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Serious diseases often require more than one approach; cell therapy could be the missing piece [in Alzheimer's Disease]

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What if ageing itself, not just individual diseases, was the root cause of the most devastating conditions we face? That question has shaped the career of Dr. Joshua Hare, a practising cardiologist and biotech founder who is betting on stem cell therapy to shift how we treat age-related illnesses. Dr. Hare shares the scientific rationale behind Longeveron's lead candidate, laromestrocel, and its potential as a safe, disease-modifying therapy for Alzheimer's. With early clinical data showing promise and regulatory pathways opening up, he believes the field may be nearing a turning point.

What led you from a background in cardiology to founding Longeveron and focusing on stem cell therapies for ageing-related diseases?

My journey began in cardiology, where my focus was on end-stage heart failure and heart transplantation, areas where age is a defining risk factor. This naturally drew me to the geroscience hypothesis, which posits that ageing itself is the primary driver behind virtually all serious diseases. Whether we are speaking about heart failure, stroke, hypertension, cancer, or Alzheimer's, the data show a consistent and exponential increase in risk with each passing decade of life.

Roughly 25 years ago, I began searching for alternatives to heart transplantation, driven by the stark reality that while nearly 100,000 patients in the United States require a new heart each year, only around 2,500 actually receive one. Around that time, cell therapy was emerging as a radical yet promising concept, offering the possibility of repairing damaged organs rather than replacing them entirely. However, early enthusiasm for embryonic stem cells was tempered by federal restrictions on funding, particularly under President George W. Bush. These constraints prompted many of us in the field to explore other approaches.

One of the most compelling alternatives turned out to be mesenchymal stem cells. As a young faculty member at Johns Hopkins, I was fortunate to have access to these cells and launched a dedicated research programme focused on their use in cardiac repair. Our work spanned everything from catheter design to delivery techniques and dosing strategies, and we were encouraged by strong preclinical results. The National Institutes of Health (NIH) also recognised the potential, funding our early clinical trials in adult patients with heart failure.

Importantly, I made a conscious decision not to cap enrolment based on age, allowing us to include patients well into their 80s. We discovered that the therapy was equally effective in older and younger participants, and more intriguingly, that the benefits extended beyond cardiac function. We observed improved mobility, better functional capacity, and an overall enhancement in quality of life. These insights led us to a broader hypothesis: that cell therapy might have utility in treating ageing itself, particularly the frailty that often accompanies it. That pivot ultimately led to the founding of Longeveron in 2014, backed by a group of private investors who recognised the promise of targeting the biology of ageing directly.

Where does Longeveron currently stand in its development journey, and what is the strategic focus of your clinical pipeline?

While we have the technical capacity to develop additional products, we made a strategic decision early on to concentrate our efforts around a single high-potential asset, laromestrocel, our mesenchymal stem cell therapy. In biotech, focus is not a luxury but a necessity. Advancing one product through the regulatory process demands both scientific precision and organisational discipline, and laromestrocel offered us the clearest path forward based on our early data.

When we established Longeveron roughly a decade ago, we identified several promising indications. We began with ageing-related frailty, where our early studies revealed not only improvements in physical function, but also intriguing signs of cognitive benefit. That observation

naturally led us to consider Alzheimer's disease, which has remained a core programme ever since. We also initiated a second lead indication in Hypoplastic Left Heart Syndrome (HLHS), a rare congenital condition that aligns with my background in advanced cardiology and paediatric heart disease.

Alzheimer's has been particularly central to our clinical efforts. We received two grants from the Alzheimer's Association in the United States to support our Phase 1 trial, which evaluated laromestrocel in older adults with mild Alzheimer's. The results were reassuring: the therapy was well tolerated, with no serious adverse events, and although the study was not powered for efficacy, we observed early signals of improvement in both cognition and quality of life across a cohort of 33 patients. These initial findings provided the momentum to advance to Phase 2.

Following our NASDAQ listing, we conducted a Phase 2a trial, the results of which were published in *Nature Medicine* in April of 2025. This randomised, double-blind, placebo-controlled study enrolled 49 patients across three dosing regimens: single, multiple, and accelerated multiple dosing. Laromestrocel again demonstrated a favourable safety profile. While the trial was not powered for definitive efficacy, we saw consistent and meaningful signals: improvements in cognitive and functional assessments, preservation of brain volume, and reduced neuroinflammation as confirmed by detailed volumetric MRI.

One particularly noteworthy outcome was the improvement observed in activities of daily living, a domain in which currently approved monoclonal antibody therapies have shown limited or no effect. Given the modest size of the study, these findings were both unexpected and encouraging, strengthening our belief in the potential of cell therapy as a novel and complementary approach to treating Alzheimer's disease.

Where does laromestrocel fit into the evolving treatment landscape for Alzheimer's disease, and what distinguishes its therapeutic potential?

Alzheimer's disease, like other advanced and multifactorial conditions, is unlikely to be addressed by a single therapeutic agent. In clinical medicine, we rarely rely on a one-size-fits-all solution; complex diseases such as heart failure or cancer are typically managed through multidrug regimens that reflect the underlying biology. Alzheimer's is increasingly understood in similar terms, with a growing recognition that amyloid plaques represent just one dimension of a much broader pathological process.

At Longeveron, we believe that laromestrocel acts primarily by modulating neuroinflammation, a mechanism supported by imaging data from our recent Phase 2a trial. Importantly, this does not position our therapy as an alternative to amyloid-targeting monoclonal antibodies, but rather as a potential complement. Serious diseases often require multiple therapeutic inputs, and Alzheimer's is no exception. Combining agents with distinct modes of action may ultimately deliver better outcomes than either approach alone.

