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NEUROREGENERATION BEYOND NEUROPROTECTION: A NEW FRONTIER IN ALZHEIMER'S DISEASE RESEARCH:THE ZEBRAFISH PARADIGM

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Abstract

Alzheimer's disease (AD) represents the most prevalent neurodegenerative disorder worldwide, characterized by progressive neuronal loss, synaptic failure, and the pathological accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles. For decades, the therapeutic landscape has been dominated by **neuroprotection**—strategies aimed at shielding existing neurons from further damage. However, the sobering reality of clinical trials reveals a critical limitation: neuroprotection alone cannot reverse the neuronal devastation already wrought by the disease. As of 2026, over 200 drug candidates have failed in Phase III trials, with most approaches focusing on amyloid clearance or anti-

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inflammatory modulation without addressing the fundamental deficit of **neuronal replacement**.

Keywords: Alzheimer's disease, neuroregeneration, neuroprotection, zebrafish (Danio rerio), adult neurogenesis, neural stem cells, amyloid-β42, glial plasticity, interleukin-4, translational neuroscience, disease-modifying therapy

Introduction

The emerging paradigm of **neuroregeneration** offers a transformative alternative. Rather than merely preserving what remains, neuroregeneration seeks to replenish lost neuronal populations, rebuild synaptic circuitry, and restore cognitive function through the activation of endogenous neural stem cells (NSCs) or the transplantation of exogenous neuronal progenitors. This shift from "protection" to "replacement" represents not merely a semantic evolution but a fundamental reconceptualization of therapeutic goals in neurodegenerative medicine.

At the forefront of this revolution stands an unlikely hero: the zebrafish (Danio rerio). This small tropical freshwater fish possesses an extraordinary capacity for central nervous system (CNS) regeneration that mammals, including humans, have largely lost during evolution. Adult zebrafish maintain robust neurogenic niches throughout their brains and can regenerate neurons after injury or disease-like insults—a capability that has made them an indispensable model for decoding the molecular machinery of successful neural repair .

This article explores how zebrafish research is illuminating the path from neuroprotection to neuroregeneration in Alzheimer's disease, examining the mechanistic insights gained from this remarkable vertebrate model and their translational potential for human therapeutic development.

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The Limitations of Neuroprotection: Why Preservation Is Not Enough

The Neuroprotective Paradigm

Traditional neuroprotective strategies in AD have targeted multiple pathological cascades: amyloid-β aggregation, tau hyperphosphorylation, neuroinflammation, oxidative stress, and mitochondrial dysfunction. While these approaches have yielded valuable mechanistic understanding, their clinical translation has been disappointing. The recent approval of lecanemab and donanemab represents a milestone in amyloid-targeting immunotherapy, yet these agents offer modest cognitive benefits primarily in early-stage patients and do not address the irreversible neuronal loss that defines advanced disease .

Neuroprotection operates on a defensive premise: identifying vulnerable neurons and fortifying them against insult. However, AD pathology begins years—perhaps decades—before clinical symptoms emerge. By the time diagnosis occurs, substantial neuronal death has already occurred in the entorhinal cortex, hippocampus, and associative neocortex. Protecting surviving neurons, while valuable, cannot reconstruct the neural networks essential for memory, learning, and executive function.

The Regenerative Imperative

Neuroregeneration introduces an offensive strategy: **replacing lost neurons**, **rebuilding synaptic connections**, and **restoring functional circuits**. This approach acknowledges that neuronal death in AD is not merely a symptom but the central pathological outcome that must be reversed. The human brain does retain limited regenerative capacity—adult neurogenesis persists in the hippocampal dentate gyrus and olfactory bulb—but this endogenous repair mechanism is profoundly impaired in AD patients .

The challenge lies not in the concept of regeneration but in the execution. Mammalian brains exhibit glial scarring, inhibitory extracellular matrix molecules, and an inflammatory milieu that actively suppresses neurogenesis

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after injury. Understanding how some vertebrates overcome these barriers is essential for designing effective regenerative therapies.

The Zebrafish Advantage: A Vertebrate Model of Successful CNS Regeneration

Why Zebrafish?

