ABL Bio Inc.
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Blood–brain barrier molecular carriers for Parkinson's disease

ABL Bio's first-in-class bispecific antibodies for Parkinson's disease combine unprecedented blood–brain barrier penetration with a robust mechanism of action for improved therapeutic efficacy. The company is looking for partners to codevelop or out-license bispecific antibodies able to penetrate the blood–brain barrier.

ABL Bio Inc. is a privately held South Korean immuno-oncology and neurodegenerative disease biotechnology research company founded in 2016. The company uses two platform technologies: bispecific antibodies (BsAbs) that bind two different antigens of interest, and antibody–drug conjugates (ADCs) that deliver small-molecule drugs to specific cells.

ABL's most advanced asset is ABL001, a BsAb targeting vascular endothelial growth factor and DLL4 that is in development for the treatment of solid tumors. The product is entering a phase 1 trial, a first for a BsAb in South Korea. On the ADC front, ABL has partnered with LegoChem Biosciences (141080 under the Korean Securities Dealers Automated Quotations market) to codevelop cancer therapeutics with high linker stability and efficient payload release.

In the neurodegenerative disorder space, the company's latest R&D program, ABL is harnessing its BsAb expertise to develop next-generation BsAbs designed to maximize blood–brain barrier (BBB) penetrance and therapeutic efficacy. The most advanced molecule is ABL301, an α-synuclein (SNCA)-targeting BsAb that penetrates the BBB via a receptor-mediated transcytosis (RMT) receptor and is in development for Parkinson's disease (PD) (**Fig. 1**).

ABL is interested in partnering on any of its programs—particularly in the neurodegenerative space—and is looking to establish codevelopment partnerships or licensing agreements to take those molecules through the later stages of drug development.

"ABL has achieved major milestones in just two years, including IND [investigational new drug] approval of ABL001 and preclinical validation of ABL301," said Sang Hoon Lee, ABL's founder and CEO. "Success with our BsAb-based drug development in oncology has allowed us to expand into CNS, an area with a huge unmet medical need and where there is potential for our BsAb-based BBB-penetrating platform."

The PD challenge

PD is the second most frequent neurodegenerative disease globally, with over 6 million affected individuals. No disease-specific therapies exist for PD; one of the main hurdles is the lack of a PD-specific mechanism of action to target.

The standard of treatment for PD includes levodopa, dopamine agonists, amantadine, anticholinergic drugs, catechol-*O*-methyltransferase inhibitors and monoamine oxidase B inhibitors, all of which treat the symptoms but not the underlying cause of PD.

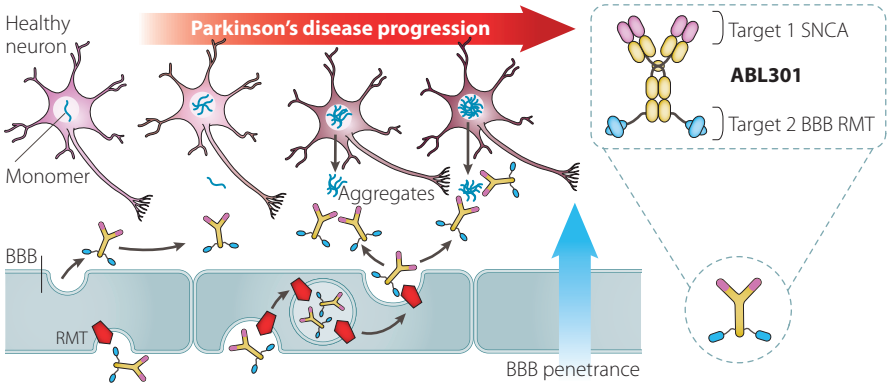

Figure 1: Molecular carriers crossing the blood–brain barrier (BBB). ABL301 penetrates brain epithelial cells, via an undisclosed receptor-mediated transcytosis (RMT) receptor. ABL301 inside RMT-coated vesicles are transported across the cell. ABL301 efficiently targets and binds to SNCA-aggregates, leading to its preferential intervention to the diseased neurons.

Immunotherapy against critical targets in the brain has been proposed as a strategy. ABL has developed a BsAb that would first target a PD-specific disease mechanism—namely, the formation of extracellular SNCA aggregates—and maximize BBB penetrance by targeting a novel RMT receptor on brain endothelial cells. The result is ABL301, a first-in-class BsAb.

ABL301—a first-in-class therapy

Building on its solid BsAb-engineering expertise, ABL set out to develop a next-generation therapeutic antibody for PD to address two main hurdles: PD specificity and BBB penetrance. The strongest genetic association found in PD is with missense and multiplication mutations of *SNCA*. The SNCA protein, which is usually present inside cells as an unfolded monomer, accumulates as multimeric aggregates (so-called Lewy bodies) inside cells of PD patients. Inhibition of the formation and intercellular transmission of such aggregates constitutes a key strategy in PD treatment.

ABL301's SNCA-aggregate-binding moiety is highly specific for SNCA, shows no cross-reactivity with other SNCA homologs *in vitro*, and has shown *in vivo* efficacy in a preclinical mouse model of PD.

A key strategy for overcoming the BBB consists of recruiting RMT systems to shuttle molecules through the brain endothelium. Three such RMT systems—transferrin receptor (TfR), insulin receptor, and low-density lipoprotein receptor–related peptide—have been used in many drug development programs. ABL301 contains a moiety that targets an undisclosed RTM system, which is present at levels similar to those of TfR in brain cells but, critically, much lower levels in other organs, which reduces the potential for side effects.

ABL301 thus combines specificity for SNCA with safe and efficient BBB penetrance. "Existing antibody therapeutics penetrate the brain with only 0.1–0.2% efficiency, a major problem for CNS drugs," said Lee. "We expect ABL301's potential for increasing brain penetrance to boost the therapeutic efficacy of SNCA-targeting drugs."

Partnering on BBB penetrance

The work conducted with ABL301 underscores ABL's commitment to develop novel, BsAb-based therapeutic strategies to overcome BBB penetrance. The company is looking to partner or out-license ABL301 for PD. "ABL is an innovative research company backed by a global network of investors and collaborators that has reached clinical stage in less than two years from its founding," said Lee. "A strong commitment in immuno-oncology and neurodegenerative disorders has allowed us to be highly productive, leading to successful global collaborations, and we are looking to expand our network of partnerships."

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