MAGIC BULLETS AGAINST TUMORS

State of the art decoration on molecular scale

'A top molecule' is how Sander van Berkel describes the discovery of BCN, made in 2010 at Radboud University in Nijmegen. Now this molecule is the basis for Synaffix, a young biotech company in Oss that now has many big pharma companies as partners. An interview with co-founder and director of R&D Operations Van Berkel and CEO Peter van de Sande about their ambitious plans for a tiny molecule.

At the beginning of the last century, the German doctor Paul Ehrlich introduced the concept of the 'magic bullet': an ideal drug that would precisely target the place in the body where it was needed and nowhere else. In practical form, these 'magic bullets' were still far beyond the reach of the medical world. Since the beginning of this century, however, the marketing authorisation of the first antibody drug conjugates (or ADCs) has given doctors the resources which go some way to achieving Ehrlich's 'magic bullets'. An ADC is, to continue using ammunition vocabulary, a 'guided missile': a destructive load (the drug) is connected to a navigation system (the antibody) that guides this load straight to its target in the human body, i.e. the tumour (see box).

As the 'Connect to Cure' part of the company name reveals, Synaffix specifically focuses on the connection between drug and antibody. While Van Berkel draws the process by which that connection is achieved on a piece of paper. Van de Sande points from his office to a tall tree outside on Pivot Park in Oss where Synaffix is based. "Remember, what Sander's drawing is not to scale. If the antibody is as big as that tree over there, we can pass through all the waving branches and attach a birdhouse to a specific branch high up in the tree. What we do is 'state of the art' decoration, but then on a molecular scale."

What did you actually have in 2010 when you thought of the possibility of building up a business?

Van Berkel: "The basis of Synaffix is bicyclononyne, or BCN for short. This is a molecule with fantastic properties: it can react very selectively, without adding a catalyst, with azide-containing molecules in any desired medium. These reactions take place very fast, without creating waste products and are very popular among people who work with biological

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systems. As researchers at Radboud University, Floris van Delft (co-founder and current Chief Scientific Officer of Synaffix, ed.) and I spent a long time working with these kinds of molecules, which finally resulted in BCN. Because it seemed to work so well and because the synthesis is so simple, we had an invention which we felt we could commercialise. The idea was initially to offer BCN and derivates to research groups and companies which, like us, are engaged in so-called click chemistry, but who can't make the molecule themselves."

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Van de Sande: "The field of click chemistry was growing exponentially in those early days and that formed the basis for the initial business model. We sold our molecules, which we had just patented (see box, ed.), on a small scale to various parties who used them for research purposes. However, we realised that this wasn't the way to get maximum value from our technology. After an in-depth market survey, we decided to focus mainly on high quality applications of our molecules in complex biomolecules, particularly in the field of ADCs for specific cancer therapies. In this application, the advantages offered by our technology come into their own."

What makes your technology so suitable for ADCs?

Van Berkel: "When we decided to focus on ADCs, we only had half of the BCN for the connection, namely the part that is attached to the drug. Thanks to targeted research, we then made a great discovery which enabled us to elegantly attach the other half to the antibody. In itself, that's a small revolution in the way in which ADCs can be made. Furthermore, with that second technology pillar, we have the ability to very simply and quickly modify all off-the-shelf antibodies to make them suitable for our technology. To continue Peter's tree analogy: to develop new ADCs we don't first need to build new trees and let them grow. We can prune any existing tree so that it becomes suitable for our technology, saving a lot of time and money."

Van de Sande: "The most important thing that we do is to increase the effectiveness and the safety of specific drugs. By doing so, we are trying to bring a cure for cancer a step closer. With our technology, we are improving the stability of the connection between antibody and medicine, also the payload. These payloads are toxic substances which are up to ten thousand times more toxic than existing chemotherapy. So you can only use such payloads if they very selectively target the tumour. If they go off track and get into the blood stream, this can cause serious side effects elsewhere in the body. In general, the greater the stability of the connection between antibody and drug, the higher the dose you can safely administer and the more effective the treatment may be. Finally Synaffix ADCs are made so that they are more homogenous than the ADCs which are currently on the market. To use the tree analogy again: we connect the payload each time to the same branch. With the commercial ADCs, the payloads are attached to different branches which means they are much less effective."

Can you already express the power of your technology in clinical terms? In other words: what advantages does it offer patients?

Van de Sande: "Our technology hasn't been tested on people yet. All the data we have are based on animal models. We usually compare Synaffix ADCs with the two ADCs which are now on the market. So we use the same antibodies and the same payloads, but then connected via our own technology. The results which we've produced so far show that Synaffix ADCs are more effective than the market products and that the side effects are considerably less harmful. But remember: at the moment these results only apply to this particular animal model and for the tumour material used. So it may be different in cancer patients. We therefore remain cautious, but on the other hand, all the test results we have so far indicate that our technology really gives better safety and effectiveness."

