Essay

Throwing Good Money, and Millions of Lives, after Bad

Marcia Triunfol *

Posted Date: 11 September 2023

doi: 10.20944/preprints202309.0705.v1

Keywords: escalation of commitment; sunk cost; Alzheimer Disease; animal models

Essay

Throwing Good Money, and Millions of Lives, after Bad

Marcia Triunfol

Publicase International; mtriunfol@publicaseinternational.com

Abstract: Escalation of commitment explains the choice for investing in an option for which great investments have previously been made even though better choices became available. The last 25 years of producing innumerous versions of Alzheimer Disease animal models with virtually no predictive validity should have exposed the fact that using animals for studying AD is clearly a failing course of action and as such should have been abandoned long ago, giving room to other alternatives to flourish. In this assay, I explore the idea that the investment in new animal models for studying Alzheimer (AD) represents a classic case of escalation of commitment, and sunk cost dilemma, in the biomedical research.

Keywords: escalation of commitment; sunk cost; Alzheimer Disease; animal models

---

In a 2013 study, Katherine Aebuthnott and Brett Dolter showed how the psychological construct known as escalation of commitment could have interfered with the need, already recognized at the time, to transition from fossil fuel production to green technologies aimed to mitigate the impacts of global warming (1). Escalation of commitment explains the choice for re-investing in an option for which great investments have previously been made even though better choices became available. The magnitude of previous investment in technologies of long history, such as fossil fuels, favors continuing investments in such technology because reduces the flexibility of decision-makers who tend to re-invest in something that is already familiar while resisting to invest in new alternatives for which the return is unknown. It is a decision-making framework that relies on conservationism and familiarity instead of exploring the value and probability of success of the available options. At the time, the authors expressed that investing in fossil fuel industries should not be publicly supported as it could impair progress and the investment in new technologies such as green alternatives. Sadly, G20 countries have invested more than $3.3 tn in fossil fuels since the Paris Climate Agreement in 2015, The Guardian reported in July 2021. Escalation of commitment can be translated into simple language as "throwing good money after bad (2).

With escalation of commitment, investments are put in a strategy that clearly has failed; it is an attempt to "rescue" investments already made in the past. The concept derives to what is known as sunk cost dilemma, which is the "tendency to continue an endevor once an investment in money, effort or time has been made"(3). It is a decision bias that makes individuals continue to invest money, time, and energy in a bad deal because of the effort that they have already put into it.

The investment in new animal models for studying Alzheimer Disease (AD) seems to represent a classic case of escalation of commitment, and sunk cost dilemma, in the biomedical research. AD is characterized by a brain degeneration that destroys many of its functions and is associated with loss of cognition and behavioral changes. The main histopathological cerebral hallmarks of AD are extracellular deposits of amyloid-β (Aβ) plaques and the presence of tau proteins in intracellular neurofibrillary tangles. However, there are still many questions on how these two proteins orchestrate the onset and progression of AD in the human brain and whether the "amyloid cascade theory" proposed in 1988, and which states that AB pathology is central to AD, holds true (4). Nevertheless, most animal models ever developed to study AD aim at replicating the presence of

 doi:10.20944/preprints202309.0705.v1

amyloid plaques in the brain; removing amyloid plaques is still an end point of many clinical trials testing new drugs to treat AD (NCT04468659, NCT05269394, among others).

According to ALZForum, a platform that provides information on AD and has a database of animal models of neurodegenerative diseases, there are more than 200 animal models for studying Alzheimer's Disease. Even though there are no established criteria to determine whether an animal model constitutes a *bona fide* representation of the human condition, three main "levels" of validity have been established to evaluate an animal model: construct, face, and predictive validities. Construct validity is *a priori* value that refers to the design of the model and how faithfully it replicates the pathogenesis of the disease; face validity is *a posteriori* value and indicates how well the model replicates biological and behavioral phenotypes and the predictive validity refers to the predictive value of the model and its translatable potential to humans.

Many different approaches have been applied to create an animal model that illustrates these three main validities. These approaches include transgenic and nongenetic methods that have led to models with very different characteristics. The first transgenic model of AD was reported by Games *et al*. in 1995 (5) followed by the Tg2576 (6) and the APP23 mouse models (6, 7). Many humanized transgenic mice carrying human AD mutations known to run in families have also been created using different mice strains (8). The first model displaying both amyloid plaques and tau tangles is the triple transgenic mouse model 3XTg (9). Of note is that cognitive deficit in these animals occur very early in the process (at 2 months of age) (10).

