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Recent Studies Towards the Synthesis of Bioactive Natural Products

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12:00 p.m. Tuesday February 26th, 2019
Bowman Oddy 2059

John A. Porco, Jr.

John A. Porco Jr. received his B.A. in chemistry in 1985 from the College of the Holy Cross and a Ph.D. in organic chemistry from Harvard University with Prof. Stuart Schreiber in 1992. From 1992-1993, he was an NSF postdoctoral fellow with Prof. Chi-Huey Wong at the Scripps Research Institute. John then spent six years in industry, first working in venture capital at Avalon Ventures, and then at Argonaut Technologies where he became Director of Parallel Medicinal Chemistry. He joined the Department of Chemistry at Boston University in 1999 as Assistant Professor and was promoted to Full Professor in September 2004. In 2002, he successfully led an effort to establish the Center for Chemical Methodology and Library Development at Boston University (CMLD-BU). Funded by the National Institutes of Health (NIH) as a Center of Excellence, the focus of the CMLD-BU was the discovery of new methodologies to produce novel chemical libraries of unprecedented complexity for biological screening. In 2014, the CMLD-BU was transitioned to the Center for Molecular Discovery (BU-CMD), an integrated infrastructure for the discovery of small molecule chemical probes.

Professor Porco's research is focused in two major areas: 1) the development of new synthetic methodologies for chemical synthesis of complex molecules and 2) synthesis of complex chemical libraries. Synthetic methodologies developed the Porco laboratory include: copper (I)-mediated formation of enamides, oxa-electrocyclization/dimerization of dienals enroute to complex epoxyquinoid frameworks; enantioselective oxidative dearomatization using chiral copper complexes and molecular oxygen; photocycloaddition using oxidopyryliums enroute to the rocaglamides and related natural products, and catalytic ester-amide exchange using group (IV) metal alkoxide-activator complexes. In the past twenty years, his research group has synthesized numerous complex natural products including torreyanic acid, the salicylate enamide macrolides lobatamide C and oximidines, the rocaglamides, silvestrol, ponapensin, secalonic acids A and D, griffipavixanthone, and kinamycin C.

In 2001, Prof. Porco received the American Cancer Society Research Scholar Award for "Studies Towards the Synthesis of Torreyanic Acid and Related Epoxyquinoids;" the Bristol-Myers Squibb Unrestricted Grant in Synthetic Organic Chemistry in 2003, a Novartis Chemistry Lectureship Award in 2009, and the ACS Arthur C. Cope Scholar Award in 2009. In addition to multiple grants from the NIH, in 2016 Prof. Porco received a prestigious five-

year MIRA (R35) grant entitled “Chemical Synthesis of Complex Natural Products for Translational Science.”

At Boston University, he has mentored 43 Ph.D. graduate students, 2 Masters students, 32 undergraduate researchers, and 48 postdoctoral fellows. Since beginning his research program, he and his colleagues have published over 200 manuscripts in peer-reviewed journals and presented over 150 invited seminars at universities, pharmaceutical companies, and conferences. In 2018, John was named the Samour Family Professor of Chemistry in the College of Arts and Sciences at Boston University.

The Porco laboratory is developing novel synthetic methodologies for concise entry to bioactive complex molecules. In a main area of interest, biomimetic approaches to natural products are being pursued as a means to formulate biosynthetic hypotheses and invent new synthetic methodology to important synthetic targets. As part of their studies, they have taken opportunities to address key questions and contemporary needs in organic chemistry including asymmetric catalysis of photocycloadditions, enantioselective dearomatization, and atropselective synthesis. Their laboratory also has a growing interest in translational collaborations with biological investigators to identify bioactive molecules.

