

COMBATting EMERGING BIOLOGICAL THREATS – PREPARING FOR THE FUTURE TODAY

Extremophile Derived Natural Products (eden) To Combat Future Threats

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Nature has long been the greatest producer of antimicrobial chemistry. However, rediscovery has plagued natural products drug discovery, causing many programs to be abandoned. Our EDeN Platform unlocks natural products from untapped sources such as Yellowstone hot springs and mud pots, which contain incredible biosynthetic diversity. We have created diverse metagenomics libraries from a variety of geothermal features (DTRA-funded), which can be screened in a high throughput manner for natural products that inhibit desired viral protein targets.

We have successfully demonstrated this "ligand fishing" in pooled metagenomic extracts with the SARS-CoV-2 N protein (DHA-funded). We have found 10 unique molecules with strong affinity for the N protein which have been reconfirmed by a second binding assay (fluorescence polarization). The N protein is a structural protein which plays a key role in viral replication, but has not been a readily "druggable" target. For this reason, we are creating PROTACs (proteolysis targeting chimeras) molecules with our hits, so that the N protein will be ubiquitinated and subsequently degraded in the host cell, thus blocking viral replication. We now have a platform in place to 1. produce viral target proteins, 2. screen for inhibitors with EDeN, 3. purify hit natural products, 4. produce PROTACs molecules with hits, 5. test for potency and toxicity.

To broaden the spectrum of our hits, we will continue to focus on viral structural proteins which are highly conserved and not typically targeted by drug companies. We will also expand our ligand fishing step to screen multiple versions of the target protein from AI-based models of protein evolution. The AI-based models will predict likely protein structures from future threats so that hits can be discovered in advance. EDeN hits from this type of high throughput screening will be well positioned to move forward in development as broad spectrum antivirals to protect the warfighter against future viral threats.