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Cancer drug developer aims to transform treatment

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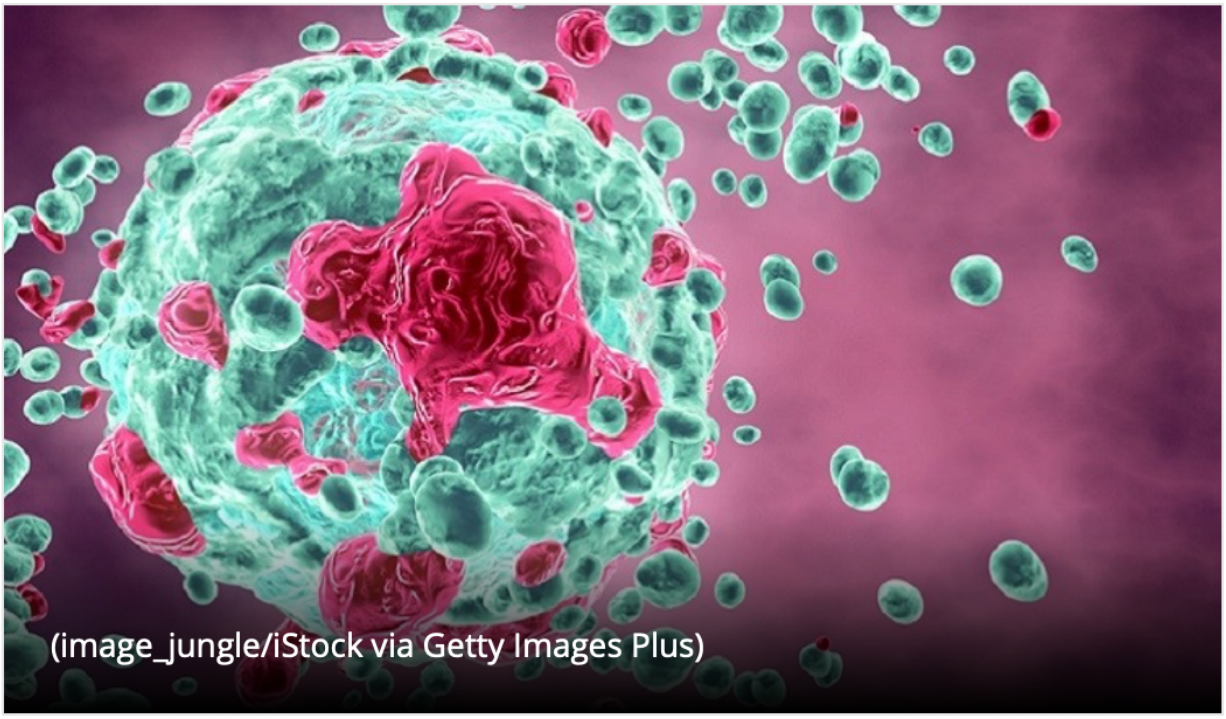

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A leader from clinical-stage pharma firm NuCana shares promising results for its ProTides therapies and hopes the drugs can elevate outcomes for patients.

Cancer continues to be one of the deadliest forces on the planet. According to the International Agency for Research on Cancer, in 2018 there were 18.1m new diagnoses around the world, and about 9.5m cancer deaths were reported.

Considering the toll cancer takes, it is hardly surprising the number of new oncological drugs created and trialed—of the 53 novel drugs approved by the US Food and Drug Administration (FDA) last year, 20 had indications related to cancers. However, while researchers continue to create new drugs that improve outcomes and tweak existing therapies, the field is not without its limitations.

Hugh Griffith of NuCana recently spoke with Outsourcing-Pharma about the firm's ProTides therapies, results from trials, and the hopes that the treatments will offer greater hope for patients.

OSP: Could you please share some more detail about the limitations of some of the most commonly used chemotherapy drugs? What problems do these limitations create for pharma firms, caregivers, patients, etc?

HG: Chemotherapy remains the cornerstone of treatment for patients with cancer. While novel medicines like immunotherapies and targeted therapies have changed the way some cancers are treated, the vast majority of cancer patients receive chemotherapy at some stage of their treatment.

Chemotherapies are still widely used because they can be very effective, but they do have limitations including toxic side effects, the fact that cancers have innate or acquired resistance to them, and the often inconvenient administration schedules they require. These limitations create a variety of problems for patients and caregivers.

> The toxicity profiles of many chemotherapies can have a detrimental impact on the quality of life of patients and can require patients to take other treatments to alleviate the symptoms caused by the side effects. Additionally, some patients cannot tolerate certain chemotherapies as the side effects are so debilitating and they need to switch to different therapies which may not be as effective at treating their cancer.