What steps will Synaffix be taking next?

Van de Sande: "The preclinical test phase will soon be completed. The aim is then to start clinical testing on cancer patients in the coming years. For this purpose, we are working together with pharmaceutical companies which use our technology in the development of their ADCs. If the first clinical results are good and new ADCs made with our technology prove to be safe and effective in people, then we'll celebrate. Because of the necessary follow up studies, it will then take at least three to five years before these drugs are actually on the market. Furthermore, in-house development of ADCs may offer a new growth perspective. But that discussion is still in an explorative phase; we must first learn to walk before we can run."

THE 'MAGIC BULLETS' OF MEDICINE: WHAT ARE ADCS?
Antibody-Drug Conjugates (ADCs) are antibodies to which a cytotoxic or cell-killing substance is attached.

Antibodies are an essential part of the human immune system and there are around 100 million different variants in the body. Each variant recognises certain foreign elements, such as bacteria and viruses and in some cases also cancer cells. Antibodies recognise so-called markers on the outside of these cells and attach themselves to them. The accuracy and selectivity with which that happens makes antibodies ideal for treatments for cancer or rheumatoid arthritis. Five of the ten best sold drugs in 2015 were based on antibodies.

In these drugs, just the binding of the antibody to its target already has a therapeutic effect. For antibodies which target cancer cells, the effect can be enhanced by attaching a toxic substance to the antibody. After binding, the resulting ADC is then absorbed by the tumour cell. Once inside the cell, the ADC is broken down, releasing the toxic load and killing the tumour cell.

Two ADCs have market authorisation: Adcetris to treat certain lymphoma and Kadcyla for breast cancer. Dozens of new ADCs, mainly targeting cancer, are currently being tested on patients in clinical trials.

How has Synaffix protected all its findings?
Van Berkel: "Our first patent application was for the BCN molecule itself, a compound claim for the connection in the field of 'metal-free click chemistry'. As we said, we then started looking for a method to use the advantages of this pioneering technology in complex biomolecules, particularly looking at high quality applications in targeted cancer treatments. The method we developed resulted in our second patent. We then focused particularly on ADCs. We protect our inventions in that field by product claims and applications, with claims for reactions and processes for making them. If you have a platform technology like ours, it's standard practice to further expand your IP portfolio. Our field is developing fast and many players are active in it. That means the bar is being raised higher and higher, forcing us to continue improving and innovating. There's a world of difference between what we can do now and a couple of years ago. So you obviously have to protect all those improvements."

Start-ups sometimes fail to realise the importance of IP protection. What made you aware of how important it is?
Van Berkel: "That was a harsh learning curve. When Floris and I were still working as researchers at the university, we developed the DBCO molecule, a precursor of BCN, and immediately published an article about it. At the time, we never thought about patenting that molecule. Now it's frequently used worldwide. We learned that whenever we discover anything, we must immediately consider whether it is interesting and relevant enough to patent. For BCN, in several respects superior to its predecessor, it was immediately clear that this should be patented. Ultimately, this led to the foundation of Synaffix."
Van de Sande: "In view of this experience, within Synaffix we agree that publishing new data comes second to patenting new discoveries. Now we keep a lid on an invention for longer so that we first really know what its potential is."

How does Synaffix protect the patent portfolio in practice?
Van de Sande: "Very simple: without patents, there's no Synaffix. The patent portfolio is clearly one of the reasons why the company exists. To start with, in our sector you have to attract investors. Furthermore, you need a well organised IP portfolio before you can launch anything on the market. In recent years, we've therefore devoted a lot time and energy to building up our IP portfolio. We now have a very complete portfolio of fifteen patents including pending applications, which is quite a lot for a young company like Synaffix. We now have such a strong position that we aren't dependent on one single patent and others not in the same field as us can be active without taking a licence on our technology."

Do you come across competitors who still try to move into your field?
Van de Sande: "We work in a sector which tends to respect patents. But if competitors see an opportunity to work around us, you have to assume that they'll try to gain an advantage. We also see cases where mainly larger pharmaceutical companies oppose patents which don't suit them. In that respect, as a small company you can't claim everything. You can't build castles in the sky; claims have to have a solid foundation and be realistic."

Synaffix has registered a number of trademarks. What is the added value of trademarks for a highly specialised business-to-business company like Synaffix?
Van de Sande: "Clients don't buy or in-license our technology because we've registered GlycoConnect or HydraSpace as a trademark, for example. In our world, trademarks are mainly very useful for communication in business development. It's nice to have a label for your technological innovations and not just have to use patent numbers or complicated descriptions. And because our trademarks sometimes give a tiny glimpse about the specific approach we use or its planned application, we can demonstrate a bit of 'category leadership'. So trademarks help us communicate our value proposition, and if they are used consistently, they certainly contribute to the company's success. "

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