American Chemical Society

National Awards Nomination Packet

Ronald Breslow Award for Achievement in Biomimetic Chemistry:2018
for: M Ghadiri

Received: 10/27/2014 *Cycle Year: 3*

"Path-pointing contributions to the de novo design of functional peptides and protein assemblies and to the probable role of peptides in the origins of life"

NOMINATOR:

Phil Baran

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Tel: (858)720-1823
Email: pbaran@scripps.eduXXX

- Have you discussed this award nomination with the nominee? *Yes*

NOMINEE:

M Ghadiri

Scripps Rsrch Inst
10550 N Torrey Pines Rd
La Jolla, CA 92037-1000
UNITED STATES

Tel: (858)784-2700
Email: rghadiri@mac.comXXX

ACS Current Member: Yes
Years of Service: 34
Date of birth: 01/01/1959
Present Position: Professor
Industry: Academia

- Does the nominee employ and require good safety protocols and practices in his/her laboratory? *Yes*
- What is the nominee's present position? *Professor*
- What professional discipline does the nominee work in? *Academia*

SUPPORTER 1

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Phil S. Baran
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September 30, 2014

Re: **ACS Breslow Award**
Candidate **M. Reza Ghadiri**

Dear Award Committee:

I write with glowing enthusiasm to nominate Reza Ghadiri for the Breslow Award. Reza has made incredibly impactful contributions to the fields of the *de novo* design of peptide and protein structures, functional peptide assemblies, bioactive agents, complex molecular networks, and to the better understanding of the probable roles of peptides in the origins of life. His work has been path-pointing to scores of people in bioorganic chemistry and he is a world recognized thought leader and innovator as evidenced by over 11,000 citations to his work (H factor = 55). I write as both his colleague and past student, having learned bioorganic chemistry from him in graduate school many years ago. Reza is one of the most creative scientists I have ever met and I routinely seek his advice for our own projects.

His contributions to the field of the *de novo* design of peptide and protein structures range from his early studies in metal ion-assisted self-organizing and self-assembling processes to induce predetermined folding of peptides and protein-like structures to the more recent design of aminoacyl transfer catalysts and the rational design of bioactive compounds based on conformationally homogeneous four-residue cyclic peptidomimetic structures. His approach to metallo-peptide and -protein designs constituted the basis for the construction and study of electron transfer in *de novo* designed protein redox systems. His influential 1993 *Nature* paper describing the synthesis and structural analyses of self-assembling peptide nanotubes marked the beginning of a new field of research in the design of functional biomaterials and bioactive agents. His contributions span the original development of the basic design concepts to their adapted use in materials science and as therapeutics. The applications include polymeric self-assembling constructs, liquid crystals, photo-switchable materials, transmembrane molecular transport systems, and electronically active complexes and nanowires. Additionally, he has introduced and developed self-assembling cyclic peptides as antimicrobial agents with *in vivo* efficacy against MRSA and VRE infections [*Nature* **2001**, *412*, 452]. Similar antiviral constructs with novel modes of action have been discovered against adenovirus, hepatitis C, and influenza infections.

Ghadiri also made seminal contributions to the advancement of peptide research through his studies in the emerging field of systems chemistry and the origin of life. His research in this area has been concerned with developing synthetic models to uncover the chemical roots of biological information processing, organization, and function. Through a series of landmark papers

appearing in *Nature* and *Science*, Ghadiri reported the first examples of self-replicating peptide structures, the disclosure of template-directed peptide ligases and the construction of a number of primary peptide networks that displayed emergent properties such as replication and symbiosis, and the only example of an experimental system that displays efficient auto- and cross-catalytic homochiral amplification and error correction properties.

He has also reported a number of pioneering studies supporting the potential roles of peptides in the origins of life. His study on the origins of homochirality remains the only experimental system that displays efficient auto- and cross-catalytic homochiral amplification and error correction properties [*Nature* **2001**, *409*, 797]. He provided the first plausible prebiotic condensation reactions, showing that carbonyl sulfide (COS, a volcanic gas) can promote efficient formation of peptides from amino acids under mild aqueous conditions [*Science* **2004**, *306*, 283]. He demonstrated that COS is also effective at promoting the synthesis of aminoacyl phosphates (amino acids + inorganic phosphate) or aminoacyl adenylates (amino acids + adenylic acid), suggesting that peptide synthesis and phosphoryl transfer reactions might have shared a common activated precursor on prebiotic Earth [*J. Am. Chem.* Soc., **2006**, *128*, 20]. And recently, he has taken a significant step toward the design of a system capable of undergoing Darwinian evolution, developing the first self-assembling sequence-adaptive peptide nucleic acid structures [*Science* **2009**, *325*, 73], supporting a potential interdependence of peptides and nucleic acids in primordial (pre-RNA World) genetic systems.

