# Yeast-Based Therapeutic Platforms for Alzheimer's Disease

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**Abstract.** *Alzheimer's* disease (AD) is a progressive neurodegenerative disorder that represents a growing global health crisis. Existing treatments provide only limited symptomatic relief and fail to stop or reverse disease progression. Therapeutic peptides and proteins such as Anticalin and neprilysin (NEP) show great potential to target the underlying mechanisms of AD by binding, degrading, or preventing the aggregation of amyloid beta (Aβ) and Tau proteins. Yet, large-scale production of biologics in mammalian cell systems is costly and restricts global accessibility. Yeast-based cell factories, especially Pichia pastoris, provide a promising alternative, combining scalability, cost-effectiveness, and safety. Through synthetic biology, fermentation optimization, and protein stabilization, yeast platforms can produce therapeutic peptides at high yield and low cost. This paper discusses the pathology of AD, the therapeutic potential of peptides, strategies for expression in yeast, and the opportunities and challenges in applying microbial systems to neurodegenerative disease treatment. Future perspectives, including CRISPR-based yeast engineering, AI-assisted protein design, and novel delivery methods, are also discussed. Yeast cell factories thus offer a pathway toward affordable peptide-based treatments for AD, bridging the gap between laboratory research and clinical application.

**Keywords:** Alzheimer's Disease; Therapeutic peptides; CRISPR; yeast engineering; AI-assisted protein design.

## 1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia worldwide, affecting over 50 million people. The disease is characterized by progressive memory loss, cognitive decline, and loss of daily functioning, imposing a huge burden on families and healthcare systems. Despite decades of research, current therapies—including acetylcholinesterase inhibitors and NMDA receptor antagonists—only alleviate symptoms temporarily [1]. Disease-modifying treatments remain elusive, highlighting the urgent need for novel approaches.

At the molecular level, AD pathology is defined by three main features: amyloid beta (Aβ) plaque accumulation, Tau protein tangles, and chronic neuroinflammation (shown in Fig. 1). These pathological factors disrupt synaptic communication, trigger neuronal death, and accelerate cognitive impairment. Therapeutic peptides and proteins offer promising strategies to directly target these mechanisms. Anticalin proteins bind to Aβ monomers or dimers, preventing their aggregation into plaques. Enzymes like neprilysin (NEP) can degrade Aβ peptides, while Tau-directed antibodies inhibit aggregation and spreading. These biologics hold potential to address AD at its roots, but their translation into widespread clinical use is hindered by the high cost and complexity of production. However, mammalian cell systems, the current standard for biologic production, are expensive and limited in scalability [2]. This creates a barrier to accessibility, especially in developing countries where healthcare budgets are constrained. As AD is a global disease, treatment must also be accessible to globalization. Yeast-based microbial cell factories, such as Pichia pastoris, present a cost-effective and scalable alternative. This paper examines yeast engineering as a platform for producing therapeutic peptides for Alzheimer's disease and highlights both the potential advantages and remaining challenges of this approach.

## 2. Peptide-Based Therapeutic Strategies for Alzheimer's Disease

The development of peptide-based therapies for AD is motivated by their ability to directly interfere with pathological proteins. Anticalins represent a new class of binding proteins that can specifically target Aβ monomers or small oligomers. By preventing aggregation at an early stage, anticalins reduce plaque formation and the associated toxicity, shown in Fig. 2 [2]. Similarly, NEP acts as a degrading enzyme, breaking down Aβ into harmless fragments. One of its unique strengths is its ability to cross the blood–brain barrier when engineered properly, enhancing therapeutic effect.

Another important direction is Tau-targeting peptides and antibodies. Tau proteins, when abnormally phosphorylated, form neurofibrillary tangles that spread from one neuron to another. Tau immunotherapy can block this process, limiting disease progression. [2-4] While promising in theory, the success of these peptides in clinical settings requires reliable, low-cost production systems that can supply enough pure and functional proteins. This is where microbial cell factories become crucial.