The production of Aβ amyloid plaques and deposition of tau tangles are still considered as face validity and still an important feature to replicate when producing an animal model for studying AD. However, it has been shown that the overexpressing of genes and promoters in these models leads to symptoms associated with AD, not being clear how to differentiate the symptoms caused by the amyloid plaques and/or tau neurofibrillary tangles from those of gene overexpression. These models greatly differ among themselves, and none displays all seven dimensions listed in the ALZForum database as important AD features: presence of amyloid plaques, presence of tangles, neuronal loss, gliosis, synaptic loss, changes in synaptic strength, and cognitive impairment. Also, when to use one model or the other is not clearly defined. A previous study indicates that the choice for which animal to use has less to do with its predictive validity or translatable potential and more with its availability (10).

None of the AD models ever developed carries any predictive validity that has been translated to humans. For instance, virtually all drugs that appear safe and effective in these animals have failed in human trials. Take for example Solanezumab, a human monoclonal antibody developed by Eli Lilly first tested in the AD PDAPP transgenic mice model where it showed to reduce the Aβ amyloid deposition significantly (11). The drug failed to reach the primary endpoint in Phase III clinical trials (12). Another example of failing drug is the monoclonal antibody Bapenizumab, acquired by Pfizer and Johnson & Johnson for 1. 5 billion dollars in 2009 (13). With a failing rate at 99.6%, the number of drugs that failed AD patients in clinical trials only keeps growing (14).

Currently, the four drugs for AD approved by regulatory agencies worldwide (donepezil, rivastigmine, galantamine, and memantine) only ameliorate some symptoms and they only work in a small number of patients. More recently, the drug Aduhelm (aducanumab, a human monoclonal antibody that selectively targets aggregated Aβ), was approved by the U.S. Food and Drug Administration for the treatment of Alzheimer's. In 2016, the molecule was first tested *in vitro* and then in the transgenic AD model Tg2576, in which it showed to cross the brain barrier and to cause a reduction of amyloid plaques (15).

The new drug was supposed to be the first disease-modifying therapy for AD. It was approved through FDA accelerated approval pathway based on the drug effects observed in a surrogate endpoint (the amyloid removal) that may predict how patients respond to the drug, even though it is not clear whether amyloid removal indeed translates into disease control, or improvement of patients' symptoms. There are many controversies surrounding Aducanumab. Its approval in Europe was refused in December 2021, which made Biogen, the drug manufacturer, to withdraw its application for marketing authorization in the region in April 2022.

 doi:10.20944/preprints202309.0705.v1

More recently, Leqembi (lecanemab) formerly known as BAN2401(and originally the monoclonal antibody mAb158) gained FDA approval in January 2023 and full approval in August of the same year. Lecanemab was extensively studied in rodent models in which showed to selectively bind and reduce soluble amyloid beta plaque (Aβ protofibrils) (16) (17). Lecanemab does reduce amyloid plaques in the brain of patients, a feature that is not yet confirmed to be the cause of symptoms observed in AD patients. However, improvement in cognition and function in AD patients has been only moderate, with patients delaying symptoms for 18 months, if compared with placebo, and having to cope with adverse events (18).

Why are studies that use animal models for Alzheimer Disease still being funded? For some, continuous funding of studies that rely on animal models to study Alzheimer Disease may be explained by the sunk cost effect. In other words, so many animal models have been produced, so much has been invested in producing animal models to study AD, including the construction of animal facilities and development of specialized training to handle the animals, that to stop using animal models altogether does not seem to be an acceptable alternative, regardless of how unreliable or non-translatable to humans the results of such studies seem to be. It is possible that quitting projects that use animal models to study AD constitutes an admission of waste and loss of money, time and resources that may be unacceptable to some.

It is important to recognize that in the same way that the discovery and use of fossil fuels were crucial for the development and progress of modern societies, the use of animals in research in the past was crucial for unveiling the fundamental basis of animal anatomy and physiology and to help us understand the basis of human biology. For centuries, animal models and animal research were the only resources available to a scientific community eager to explore and understand our own nature and to discover new compounds, treatments, and vaccines to care for a growing population.

However, this is no longer our reality today. Since the discovery of the DNA molecule by Watson, Crick and Franklin in the 1950's, which launched the molecular biology era, we have been developing techniques that do not rely on *in vivo* studies but instead explore smaller biological parts such as tissues, cells and molecules to shed light on how our bodies work in health and disease. By employing innovative approaches like organoids, induced pluripotent stem cells (iPSCs), computational models, and organ-on-a-chip technologies, we have accelerated our understanding of human biology at an unprecedented pace, surpassing what was achievable using traditional animal models.

Animal models for studying AD do carry construct and face validities, with each model displaying one or another feature of AD. However, the last 25 years of producing innumerous versions of AD animal models with virtually no predictive validity should have exposed the fact that using animals for studying AD is a failing course of action and as such should have been abandoned long ago, giving room to other alternatives to flourish.

