After more than 2 decades of development, two Mn(III) N-substituted ortho pyridylporphyrins and potent SOD mimics, MnTE-2-PyP^{5+} (BMX-010) and MnTnBuOE-2-PyP^{5+} (BMX-001) (collectively abbreviated as MnPs), have progressed to 4 clinical trials. In two trials MnTnBuOE-2-PyP^{5+} has been tested on its ability to radioprotect normal tissue with glioma and head and neck (H&N) cancer patients, while simultaneously radiosensitize tumors. In parallel, another metal-based similarly potent but structurally very different SOD mimic, Mn(II) pentaaza macrocycle, GC4419, has been tested on identical application - radioprotection of normal tissue with H&N cancer patients.

MnPs were originally developed as SOD mimics based on structure-activity relationships between their thermodynamic and kinetic properties: redox-activity described by the reduction potential of the Mn site, $E_{1/2}$ for Mn$^{III}$/Mn$^{II}$ redox couple and ability to catalyze the disproportionation of superoxide into oxygen and hydrogen peroxide. Yet over years we learned that such metal complexes, lacking complex protein structures that would have imposed specificity towards $O_2^-$, react with many other reactive species such as peroxynitrite, hydrogen peroxide, nitric oxide, hypochlorite, ascorbate and simple and protein thiols. The reactivity of MnPs with thiols (cysteines) of critical cellular proteins appears to be their major \textit{in vivo} action (largely facilitated by ascorbate) which impacts cellular transcriptional activity and in turn cellular metabolism. The reactions of MnPs with cellular proteins are of pro-oxidative character as they involve MnP/H$_2$O$_2$/GSH-driven catalysis of protein cysteine oxidation/S-glutathionylation with subsequent modification of protein function. Among those proteins, master transcription factor, NF-$\kappa$B, was recently identified as a major target of MnPs and of several other classes of redox-active compounds such as Mn(III) salens, flavonoids and nitroxides. Also Nrf2, a major transcription factor that controls cellular redox environment, has recently emerged as a key target in the actions of MnPs and other redox-active drugs.

Most importantly, Mn porphyrins inflict \textit{differential effects} on normal vs tumor cell/tissue -- a driving force for their progress towards clinical trial. Such effects arise from differences in the redox environments of those tissues, primarily levels of H$_2$O$_2$ and MnPs - both key reactants in the process of protein S-glutathionylation. This in turn results in different yields of S-glutathionylation of proteins with their subsequent inactivation. Consequently physiological state of normal tissue gets restored, while tumor undergoes death. No studies have thus far explored \textit{differential effects} in the same animal, while they are essential for understanding the extremely intricate interactions of metal-based drugs with complex milieu of the cell. The progress of SOD mimics into clinical trials justifies further studies of the molecular mechanisms of their actions.

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