Aside from his scientific contributions he has educated more than 30 graduate and postdoctoral scholars that have gone on to successful careers in prominent academic posts. The practical utility of his remarkably creative approaches are readily apparent in the scores of people that have used his concepts to design functional materials. From a purely objective standpoint, Reza Ghadiri has made profound, compelling, and pioneering contributions to bioorganic chemistry and thus is most deserving of this great honor. He exemplifies the intrinsic creativity that is the essence of the Ronald Breslow.

Yours truly,

Phil S. Baran, Ph.D.
Department of Chemistry
The Scripps Research Institute

Curriculum Vita **M. Reza Ghadiri, Ph.D.**

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Phone: (858) 784-2700
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Education:

Undergraduate:	University of Wisconsin-Milwaukee
	B.A., Chemistry, 1982
Graduate:	University of Wisconsin-Madison
	Ph.D., Chemistry, 1987
Postdoctoral:	The Rockefeller University, 1987-1989

Research and Professional Appointments:

1982-1987: Research Associate, Department of Chemistry, University of Wisconsin-Madison. Synthetic Organic Chemistry, Ph.D. thesis title: Alkylations via Lewis acid promoted substitutions of sulfones (Advisor: Professor Barry M. Trost).

1987-1989: Postdoctoral Research Fellow, Rockefeller University, Bioorganic Chemistry, Enzymology and Molecular Biology (Advisor : Professor Emil T. Kaiser).

1989-1994: Assistant Professor; 1995-1997: Associate Professor, Departments of Chemistry and Molecular Biology, The Scripps Research Institute, La Jolla, California.

1996- present: Member, the Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, California.

1998- present: Professor, Departments of Chemistry, The Scripps Research Institute, La Jolla, California.

Awards and Fellowships:

Rockefeller Postdoctoral Fellow 1987-1989
Searle Scholars Award 1991-1994
Arnold and Mabel Beckman Young Investigator Award 1991-1993
Alfred P. Sloan Research Fellow 1993-1995
Eli Lilly Grantee 1994-1995
American Chemical Society Award in Pure Chemistry 1995
Feynman Prize in Nanotechnology 1998
Arthur C. Cope Scholar Award, American Chemical Society 1999
Visiting Professor, University of Santiago, Spain 2000
Elected Fellow, American Association for the Advancement of Science 2001
Vincent du Vigneaud Award, American Peptide Society 2010

Research Interests:

- *De novo* design of synthetic peptides and catalysts.
- Rational design of intrasterically regulated semi-synthetic enzymes for nucleic acid diagnostics and programmed enzyme therapeutics.
- Prebiotic chemistry, design of self-replicating molecular systems, complex self-organized networks, and adaptive informational biopolymers.
- Self-assembling peptide nanotubes in the design of adaptive biomaterials and antimicrobial therapeutics.
- Design and discovery of bioactive agents that remodel the epigenetic network processes and organization.
- Single-molecule nanopore DNA sequencing.
- DNA-based molecular computation.
- Design of HDL-mimetic nanolipopeptides as anti-atherosclerotic agents.

Publications: ~106

Plenary and Named Lectureships: ~30

Invited Lectures: ~230

Reza Ghadiri, Ph.D.

List of 20 Significant Publications:

1. Ghadiri, M. R.; Granja, J. R.; Milligan, R. A.; McRee, D. E ; Khazanovich, N. "Self-Assembling Organic Nanotubes Based on a Cyclic Peptide Architecture". *Nature* **1993**, *366*, 324-327.

2. Ghadiri, M. R.; Granja, J. R.; Buehler, L. "Artificial Transmembrane Ion Channels From Self-Assembling Peptide Nanotubes" *Nature* **1994**, *369*, 301-304.

3. Lee, D. H.; Granja, J. R.; Martinez, J. A.; Severin, K.; Ghadiri, M. R. "A Self-Replicating Peptide". *Nature* **1996**, *382*, 525-528.