Cancers can also develop resistance to chemotherapies or in some cases they will already have these resistance mechanisms in place which means that they are resistant to chemotherapy before they have been exposed. In each of these scenarios, chemotherapy will not be as effective and patients must either switch to another therapy that may be less effective at treating their particular cancer type or stop therapy altogether. Both of these scenarios are likely to result in worse outcomes for patients.

Some chemotherapies, such as fluorouracil (5-FU), have poor pharmacokinetic profiles and thus require administration via a continuous infusion through a portable infusion pump which can be uncomfortable, inconvenient, and limits the activities of patients.

In the case of 5-FU, patients typically require a 46-hour continuous infusion every two weeks and are required to visit their clinic to have the infusion pump attached and then again to have the pump removed. This has a significant impact on the quality of life of patients and adds a substantial burden to healthcare systems compared to other administration schedules such as shorter infusions that can be completed within a few hours in a single visit.

OSP: Please tell us about how ProTides overcome these challenges, more efficiently target resistance mechanisms, and hopefully yield better results/outcomes for cancer patients.

Hugh Griffith, CEO, NuCana

HG: Nucleoside analogs are one of the most widely used classes of chemotherapy used to treat cancer, but cancer resistance mechanisms exist that limit their use. The three key cancer resistance mechanisms are:

- Uptake- Insufficient expression of membrane transporters which are required for cellular uptake
- Activation- Rate-limiting phosphorylation step which is required for activation
- Breakdown- Susceptible to breakdown releasing toxic by-products

ProTides have specific properties that allow them to overcome these cancer resistance mechanisms:

- ProTides' properties allow them to enter cells independently of transporters
- ProTides are pre-activated thus bypass the rate limiting phosphorylation step that is required for nuceloside analogs
- ProTides are resistant to breakdown by enzymes such as deaminases and dehydrogenases

As a result, ProTides generate much higher levels of the active anti-cancer metabolites inside tumor cells compared to nucleoside analogs, giving ProTides the potential to be more effective than the current standards of care. Furthermore, as ProTides are not broken down by deaminases and dehydrogenases, they avoid the generation of some of the toxic metabolites that can result in unwanted side effects.

OSP: Please tell us about ProTides' history, chemistry's use in other therapeutic areas (you mentioned Gilead's hepC and HIV drugs), and types of cancer you're most hopeful about the potential with.

HG: ProTide technology was invented by our late chief scientific officer Christopher McGuigan, professor at Cardiff University. The unique feature of his discovery was the specific combinations of aryl, ester, and amino acid groups (phosphoramidate motifs) that protect the activated nucleotide analog. This phosphoramidate chemistry approach is the key to the ProTide technology.

Every ProTide grouping is distinct, and Professor McGuigan and his team synthesized and tested thousands of compounds in order to identify the optimal phosphoramidate motif for each underlying nucleoside analog.

Professor McGuigan's work helped lead to the development of several FDA-approved antiviral ProTides, including Gilead's sofosbuvir, (Sovaldi), and tenofovir alafenamide fumarate (TAF), a ProTide transformation of tenofovir (Viread). The Sovaldi and TAF franchises were the two most successful drug launches in the history of medicine as measured by their first twelve months of revenue post-launch.

Most recently Gilead's ProTide remdesivir (Veklury), was approved for the treatment of patients with COVID-19.

ProTides are rationally designed to overcome the limitations of nucleoside analogs. Our researchers have invested over two decades of work in designing, synthesizing, and screening ProTides designed to overcome the key cancer cell resistance mechanisms and improve the survival outcomes for patients. Having created thousands of ProTides, we have considerable insight in understanding phosphoramidate chemistry and how our selected ProTides are able to exert their anti-cancer effects.

We currently have three ProTides in the clinic: Acelarin, NUC-3373, and NUC-7738.

Acelarin is a ProTide transformation of gemcitabine so the obvious cancer types for it are cancers where gemcitabine is commonly used such as biliary tract cancer, bladder, breast, lung, pancreatic and ovarian cancer. However, it has the potential to be used in a wide variety of cancers beyond those traditionally treated with gemcitabine.

NUC-3373, our second ProTide to enter clinical development, is a ProTide transformation of 5-FU so the obvious cancer types for it are cancers where 5-FU is commonly used such as colorectal, gastric, pancreatic, head/neck, and breast cancer. It also has the potential to be used in a wide variety of cancers beyond those traditionally treated with 5-FU.

