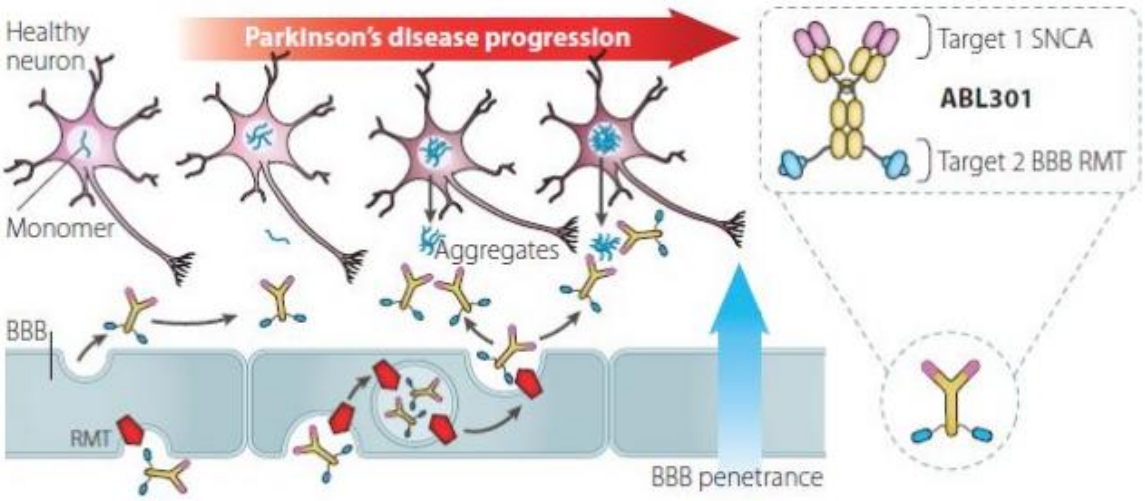
ABL301

ABL301, 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.

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.



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.

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.”

neurodegenerative disorders has allowed us to be highly productive, leading to successful global collaborations.