

# Richard Hargreaves - Senior Vice President, Neuroscience Thematic Research Center, Bristol Myers Squibb

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*By pursuing both fronts, disease modification and symptom management, we aim to deliver a more comprehensive and humane approach [to Alzheimer's Disease]*

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*As neuroscience reclaims a place at the top table of pharmaceutical innovation, Bristol Myers Squibb (BMS) is quietly reshaping its presence in the field. Spearheaded by its Neuroscience Thematic Research Center, the company is pursuing a dual mandate: to slow the progression of diseases like Alzheimer's while also addressing their most disruptive symptoms. In this interview, Richard Hargreaves, Senior Vice President and Head of Neuroscience, discusses how BMS is navigating this high-stakes landscape, bridging psychiatry and neurology, embracing emerging diagnostics, and rethinking what impact on brain health can look like. As he puts it, "We are putting the CNS back into BMS."*

## **How has Bristol Myers Squibb renewed its focus on neuroscience, and what role does the Neuroscience Thematic Research Center play in that strategy?**

BMS's return to neuroscience was catalysed by the integration of Celgene in 2019, which brought with it a foundational team and a renewed opportunity to engage meaningfully with brain diseases. At that time, many pharmaceutical companies had stepped away from neuroscience, discouraged by scientific setbacks and the complexity of the field. As a result, much of the expertise shifted to venture-backed biotechs, and it became clear that advancing innovation in this space would

require a more collaborative, outward-facing model.

Our Neuroscience Thematic Research Center was intentionally built with a small internal footprint and a strong emphasis on external partnerships. That model has given us the agility to work with the most promising academic and biotech collaborators worldwide. Many of the assets now in our pipeline reflect the success of this approach. While our early efforts were focused on neurodegenerative diseases and disease-modifying strategies, we have since broadened our scope to include symptom management, most notably through the acquisition of Karuna Therapeutics and its lead asset, KarXT, which has also re-established our presence in psychiatry.

Today, we remain a focused team, but one embedded in a network of global innovation. We continue to work across both internal and external channels to advance neuroscience programmes with the potential to make a real impact. Internally, a phrase that resonates with our team, and that we have embraced as a kind of mission statement, is that we are “Putting the CNS back into BMS.” It reflects both a strategic intent and a renewed sense of purpose.

### **What underpins BMS’s dual commitment to slowing Alzheimer’s disease progression and alleviating its symptoms?**

Alzheimer’s disease demands a multifaceted response. It is not only a condition marked by gradual neurodegeneration but also one in which behavioural and psychiatric symptoms – such as agitation, aggression, and psychosis – can become the most distressing and disruptive features for both patients and caregivers. At BMS, we have deliberately adopted a dual approach that seeks to address the full continuum of care: intervening in the underlying pathology while also managing the symptoms that most acutely affect the quality of life.

From a biological perspective, Alzheimer’s begins with the early deposition of amyloid-beta, often years before symptoms appear, followed by the emergence and spread of tau pathology, particularly in the form of neurofibrillary tangles. These tau aggregates are more closely correlated with clinical symptoms and cognitive decline. To address this cascade, we are advancing an anti-tau monoclonal antibody that targets the microtubule-binding region (MTBR) of the tau protein, aiming to halt the propagation of these toxic aggregates.

At the same time, we are developing next-generation anti-amyloid antibodies equipped with technologies that allow us to significantly enhance the penetration of molecules across the blood-brain barrier, such as transferrin receptor-mediated transporters. This improved delivery

mechanism allows higher concentrations of antibodies to reach the brain, potentially enabling lower doses, safer profiles, and more convenient administration, possibly shifting from intravenous infusions to subcutaneous injections. Early data also suggest that therapies with this technology may reduce the incidence of amyloid-related imaging abnormalities (ARIA), as they engage with brain regions less burdened by vascular amyloid, thereby reducing the likelihood of inflammatory responses.

Beyond amyloid and tau, we are exploring approaches that target the neuroinflammatory processes associated with protein aggregation, with a long-term view towards combination therapies that may ultimately yield broader and more durable benefits. While halting the disease entirely remains a long-term aspiration, providing patients and caregivers with meaningful symptom relief is an equally important and more immediate goal. By pursuing both fronts simultaneously – disease modification and symptom management – we hope to offer a more comprehensive and humane approach to one of the most challenging conditions in medicine.

### **What prompted BMS's acquisition of Karuna Therapeutics, and how does KarXT align with your ambitions in Alzheimer's and neuroscience?**

The acquisition of Karuna Therapeutics was a deliberate move to expand our reach beyond neurodegeneration and into psychiatry, an area that not only complements our scientific ambitions but also directly supports our commitment to delivering comprehensive care in Alzheimer's disease. KarXT, Karuna's lead candidate, is a selective M1/M4 muscarinic receptor agonist and represents the first novel treatment for schizophrenia in decades. That in itself is a meaningful advance, particularly for a condition that remains one of the most pervasive and underserved in global mental health.

What made the opportunity especially compelling was KarXT's potential application in Alzheimer's-related psychosis, an area where existing treatment options are limited and often burdened by significant side effects. While our initial trials focus on psychosis, the mechanism of action also offers a rational path toward addressing agitation and cognitive decline, symptoms that are equally disruptive and often the tipping point for families seeking institutional care.

This move also allowed us to reconnect with a field we know well. BMS has a long-standing heritage in psychiatry and KarXT offered a natural bridge between that legacy and our current neuroscience strategy. While our work in Alzheimer's has largely focused on modifying disease biology, we recognise that symptomatic relief – particularly in the behavioural and cognitive domains – is

critical for patients and caregivers. KarXT strengthens our ability to deliver on both fronts.

