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A rational drug engineering approach could breathe new life into drug development

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A new strategy for engineering protein fusions—to make specific cell-targeted drugs without side effects—could enable a safer, more potent class of protein drugs. A team at the Wyss Institute for Biologically Inspired Engineering designed a better variant of the widely-used drug erythropoietin (EPO), showing how rational design can improve in vivo efficacy and safety of protein therapeutics, reduce potential side effects, and also accelerate new drug development. The findings were published online April 25 in the *Proceedings of the National Academy of Sciences* journal.

"Our concept is completely general," said Pamela Silver, Ph.D., the study's corresponding author, who is a Wyss Institute Core Faculty member, the Eliot T. and Onie H. Adams Professorship of Biochemistry and Systems Biology at Harvard Medical School (HMS), and a founder of the HMS Department of Systems Biology. "We can reduce the toxicity of approved protein drugs, and may also be able to rehabilitate protein fusion drugs that have so far failed in clinical trials due to unacceptable side effects."

Like many drugs, protein therapeutics can cause unwanted side effects. Such has been the case for erythropoietin (EPO), a natural hormone secreted by the kidneys to increase red blood cell production, of which laboratory-synthesized variants have been widely used to treat anemia stemming from kidney disease or chemotherapy.

However, EPO not only activates red blood cell production but can also

cause dangerous complications, such as blood clotting and boosted blood vessel growth. As a result, patients treated with EPO often suffer from higher rates of heart attack, stroke, and accelerated tumor growth. Therefore, the FDA has issued its strictest warning - a black box label advising of serious hazards associated with the drug - for the use of EPO drugs. To combat this problem, the Wyss team rationally designed a more effective, multi-part drug molecule.

"Compared to currently available EPO drugs, our molecule is engineered to prevent EPO from binding to and activating cells that promote side effects such as blood clotting or tumor growth," said Jeffrey Way, Ph.D., Wyss Institute Senior Staff Scientist and the senior author on the study. "This cell-targeted EPO approach demonstrates a new theoretical basis for the rational design of engineered protein fusion drugs."

First, the team genetically mutated EPO protein, reducing its ability to bind to cell receptors. Then, using a chain of amino acids as a flexible linker, they attached mutated EPO to a specific antibody fragment. The antibody fragment was selected because it uniquely binds to the cell membranes of red blood cell precursors while avoiding other types of blood cells that control clotting and vessel growth.

When the team's fusion protein molecules were delivered to mice, the antibody fragments piloted toward and bound to the membranes of red blood cell precursors, towing along EPO molecules on the other end of their linkers. In such close proximity to the surface of the cells, a high concentration of tethered EPO bounced around until they ultimately toggled into place on the cell's receptors. In this way, side effects were avoided and only red blood cell production was increased.

"Our rational design strategy is unique compared to current industry approaches," said the study's first author Devin Burrill, Ph.D., who is a National Institutes of Health (NIH) National Research Service Award

(NRSA) Postdoctoral Fellow at the Wyss Institute. "Our goal is to use our method to advance predictive drug design and minimize the time between drug concept and commercialization."

"The principles of synthetic biology influenced our efforts," said Wyss Core Faculty member James Collins, Ph.D., co-author on the study, who is Termeer Professor of Medical Engineering & Science and Professor of Biological Engineering at the Massachusetts Institute of Technology (MIT)'s Department of Biological Engineering. "In drug development, the focus is typically on increasing the strength of interaction with a drug target, but here we found that weakening an interaction was useful. This illustrates how we need to adopt alternative, non-traditional approaches if we want to build complex, multi-part therapeutics."

The specific, cell-targeted approach could be applied quite broadly. The Wyss team has unveiled not only a novel design of their "targeted EPO", but also "targeted interferon alfa", a cancer drug that can otherwise cause side effects including flu-like symptoms, mood fluctuations, and depression.

"This is another great example of how using a synthetic 'bottom-up' engineering approach and leveraging the power of biological design - this time at the scale of individual molecules interacting on cell membranes - can lead to breakthrough technologies for medicine that overcome limitations that hold back more conventional approaches," said Wyss Institute Founding Director Donald Ingber, M.D., Ph.D., who is also the Judah Folkman Professor of Vascular Biology at Harvard Medical School and the Vascular Biology Program at Boston Children's Hospital and Professor of Bioengineering at Harvard's John A. Paulson School of Engineering and Applied Sciences.

More information: Targeted erythropoietin that selectively stimulates red blood cell expansion in vivo, *PNAS*,

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