THERAPEUTIC LANDSCAPE OF NEUROINFLAMMATION

An overview of current therapeutic strategies targeting neuroinflammation through distinct mechanisms of microglial modulation.

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KEY TAKEAWAY

Neuroinflammation is an increasingly explored therapeutic target in AD, but the field remains early-stage. Clinical evidence is needed to determine which mechanisms can deliver meaningful disease modification.

OPPORTUNITIES

Address broader AD pathophysiology
Target inflammatory processes contributing to synaptic dysfunction and neuronal damage, beyond amyloid and tau.

Differentiate from existing approaches
Offer a distinct mechanism for disease modification where current treatments have limited impact on disease progression.

Expand therapeutic options
Successful clinical validation could add a differentiated mechanism to the AD treatment landscape.

CHALLENGES

Limited clinical validation
Most approaches remain preclinical or early-stage, with limited evidence of clinical benefit.

Biological complexity
Neuroinflammatory pathways are heterogeneous, making effective target selection challenging.

Patient selection
Identifying patients with relevant neuroinflammatory biology may be critical to efficacy.

FUTURE DIRECTIONS

Clinical validation
Determine which mechanisms translate into meaningful disease modification.

Biomarker-led development
Use biomarkers to support target engagement and patient selection.

Mechanism prioritisation
Use clinical evidence to identify the most promising approaches.

1. FOUR APPROACHES TO MODULATING MICROGLIAL DYSFUNCTION

1 ENHANCE PROTECTIVE MICROGLIAL FUNCTION

Promote protective microglial states that support neuronal health and resilience. Enhance beneficial functions such as debris clearance and tissue repair.

EXPECTED OUTCOMES
- Improved debris-clearance
- Increased neuronal support
- Reduced neurodegeneration

2 BLOCK MICROGLIAL INFLAMMATORY SIGNALLING

Suppress chronic inflammatory signalling that contributes to neuronal damage. Target pro-inflammatory mediators and pathways such as TNF and NLRP3.

EXPECTED OUTCOMES
- Reduced cytokine release
- Lower inflammasome activation
- Decreased neurotoxicity

3 REMOVE UPSTREAM PATHOLOGICAL TRIGGERS

Prevent pathological signals from initiating microglial activation. Target upstream triggers before they drive downstream neuroinflammation.

EXPECTED OUTCOMES
- Reduced complement activation
- Prevents chronic inflammation
- Preserves BBB integrity

4 REPROGAM THE NEUROIMMUNE SYSTEM

Shift the neuroimmune environment towards a more protective state. Alter immune-cell states and responses to restore healthier immune regulation.

