HOW SEA SQUIRTS CAN HOLD THE KEY TO TREATING COVID-19

The development of vaccines and therapeutics against the novel SARS-CoV2 virus have dominated global news and drug development efforts since the novel coronavirus has changed the lifestyle of almost every person on the planet. The current standard of care for patients infected with SARS-CoV2 includes oxygen therapy and ventilation to assist in respiration along with dexamethasone (a steroid) and remdesivir, an antiviral therapy that has so far shown limited efficacy. Given the high incidence rate and hospitalization rate, there is a strong momentum to repurpose existing antiviral therapies that have known safety profiles to treat COVID-19.

Typical antiviral drugs target viral proteins, so the long-term efficacy of these drugs can reduce if the targeted viral proteins mutate such that they are no longer inhibited by the antiviral therapy. A new approach to developing therapies against SARS-CoV2 is to target host cell machinery. Coronaviruses like SARS-CoV2 are large RNA viruses so once they infect the cell via attachment of the spike protein to cell surface receptors, the first step is for the genomic RNA to be uncoated from the viral capsid and translated to functional proteins. Some of the proteins form the viral replication transcription complex, while others are involved in mRNA translational control and proteolytic cleavage. Essentially, the virus hijacks the host cell translational machinery to start its replication cycle.

A recent report from Kris White and colleagues at the Icahn School of Medicine at Mount Sinai showcases an example of repurposing an oncology therapeutic, plitidepsin (Aplidin®), for COVID-19[1]. Plitidepsin inhibits eEF1A or eukaryotic Elongation Factor 1A that is a critical component of the translation machinery. Plitidepsin is a member of the didemnins class of compounds and is a cyclic depsipeptide (which is a peptide that forms a cyclic structure via an ester bond). It was originally extracted from *Aplidium albicans*, a rare sea squirt found in the shallow waters off the coast of Ibiza, Spain and is being clinically tested to treat multiple myeloma patients in conjunction with dexamethasone. In a phase III trial, patients treated with plitidepsin and dexamethasone had a 35% reduction in disease progression compared to dexamethasone alone[2]. Additionally, plitidepsin was found to have a good safety profile with the most common side effects being fatigue, muscle pain and nausea[3].

Plitidepsin was tested in *in vitro* and *in vivo* models of SARS-CoV2 and was found to be over 25-fold more potent than remdesivir that has received emergency use authorization to treat patients with COVID-19. Through the use of drug resistant mutant eEF1A, the researchers identified that the effect on SARS-CoV2 was due to the inhibition of eEF1A function in the translational machinery. Plitidepsin was also found to reduce viral protein expression in infected cell lines. Following the cell line data, the researchers tested the effects of plitidepsin in 2 mouse models of SARS-CoV2 and showed reductions in viral load and lung inflammation in plitidepsin treated mice[1]. PharmaMar, the company that developed plitidepsin for cancer indications has recently completed a clinical trial where the efficacy of plitidepsin on COVID-19 was evaluated on 46 COVID-19 patients who had required hospitalization. The study results were dramatic and showed an average 70% reduction in viral load 15 days post treatment along with reduction in inflammation and clinical improvement.

Based on these reports that demonstrate efficacy, plitidepsin appears to be a viable therapeutic for COVID-19 with a good safety profile. This is another example of a therapy identified in a marine animal that can be a game changer in the fight against disease.

References:
[1] https://science.sciencemag.org/content/early/2021/01/22/science.abf4058
[2] https://news.cancerconnect.com/multiple-myeloma/aplidin-improves-progression-free-survival-in-multiple-myeloma-_luAUQxHPkGA65_jh4Z-0Q
[3] https://pubmed.ncbi.nlm.nih.gov/31240472/