Intrathalamic Delivery of AVB-101 Rescues Pathology in Progranulin Deficient Mice and Achieves Widespread Cortical Expression in Two Large Animal Models

Shaw CE,1 Lee DY,2 Allison J,1 Bekele Y,1 Rosseini P,1 Joubert R,3,5 Walker Z,1,2 Furtado J,1,2 Gamus M,1,2 Fernandes A,1,2 Brock G,1 Miranda CJ,2 and Lee YB1

1United Kingdom Dementia Research Institute, Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neurosciences, King’s College London, London, UK; 2Aviabio Ltd, London, UK

Introduction

• Frontotemporal dementia (FTD) affects >30,000 patients in the United States of America and >75,000 patients in Europe causing a progressive decline in behaviour, personality, executive function and/or language, with death 2-12 years after initial symptom onset10.11.12.
• The burden associated with FTD is significant and costly, and currently no disease modifying therapies are available3.10.11.12.
• FTD caused by loss-of-function mutations in the GRN gene (FTD-GRN) production that increases microglial activation, accelerates neurodegeneration, and leads to pathognomonic transsynaptic spongiform vacuolation in the CNS10.11.12.
• FTD-GRN expression has been demonstrated to reduce the pathogenicity of mutant tau protein into non-pathogenic forms10.11.12.
• In a transgenic murine model for FTD-GRN, AVB-101 administered via the intracisternal magna route achieves FTD-GRN levels observed in healthy human controls (Figure 5A) while intrathalamic delivery of AVB-101 at a dose of 1x1011 vg, 100 times greater than the intracisternal magna route, was not protective (Figure 5B).
• Intrathalamic delivery of AVB-101 resulted in widespread distribution across brain regions (Figure 6).
• The intrathalamic delivery route decreased liver exposure and shedding versus intracisternal magna delivery as determined by quantitative polymerase chain reaction with undetectable levels of AVB-101 vector in liver biopsy following intrathalamic administration (Figure 5C).

Results

AVB-101 substantially reduces pathology in Grn knock-out mice

• AVB-101 was administered intrathalamically to Grn−/− mice to assess impact on FTD-GRN disease pathology – Without intervention, Grn−/− mice develop extensive lipofuscinosis and age-dependent neuroinflammation.
• Intrathalamic delivery of AVB-101 in young Grn−/− mice (8 weeks) reduced age-related levels of lipofuscinosis (subcortex mitochondrial and adrenoleukodystrophy triphosphate synthase (SCMAGAL) across all doses (Figure 2).
• Intrathalamic delivery of AVB-101 in older Grn−/− mice (28 weeks) reduced levels of microglial activation, as measured by cluster of differentiation 68 (CD68) expression, throughout the central nervous system (CNS) (Figure 3).

Intrathalamic administration of AVB-101 to sheep led to targeted and robust cortical human progranulin (hPGRN) expression without microglial activation

• AVB-101 was administered to sheep via conventional intravenous delivery under anaesthetic guidance. Animals were sacrificed after four weeks or 16 weeks. The treatment was dosed with or without gadolinium-based contrast agent.
• The ovine model was chosen as sheep brains are more comparable to the human brain in size versus the brain of a macaque and sheep are widely used in animal models in neurological research.
• AVB-101 achieved robust hPGRN expression in the primate cortex without microglial activation (Figure 4A) and hPGRN was detected in 60–75% of neuronal nuclear protein (NeuN) positive neurons in the sheep thalamic cortex (Figure 4B).
• Intrathalamic delivery of AVB-101 results in a dose-dependent increase of hPGRN in the cerebral spinal fluid (CSF) and normal to supraphysiological levels of the hPGRN protein in various brain areas affected in FTD (Figure 4C and D).
• hPGRN levels in serum remained undetectable before and after AVB-101 treatment.

Intrathalamic administration of AVB-101 into the thalamus of control and AVB-101-treated young Grn−/− mice. Infused at 8 weeks, imaged 12 weeks post AVB-101 delivery (representative images).

Conclusions

• AVB-101 is a gene delivery vehicle for the treatment of FTD-GRN, with potential for TDP-43 accumulation9.
• AVB-101 was administered to Grn−/− mice to assess impact on FTD-GRN disease pathology – Without intervention, Grn−/− mice develop extensive lipofuscinosis and age-dependent neuroinflammation.
• Intrathalamic delivery of AVB-101 in young Grn−/− mice (8 weeks) reduced age-related levels of lipofuscinosis (subcortex mitochondrial and adrenoleukodystrophy triphosphate synthase (SCMAGAL) across all doses (Figure 2).
• Intrathalamic delivery of AVB-101 in older Grn−/− mice (28 weeks) reduced levels of microglial activation, as measured by cluster of differentiation 68 (CD68) expression, throughout the central nervous system (CNS) (Figure 3).
• Intrathalamic delivery of AVB-101 to sheep led to targeted and robust cortical human progranulin (hPGRN) expression without microglial activation.
• AVB-101 was administered to sheep via conventional intravenous delivery under anaesthetic guidance. Animals were sacrificed after four weeks or 16 weeks. The treatment was dosed with or without gadolinium-based contrast agent.
• The ovine model was chosen as sheep brains are more comparable to the human brain in size versus the brain of a macaque and sheep are widely used in animal models in neurological research.
• AVB-101 achieved robust hPGRN expression in the primate cortex without microglial activation (Figure 4A) and hPGRN was detected in 60–75% of neuronal nuclear protein (NeuN) positive neurons in the sheep thalamic cortex (Figure 4B).
• Intrathalamic delivery of AVB-101 results in a dose-dependent increase of hPGRN in the cerebral spinal fluid (CSF) and normal to supraphysiological levels of the hPGRN protein in various brain areas affected in FTD (Figure 4C and D).
• hPGRN levels in serum remained undetectable before and after AVB-101 treatment.

Intrathalamic delivery of AVB-101 delivered by intrathalamic infusion constitutes a novel and promising approach to address neurodegenerative diseases involving FTD-GRN, with potential for TDP-43 accumulation9.