ProTide man Chris McGuigan hopes to make NuCana the next Gilead

Edinburgh, U.K., 15th July 2015: There aren't many privately held UK-based pharmaceutical companies that can boast of appointing an inventor behind one of the world's biggest selling drugs to its management team. But Nucana's new CSO is Professor Chris McGuigan, the man behind ProTides, a technology used in drugs such as Gilead Sciences' Sovaldi (sofosbuvir). Here he tells Scrip what prompted him to cut down on his academic commitments for the first time in his career to take up a management position at a little-known oncology firm.

"The ProTide technology has been successfully applied to antiviral nucleosides, by companies such as Gilead, with remarkable improvements in efficacy and tolerability. Nucana is advancing this into oncology and the results from the recently completed Phase I/II study have shown the potential of ProTides to define a new era in cancer treatment," he explains.

Prof McGuigan has been working on ProTides for 30 years. "The first paper disclosing the ProTide structure was published in 1995. So it is exactly 20 years since I filed the patent and disclosed the structure," he says.

The hepatitis C glory went to Gilead, but for a while it was all looking very different.

"I worked very extensively with GlaxoSmithKline in Research Triangle Park North Carolina on hepatitis B, then with Roche Palo Alto on hepatitis C, and then we had quite a breakthrough which we licensed out to a start-up company in Atlanta called Inhibitex. We had a really promising clinical candidate that flew through Phase I and Phase II trials for hepatitis C. For a while it looked like we had the most powerful hepatitis C drug in the class with Inhibitex. The company raised around $99m to fund that compound, it was called '189, and in the end the firm was bought out by BMS [Bristol-Myers Squibb] for $2.5bn, so it was a good return on investment for them, but sadly the drug didn't progress as there were some toxicity issues. But the son of '189, inspired by it, is the drug that became Sovaldi. Other pharma continued applying our ProTide technology to their drugs in parallel to the work Inhibitex was doing. And as fate would have it, ours crashed in Phase III and theirs went through Phase III and led to the $10bn Sovaldi. So Sovaldi is a ProTide."

The same technology invented by Prof McGuigan and powering Sovaldi powers Nucana's lead drug candidate, Acelarin, "and powers the whole Nucana family." Acelarin is a ProTide version of gemcitabine.

With ProTides established in the antiviral space, Prof McGuigan started working with Nucana about six years ago to apply the ProTide technology to oncology. "I've got an exclusive deal so all my oncology ProTide work is done solely through Nucana," says Prof McGuigan.

April 2014 saw Nucana announce a hefty $57m series B financing which included Sofinnova Ventures, Sofinnova Partners, Morningside Ventures, Alida Capital International and the Scottish Investment Bank.

So what prompted Prof McGuigan to join the company now?

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"I am offered management positions relatively often and I generally do not take them up in order to concentrate on feeding the pipeline of drugs, although I sometimes take on board positions. But for the first time, I have taken a cut in my university position in order to release me formally for one day a week so I can support Nucana. I've done it because I am extremely excited about the prospects for Acelarin and extremely enthusiastic about the management team [Hugh Griffiths and Chris Wood, formerly of Bioenvision, which was acquired by Genentech] and I want to make sure that I am doing everything I can to get this dug through. What I've seen from our recent data suggests it's going to transform the chemotherapy of cancer. "

Nucana completed a Phase I/II trial of Acelarin in a wide range of tumor types and reported the data at this year's ASCO meeting. "With a known drug like gemcitabine there are certain tumor types that it's used for. What was striking but makes sense from our mechanism is when you ProTide it, it then starts accessing different tissues and appears effective against different tumor types. When you look at the range of tumors [in the Phase I/II Acelarin trial] where we had really good disease control, it's much broader than the indications that gemcitabine is currently used for. For example, gemcitabine is not at all famous for its use in gynecological and ovarian cancer, whereas ovarian patients did really well in our trial."

According to Prof McGuigan, there were 18 patients with gynecological cancers in the Phase I/II trial, of whom 14 took two courses of the drug. Of those, 13 out of 14 had disease control "which is remarkable because they all came into the trial without disease control. To stop the tumors growing and in two cases achieve a partial response, shrinking the tumors 30% or more, is staggering."

