Axial Therapeutics
axialtx.com

Harnessing the gut–brain axis to develop CNS therapeutics

Axial Therapeutics focuses on the gut–brain axis to develop therapeutics to mitigate central nervous system disorders and conditions. The company has built a pipeline of novel small molecules with lead programs in autism spectrum disorder and Parkinson's disease.

Axial Therapeutics is a clinical-stage biopharmaceutical company harnessing the gut–brain axis (G–BA) to develop safe and effective therapies for patients impacted by central nervous system (CNS) disorders and conditions. Using its 'omics' platform, the company has built a deep pipeline of gut-restricted small molecules based on pioneering research from its cofounder, Sarkis Mazmanian, and his lab at the California Institute of Technology. Axial's pipeline has significant potential for mitigating underlying disease pathology and resulting symptoms.

"Targeting diseases believed to be of CNS origin via the gut microbiome is a disruptive concept," said David Donabedian, CEO and cofounder of Axial. "There's a growing body of evidence about the G–BA, and our 'omics' platform allows us to see constellations where others only see stars, putting us at the forefront of scientific research validating the G–BA in CNS diseases and developing innovative, safe and effective therapies."

Axial's lead programs include AB-2004, a gut-restricted, first-in-class compound poised to first redefine the treatment of irritability in children with autism spectrum disorder (ASD), and AB-4166, an oral compound that reduces gastrointestinal (GI) symptoms, i.e., colonic dyskinesia in patients with Parkinson's disease (PD). Other programs in preclinical development include additional small molecules for PD, a rare CNS disorder, and most recently oncology (Fig. 1).

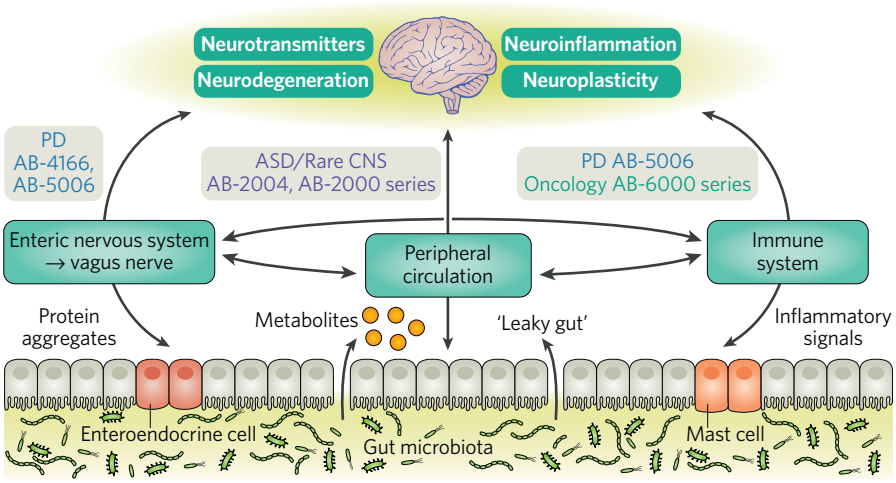

Fig. 1 | Harnessing the gut–brain axis to treat CNS disorders. Axial's therapies target specific processes including the enteric nervous system, the immune system and neuroactive microbial metabolites (NMMs) in peripheral circulation. ASD, autism spectrum disorder; CNS, central nervous system; PD, Parkinson's disease.

The gut–brain axis in CNS disease

Axial has developed a unique platform that combines the study of human samples and experimental approaches with proprietary in vivo models to establish the role of the gut microbiome in diseases to identify novel G–BA-specific targets. Once a novel target is validated, Axial designs and develops new chemical entities. The Axial approach has two distinct and critical advantages over other approaches. By targeting the gut microbiome, the challenge of crossing the blood–brain barrier is eliminated. Additionally, the gut-restricted therapies minimize systemic exposure, resulting in exceptional safety profiles.

Studies have revealed profound differences between the gut microbiomes of children with ASD and those of typically developing children. These differences result in altered concentration profiles of certain bacteria-derived metabolites, including levels of so-called neuroactive microbial metabolites (NMMs) that are produced in the gut, but reach the brain, altering neuronal networks and actively contribute to ASD and other CNS disorders.

Axial's AB-2004 is designed to remove NMMs linked to ASD-associated behaviors with high affinity and selectivity. The compound effectively removes the NMMs in the gut, limiting their impact on the brain.

In a phase 1b/2a open-label clinical trial of males aged 12 to 17 with ASD, AB-2004 exhibited a favorable safety profile with no drug-related adverse events. Importantly, levels of key NMMs, including 4-ethylphenylsulfate (4-EPS), p-cresol sulfate (p-CS) and indoxyl sulfate (IS) were substantially reduced in plasma and urine. With >90% adherence to the dosing regimen, significant improvements in subjects with high irritability and high anxiety scores were observed.

Axial has initiated activities for a pediatric phase 2b randomized, double-blind, placebo-controlled study for irritability associated with ASD. The company plans to file an IND in the last quarter of 2020 and seek US Food and Drug Administration breakthrough/fast-track therapy designation.

A gut–amyloid link in Parkinson's disease

Parkinson's disease is a neurodegenerative disorder characterized by motor impairment resulting from damage to the dopaminergic neurons of the substantia nigra and the formation of α-synuclein inclusion bodies (Lewy pathology) in several other brain regions. Certain gut bacteria produce amyloids that accelerate α-synuclein propagation from the gut to the brain. In preclinical PD models, the bacterial amyloid CsgA, the major curli subunit, induces α-synucleinopathy and a PD phenotype.

Small molecules developed by Axial block CsgA aggregation resulting in reduced α-synucleinopathy and overall motor improvement. In a small study with PD subjects exhibiting elevated bacterial amyloid levels and GI symptoms, AB-4166 demonstrated improvements in GI symptoms such as constipation and a reduction in colonic dyskinesia while maintaining a strong safety profile. A new more potent chemical entity, AB-5006, is in late stage preclinical development.

Axial is seeking collaborators interested in leveraging its omics platform to identify new targets and advance the development of its pipeline.

"Not long ago, neuroscientists would never have believed that a therapeutic targeting the gut and not the brain, could have an impact on CNS disorders and conditions," said Donabedian. "With our platform and groundbreaking approach, we look forward to bringing new treatments to the market and improving the lives of patients and families worldwide."

CONTACT
David H. Donabedian, Cofounder & CEO
Axial Therapeutics
Waltham, MA, USA
Tel: +1-781-701-8468
Email: david@axialtx.com