CLINICAL IMPLICATIONS OF BASIC RESEARCH

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PARP Inhibitors and Parkinson's Disease

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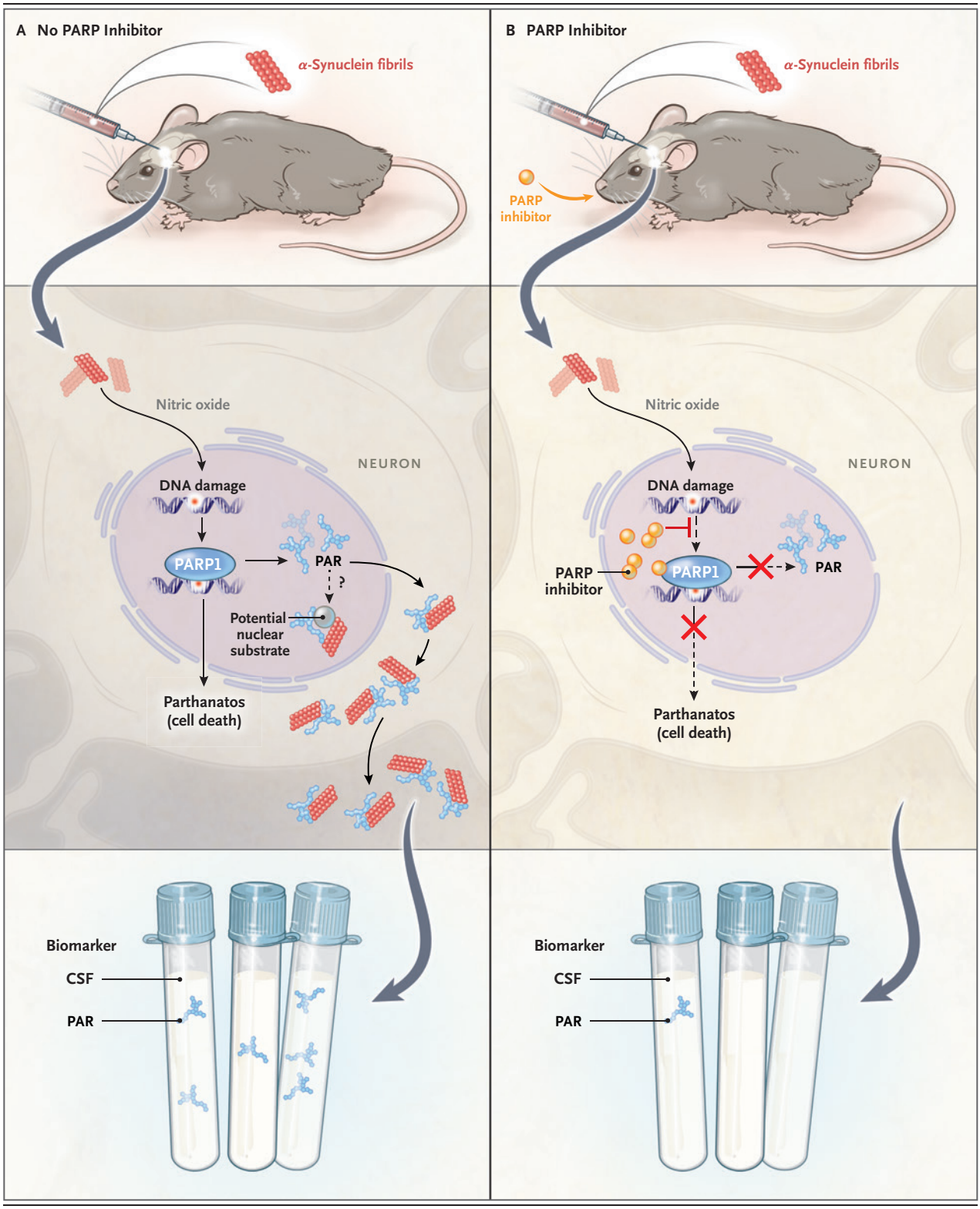
Parkinson's disease is a common and debilitating age-related neurodegenerative disease that is increasing rapidly in prevalence and is expected to affect 14 million people worldwide by 2040. The disorder is defined pathologically by the accumulation of a misfolded protein, α-synuclein, and the death of dopaminergic neurons in the substantia nigra. Despite extensive research, there remain fundamental questions about the mechanisms underlying α-synuclein toxicity and debates about the role of different forms of α-synuclein, cell-to-cell (prionlike) transmission of toxic α-synuclein, nuclear events, and cell-death mechanisms. Furthermore, clinical trials are hampered by a lack of biomarkers, challenges in translating discoveries in model systems to humans, and the number of patients and intensive resources required to conduct large trials. Drug repurposing has emerged as a promising therapeutic strategy to reduce the costs and safety failures associated with the development of new drugs.[1]

