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Trends in Alzheimer's Disease management: 2024 a year of hope

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Trends in Alzheimer's Disease management: 2024 a year of hope

By Vanja Nagy, PhD

More than 50 million people worldwide suffer from dementia, a number that is estimated to reach 139 million by 2050 (WHO).

Thanks to improved healthcare, sanitation and medical advances, life expectancy has more than doubled in the last 100 years, significantly aging the world's population. Incidence of age-related diseases is increasing together with the increasing number of individuals over the age of 65, creating an enormous societal and financial burden on the medical establishment (**Figure 1**). The leading cause of age-related dementia is Alzheimer's Disease (AD), that represents at least 70% of all dementia cases. Currently, there is no cure for AD, creating an increasing international crisis prompting global leaders to set an ambitious deadline for curing or preventing AD[1].

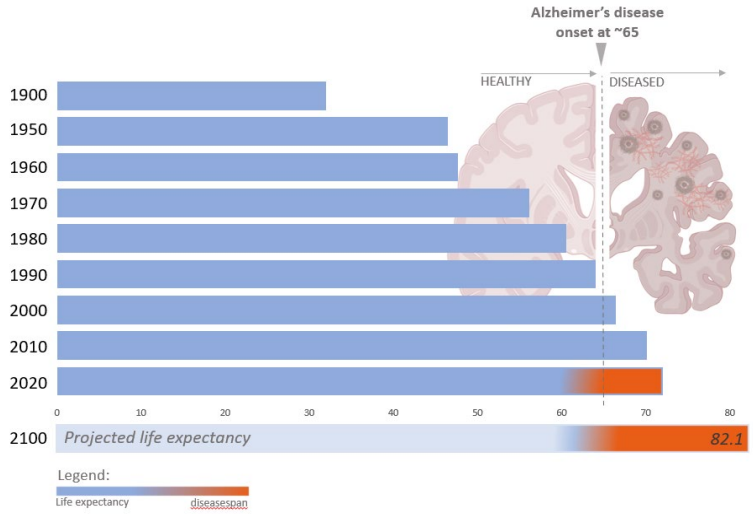

Figure 1. Increased disease risk in the growing aging population. Lifespan (blue bars) has significantly increased since 1900, while healthspan, has not. Chronic, age-related diseases (orange) are currently estimated to last ~10 years, a number only to increase as life expectancy increases. Almost 40% of people over the age of 85 are diagnosed with Alzheimer's disease, with an average onset at 65 years of age. (Created with BioRender.com)

Molecular hallmarks and genetics of Alzheimer's Disease

AD is currently thought to be irreversible, age-associated neurodegenerative disease marked by toxic extracellular amyloid-beta (Aβ) deposits, intracellular neurofibrillary tangles caused by hyperphosyphorylated tau (p-tau), and selective neuronal death. There are two types of AD, early-onset familial AD, caused by autosomal dominant inheritance of mutations in several genes (amyloid precursor protein, presenilin 1 and 2), or late-onset AD which can be caused by a myriad of life-style factors. The primary genetic risk factor for late-onset is alipoprotein E (ApoE) ε4 allele, as well as polymorphisms (variants) in additional lipid trafficking/metabolism related genes including *TREM2, APOJ, PICALM, ABCA1, SREBP-2 and ABCA7*.

Since the first description of the disease in 1906 by a German psychiatrist and neuropathologist, Alois Alzheimer (1864-1915), the prevailing theory on the pathophysiology of the disease called the “Amyloid Hypothesis” emerged. According to the hypothesis, Aβ accumulation triggers local inflammation, oxidation, excitotoxicity and tau hyperphosphorylation. These events are followed by neuronal cell death, causing an imbalance of neurotransmitters and finally behavioral effects and cognitive deficiencies that define the disease. However, the Amyloid hypothesis, largely developed by the study of familial AD, has been challenged by a number of observations: Aβ is important to the healthy brain and deposits were noted in asymptomatic individuals; while Aβ is expressed throughout the brain AD is manifested in discrete regions; the levels of Aβ do not reflect pathogenicity and are not tightly correlated with disease progression, at least not as well as p-tau.