4. Severin, K.; Lee, D. H.; Kennan, A. J.; Ghadiri, M. R. "A Synthetic Peptide Ligase", *Nature* **1997**, *389*, 706-709.

5. Lee, D. H.; Severin, K.; Yokobayashi, Y.; Ghadiri, M. R. "Emergence of Symbiosis in Peptide Self-Replication Through a Hypercyclic Network", *Nature* **1997**, *390*, 591.

6. Severin, K.; Lee, D. H.; Martinez, J. A.; Vieth, M.; Ghadiri, M. R. "Dynamic Error-Correction in Autocatalytic Peptide Networks", *Angew. Chem. Int. Ed.* **1998**, *37*, 126-128.

7. Clark, T. D.; Buehler, L. K.; Ghadiri, M. R. "Self-Assembling Cyclic β^3-Peptide Nanotubes as Artificial Transmembrane Ion Channels", *J. Am. Chem. Soc.* **1998**, *120*, 651-656.

8. Bong, D. T.; Steinem, C.; Janshoff, A.; Johnson, J. E.; Ghadiri, M. R. "A Highly Membrane Active Peptide in Flock House Virus: Implications for the Mechanism of Nodavirus Infection". *Chem. Biol.* **1999**, *6*, 473-481.

9. Saghatelian, A.; Yokobayashi, Y.; Soltani, K.; Ghadiri, M. R. "A Chiroselective Peptide Replicator", *Nature* **2001**, *409*, 797-801.

10. Fernandez-Lopez, S.; Kim, H. S.; Choi, E. C.; Delgado, M.; Granja, J. R.; Khasanov, A.; Kraehenbuehl, K.; Long, G.; Weinberger, D. A.; Wilcoxen, K.; Ghadiri, M. R. "Antibacterial Agents Based on the Cyclic *D,L*-α-Peptide Architecture", *Nature* **2001**, *412*, 452-455.

11. Sánchez-Quesada, J.; Isler, M. P.; Ghadiri, M. R. "Modulating Ion Channel Properties of Transmembrane Peptide Nanotubes Through Heteromeric Supramolecular Assemblies", ,*J. Am. Chem. Soc.* **2002**, *124*, 10004-10005.

12. Ashkenasy, G.; Jagasia, R.; Yadav, M.; Ghadiri, M. R. "Design of a Directed Molecular Network", *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 10872–10877.

13. Leman, L.; Orgel, L.; Ghadiri, M. R. “Carbonyl Sulfide-Mediated Prebiotic Formation of Peptides”, *Science* **2004**, *306*, 283-286.

14. Horne, S. W.; Wiethoff, C. M.; Cui, C.; Wilcoxen, K. M.; Amorin, M.; Ghadiri, M. R.; Nemerow, G. R. “Antiviral Cyclic D,L-α-Peptides: Targeting a General Biochemical Pathway in Viral Infections”, *Bioorg. Med. Chem.* **2005**, *13*, 5145-5153.

15. Wilcoxen, K. M.; Leman, L. J.; Weinberger, D. A.; Huang, Z.-Z.; Ghadiri, M. R. “Biomimetic Catalysis of Intermodular Aminoacyl Transfer”, *J. Am. Chem.* Soc., **2007**, *129*, 748-749.

16. Beierle, J. M.; Horne, W. S.; van Maarseveen, J. H.; Waser, B.; Reubi, J. C.; Ghadiri, M. R. “Conformationally Homogeneous Heterocyclic Pseudo-Tetrapeptides as Three-Dimensional Scaffolds for Rational Drug Design: Mapping the Structural Basis Set and Application to the Design of Receptor-Selective Somatostatin Analogues”, *Angew. Chem. Int. Ed.* **2009**, *48*, 4725-4729.

17. Ura, Y.; Beierle, J. M.; Leman, L. J.; Orgel, L. E.; Ghadiri, M. R. “Self-Assembling Sequence-Adaptive Peptide Nucleic Acids”, *Science* **2009**, *325*, 73-77.

18. Montero, A.; Gastaminza, P.; Law , M.; Cheng, G.; Chisari, F. V.; Ghadiri, M. R. “Self-Assembling Peptide Nanotubes with Antiviral Activity Against Hepatitis C Virus”, *Chem. Biol.* **2011**, *18*, 1453-1462.

