

## CURRICULUM VITAE

### Christopher T. Seto

Associate Professor  
Department of Chemistry, Brown University

### Education

University of Chicago  
B.S. in Chemistry with General Honors: 1982 - 1986  
Research Advisor: Professor Philip E. Eaton  
Harvard University  
M.A. in Organic Chemistry: 1986 - 1988  
Ph.D. in Organic Chemistry: 1988 - 1992  
Research Advisor: Professor George M. Whitesides

### Professional Appointments

University of California, Berkeley  
Postdoctoral Fellow: 1992 - 1994  
Research Advisor: Professor Paul A. Bartlett  
Brown University  
Assistant Professor of Chemistry: July 1994 – July 2000  
Associate Professor of Chemistry: July 2000 - Present

### Publications

1. "Description of the Cytotoxic Effect of a Novel Drug Abietyl-Isothiocyanate on Endometrial Cancer Cell Lines" Horan, T. C.; Zompa, M. A.; Seto, C. T.; Kim, K. K.; Moore, R. G.; Lange, T. S. *Invest. New Drugs* **2011**, *29*, In Press.
2. "Kinetic Delay of Cyclization/Elimination-Coupled Enzyme Assays: Analysis and Solution" Xue, F.; Seto, C. T. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1069.
3. "The Binding Site of Zinc and Indium Metal to Amino Acid Derivatized Squarate Complexes – Implications in Inhibitor and Mediator Designs" Ramroop-Singh, N.; Narinesingh, D.; Singh, G.; Seto, C. T.; Comeau, A. B. *Bioorganic Chem.* **2010**, *38*, 234.
4. "A Focused Library of Protein Tyrosine Phosphatase Inhibitors" Comeau, A. B.; Critton, D. A.; Page, R.; Seto, C. T. *J. Med. Chem.* **2010**, *53*, 6768.
5. "Enantioselective Synthesis of 1-Aryltetrahydroisoquinolines" Wang, S.; Onaran, M. Burak; Seto, C. T. *Org. Lett.* **2010**, *12*, 2690.
6. "Fluorogenic Peptide Substrates for Serine and Threonine Phosphatases" Xue, F.; Seto, C. T. *Org. Lett.* **2010**, *12*, 1936.
7. "Macrocyclic Inhibitors of the Serine Protease Plasmin" Xue, F.; Seto, C. T. *J. Enz. Inh. Med. Chem.* **2009**, *24*, 779.
8. "Development of a Specific Inhibitor for the Placental Protease, Cathepsin P" Hassanein, M.; Xue, F.; Seto, C. T.; Mason, R. W. *Arch. Biochem. Biophys.* **2007**, *464*, 288.