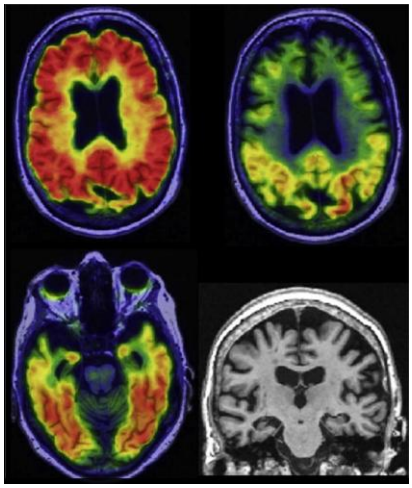


**Figure 1:** Alzheimer's disease with dementia [2]

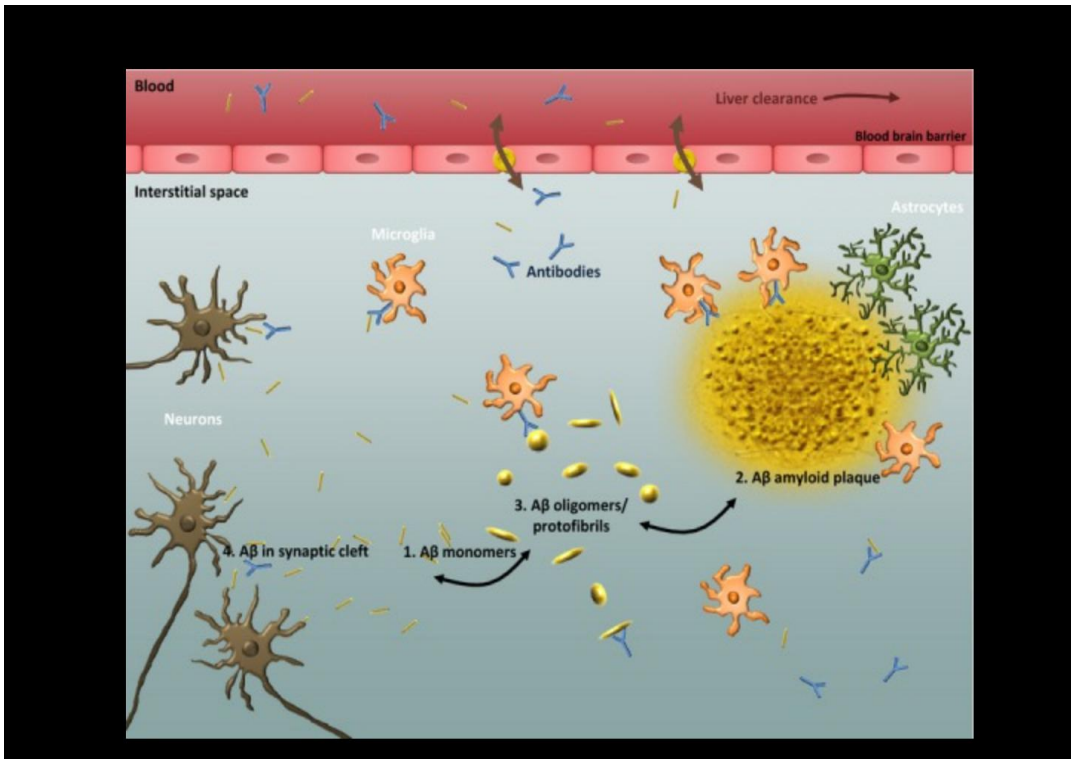



**Figure 2:** Possible targets for immunotherapy [3]

## 3. Microbial Cell Factories and Yeast Expression

Microbial cell factories are genetically engineered systems designed to produce target proteins efficiently. Two common hosts are *Escherichia coli* and *Pichia pastoris* [4,5,6]. *E. coli* is widely used due to its rapid growth and ease of genetic manipulation [7,8]. However, it cannot perform eukaryotic post-translational modifications, such as glycosylation, which are often essential for therapeutic proteins [9]. Misfolding and formation of inclusion bodies are frequent problems, and the presence of endotoxins adds safety concerns [10]. By contrast, Pichia pastoris offers a more suitable platform [11]. It combines the advantages of yeast (safety, absence of endotoxins, scalability) with certain features of higher eukaryotes, including protein folding and glycosylation [12]. It can reach very high cell densities in bioreactors, making it ideal for large-scale production. Proteins can be secreted into the culture medium, simplifying purification [13-15]. These properties make Pichia an attractive candidate for producing therapeutic peptides for AD [16].

