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David H. Crean, Ph.D., is a San Diego-based venture capitalist and strategic advisor with over 30 years of experience in life sciences and healthcare. Drawing on a deep personal connection to Alzheimer's disease as well as decades of experience as a scientist and investor, Crean casts his eye over the massive progress that has been made in diagnosis, treatment and understanding of Alzheimer's; the exciting myriad of treatments in the pipeline; and the geopolitical tensions currently threatening the investment climate.

Why is Alzheimer's disease so important to you personally?

My father has Alzheimer's; he was diagnosed with mild cognitive impairment about seven or eight years ago, and it's only gotten worse. By the time the two recently approved antibodies became available, he no longer qualified because his condition had progressed.

He is based in New York and I'm in San Diego, so I manage a long-distance caretaker relationship. This disease takes a terrible toll, not just on the patient but on their caregivers and families, and that's why I felt like I had to do something to give back, raise awareness, and advocate for increased research funding. I therefore got involved with my local branch of the Alzheimer's Association and have served on the board in various roles, now as chairman emeritus.

For the past two decades, Alzheimer's has been a field without new therapeutic options, although a couple of recent approvals have provided some cause for optimism. From an investment perspective, how different are things in 2025 compared to five years previously?

The advancements over the past five to ten years have been remarkable. 20 years ago, drugs like memantine only addressed signs and symptoms of Alzheimer's disease, but we are now finally targeting the root causes of the disease, or at least the biological mechanisms behind it.

Even though Biogen's launch of Aduhelm (aducanumab) was an epic failure, the rollout of other anti-amyloid beta antibodies such as lecanemab and donanemab has been hugely encouraging.

That said, I do have some hesitation about the changing landscape in Washington DC, with cuts to National Institutes of Health (NIH) funding. NIH, and the National Institute on Aging (NIA) underneath it, has made truly significant investments in the field, not just in basic research to better understand mechanisms and targets, but also in clinical development, contributing to the advancement of disease-modifying drugs.

It's also not just about therapeutics. We've seen major improvements in diagnostic tools like blood biomarkers and PET scans, as well as in behavioural studies, lifestyle interventions, genetic factors, and caregiving science. Overall, there's now a much more comprehensive approach that increasingly addresses the underlying causes of the disease.

Researchers are now looking at a range of biological mechanisms. Of course, we still focus on amyloid beta and tau tangles, but there's growing interest in other targets such as microglia, which play a role in regulating neural inflammation and neuroinflammatory diseases.

Additionally, just this month I spoke with a US-based group looking to start a venture fund specifically focused on vaccine technology for Alzheimer's. Given the anti-vaccine stance of some members of the current administration, I have some doubts about how this could play out politically, but I like the approach from a scientific perspective and am going to be watching it closely.

The key takeaway is that there is now lots of diversity, not just in terms of biological mechanisms but also approaches. As a researcher, investor, and advocate, I truly believe that Alzheimer's treatment is going to evolve in the same way that cancer treatment has, utilising multiple approaches. There will not be a single wonder drug that works for everyone. Instead, a patient

might take an anti-amyloid beta antibody to target plaques in the brain but combine it with a small-molecule drug to address neuroinflammation

The likes of Eli Lilly, Roche, and Biogen have made significant bets on Alzheimer's, yet it is predominantly smaller biotechs driving early innovation. Given this landscape, what M&A trends are you anticipating over the coming years?

Looking at how big and mid-sized pharma companies are expanding their portfolios in this space, I only see M&A activity increasing.

Right now, we have two generally approved therapies worldwide, lecanemab and donanemab, though their market expansion is still a challenge. However, in the broader pipeline, both pharmacological and non-pharmacological, there are so many different targeted disease pathways emerging. There's amyloid, inflammation, and multi-target approaches, as well as something I'm watching closely: GLP-1 drugs. These are the medications from Novo Nordisk and Eli Lilly currently being used to treat obesity and diabetes. Novo Nordisk is set to report its first highly anticipated findings at the Clinical Trials on Alzheimer's Disease (CTAD) conference in November.

More broadly, how different companies are approaching Alzheimer's pharmacologically, across phase one, phase two, and even phase three and four trials, is going to keep driving partnerships and M&A activity. It's not just going to be two antibodies on the market forever. There's a growing focus on earlier intervention and prevention. This will call for long, expensive studies that require time, effort, and a lot of patience, but the potential impact is enormous.

Beyond drugs, we're also seeing some interesting developments in medical devices. A Boston-based company called Sinaptica Therapeutics, for example, shared an early-stage cost-effectiveness analysis of their therapy for Alzheimer's disease at the ISPOR Europe 2024 Annual Meeting in Barcelona, Spain, in late October 2024. They are working on a device that stimulates specific areas of the brain, which seems to trigger significant neuroplasticity. This essentially reorganises the brain's structure and function and has shown some remarkable cognitive improvements in early studies. As a seasoned venture capitalist, I am generally a little sceptical about medtech, but there is definitely something happening there.

How do pricing and reimbursement dynamics affect investment in this space? And what lessons have been learned from the Aduhelm experience?

