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Scientists profile FDA-approved drugs to potentially treat hundreds of genetic disorders

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Nonsense-mediated RNA decay, or NMD, is an evolutionarily conserved molecular mechanism in which potentially defective messenger RNAs, or mRNAs, are degraded. By reducing errors in gene expression, it serves as an RNA quality control and gene regulatory mechanism. Its disruption can lead to neurological disorders, immune diseases, cancers, and other pathologies.

A team of biomedical scientists at the University of California,

Riverside, has designed a simple and robust method to determine the effects of drugs on NMD. The researchers profiled all current Food and Drug Administration-approved drugs to identify NMD modulators, which could potentially help treat hundreds of disorders associated with NMD.

"These drugs, by modulating cellular NMD efficiency, can potentially alleviate symptoms of genetic disorders caused by nonsense mutations," said Sika Zheng, an associate professor of biomedical sciences in the School of Medicine, who led the study that appears in the journal *Molecular Therapy - Nucleic Acids*. "Two examples are Duchenne muscular dystrophy and cystic fibrosis."

Cells have surveillance mechanisms to target defective mRNAs. Without these mechanisms, which operate in the cell nucleus and cytoplasm, errors in the synthesis of proteins could result. NMD is one of the best-studied RNA surveillance pathways. The term "nonsense" in its name refers to a type of mutation. NMD plays an important role in cell cycle regulation, cell viability, and DNA damage response. It also serves as a barrier to virus infection.

"NMD degrades aberrant mRNAs and prevents their expression," Zheng said. "More than 20% of monogenic diseases—which means hundreds of rare diseases, including sickle cell anemia—are attributed to genetic mutations directly targeted by NMD. Excessive aberrant mRNAs also play a role in Lou Gehrig's disease and myelodysplastic syndromes. Therefore, NMD modulation can help modify diseases outcomes. Several NMD modulators we identified can be tested in animal models of aforementioned diseases."

Zheng explained that current FDA-approved drugs are not known to target NMD. They have not been examined closely for their effect on cellular NMD activity. For this study, Zheng and his team first

developed a robust sensitive assay or test, termed AS-NMD assay, that quantitatively measures cellular NMD activity. They then obtained a library of 704 FDA-approved drugs. They treated cells with each of these drugs and measured the cellular responses using the AS-NMD assay.

"We wanted to know whether the FDA-approved drugs can be repurposed to modulate NMD," he said. "So we treated cells with each FDA-approved drug and tested whether cellular NMD activity was affected. We found one drug had a strong effect on NMD; four drugs had mild effects. We now have solid information for the effect of 704 FDA-approved drugs on NMD. What made this possible is the method we developed, without which profiling 704 drugs to such a precision level would be unthinkable. Old methods are either too tedious or not precise enough."

Zheng believes the NMD-modulatory drugs should be further investigated for their molecular targets and be optimized and repurposed for NMD-associated diseases.

"Nonsense mutation-associated disorders are orphan diseases with a wide range of varied symptoms," he said. "We should think of targeting their commonality: the associated NMD pathway."

Next, the research team plans to do animal testing of some drug candidates. They also plan to scale up their assay to profile larger chemical libraries.

Zheng was joined in the study by Jingrong Zhao, Zhelin Li, Ruchira Puri, Kelvin Liu, and Israel Nunez at UCR; and Liang Chen at the University of Southern California.

More information: Jingrong Zhao et al, Molecular profiling of

individual FDA-approved clinical drugs identifies modulators of nonsense-mediated mRNA decay, *Molecular Therapy - Nucleic Acids* (2021). DOI: 10.1016/j.omtn.2021.12.003

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