**How is BMS balancing internal innovation with external collaboration in neuroscience, and how do you define your Center's strategic role?**

Our Neuroscience Thematic Research Center is intentionally compact. Rather than pursuing breadth our scope is sharply focused by a research framework that includes causal human biology, matching molecules to mechanisms and efficient paths to value creation with clinical proof of concept. This means relying heavily on human genetic evidence to select targets, pairing them with the most appropriate therapeutic modality, whether that be antisense oligonucleotides, RNA-silencing technologies, small molecules, protein degraders, or, increasingly, cell therapies and innovative biomarker-driven early clinical development.

This disciplined approach allows us to focus on diseases where the biological rationale is strongest – such as amyotrophic lateral sclerosis (ALS), Huntington's disease, and Parkinson's disease – where we believe intervention has the greatest potential to alter disease course. In other domains, particularly psychiatry and Alzheimer's disease, where the mechanistic landscape is more complex and the timelines to proof of concept are longer, we look outward. The innovation coming from biotech and academic labs is invaluable, and we see our role as identifying and enabling the most promising ideas rather than replicating them internally.

In Alzheimer's, for example, we are already advancing multiple programmes, including an anti-MTBR tau antibody, next-generation anti-amyloid therapies, and approaches targeting neuroinflammation. But each of these demands significant investment, both scientific and operational, and we are highly selective in what we choose to progress. You cannot meaningfully pursue ten long-cycle clinical programmes in parallel, so we prioritise those where there is a credible and timely path to proof of concept.

That translational window, the moment a molecule begins to declare itself, is where we place considerable emphasis. We view this stage as the critical value-creation period, and we have built strong internal capabilities to support it. Our translational science team works closely with biomarkers and imaging tools, including PET tracers for pathology and target engagement, allowing us to assess biological activity early and reliably. This enables better-informed decisions, reduces the risk of late-stage failure, and ensures that our resources are focused where they can deliver the greatest impact.

So while we remain highly collaborative, we are not simply aggregators. We operate at the intersection of rigorous internal science and strategic external engagement, grounded in a framework that combines biological plausibility, therapeutic modality, and translational feasibility. That balance, between precision and ambition, is what defines our role within BMS neuroscience.

### **How are advances in diagnostics and imaging reshaping Alzheimer's clinical research and patient selection?**

Recent developments in diagnostics have fundamentally changed how we conduct clinical research on Alzheimer's disease. Perhaps the most significant shift is our ability to more confidently identify patients who truly have the condition. In the past, diagnostic certainty often came only after death, which meant that many trials enrolled individuals with other forms of dementia, undermining the precision and interpretability of outcomes. Today, tools such as plasma p-tau217 allow us to detect amyloid pathology, a defining early feature of Alzheimer's, through a simple blood test.

This progress has transformed patient selection. We can now segment trial populations more accurately, recruit patients earlier in the disease process, and monitor progression in living individuals with far greater fidelity. These capabilities are allowing us to design trials that are not only more targeted but also more likely to yield meaningful insights.

Looking ahead, the implications are even broader. If we can identify biological changes long before clinical symptoms emerge, we may eventually shift from reactive treatment to proactive intervention, even prevention. It is an evolution that, as my colleague Ken Rhodes commented, brings Alzheimer's research closer to fields like cardiovascular and metabolic disease, where risk is assessed through panels of biomarkers and therapeutic strategies are tailored accordingly.

These advances do more than improve trial design, they refine the kinds of questions we are able to ask. And in doing so, they bring us closer to answers that matter, not just for science, but for the lives of patients and families navigating this profoundly challenging disease.

### **Some of our other interviewees have characterised the current sentiment in Alzheimer's research as one of 'cautious optimism.' Would you agree?**

'Cautious optimism' is an apt way to describe the current mood within the Alzheimer's research community. We have seen significant progress, particularly in our understanding of the disease's

underlying biology and how to design studies that more accurately capture meaningful outcomes. The years spent attempting to validate the amyloid hypothesis were not wasted, they taught us how to do the best clinical trials using the right biomarkers to choose the right patients at the right time in their disease, thereby letting us ask more precise and relevant clinical questions. That learning has created a more robust foundation for the next wave of innovation.

One area we continue to watch with particular interest is the development of mid-domain and microtubule-binding region (MTBR) tau antibodies. While the results from one recent trial were inconclusive, others such as our BMS TargetTau study are ongoing, and we may yet see a clearer signal of activity. At the same time, there is encouraging progress in the next generation of brain transporter-enabled amyloid-targeting therapies, many of which have improved delivery that may enhance safety and ease of use. Within our own pipeline, we are also exploring novel mechanisms, including endocannabinoid enhancement through dual FAAH/MAGL inhibitors and eIF2B activators, which could offer new ways of addressing both the symptoms and progression of the disease.

Yet despite this momentum, the unmet need remains immense. We still need therapies that can markedly alter the course of Alzheimer's disease, and even as we make strides in disease modification, there is a parallel need to manage the symptoms that continue to take a toll on patients and caregivers alike. That dual challenge, biological and experiential, remains central to our focus.

Still, the field is far better equipped than it was even five years ago. With more refined tools, deeper biological insight, and stronger translational capabilities, we are finally in a position to address the continuum of Alzheimer's disease by conducting clinical trials tailored to meaningfully test the mechanisms and hypotheses we believe in. So yes, the optimism is real, but it is rightly tempered by the scale and complexity of the task ahead.

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