

Scientific Lecture – Garland R. Marshall

SYNZYMES: SOD Mimetics – From Discovery to the Clinic

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The design and synthesis of drug-like compounds that displayed catalytic activity equivalent to one of nature's most efficient enzymes, superoxide dismutase (SOD), was accomplished by Dennis Riley while a Senior Research Fellow at Monsanto [1]. Superoxide dismutases are a class of oxido-reductase enzymes that contain either Cu, Fe or Mn at the active site and catalyze the dismutation of superoxide, the one-electron reduction product of molecular oxygen to oxygen and hydrogen peroxide. Why generate a drug that can convert superoxide to hydrogen peroxide as the body contains both manganese SOD in the mitochondria and iron/copper SOD elsewhere? The answer is the ubiquitous role of superoxide in pathology, e.g., inflammation, reperfusion injury, shock, arthritis, asthma, etc. [2]

The evolution of the design of this synzyme from an initial understanding of the structure and mechanisms of superoxide dismutases to a cyclic pentaazacrown complex of manganese with three exocyclic rings (M40403) will be used to illustrate the breakthroughs in understanding that occurred. The therapeutic opportunities and potential side effects of the use of an exogenous catalyst to remove superoxide will be discussed, and the rationale for choice of clinical target explained. In particular, the molecular basis of catalysis for this class of SOD mimetics is sufficiently well understood [3] that the relative enzymatic activity for a proposed analog can be accurately predicted [4, 5]. Computer-aided design was used extensively to screen for analogs with enhanced stability and catalytic activity [6].

References

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