

Gene therapy as the enabling technology for translating neurotrophic factors: Developing and establishing clinical proof of concept for AAV2-Neurturin in Parkinson's disease

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The two independent fields of gene therapy and neurotrophic factors share a history of both showing early promise as transformational, therapeutic technologies, following by initial difficulties in the clinic. However, significant progress has been made in both fields, supporting the conclusion that gene transfer can now provide the 'enabling technology' to overcome the delivery issues plaguing the translation of neurotrophic factors to the clinic. This may be best exemplified by AAV2-neurturin (CERE-120), a viral-vector construct designed to deliver the neurotrophic factor, neurturin (NRTN) to the degenerating nigrostriatal neurons in Parkinson's disease. A dozen nonclinical publications established the safety of CERE-120 and its ability provide long-term, biologically active NRTN to targeted nigrostriatal neurons. Three clinical trials have been completed (while a 4th, multi-center controlled trial has completed all dosing and is evaluating subjects for further safety and efficacy). Eighty Parkinson's disease (PD) subjects have been dosed with CERE-120 (some over 7 years ago) with no serious safety issues identified, while long-term, targeted expression has been confirmed in human PD brains (4+ years). A prior double-blind, controlled Phase 2a trial established clinical 'proof of concept' via significant benefit on several protocol-prescribed, blinded motor and quality-of-life endpoints at 12months, and an even greater number of endpoints showing benefit at 18months. Although no measure favored the sham control, the trial failed to meet the primary endpoint (UPDRS motor-off at 12months) and another multi-center Phase 2b trial was designed and launched, optimizing the neural targeting and dose level on the basis of insight gained from the initial, Phase 2a controlled trial. This review summarizes how gene therapy solved the major delivery issues for neurotrophic factors, using CERE-120 as a tangible example, and describes in detail, the strategies applied as CERE-120 was developed pre-clinically and clinically, eventually demonstrating clinical 'proof-of-concept'.

Biography

Bartus was trained in the neurosciences, receiving his PhD at age 25 and focusing his 30+ year-career on translational R&D, primarily at multi-national pharmaceutical as well as development-stage biotech companies. However, he has also maintained strong academic/scientific ties, publishing over 250 scientific articles (he is listed by the Institute of Scientific information (ISI) as a "Highly Cited Researcher", placing him in the top 0.5% of all scientists), serving as the founding/inaugural Editor-in-Chief for Neurobiology of Aging (for 10 years) and serving on numerous elite committees and panels for the United States Congress, Secretary of HHS, FDA and several different branches of NIH. He has been involved in the research and development of well over a dozen novel products that advanced into human clinical testing, nearly half of which have received regulatory approval. Since joining Ceregene 10 years ago, Dr. Bartus has been the main architect for all their gene therapy products, and has directed the nonclinical, clinical and regulatory activities from concept to 'clinical proof of concept' for AAV2-NRTN (CERE-120) for Parkinson's disease.

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