Zebrafish offer a unique combination of experimental tractability and biological relevance. As vertebrates, they share approximately 70% genetic homology with humans, including conservation of key genes involved in neurodegeneration such as APP (amyloid precursor protein), PSEN1/2 (presenilins), and MAPT (tau). Their brains exhibit complex architecture with recognizable homologs of mammalian structures including the telencephalon, diencephalon, cerebellum, and optic tectum .

Zebrafish as an emerging model system for Alzheimer's disease research, showing embryonic, larval, and adult stages with key experimental advantages including optical clarity, genetic malleability, and vertebrate neural structure

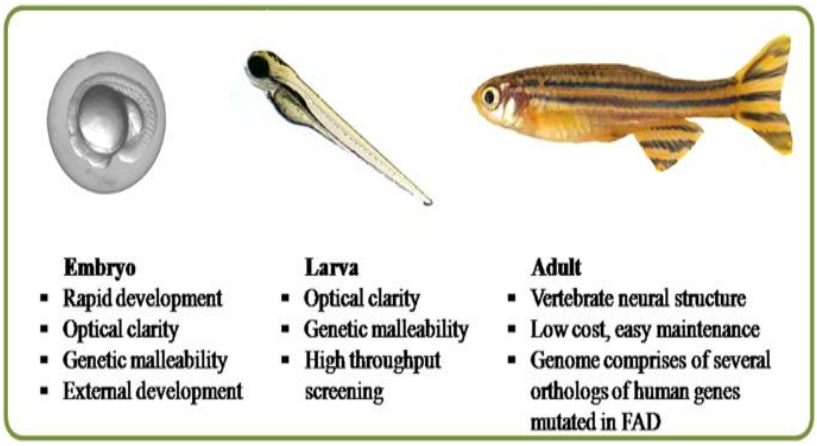

Figure 1. Zebrafish as a model system for Alzheimer's disease research. The species offers optical clarity in early developmental stages, high genetic malleability, and conservation of vertebrate neural structures including homologs of human brain regions affected in AD. (Adapted from Nature Communications)

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Critically, unlike mammals, zebrafish maintain extensive neurogenic zones throughout adulthood. Radial glia cells—functionally equivalent to mammalian neural stem cells—persist in ventricular niches across the telencephalon, diencephalon, and cerebellum, continuously generating new neurons that integrate into existing circuits .

Regenerative Neurogenesis in the Adult Zebrafish Brain

When injury or disease-like insult occurs, zebrafish mount a robust regenerative response. Following mechanical lesion or toxic insult, quiescent radial glia re-enter the cell cycle, proliferate, and differentiate into region-appropriate neuronal subtypes. These newborn neurons migrate to injury sites, extend axons and dendrites, and functionally integrate into pre-existing neural networks, restoring both structural integrity and behavioral function .

This regenerative capacity extends to the retina, spinal cord, and brain. In the retina, Müller glia dedifferentiate into progenitor-like cells upon injury, generating all retinal neuron types. In the spinal cord, ependymo-radial glia form a “glial bridge” rich in laminin and fibronectin that guides axon regrowth. The brain itself can recover from substantial neuronal loss while maintaining circuit integrity—a feat impossible in mammalian models .

Modeling Alzheimer’s Disease in Zebrafish: The Aβ42 Paradigm

Creating an AD-Like Phenotype

To study Alzheimer’s pathophysiology, researchers developed a microinjection-based model in which synthetic amyloid-β42 (Aβ42) peptide is directly introduced into the adult zebrafish brain. Aβ42 is the most toxic form of amyloid, forming oligomers and fibrils that aggregate into plaques—the pathological hallmark of AD .

