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Targeting mitochondrial dysfunction across the lifespan: Role of bezafibrate in neurodevelopment and neurodegeneration

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Neurodevelopmental and neurodegenerative disorders were long regarded as distinct entities, traditionally defined by their age of onset and clinical trajectory, as early-life disturbances in neuronal differentiation, synaptic assembly, and circuit maturation versus progressive synaptic failure, protein aggregation, and neuronal death during ageing. Increasing evidence now demonstrates that these are not isolated conditions but rather two temporal phases along a shared continuum (Hickman et al., 2022).

Mitochondrial dysfunction is central to this continuum, which undermines both the formation and maintenance of neuronal–glial networks. Deficits in biogenesis, oxidative phosphorylation, and metabolic resilience, together with altered fusion/fission dynamics, defective mitophagy (PINK1/Parkin), and impaired Ca^{2+} buffering, compromise synaptogenesis and heighten vulnerability to later degeneration. Mitochondrial programs in glia are also critical: astrocytic biogenesis supports maturation and synaptogenesis (Zehnder et al., 2021). Early bioenergetic failure, therefore, seeds vulnerabilities that accelerate neurodegeneration under age-related stress.

Within this framework, bezafibrate, a pan-peroxisome proliferator-activated receptor (PPAR) agonist used clinically for dyslipidemia, emerges as a modulator of mitochondrial health and synaptic function. By activating PPARα/δ/γ upstream of peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α)–nuclear respiratory factor 1 (NRF1/2)–mitochondrial transcription factor A (TFAM) cascade, it enhances biogenesis, oxidative phosphorylation, and overall cellular resilience. Across models, from tauopathy organoids (Cordella et al., 2025) and endothelial cells in 22q11.2DS (Crockett et al., 2025), to astrocytic maturation and Alzheimer's models (Lu et al., 2023), bezafibrate consistently restores mitochondrial function and rescues both developmental and degenerative phenotypes (**Figure 1**).

Neurodevelopment–neurodegeneration continuum: The link between early neurodevelopmental vulnerability and late neurodegenerative decline has gained significant traction from two complementary perspectives. Hickman et al. (2022) proposed that many neurogenetic disorders extend across the lifespan, evolving from aberrant development to degeneration, with mitochondria and synapses as shared mechanistic hubs. This framework positions neurodevelopment and neurodegeneration as phases of a single biological trajectory, with distinct yet interdependent contributions from neurons, astrocytes, and oligodendrocytes.

Key lines of evidence include: (i) Genetic overlap. Genes such as microtubule associated protein tau (*MAPT*), amyloid precursor protein (*APP*), and leucine-rich repeat kinase 2 (*LRRK2*) regulate neuronal growth, axonal transport, and pruning during development, but later drive aggregation and degeneration. (ii) Early signatures of late disease. Misfolded proteins, hyperphosphorylated tau, and mitochondrial deficits emerge decades before onset, often during neurodevelopmental phases; e.g., abnormal tau phosphorylation in presymptomatic MAPT carriers. (iii) Shared pathways. Altered lipid metabolism, oxidative stress, impaired glial maturation, and disrupted synaptic connectivity are features common to autism, schizophrenia, and dementias. Additional convergent mechanisms include autophagy–mitophagy (PINK1/Parkin), complement-mediated pruning, and mTOR-dependent programs coordinating synaptic and myelin plasticity (Hickman et al., 2022). (iv) Clinical overlaps. The 22q11.2 deletion syndrome presents with autism or attention deficit hyperactivity disorder in childhood, schizophrenia in adolescence, and Parkinson's disease in adulthood (Crockett et al., 2025; Rao et al., 2025). This "phenotypic cascade" illustrates how a single genetic lesion yields developmental, psychiatric, and degenerative manifestations.