Safety remains a critical part of this discussion. While monoclonal antibodies have demonstrated efficacy in amyloid clearance, they are associated with amyloid-related imaging abnormalities (ARIA), including brain oedema and microhaemorrhages, particularly in individuals who carry the APOE4 genotype. In contrast, our trial included APOE4 carriers, including homozygotes, and we observed no ARIA events. That difference, coupled with the improvements we saw in cognition, activities of daily living, and brain volume preservation, reinforces our conviction that laromestrocel offers both safety and efficacy advantages in this setting.

Following these findings, we engaged with the US Food and Drug Administration and secured both Regenerative Medicine Advanced Therapy (RMAT) and Fast Track designations, which allow for closer interaction with the agency and access to expedited review pathways. In our end-of-Phase 2 Type B meeting, the FDA endorsed a seamless, adaptive Phase 2/3 trial design and confirmed that a Biologics License Application (BLA) could be submitted based on positive interim data. Launching this pivotal trial is now our next critical milestone.

How are shifting regulatory frameworks and tightening funding conditions in the US influencing your strategy as a clinical-stage biotech?

We are operating in a moment of real transition for the biotech sector in the United States. On one hand, the FDA – under Dr Martin Makary's leadership – is clearly working to accelerate therapeutic development through regulatory innovation and closer collaboration with companies like ours. On the other hand, there are strong headwinds. Proposed cuts to NIH funding, reportedly over 40%, threaten the stability of public-sector research, while access to private capital has become more limited than in recent years. Overlaying this is a broader geopolitical climate marked by tensions with China, a country that plays a significant role in the global innovation ecosystem.

From my perspective, this is less about a retreat from innovation than a rebalancing of where and how that innovation is funded. It appears that many traditional government functions are being shifted toward the private sector. Whether this yields a more efficient system or creates further

strain remains to be seen. What is clear is that companies like ours must stay agile. If public support continues to recede, then private capital must fill the gap, and we will do everything necessary to maintain momentum toward approval.

The impact on academic research could be even more severe. University laboratories have long depended on NIH grants to sustain their operations, and a reduction of this magnitude could compromise critical programmes. I see this dual reality firsthand, not only through my role at Longeveron, but also as the head of a research lab at the University of Miami. In both capacities, the imperative is the same: to move forward, adapt to changing conditions, and remain committed to reaching the next milestone. We are pursuing approval with purpose and resolve, regardless of how the external environment may shift.

How important are partnerships to your future development plans, and what shape might those collaborations take?

Partnerships are going to be fundamental as we move into the next phase of clinical development. Conducting a Phase 3 trial in Alzheimer’s disease is an immense undertaking, and given current funding constraints, it would be unrealistic to attempt it without a strategic partner. We are actively engaged in identifying the right collaborators who can help us scale the programme and navigate the regulatory path efficiently.

Recent regulatory initiatives could make this process even more compelling. The FDA has introduced a pilot programme aimed at reducing the time from submission to approval, potentially compressing review timelines from ten months to just two. This approach would allow companies to submit their full BLA in advance and trigger formal review upon the availability of clinical data. If we are able to secure a partner, complete the pivotal trial, and align with this accelerated pathway, it could significantly enhance both the strategic value of laromestrocel and our ability to bring the therapy to patients more rapidly.

We see forums like the recent BIO International Convention in Boston as vital platforms for building these relationships. Events like these allow us to present our data, engage directly with stakeholders across the pharmaceutical, biotech, and academic sectors, and lay the groundwork for future collaboration. As we prepare for our pivotal study, forging the right partnership is not only essential, it is central to our long-term strategy.

To what extent is the industry embracing your approach to Alzheimer's, and what challenges remain in advancing the adoption of cell therapy more broadly?

There is increasing recognition that neuroinflammation plays a critical role in Alzheimer's disease, particularly as a therapeutic target beyond the more established amyloid and tau pathways. This shift is becoming more visible in industry strategy. Sanofi's recent USD 470 million acquisition of Vigil Neuroscience, centred on a small-molecule programme targeting neuroinflammation, reflects growing interest from major pharmaceutical players.

Nonetheless, while the scientific rationale for cell therapy is compelling, broad adoption within the neurodegenerative space has been slower. Larger companies remain cautious, often preferring to wait for regulatory approval before moving decisively into the field. The concerns typically cited – manufacturing complexity, cost, and delivery – are valid, but I believe the deeper issue is one of mindset. Cell therapy represents a departure from conventional modalities, and such shifts rarely happen without initial resistance.

We have seen this dynamic before. When gene therapy first emerged, it faced significant scepticism. Yet once Spark Therapeutics gained FDA approval for Luxturna – the first gene therapy for an inherited disease – and was subsequently acquired for USD 4 billion by Roche, the landscape changed. That milestone validated the field and unlocked a wave of investment, partnerships, and innovation. I believe cell therapy is approaching a similar inflexion point.

The FDA's recent approval of Mesoblast's mesenchymal precursor cell therapy Ryoncil in the US may mark the beginning of that transition. As precedent builds and confidence in the modality grows, we may start to see the same pattern: increased activity from large players once early risks have been mitigated. Our role is to help accelerate that evolution, not only by generating robust clinical evidence, but also by demonstrating that cell-based therapies can be viable, scalable, and highly complementary to existing approaches in Alzheimer's disease.

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