This model recapitulates key features of human AD pathology:

- **Neuronal death** in affected regions

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- **Neuroinflammation** with microglial/macrophage activation
- **Synaptic degeneration** and impaired neurotransmission
- **Memory and learning deficits** measurable through behavioral assays
- **Aβ42 aggregation** forming toxic deposits

Neurotoxic agents and Alzheimer's disease pathology in zebrafish models, showing how various insults including amyloid beta, metals, and neurotoxins induce AD-like degenerative changes

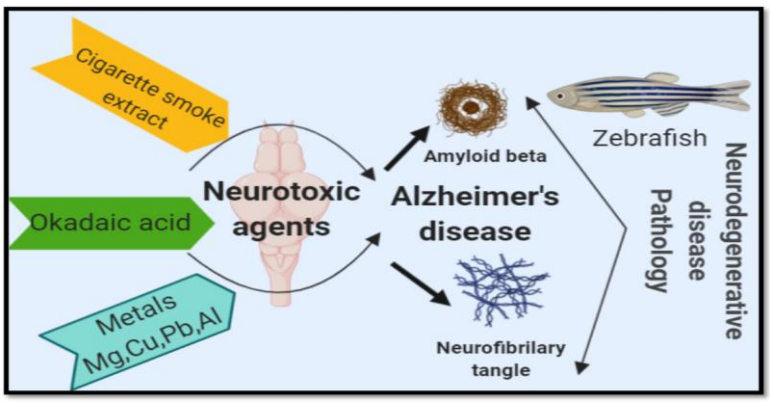

Figure 2. Zebrafish as a tool for modeling neurotoxin-induced neurodegeneration. Various insults including amyloid-β, metals, and cigarette smoke extract induce AD-like pathology, enabling mechanistic study of disease processes and therapeutic screening. (Adapted from Springer Neurotoxicity Research)

The Surprising Response: Regeneration Rather Than Degeneration

Herein lies the zebrafish's most valuable lesson. Rather than succumbing to Aβ42 toxicity, adult zebrafish mount a **compensatory regenerative response**. Neural stem/progenitor cells (NSPCs) in the ventricular zones dramatically increase their proliferation rate. These proliferating cells differentiate into mature neurons that migrate toward injury sites and integrate into damaged circuits.

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This regenerative neurogenesis is not merely a passive reaction but an active, coordinated repair program. Single-cell transcriptomics and spatial proteomics analyses have revealed that Aβ42 insult triggers a precise molecular cascade that transforms the brain's response from potential degeneration to successful regeneration. The zebrafish brain effectively treats Aβ42 toxicity as a **regenerative stimulus** rather than an irreversible death sentence .

Molecular Mechanisms: Decoding the Regenerative Program

The IL4-STAT6 Axis: Immune-Neural Crosstalk

One of the most striking discoveries from zebrafish AD models involves **Interleukin-4 (IL4)**, an anti-inflammatory cytokine traditionally associated with immune modulation. In mammals, chronic neuroinflammation in AD suppresses IL4 signaling, creating a pro-inflammatory environment that impairs neurogenesis. Zebrafish, however, exhibit a fundamentally different immune-neural interaction .

Upon Aβ42 exposure, zebrafish brains upregulate IL4 expression. This cytokine directly binds to IL4 receptors expressed uniquely on neural stem cells—the only non-immune cell type in the brain bearing this receptor. IL4 signaling through the STAT6 transcription factor activates a pro-neurogenic program, stimulating NSPC proliferation and subsequent neuronal differentiation.

Comparison of neural stem cell responses to amyloid-β in mouse versus zebrafish models, showing divergent outcomes due to differential IL4 signaling and inflammatory environments

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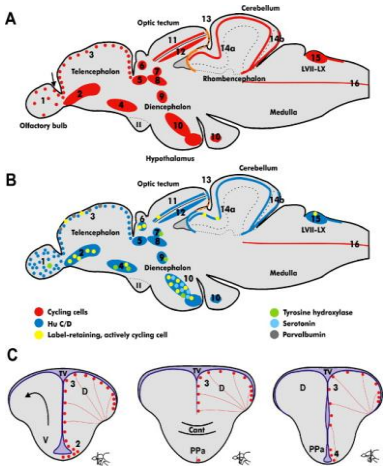

Figure 3. Divergent neural stem cell plasticity in mouse and zebrafish Alzheimer's models. While amyloid-β induces chronic inflammation that suppresses neurogenesis in mammals, zebrafish mount an IL4-mediated anti-inflammatory response that promotes regenerative neurogenesis and neuronal replacement. (Adapted from Developmental Biology)

This IL4-STAT6 axis represents a master regulatory switch that determines whether the brain degenerates or regenerates. In mouse AD models, restoring IL4 signaling rescues neurogenesis and improves cognitive outcomes—demonstrating the translational potential of this zebrafish-derived mechanism .