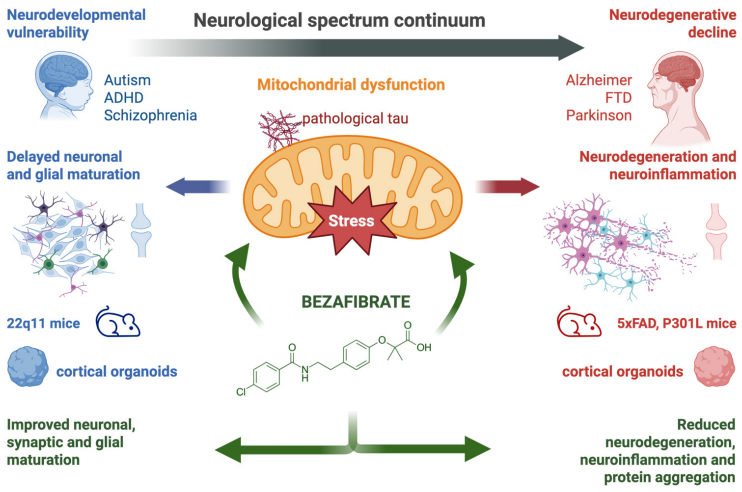

Figure 1 | **Neurological spectrum continuum and the therapeutic role of bezafibrate.**
The schematic illustrates the continuum of brain disorders across the lifespan, from neurodevelopmental vulnerability (left; autism, ADHD, schizophrenia, delayed neuronal and glial maturation, exemplified by 22q11.2 models and cortical organoids) to neurodegenerative decline (right; Alzheimer's disease, frontotemporal dementia, Parkinson's disease, characterized by pathological tau, neurodegeneration and neuroinflammation, modeled in 5×FAD and P301L mice, as well as cortical organoids). At the center lies mitochondrial dysfunction, depicted as a common mechanistic hub linking early- and late-life brain disorders. Bezafibrate, a pan-PPAR agonist, acts on this central node to restore mitochondrial function, leading to improved neuronal, synaptic and glial maturation on the developmental side and reduced neurodegeneration, neuroinflammation and protein aggregation on the degenerative side. Created with BioRender.com. ADHD: Attention deficit hyperactivity disorder; FTD: frontotemporal dementia; PPAR: peroxisome proliferator-activated receptor.

This conceptual framework suggests the need for therapies that transcend developmental and degenerative boundaries. In practice, such approaches include interventions reinforcing mitochondrial PPAR–PGC-1α–NRF1/2–TFAM axis, modulating synaptic and pruning pathways, and designing lifespan-orinented trials using biomarkers that bridge youth and aging (Uittenborgaard et al., 2014).

Tauopathies in cortical and retinal models: Tauopathies represent a clear illustration of the neurodevelopment–neurodegeneration continuum. In cortical organoids carrying the MAPT IVS10+16 mutation, tau dysregulation disrupted neuronal differentiation, reduced synaptic gene expression, and impaired calcium-dependent network activity (Cordella et al., 2025). These organoids also displayed mitochondrial dysfunction, tau hyperphosphorylation, and aggregation. Such deficits coincided with downregulated synaptic programs and diminished spontaneous calcium synchrony.

Treatment with bezafibrate restored mitochondrial biogenesis, rescued synaptic maturation, and normalized network activity (Cordella et al., 2025), likely through activation of the PGC-1α pathway, increasing mtDNA copy number and respiratory gene expression to support network recovery. Parallel findings in retinal organoids confirmed that tau mutations impair neuronal differentiation and connectivity, highlighting retinal models as accessible systems for studying tau pathology (Mautone et al., 2025). These alterations disrupted lamination and photoreceptor/retinal ganglion cell maturation, revealing how tau mutations derail early developmental processes and predispose to later degeneration. Moreover, MAPT mutations delayed glial maturation, with downregulation of myelination genes (myelin basic protein [*MBP*], oligodendrocyte transcription factor 2 [*OLIG2*], and galactocerebrosidase [*GALC*]) and reduced glial fibrillary acidic protein [*GFAP*]) expression (Cordella et al., 2025). Thus, tau impacts both neuronal and glial compartments, reinforcing the concept that neuro-glial developmental delay fuels degenerative progression. Glia-intrinsic bioenergetic and transcriptional programs support axons and synapses; their delay compromises myelination, metabolic coupling, and plasticity, amplifying neuronal loss.

Beyond tauopathies, 22q11.2 patient-derived cortical organoids demonstrated DGCR8 haploinsufficiency leading to defective miRNA biogenesis, delayed maturation, reduced dendritic complexity, and attenuated calcium responses (Rao et al., 2025). These defects mirror those observed in tauopathy organoids and illustrate how patient-derived systems can capture both genetic and epigenetic contributors to the continuum. More broadly, organoids enable causal investigation of convergent pathways, such as mitochondrial quality control, miRNA-mediated timing, and synaptic pruning, and provide platforms to evaluate cross-cutting therapeutic approaches, including PPAR agonists and autophagy modulators.

