Published in final edited form as:
Brain Res. 2011 September 2; 1410: 120–121. doi:10.1016/j.brainres.2011.07.001.

Climbing STAIRs towards clinical trials with a novel PARP-1 inhibitor for the treatment of ischemic stroke

Andria L. Ford, MD[2] and **Jin-Moo Lee, MD, PhD**[1,2]

[1]The Hope Center for Neurological Disorders, Washington University School of Medicine

[2]The Department of Neurology, Washington University School of Medicine

For almost three decades, poly(ADP-ribose) polymerase-1 (PARP-1) has been actively investigated as a potential therapeutic target for a variety of diseases including diabetes, myocardial infarction, stroke, and cancer. Already in Phase III studies for the treatment of breast cancer, PARP-1 inhibitors have not yet made it past preclinical studies for cerebral ischemia. In this issue of Brain Research, Matsuura et al [1] report an extensive series of experiments with MP-124, a novel PARP-1 inhibitor, in a non-human primate stroke model, and the drug is now poised to take its first step into human clinical trials.

Poly(ADP-ribosyl)ation, an important post-translational modification that modulates response to cellular stress, is carried out by PARP-1, an abundant, highly-conserved intranuclear polymerase. Under states of mild genotoxic stress, PARP-1 is activated and plays a central role in DNA repair by recruiting and increasing accessibility to DNA repair enzymes. [2] A zinc-finger binding domain recognizes breaks in double-stranded DNA and activates a catalytic domain which polymerizes a chain of ADP-riboses onto histones utilizing nicotinamide adenine dinucleotide (NAD+) as a source for the ADP-ribose. [3] In the setting of cancer treatment, PARP-1 orchestrates the repair of damaged DNA induced by chemotherapeutic agents leading to drug resistance. Thus, PARP-1 inhibitors compromise cancer cell DNA repair mechanisms, potentiating chemotherapeutic efficacy. During conditions of extreme energetic stress, as seen in ischemia, PARP-1 overactivation turns deleterious due to massive NAD+ consumption. Because NAD+ biosynthesis requires ATP, its depletion in ischemic cells results in precipitous drops in ATP, mitochondrial dysfunction, and necrosis. [4, 5] Proof of principle that PARP-1 inhibition could reduce ischemic injury by preserving energy stores was demonstrated by genetic disruption of PARP-1 in mice undergoing middle cerebral artery occlusion (MCAO). [6, 7]. Knockout mice demonstrated smaller cerebral infarcts compared to wildtype littermates. Subsequent studies have suggested that PARP-1 inhibition may also prevent the activation of inflammatory pathways which may contribute to ischemic injury, and potentially open a much longer therapeutic window. [3, 8]

So why are PARP-1 inhibitors for ischemic stroke lagging so far behind clinical trials for treatment of cancer and other diseases? Unclear, but one cannot help but speculate that this may be due to reticence on the part of pharmaceutical companies to pursue neuroprotective

Correspondence: Jin-Moo Lee Department of Neurology 660 S. Euclid Ave, Campus Box 8111 St. Louis, MO 63110 Tel #: (314) 747-1138 Fax #: (314) 362-2244 leejm@wustl.edu.

agents for the treatment of acute ischemic stroke in light of the large series of clinical trial failures in the 1990's. These failed clinical trials fueled introspection in the field of stroke neurology, culminating in a re-examination of the process by which candidate drugs are translated to human stroke trials within a conference of industry representatives and academicians known as Stroke Therapy Academic Industry Roundtable (STAIR). [9, 10] A set of recommendations for the preclinical development of acute ischemic stroke therapies emerged and included: 1) defining the therapeutic time window in a well-characterized model; 2) using blinded, physiologically-controlled reproducible studies; 3) measuring both histological and functional outcomes assessed acutely and long-term; 4) testing in rodent models, followed by gyrencephalic species; and 5) using both permanent and transient occlusion models. Despite the field's desperate need for an effective neuroprotectant in acute ischemic stroke, clinical trials for this population have precipitously declined.

In this setting, we now see very promising preclinical results from Matsuura et al., who build upon their previous work in rodent focal ischemia, [11] now testing MP-124 in a non-human primate model. This series of experiments puts MP-124 through a tough set of tests in a variety of ischemia settings (permanent and transient focal ischemia) using multiple endpoints (behavioral, histological, and MR imaging), examining both short-term (28 hours) and long-term (7 day, 30 day) outcomes. Consistently, the authors find that MP-124 is efficacious in both permanent and transient ischemia models in behavioral, histological, and MR imaging endpoints. Because of previous reports that PARP-1-related cell death pathways may differ between genders, [12] the authors examined female monkeys separately from males, finding that the compound appears to be effective in both genders although their female numbers are small (N=12, of which 5 died). The authors also found that MP-124 was efficacious even if given 6 hours after ischemia onset, suggesting that the therapeutic time window for treatment is quite wide. Impressively, the investigators have adhered closely to the original STAIR criteria and in many cases gone beyond expectations.

