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Silencing the Huntington's disease gene: Promises, obstacles and solutions

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The genetic mutation that causes Huntington's disease (HD) was discovered in 1993 after a sustained international effort that focused on the large Venezuelan pedigree. Among the St. Viteros (the Venezuelan HD people), there was an expectation, if not a promise, that the same international efforts would lead to a definitive cure. Among the scientists, the HD gene discovery fueled new research to understand how the mutated huntingtin (htt) protein causes cellular dysfunction and death. New insights into how the abnormal htt protein caused disturbances of many cellular functions (mitochondrial energy production, gene transcription, neurotansmission) led to promises of novel disease-modifying medications. The therapeutic promise of silencing mutant htt expression was demonstrated in a tetracycline-regulated conditional mouse model of HD in 2010. In these mice the HD gene could be turned on and off. When the gene was "on", cellular inclusions of htt protein and motor dysfunction developed. When the gene was "turned off" inclusions disappeared and behavioral changes improved. Blood-brain barrier and other factors make it difficult to deliver large molecules like siRNA or antisense oligonucleottides (ASOs) to brain. Delivery of the siRNA requires a surgical intervention. Entire brain needs to be treated with the siRNA because over time all brain cells become affected; surgical approach must make sure the siRNA selectively suppresses the mutated gene and avoids "off-target" effects. Anti-htt siRNA may affect the normal HD allele. One approach to be discussed in detail is the development in the author's laboratory of nanocarriers that can deliver siRNA or other nucleic acid payloads from nasal epithelium to brain.

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