22q11.2 deletion syndrome — development meets degeneration: The 22q11.2 deletion syndrome exemplifies a disorder spanning neurodevelopmental and neurodegenerative spectra. Children frequently present with autism and attention deficit hyperactivity disorder, adolescents with schizophrenia (Rao et al., 2025), and adults exhibit an elevated risk of Parkinson's disease. This lifespan progression suggests that dosage-sensitive genes within the deleted interval generate enduring vulnerabilities that first disrupt circuit assembly and later accelerate neurodegenerative processes.

Crockett et al. (2025) found that induced pluripotent stem cell-derived brain endothelial cells from 22q11.2 patients exhibit pronounced mitochondrial dysfunction, compromising blood–brain barrier (BBB) integrity and cognitive performance. In mouse models, bezafibrate treatment restored respiration, stabilized the BBB, and rescued social memory (Crockett et al., 2025). These effects reflect pan-PPAR activation of the PGC-1α pathway, enhancing mitochondrial biogenesis, oxidative phosphorylation, and tight-junction gene expression, thereby reducing barrier leakage and neuroinflammation.

Complementing this vascular perspective, Rao et al. (2025) demonstrated that 22q11.2 organoids follow asynchronous developmental trajectories, with progenitors persisting in proliferative states and generating fewer mature neurons. This phenotype was linked to DGCR8 haploinsufficiency and disrupted miRNA pathways (Rao et al., 2025). Such alterations mistime transcriptional programs governing neuronal differentiation, dendritic formation, and activity-dependent synaptic maturation, leading to under-connected and metabolically fragile circuits. Collectively, 22q11.2DS pathology combines neurovascular mitochondrial dysfunction with neuronal developmental delay, explaining its psychiatric and degenerative manifestations across the lifespan. This convergence

highlights therapeutic targets, such as mitochondrial modulators, capable of addressing multiple disease phases.

Astrocytes at the nexus of development and degeneration: Astrocytes, once viewed as passive supportive cells, are now recognized as active regulators of synapse formation, neurotransmitter recycling, and metabolic coupling. In schizophrenia and related disorders, astrocytes display impaired differentiation, abnormal glutamate handling, and mitochondrial deficits (de Oliveira Figueiredo et al., 2022). Transplantation studies confirm that glial progenitors derived from patients can autonomously drive cognitive and behavioral dysfunction. Converging mechanisms include diminished glutamate clearance (excitatory amino acid transporter 2/ glutamate transporter 1), impaired K^+ buffering (Kir4.1), altered gap-junction coupling (connexin-43), and weakened lactate shuttling (monocarboxylate transporter 1/monocarboxylate transporter 4), all of which undermine synaptic homeostasis and plasticity.

Our MAPT organoid study revealed that tau mutations delay both neuronal specification and glial maturation. Reduced GFAP expression and downregulation of myelination genes indicate compromised astrocytic and oligodendrocytic trajectories (Cordella et al., 2025). This finding links tau pathology to glial developmental failure, destabilizing neuronal networks and predisposing them to degeneration. Functionally, delayed astrocyte and oligodendrocyte programs disrupt metabolic coupling, myelination timing, and activity-dependent pruning (e.g., complement-mediated), increasing network noise and lowering the threshold for degenerative cascades.

Mitochondrial regulation of astrocytic maturation: Mitochondrial biogenesis, driven by PGC1α and regulated by metabotropic glutamate receptor 5 (mGluR5) signaling, is essential for postnatal astrocytic arborization and synapse support (Zehnder et al., 2021). Activity-dependent mGluR5 signaling couples neuronal activity to astrocytic PGC1α programs, boosting mitochondrial content and respiratory capacity to sustain arborization and synaptogenesis. Loss of PGC1α disrupts astrocytic morphology and reduces synaptogenesis, whereas re-expression restores both, normalizing mitochondrial networks and synaptic support. This identifies astrocytic mitochondria as promising therapeutic targets in disorders characterised by impaired neural wiring. Reinforcing the PPAR–PGC1α axis (e.g., with bezafibrate) could synergize with the physiological mGluR5–PGC1α program (Zehnder et al., 2021).

In addition, bezafibrate may engage the pregnane X receptor, a nuclear receptor with overlapping lipid-sensing and detoxification roles that intersect PPAR signaling. Crosstalk between pregnane X receptor and PPAR pathways can modulate mitochondrial and peroxisomal gene expression, influencing lipid oxidation, xenobiotic metabolism, and redox balance. Through partial pregnane X receptor activation, bezafibrate could thus fine-tune mitochondrial resilience in astrocytes, integrating metabolic and antioxidant responses within the broader transcriptional network governing astrocytic maturation.