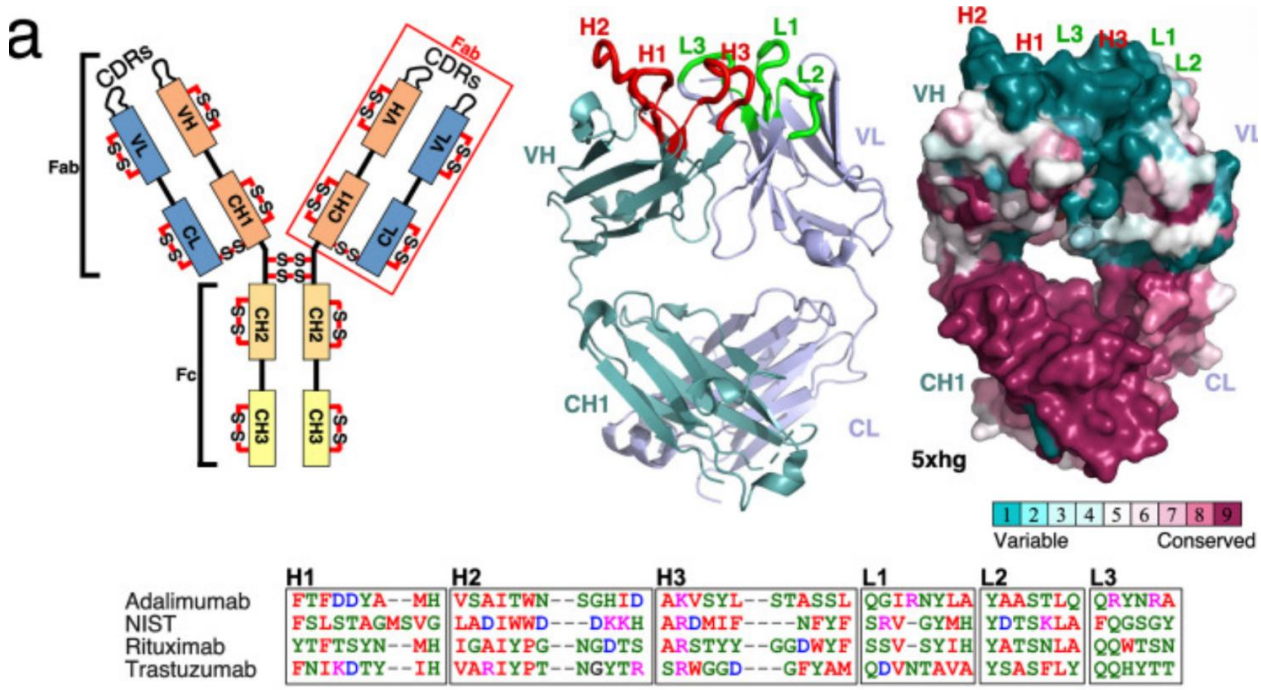



**Figure 3:** Design of the single chain Fab constructs [14]

Producing therapeutic peptides in yeast requires careful design and optimization shown in Fig. 3. At the genetic level, codon optimization ensures compatibility between human genes and yeast translation machinery. Fusion tags such as His-tags or TEV cleavage sites are commonly introduced to facilitate purification and processing [14,15,17]. At the fermentation level, fed-batch cultivation and high-cell-density fermentation maximize protein yield [17]. Co-expression of chaperones can assist in proper folding, reducing the risk of misfolded or inactive proteins. Post-production stabilization methods, such as PEGylation, can improve peptide stability and circulation time in the body [18]. Successful case studies already exist, with antibodies, enzymes, and small therapeutic peptides expressed at high levels in Pichia [12,16,17]. These examples, shown in Fig. 4, demonstrate the feasibility of yeast-based systems for scalable and cost-effective production.

