# Biochemists streamline construction method for human artificial chromosomes

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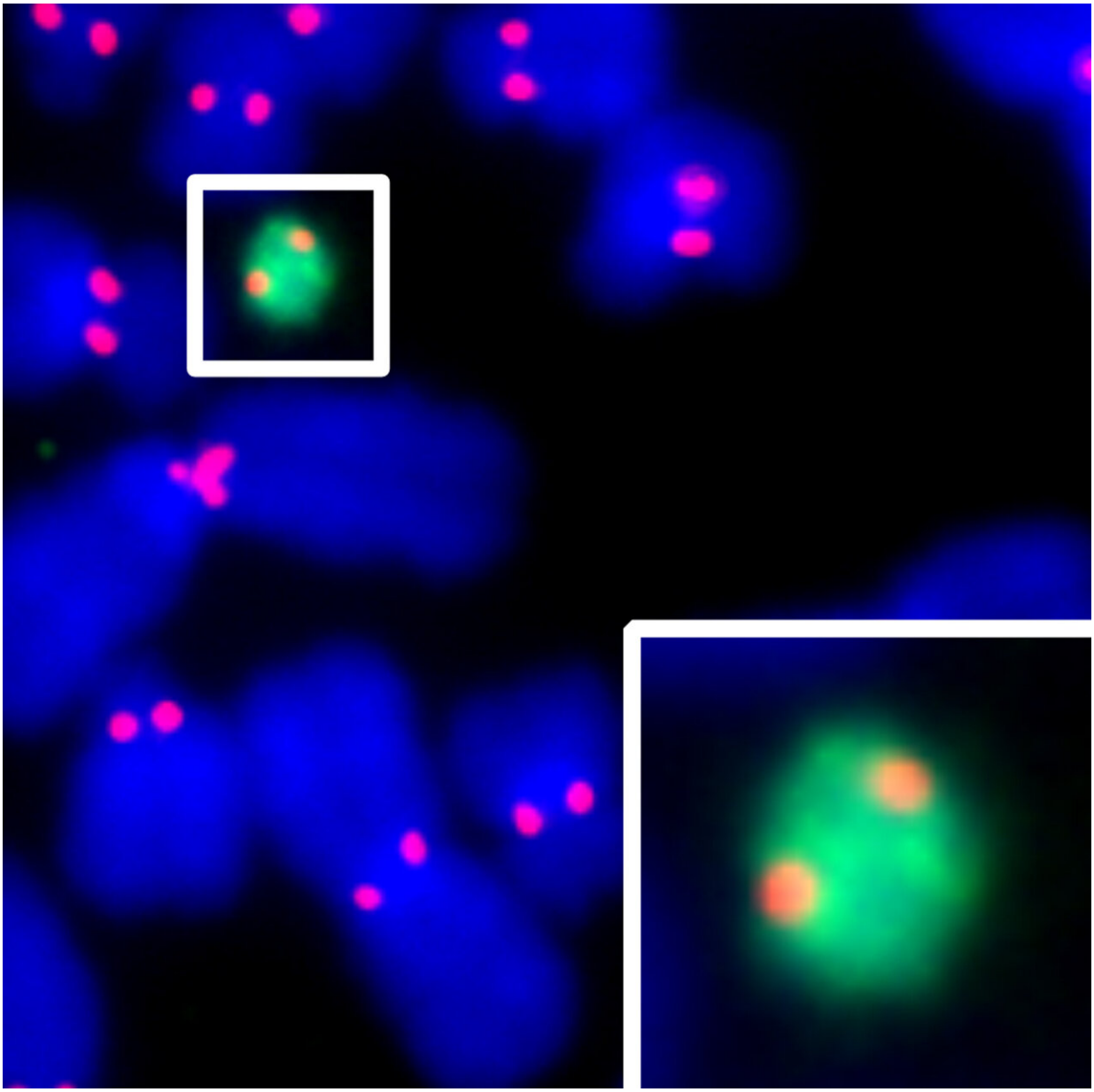

Human artificial chromosome (HAC, green) with two sister centromeres (red), similar to that of the natural host chromosomes (blue). Credit: Glennis Logsden, Penn Medicine, *Cell*

For the past 20 years, researchers have been trying to perfect the construction of human artificial chromosomes, or HACs for short. In a paper published today in *Cell*, Penn researchers describe a new way to form an essential part of the artificial chromosome, called the centromere, by bypassing the biological requirements needed to form a natural one. Simply put, they biochemically delivered a protein called CENP-A directly to HAC DNA to simplify the building of a HAC in the lab.

"Our developments streamline the construction and characterization of HACs to aid in efforts to make synthetic whole human chromosomes," said Ben Black, Ph.D., a professor of Biochemistry and Biophysics in the Perelman School of Medicine at the University of Pennsylvania, who has dedicated decades to understanding the process.

HACs essentially function as new mini-chromosomes carrying engineered sets of genes that are inherited alongside a cell's natural set of chromosomes. Bioengineers envision HACs performing all sorts of jobs, including delivering large proteins for gene therapy or transporting suicide genes to fight cancer.

"Think of the HACs we build now as model-sized chromosomes," said first author Glennis Logsdon, Ph.D., a doctoral student in Black's lab at the time of the study and now a postdoctoral fellow at the University of Washington. "By being able to build a centromere on a HAC in a more straightforward way, we are closer to scaling up to full-size chromosomes."

Inheritance of HACs from mother to daughter cells during division is key, and this speaks to the importance of the centromere—the cinched area of duplicated chromosomes responsible for holding together pairs of "sister" chromosomes created when cells divide. Without it, whole chromosomes can be lost during cell division.

For cell replication to occur, human centromeres are not simply coded by a DNA sequence, unlike baker's yeast long used synthetic chromosome research. For example, mammals depend on the CENP-A protein to specify centromere location on chromosomes for precise cell division.

Prior attempts to form HAC centromeres in test tubes only happened rarely when they "encountered" CENP-A, and this unlikely event only occurred at highly repetitive DNA sequences on the HAC genome. "Highly repetitive DNA, however, is the scourge of molecular biologists because it is the most difficult to work with using the approaches we have now, which are designed for non-repetitive DNA," Black said.

Black's team bypassed the repetitive DNA altogether by delivering CENP-A directly to the HAC DNA. Their work-around involves "forcing" CENP-A to associate with non-repetitive DNA sequences to form a new centromere for the HAC.

"We've taken our centromere bypass method to make a fully functional HAC without the cloning nightmares that repetitive centromere DNA has presented to mammalian chromosome engineers through the last two decades," Black said. "Building on our success, we and others in the synthetic chromosome field will now have a real chance to attain what has only been achieved so far in yeast cells."

One of the next steps for this area of synthetic biology will be to link the Black lab's centromere to sets of genes that others have designed. This

step-by-step construction project is the goal of the Human Genome Project-Write, a collaboration to build that life-size synthetic chromosome. The Penn team's contribution will help speed creating useful research and clinical tools based on synthetic chromosomes.

**More information:** Logsdon et al. "Human Artificial Chromosomes that Bypass Centromeric DNA," *Cell* (2019). DOI: 10.1016/j.cell.2019.06.006

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