Copying cancer cell carbohydrates for inclusion in a vaccine that activates the immune system

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Professor Mads Hartvig Clausen and Postdoc Cecilia Romanò. Credit: Mikal Schlosser/Technical University of Denmark

The surface of all cells is covered with carbohydrates. On cancer cells, however, the carbohydrates often differ from the carbohydrates located on the surface of healthy cells. Professor Mads Hartvig Clausen and Postdoc Cecilia Romanò from DTU Chemistry are trying to exploit this difference to develop a cancer vaccine.

"With such a vaccine, it will be possible to teach our immune system to recognize the difference between a healthy cell and a cancer cell, so that the cancer cells are attacked and destroyed by the immune cells," says Mads Hartvig Clausen.

The vaccine is based on imitations of the surface carbohydrates of cancer cells—which are called tumor associated carbohydrate antigens (TACA)—and which DTU chemists can produce artificially in the laboratory using chemical synthesis.

"The carbohydrates are only found in small quantities on the surface of cancer cells, but we can produce large quantities in the laboratory. When the vaccine is injected under the skin, the immune system will be presented with our copies of the TACAs. They are to act as antigens, which means that they must activate the immune system to produce antibodies. The idea is that if a person's immune system subsequently encounters these carbohydrates because he or she has developed cancer, it will be able to recognize them and consequently combat the cancer cells," says Mads Hartvig Clausen.

The concept sounds surprisingly simple. Yet the chemists have already faced a number of challenges that needed to be addressed before they were ready with an initial cancer vaccine candidate. And the chemists were aware that they needed close collaboration with other disciplines at DTU if they were to succeed with their ambition:

"When we started, we knew the strong competences that exist at DTU in immunology and drug delivery. We're experts in chemical synthesis, but we need to collaborate on the other aspects if we're to succeed in developing the vaccine, and we therefore got together with colleagues from DTU Health Tech and DTU Bioengineering," explains Mads Hartvig Clausen.

Friend of carbohydrates

The first challenge for Mads Hartvig Clausen and Cecilia Romanò was to select the types of TACAs to be produced in the laboratory. Because—with cancer—there is not just one kind of carbohydrate on the surface of all cancer cells. The TACAs vary from cancer type to cancer type, just as each cancer type has several types of TACAs on the surface of the cells. At DTU, the choice fell on a group of carbohydrates associated with malignant melanoma cancer, neuroblastoma (a type of tumor in the body of children) and small cell lung cancer.

"These are primarily three cancers that have the same type of carbohydrate on their cell surface, namely the carbohydrates known as gangliosides. They can be produced in the laboratory from simple sugars that we can buy for this purpose," says Cecilia Romanò.

The next challenge was to ensure that the carbohydrate activates an immune response in the body when injected. Here, there is an obstruction, as the body is 'a friend of carbohydrates'—meaning that a carbohydrate is generally not a very strong antigen, according to the two chemists.

"Carbohydrates generally don't activate a particularly strong response from our immune system. Therefore, we had to find a way to help our artificial carbohydrates elicit the desired immune response," says Cecilia Romanò.

Having to amplify the effect of a pharmaceutical is a well-known challenge, and the solution may be to use an excipient—an adjuvant. Mads Hartvig Clausen and Cecilia Romanò chose to use the excipient α-galactosylceramide as an adjuvant. This is a substance consisting of both carbohydrates and fatty acids—a so-called glycolipid—which stimulates the immune system. To boost the immune response further, the chemists

compounded the antigen and the adjuvant in the laboratory. This means that they 'coupled' their selected TACA with α-galactosylceramide, so that they became one compound instead of two 'loose substances.'

"We've subsequently demonstrated that it gives a stronger immune response when the two substances are joined than if they are given individually," explains Mads Hartvig Clausen.

Assimilation in the body is ensured

Before the chemists could come as far as to inject their antigens, they were aware that something was needed to help the substances be assimilated in the immune system.

"We needed a kind of carrier to ensure that the immune system is able to detect and respond to our antigens. Otherwise, we will not be able to start the cascade of events which makes up an immune response and which results in the actual production of antibodies," explains Mads Hartvig Clausen, who approached his colleagues at DTU Health Tech, Associate Professor Jonas Henriksen and Professor Thomas Andresen.

They have been collaborating for many years, and the chemists were familiar with their colleagues' work with liposomes (a fat globule the size of a nanoparticle) that can be used for drug delivery and vaccine formulation.

Mads Hartvig Clausen and Cecilia Romanò were thus able to have their cancer antigens 'mounted' on a liposome, which was well described and with documented assimilation by the immune system.

Immune system is activated in mice

The chemists could now start testing their vaccine. So far, they have performed one trial with mice. They were all cancer-free, because the researchers were initially interested in finding out whether their vaccine would create the desired immune response at all.

The results were really good, say Mads Hartvig Clausen and Cecilia Romanò.

"We've shown that our vaccine triggered the immune system of the mice into producing antibodies that can recognize cancer cells with our selected carbohydrate on the surface. The antibodies can also communicate that components from the immune system—the so-called complement system—can kill cancer cells in the laboratory," say the two chemists.

In the next two to three years, the researchers will optimize the vaccine and further understand the immune response. The next step will be testing on mice with cancer to see if the antibodies produced by the vaccine will fight the disease. In parallel, the researchers have applied for and received funding for starting a process with a consultant that will pave the way for getting the vaccine out of the laboratory and onto a commercial market.

"If society is to benefit from our vaccine one day, we will need a company to take over our invention, so that it can be tested in humans and then—hopefully—be put into production," says Mads Hartvig Clausen.

The researchers hope to be able to hand over their cancer vaccine candidate to a pharmaceutical company in about three years.

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