Scientists engineer one protein to fight cancer and regenerate neurons

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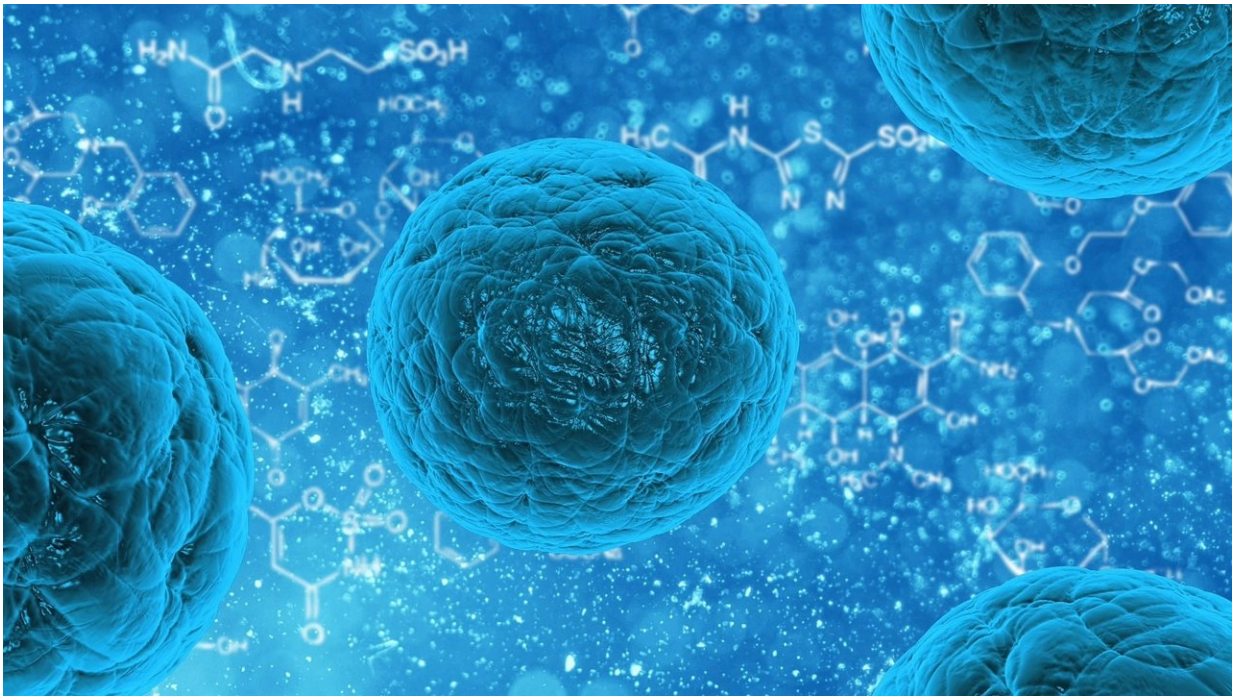

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Our lungs, bones, blood vessels and other major organs are made up of cells, and one way our bodies keep us healthy is by using protein messengers known as ligands that bind to receptors on the surfaces of cells to regulate our biological processes. When those messages get garbled, it can make us ill with a host of different diseases.

Now a team led by Stanford bioengineer and department chair Jennifer Cochran has tweaked one ligand in slightly different ways to produce two startlingly different results. One set of alterations caused neuronal cells to regenerate, while different tweaks to the same protein inhibited lung tumor growth.

The experiments her team described in the *Proceedings of the National Academy of Sciences* were performed on rat and human cells or in mice that model actual diseases and are still far from being tested in humans. But the results show how scientists are becoming increasingly adept at tinkering with the body's protein-based control mechanisms to help vital organs heal themselves.

"These proteins can hopefully one day be used to treat neurodegenerative disease, as well as cancers and other disorders such as osteoporosis and atherosclerosis," Cochran said.

Her lab studies how ligands and receptors work together to deliver messages to cells, and how these interactions can be engineered to create potent therapeutic agents. Shape is the critical concept. Like all proteins, ligands and receptors are made up of many different amino acids strung together like pearls and folded into distinct three-dimensional shapes. A ligand with the right shape fits its matching receptor like a key fits a lock.

By using sophisticated molecular engineering techniques, the researchers can change the lineup of amino acids in a ligand, essentially making millions of keys that they then screen to see which might unlock its matching receptor in some desirable way. A key that fits better and trips the lock more efficiently -scientists call this a superagonist—might transmit messages instructing cells to grow more robustly. Bioengineering can also be used to turn ligands into antagonists—keys that also fit the receptor lock, but in a way that blocks the signal and thus

might retard a function like cell growth.

Last year, Cochran collaborated with UC San Francisco cancer researcher Alejandro Sweet-Cordero to publish a paper showing how an engineered version of the receptor protein CNTFR, helped stop lung tumor growth in rodents.

The new experiments build on that work as a research team led by graduate student Jun Kim engineered the ligand known as CLCF1 which binds with the CNTFR receptor. By making one set of amino acid alterations in CLCF1, Kim turned that ligand into a superagonist. When they added this superagonist to a tissue culture of injured neuronal cells, the engineered CLCF1 increased the messaging signals that promote the growth of axons, the fibers that transmit nerve impulses, suggesting that this modified ligand was encouraging wounded neurons to regenerate themselves.

Conversely, Kim and his fellow researchers showed that, by introducing a few additional amino acid alterations to CLCF1, they could turn this ligand into a potent antagonist that could inhibit the growth of lung tumors in mice, suggesting a different possible medicinal use for this variant of the molecule.

Cochran has spent her career developing novel engineered proteins as therapeutic candidates for oncology and regenerative medicine applications. Several of the molecules discovered in her lab have moved forward into early through late stage pre-clinical development, with her most advanced therapeutic, a treatment for ovarian and kidney cancer, now in human trials. She is optimistic that engineered ligands and receptors will continue to prove to be a promising class of drugs to fight illness and maintain health.

"I have long been fascinated with how proteins function as nature's

molecular machines, and how the tools of engineering allow us to shape protein structure and function with the creativity of an artist, in this case using amino acids as our palette."

More information: Jun W. Kim el al., "Engineering a potent receptor superagonist or antagonist from a novel IL-6 family cytokine ligand," *PNAS* (2020). www.pnas.org/cgi/doi/10.1073/pnas.1922729117

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