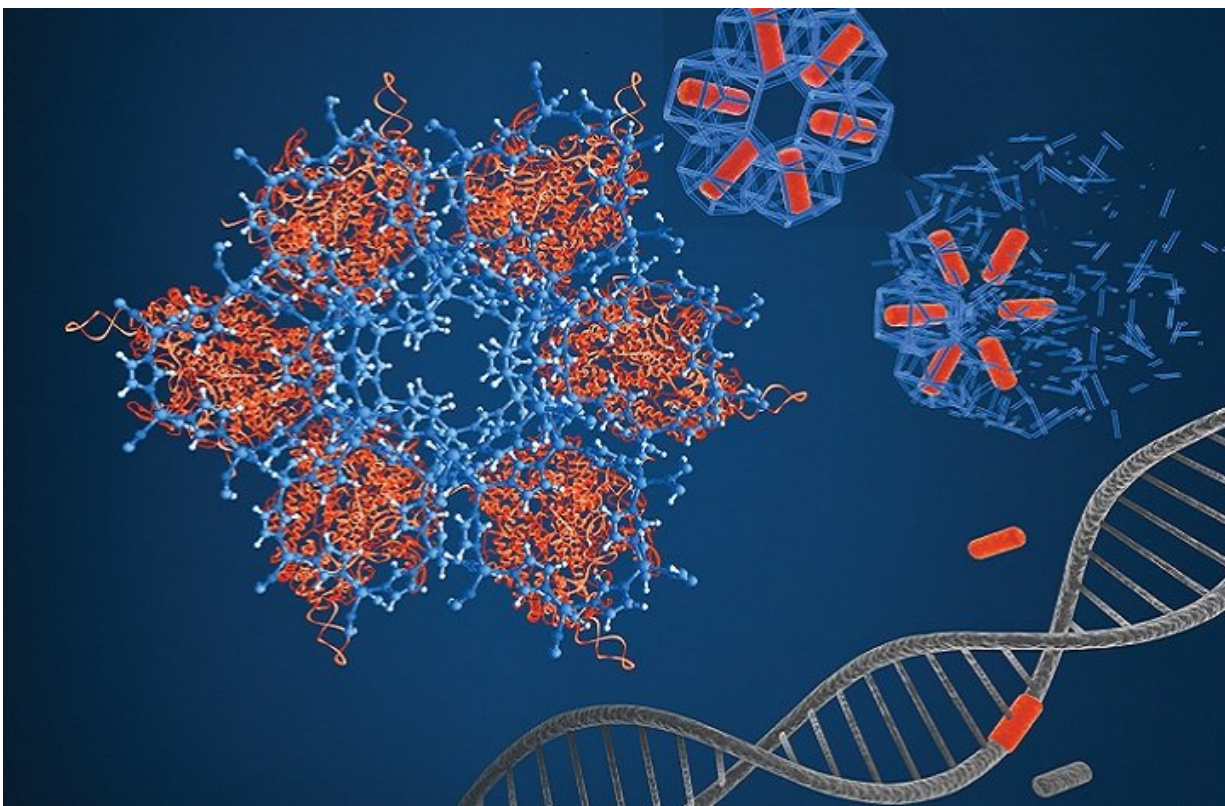


A delivery platform for gene-editing technology

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The zeolitic imidazolate framework forms a cage-like scaffold over the CRISPR/Cas9 machinery. Credit: Reprinted (adapted) with permission from Alsaiani, S.K., Patil, S., Alyami, M., Alamoudi, K.O., Aleisa, F.A., Merzaban, J., Li M. & Khashab, N.M. Endosomal escape and delivery of CRISPR/Cas9 genome editing machinery enabled by nanoscale zeolitic imidazolate framework. *Journal of the American Chemical Society* 140, 143–146 (2018). © 2018 American Chemical Society; KAUST Xavier Pita and Heno Huang

A new delivery system for introducing gene-editing technology into cells could help safely and efficiently correct disease-causing mutations in patients. The system, developed by KAUST scientists, is the first to use sponge-like ensembles of metal ions and organic molecules to coat the molecular components of the precision DNA-editing technology known as CRISPR/Cas9, allowing efficient release of the genome-editing machinery inside the cell.

"This method presents an easy and economically feasible route to improve on the delivery problems that accompany RNA-based therapeutic approaches," says Niveen Khashab, the associate professor of chemical sciences at KAUST who led the study. "This may permit such formulations to be eventually used for treating genetic diseases effectively in the future."

CRISPR/Cas9 has a double delivery problem: For the gene-editing [technology](#) to work like a molecular Swiss Army knife, both a large protein (the Cas9 cutting enzyme) and a highly charged RNA component (the guide RNA used for DNA targeting) must each get from the outside of the cell into the cytoplasm and finally into the nucleus, all without getting trapped in the tiny intracellular bubbles that are known as endosomes.

To solve this problem, Khashab and her lab turned to a nano-sized type of porous material known as a zeolitic imidazolate framework, which forms a cage-like structure into which other molecules can be placed. The researchers encapsulated the Cas9 protein and guide RNA in this material and then introduced the resulting nanoparticles into hamster [cells](#).

The encapsulated CRISPR-Cas9 constructs were not toxic to the cells. And because particles in the coating material become positively charged when absorbed into endosomes, they caused these membrane-bound

bubbles to burst, freeing the CRISPR-Cas9 machinery to travel to the nucleus, home to the cell's genome. There the gene-editing technology could get to work.

Using a guide RNA designed to target a gene that caused the cells to glow green under fluorescent light, Khashab and her team showed that they could reduce the expression of this gene by 37 percent over four days with their technology. "These cage-like structures are biocompatible and can be triggered on demand, making them smart options to overcome delivery problems of genetic materials and proteins," says the study's first author Shahad Alsaieri, a Ph.D. student in Khashab's lab.

The researchers plan to test their system in human cells and in mice, and eventually, they hope, in clinical trials.

More information: Shahad K. Alsaieri et al, Endosomal Escape and Delivery of CRISPR/Cas9 Genome Editing Machinery Enabled by Nanoscale Zeolitic Imidazolate Framework, *Journal of the American Chemical Society* (2017). [DOI: 10.1021/jacs.7b11754](https://doi.org/10.1021/jacs.7b11754)

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