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Effective antiviral drugs for multiple influenza A strains could work by attacking combined RNA targets

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Influenza A is one of the most prolific and diverse viruses on Earth; its ability to rapidly mutate to resist treatment challenges the management of future pandemics. Now, A*STAR researchers have identified thousands of segments of RNA that could act as potential new antiviral drug targets, and provide protection against all strains of influenza A.

During a pandemic, which could take only two months to spread across the world, the creation of a new vaccine to target a specific strain of influenza A could take up to six months. A new avenue being explored includes antiviral drugs created using so-called antisense oligonucleotides (AONs)—synthetic polymers that can block disease progression by altering viral RNA activity.

"The next influenza A pandemic is inevitable, given how easy it is for an animal-based subtype to mutate and infect humans," says Keng Boon Wee at the A*STAR Institute of High Performance Computing, who worked on the project with scientists across Singapore. "To make use of AONs, we need to identify specific RNA target sites found across all viral subtypes and strains. In the case of influenza A this means searching through almost 36,000 strains. We used computer simulations to hunt for RNA target sites in all current influenza A subtypes."

At first, the team thought they might find one target site that would protect against all subtypes. It became apparent, however, that this was

simply impossible, because no single site is shared by all RNA sequences. Instead, the researchers realized they should search for 'pairs' of sites that, if targeted simultaneously by AONs, could provide multi subtype protection.

"Our initial search uncovered thousands of potential pairs," says Wee. "While we were pleasantly surprised that only two target sites are sufficient to address all strains from all subtypes simultaneously, we were very excited at the enormous potential to combine these pairs to create even more targets."

The team discovered that carefully-selected pair combinations could significantly increase a new drug cocktail's 'hedge factor'—the time it takes for a virus to become drug resistant. By targeting pair combinations, antiviral drugs based on AONs could be developed that can provide long-term protection against all influenza A subtypes and strains.

"Even when we remove targets that cannot be used due to unwanted effects, the potential target space is huge," says Wee. "Our technique is also applicable to other viruses, including HIV. We hope to work with experimental virologists to validate our combinatorial pairs and develop corresponding RNA therapeutics."

More information: Keng Boon Wee et al. Discovery of Influenza A Virus Sequence Pairs and Their Combinations for Simultaneous Heterosubtypic Targeting that Hedge against Antiviral Resistance, *PLOS Computational Biology* (2016). DOI: 10.1371/journal.pcbi.1004663

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