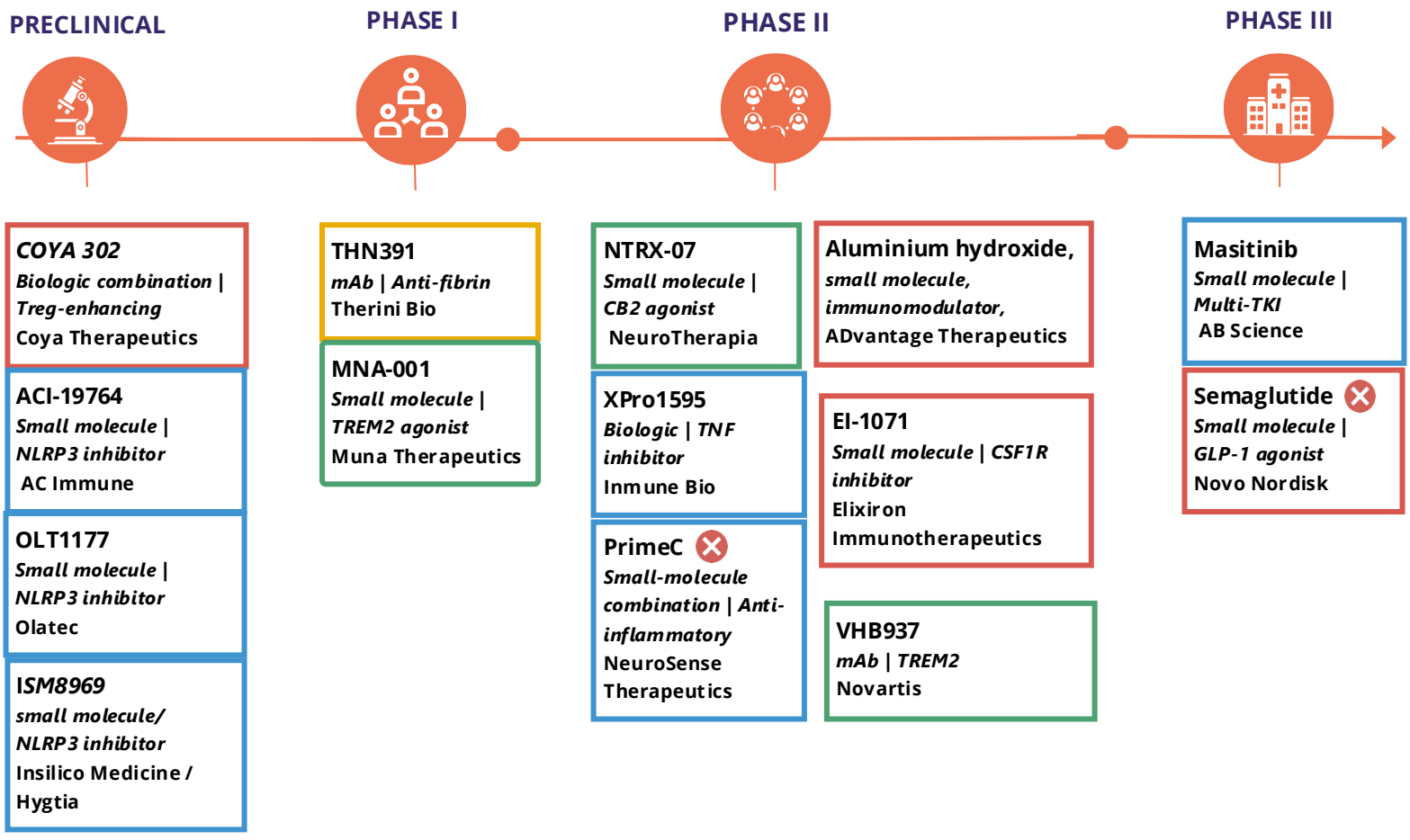
EXPECTED OUTCOMES
- Immune reset and recalibration
- Long-term disease modification
- Enhanced neuroprotection

2. MECHANISM COMPARISON

	ENHANCE PROTECTIVE MICROGLIAL FUNCTION	BLOCK MICROGLIAL INFLAMMATORY SIGNALLING	REMOVE UPSTREAM PATHOLOGICAL TRIGGERS	REPROGRAM THE NEUROIMMUNE SYSTEM
PRIMARY AIM	Promote repair and resilience	Reduce inflammation and neurotoxicity	Prevent chronic inflammation	Restore long-term immune homeostasis
HOW/ APPROACH	Enhance protective signalling and promote phagocytic clearance of cellular debris	Reduce cytokine release and inflammasome activation, limiting downstream neurotoxicity	Block pathological signals before they trigger microglial activation and downstream inflammation	Modulate immune-cell states and restore a more protective neuroimmune balance
PIPELINE	3 assets · Latest: Phase II	6 assets · Latest: Phase III*	1 asset · Phase I	4 assets · Latest: Phase II*

* Latest phase includes a Phase III programme/trial that has subsequently been terminated; latest active development is Phase II.

3.CLINICAL DEVELOPMENT LANDSCAPE



*Clinical stage shown at the programme/asset level; stage may vary by indication and specific candidate. ✕ Indicates an AD clinical trial/programme that has been terminated. **For semaglutide, Phase 3 AD trials did not demonstrate a significant clinical benefit, although GLP-1 receptor agonism remains under investigation for its potential effects on neuroinflammation and other disease-related pathways. ISM8969 is currently being developed for Parkinson's disease (PD), not AD.