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AN AUDIENCE WITH...

Norbert Bischofberger


Gilead

When Norbert Bischofberger joined Gilead Sciences in 1990, the 3-year-old company was focused on developing antisense drugs. Bischofberger has since helped the company re-invent itself as an antiviral powerhouse, and nearly 90% of its US$26 billion in annual sales came from HIV, hepatitis C virus and hepatitis B virus products last year. After heading up preclinical development for a few years, he took over responsibility for development efforts in 2000 and became CSO in 2007. He is also one of the inventors of oseltamivir, which Gilead licensed to Roche in 1996. Bischofberger has now stepped down from his role as CSO. He spoke with **Asher Mullard** about remaining antiviral opportunities, Gilead's pivot to oncology and the need for a societal discussion of drug costs.

Whereas many large pharma CSOs have a medical and biology background, your PhD was in chemistry. Does this give you a different perspective on drug development than your CSO peers?

Yes I trained in chemistry at the PhD level. But I did my postdoc with George Whitesides at Harvard in applied enzymology, so that was a bit of a mixture of biology and chemistry. Then I worked on molecular biology at Genentech, and at Gilead I started in research but then took over responsibility for preclinical development, dealing with everything from pharmacology and in vitro metabolism to ADME (absorption, distribution, metabolism and excretion) and toxicology. In 1999 I took over the development side of things at Gilead, and since then I've spent most of my time working on development issues. So I used to be a chemist a long time ago, but I've actually now worked on everything except for product pricing and commercialization.

Here at Gilead, one of our secrets at the very top level is that we really seek to understand the whole spectrum of drug development. Sometimes I see people working on elegant biology problems, but in order to make a product you have to get more than just the biology right. You have to get the chemistry right as well. And sometimes I look at a molecule and say, this is hopeless. Another thing that I think is often underappreciated is the manufacturing side of chemistry. We learned a lot with Tamiflu (oseltamivir). The starting material for that synthesis was extremely expensive, so we had to look for other starting materials and that led us to the Chinese spice star anise. But it took us a lot of work to get there.

Ultimately, we are looking for a product that we can give to patients that insurance companies will reimburse and that we can make at the appropriate cost. I'm always thinking "what is the product, and what are the hurdles that have to be overcome to make it into a product". And that's why it's good to have seen the whole drug discovery spectrum, from lead optimization to clinical trials, approvability, labelling, commercialization and reimbursement. That's how we look at it.

During your time at Gilead, you've brought more than 25 products to market. Most of these have been antivirals. What's next in antiviral R&D?

So hepatitis C to start off with — we're done. Really there is nothing left to do. We have developed a single pill administered once daily that is very well tolerated and leads to cure rates of ≥90% within 8 to 12 weeks of treatment. We stopped our hepatitis C research around 3 years ago.

We've also made huge progress with HIV. We have developed a small, safe, well-tolerated pill with response rates of ~90%. Over the years we've really optimized the HIV drugs to the point where there's not much left to do for treatment-naive patients. We're still working on long-acting injectables, which some patients might prefer. And we are still working on a once-daily pill for highly treatment-experienced patients who have developed resistance to other drugs. But a lot of the work on maintenance therapy is done.

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The next big step here is cure, because HIV is still a chronic viral disease that we can't fully clear. The big question is, can we elicit the immune system to clear the virus? We call this the kick-and-kill approach. The challenge with HIV infection is that the virus hides in non-replicating $CD4^+$ T cells. If you can kick these cells to wake them up, so to speak, then the virus will start reproducing, which kills the cell. And if subjects are well controlled on antivirals, then the virus can't go anywhere. We are looking at using a TLR7 agonist to deliver the kick, and a broadly neutralizing antibody to help control the awakened virus.

In monkey models of HIV, we just showed that this combination can actually cure monkeys of their simian–human immunodeficiency virus infections. It's very exciting stuff. Of course whether it will work in humans remains to be seen. But for us, the chances of success are reasonable and it's certainly worth spending the money on this.

Our best chance of success here is probably if we can deliver this combination early after an infection, when the viral diversity is minimal. If you try kick and kill in someone who has been infected for 10 years, you have so many quasispecies of HIV that a broadly neutralizing antibody is not enough to control everything.

And, a quick word about hepatitis B. We have really good drugs that patients can take long term to suppress the virus.

