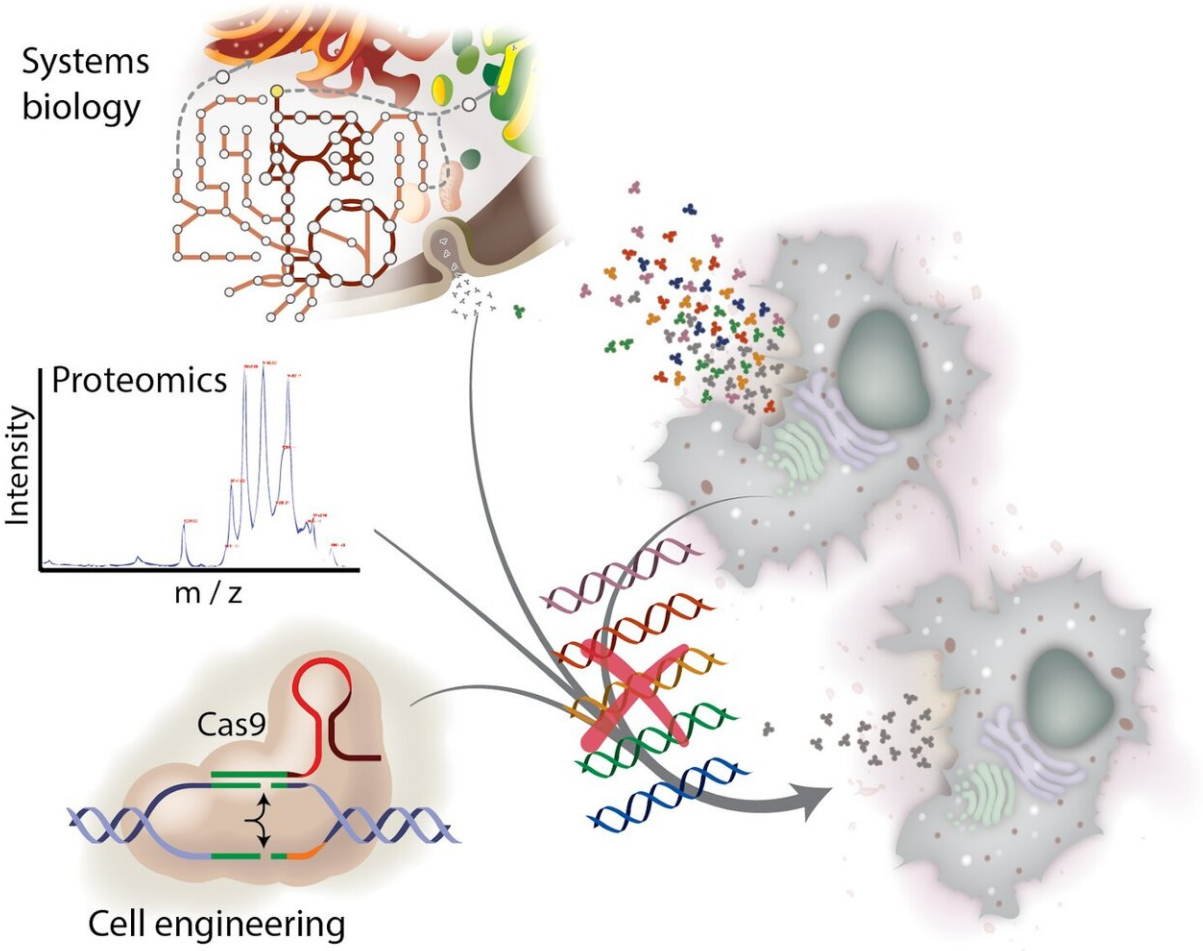
Making recombinant-protein drugs cheaper

April 23 2020, by Daniel Kane



Cleaning up CHO cells for improved drug production involves an interdisciplinary research approach. By cleaning up mammalian cell lines that produce recombinant-protein drugs, researchers forge a path to purer, cheaper drugs that treat cancer, arthritis and other complex diseases. Credit: University of California - San Diego

The mammalian cell lines that are engineered to produce high-value recombinant-protein drugs also produce unwanted proteins that push up the overall cost to manufacture these drugs. These same proteins can also lower drug quality. In a new paper in *Nature Communications*, researchers from the University of California San Diego and the Technical University of Denmark showed that their genome-editing techniques could eliminate up to 70 percent of the contaminating protein by mass in recombinant-protein drugs produced by the workhorses of mammalian cells—Chinese Hamster Ovary (CHO) cells.