Selected Recent Scientific Contributions from list of ~215:

1. “Small Molecule Amyloid Protein Precursor Processing Modulators Lower Amyloid Peptide Levels via cKit Signaling." Chen, C. D.; Zeldich, E.; Khodr, C.; Camara, K.; Tung, T. Y.; Lauder, E. C.; Mullen, P.; Polanco, T. J.; Liu, Y. Y.; Zeldich, D.; Xia, W.; Van Nostrand, W. E.; Brown, L. E.; Porco, J. A., Jr.; Abraham, C. R. *J. Alzheimers Dis.* **2019**, *67*, 1089.
2. “Oxo-aglaiastatin-Mediated Inhibition of Translation Initiation." Maiga, R. I.; Cencic, R.; Chu, J.; Waller, D. D.; Brown, L. E.; Devine, W. G.; Zhang, W.; Sebag, M.; Porco, J. A., Jr.; Pelletier, *J. Sci. Rep.* **2019**, 1265.
3. “Isolation and Synthesis of Novel Meroterpenoids from Rhodomyrtus tomentosa: Inverstigation of a Reactive Enetrione Intermediate." Qin, X.-J.; Rauwolf, T. J.; Li, P.-P.; Liu, H.; McNeely, J.; Hua, Y.; Liu, H.-Y.; Porco, J. A., Jr. *Angew. Chem. Int. Ed.* **2019**.
4. “Structural Basis for Species-Selective Targeting of Hsp90 in a Pathogenic Fungus." Whitesell, L. et. al. *Nat. Commun.* **2019**, *10*, 402.
5. “Discovery of Macrocylic Inhibitors of Apurinic/Apyrimidinic Endonuclease 1." Trilles, R.; Beglov, D.; Chen, Q.; He, H.; Wireman, R.; Reed, A.; Chennamadhavuni, S.; Panek, J. S.; Brown, L. E.; Vajda, S.; Porco, J. A., Jr.; Kelley, M. R.; Georgiadis, M. M. *J. Med. Chem.* **2019**.
6. “METTL13 Methylation of eEF1A Increases Translational Output to Promote Tumorigenesis." Liu, S. et. al. *Cell* **2019**, *176*, 1.
7. “Chemical Synthesis Enables Structural Reengineering of Aglaroxin C Leading to Inhibition Bias for Hepatitis C Viral Infection." Zhang, W.; Liu, S.; Maiga, R. I.; Pelletier, J.; Brown, L. E.; Wang, T. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2019**.
8. “Asymmetric Synthesis of Griffipavixanthone Employing a Chiral Phosphoric Acid-Catalyzed Cycloaddition." Smith, M. J.; Reichl, K. D.; Escobar, R. A.; Heavey, T.; Coker, D. F.; Schaus, S. E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2019**, *141*, 148.

9. “Sensitization of Renal Carcinoma Cells to TRAIL-induced Apoptosis by Rocaglamide and Analogs." Nalli, A. D.; Brown, L. E.; Thomas, C. L.; Sayers, T. J.; Porco, J. A., Jr.; Henrich, C. *J. Sci. Rep.* **2018**.
10. “Asymmetric Synthesis of Gonytolide A: Strategic Use of an Aryl Halide Blocking Group for Oxidative Coupling." Wu, X.; Iwata, T.; Scharf, A.; Qin, T.; Reichl, K. D.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2018**, *140*, 5969.
11. “Rocaglates as Dual-Targeting Agents for Experimental Cerebral Malaria." Langlais, D.; Cencic, R.; Moradin, N.; Kennedy, J. M.; Ayi, K.; Brown, L. E.; Crandall, I.; Tarry, M. J.; Schmeing, M.; Kain, K. C.; Porco, J. A., Jr., Pelletier, J.; Gros, P. *Proc. Natl. Acad. Sci.* **2018**, *115*, E2366.
12. “Biomimetic Total Synthesis of (+/-)-Griffipavixanthone via a Cationic Cycloaddition-Cyclization Cascade.” Reichl, K. D.; Smith, M. J.; Song, M. K.; Johnson, R. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2017**, *139*, 14053.
13. “Tight Coordination of Protein Translation and HSF1 Activation Supports the Anabolic Malignant State.” Santagata, S.; Mendillo, M.L.; Tang, Y.-C.; Subramanian, A.; Perley, C.C.; Roche, S..; Wong, B.; Narayan, R.; Kwon, H.; Koeva, M.; Amon, A.; Golub, T.R.; Porco, J.A. Jr.; Whitesell, L.; Lindquist, S., *Science* **2013**, *341*, 1238303.

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