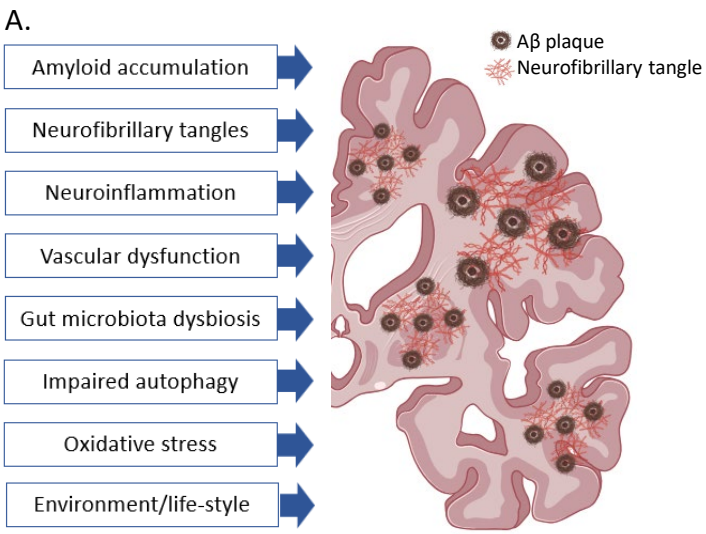

Figure 2A. **Challenging the Amyloid hypothesis** are a myriad of factors described to cause or contribute to the progression and pathology of AD, listed on the left. (Created with BioRender.com)

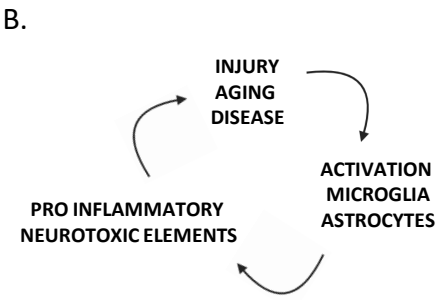

Figure 2B. **Cyclical role of inflammation in AD.** Injury, disease or aging contribute to activation of microglia and astrocytes which, in turn, release proinflammatory and neurotoxic elements exacerbating disease. Created with BioRender.com.

It is now clear that AD is a complex, multifactorial disease that is associated with vascular dysfunction, diabetes, infection, inflammation, mitochondrial dysfunction and oxidative stress, impaired autophagy, innate immune system dysfunction, gut microbiome alterations and a variety of environmental and life-style factors to name a few (**Figure 2**). Of particular importance is neuroinflammation, a critical event found not only in AD but in many other neurodegenerative disorders. While microglia and astrocytes, cells that mediate brain inflammatory processes, are activated to clear the increasing Aβ levels, they also release highly potent and damaging inflammatory molecules, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1 β, IL-16 and reactive oxygen species (ROS) that further exacerbate the disease. Therefore, neuroinflammation targeted-therapies have been gaining attention as an additional approach for slowing progression of AD.

Another area of active research for potential therapeutic targets was ignited by the recognition that a large number of genes involved in lipid metabolism and trafficking serve as risk genes in AD, and that one of the defining characteristics of AD dementia and vascular dementia is lipid dyshomeostasis.

Symptoms and diagnosis

Notable symptoms of AD can appear as long as 20 years after the onset of the molecular pathology described above. Symptoms include memory loss, challenges in planning, difficulty completing familiar tasks, confusion with time or place, trouble understanding visual images and spatial relationships, trouble with speaking or writing, misplacing things, decreased or poor judgement, withdrawal from social activities, and changes in mood or personality (Source: Alzheimer's Association). As AD is a complex and progressive disease, early diagnosis and detection is difficult. There is not one definitive and conclusive laboratory test, however, AD is diagnosed in symptomatic patients by various means that may include neurological evaluations, cognitive and functional assessments, brain imaging (MRI, CT, PET) to determine structural brain changes or Aβ levels, and cerebrospinal fluid or blood tests for multiple markers. Definitive, accurate, sensitive and non-invasive diagnostics and biomarkers are sorely needed to identify patients early enough for available treatments which are most effective before the noticeable behavioral symptoms take effect.

Available FDA approved therapies for AD

Currently there are a few marketed therapies for only treating or slowing symptoms of AD, all of which target mild to moderate stages of the disease prescribed alone or in combination (**Table 1**). Cholinesterase inhibitors (Donepezil, Rivastigmine, Galantamine) that have been in use for several decades are effective in temporarily alleviating memory deficiencies and improving cognitive processes, however, they do not address the underlying cause or slow the rate of progression of the disease, even if used in combination with NMDA receptor antagonist, Memantine, calling for expanded efforts in search and development.