9. "A Two Stage Click-Based Library of Protein Tyrosine Phosphatase Inhibitors" Xie, J.; Seto, C. T. *Bioorg. Med. Chem.* **2007**, *15*, 458.
10. "Structure-Activity Studies of Cyclic Ketone Inhibitors of the Serine Protease Plasmin: Design, Synthesis and Biological Activity" Xue, F.; Seto, C. T. *Bioorg. Med. Chem.* **2006**, *14*, 8467.
11. "Enantioselective Addition of Vinylzinc Reagents to 3,4-Dihydroisoquinoline *N*-Oxide" Wang, S.; Seto, C. T. *Org. Lett.* **2006**, *7*, 3979.
12. "Squaric Acid-Based Peptidic Inhibitors of Matrix Metalloprotease-1 (MMP-1)" Onaran, M. B.; Comeau, A. B.; Seto, C. T. *J. Org. Chem.* **2005**, *70*, 10792.
13. "Selective Inhibitors of the Serine Protease Plasmin: Probing the S3 and S3' Subsites Using a Combinatorial Library" Xue, F.; Seto, C. T. *J. Med. Chem.* **2005**, *48*, 6908.
14. "Using Enzyme Inhibition as a High Throughput Method to Measure the Enantiomeric Excess of a Chiral Sulfoxide" Sprout, C. M.; Seto, C. T. *Org. Lett.* **2005**, *7*, 5099.
15. "Enantioselective Addition of Vinylzinc Reagents to Aldehydes Catalyzed by Modular Ligands Derived from Amino Acids" Richmond, M. L.; Sprout, C. M.; Seto, C. T. *J. Org. Chem.* **2005**, *70*, 8835.
16. "A Comparison of Cyclohexanone and Tetrahydro-4H-thiopyran-4-one 1,1-dioxide as Pharmacophores for the Design of Peptide-Based Inhibitors of the Serine Protease Plasmin" Xue, F.; Seto, C. T. *J. Org. Chem.* **2005**, *70*, 8309.
17. "A Positional Scanning Approach to the Discovery of Dipeptide-Based Catalysts for the Enantioselective Addition of Vinylzinc Reagents to Aldehydes" Sprout, C. M.; Richmond, M. L.; Seto, C. T. *J. Org. Chem.* **2005**, *70*, 7408.
18. "Investigations of Linker Structure on the Potency of a Series of Bidentate Protein Tyrosine Phosphatase Inhibitors" Xie, J.; Seto, C. T. *Bioorg. Med. Chem.* **2005**, *13*, 2981.
19. "Solid-Phase Synthesis of Chiral *N*-Acylethylenediamines and Their Use as Ligands for the Asymmetric Addition of Alkylzinc and Alkenylzinc Reagents to Aldehydes" Sprout, C. M.; Richmond, M. L.; Seto, C. T. *J. Org. Chem.* **2004**, *69*, 6666.
20. "Parallel Synthesis of a Library of Bidentate Protein Tyrosine Phosphatase Inhibitors that are Based on the  $\alpha$ -Ketoacid Motif" Chen, Y. T.; Seto, C. T. *Bioorg. Med. Chem.* **2004**, *12*, 3289.
21. "Squaric Acids: A New Motif for Designing Inhibitors of Protein Tyrosine Phosphatases" Xie, J.; Comeau, A. B.; Seto, C. T. *Org. Lett.* **2004**, *6*, 83.
22. "Using a Lipase as a High Throughput Screening Method for Measuring the Enantiomeric Excess of Allylic Acetates" Onaran, M. B.; Seto, C. T. *J. Org. Chem.* **2003**, *68*, 8136.
23. "Modular Ligands Derived from Amino Acids for the Enantioselective Addition of Organozinc Reagents to Aldehydes" Richmond, M. L.; Seto, C. T. *J. Org. Chem.* **2003**, *68*, 7505.