The Serotonin-BDNF-NGFR Pathway

Beyond IL4, zebrafish research has uncovered a neurotransmitter-mediated regenerative axis. Following Aβ42 insult, serotonergic signaling increases, triggering brain-derived neurotrophic factor (BDNF) release. BDNF activates the nerve growth factor receptor (NGFR, also known as p75NTR) on astroglial cells, inducing their transformation from a reactive, scar-forming state into a pro-neurogenic phenotype capable of generating new neurons .

This **neuron-glia interaction** is particularly significant because mammalian astrocytes typically form glial scars that inhibit regeneration. In zebrafish, NGFR

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signaling imposes a neuro-regenerative fate on astroglia, enabling them to contribute to neuronal replacement rather than impeding it. Recent work has successfully translated this mechanism to mouse AD models, where NGFR activation in astrocytes reduced amyloid plaques, decreased tau phosphorylation, and promoted the generation of new neurons from glial precursors .

Context-Specific Signaling Networks

Single-cell transcriptomic analyses of zebrafish brains following Aβ42 exposure have revealed injury-induced progenitor states regulated by a complex network of transcription factors including ascl1a, lin28, sox2, and stat3. These regulators orchestrate the transition from quiescence to proliferation, followed by neuronal differentiation and circuit integration .

Notably, zebrafish regeneration involves transient suppression of Notch signaling—normally required for stem cell maintenance—coupled with context-specific activation of Wnt/β-catenin and fibroblast growth factor (FGF) pathways. This dynamic signaling environment enables rapid expansion of the progenitor pool followed by timely differentiation, avoiding the uncontrolled proliferation seen in pathological conditions .

Aging and Regenerative Capacity: Lessons from the Zebrafish Lifespan

The Age-Related Decline

A critical question for translational application concerns the impact of aging on regenerative capacity. AD is predominantly a disease of aging, and any regenerative strategy must function in aged brains. Zebrafish studies comparing young (6-month) and old (24-month) fish have revealed important insights .

While aging does not significantly reduce the rate of NSPC proliferation in zebrafish, it markedly impairs the **neurogenic response**—the efficiency with which proliferating cells differentiate into functional neurons. Aged fish also exhibit diminished microglial/macrophage activation following Aβ42 exposure,

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suggesting that the immune system's capacity to coordinate regenerative signaling declines with age.

Neural stem cell proliferation zones in the adult zebrafish brain, showing distribution of cycling cells, neuronal markers, and label-retaining cells across major brain regions

