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As the neuroscience field gains unprecedented momentum, Roche is taking a leading role in redefining how neurodegenerative diseases like Alzheimer's are understood, diagnosed, and treated. Dr Azad Bonni, Senior Vice President and Global Head of Neuroscience and Rare Diseases at Roche's Pharma Research and Early Development (pRED), brings a unique perspective shaped by decades in academic neuroscience and clinical neurology. In this interview, Bonni discusses the scientific breakthroughs, diagnostic innovations, and strategic integration across pharma and diagnostics that are driving a new therapeutic frontier.

How have your academic and clinical experiences shaped your leadership of neuroscience and rare disease research at Roche?

In my role as Senior Vice President and Global Head of Neuroscience and Rare Diseases at Roche's Pharma Research and Early Development (pRED) division, I lead the strategy and execution of research and early clinical development programmes spanning from discovery through to completion of Phase II proof-of-concept trials. While my core remit lies within neuroscience and rare diseases, I also contribute more broadly to strategic decision-making across therapeutic areas as a member of the pRED leadership team.

My journey to Roche followed a long and rewarding academic career. I previously served as Head of Neuroscience at Washington University in St. Louis and, before that, spent several years at Harvard Medical School, where I led an independent laboratory and held a tenured professorship. Alongside my scientific training, I am a neurologist by background, having earned my medical degree at Queen's University in Kingston, Ontario, and completed neurology training at McGill University. To this day, I maintain a part-time clinical practice in Canada, which continues to inform my understanding of patients' lived experiences.

This dual perspective as both a clinician and a scientist profoundly shapes the way I approach drug development. I bring to Roche a deep commitment to scientific rigour, tempered by an appreciation of the real-world needs of patients. The decision to transition from academia to industry was not abrupt but rather driven by a sense that the time was right. Advances in human genetics, an increasingly nuanced understanding of neurological disease mechanisms, and the maturation of powerful new technologies have coalesced to create unprecedented opportunities for innovation. I genuinely believe that we stand at the threshold of a new era in neuroscience, and that the 2020s and 2030s will be marked by profound therapeutic breakthroughs that were once out of reach.

What scientific and technological breakthroughs have most significantly transformed the current era of neuroscience research and development?

The transformation of neuroscience R&D over the past decade reflects a decisive break from the historical pattern of infrequent therapeutic advances to one marked by accelerating innovation. Roche's own legacy in this field serves as a useful lens through which to view this evolution: the identification of benzodiazepines in the 1960s; the development of levodopa + benserazide in the 1970s as symptomatic treatment for Parkinson's disease; and the approval of alteplase, a tissue plasminogen activator (tPA) for acute ischaemic stroke, in the 1990s. These advances, while impactful, occurred at long intervals. In contrast, since 2017, the pace has shifted dramatically, with four major therapies brought to market: ocrelizumab for multiple sclerosis, risdiplam for spinal muscular atrophy, satralizumab for neuromyelitis optica spectrum disorder, and delandistrogene moxeparvovec-rokl for Duchenne muscular dystrophy.

This progression is not coincidental but rather the result of three converging forces: major strides in human genetics, deepening biological understanding of disease mechanisms, and the emergence of enabling technologies. The previous model of developing molecules targeting

neurotransmitter receptors and then searching retrospectively for indications has largely been superseded in neurology by a target-driven approach grounded in robust biological evidence. Today, drug discovery in this space is increasingly focused on high-confidence mechanisms, some of which, like CD20 targeted by ocrelizumab and amyloid-beta (Aβ) in Alzheimer's disease, have already achieved clinical validation. Numerous additional targets, while not yet validated in humans, are supported by compelling preclinical data and offer substantial therapeutic promise.

The key to enabling this paradigm shift has been the advancement of biomarkers, particularly in Alzheimer's disease, where decades of clinical trial failures have paradoxically catalysed remarkable progress in diagnostics. Biomarker development is now gathering momentum across other neurological indications as well. In parallel, innovation in clinical endpoints historically limited by noise and variability is underway, with Roche leading efforts in areas such as Parkinson's disease. Further upstream, the adoption of human-derived model systems is enhancing translational accuracy, while computational approaches, still in their early stages within neurology, are beginning to support more predictive and data-driven discovery.

Together, these scientific and technological inflection points are ushering in a new chapter in neuroscience, one defined not by incremental progress, but by the real possibility of therapeutic breakthroughs grounded in biological precision.

In what ways does trontinemab, through its use of the Brainshuttle platform, represent a new therapeutic paradigm for Alzheimer's disease?