24. "Chiral *N*-Acyl-ethylenediamines as New Modular Ligands for the Catalytic Asymmetric Addition of Alkylzinc Reagents to Aldehydes" Sprout, C. M.; Seto, C. T. *J. Org. Chem.* **2003**, *68*, 7788.
25. "Peptidic  $\alpha$ -Ketocarboxylic Acids and Sulfonamides as Inhibitors of Protein Tyrosine Phosphatases" Chen, Y. T.; Xie, J.; Seto, C. T. *J. Org. Chem.* **2003**, *68*, 4123.
26. "Divalent and Trivalent  $\alpha$ -Ketocarboxylic Acids as Inhibitors of Protein Tyrosine Phosphatases" Chen, Y. T.; Seto, C. T. *J. Med. Chem.* **2002**, *45*, 3946.
27. "Inhibitors of Plasmin that Extend into Both the S and S' Binding Sites: Cooperative Interactions Between S1 and S2" Abato, P.; Yuen, C. M.; Cubanski, J. Y.; Seto, C. T. *J. Org. Chem.* **2002**, *67*, 1184.
28. "EMD<sub>ee</sub>: An Enzymatic Method for Determining Enantiomeric Excess" Abato, P.; Seto, C. T. *J. Am. Chem. Soc.* **2001**, *123*, 9206.
29. " $\alpha$ -Ketocarboxylic Acid-Based Inhibitors of Protein Tyrosine Phosphatases" Chen, Y. T.; Onaran, M. B.; Doss, C. J.; Seto, C. T. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1935.
30. "Biotinylation of Substituted Cysteines in the Nicotinic Acetylcholine Receptor Reveals Distinct Binding Modes for  $\alpha$ -Bungarotoxin and Erabutoxin a" Spura, A.; Riel, R. U.; Freedman, N. D.; Agrawal, S.; Seto, C. T.; Hawrot, E. *J. Biol. Chem.* **2000**, *275*, 22452.
31. "The Effects of Buffers on the Thermodynamics and Kinetics of Binding Between Positively-Charged Cyclodextrins and Phosphate Ester Guests" Ghosh, M.; Zhang, R.; Lawler, R. G.; Seto, C. T. *J. Org. Chem.* **2000**, *65*, 735.
32. "Inhibition of Phosphatase Activity by Positively-Charged Cyclodextrins" Ghosh, M.; Sanders, C. T.; Zhang, R.; Seto, C. T. *Org. Lett.* **1999**, *1*, 1945.
33. "A Combinatorial Library of Serine and Cysteine Protease Inhibitors that Interact with Both the S and S' Binding Sites" Abato, P.; Conroy, J. L.; Seto, C. T. *J. Med. Chem.* **1999**, *42*, 4001.
34. "4-Heterocyclohexanone-Based Inhibitors of the Serine Protease Plasmin" Sanders, T. C.; Seto, C. T. *J. Med. Chem.* **1999**, *42*, 2969.
35. "Hydrolysis of Amides Catalyzed by 4-Heterocyclohexanones: Small Molecule Mimics of Serine Proteases" Ghosh, M.; Conroy, J. L.; Seto, C. T. *Angew. Chemie. Int. Ed.* **1999**, *38*, 514 - 516.
36. "Synthesis of Cyclohexanone-Based Cathepsin B Inhibitors that Interact with Both the S and S' Binding Sites" Conroy, J. L.; Abato, P.; Ghosh, M.; Austermuhle, M. I.; Kiefer, M. R.; Seto, C. T. *Tetrahedron Lett.* **1998**, *39*, 8253 - 8256.
37. "<sup>13</sup>C NMR Studies Demonstrate that Tetrahydropyranone-Based Inhibitors Bind to Cysteine Proteases by Reversible Formation of a Hemithioketal Adduct" Conroy, J. L.; Seto, C. T., *J. Org. Chem.* **1998**, *63*, 2367.
38. "Using the Electrostatic Field Effect to Design a New Class of Inhibitors for Cysteine Proteases" Conroy, J. L.; Sanders, T. C.; Seto, C. T. *J. Am. Chem. Soc.* **1997**, *119*, 4285.

