

# Philosophy of Medicine

Letter

## Interventional Philosophy in Medicine: Formulating Hypotheses

Timothy Daly<sup>1</sup>

<sup>1</sup> Department of Philosophy, Sorbonne Université, Paris, France; Bioethics Program, FLACSO, Buenos Aires, Argentina. Email: [tdaly@flacso.org.ar](mailto:tdaly@flacso.org.ar)

Advocates of philosophy in science and biomedicine argue that philosophers can embed their ideas into scientific research in order to help solve scientific problems (Pradeu et al. 2021). One successful example of this is the philosopher Thomas Pradeu's essay, with Sébastien Jaeger and Eric Vivier, titled "The Speed of Change: Towards a Discontinuity Theory of Immunity?" published in *Nature Reviews Immunology* (2013).

For my PhD in philosophy of science on Alzheimer's disease embedded in a neurology environment, I was interested in the relationship between theory and practice, with a particular focus on the dominant "amyloid cascade hypothesis" of Alzheimer's disease that has existed since the turn of the 1990s (Hardy and Higgins 1992; Hardy 2006; Herrup 2015; Kepp et al. 2023). According to this hypothesis, one of the brain proteins that defines Alzheimer's disease—beta-amyloid—also causes it when it accumulates (Hardy and Higgins 1992). Thus, according to the hypothesis's proponents, removing amyloid from the brain should be the priority for developing therapeutics. However, given the absence of effective treatments for Alzheimer's disease based on this strategy, I was interested in whether this hypothesis represented a premature convergence of consensus around an untrue idea of what causes disease.

Debate around amyloid and Alzheimer's has been active for decades and perhaps its most famous defender, the neurogeneticist Sir John Hardy, has long argued that its critics have "failed to come up with a viable alternative" (Hardy 2006, 153). In the words of the critics themselves, moving beyond the centrality of amyloid tends to leave researchers with "no clear guidance as to how to focus our quest to understand and treat AD" (Herrup 2015, 797) as the focus shifts to studying the "concerted activity of many pathogenic factors" (Kepp et al. 2023, 3969). Thus, in spite of mounting evidence against the amyloid cascade hypothesis, as the philosopher of science Thomas Kuhn (1922–1996) argued, "Once it has achieved the status of a paradigm, a scientific theory is declared invalid only if an alternative candidate is available to take its place" (1970, 77).



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So, putting forward an actionable alternative to the amyloid cascade hypothesis emerges as one way in which a philosopher of science working within Alzheimer's research can use their expertise to intervene and "solve a scientific problem" (Pradeu et al. 2021, 31). Work from my PhD led me to argue that two criteria may have played an important role in the widespread acceptance of the amyloid cascade hypothesis: the concision and clarity of the 1,150-word article defending it in 1992 (Hardy and Higgins 1992), making for a wide readership of these ideas (Daly 2023), and the high pathophysiological specificity of amyloid metabolism's association with Alzheimer's disease as opposed to other putative causes that are almost always involved in the etiology of other conditions (Daly, Henry, and Bourdenx 2023).

The conjunction of these two criteria led me to reach out to three critics of the hypothesis—scientists Karl Herrup and Kasper Kepp, authors of the aforementioned critical articles (Herrup 2015; Kepp et al. 2023)—and, in particular, the neurologist Alberto J. Espay, who has invested considerable energy into putting forward a different paradigm for understanding the relationship between protein and neurodegenerative diseases. His work maintains a focus on the specificity of proteins that define these conditions but may not necessarily cause them. Instead, he has invited researchers to consider what is lost when proteins accumulate in neurodegenerative disorders, rather than what is gained. His idea is that the loss of functional, soluble protein during the process of aggregation is more detrimental to the brain than the corresponding accrual of insoluble clumps of protein—in other words, the problem is *proteinopenia*, rather than *proteinopathy* (Espay and Okun 2023).

Over the course of ten months and at least as many drafts, the four of us worked on formulating a 1,300-word paper, "The Proteinopenia Hypothesis: Loss of A $\beta$ 42 and the Onset of Alzheimer's Disease," which was recently published in a Q1 science journal, *Ageing Research Reviews* (Espay et al. 2023). Though I cannot speak on behalf of my colleagues, from my point of view, the goal of the paper was to stimulate healthy and reasonable competition between hypotheses in a field dominated by monolithic thinking about disease. Ultimately, time will tell whether competition between hypotheses of Alzheimer's disease is feasible or even desirable.

In the meanwhile, I encourage other philosophers of medicine to draw on their expertise within their own domain of study to identify problems relevant to scientific practice and patients awaiting solutions, so as to intervene and put their unique skills toward solving them.

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