Generic name	Developed/Marketed by	Molecular target
donepezil hydrochloride	Eisai Inc/Pfiser	AChE
AstroStem	Biostar Stem Cell Research Institute	N/A
cerebroprotein hydrolysate	Alniche Life Sciences Pvt Ltd/Ikon Remedies Pvt Ltd/ Invivion Medi Sciences Pvt Ltd	N/A
galantamine hydrobromide		AChE
idebenone	Takeda Pharmaceuticals Company	N/A
lecanemab	Eisai Inc/Biogen Inc	Aβ
levetiracetam	Ikon Remedies Pvt Ltd/Innovative Pharmaceuticals/ Merryl Pharma Pvt Ltd	Synaptic Vesicle Glycoprotein 2A (SV2A); Voltage Dependent N Type Calcium Channel Subunit Alpha 1B (CACNA1B)
memantine	Merz	Glutamate Ionotropic Receptor NMDA Type Subunit (NMDAR or GRIN)
monosodium luminol	Bach Pharma Inc	Nuclear Factor Erythroid 2 Related Factor 2 (NRF2)
piracetam	UCB Pharma	AMPA receptor
procaine hydrochloride	Shandong Hualu Pharmaceutical Co Ltd	Cortisol; Voltage Gated Sodium Channel (SCN)
quetiapine fumarate	Daksh Pharmaceuticals Pvt Ltd	5-Hydroxytryptamine Receptor 2A (5 HT2A); D2 Dopamine Receptor (DRD2)
risperidone	Janssen	5-Hydroxytryptamine Receptor 2A (5 HT2A); D2 Dopamine Receptor (DRD2)
sodium oligomannate	Shanghai Green Valley Pharmaceutical Co Ltd	Aβ
vinpocetine	Innovative Pharmaceuticals	N/A
rivastigmine	Novartis	AChE/BChE

Table 1. **Currently available therapies for Alzheimer's disease**. Companies that originally developed or marketed the assets are listed in second column, and molecular target in the third, if known. N/A not applicable defines unknown or undisclosed targets. (Source: GlobalData)

New treatment: antibodies directed against Aβ

Anti Aβ antibodies are the first novel FDA approved therapies for Alzheimer's in 20 years, and the first ever disease modifying therapies on the market.

In the past few years, much excitement has been focused on the development of antibodies targeted against Aβ: aducanumab, under the brand name Aduhelm (Biogen Inc, FDA approved in 2021), lecanemab, under the brand name Lequembi (Biogen Inc/Eisai Co Ltd, FDA approved in 2023), and donanemab (Eli Lilly and co., FDA approval expected in 2024) (**Table 2**). Anti-amyloid antibodies together with a new acetylcholinesterase inhibitor, benzgalantamine, under the brand name Memogain (AlphaCognition Inc), are in pre-registration phase. Fueled by the Aβ hypothesis, it was posited that identifying an antibody that would clear Aβ accumulation from the brain would also alleviate, if not reverse, the main symptoms of AD. Aducanumab was the first disease modifying therapy targeting Aβ to be FDA approved in 2021, a controversial decision that was met by skepticism due to controversial clinical trial results and doubts regarding risk-to-benefit ratios[2]. Lacanemab received full FDA approval in July of 2023, and is indicated for patients with early AD. In phase III clinical trials (Clarity AD), it was shown to effectively remove Aβ, reduce p-tau and to slow the decline of cognitive parameters by 27%, and prevent the decline in quality of life by 56%[3]. Clinical trials of donanemab on the other hand, report that 40% of patients experienced almost 90% of Aβ clearance within the first 6 months of therapy and, more importantly, ~47% of participants had no clinical progression for 1 year[4]. This treatment, like the others, is more effective in patients in earlier stages of the disease. FDA approval is expected this year. While these results are a cause for optimism, whether they are enough to justify the cost, and more importantly, the potential safety issues, including infusion reactions, amyloid-related imaging abnormalities (ARIA), brain edemas and potentially death, remains to be seen. Nevertheless, these treatments are the first to be approved in 20 years, and the first disease modifying therapies to be developed for AD. What is clear, as significant reduction of Aβ from the brain still did not impressively reverse or cure the disease, much more work needs to be done for second generation Aβ antibodies with less side effects, or more importantly, development of additional disease modifying therapies that target different aspects of AD pathology. In line with this sentiment, at the end of January 2024, Biogen announced that it will discontinue the development and commercialization of the controversial Aduhelm, terminate the associated clinical trial and discontinue the license for aducanumab to be able to focus on other AD drug candidates in its pipeline.

