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 using a combination of biochemistry, genetics, genomics and a deep understanding of enzyme mechanisms and microbial metabolism and physiology.

New enzymes often arise from physiologically irrelevant side-activities of existing enzymes. Although these “promiscuous” activities are usually 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 use experimental evolution to address fundamental questions about the processes by which new enzymes and metabolic pathways emerge, with an emphasis on identifying the molecular and cellular mechanisms by which mutations enhance fitness.

The initial stage of evolution of a new enzyme often involves gene amplification to provide higher levels of an inefficient enzyme, followed by mutations that improve the newly needed activity in some alleles while others continue to provide the ancestral function. We have examined the earliest stage of this process by characterizing the effect of segmental amplification on the levels of mRNAs and proteins produced from coamplified genes and amplicon remodeling that removes extra copies of coamplified genes that do not contribute to enhanced fitness.

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?

We have recently turned our attention to the potential of genes acquired by horizontal gene transfer (HGT) to contribute to novel metabolic pathways. HGT is rampant among microbes and provides an additional source of catalytic capability that can be utilized to address an environmental challenge or opportunity. We are investigating the mechanisms by which horizontally transferred genes are “domesticated” when they arrive in a new host genome.

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

Scientific Appointments

1999-2003	NSF Molecular Biochemistry Panel
2000	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	NIH MSFE study section, Special Emphasis Panel and Grand Opportunity grant study section
2010	NIH Genetic Variation and Evolution study section, 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	NIH Biological Chemistry and Macromolecular Biophysics B special study section
2012	NSF Molecular Biochemistry Panel
2013	NIH Glue Grant study section, NIH U54 study section
2014	NIH Genetic Variation and Evolution study section
2014-2016	Editorial Review Board, *Journal of Biological Chemistry*
2017	AbSciCon 2017 Session organizer, Origin and Evolution of Life: Evolution/Genetics: Experimental Microbial Evolution
2018	NIH Genetic Variation and Evolution study section
2019	NIH R25 study section
2020	NIH R35 study section
2021	NIH R24 study section
2022	NIH Fellowship study section
2022-	co-Theme Organizer, American Society for Biochemistry and Molecular Biology 2024 Annual Meeting
2022-	External Advisory Board, Arizona State University BII: Mechanisms of Cellular Evolution Center
2022-	Steering Committee, NASA *LIFE* Research Coordination Network
2023	Co-Vice Chair, Gordon Research Conference on Molecular Mechanisms in Evolution

2023	NIH K99 study section
2024	Theme Leader, Cool and Novel Enzymes, ASBMB 2024
2024	Session chair, AbSciCon
2025	Co-Chair, Gordon Research Conference on Molecular Mechanisms in Evolution

Honors

1980	A. B. *summa cum laude*, Harvard University
1980	Phi Beta Kappa
1987-1988	Anna Fuller Fund Fellow
1991	University of Colorado Junior Faculty Development Award
1998	Mortar Board National Honor Society Outstanding Professor
2003-2005	Kavli Frontiers of Science Fellow

C. Publications

Widney, KA, Phillips, LC, Rusch, LM and Copley, SD. "A cheater founds the winning lineages during evolution of a novel metabolic pathway", BioRxiv https://doi.org/10.1101/2025.01.26.634942

Lynch, MD, Lipscomb-Warnecke, T, Hogsett, D, Louie, MTM, Copley, S, Evans, R, Lipscomb, M, and Liao, HH. "Microorganisms and methods for the production of fatty acids and fatty acid derived products", US Patent 11408013, 2024

Newton, MS, Azadeh, AL, Morgenthaler, AB and Copley, SD. "Overturning a decades-old paradigm: ProB and ProA do not channel the unstable intermediate in proline synthesis after all", *Proc. Natl. Acad. Sci. USA* **121** (46) e2413673121, 2024, doi: https://doi.org/10.1073/pnas.2413673121

Yang, D-D, Rusch, LM, Widney, KA, Morgenthaler, AB and Copley, SD. "Synonymous edits in the *E. coli* genome have substantial and condition-dependent effects on fitness", *Proc. Natl. Acad. Sci. USA*, **121** (5) e2316834121, 2024, https://doi.org/10.1073/pnas.2316834121

Fritts, RK, Ebmeier, CC and Copley, SD. "The transcriptomic and proteomic ramifications of segmental amplification", BioRxiv [Preprint] Nov 21, 2023, https://doi.org/10.1101/2023.11.21.568005.

Copley, SD, Newton, MS and Widney, KA. "How to recruit a promiscuous enzyme to serve a new function", *Biochemistry* **62**, 300-308, 2023. (Special issue in honor of Professor Dan Tawfik), https://doi.org/10.1021/acs.biochem.2c00249

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Copley, SD, Babbs, S and Losoff, B. "Science and society: Integrating historical science materials into an undergraduate biology course", *CourseSource***,** 2021, 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, https://doi.org/10.1016/j.sbi.2021.03.001

Copley, SD. "Evolution of new enzymes by gene duplication and divergence", *FEBS J.* **287**, 1262-1283, 2020, https://doi.org/10.1111/febs.15299

Copley, SD. "The physical basis and practical consequences of biological promiscuity", *Phys. Biol.***17**, 051001, 2020, DOI 10.1088/1478-3975/ab8697

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 recombineering in *Escherichia coli*", *ACS Synth. Biol.* **9**, 1083-1099, 2020. PMID 32298586, https://doi.org/10.1021/acssynbio.9b00440

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.

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*", *Proc. Natl. Acad. Sci. USA* **116**, 24164-24173, 2019. PMID 31712440,https://doi.org/10.1073/pnas.1915569116

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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 Genet.* **14**, e1007615, 2018. PMID 30148850, https://doi.org/10.1371/journal.pgen.1007615

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