Trontinemab is the first therapeutic candidate to apply Roche's Brainshuttle platform in a prevalent neurological condition, offering a novel solution to one of the field's most persistent challenges: delivering large molecules across the blood–brain barrier. The antibody is engineered to bind the transferrin receptor (TfR1), enabling receptor-mediated transcytosis through cerebral capillaries into the brain parenchyma, without interfering with iron transport or becoming trapped in endosomal compartments. Once in the brain, its Fc effector function, masked during circulation, is activated upon binding Aβ plaques, triggering localised microglial clearance with minimal systemic immune activation.

In Phase IIa trials, trontinemab demonstrated rapid and profound amyloid clearance: over 80 percent of participants in the 3.6 mg/kg cohort became amyloid-negative by week 28, as determined by positron emission tomography (PET) and defined by the 24 centiloid threshold. This rate of clearance significantly exceeds that of conventional monoclonal antibodies, which often

require months to reach similar outcomes. Rapid plaque reduction has been correlated with improved clinical benefit, reinforcing trontinemab's best-in-class potential. The candidate has also shown a notably low incidence of amyloid-related imaging abnormalities (ARIA), likely attributable to its lower dosing and its unique entry pathway via capillaries rather than perivascular spaces, where toxicity is more frequently observed. Preclinical data further indicate broader and more uniform brain distribution than existing therapies. Together, these findings support Roche's decision to advance trontinemab into Phase III pivotal phase, positioning it as a potentially transformative asset in the treatment of Alzheimer's disease.

How is Roche leveraging strategic partnerships and collaborative initiatives to accelerate innovation in Alzheimer's research and development?

The recent wave of promising results in Alzheimer's disease, including those observed with trontinemab, has brought renewed energy to the field and, with it, a strong case for greater collaboration across the biopharmaceutical landscape. This resurgence is fuelling not only scientific ambition but also a spirit of shared progress, where partnerships – whether between large pharmaceutical companies and smaller biotechs or through industry-wide consortia – are becoming central to research acceleration.

In particular, pre-competitive collaboration around biomarker development, longitudinal cohort studies, and data integration offers a powerful mechanism to deepen our understanding of disease pathways and therapeutic response. These efforts allow for mutual learning and collective problem-solving in areas where no single actor possesses all the answers. In such a complex and historically under-served field as neurology, especially Alzheimer's, collaboration is no longer optional but essential. It provides both a scientific imperative, advancing knowledge through shared insight, and a strategic advantage, enabling more efficient resource allocation, faster validation, and ultimately, better outcomes for patients.

What impact do you foresee from recent Alzheimer's approvals on diagnosis, access, and the shift towards prevention, and how is Roche positioned to lead this evolution?

The approval of anti-amyloid antibodies in the US have brought renewed momentum to the Alzheimer's field, signalling a shift from therapeutic promise to clinical reality. Yet meaningful patient access remains constrained by the complexity of diagnosis, which continues to rely heavily

on PET and cerebrospinal fluid (CSF) analysis, methods that are often invasive, expensive, or inaccessible at scale. Roche, uniquely positioned with integrated capabilities in both pharmaceuticals and diagnostics, is advancing a new diagnostic paradigm. Its ongoing development of blood-based biomarkers, including phosphorylated tau 181 (pTau181) as a high negative predictive value rule-out test and phosphorylated tau 217 (pTau217) as a confirmatory marker, could significantly streamline diagnosis and enable earlier, broader therapeutic intervention.

Beyond diagnosis, these innovations lay the groundwork for a future defined not only by treatment but also by prevention. Much like lipid screening and statin therapy transformed cardiovascular care, a similar model may emerge for Alzheimer's: identifying individuals with asymptomatic amyloid pathology and intervening well before cognitive decline sets in. It is estimated that by their sixties, approximately 40 percent of individuals already exhibit amyloid accumulation, a figure that escalates with age and contributes to projections of over 150 million dementia cases globally by 2050. In parallel to its work on trontinemab, Roche is developing the gamma-secretase modulator nivegacetor, now in Phase IIa, which modulates the enzyme to reduce amyloidogenic peptides Aβ40 and Aβ42 while promoting the formation of shorter, non-aggregating forms such as Aβ37 and Aβ38. The dual approach, addressing both upstream production and downstream accumulation, exemplifies a holistic strategy to reshape the Alzheimer's landscape. It also reflects Roche's enduring commitment to the field, not only as a scientific leader, but as a company that has remained steadfast through decades of challenges, contributing to a future where early diagnosis, prevention, and effective treatment converge.

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