MILLER INSTITUTE NEWSLETTER

Fall 2004

Miller Fellow Focus: Olafur Magnusson

Ever since Franz Hofmeister and Emil Fischer discovered that proteins were polymers made of amino acids over 100 years ago, biochemists have been fascinated by the structure and function of proteins. Enzymology is a sub-field of biochemistry that focuses on the studies of biological catalysts, most of which are proteins. Enzymes are the catalysts of life – a fact that is sometimes underappreciated in the modern era of genes and genomics. Enzymes are involved in nearly all of the chemical reactions that occur in all living organisms, ranging from primary metabolic pathways such as the breakdown of sugars to very complex and highly regulated signaling cascades. Another more pragmatic fact, which is often overlooked, is that most drugs on the market today affect the activity of certain enzymes in our bodies. For example, common household medications like aspirin and ibuprofen both inhibit (albeit via different mechanisms) the activity of an important enzyme in steroid metabolism named prostaglandin synthase, also called cyclooxygenase (COX). Understanding how enzymes work is thus a very important task, but even despite studies in the last 100 years there is still a lot to learn about enzyme function and new and exciting enzyme-catalyzed reactions continue to be discovered.

Olafur Magnusson is a 3rd year Miller Fellow in the Department of Chemistry, hosted by Professor Judith P. Klinman. He has been interested in enzymes ever since enrolling in the undergraduate biochemistry program at the University of Iceland in 1991. He continued to pursue this interest as a graduate student at the University of Wisconsin-Madison - a pursuit that continues to this date. He is particularly interested in two aspects of enzyme function, one being the facilitation of seemingly obscure and difficult chemical reactions, which often involve the use of highly reactive free radicals that can be generated via the use of certain coenzymes. His second main interest is the function and biosynthesis of coenzymes. But what are coenzymes? If one looks at the twenty amino acids that nature has at its disposal to make proteins, it is evident that the chemical and functional diversity of the amino acids is very limited. Only a few amino acids have chemically reactive groups and the type of chemistry is limited to acid/base and simple nucleophilic catalysis. Some enzymes have circumvented this problem through post-translational modification of certain amino acid residues in order to increase their chemical weaponry. However, by far the most common method that enzymes utilize to increase their range as catalysts is by recruiting coenzymes. Coenzymes (also called cofactors or prosthetic groups) are small organic molecules or metals and/or metal clusters that increase the functional diversity of enzymes enormously. Coenzymes are usually bound tightly and in a specific manner to enzymes that require their services. The site where the coenzyme is bound to its respective enzyme is "where the action takes place".

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Miller Fellow Olafur Magnusson

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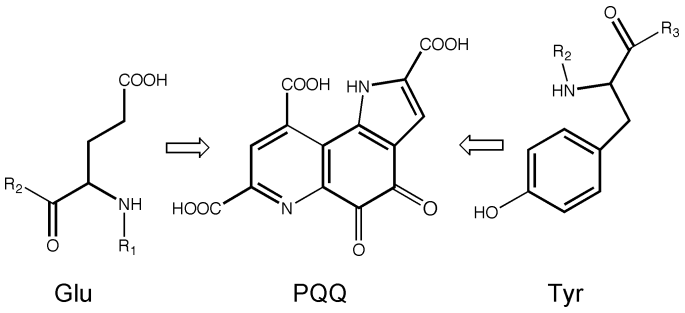
Deadlines to note:

Wednesday, September 22
Miller Professor applications due

Monday, September 27
Visiting Miller Professor Nominations due

Monday, October 4
Miller Fellow nominations due

Some of the most important types of coenzymes are those involved in oxidation/reduction (redox) reactions. Magnusson's work at Berkeley has been focused on understanding the biosynthetic pathway and the role of all the enzymes required putting together one such coenzyme named pyrroloquinoline quinone (PQQ). This coenzyme is essential for many bacteria that utilize small alcohols and simple sugars as carbon and energy sources. PQQ also appears to be important for eukaryotes, although its role is not fully understood and still controversial. Recent studies have shown the importance of PQQ in mammals. Most notably, a group of researchers found a potential role for the coenzyme in the breakdown pathway of the amino acid lysine. This suggests that PQQ should now be classified as a new B-vitamin in mammals.