Novel studies also highlight tau–astrocyte interactions: astrocytes internalise extracellular paired helical filament tau, triggering mitochondrial remodeling and altering vesicular regulation (Zufferey et al., 2025). Initially adaptive, tau-induced mitochondrial changes and calcium perturbations may impair glutamate clearance and lactate shuttling, driving excitotoxicity and facilitating tau propagation. Thus, astrocytes act as both victims and mediators of tau-driven degeneration.

Together, these findings place astrocytes and their mitochondrial health at the center of the developmental–degenerative continuum. The mGluR5–PGC1α pathway offers a testable therapeutic lever to stabilize astrocytic maturation and circuit homeostasis.

Comparative insights — *in vitro* and *in vivo* models: Induced pluripotent stem cell-derived organoids recapitulate human-specific developmental trajectories (D'Antoni et al., 2023). Cortical and retinal organoids reproduce early neuronal and glial differentiation, revealing developmental deficits that are often absent in adult models (Cordella et al., 2025; Mautone et al., 2025; Rao et al., 2025). The advent of assembloids incorporating microglia, vasculature, and BBB-on-chip systems further extends their ability to capture immune and neurovascular contributions (D'Antoni et al., 2023).

Nevertheless, organoids lack vascularization and systemic inputs, limiting their relevance for late-stage disease mechanisms. Animal models, by contrast, can address aspects of ageing, immune regulation, and behavior. Bezafibrate has been shown to improve cognition in 5×FAD mice (Lu et al., 2023) and to increase astrocytic PGC1α expression, enhancing synaptic function (Zufferey et al., 2025).

An integrated experimental pipeline is therefore needed: organoids for identifying early developmental defects, animal models for systemic validation, and phase 0/II clinical trials incorporating biomarker anchoring. Cross-platform readouts, such as mitochondrial activity assays, astrocytic calcium imaging, and network synchrony measurements, should enable direct translation from experimental models to patients.

Implications and future directions: Viewing brain disorders through a lifespan lens carries major implications: (i) Early therapeutic windows: Detecting mitochondrial and synaptic deficits in children with genetic risk factors could allow intervention before irreversible degeneration, including targeting the mGluR5–PGC1α axis during astrocytic maturation. (ii) Targeting glia: Treatments should extend beyond neurons to include astrocytes and endothelial cells, key regulators of circuit stability, and oligodendrocytes with their energy-intensive myelination programs. (iii) Accessible biomarkers: Retinal imaging, BBB assays, and astrocytic metabolic markers may serve as non-invasive efficacy readouts. Integrating mitochondrial biomarkers with functional measures (such as cognitive or visual assessments) would facilitate longitudinal monitoring across the lifespan. (iv) Patient-specific testing: induced pluripotent stem cell-derived cortical, retinal, and astrocytic organoids provide precision platforms for n-of-1 drug testing tailored to individual genetic backgrounds. (v) Drug repurposing: Bezafibrate, with its strong safety profile, remains a promising candidate for clinical trials across both neurodevelopmental and neurodegenerative contexts. Combination strategies, such as bezafibrate with activity-based interventions engaging the mGluR5–PGC1α pathway, deserve formal evaluation. (vi) Lifespan clinics: Clinical models should bridge pediatric and geriatric services, reflecting shared underlying biology. Multidisciplinary clinics could harmonize biomarkers and interventions across age groups.

Future clinical studies should evaluate bezafibrate in neurodevelopmental and neurodegenerative settings, employing CNS-relevant mitochondrial and functional biomarkers to assess target engagement and efficacy across the lifespan.

Conclusion: Neurodevelopmental and neurodegenerative disorders are not discrete categories but rather expressions of shared vulnerabilities unfolding over time. Mitochondria, astrocytes, and synapses form the critical nexus where developmental derailment transitions into degenerative decline. Evidence from tauopathy cortical and retinal organoids, 22q11.2 deletion syndrome, and animal studies demonstrates that bezafibrate can rescue both developmental and degenerative phenotypes, underscoring its promise as a cross-cutting therapeutic. The convergence of physiological (mGluR5–PGC1α) and pharmacological (PPAR–PGC1α) pathways, particularly within astrocytes, provides a coherent framework for intervention across the lifespan.

Embracing this continuum model, in which neurodevelopment and neurodegeneration represent sequential stages of a single trajectory, is essential for strategies aiming to preserve brain health throughout life. This paradigm supports preventive trials in at-risk youth and disease-modifying interventions in adults using shared, mitochondria-centered endpoints.

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