19. Hutt, D. M.; Olsen, C. A.; Vickers, C. J.; Herman, D.; Chalfant, M.; Montero, A.; Leman, L. J.; Burkle, R.; Maryanoff, B. E.; Balch, W. E.; Ghadiri, M. R. “Potential Agents for Treating Cystic Fibrosis: Cyclic Tetrapeptides that Restore Trafficking and Activity of DF508-CFTR”, Med. Chem. Lett. **2011**, *2*, 703-707.

20. Zhao, Y.; Imura, T.; Leman, L. J.; Curtiss, L. K.; Maryanoff, B. E.; Ghadiri, M. R. “Mimicry of High-Density Lipoprotein: Functional Peptide–Lipid Nanoparticles Based on Multivalent Peptide Constructs”, *J. Am. Chem. Soc.* **2013**, *135*, 13414–13424.

Wiess School of Natural Sciences
K.C. Nicolaou, Ph.D.
Department of Chemistry
Harry C. and Olga K. Wiess Professor of Chemistry

October 23, 2014

Dear Committee Members:

I am writing to provide you with this letter of support for Reza Ghadiri's nomination for the 2016 ACS Breslow Award in Biomimetic Chemistry.

Reza has done some stunning work in the area of peptide design, synthesis and biological evaluation. He found that carefully designed peptides can assemble under certain conditions into nanotubes and other structural motifs which can give rise to functional biomaterials and biologically active agents. He also contributed to the origins of life field through these self-assembling and self-replicating peptides and to drug discovery through his synthetic efforts on cyclic peptides. His original and imaginative works in these areas are pioneering and path-pointing.

In brief, Reza's scientific contributions to chemistry are extremely important and highly relevant to the scope of the ACS Breslow Award for which I endorse with great enthusiasm, believing that he is a highly deserving candidate whose name on the lists of previous winners will be highly appropriate and most luminous.

Cordially,

K.C. Nicolaou, Ph.D.

KCN/vbna

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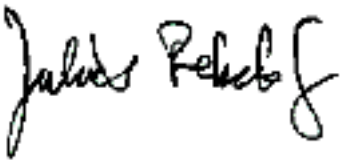
September 26, 2014

I am pleased to write in support of my colleague Reza Ghadiri for the **Ronald Breslow Award for Achievement in Biomimetic Chemistry**. Phil Baran is writing the primary nomination and I present below my perspective on Ghadiri's contributions to peptide chemistry.

Reza burst on the scene with peptide nanotubes in 1993 and has been a force and peptide chemistry ever since. The nanotubes showed that peptides could be propped open into a macrocyclic conformation by judicious use of alternating D and L amino acids. These assemble spontaneously and create channels in biological membranes. He did a splendid job in showing that they have profound physiological effects, for example as transporters of glucose and as antiviral agents. This work also led to the first application of olefin metathesis in supramolecular chemistry: specifically, he pioneered the use of Grubbs' catalyst for fixing peptide conformations. This reaction was applied later by many others to stabilize peptide alpha helices.

Reza also devised the first synthetic peptide ligase but my greatest admiration is for his work on self-replicating peptides. In 1986 von Kiedrowski showed that nucleic acids could act as templates for their own formation, but this was hardly news to anyone since the discovery of the DNA structure. What Reza showed was that *even peptides could do this*; that any merely self-complementary system was the fundamental unit required. With his helical peptide systems he was able to show all of the important molecular effects in evolution: recognition-based autocatalysis, exponential growth, error-correction, reciprocity and many of the key features of what was not yet, but later became known as systems chemistry. Ghadiri ripped open the straitjacket of nucleic acid only replication and retailored it to include self-replicating molecules from peptide chemistry. To further place peptides nearer the origins of life, Reza teamed with Leslie Orgel to show that peptides could be formed in prebiotic like soups through the agency of carbonyl sulfide. This expanded the types of backbones for information-bearing structures beyond carbohydrates. Reza's studies inspired the Eschenmoser school to incorporate peptide-like scaffolds as possible precursors to RNA. In short, Reza Ghadiri has an admirable reputation for innovation and creative thinking in peptide chemistry that makes him an ideal candidate for the Breslow Award.

Sincerely yours,



Julius Rebek, Jr., Director
The Skaggs Institute for Chemical Biology