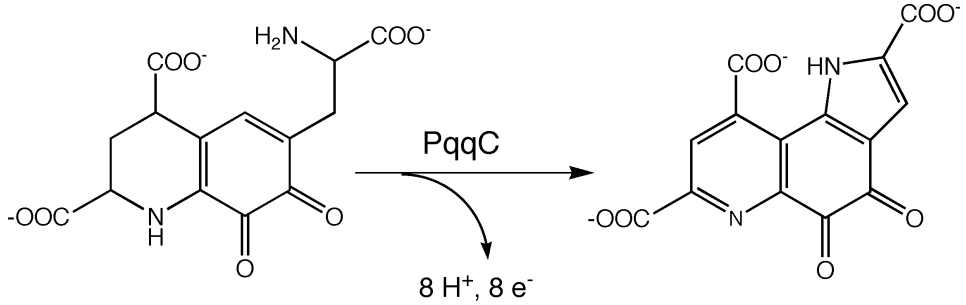


Biosynthesis of PQQ from amino acid precursors

Elegant labeling studies done in the late 80's showed that all carbon and nitrogen atoms of PQQ are derived from the amino acids glutamate (Glu) and tyrosine (Tyr). More recent genetic studies have identified all the genes required for the assembly of the coenzyme with the interesting identification of a short gene that encodes for a small peptide, which contains completely conserved Glu and Tyr residues. This and other observations have led to the conclusion that this peptide serves as a direct precursor for PQQ. Through a collaborative effort, Magnusson, Robert Schwarzenbacher at the Burnham Institute in LaJolla, CA and Hirohide Toyama at the Yamaguchi University in Japan have recently elucidated the last step in PQQ biosynthesis. This reaction involves a ring closure and an amazing eight-electron oxidation of a precursor molecule to produce PQQ. The reaction is catalyzed by an enzyme we call PqqC (nomenclature derived from genes in a transcriptional operon: pqqA-pqqF). Oxidation of eight electrons by one enzyme is an unprecedented process in biological systems, but perhaps more interestingly the enzyme itself does not require a coenzyme to catalyze this reaction. Based on structural and biochemical studies they have recently proposed a reaction mechanism that explains how the enzyme is able to accomplish this seemingly improbable task. Magnusson is currently trying to understand the function of other enzymes involved in PQQ biosynthesis. Through a combination of biochemical, kinetic, structural, spectroscopic and genetic methods, they hope to be able to assign functions for all the enzymes in the pathway.

When not found in the laboratory, Magnusson likes to spend quality time with his family – his wife Selma and their three-year old son Kjartan Isak. As this piece goes to press they are anxiously awaiting the arrival of their second child, due late August. They like to spend time traveling around Northern California, and when given the chance he tries to go hiking and climbing mountains in the high Sierra-Nevada mountain range and the volcanoes of the Cascades.


Olafur Magnusson with his wife Selma and their son Kjartan Isak.



Reaction catalyzed by PqqC

Next Steps

The Miller Institute congratulates outgoing Miller Fellows on their next endeavors.

ALISON GALVANI
Assistant Professor
Yale University, School of Medicine

CLARISSA HENRY
Assistant Professor, Biological Sciences
University of Maine

AARON VAN HOOSER
Postdoctoral Fellow, Molecular & Cell Biology
University of California, Berkeley

BENJAMIN MCCALL
Assistant Professor, Chemistry
University of Illinois, Urbana-Champaign

SHEILA PATEK
Assistant Professor, Integrative Biology
University of California, Berkeley

ANNE PRINGLE
Assistant Professor
Harvard University

JEFFREY TOWNSEND
Assistant Professor
University of Connecticut

MICHAEL ZACH
Glenn Seaborg Postdoctoral Fellow
Argonne National Laboratory

ROBERT ZILLICH
Research Fellow
Fraunhofer Institut fur Techno- und Wirtschaftsmathematik
Kaiserslautern, Germany

Awards

David Aldous (Miller Professor, Spring 1993) and **Paul A. Alivisatos** (Miller Professor, 2001-02) were elected to the American Academy of Arts and Sciences as fellows.