The study has important implications with regard to future human studies in acute ischemic stroke. Moving forward cautiously, however, not long ago, the free radical scavenger NXY-059 underwent preclinical tests which followed the STAIR criteria (including studies in non-human primates) [13, 14], only to fail in clinical trials. [15] Although controversy exists as to how well the STAIR criteria were followed (concern for unblinded assessments in the previous rodent experiments and the lack of confirmation of arterial occlusion, both of which were followed in the current study of MP-124), [16] the disappointing results, nonetheless, led to updated STAIR recommendations which encouraged investigators to: randomize subjects, utilize a priori inclusion/exclusion criteria and sample size calculations, report reasons for excluding animals from the final data analysis, disclose conflicts of interest, study aged animals with comorbid conditions in both genders, evaluate medication interactions, and study relevant biomarkers. [17] Consequently, while Matsuura et al. have largely succeeded in preparing MP-124 for the next step, it may be wise to heed the updated STAIR recommendations, including the replication of results in an independent laboratory and additional studies in aged animals (not necessarily in primates). Ultimately, if this compound moves forward to human clinical trials, the current study will serve not only as a preclinical test of MP-124, but will also test the utility of the STAIR criteria once again.

References

1. Matsuura S, et al. MP-124, a novel poly(ADP-ribose)polymerase-1 (PARP-1) inhibitor, ameliorates the ischemic brain damage in non-human primate model. Brain Res. 2011
2. Ferraris DV. Evolution of poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors. From concept to clinic. J Med Chem. 2010; 53(12):4561–84. [PubMed: 20364863]

3. Szabo C, Dawson VL. Role of poly(ADP-ribose) synthetase in inflammation and ischaemia-reperfusion. Trends Pharmacol Sci. 1998; 19(7):287–98. [PubMed: 9703762]
4. Graziani G, Szabo C. Clinical perspectives of PARP inhibitors. Pharmacol Res. 2005; 52(1):109–18. [PubMed: 15911339]
5. Pacher P, Szabo C. Role of the peroxynitrite-poly(ADP-ribose) polymerase pathway in human disease. Am J Pathol. 2008; 173(1):2–13. [PubMed: 18535182]
6. Endres M, et al. Ischemic brain injury is mediated by the activation of poly(ADP-ribose)polymerase. J Cereb Blood Flow Metab. 1997; 17(11):1143–51. [PubMed: 9390645]
7. Eliasson MJ, et al. Poly(ADP-ribose) polymerase gene disruption renders mice resistant to cerebral ischemia. Nat Med. 1997; 3(10):1089–95. [PubMed: 9334719]
8. Szabo C, et al. Inhibition of poly (ADP-ribose) synthetase attenuates neutrophil recruitment and exerts antiinflammatory effects. J Exp Med. 1997; 186(7):1041–9. [PubMed: 9314553]
9. Recommendations for standards regarding preclinical neuroprotective and restorative drug development. Stroke. 1999; 30(12):2752–8. [PubMed: 10583007]
10. Recommendations for clinical trial evaluation of acute stroke therapies. Stroke. 2001; 32(7):1598–606. [PubMed: 11441207]
11. Egi Y, et al. Neuroprotective effects of a novel water-soluble poly(ADP-ribose) polymerase-1 inhibitor, MP-124, in in vitro and in vivo models of cerebral ischemia. Brain Res. 2011; 1389:169–76. [PubMed: 21420942]
12. McCullough LD, et al. Ischemic nitric oxide and poly (ADP-ribose) polymerase-1 in cerebral ischemia: male toxicity, female protection. J Cereb Blood Flow Metab. 2005; 25(4):502–12. [PubMed: 15689952]
13. Marshall JW, et al. NXY-059, a free radical--trapping agent, substantially lessens the functional disability resulting from cerebral ischemia in a primate species. Stroke. 2001; 32(1):190–8. [PubMed: 11136936]
14. Marshall JW, et al. Functional and histological evidence for the protective effect of NXY-059 in a primate model of stroke when given 4 hours after occlusion. Stroke. 2003; 34(9):2228–33. [PubMed: 12920263]
15. Shuaib A, et al. NXY-059 for the treatment of acute ischemic stroke. N Engl J Med. 2007; 357(6): 562–71. [PubMed: 17687131]
16. Savitz SI. A critical appraisal of the NXY-059 neuroprotection studies for acute stroke: a need for more rigorous testing of neuroprotective agents in animal models of stroke. Exp Neurol. 2007; 205(1):20–5. [PubMed: 17408618]
17. Fisher M, et al. Update of the stroke therapy academic industry roundtable preclinical recommendations. Stroke. 2009; 40(6):2244–50. [PubMed: 19246690]