T-cell biofactories find, fight disease in one fell swoop

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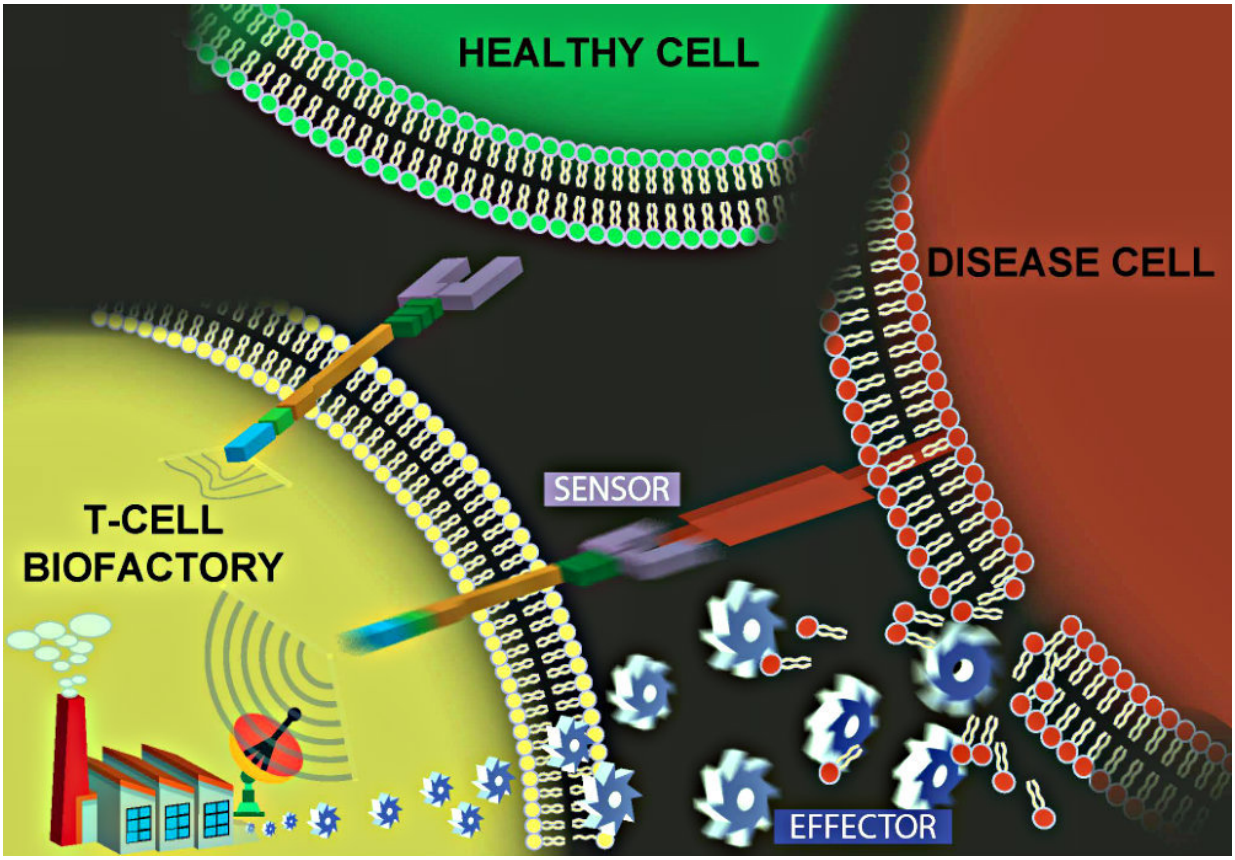

The sensor molecule on the surface of the T-cell biofactory interacts with the diseased cell but not the healthy cell. The factory then produces therapeutic effector proteins that attack and destroy the diseased cell. Credit: Parijat Bhatnagar, SRI International, Menlo Park, CA.

NIBIB-funded researchers have transformed T cells into drug factories engineered to find cells carrying specific diseases in the body—and then produce therapeutic proteins localized to the diseased cells.

Senior author Parijat Bhatnagar, Ph.D., director of cell-based medicine at the SRI International Center for Chemical Biology, Menlo Park, California, and his colleagues engineered the T-cell "biofactories" to directly target cell-based disease in the body while minimizing damage to surrounding healthy cells. The work is reported in the September issue of *Advanced Biosystems*.

"The researchers have taken the T cell that moves through the body and destroys cells that appear abnormal and added some extra therapeutic sense-and-respond functionality," explains David Rampulla, Ph.D., director of the program in Synthetic Biology for Technology Development at the National Institute of Biomedical Imaging and Bioengineering. "This new cell-based tool directs the T-cells to target specific diseases. The work is an excellent example of synthetic biology, which involves the re-design of existing, natural biological systems for tailored purposes."

"The T cell naturally moves into tissues from the blood, a process known as extravasation, patrolling for abnormal cells," explains Bhatnagar. "We have engineered a new signaling pathway in the T cell that capitalizes on this innate extravasation capability. It transforms the T cell into a cell-based drug delivery system, that we call a T-cell biofactory. This can be engineered to seek out a specific disease in an individual, such as a viral infection or a certain type of cancer and then synthesize a therapeutic protein to neutralize the disease."

For example, to kill a cell carrying a flu virus, the researchers would insert a DNA sequence that encodes a flu-recognizing protein on the surface of the T-cell biofactory. That module is called the sensor. The

other important DNA sequence is the one that encodes for a therapeutic protein that specifically neutralizes the flu virus. That module is called the effector. The effector is activated when the sensor recognizes the flu-infected host cell. These DNA sequences are modular and can be exchanged to redirect the T-cell biofactory to different disease targets.

The first test of activity and specificity of T-cell biofactory in an animal model was demonstrated in mice carrying human ovarian tumors. For the test, the sensor module was a protein that binds to the ovarian cancer cells. Instead of an effector protein that kills tumors, the researchers inserted a gene that makes a bioluminescent reporter protein. The bioluminescence allowed the team to visualize whether binding of the T-cell biofactory to the ovarian cancer cells caused the effector protein to be released within the tumor. The control biofactory did not contain the sensor module.

Twenty-four hours after injection, the test T-cell biofactory released significantly higher amounts of reporter protein compared with the control biofactory. The bioluminescence peaked at 48 hours and continued to be expressed for 72 hours.

"This first test demonstrated the feasibility of a T-cell based system that can be directed against a specific cell-based disease to express an effector protein at the site of disease," said Bhatnagar."We are enthusiastic about our initial results and the promise of a system that avoids systemic infusion of drugs, where they often damage healthy as well as diseased tissues. Our reprogrammable system will instead synthesize therapeutic proteins only when the biofactory encounters the diseased cell, limiting damage to normal tissues."

More information: Claire E. Repellin et al. Modular Antigen-Specific T-cell Biofactories for Calibrated In Vivo Synthesis of Engineered Proteins, *Advanced Biosystems* (2018). DOI: 10.1002/adbi.201800210