Stéphane Bodin (Miller Fellow, 2002-05) received an award for his PhD work from the Academie des Sciences et Belles Lettres (Academy of Sciences and Literature) of France.

F. Michael Christ (Miller Professor, 2000-01) was presented with the 2004 Distinguished Teaching Award, which is bestowed by the Berkeley Division of the Academic Senate's Committee on Teaching. The award is the campus's highest honor for teaching.

Charles Harris (Miller Professor, 1984-85) will assume the role of Dean of College of Chemistry in 2005.

Richard Karp (Miller Professor, 1980-81) was awarded the Franklin Medal honoring lifetime achievement in science.

Simon A. Levin (Visiting Miller Professor, Spring 2003) has been awarded the Dr A.H. Heineken Prize for Environmental Sciences 2004 by the Royal Netherlands Academy of Arts and Sciences.

Karl S. Pister (Miller Professor, 1962-63) is the 2004 winner of the TAM Distinguished Alumni Award, which is sponsored by the Department of Theoretical and Applied Mechanics (TAM), University of Illinois at Urbana-Champaign, and the TAM alumni Association Board of Directors.

Lisa Pruitt (Miller Professor, Fall 2000) received the 2003 Presidential Award for Excellence in Science, Mathematics and Engineering Mentoring, awarded by the U.S. President.

Several Miller Institute members were elected to the National Academy of Sciences in April.

- **Paul Alivisatos** (Miller Professor, 2001-02), Chemistry and Materials Science
- **Philip H. Bucksbaum** (Visiting Miller Professor, Fall 1996), Physics
- **Raymond Jeanloz** (Executive Director, 1998-2003; Miller Professor, Fall 1992), Earth & Planetary Science, Astronomy
- **Nicholas M. Katz** (Visiting Miller Professor, Spring 1993), Mathematics
- **Stephen L. Mayo** (Miller Fellow 1987-89), Biology and Chemistry
- **Erin K. O'Shea** (Miller Fellow, 1992-93), Biochemistry and Biophysics
- **George F. Oster** (Executive Committee Member; Miller Professor 1983-84, 2003-04), Cell & Developmental Biology, Environmental Science, Policy and Management

Botanical Gardens Tour and Picnic Lunch
July 13, 2004

Executive Committee Member Alberto Grunbaum and Miller Professor Kenneth Raymond

Miller Fellows Raghuveer Parthasarathy and Matthew Reidenbach

Miller Fellows Elchanan Mossel and Yi Cui

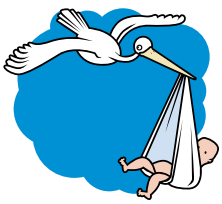
Miller Fellows Jeffrey Townsend and Ioana Dumitriu

ScienceMatters@Berkeley

From The Berkeleyan: The College of Letters & Science has teamed up with the College of Chemistry to launch ScienceMatters@Berkeley (http://sciencematters.berkeley.edu), a monthly online research magazine that will highlight groundbreaking research in the physical and biological sciences. Former Miller Professor Paul Alivisatos and Miller Symposium Speaker Chung-Pei Ma were among the science faculty whose work was profiled in the first issue of ScienceMatters@Berkeley.

