Anti-cancer drug derived from fungus shows promise in clinical trials

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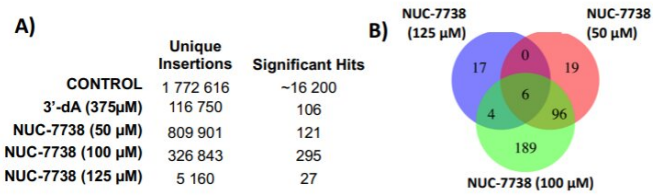

Figure 1. Genome wide haploid genetic screen identifies genes necessary for the activity of 3'-dA and NUC-7738. A) Number of unique gene trap sense insertions and significant gene hits found in the haploid genetic screen. B) Venn diagram indicating the overlap of significant hits found for NUC-7738 treatment. Credit: 10.1158/1078-0432.CCR-21-1652

A new industry-academic partnership between the University of Oxford and biopharmaceutical company NuCana as found that chemotherapy drug NUC-7738, derived from a Himalayan fungus, has 40 times greater potency for killing cancer cells than its parent compound.

Oxford University researchers have worked in collaboration with industry leaders NuCana to assess a novel chemotherapy drug derived from a fungus. A study in *Clinical Cancer Research* has shown that the new drug NUC-7738, developed by NuCana, has a up to 40 times greater potency for killing cancer cells than its parent compound, with limited toxic side effects.

The naturally-occurring nucleoside analog known as Cordycepin (a.k.a 3'-deoxyadenosine) is found in the Himalayan fungus Cordyceps sinensis and has been used in traditional Chinese medicine for hundreds of years to treat cancers and other inflammatory diseases. However, it breaks down quickly in the blood stream, so a minimal amount of cancer-destroying drug is delivered to the tumor. In order to improve its potency and clinically assess its applications as a cancer drug, biopharmaceutical company NuCana has developed Cordycepin into a clinical therapy, using their novel ProTide technology, to create a chemotherapy drug with dramatically improved efficacy.

Once inside the body, Cordycepin requires transport into cancer cells by a nucleoside transporter (hENT1), it must be converted to the active anti-cancer metabolite, known as 3'-dATP, by a phosphorylating enzyme (ADK), and it is rapidly broken down in the blood by an enzyme called ADA. Together, these resistance mechanisms associated with transport, activation and breakdown result in insufficient delivery of anti-cancer metabolite to the tumor. NuCana have utilized novel ProTide technology to design a therapy that can bypass these resistance mechanisms and generate high levels of the active anti-cancer metabolite, 3'-dATP, inside cancer cells.

ProTide technology is a novel approach for delivering chemotherapy drugs into cancer cells. It works by attaching small chemical groups to nucleoside analogs like Cordycepin, which are then later metabolized once it has reached the patient's cancer cells, releasing the activated drug. This technology has already been successfully used in the FDA approved antiviral drugs Remsidivir and Sofusbuvir to treat different viral infections such as Hepatitis C, Ebola and COVID-19.

The results of the study published in *Clinical Cancer Research* suggest that by overcoming key cancer resistance mechanisms, NUC-7738 has greater cytotoxic activity than Cordycepin against a range of cancer cells.

Oxford researchers and their collaborators in Edinburgh and Newcastle are now assessing NUC-7738 in the Phase 1 clinical trial NuTide:701, which tests the drug in patients with advanced solid

tumors that were resistant to conventional treatment. Early results from the trial have shown that NUC-7738 is well tolerated by patients and shows encouraging signs of anti-cancer activity.

Further Phase 2 clinical trials of this drug are now being planned in partnership with NuCana, to add to growing number of ProTide technology cancer drugs that are being developed to treat cancer.

More information: Hagen Schwenzer et al, The novel nucleoside analogue ProTide NUC-7738 overcomes cancer resistance mechanisms in vitro and in a first-in-human Phase 1 clinical trial, *Clinical Cancer Research* (2021). DOI: 10.1158/1078-0432.CCR-21-1652

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