AACR20: translating oncolytic viruses in the clinic, an interview with Yuman Fong

We spoke with Dr. Yuman Fong (Chief of Surgery, City of Hope cancer center, CA, USA) about his recent work presented at the American Association for Cancer Research (AACR; 27–28 April 2020), titled, 'A first-in-human phase 1 ascending, multiple dose, safety and tolerance study of Vaxinia (CF33-hNIS), a novel chimeric oncolytic poxvirus, administered intratumorally or intravenously in adult patients with mixed advanced solid tumors (MAST)'. Fong's research interests over the last 25 years have been designing viruses and cells to be used for anticancer therapy.

Can you tell us about the work you will be presenting at the AACR Virtual Annual Meeting I?

To set the background, we have had data that viruses kill cancer for over 100 years. However, up until around the 1960s science had not progressed enough to utilize this information. Once the field of virology had matured enough, researchers started to use natural viruses in human trials. However, nature's viruses were too toxic to sustain the field. Fast-forward to the 1990s and genetic engineering began to allow the manipulation of viruses and over the past 30 years many viruses have been put to trials. Over the years, we have seen many promising viruses in human trials. The problem is that we were so afraid of toxicity that we attenuated a whole generation of viruses far too much and they were so safe that they did not effectively kill cancer. In total, two viruses have made it to the clinic as medicine, one in China and a Herpes Simplex Virus used for melanoma approved in the USA.

Around five years ago, several groups, including my own, decided to engineer viruses to be safe in humans but make them more specific and more toxic to cancer. We noted that in the 1990s, viruses can also work as an immunotherapy by stimulating the immune system to kill cancer, as well as direct lysis. Therefore, for this next generation of viruses, we are trying to find the best agents to turn on the immune system, whilst turning down the ability of immunosuppressive cells to hid cancer from the immune system.

The work I am presenting at AACR is the preclinical data and clinical design of a first-in-man clinical trial plans for a virus, CF33, that we have designed. We tested the virus against the National Cancer Institute 60 (NCI60) cancer cell lines that are used to screen how effective a potential anticancer agent is. Our agent was found to be have activity against all cell lines and later on, was proven to be safe in animal models. Once these initial results had been confirmed, we combined the virus with anti-PDL1 antibody, an immunotherapy molecule. By doing this we hope to harness the immune stimulatory effects of the virus whilst inhibiting the immunosuppressive cells that protect cancer. Human testing is due to start later this year.

What do you think are the major challenges with using genetically modified viruses to target cancer cells?

The challenges are three-fold. First, viruses are so different to regular chemotherapies, immunotherapies, or small molecules. The usual rules of developing these anticancer agents don't apply to live preparations of viruses. This makes it difficult for getting viruses into trials and through the regulatory path. However, this is getting easier now that there has been over 20 years of trials investigating viruses, so people are starting to become comfortable with the new rules. Second, we know that viruses are likely to work best in a combination with other agents. However, it is a challenge to do a combination trial with agents that are very novel. This slows the process down. There are ongoing discussions in the field of how we can speed viruses to and through multiagent clinical trials to be able to save as many lives as possible. Third, is the COVID-19 crisis. Many labs have had to shut down including academic and those on the clinical trial development side. Again,

this drastically slows the process down. I'm hoping that we will soon emerge and get back to killing cancer and saving cancer patient lives.

How do you think these challenges could be overcome?

For the first challenges, I think the clinical trial methodology will need to be different for viruses. Not only how we measure toxicity but also how we assess dose escalation and ensuring that we can measure whether the immune system has been turned on. Sorting out optimal viral clinical trial set-up is key. After that, we need to ensure that the system is rapidly moving along towards combination trials. Many groups are pushing for this now and a consensus agreement of how to get through single agent development and into combination agent studies will be an important step. Finally, the COVID-19 part will be harder to overcome. We need to make sure we contain the SARS-CoV-2 infection so that people can safely get back to work in all industries, but particularly those related to cancer and healthcare.

What do you think are the next steps for translating research surrounding viruses into the oncology clinic?

I think a number of things need to happen. For example, trying to figure out all of the best candidates for active next generation viruses. We have a very promising candidate and we are hoping that other candidates will emerge. We need to make sure all of our colleagues with active viruses can also move forward as I believe these agents will be complimentary to each other. The next step will be partnering with other researchers that have promising immunotherapy agents. There is already good preliminary data that suggests combinations of viruses with check-point inhibitors, and with cell therapies are likely to be highly effective against cancer.

How do you think the field of cancer research will evolve over the next decade?

I believe that it will be a partnership between groups making small molecules, immunotherapies, cell therapies and oncolytic viral therapies. Leveraging the best experts in each of these fields in order to design the best combination therapies will give us the greatest pace going forward to resolve the hard to treat cancers. The reason I say that is because viruses and immune cells have the potential to attack cancers that are the hardest to treat by chemotherapy. The natural response to viral infection is to turn on apoptosis, which is also how some cancers evade chemotherapy and radiation therapy. Therefore, viruses have adapted ways to turn apoptosis off. The anti-apoptotic proteins in viruses are really important for a virus to cause propagation of infection. Exploiting all of these agents is highly likely to result in more effective ways to fight cancer. To summarize, the field of cancer research will hopefully evolve to figure out what agents are needed, at what time and in what combinations. That is when we will truly have personalized and precision medicine.