39. "Chorismate-Utilizing Enzymes Isochorismate Synthase, Anthranilate Synthase and *p*-Aminobenzoate Synthase: Mechanistic Insight Through Inhibitor Design" Kozlowski, M. C.; Tom, N. J.; Seto, C. T.; Sefler, A. M.; Bartlett, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2128.
40. "Non-Covalent Synthesis: Using Physical-Organic Chemistry to Make Aggregates" Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, *28*, 37.
41. "Design and Synthesis of Hydrogen-Bonded Aggregates. Theory and Computation Applied to Three Systems Based on the Cyanuric Acid-Melamine Lattice" Simanek, E. E.; Mammen, M.; Gordon, D. M.; Chin, D.; Mathias, J. P.; Seto, C. T.; Whitesides, G. M. *Tetrahedron* **1995**, *51*, 607.
42. "Structural Preferences of Hydrogen-Bonded Networks in Organic Solution - the Cyclic CA<sub>3</sub>-M<sub>3</sub> 'Rosette'" Mathias, J. P.; Simanek, E. E.; Zerkowski, J. A.; Seto, C. T. Whitesides, G. M. *J. Am. Chem. Soc.* **1994**, *116*, 4316.
43. "Self-Assembly Through Hydrogen Bonding: Preparation and Characterization of Three New Types of Supramolecular Aggregates Based on Parallel Cyclic CA<sub>3</sub>-M<sub>3</sub> 'Rosettes'" Mathias, J. P.; Seto, C. T.; Simanek, E. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1994**, *116*, 1725.
44. "Design of Organic Structures in the Solid State: Molecular Tapes Based on the Network of Hydrogen Bonds Present in the Cyanuric Acid-Melamine Complex" Zerkowski, J. A.; MacDonald, J. C.; Seto, C. T.; Wierda, D. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1994**, *116*, 2382.
45. "(Z)-9-Fluoro-EPSP is Not a Substrate for EPSP Synthase: Implications for the Enzyme Mechanism" Seto, C. T.; Bartlett, P. A. *J. Org. Chem.* **1994**, *59*, 7130.
46. "Design, Preparation, and Characterization of Hydrogen Bonded Supramolecular Aggregates Based on the Cyanuric Acid-Melamine Lattice" Mathias, J. P.; Simanek, E. E.; Seto, C. T.; Whitesides, G. M. *Macromol. Symp. (International Symposium on New Macromolecular Architectures and Supramolecular Polymers, 1993)*, **1994**, *77*, 157.
47. "Self-Assembly Through Hydrogen Bonding: Preparation of a Supramolecular Aggregate Composed of Ten Molecules" Mathias, J. P.; Simanek, E. E.; Seto, C. T.; Whitesides, G. M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1766.
48. "Synthesis, Characterization, and Thermodynamic Analysis of a 1+1 Self-Assembling Structure Based on the Cyanuric Acid-Melamine Lattice" Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1993**, *115*, 1330.
49. "Molecular Self-Assembly through Hydrogen Bonding: Aggregation of Five Molecules to Form a Discrete Supramolecular Structure" Seto, C. T.; Mathias, J. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1993**, *115*, 1321.
50. "Molecular Self-Assembly through Hydrogen Bonding: Supramolecular Aggregates Based on the Cyanuric Acid-Melamine Lattice" Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1993**, *115*, 905.

51. "Self-Assembly Through Hydrogen Bonding: Structures Based on Cyanuric Acid-Melamine" Mathias, J. P.; Seto, C. T.; Whitesides, G. M. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)*, **1993**, 34, 92.
52. "Solid-State Structures of 'Rosette' and 'Crinkled Tape' Motifs Derived from the Cyanuric Acid-Melamine Lattice" Zerkowski, J. A.; Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1992**, 114, 5473.
53. "Molecular Recognition in Gels, Monolayers, and Solids." Prime, K. L.; Chu, Y.-H.; Schmid, W.; Seto, C. T.; Chen, J. K.; Spaltenstein, A.; Zerkowski, J. A.; Whitesides, G. M. *Macromolecular Assemblies*; Stroeve, P.; Balazs, A. C., Eds.; ACS Symposium Series; American Chemical Society, **1992**.
54. "Designed Ordered Molecular Arrays in Two and Three Dimensions" Folkers, J. P.; Zerkowski, J. A.; Laibinis, P. E.; Seto, C. T.; Whitesides, G. M. *Supramolecular Architecture: Synthetic Control in Thin Films and Solids*; Bein, T., Ed.; ACS Symposium Series No. 499; American Chemical Society, **1992**.
55. "Self-Assembly Through Networks of Hydrogen Bonds" Mathias, J. P.; Seto, C. T.; Zerkowski, J. A.; Whitesides, G. M. *Symposium Proceedings: Molecular Recognition: Chemical and Biochemical Problems II*; Roberts, S. M., Ed.; The Royal Society of Chemistry, **1992**.
56. "Molecular Self-Assembly and Nanochemistry: A Chemical Strategy for the Synthesis of Nanostructures" Whitesides, G. M.; Mathias, J. P.; Seto, C. T. *Science* **1991**, 254, 1312.
57. "Self-Assembly of a Hydrogen-Bonded 2+3 Supramolecular Complex" Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1991**, 113, 712.
58. "Self-Assembly Based on the Cyanuric Acid-Melamine Lattice" Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, 112, 6409.
59. "Design of Organic Structures in the Solid State: Hydrogen-Bonded Molecular 'Tapes'" Zerkowski, J. A.; Seto, C. T.; Wierda, D. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, 112, 9025.