With the team's CRISPR-Cas mediated gene editing approach, the researchers demonstrate a significant decrease in purification demands across the mammalian cell lines they investigated. This work could lead to both lower production costs and higher quality drugs.

Recombinant proteins currently account for the majority of the top drugs by sales, including drugs for treating complex diseases ranging from arthritis to cancer and even combating infectious diseases such as COVID-19 by neutralizing antibodies. However, the cost of these drugs puts them out of reach of much of the world population. The high cost is due in part to the fact that they are produced in cultured cells in the laboratory. One of the major costs is purification of these drugs, which can account for up to 80 percent of the manufacturing costs.

In an international collaboration, researchers at the University of California San Diego and the Technical University of Denmark recently demonstrated the potential to protect the quality of recombinant protein drugs while substantially increasing their purity prior to purification, as reported in the study entitled "Multiplex secretome engineering enhances recombinant protein production and purity" published in April 2020 in the journal *Nature Communications*.

"Cells, such as Chinese hamster ovary (CHO) cells, are cultured and

used to produce many leading drugs," explained Nathan E. Lewis, Associate Professor of Pediatrics and Bioengineering at the University of California San Diego, and Co-Director of the CHO Systems Biology Center at UC San Diego. "However, in addition to the medications we want, the cells also produce and secrete at least hundreds of their own proteins into the broth. The problem is that some of these proteins can degrade the quality of the drugs or could elicit negative side effects in a patient. That's why there are such strict rules for purification, since we want the safest and most effective medications possible."

These host cell proteins (HCPs) that are secreted are carefully removed from every batch of drug, but before they are removed, they can degrade the quality and potency of the drugs. The various steps of purification can remove or further damage the drugs.

"Already at an early stage of our research program, we wondered how many of these secreted contaminating host cell proteins could be removed," recounted Director Bjorn Voldborg, Head of the CHO Core facility at the Center of Biosustainability at the Technical University of Denmark.

In 2012 the Novo Nordisk Foundation awarded a large grant, which has funded ground-breaking work in genomics, systems biology and large scale genome editing for research and technology development of CHO cells at the Center for Biosustainability at the Danish Technical University (DTU) and the University of California San Diego. This funded the first publicly accessible genome sequences for CHO cells, and has provided a unique opportunity to combine synthetic and systems biology to rationally engineer CHO cells for biopharmaceutical production.

"Host cell proteins can be problematic if they pose a significant metabolic demand, degrade product quality, or are maintained

throughout downstream purification," explained Stefan Kol, lead author on the study who performed this research while at DTU. "We hypothesized that with multiple rounds of CRISPR-Cas mediated gene editing, we could decrease host cell protein levels in a stepwise fashion. At this point, we did not expect to make a large impact on HCP secretion considering that there are thousands of individual HCPs that have been previously identified."

This work builds on promising computational work published earlier in 2020.

Researchers at UC San Diego had developed a computational model of recombinant protein production in CHO cells, published earlier this year in *Nature Communications*. Jahir Gutierrez, a former bioengineering Ph.D. student at UC San Diego used this model to quantify the metabolic cost of producing each host cell protein in the CHO secretome, and with the help of Austin Chiang, a project scientist in the Department of Pediatrics at UC San Diego, showed that a relatively small number of secreted proteins account for the majority of the cell energy and resources. Thus the idea to eliminate the dominant contaminating proteins had the potential to free up a non-negligible amount of cellular resources and protect drug quality. The authors identified and removed 14 contaminating host-cell proteins in CHO cells. In doing this they eliminated up to 70 percent of the contaminating protein by mass and demonstrated a significant decrease in purification demands.

These modifications can be combined with additional advantageous genetic modifications being identified by the team in an effort to obtain higher quality medications at lower costs.

More information: Jahir M. Gutierrez et al, Genome-scale reconstructions of the mammalian secretory pathway predict metabolic costs and limitations of protein secretion, *Nature Communications*

(2020). DOI: 10.1038/s41467-019-13867-y

Stefan Kol et al. Multiplex secretome engineering enhances recombinant protein production and purity, *Nature Communications* (2020). DOI: 10.1038/s41467-020-15866-w

Provided by University of California - San Diego

Citation: Making recombinant-protein drugs cheaper (2020, April 23) retrieved 3 May 2024 from https://phys.org/news/2020-04-recombinant-protein-drugs-cheaper.html

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