The Aduhelm saga was a disaster. Mark my words, one day the Harvard Business Review will use this episode as a case study on how *not* to launch a drug! Biogen thought that, given that nothing new had come along in 17 years and that their drug targeted the biology of the disease rather than just the symptoms, they could get away with pricing it at USD 56,000 per patient per year. This was a ridiculous decision, and a clear reflection of insufficient market research on pricing. It was a massive failure, not just from a business perspective, but from a health economics standpoint.

When you develop innovative drugs or devices, it's not just about safety and efficacy, there are two other key questions: what's the price and who's going to pay for it? Biogen failed spectacularly on both fronts. And, given they couldn't make an economic case for it in the US, there was even less chance of success in markets with higher levels of price regulation such as the UK.

Lessons have been learned, and lecanemab and donanemab have been priced much more reasonably, in the USD 25,000 to 30,000 range. The bigger issue here is the impact on Medicare and Medicaid in the US as well as in global health systems. With dementia rates rising in an aging population, how are we going to afford these treatments? Figuring out how to pay for these therapies – whether through subsidies or full coverage – has to be part of every major health system's agenda.

The Trump administration is undertaking a massive cost-cutting programme across the Federal government, including proposing to cap NIH indirect cost reimbursements at 15 percent. This potentially puts the USD four billion spent on Alzheimer's medical research annually under threat. How do you anticipate this will affect investment in Alzheimer's research and potentially America's leadership in this area?

I am really concerned about the impact on innovation, not just in the US, but globally. The NIH, Food & Drug Administration (FDA), Centers for Disease Control (CDC), and other agencies play a critical role in advancing science and approving new treatments. If their budgets are slashed, it's going to slow down everything from grant approvals to regulatory reviews and funding for new technologies. Additionally, the appointment of a vaccine-sceptic as head of Health & Human Services (HHS) adds to the atmosphere of uncertainty. If a researcher submits a new application for review, they will now be less sure as to what to expect, which has knock-on effects on all areas of medical research, not just Alzheimer's.

The cuts being made are seemingly indiscriminate, which to me seems crazy, and – if the goal is for the US to remain competitive in innovation with countries like China – this is not the way to do

it.

What impact are these cuts having on some of the biotechs that you advise?

I spend a significant amount of time advising CEOs, many of whom rely on NIH grants, and a lot of them are panicking. A few weeks ago, they were scrambling to pull down as much grant money as possible before January 21st, and now they're left wondering what to do.

Many will need to figure out alternative funding strategies. When I talk to biotech CEOs about raising equity, they often worry about dilution, giving up company ownership. But as I tell them, I'd rather see them have money than no money. Don't get caught up in ownership concerns if it means you cannot advance your company and technology.

Some companies have already secured their grants, only to have portions of the funding pulled back. What I'd like to see, given the uncertainty around public funding, is for private investors, people like me and others, step up and help fill that gap. Institutional investors, venture capitalists, and private firms have an important role to play here. Maybe that means launching new funds or investment firms specifically for this purpose.

2024 was not a great year for biotech investment, but what are the bright spots you see for 2025?

2024 was a disappointing year. IPOs were not particularly strong and, while we now have a long queue of companies lined up to go public, things have been slow in the first few months of the year.

M&A was muted last year too. While there have been a few deals announced so far in 2025 – such as J&J's USD 14.6 billion acquisition of the neuroscience biotech Intra-Cellular Therapies – it has been pretty quiet.

Everybody expected 2025 to be a big M&A year, and while I think it will improve, I do not expect the IPO market to properly pick up until towards the end of the year. I think we may have to wait until 2026 for the real bounce-back

The political uncertainty I mentioned previously is playing a role. We've got a new administration that wants to slap tariffs on everyone, which is creating additional instability. Geopolitical tensions

are escalating, consumer confidence is dipping again, and there is a real risk of an economic downturn. The Federal Open Market Committee initially projected three rate cuts this year, but now there may be only one, or possibly none.

What's your advice for biotech CEOs and entrepreneurs in the Alzheimer's space over the next year or two?

The main point is to keep focusing on innovation. There are so many great ideas out there, and this isn't going to be a one-and-done situation. Alzheimer's treatments won't just rely on a single antibody, we're going to see diverse approaches for treating neurodegenerative diseases, whether Alzheimer's, ALS, Parkinson's, Huntington's, or others. There's a massive unmet medical need, and innovation always rises to the top. Globally, we're doing incredible work in this space and need to keep pushing forward. Hopefully, the capital markets will align over time.

This is particularly important as, right now, there are still some strong headwinds. IPOs are slow, M&A is muted, and investors, especially limited partners, are cautious. For them, the return on investment comes from IPOs or acquisitions. When those aren't happening, they don't get their returns, which slows the cycle of reinvestment and contributed to this period of uncertainty.

With all of that in mind, my advice to CEOs and entrepreneurs would be threefold: buckle up, as things are going to get bumpy; be capital-efficient and spend wisely; and don't spread yourself too thin, i.e. pick one target or one program and go deep rather than chasing five different ideas at once.

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