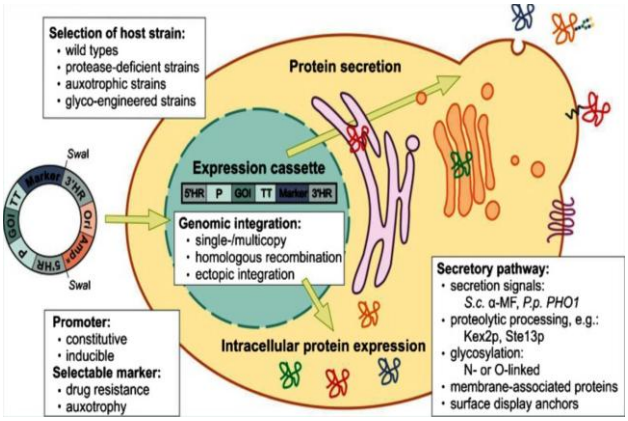



**Figure 4.** General considerations for heterologous gene expression in P.pastoris.Expression.[12]

## 4. Discussion

The global burden of AD is rapidly increasing, creating an urgent demand for effective and affordable therapies [18]. Yeast cell factories offer the opportunity to reduce production costs, making advanced biologics accessible to more patients, including those in developing countries. In addition, yeast systems are highly adaptable, allowing for the production of diverse therapeutic formats ranging from enzymes to antibodies [12,16]. Nevertheless, challenges remain. Yeast glycosylation patterns differ from humans, which can affect protein function and immunogenicity [19]. Secretion yields may be low, requiring further optimization. Misfolding and degradation also pose risks [13]. Finally, regulatory approval for yeast-produced biologics requires rigorous demonstration of safety, purity, and efficacy. Overcoming these barriers will be essential for clinical translation [18].

The future of yeast-based peptide production will be shaped by advances in synthetic biology and computational tools shown in Figure 5 below[16]. CRISPR-Cas systems allow precise editing of yeast genomes, enabling pathway optimization and targeted expression [16,17]. AI-assisted design can accelerate codon optimization, promoter selection, and protein engineering, making the process faster and more predictable. Novel drug delivery methods are another promising direction . Oral or inhaling formulations of peptides could improve patient compliance and accessibility. Bridging microbial production with clinical applications will also require interdisciplinary collaboration, combining synthetic biology, protein engineering, and clinical science [18].

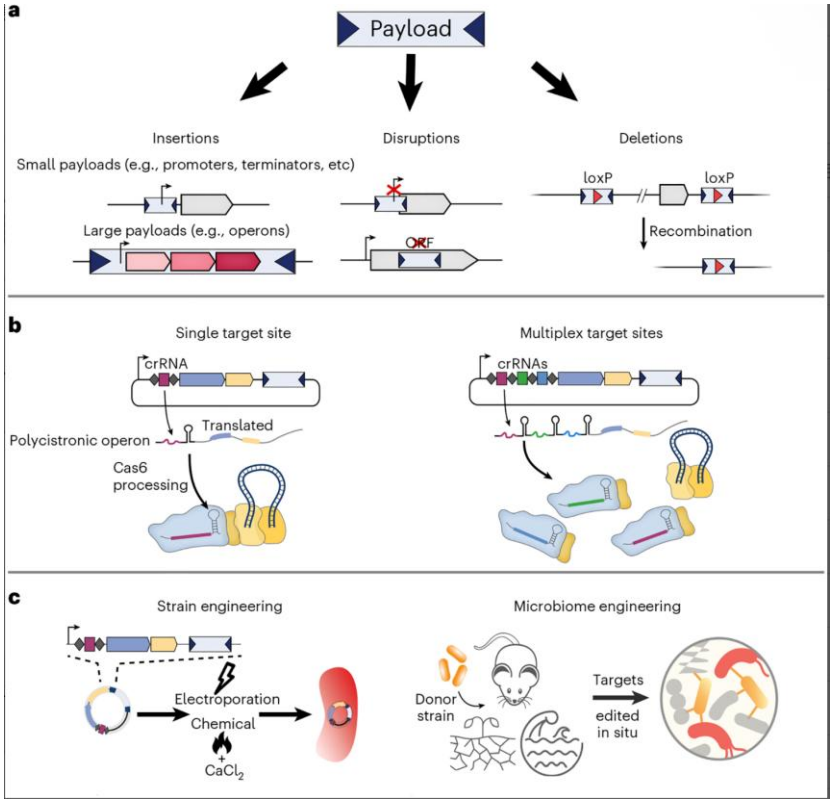



**Figure 5.** Future perspectives: integration of CRISPR technologies [16].

## 5. Conclusion

Engineering yeast-based cell factories represent a powerful strategy for producing therapeutic peptides against Alzheimer's disease. By combining genetic optimization, fermentation engineering, and stabilization methods, yeast platforms such as Pichia pastoris can produce biologics at high yield and low cost. This approach addresses one of the greatest obstacles in AD therapy: accessibility. With the integration of CRISPR, AI-assisted design, and novel drug delivery systems, yeast-based production could become a cornerstone of next-generation AD treatments. Ultimately, interdisciplinary efforts that unite synthetic biology, protein engineering, and clinical research will be required to translate these advances into effective, affordable, and globally accessible therapies.

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