Name	Company	Target	FDA approval
Aducanumab	Biogen Inc.	Aggregated Aβ	2021 Discontinued
Lecanemab	Biogen Inc/Eisai Co Ltd	Aβ protofibrils	2023
Donanemab	Eli Lilly and co.	Aβ plaques	Expected 2024

Table 2. **Summary of marketed anti- Aβ antibodies.** Each target Aβ at different stages of aggregation, all are most effective when given at the early phase of the disease.

Current novel therapies in development

As the anti-Aβ antiboby treatments confirm, clearing Aβ from the brain is not sufficient for complete obliteration of the complex disease and calls for novel targets and combination therapies. Indeed, this thriving research space has ushered novel innovations into development. There are currently 26 drugs in Phase III, most of which are small molecules, 5 antibodies targeting Aβ, tau or APP (3 of which are in preregistration phase mentioned above), a recombinant peptide from Novo Nordisk AS, and a stem cell therapy from CellTex Therapeutics Corp (Source: GlobalData). Most small molecules in development target the usual suspects, including acetyl- and butyryl-cholinesterases, Aβ and tau aggregates, serotonin receptors, alpha-2 adrenergic receptors, and sigma-1 receptors. Standing out from the rest is buntanetap tartrate (Annovis Bio Inc), orally available small molecule that targets mRNA of amyloid precursor protein, tau and α-synuclein and reduces their toxic protein levels likely restoring proteostasis in both AD and Parkinson's Disease[5].

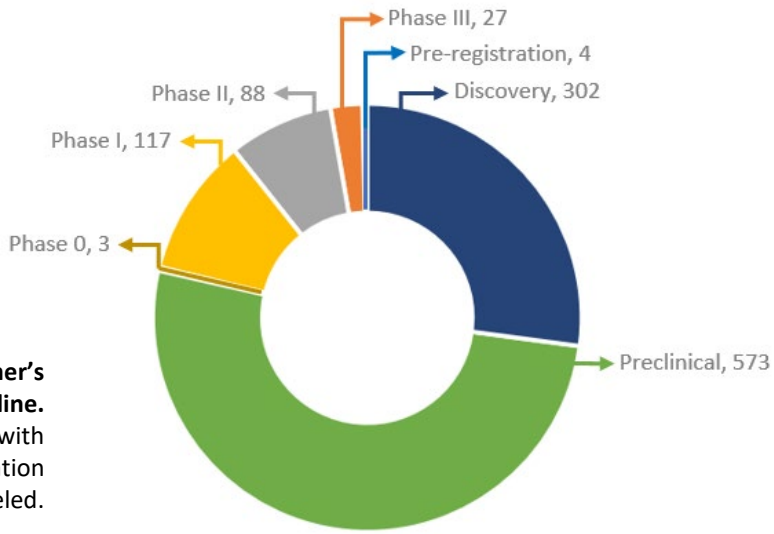

Figure 3. Current status of Alzheimer's disease drug development pipeline. Number of drugs in development with Alzheimer's disease as lead indication by development stage, as labeled. (Source: GlobalData)

Of particular interest are compounds that aim to alleviate neuroinflammatory cascades that accompany AD and most other neurodegenerative disorders. NE-3107 (BioVie Inc), adrenal sterol metabolite for example, targets ERK1/2, which inhibits major inflammatory mediators and modulates insulin responses. Likewise, semaglutide or NN-6535, Ozempic from Novo Nordisk AS, is a recombinant peptide selectively binding to glucagon-like peptide-1 receptor, increasing glucose-dependent insulin secretion marketed for type II diabetes mellitus and obesity. As insulin resistance is a well-documented molecular link to dementia and cognitive impairment, it is not surprising that semaglutide is also being developed for AD. It was shown to reduce neuroinflammation, oxidative stress and decrease Aβ and p-tau aggregation positioning it as another promising alternative to Aβ antibody treatments.

Together with 81 assets in phase II, 117 in phase I, and hundreds in preclinical and discovery phases, it is clear that this R&D area is a competitive and expanding space (**Figure 3**).

