

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	Biorganic chemistry

A. Personal Statement

My 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 un-catalyzed 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.

Fitness is a characteristic of a microbe, not just a single inefficient enzyme. 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. We are working on identifying the mechanism by which each mutation contributes to the fitness of the microbe.

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 investigating several examples of this phenomenon, including pathways that can reconstitute biosynthesis of the cofactor PLP in *E. coli* when an essential gene is deleted, and a pathway for degradation of the toxic pesticide pentachlorophenol in a bacterium isolated from a highly contaminated site.

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, *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, ad hoc reviewer
2019 NIH R25 study section

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

C. Publications

Morgenthaler, A.B., Kinney, W.R., Ebmeier, C.C., Walsh, C.M., Snyder, D.J., Cooper, V.S., Old, W.M. and Copley, S.D. "Mutations that improve the efficiency of a weak-link enzyme are rare compared to adaptive mutations elsewhere in the genome". *eLife* **8**:e53535, 2019 DOI: [10.7554/eLife.53535](https://doi.org/10.7554/eLife.53535).

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- 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.
- Kristofich, JohnCarlo, Morgenthaler, Andrew B., Kinney, Wallis R., Snyder, Daniel J., Ebmeier, Christopher C., Old, William M., Cooper, Vaughn S., and Copley, Shelley D. "Synonymous mutations make dramatic contributions to fitness when growth is limited by a weak-link enzyme", *PLoS Genetics*, **14**, e1007615, 2018.
- Mikkonen, A., Yläntä, K., Tirola, M., Dutra, L. A. L., 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, Shelley D. "Shining a light on enzyme promiscuity", *Curr. Opin. Struct. Biol.* **47**, 67-75, 2017.
- Kershner, J. P., Yu McLoughlin, S., Kim, J., Morgenthaler, A., Ebmeier, C. C., Old, W. M., Copley, S. D. "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.
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- Rudolph, J., Erbse, A. H., Behlen, L. and Copley, S. D. "A radical intermediate in the conversion of pentachlorophenol to tetrachlorohydroquinone in *Sphingobium chlorophenolicum*". *Biochemistry* **56**, 6539-6549, 2014. PMID: 25238136
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D. Funding

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| NIH/NIGMS R01GM134044
8/12/19 – 7/31/23
\$226,653 annual direct costs
Gene Duplication and Divergence: the Bigger Picture | Copley (PI) |
| NIH/NIGMS R01GM124365
9/1/17 – 8/31/21
\$203,000 annual direct costs
The Cellular and Molecular Effects of Synonymous Mutations | Copley (PI) |
| NASA Astrobiology Institute NNA15BB04A
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\$120,000 annual direct costs to Copley lab
Reliving the History of Life: Experimental Evolution of Major Transitions | Copley (co-I), Rosenzweig (PI) |