High-tech method for uniquely targeted gene therapy

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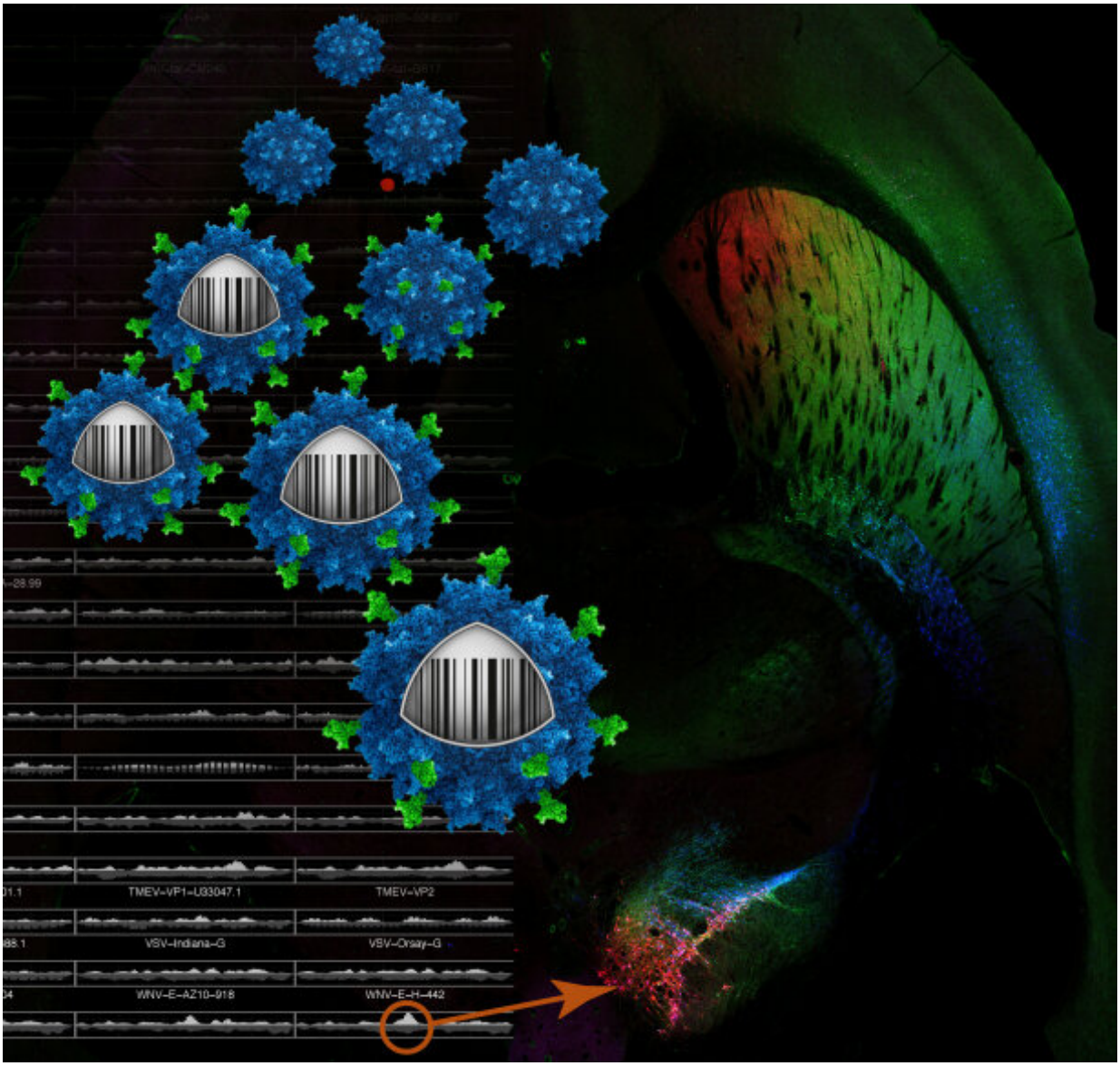

An illustration of when a virus shell reaches the dopamine-producing nerve cells

that die in Parkinson's disease. Credit: Tomas Björklund

Neuroscientists at Lund University in Sweden have developed a new technology that engineers the shell of a virus to deliver gene therapy to the exact cell type in the body that needs to be treated. The researchers believe that the new technology can be likened to dramatically accelerating evolution from millions of years to weeks.

Several of the new revolutionary treatments that have been used clinically in recent years to treat complex diseases—such as spinal muscular atrophy and enzyme deficiency—are based on gene therapy.

With gene therapy, the genetic material is controlled or altered using biological drugs. Examples of this are the gene scissors CRISPR / Cas9 and the so-called CAR-T cells that are used to treat various forms of cancer. This type of treatment is often engineered by growing viruses in the laboratory. The viruses are altered so that they are harmless and can deliver new genetic material to the body's cells, replacing the damaged genome. The virus's own genome, which is required for it to spread, has been completely removed.

In the last five years, neuroscientist Tomas Björklund and his research group have developed a process that tailors these virus shells, or virus capsids, so that they can reach precisely the cell type in the body that needs to be treated, for example nerve cells. The process combines powerful computer simulations and modeling with the latest gene technology and sequencing technology.

"Thanks to this technology, we can study millions of new virus variants in cell culture and animal models simultaneously. From this, we can subsequently create a computer simulation that constructs the most

suitable virus shell for the chosen application– in this case, the dopamine-producing nerve cells for the treatment of Parkinson's disease," says Tomas Björklund, senior lecturer in translational neuroscience at Lund University.

"You can view this as dramatically speeding up evolution from millions of years to weeks. The reason we can do this is that we study each "generation" of the virus in parallel with all the others in the same nerve cells. Unlike evolution, where only the best suited live on to the next generation, we can also learn what makes the virus work less well through this process. This is crucial when building computer models that interpret all the information," he continues.

With the new method, researchers have been able to significantly reduce the need for laboratory animals, as millions of variants of the same drug are studied in the same individual. They have also been able to move important parts of the study from animals to cell culture of human stem cells.

"We believe that the new synthetic virus we succeeded in creating would be very well suited for gene therapy for Parkinson's disease, for example, and we have high hopes that these virus vectors will be able to be put into clinical use. Together with researchers at Harvard University, we have established a new biotechnology company in Boston, Dyno Therapeutics, to further develop the virus engineering technology, using artificial intelligence, for future treatments," concludes Tomas Björklund.

More information: Marcus Davidsson et al. A systematic capsid evolution approach performed in vivo for the design of AAV vectors with tailored properties and tropism, *Proceedings of the National Academy of Sciences* (2019). DOI: 10.1073/pnas.1910061116

Provided by Lund University