Public funding for CNS disease research

Investments into basic AD research from governmental institutions or private donations has been steadily on the rise to support academic research efforts in identifying basic disease mechanisms, novel engageable targets, accurate diagnostic methods and sensitive biomarkers. Indeed, "neuroscience" and "brain disorders" are projected to be in the top 10 funded fields in 2024 by the National Institutes of Health (NIH), biggest funding agency in the USA (Source: https/report.nih.gov). Topics pertaining to aging, neurodegeneration and Alzheimer's Disease have seen a steady increase in NIH funding over the past decade, estimated to equal ~$6.3Bn, $5.0Bn and $3.5Bn in 2024, respectively (**Figure 4**). In contrast, in Europe, according to *Alzheimer Europe* European governments' funding of basic research related to dementia dropped to €65M in 2020 from the peak in 2016 of € 190M.

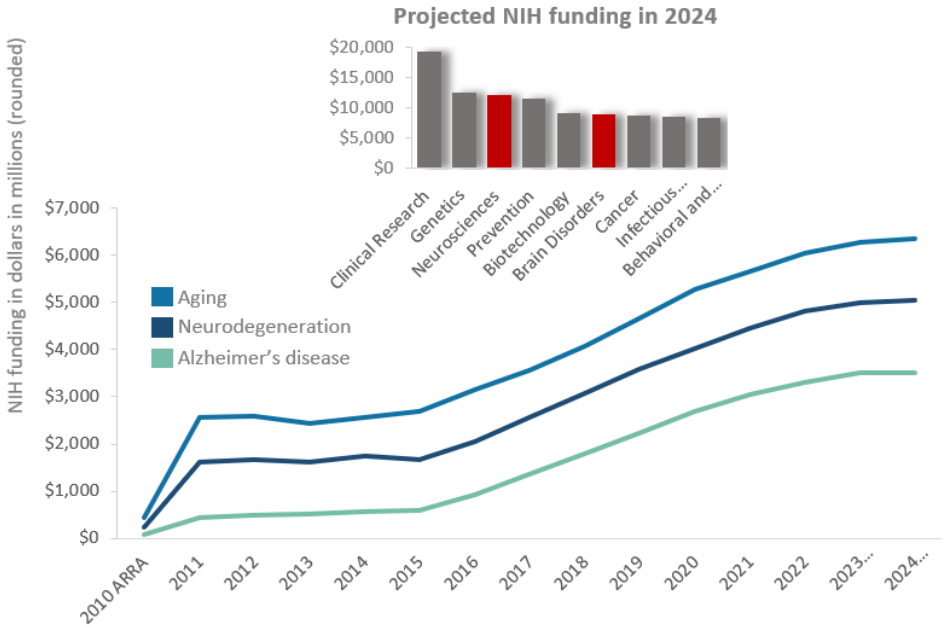

Figure 4. NIH funding for aging, neurodegeneration and Alzheimer's disease research has been increasing in the last decade. Following a boost in funding by the American Recovery and Reinvestment Act (ARRA) in 2010, NIH funding has slowly been increasing for these three topics. Projected for funding in 2024 topics focused on brain research and disorders will stay in the top 10 funded (red bars, inset). (Source: report.nih.gov/funding/)

Private/venture investment in CNS disease therapy development

According to *Future Market Insights* the neurodegenerative disease market value is expected to increase by $50Bn in the next 10 years. It is therefore, not a surprise that private venture and investment industry has taken note. While there was a significant drop in investments, central nervous system indications has led the pack and is showing recovery in 2023, a significant achievement in an economically difficult period (**Figure 5**). The interest from VCs in this space is particularly important in the European CNS research ecosystem that cannot rely on governmental funding as much as their American colleagues.