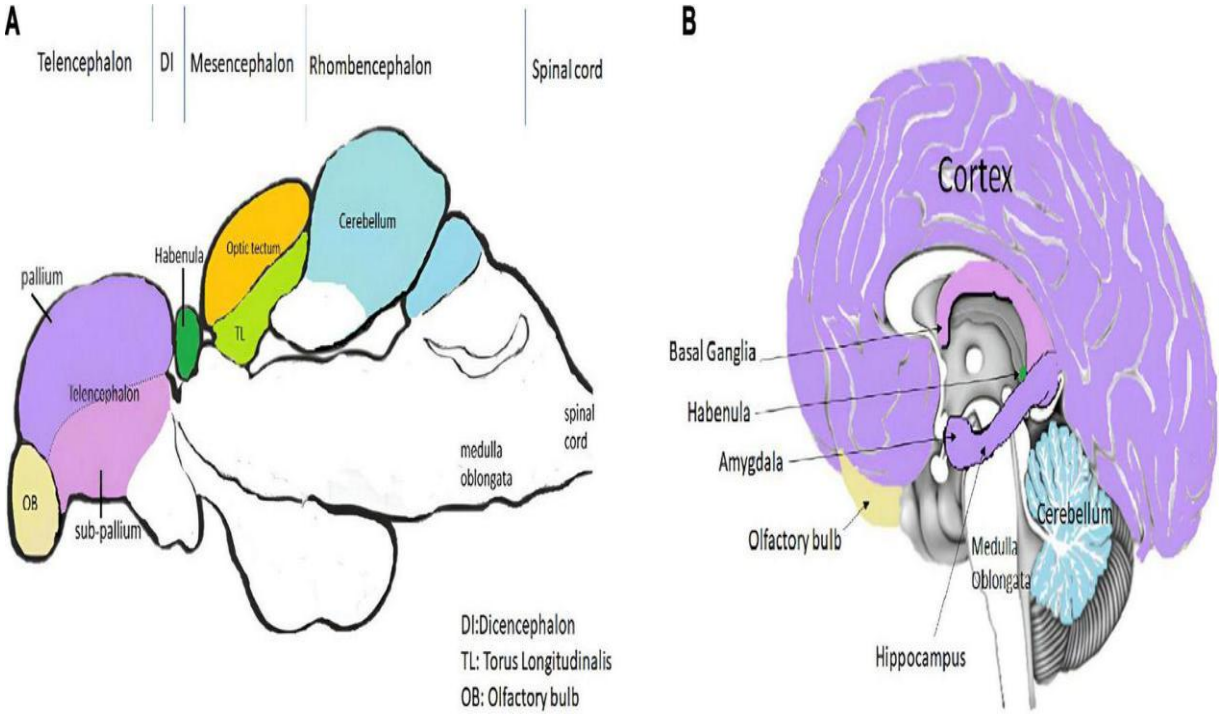

Figure 4. Neurogenic niches in the adult zebrafish brain. Cycling cells (red), newly born neurons (blue), and label-retaining stem cells (yellow) are distributed across ventricular zones in the telencephalon, diencephalon, and cerebellum, enabling lifelong neuronal replacement. (Adapted from Frontiers in Behavioral Neuroscience)

Implications for Human Therapy

These findings suggest that regenerative therapies in elderly AD patients may require dual approaches: not only stimulating stem cell proliferation but also

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enhancing the differentiation and maturation of newborn neurons. The zebrafish model indicates that addressing age-related immune dysfunction—particularly restoring the coordinated inflammatory response necessary for regeneration—may be as important as direct stem cell activation .

Translational Pathways: From Zebrafish to Human Therapy

3D Human Neurogenesis Assays

Validating zebrafish discoveries for human application requires robust in vitro models. Hydrogel-based three-dimensional (3D) human neurogenesis assays have emerged as powerful tools for this translation. These systems culture human neural stem cells in biohybrid starPEG-heparin matrices that mimic the brain's extracellular environment, enabling the study of Aβ42-induced toxicity and therapeutic intervention in a human cellular context .

Using these 3D assays, researchers confirmed that Lipocalin-2 (Lcn2)—a protein elevated in postmortem AD brains—suppresses human neurogenesis and promotes reactive gliosis. Blocking Lcn2's receptor, Slc22a17, restored pro-neurogenic effects similar to those observed with NGFR activation in zebrafish. This cross-species validation strengthens the case for targeting glial plasticity as a regenerative strategy in human AD .

Cellular Reprogramming and In Vivo Conversion

Building on zebrafish insights into glial plasticity, recent advances enable direct reprogramming of mammalian astrocytes into neurons. In mouse AD models, forced expression of neurogenic transcription factors (such as NeuroD1 or Ascl1) in reactive astrocytes converts them into functional neurons that integrate into existing circuits and improve cognitive performance.

However, this approach faces challenges including incomplete reprogramming, heterogeneity of converted cells, and potential disruption of astrocytic support functions. Zebrafish studies suggest that **physiological activation** of endogenous

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reprogramming pathways—such as NGFR or IL4 signaling—may offer safer, more physiologically integrated alternatives to forced genetic manipulation .

Biomarker-Guided Regenerative Strategies

The emerging framework of P4 medicine (Predictive, Preventive, Personalized, Participatory) offers a roadmap for implementing neuroregeneration in clinical practice. Multi-omic profiling—including genomics, proteomics, metabolomics, and lipidomics—can identify patient subgroups most likely to benefit from regenerative interventions based on their molecular signatures.

