Designing drugs and their antidotes together improves patient care

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Imagine a surgical patient on a blood-thinning drug who starts bleeding more than expected, and an antidote that works immediately - because the blood thinner and antidote were designed to work together. Researchers at Duke University Medical Center have engineered a way to do this for an entire, versatile class of drugs called aptamers and published their findings in *Nature Medicine*.

"With any anticoagulant, you are trying to reduce your chances of having clotting because it can lead to a heart attack or stroke during treatment," said Bruce Sullenger, Ph.D., senior author and Vice Chair for Research and Joseph W. and Dorothy W. Beard Professor of Surgery. Yet bleeding is a common side effect during and after treatments that require anticoagulation therapy such as surgery or angioplasty.

These new antidotes may give doctors a way to quickly and precisely put the brakes on an anticoagulant if bleeding becomes a problem or neutralize other adverse events or toxicities.

Duke researchers have just completed a series of successful clinical trials in patients taking a blood-thinner aptamer and an antidote engineered to reverse the effects of the aptamer.

"We have shown that this type of antidote can reverse the action of any of the aptamer drugs, and there are many aptamers in development," Sullenger said. Their approach amounts to a universal antidote to the entire aptamer family. "We predict that this advance will significantly

expand the number of diseases that can be more safely treated using antidote-controllable therapeutic agents," he said.

The new approach, called RNA-based aptamer technology, "provides the opportunity to make safer drugs," said Sullenger, who also directs the Duke Translational Research Institute. "And now that we can engineer a universal antidote for aptamers, we can in principle for the first time afford to provide additional control over drugs for patients and their physicians."

Aptamers are oligonucelotides, short stretches of nucleic acid that bind to a specific target molecule. If a patient takes an aptamer drug, the drug is the only free oligonucleotide in the body.

The researchers studied eight aptamer drugs and showed that the antidotes they introduced could reverse the activity of any of the drugs, regardless of the sequence, shape or target of the drug.

One advantage of aptamer drugs, as opposed to antibody-based drugs, is that nucleic acids aren't typically recognized by the human immune system as foreign agents. Aptamers do not generally trigger an immune response, Sullenger said.

"This technology could be applied to any oligonucleotide-based therapeutic that is free in a patient's circulation," said lead author Sabah Oney, Ph.D., formerly with the Sullenger laboratory and now a senior scientist at b3bio, a biotechnology company Sullenger helped co-found in the Research Triangle Park.

"With the ever-increasing number of such drugs in clinical trials, we believe that this discovery can have very broad applications and improve the safety profile of these therapeutics," Oney said. "This could be rapidly translated into the clinic, and lead to a whole new class of safer

therapeutic agents."

To date, one aptamer has been approved by the U.S. Food and Drug Administration, a drug for macular degeneration, a cause of blindness. Several others are being tested and developed for use in cardiovascular, hematology and cancer patients.

"This research potentially represents the next frontier of controlled therapeutics using nucleic acids as highly selective antithrombotics and neutralizing polymers," said Richard C. Becker, M.D., Professor of Medicine in the Duke Divisions of Cardiology and Hematology and a scientist in the Duke Clinical Research Institute (DCRI) who has worked on clinical trials with the aptamer antidotes. "The translational platform for antithrombotic therapy pioneered by the Sullenger laboratory in collaboration with the DCRI underscores the unlimited potential of clinicians and scientists collaborating with purpose and commitment to advance patient care."

"Future optimization should further improve the potency of sequestering the aptamers from circulation, which will then spur the development of many new aptamer drugs," said Kam Leong, a James B. Duke professor of biomedical engineering and co-author of the study.

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