COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

A New Class Of RNA For Immediate, Broad-spectrum & Precision Antiviral Protection

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Problem: There is an urgent need to develop broad-spectrum countermeasures that can safely protect warfighters against unpredictably evolving viral threats (both natural and engineered). State-of-the-art antiviral countermeasures are variant-specific small molecules, antibodies, or vaccines. Each time a new viral variant emerges, these (billion-dollar) countermeasures developed against last year's threats are rendered unprotective and obsolete—threatening warfighter safety and operational readiness. Host-directed therapeutics have been proposed as promising alternatives to current narrow-spectrum countermeasures. Yet, the off-target toxicity associated with systemically targeting essential human proteins has limited the long-term and prophylactic use of host-directed therapies, even when FDA-approved. This is a specific concern for warfighters who need to maintain peak physiology and who often require prophylaxis to maintain operational readiness. Prophylaxis is essential for acute viral threats—especially aerosolized threats—which are often transmitted before individuals know they are infected and can initiate therapeutic treatment to control infection and spread. In summary, existing host-acting therapeutics lack the safety profiles required for antiviral preparedness and existing direct-acting therapeutics are bespoke and variant-specific (and impossible to modularly adapt to new threats in time to prevent deadly outbreaks).

Solution: Here we describe a next-generation platform technology that fuses the safety (i.e. precision) advantages of direct-acting therapeutics and the efficacy (i.e. broad-spectrum) advantages of host-acting therapeutics—in single molecules that can be developed against any viral threat in less than 14 days. Known as encrypted RNA (encRNA), the platform-derived countermeasures are direct-acting nucleic acids that encode host-acting immunotherapeutic proteins—but only produce these immunomodulatory payloads when directly bound, transcribed, and amplified ("decrypted") by viral protein domains (e.g. replicase domains) conserved across a viral species. Given their dependence on viral infection, encRNAs remain translationally silent and inactive in uninfected cells and individuals. encRNAs are therefore designed to have no impact on warfighter performance when administered as prophylactics. encRNAs can also be administered as variant-proof therapeutics after viral infections. Autonomous has shown that a single encRNA confers resistance-proof efficacy against every variant of a viral pathogen—whether administered prophylactically or therapeutically. Autonomous has also developed an inhalable lipid nanoparticle (LNP) to make encRNA self-administrable via handheld, FDA-approved nebulizers. The resulting encRNA-LNPs are shelf-stable at 4 °C—to enable stockpiling and far-forward use. In vivo Validation: Strikingly, a single inhaled dose of a platform-derived encRNA-LNP immediately protects against lethal viral infections in multiple preclinical animal models—for multiple viral threats (e.g. SARS-CoV-2 and influenza). Platform Capability: In a DTRA-funded (BAT-CAVE) effort, we developed pan-variant encRNA candidates against currently untreatable alphavirus threats (VEEV and EEEV) in just 14 days. These countermeasures were developed from (digital) viral genome sequences alone—without the need to obtain viral or nucleic acid samples. The same plug-and-play platform has now been used to rapidly develop encRNA-LNP candidates against 8 different viral families, including: Nipah, Ebola, Marburg, and pandemic influenza. Each platform-derived encRNA leverages the same LNP, host-acting payload, and CMC. Notably, the same encrypted RNA platform can be used to encode and control virtually any protein payload, enabling the possibility of programmable RNA immunity in vivo. Further, by conferring protection that is not variant-specific, encRNAs could enable us to protect against the future—against the unknown and inevitable threats that cannot be predicted or hard-coded into any existing vaccine or antibody technology.

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