Digital biomarkers derived from smartphone accelerometry, speech analysis, and sleep architecture monitoring enable longitudinal tracking of subtle cognitive changes, potentially identifying candidates for regenerative therapy during the preclinical or mild cognitive impairment (MCI) stage when neurogenic interventions may be most effective .

Challenges and Future Directions

The Blood-Brain Barrier and Delivery

A significant hurdle for regenerative therapeutics is delivery to the CNS. Biologics such as recombinant IL4, BDNF, or NGFR agonists must cross the blood-brain barrier (BBB), which is compromised but not absent in AD. Nanoparticle-based delivery systems, focused ultrasound BBB opening, and intrathecal administration represent promising approaches under active investigation.

Circuit Integration and Functional Recovery

Generating new neurons is necessary but not sufficient for cognitive recovery. Newborn neurons must extend appropriate axonal and dendritic projections, form functional synapses with existing circuits, and assume correct physiological roles. Zebrafish research indicates that the adult brain retains remarkable capacity for

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circuit plasticity, but the mechanisms ensuring correct integration remain incompletely understood.

Safety and Tumorigenicity

Stimulating stem cell proliferation carries inherent risks, including tumorigenesis. Zebrafish studies reveal that regenerative neurogenesis is tightly self-limiting—proliferation ceases once injury is resolved, and ectopic growth is prevented by Notch reactivation and contact inhibition. Understanding these endogenous braking mechanisms is essential for designing safe regenerative therapies.

Comparative Overview: Neuroprotection vs. Neuroregeneration

Feature	Neuroprotection	Neuroregeneration
Primary Goal	Preserve existing neurons	Replace lost neurons and rebuild circuits
Mechanism	Anti-oxidant, anti-inflammatory, anti-apoptotic	Stem cell activation, neurogenesis, synaptogenesis
Therapeutic Window	Early to mid-stage disease	Potentially all stages, including advanced
Key Targets	Amyloid-β, tau, microglia, mitochondria	Neural stem cells, astroglia, neurotrophic factors
Zebrafish Insight	Limited—mammalian models dominate	Extensive—zebrafish reveal successful regeneration programs
Clinical Status (2026)	Lecanemab/donanemab approved (modest efficacy)	Preclinical/clinical trials for stem cell therapies
Limitations	Cannot reverse existing damage	Requires functional circuit integration; safety concerns
Complementary Role	Prevents further loss	Restores what has been lost

Table 1. Comparative analysis of neuroprotective versus neuroregenerative therapeutic strategies in Alzheimer's disease, highlighting the distinct mechanisms, targets, and clinical considerations of each approach.

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Conclusions

The zebrafish model has fundamentally reshaped our understanding of what is possible in Alzheimer's disease therapy. By demonstrating that vertebrate brains can mount successful regenerative responses to amyloid-β toxicity, this remarkable organism has challenged the long-held assumption that neuronal loss in AD is irreversible.

Key insights from zebrafish research point toward a new therapeutic paradigm:

- **Neuroregeneration is biologically feasible** even in the context of amyloid-β pathology, provided the correct molecular signals are activated.
- **Immune-neural crosstalk**—particularly IL4-mediated anti-inflammatory signaling—determines whether the brain degenerates or regenerates.
- **Glial plasticity** represents a powerful, underexploited resource; astroglia can be reprogrammed from scar-forming to neuron-generating phenotypes.
- **Aging impairs regenerative efficiency** primarily at the level of neuronal differentiation and immune coordination, not stem cell proliferation itself.
- **Translational validation** through 3D human neurogenesis assays and mammalian models confirms the cross-species relevance of zebrafish-derived mechanisms.

As we move beyond the neuroprotection paradigm, the integration of regenerative strategies with existing protective approaches offers the most promising path forward. The future of Alzheimer's therapy likely lies not in choosing between protection and regeneration, but in **sequencing and combining** these strategies: neuroprotection to halt progression during early stages, followed by neuroregeneration to restore function in affected circuits.

The zebrafish has shown us that vertebrate brains can heal themselves. Our challenge now is to translate that biological wisdom into human therapeutic reality.

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