousands of small clusters of synonymous mutations in *E. coli* that have unexpectedly high impacts on fitness during growth on a sub-optimal carbon source. We are delving into the mechanisms by which these mutations affect the levels of the mRNA and the encoded protein, and the function of the system as a whole.

### B. Positions and Honors

#### Positions Held

1990-1998	Assistant Professor of Chemistry and Biochemistry, University of Colorado at Boulder
1990 – present	Fellow, Cooperative Institute for Research in Environmental Sciences, University of Colorado at Boulder

1998-1999	Associate Professor of Chemistry and Biochemistry, University of Colorado at Boulder
2000-2004	Associate Professor of Molecular, Cellular, and Developmental Biology, University of Colorado at Boulder
2004-present	Professor of Molecular, Cellular, and Developmental Biology, University of Colorado at Boulder
2012-2015	Associate Chair of Molecular, Cellular, and Developmental Biology, University of Colorado at Boulder

### **Other Experience**

1999-2003	NSF Molecular Biochemistry Panel
2000	Ad hoc reviewer, NIH Physical Biochemistry Study Section
2001	Nominating Committee, Biological Division of the American Chemical Society
2002-2004	Councilor, Biological Division of the American Chemical Society
2003-2004	Associate, Committee on Environmental Improvement, American Chemical Society
2003-2005	Editorial Board, Bioorganic Chemistry
2003	Co-Vice Chair, Gordon Conference on Enzymes, Coenzymes, and Metabolic Pathways
2003-2004	NIH Biochemistry Study Section
2003-2011	Member of Faculty of 1000
2004	Co-Chair, Gordon Conference on Enzymes, Coenzymes, and Metabolic Pathways
2004-2005	Member, Japanese-American Frontiers of Science Symposium Planning Committee
2004-2005	Member, National Research Council Space Studies Board Committee on Limits of Life in the solar System
2004-2007	NIH Genetic Variation and Evolution Study Section
2009	Ad hoc reviewer, NIH MSFE study section, Special Emphasis Panel and Grand Opportunity grant study section
2010	Ad hoc reviewer, NIH Genetic Variation and Evolution study section and EUREKA Review Panel
2010-2013	Biocatalysis Organizing Committee, Society for Industrial Microbiology Annual Meeting
2012	Chemical and Systems Biology Theme Organizer, ASBMB 2013 Annual Meeting
2012	Reviewer, NIH Biological Chemistry and Macromolecular Biophysics B special study section
2012	NSF Molecular Biochemistry Panel
2013	Review teams for NIH Glue and U54 grants
2014	NIH Genetic Variation and Evolution Study Section, ad hoc reviewer
2014-2016	Editorial Review Board, <i>Journal of Biological Chemistry</i>
2017	AbSciCon 2017 Session organizer, Origin and Evolution of Life: Evolution/Genetics: Experimental Microbial Evolution
2018	NIH Genetic Variation and Evolution Study Section, ad hoc reviewer
2019	NIH R25 study section
2020	NIH R35 study section
2021	NIH R24 study section
2023	Co-Vice Chair, Gordon Research Conference on Molecular Mechanisms in Evolution
2025	Co-Chair, Gordon Research Conference on Molecular Mechanisms in Evolution

### **Honors**

1980	A. B. <i>summa cum laude</i> , Harvard University
1980	Phi Beta Kappa
1987-1988	Anna Fuller Fund Fellow

1991  
1998

University of Colorado Junior Faculty Development Award  
Mortar Board National Honor Society Outstanding Professor