## Patents

Patent Application "Alpha-Ketocarboxylic Acid Based Inhibitors of Protein Tyrosine Phosphatases." US Application No. 10/117,699, Filed April 5, 2002.

Provisional Patent Application "Fluorogenic Substrates For Protein Phosphatases and Assays Incorporating the Substrates"  
Docket No. BU2007-12, Filed November 15, 2007.

## Current Research

The Seto research group continues to focus on two areas within bioorganic chemistry. First, we are developing an activity based probe for the serine and threonine phosphatase class of enzymes. These phosphatases play important roles in a variety of human pathogenic conditions including cystic fibrosis (PP2C), immunosuppression (PP2B) and cardiovascular disease (PP1 and PP2A). The probe is designed to react covalently and specifically with only

the *active* form of the phosphatases, as opposed to inactive pro-enzyme species, or other forms of the enzyme that are deactivated by post-translational modification, or lack thereof. These probes should prove useful for discovering unknown phosphatases, for clarifying the role that phosphatases play in disease, and investigating the selectivity of drugs that are targeted against this class of proteins. Michael Zompa, the graduate student working on this project, anticipates that synthesis of the probe will be complete in the next several months, and plans its biological evaluation during the summer.

The Ras family of proteins initiate intracellular signals that control the growth and differentiation of cells. Regulating the activity and trafficking of these proteins is vital since mutant forms of Ras that permanently switch on its activity results in uncontrolled cell growth. Thus, mutations in Ras proteins are found in more than 20% of all human cancers, and in greater than 90% of pancreatic cancer cases. We are developing a second type of activity based probe that targets acyl protein thioesterases. These enzymes control the cycling of Ras proteins between the cell membrane, where Ras exerts its biological effects, and the Golgi apparatus. Ras proteins are post-translationally modified (palmitoylated on two cysteine residues) in the Golgi apparatus. This modification initiates trafficking of Ras to the cell membrane, where the palmitoylated cysteine residues anchor the protein to the plasma bilayer. Acyl protein thioesterases hydrolyze the palmitoyl groups off of Ras, resulting in its deactivation and transport back to the Golgi. Our probes are designed to react specifically with these thioesterases, as opposed to other classes of hydrolases, and can be useful tools for understanding how these enzymes control protein trafficking, and their relationship to human diseases such as cancer. Yiming Chen is close to completing synthesis of a first generation probe, and hopes to begin its evaluation over the next several months.

We also have ongoing collaborations with Professor Rebecca Page (Brown, Biomed) on protein tyrosine phosphatase inhibitors, and with Professor William Atkins (University of Washington, Medicinal Chemistry) on triazole inhibitors of cytochrome P450 enzymes.

### **Service to the University**

2003-04 – Ad Hoc Committee on Postdoctoral Researchers  
2010 – Reviewer for ADVANCE Career Development Awards  
2007-10 – University Resources Committee

### **Service to the Profession**

Ad Hoc Member – Bioorganic and Natural Products Study Section of the NIH - October, 2000  
Ad Hoc Member – Bioorganic and Natural Products Study Section of the NIH - June, 2002  
Ad Hoc Member – ZRG1 SSS-L Study Section of the NIH - June, 2004  
Ad Hoc Member - ZRG1 BCMB-L Study Section of the NIH – July, 2005  
Ad Hoc Member - BCMB-L11S Study Section of the NIH – June, 2006  
Discussion Leader – Stereochemistry Gordon Research Conference – 2010  
Charter Member – NIH Synthetic and Biological Chemistry B Study Section – 2007-2011

### **Service to the Community**

Chemistry demonstration at Primrose Hill Elementary School – Barrington, RI – 2004  
Chemistry demonstration at Primrose Hill Elementary School – Barrington, RI - 2006

### **Honors and Awards:**

- Eli Lilly Predoctoral Fellow - Harvard University: 1991 - 1992

- United States Army Medical Research and Materiel Command: Breast Cancer Research Initiative - Career Development Award - Brown University: 1996 - 2000
- Salomon Faculty Research Award - Brown University: 1996 - 1998
- Award for Outstanding Academic Advising - Brown University: 2000