Therapeutic Applications of Biomimetic Catalysis: Synthetic Porphyrins to Decompose Peroxynitrite

*First Place, **2009 NYCS Spring Symposium Graduate Student Poster Contest**, Princeton, March 2009*

Jyoti R. Tibrewala (Advisor: Prof. John T. Groves)

Department of Chemistry, Princeton University, Princeton, NJ 08544

e-mail: jtibrewa@princeton.edu; jtgroves@princeton.edu

Enzymatic catalysis continues to inspire synthetic chemists, because of the ease and efficiency with which Nature facilitates such challenging transformations. In addition to aiding reactions of synthetic utility, the biomimetic strategy can also guide the design of drugs containing enzymatic structural motifs to catalyze reactions of biological interest. Such an approach has been taken to further our understanding of oxidative and nitrosative stress. These molecular processes are caused by reactive oxygen and nitrogen species (ROS and RNS, respectively), which are upregulated under inflammatory conditions. One of the major RNS believed to be at work is peroxynitrite ($ONOO^-$), itself the product of two such species, superoxide ($O_2^{\cdot -}$) and nitric oxide (NO). Peroxynitrite is believed to be more reactive than either of its precursors, and it is capable of oxidizing and nitrating proteins, lipids, and DNA. Indeed, peroxynitrite-mediated biological injury has been documented in animal models of such diseases as diabetes and arthritis; these reports solidify the link between peroxynitrite and disease, and they clearly demonstrate the need for an effective therapeutic strategy.[1, 2]

Our group has demonstrated that synthetic metalloporphyrins can catalytically decompose peroxynitrite; in a peroxidase-like mechanism, peroxynitrite is converted to the benign isomer nitrate.[3] The iron porphyrins developed in our group comprise the most reactive catalysts reported to date, exhibiting rate constants exceeding 10^6 $M^{-1}s^{-1}$ in reaction with peroxynitrite. The high reactivity seen in the laboratory translates into such *in vivo* effects as amelioration of protein tyrosine nitration in rodent models of diabetes.[4] Particularly effective are the 2-pyridyl porphyrin class of catalysts, in which *meso*-tetrakis(2-pyridyl) porphyrin is tetraalkylated and then metallated. The current "world record" catalyst, FP15, was developed in our group, and it continues to be studied in animal models of numerous diseases.[5]

Most recently, we have identified a next-generation catalyst which kinetically outcompetes our own FP15 by a factor of two. The new compound, FP23, was also studied in a laboratory model of protein tyrosine nitration; FP23 significantly reduces the incidence of phenolic nitration, comparing favorably to earlier catalysts. On the synthetic side, we have studied the alkylation step closely, and we have quantified all of the rotational isomers formed. Furthermore, we have optimized all steps of the synthesis, which is scalable, affording up to 1.7 g of FP23 at a time. Future work on this project will include *in vivo* assessment of catalyst activity. In collaboration with the National Institutes of Health, we plan to study the effects of FP23 in ischemia/reperfusion injury and heart failure in mice. We also plan to study our synthetic metalloporphyrins in cell culture, in order to better understand their modes of action *in vivo*.

1. Winterbourn, C. C., Reconciling the chemistry and biology of reactive oxygen species. *Nature Chemical Biology* **2008,** 4, (5), 278-286.

2. Szabo, C.; Ischiropoulos, H.; Radi, R., Peroxynitrite: biochemistry, pathophysiology and development of therapeutics. *Nature Reviews Drug Discovery* **2007,** 6, (8), 662-680.

3. Shimanovich, R.; Groves, J. T., Mechanisms of Peroxynitrite Decomposition Catalyzed by FeTMPS, a Bioactive Sulfonated Iron Porphyrin. *Archives of Biochemistry and Biophysics* **2001,** 387, (2), 307-317.

4. Szabo, C.; Mabley, J. G.; Moeller, S. M.; Shimanovich, R.; Pacher, P.; Virag, L.; Soriano, F. G.; Van Duzer, J. H.; Williams, W.; Salzman, A. L.; Groves, J. T., Part I: Pathogenic Role of Peroxynitrite in the Development of Diabetes and Diabetic Vascular Complications: Studies with FP15, A Novel Potent Peroxynitrite Decomposition Catalyst. *Molecular Medicine* **2002,** 8, (10), 571-580.

5. Drel, V. R.; Pacher, P.; Vareniuk, I.; Pavlov, I. A.; Ilnytska, O.; Lyzogubov, V. V.; Tibrewala, J.; Groves, J. T.; Obrosova, I. G., A peroxynitrite decomposition catalyst counteracts sensory neuropathy in streptozotocin-diabetic mice. *European Journal of Pharmacology* **2007,** 569, (1-2), 48-58.

Acknowledgements: We thank the NIH (R37 GM36298, MERIT Award), the New Jersey Commission on Science and Technology, and the 2007/2008 Merck-Patchett Summer Fellowship, for generous support of this research.