A little over half of the patients that came into the trial showed some response. "If you look at those that received two courses, it goes up to 78% achieving disease control. In these early first in man trials, you're getting patients rather late. You're fourth or fifth or sixth line, after all other options have been used, and often the patients are quite advanced. Obviously as we move to Phase III and beyond, we're hoping that a label might allow us to access patients earlier, second line for example, and they might not be so sick and we might get a better impact."

Nucana plans to begin a 328-patient Phase III trial in pancreatic cancer shortly, another in ovarian cancer towards the end of this year or early next year, and a third in biliary cancer in 2016.

And it's not all just about Acelarin. "There is a second-in-class that's just about to enter the clinic, and a third in class that's just left my lab. In fact we're hoping to have four ProTides for different tumor types in clinical trials over the next couple of years. I know ProTides better than anyone else in the world so I am in a good position to try and advise the company as we go forward."

Modified DNA components

So what exactly are ProTides? Prof McGuigan explains further. "They are based around nucleoside analogues, so slightly modified components of DNA. Nucleoside drugs dominate the antiviral space, and even in oncology, around one in five drugs are nucleosides, such as gemcitabine from Eli Lilly."

But nucleoside drugs have several problems that limit their use. In particular, the tumor cell – either innately or after a few rounds of therapy – learns how to evade the activity of the drug and presents resistance so the patient may do well for a few months and then will fail to respond.

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"In particular, there are three steps that the cancer cell very quickly learns to overcome the drug. One is that all of these drugs require a transporter protein to drag them in to the cell. They can't go in passively as they're not lipid soluble. If that protein is absent or the cell learns to down-regulate it, the drug can't get into the cancer cell and that is the end of the drug's utility. Then once inside, many of these drugs are hit by deactivating enzymes so with gemcitabine there is a particular one called deaminase, and again patients that up-regulate the deaminase do very poorly on the drug. And then finally, all of these nucleoside drugs need phosphorylating in order to work and that is done by a kinase. Again, patients that don't have a kinase do really poorly, patients that have the kinase do very well. So a combination of the three: transporter, deaminase and kinase, predicts how well a patient will do. "

It is estimated that 70-90% of cancer patients have at least one resistance mechanism to nucleoside analogs. "In pancreatic adenocarcinoma, if a patients lack one of those three, they will live for about three months, but if they have all three, they will live for about 12 months," says Prof McGuigan.

"With ProTides I designed a new motif which in principle can be bolted on to any nucleoside drug to overcome all three problems. So first of all we bolt a phosphate on already, so we don't need the kinase, then we protect or mask the phosphate so it doesn't need a transporter. These agents can zip into cells like lipids. Then the lipid we've put on, the protecting group, protects it from the deaminase, which can't recognize it so can't deactivate it."

But the final piece of the puzzle "and what has taken us 20 years," was to design the protecting group, such that it would fall off inside cells and liberate the active phosphate. "That was really difficult," he says.

Personalizing ProTides

As Nucana nears registrational trials, it is working actively to find diagnostic technologies that will help identify a patient "as lacking a transporter, as having high levels of deactivating enzymes, as lacking a kinase, as then they would be clearly indicated towards our therapy," explains Prof McGuigan. "We would hope that our therapies would do better than existing therapies for that patient population."

Partnering

Nucana has gone public with its first-in-class (a ProTide version of gemcitabine) and second-in-class compound (a ProTide version of 5FU [fluorouracil]), and they are both old drugs that have long been off patent.

It hasn't gone public with its next two programs. "With these drugs, we may well be in a territory where a drug is not off patent or indeed an agent that is not an approved drug. There are a number of cases where we have taken a candidate which has either failed in the clinic or not yet reached clinic and we find that when we bolt the ProTide on that we can change its properties." Partnering in these circumstances is on the table.

"Management is constantly looking at what is the best way forward to maximize shareholder value. At the moment the company is very well capitalized. Sofinnova and others have been very supportive and there's a lot of money in the bank. And Nucana is very careful how it spends money."

Prof McGuigan believes the company has enough cash in the bank to get through to registration without another fundraising. "We're in a good position to go it alone, and I am extremely excited. Acelarin looks to me like an approvable drug."