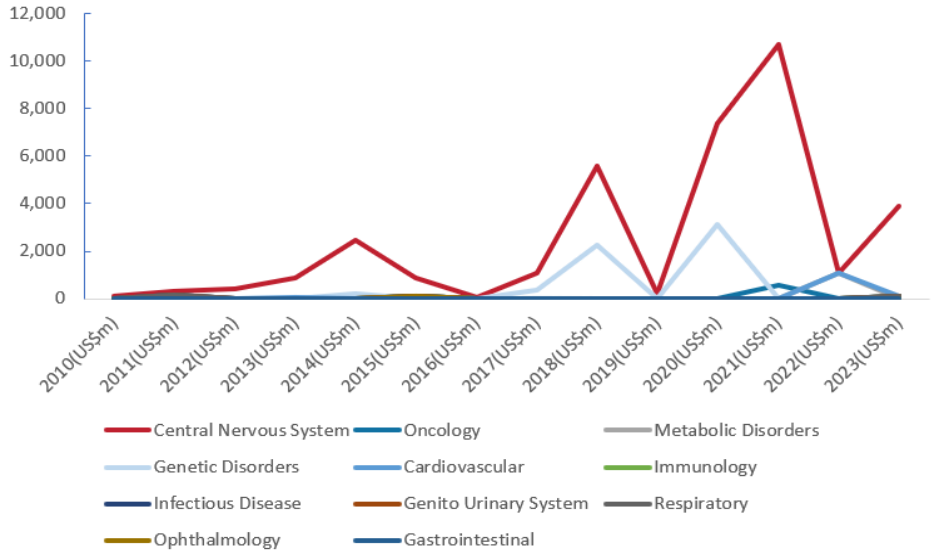

Figure 5. CNS is a leading Venture Capital investment field. While private funding is fickle and has significantly dropped from its peaks in 2021 to 2022 for the CNS space (red line), there is a strong recovery in 2023. **(**Source: GlobalData)

While major M&A pharmaceutical deals continued to favor the oncology space in 2023, CNS with 21% of market share was in second place with 3 large deals: Bristol Squibb Meyers (BMS)-Karuna ($14Bn), AbbVie-Cerevel ($8.7Bn) and Biogen-Reata ($7.3Bn) (Source GlobalData). BMS sought to strengthen its CNS pipeline with the Karuna deal, as the latter is expecting an FDA decision on its novel Schizophrenia treatment, KarXT (trospium chloride and xanomeline), in September 2024. KarXT is a small molecule agonist of the muscarinic acetylcholine receptor M1-4, with Schizophrenia as a lead indication, that also shows promise for treatment of several other CNS indications including AD. AbbVie is continuing to expand its already strong portfolio of CNS assets by acquiring Cerevel. Similarly to KarXT from Karuna, Cerevel is developing a modulator of the muscarinic acetylcholine receptor M4, emraclidine, currently in phase II for Schizophrenia, that likewise will be explored for its therapeutic potential in AD. Biogen, on the other hand, strengthened its rare disease portfolio by the acquisition of Reata and its lead FDA approved asset, SKYCLARYS® (omaveloxolone), for treatment of Friedreich ataxia.

Concluding remarks

In an atmosphere of high global inflation and risk aversion from financiers, we are nevertheless seeing a slow return of investment from a downward spiral after the 2021 peaks that should benefit breakthrough research in the CNS disease space. With the looming loss of revenue amounting to $118Bn (in the first year of expiry alone) from the expected historic patent cliffs in the pharma sector (Source: Evaluate Pharma), there will be a rush to close the pipeline gaps in major pharma giants that should fuel diverse investment in early-stage innovative technologies, set to serve a great number of patients suffering from chronic and debilitating diseases. During this stingy period, reliance on non-traditional investments in the early phases of biotechnology development to de-risk assets to pique pharma interest will be paramount, especially in Europe.

On the heels of anti-Aβ antibody approvals and clinical trials with mixed reviews, it is clear that investors will be looking for the innovative and bold new approaches for the treatment of not only Alzheimer's Disease but also other neurodegenerative diseases. Rational combinatorial therapies hitting more than 1 target to combat complex diseases will be of particular interest. The need for these therapies is only growing, and with revived research and investment activity in this space, we could be seeing a new blockbuster around the corner.

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Biosketch:

Vanja is a neuroscientist with 25 years of experience in academic research. She joined CEBINA in 2023 as the Neuroscience Program Director overseeing the acceleration program DanubeNeuro focused on innovative solutions in the field of aging and neurodegeneration.

Vanja obtained her PhD in Basic Biomedical Sciences at the Icahn School of Medicine at Mount Sinai (MSSM), USA, where she elucidated novel molecular pathways supporting synaptic function underlining learning and memory. Following two postdocs at MedILS, Croatia and IMBA, Austria, in 2016 she established her independent research group and co-founded the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, in Vienna, Austria, that focused on uncovering genetic causation and potential therapeutic interventions of neurological disorders. During this time, she was also Adjunct Principal Investigator at CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, and a Lecturer at the Medical University of Vienna.

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