Alzheimer's Disease is likely the single disease with the highest number of unique animal models ever created, which greatly increases the burden of sunk costs and the escalation of commitment. Take an appealing idea (that beta amyloid deposition is the main cause of AD and thus by clearing the plaques a positive effect should be observed), build models that confirm the appealing idea (different strategies have been successfully used to clear amyloid plaques in different AD animal models), invest millions of dollars to build different versions of the model that confirms the appealing idea (there are currently more than 200 models) and besides creating one more classic instance of confirmation bias in science, a perfect scenario for the escalation of commitment has been born!

As far as animal models is concerned, a behavioral study published in the prestigious journal Science has shown that the sensitive humans show towards sunk cost is similar to that observed in mice and rats (19). No wonder why we keep investing in animal models for studying Alzheimer's disease.

References

1. Arbuthnott KD, Dolter B. Escalation of commitment to fossil fuels. Ecological Economics2013. p. 7-13.
2. Staw BM. The Escalation of Commitment To a Course of Action. Academy of Management Review. 1981;6(4):577-87.
3. Arkes HR, Blumer C. The psychology of sunk cost. Organizational Behavior and Human Decision Processes. 1985;35(1):124-40.
4. Morris GP, Clark IA, Vissel B. Questions concerning the role of amyloid-β in the definition, aetiology and diagnosis of Alzheimer's disease. Acta neuropathologica. 2018;136(5):663-89.
5. Games D, Adams D, Alessandrini R, Barbour R, Borthelette P, Blackwell C, et al. Alzheimer-type neuropathology in transgenic mice overexpressing V717F β-amyloid precursor protein. Nature1995. p. 523-7.
6. Hsiao K, Chapman P, Nilsen S, Ec C, Harigaya Y, Younkin S, et al. Correlative Memory Deficits, AP Elevation, and Amyloid Plaques in Transgenic Mice. Science. 1996;258(1 996):7-10.
7. Sturchler-Pierrat C, Abramowski D, Duke M, Wiederhold KH, Mistl C, Rothacher S, et al. Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology. Proceedings of the National Academy of Sciences of the United States of America. 1997;94(24):13287-92.
8. Drummond E, Wisniewski T. Alzheimer's Disease: Experimental Models and Reality. 2017.
9. Oddo S, Caccamo A, Kitazawa M, Tseng BP, LaFerla FM. Amyloid deposition precedes tangle formation in a triple transgenic model of Alzheimer's disease. Neurobiology of Aging. 2003;24(8):1063-70.
10. Veening-Griffioen DH, Ferreira GS, van Meer PJK, Boon WPC, Gispen-de Wied CC, Moors EHM, et al. Are some animal models more equal than others? A case study on the translational value of animal models of efficacy for Alzheimer's disease. European Journal of Pharmacology. 2019;859(July).
11. DeMattos RB, Bales KR, Cummins DJ, Dodart JC, Paul SM, Holtzman DM. Peripheral anti-Aβ antibody alters CNS and plasma Aβ clearance and decreases brain Aβ burden in a mouse model of Alzheimer's disease. Proceedings of the National Academy of Sciences of the United States of America. 2001;98(15):8850-5.
12. Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al. Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease. New England Journal of Medicine. 2014;370(4):311-21.
13. Sheridan C. JandJ's billion dollar punt on anti-amyloid antibody. Nature Biotechnology. 2009;27(8):679-81.
14. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimer's research & therapy. 2014;6(4):37-.
15. Kastanenka KV, Bussiere T, Shakerdge N, Qian F, Weinreb PH, Rhodes K, et al. Immunotherapy with Aducanumab Restores Calcium Homeostasis in Tg2576 Mice. J Neurosci. 2016;36(50):12549-58.
16. Lord A, Gumucio A, Englund H, Sehlin D, Sundquist VS, Söderberg L, et al. An amyloid-beta protofibril-selective antibody prevents amyloid formation in a mouse model of Alzheimer's disease. Neurobiol Dis. 2009;36(3):425-34.
17. Tucker S, Möller C, Tegerstedt K, Lord A, Laudon H, Sjödahl J, et al. The murine version of BAN2401 (mAb158) selectively reduces amyloid-β protofibrils in brain and cerebrospinal fluid of tg-ArcSwe mice. J Alzheimers Dis. 2015;43(2):575-88.
18. Swanson CJ, Zhang Y, Dhadda S, Wang J, Kaplow J, Lai RYK, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Alzheimers Res Ther. 2021;13(1):80.
19. Sweis BM, Abram SV, Schmidt BJ, Seeland KD, Iii AWM, Thomas MJ, et al. Sensitivity to "sunk costs" in mice, rats, and humans Brian. Science. 2018;361(6398):178-81.