NUC-7738 is our third ProTide to enter clinical development and it is a transformation of a novel nucleoside analog called 3'-deoxyadenosine (3'-dA) often referred to as cordycepin. 3'-dA has potent anticancer activity *in vitro* against a broad range of cancer cell lines but was never successfully developed in the clinic due to its rapid breakdown by adenosine deaminase which is present in high levels in human serum.

We are currently in a Phase I study with NUC-7738 and have seen promising activity in multiple cancer types. We feel it has the potential to be successfully developed in a wide range of solid and hematologic malignancies.

OSP: What can you tell us about the colorectal and biliary cancer trials? Any details about scope, progress, etc. would be welcome.

HG: We are currently investigating NUC-3373 in patients with colorectal cancer in a three-part Phase Ib study called NuTide:302.

In Part 1 of the study, we have assessed weekly (q1w) and alternate weekly (q2w) doses of NUC-3373 with or without leucovorin (LV). The objective of this part of the study was to ascertain whether LV has an impact on the PK and safety profile of NUC-3373.

LV had no impact on NUC-3373's favorable PK and safety profile so will be included in regimens that will be explored in Parts 2 and 3 of the study. Although Part 1 of the study was aimed at exploring PK and safety endpoints, we also observed that NUC-3373 has promising anti-cancer activity. These observations are all-the-more encouraging because the patient population included in Part 1 are heavily pretreated, having received on average four prior lines of chemotherapy and as such they typically do not respond well to subsequent therapy and are very sensitive to side effects.

We are currently in Part 2 of the study which is assessing increasing doses of NUC-3373 in weekly and alternate weekly schedules in combination with leucovorin and either oxaliplatin (NUFOX) or irinotecan (NUFIRI). The objective of this part of the study is to establish the dose and schedule of NUC-3373 in combination with leucovorin and oxaliplatin or irinotecan to be further examined in expansion cohorts in Part 2.

Part 3 of the study will open in parallel to the expansion cohorts in Part 2 and will establish the optimal combinations of NUFOX and NUFIRI with EGFR and VEGF inhibitors.

Due to the promising efficacy and safety signals that we have observed in the NuTide:302 study, we are in the process of amending the protocol to allow the inclusion of additional patient populations. We are also planning a Phase III study which we plan to initiate by the end of 2021. The exact design of the study and the timing of initiation will depend on meetings we will have with the FDA.

NuTide:121 is our ongoing Phase III study investigating Acelarin plus cisplatin compared to gemcitabine plus cisplatin in patients with advanced biliary tract cancer as their first-line treatment. This is a significant unmet medical need because no drug has ever been approved for this patient population and the median life expectancy for a newly diagnosed biliary tract cancer patient with the current global standard of care, gemcitabine plus cisplatin, is only 11.7 months.

Our NuTide:121 study will enroll up to 828 patients in approximately 125 sites in 15 countries and continues to recruit well despite the challenges that the COVID pandemic has created. Our study is primarily measuring overall survival, but also includes interim analyses based on overall response rate that may enable an accelerated approval filing in the US. We are on course to recruit a sufficient number of patients in 2021 to enable the first interim analysis to occur in 2022.

OSP: Congratulations on the $80m funding raise; could you please tell us what that infusion of funds says about your company and the potential of ProTides?

We successfully raised $80m in a follow-on public offering on Nasdaq in September 2020. The financing was led by Abingworth, one of the world's leading health care investors and a new investor to NuCana.

Abingworth's managing partner, Bali Muralidhar, has joined our Board. We also attracted a broad mix of existing and new institutional investors. These funds provide us with a robust cash position and we believe will enable us to file new drug applications for our first two ProTides, Acelarin, and NUC-3373.

We think that being able to attract such a group of investors to NuCana is a testament to the potential that our ProTides have to transform the treatment of patients with cancer. We believe it is also a vote of confidence in the strategy and the team that we have assembled to bring these important new compounds through clinical development and to the market.

OSP: Do you have anything to add—about the company, ProTides, other products/projects NuCana has in the works, or anything else?

HG: At NuCana, our mission is to pioneer a new era in oncology. We strive to do this by applying our ProTide technology to transform some of the most widely prescribed chemotherapy agents, nucleoside analogs, into more effective and safer medicines.

Our ProTide technology can be applied to many existing and novel nucleoside analogs. So, it is a true platform that can generate many potential new medicines. We currently have three compounds in the clinic and are working on many others in pre-clinical development. Of the three clinical-stage assets, two are transformations of widely used anti-cancer medicines, and the third is a transformation of a very novel nucleoside analog that has exquisite anti-cancer properties but was not successfully developed historically due to resistance mechanisms that were encountered.

By applying our ProTide technology, we believe we have overcome these limitations and have already seen some very promising results in patients with cancer.