### **C. Publications**

- Morgenthaler, AB, Fritts, RK and Copley, SD. "Amplicon remodeling and genomic mutations drive population dynamics after segmental amplification", *Mol. Biol. Evol.* msab289, 2021.
- Copley, SD, Babbs, S and Losoff, B. "Science and society: Integrating historical science materials into an undergraduate biology course", *CourseSource*, 2021, doi [10.24918/cs.2021.23](https://doi.org/10.24918/cs.2021.23).
- Copley, SD. "Setting the stage for evolution of a new enzyme", *Curr. Opin. Structural Biol.*, **69**, 41-49, 2021.
- Copley, SD. "Evolution of new enzymes by gene duplication and divergence", *FEBS J.* **287**, 1262-1283, 2020.
- Copley, SD. "The physical basis and practical consequences of biological promiscuity", *Phys. Biol.* **17**, 051001, 2020.
- Choudhury, A, Fankhauser, RG, Freed, EF, Oh, EJ, Morgenthaler, AB, Bassalo, MC, Copley, SD, Kaar, JL and Gill, RT. "Determinants for efficient editing with Cas9-mediated recombining in *Escherichia coli*", *ACS Synth. Biol.* **9**, 1083-1099, 2020. PMID 32298586
- Morgenthaler, AB, Kinney, WR, Ebmeier, CC, Walsh, CM, Snyder, DJ, Cooper, VS, Old, WM and Copley, SD. "Mutations that improve the efficiency of a weak-link enzyme are rare compared to adaptive mutations elsewhere in the genome". *eLife* **8**:e53535, 2019. PMID: 31815667 DOI: [10.7554/eLife.53535](https://doi.org/10.7554/eLife.53535).
- Kim, J, Flood, JJ, Kristofich, M, Gidfar, C, Morgenthaler, AB, Fuhrer, T, Sauer, U, Snyder, D, Cooper, VS, Ebmeier, CC, Old, WM, and Copley, SD. "Hidden resources in the *E. coli* genome restore PLP synthesis and robust growth after deletion of the "essential" gene *pdxB*", *PNAS* **116** (48), 24164-24173, 2019. PMID 31712440
- Flood, J.J. and Copley, S.D. "Genome-wide analysis of transcriptional changes and genes that contribute to fitness during degradation of the anthropogenic pollutant pentachlorophenol by *Sphingobium chlorophenolicum*", *mSystems*, **3**, e00275-18, 2018. PMID: 30505947
- Kristofich, J-C, Morgenthaler, AB, Kinney, WR, Snyder, DJ, Ebmeier, CC, Old, WM, Cooper, VS, and Copley, SD. "Synonymous mutations make dramatic contributions to fitness when growth is limited by a weak-link enzyme", *PLoS Genetics*, **14**, e1007615, 2018. PMID 30148850
- Mikkonen, A, Yläntä, K, Tiirola, M, Dutra, LAL, Salmi, P, Romantschuk, M, Copley, S, Ikäheimo, J, Sinkkonen, A, "Successful aerobic bioremediation of groundwater contaminated with higher chlorinated phenols by indigenous degrader bacteria". *Water Res.* **138**, 118-128, 2018.
- Copley, SD. "Shining a light on enzyme promiscuity", *Curr. Opin. Struct. Biol.* **47**, 67-75, 2017.
- Kershner, JP, Yu McLoughlin, S, Kim, J, Morgenthaler, A, Ebmeier, CC, Old, WM, Copley, SD. "A synonymous mutation upstream of the gene encoding a weak-link enzyme causes an ultrasensitive response in growth rate." *J. Bacteriol.* **198**, 2853-2863, 2016. PMID 27501982
- Thiaville, J, Flood, J, Yurgel, S, Prunetti, L, Elbadawi-Sidhu, M, Hutinet, G, Forouhar, F, Zhang, X, Ganesan, V, Reddy, P, Fiehn, O, Gerlt, J, Hunt, J, Copley, SD, De Crecy-Lagard, V. "Members of a novel kinase family (DUF1537) can recycle toxic intermediates into an essential metabolite", *ACS Chemical Biology*, **11**, 2304-2011, 2016.
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- Copley, SD. "An evolutionary perspective on protein moonlighting", *Biochemical Society Transactions*, **42**, 1684-1691, 2014.
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- Kim, J and Copley, SD. "The orphan protein bis- $\gamma$ -glutamylcystine reductase joins the pyridine nucleotide-disulfide reductase family", *Biochemistry*, **52**, 2905-2913, 2013. PMID: 23560638
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- Hlouchova, K, Rudolph, J, Pietari, JMH, Behlen, LS, Shoemaker, RK and Copley, SD. "Pentachlorophenol hydroxylase, a poorly functioning enzyme required for degradation of pentachlorophenol by *Sphingobium chlorophenolicum*", *Biochemistry* **51**, 3848-3860, 2012. PMID: 22482720
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#### D. Funding

NASA Exobiology 1/15/21-1/14/24 \$555,750 Confronting a Conundrum: the Prevalence of Loss-of-function Mutations in Evolution	Copley (PI)
NIH/NIGMS R01GM134044 8/12/19 – 7/31/23 \$1,420,133 Gene Duplication and Divergence: the Bigger Picture	Copley (PI)
NIH/NIGMS R01GM124365 9/1/17 – 8/31/21, in no-cost extension \$1,281,317 The Cellular and Molecular Effects of Synonymous Mutations	Copley (PI)
NIH/NIGMS R01GM135364 5/1/20-2/29/24	Copley (PI)

\$1,390,009  
Promiscuity, Serendipity and Metabolic Innovation