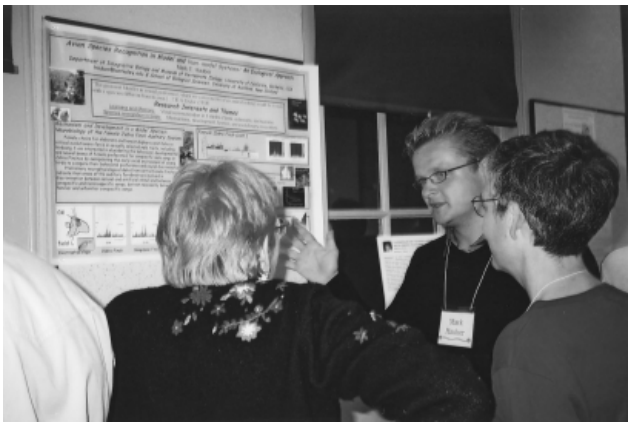
Birth Announcement

Congratulations to Former Miller Fellow Clarissa Henry and Thane Fremouw on the birth of their son, Rowen, who was born on May 10, 2004.

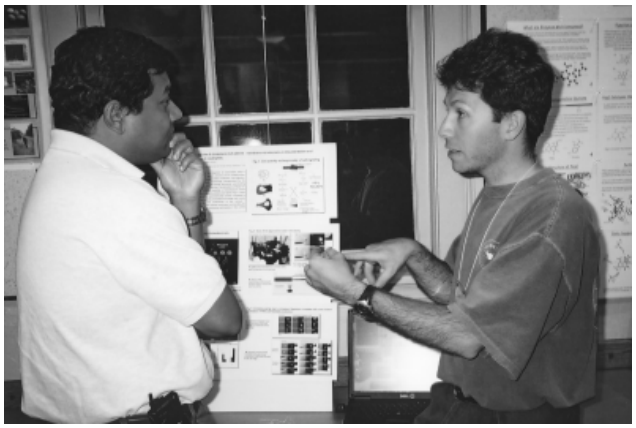


The Miller Institute's
Eighth Annual Interdisciplinary Symposium
June 2004

Former Miller Fellow Lincoln Greenhill and Miller Fellow Alice Shapley



Miller Fellow Mark Hauber explains his research to Speaker JoAnne Stubbe and Miller Professor Ellen Simms



Former Miller Professor Arunava Majumdar and Miller Fellow Stéphane Bodin

Miller Fellows Subhadeep Gupta and Eric Ford

Former Miller Fellows Sheila Patek and Anne Pringle with Executive Committee Member Mimi Koehl

Miller Fellows Ioana Dumitriu, Elena Mantovan, Alex Thompson, Raghuveer Parthasarathy, Yann Capdeville and Olafur Magnusson

Miller Institute News
Fall 2004
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Publications

The following Miller Institute members have recently published works resulting from research during their Miller Institute terms. For more information about these publications, please visit the Miller Institute's website at: http://millerinstitute.berkeley.edu/news/publications.htm.

Anil Chopra
Miller Professor, 2003-04

Yi Cui
Miller Fellow, 2003-06

Imke de Pater
Miller Professor, 2003-04

Clarissa Henry
Miller Fellow, 2001-04

Cynthia Jameson
Visiting Miller Professor, Spring 2001

Judith Klinman
Miller Professor, 2003-04

Xanthippi Markenscoff
Visiting Miller Professor, Fall 2003

Benjamin McCall
Miller Fellow, 2001-04

Sheila Patek
Miller Fellow, 2001-04

Anne Pringle
Miller Fellow, 2001-2004

Aziz Sancar
Visiting Miller Professor, Spring 2002

Martin Scharlemann
Miller Professor, Fall 2001

Montgomery Slatkin
Miller Professor, Spring 2004

Aaron van Hooser
Miller Fellow, 2001-04

Michael Zach
Miller Fellow, 2002-04

Robert Zillich
Miller Fellow, 2001-04

The Miller Institute is "dedicated to the encouragement of creative thought and the conduct of research and investigation in the field of pure science and investigation in the field of applied science in so far as such research and investigation are deemed by the Advisory Board to offer promising approach to fundamental problems."