Kam et al.[2] recently described a new mechanism driving α-synuclein toxicity, as well as a potential biomarker and a "repurposing" target: poly(adenosine 5′-diphosphate-ribose) (PAR) and PAR polymerase 1 (PARP1), respectively. PARP1 modifies nuclear proteins by adding units of PAR to them, a process known as polyADP-ribosylation. Since the discovery of this protein's role in DNA damage repair, PARP1 has been found to participate in several cellular processes, including the regulation of chromatin structure, alterations in transcriptional machinery, RNA processing, and parthanatos (PARP1-dependent cell death, a form of programmed cell death). PARP1 represents an attractive therapeutic target for drug repurposing because inhibitors have been approved by the Food and Drug Administration to treat several types of cancer.

In their recent study, Kam et al. defined a new role for PAR and PARP1 in α-synuclein toxicity. They used a relatively new but experimentally powerful animal model of Parkinson's disease and related α-synucleinopathies in which α-synuclein fibrils that are formed in vitro (preformed fibrils) are injected directly into the mouse brain. The preformed fibrils seed the aggregation of endogenous α-synuclein and promote prionlike spread of the protein. The authors identified a feed-forward loop in which α-synuclein preformed fibrils increase nitric oxide–mediated DNA damage, which in turn activates PARP1, generating PAR and causing cell death through the parthenatos cell-death pathway. Furthermore, PAR interacts directly with α-synuclein, accelerating its fibril-

Figure 1 (facing page). PARP1 as a Therapeutic Target for α-Synucleinopathies.

As shown in Panel A, Kam et al.[2] identified a feed-forward loop in which α-synuclein preformed fibrils injected into mouse brain induce nitric oxide–mediated DNA damage; this activates poly(adenosine 5′-diphosphate-ribose) (PAR) polymerase 1 (PARP1), which generates PAR. In turn, PAR interacts directly with α-synuclein to accelerate α-synuclein fibrillization and neurotoxicity in the cytoplasm, extracellular space, and also possibly in the nucleus with respect to the fibrillar nuclear α-synuclein inclusions found in multiple-system atrophy. Patients with Parkinson's disease have an increased level of PAR in the cerebrospinal fluid (CSF), which makes PAR a candidate biomarker. As shown in Panel B, PARP inhibitors block the formation of PAR, thereby reducing α-synuclein fibrillization, spread, and related cell death through the parthanatos pathway. If PAR were validated as a biomarker, PARP inhibitors would be predicted to reduce levels of PAR in the CSF.



lization in vitro and promoting both α-synuclein toxicity and spread in vivo. The authors then showed that toxicity is abrogated in PARP1 knockout mice, or through the administration of inhibitors of PARP1 or nitric oxide synthase. Finally, they found higher levels of PAR in the cerebrospinal fluid (CSF) of persons with Parkinson's disease than in that of unaffected persons, which raises the possibility of PAR as a potential biomarker.

The current work intersects with numerous exciting questions in the α-synuclein field. For one, there is growing evidence in model systems to support cell-to-cell transmission of α-synuclein,[3] but this is inherently challenging to confirm in humans. Because PARP1 inhibitors act at least in part by reducing the spread of α-synuclein, clinical efficacy of PARP1 inhibitors in Parkinson's disease could provide indirect evidence supporting α-synuclein transmission in patients. In addition, certain variants of α-synuclein would seem to be more toxic than others,[4] which raises the possibility of strain-specific association with PAR. Finally, there is emerging evidence of direct nuclear toxicity of aggregating proteins (including but not limited to α-synuclein[5]) in neurodegenerative disease. Given the normal nuclear localization of PARP1, the enzyme might promote the formation of toxic nuclear α-synuclein species, either through direct binding of PAR to α-synuclein or through polyADP-ribosylation of another nuclear substrate (Fig. 1).

The new work of Kam et al. prioritizes PARP1 inhibition as a therapeutic target in Parkinson's disease and highlights areas for further investigation. Additional work will be needed to validate PAR in the CSF as a biomarker and assess the safety of PARP1 inhibitors in the context of longer-term administration for progressive neurodegenerative disease. PARP1 inhibition may have relevance to α-synucleinopathies other than Parkinson's disease, such as dementia with Lewy bodies and multiple-system atrophy. Dementia with Lewy bodies imposes a greater disease burden than Parkinson's disease, and multiple-system atrophy may offer certain advantages in terms of clinical trials given its orphan-disease status and potentially shorter expected duration of therapy because of the rapidly progressive nature of the disease. The substantive report by Kam et al. illustrates the importance of rigorous long-term basic research efforts in moving mechanism-based therapies toward clinical practice.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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