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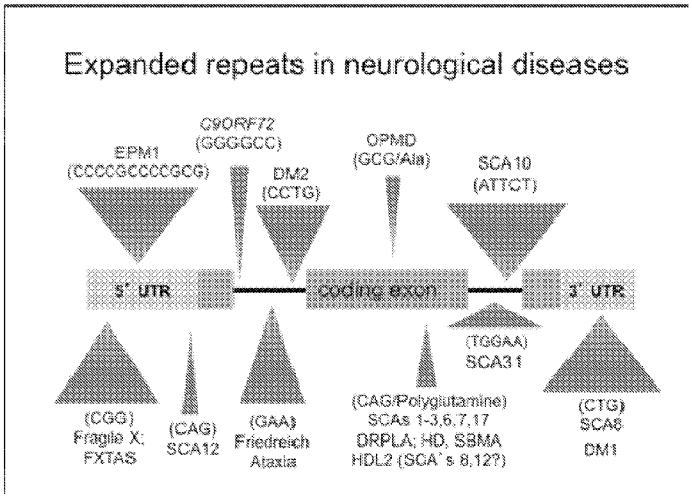


FIG. 1

(57) Abstract: The invention provides for delivery, engineering and optimization of systems, methods, and compositions for manipulation of sequences and/or activities of target sequences. Provided are delivery systems and tissues or organ which are targeted as sites for deliver}'. Also provided are vectors and vector systems some of which encode one or more components of a SIN CRISPR complex, as well as methods for the design and use of such vectors. Also provided are methods of directing SIN CRISPR complex formation in eukaryotic cells to ensure enhanced specificity for target recognition and avoidance of toxicity and to edit or modify a target site in a genomic locus of interest to alter or improve the status of a disease or a condition.

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