New strategy develops two prototype drugs against cancer, retinal diseases

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A comprehensive drug development strategy that starts with extensive screening of potential targeting agents and then narrows down to a small-molecule prototype has yielded two potential drugs that block cancer-promoting pathways in novel ways, a team led by scientists at The University of Texas M. D. Anderson Cancer Center reports in two papers published back-to-back online at the *Proceedings of the National Academies of Science*.

"The conceptual advance here is to demonstrate how to go rapidly from screening to structural-functional analysis to drug prototype in a few years," said co-senior author Wadih Arap, M.D., Ph.D., of the David H. Koch Center at M. D Anderson.

"The practical outcome is a pair of new drug candidates, one that acts as a decoy to inhibit a cancer-promoting pathway and another that blocks angiogenesis, the development of new blood vessels, which has the potential to treat both cancer and retinopathies that cause blindness," said co-senior author Renata Pasqualini, Ph.D., also of the David H. Koch Center.

The strategy begins with the screening of millions of peptides - short combinations of at least two amino acids, the building blocks of proteins. Once a peptide is found that binds the target, a durable drug called a peptidomimetic is made from short combinations of non-natural amino acids.

For proof of concept, the team targeted the epidermal growth factor receptor pathway (EGFR) and the vascular endothelial growth factor receptor pathway (VEGFR).

EGFR is overexpressed on the cell surfaces of a number of cancers, including lung, colon, and head and neck. Epidermal growth factor binds to the receptor and causes cells to divide. It is currently treated with two types of drugs, antibodies that block the receptor and small kinase inhibitors. VEGFR is overexpressed in the cancer vascular system and is central to the formation of new blood vessels (angiogenesis) that accompany tumor growth

Drugs reduce tumor volume, blood vessel growth in mice

The researchers created a decoy that lures EGF away from its receptor. In a mouse model of head and neck cancer, mice that received the decoy had a median tumor size half that of those in control groups.

They also demonstrated that the drug prototype could also serve as a decoy for cetuximab, an antibody drug that blocks the pathway by plugging into the EGFR. When the peptidomimetic and cetuximab were introduced into human colon and head and neck cancer cell lines, the small drug inhibited the antibody's action.

For VEGFR, the team discovered a peptide that binds to the receptor, inhibiting angiogenesis. In a series of mouse model experiments, treated mice showed reductions in the number of blood vessels ranging from 37 percent to 72 percent.

In an animal model of retinopathy - overgrowth of blood vessels in the eye that can cause blindness - mice treated with the peptide had a 59

percent reduction in angiogenesis compared to control mice. A separate test of the peptidomimetic in an eye drop formulation resulted in a 53 percent reduction in abnormal retinal blood vessel growth.

This raises the possibility of developing an easily administered treatment for diabetic retinopathy or retinopathy of prematurity, Arap said. Preclinical studies continue for both cancer and retinopathy applications. Using small molecules to bind to the receptor site is a new approach to inhibiting VEGFR.

Screening, winnowing and developing the peptides

The group's approach begins by screening the target receptors with a phage display library used by Arap and Pasqualini. This method screens billions of viral particles that each display a different peptide on its outer coat to find those that fit into the receptor like a key goes into a lock.

Candidate peptides are next winnowed by using structural and functional analysis. Once a peptide is identified and tested, the researchers take an additional step to synthesize a new version of the peptide more suited for use as a drug.

L-amino acids and proteins are the building blocks of life but are easily degraded by cellular protein recycling machinery, making peptide-based drugs more vulnerable to destruction. Through a process called retro-inversion, the group chemically synthesizes a mirror image peptidomimetic using D amino acids along with a reversed peptide sequence. The resulting products are more durable but still target the receptor.

For example the peptide that targets VEGFR is called RPL, letters that represent three natural amino acids that make up the peptide. The retro-inverted D-peptidomimetic is D(LPR). For the EGFR decoy, the natural

peptide CVRAC becomes the D-peptidomimetic D(CARVC).

The two prototype drugs will need to be further refined in preclinical models and later tested in clinical trials before they can become available for general use.

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