Lost in translation: Parkinson's disease research undercut by study design

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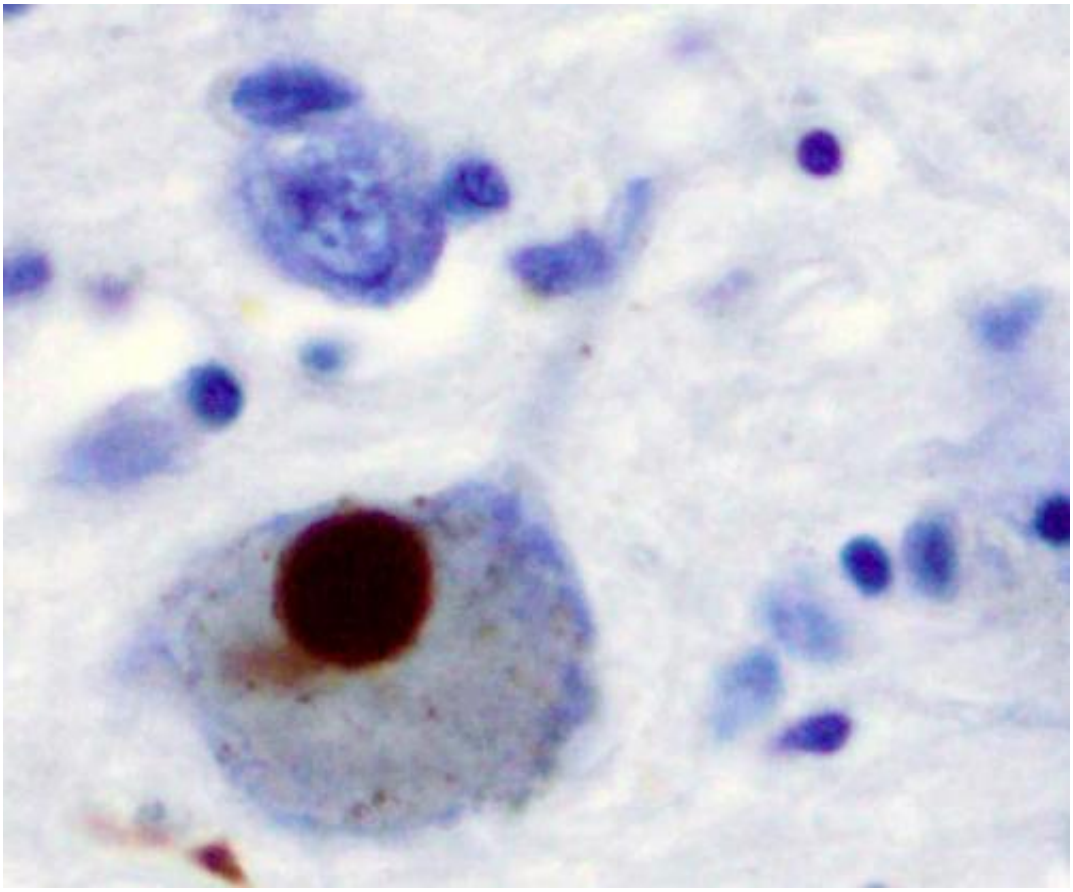

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

In a review of animal studies of Parkinson's disease therapies, Yale

researchers identified trends that may contribute to the lack of success in human clinical trials. Their finding provides insight to investigators who seek new therapies to slow the progression of the disease.

The study was published Feb. 9 by *PLOS ONE*.

Many potential therapies for Parkinson's disease that are successful in animal studies fail in human trials, said the researchers at Yale and Albert Einstein College of Medicine. While flaws in study design and reporting in a variety of diseases have been publicized, the research team decided to examine the impact of other study design issues on the development of new therapies.

The research team reviewed more than 500 animal and human studies of Parkinson's disease published over the last 40 years. They compared the design of studies for therapies that targeted symptoms with those intended to slow progression of the disease. In addition to previously described design oversights, such as randomization and blinding, they explored whether the study design in animals was aligned with the intended purpose of the therapy in humans.

The researchers found that in studies of therapies to delay the disease, the intervention was given to animals too early—either prior to or soon after disease onset. That stands in stark contrast to how human patients are typically treated.

Additional study shortcomings included a preference for young male animal subjects, a singular time point to assess the outcome, use of measures not validated in clinical settings, and dependence on non-progressive models of Parkinson's disease. These were all factors that impaired the generalizability of results from relatively narrowly defined animal systems to a more complex system, such as humans, the researchers report.

"These data suggest that study designs in animals, particularly mice, are perpetuated based on accepted norms despite little evidence for translation to humans," said first author Caroline Zeiss, professor of comparative medicine at Yale.

"Reproducibility and translation are related but distinct issues—our study focuses predominantly on factors affecting translation. Unless study designs in animals change to reflect the human disease more accurately, proposed measures to improve reproducibility are unlikely to have a significant impact on translation of new therapies to the clinic," Zeiss noted.

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