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But, again, it's a chronic viral disease and only spontaneously clears in a low percentage of patients. If we could increase that to 15–30%, that would be a huge contribution to the health system.

We have one programme in Ebola, but of course that's not a commercial opportunity and Ebola has nearly disappeared so it's difficult to do a study.

Another thing we're working on preclinically is a broad spectrum anti-respiratory virus programme. Flu, paraflu, respiratory syncytial virus, coronavirus and rhinovirus all cause very similar symptoms, even though virologically they are completely different from one another. If we could come up with something that has broad-spectrum activity against at least some of these, that could be very useful. These viruses all encode polymerases. And we have a large library of polymerase-inhibiting nucleosides that we made in our hepatitis C programme, so we are looking at expanding that library and testing it for somewhat broader spectrum activity.

Q ***How would you compare the scope of these viral programmes now versus the opportunity when Gilead started?***

There are still millions of people with hepatitis C. That market has not disappeared. But it is clearly shrinking, and that's a good thing. HIV and hepatitis B are still chronic viral diseases, but the barrier to entry for new drugs here has gone way up because we already have really safe, very effective therapies. So, yes, unless a new virus shows up, the viral space is somewhat more limited than it was when we started working in this area.

Q ***And this has driven Gilead's growing interest in oncology, and your US$12 billion acquisition of Kite Pharma last year?***

As we've become a bigger company by market capitalization, Wall Street has become more concerned about our growth and what's next for us. Clearly oncology can be a big growth area, and that's why we went into it. We looked into oncology opportunities in great detail. We looked at immuno-oncology, and decided it's an extremely competitive space and that we don't really have anything to offer there. We looked at targeted therapies, and didn't really find anything that was scientifically interesting enough and reasonable in terms of commercial pricing. And then we decided on cell therapy. The data that both Novartis and Kite have generated is really incredible. And we think chimeric antigen receptor (CAR) T cells have the potential to be further expanded into other B cell malignancies, into earlier lines of therapy and ultimately even into solid tumours. We think that could make a really big difference, so that's currently one of our focuses.

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Q ***You mentioned earlier that manufacturing is underappreciated in drug development. CAR T manufacturing is particularly challenging, especially for the first-generation autologous therapies that need to be tailored to each patient. What do you think about the potential for allogeneic CAR Ts, and competition from contenders in this space, including recently launched Allogene Therapeutics?***

Clearly the future of autologous CAR Ts is going to require an increase in the efficiency of manufacturing. And maybe we can localize manufacturing at a few sites. But another approach is of course to work on allogeneic cells.

These are conceptually fairly straightforward — you simply knock out the major histocompatibility complex or the human leukocyte antigen (HLA) on donor T cells. And we have a collaboration with Sangamo Therapeutics to do this with zinc-finger nucleases. But allogeneic CAR Ts will bring their own challenges as well. For one thing, if you don't have HLA on the surface of a cell, the immune system will recognize these cells as non-self and destroy them. So you are probably going to see less persistence of these CAR T cells. There is still lots of work to do here.

Q ***Your first generation CAR T is currently priced at nearly $375,000, drawing affordability concerns. You've been here before, when you launched your HCV drugs at a cost of $84,000 per course of treatment. Thoughts on the current cost of drugs?***

It's true; we were in the limelight unfortunately with hepatitis C drugs. But when we talked privately with insurance companies, I don't think they had a problem with the price. After all, the total cost of the alternative then — interferon plus ribavirin — was estimated to be $160,000. The problem they had was with volume; there were so many patients that immediately wanted to go into treatment, and there just wasn't the money in the system to pay for it all at once. And now the price for hepatitis C therapies is a fraction of what it used to be. So that has really gone away.

At the moment we haven't heard criticism of the price of CAR Ts. And this is because these CAR Ts are so far only being used in a relatively small patient population. And, the alternative is death. They really are life-saving therapies. If they become more broadly used, and move into earlier lines of therapy, the current price is not one that the system can afford.

You know, though, in my own opinion our hepatitis C treatment was cost effective. It is a great therapy that provides a cure and eliminates comorbidities. That's also true for our HIV drugs. But when I look at some of the oncology drugs where the benefit is just a few months of survival and they cost $100,000 or more, I do think we really need to have a debate in society about whether the pricing is right.

[After the interview, Bischofberger left Gilead to become CEO of cancer biotech Kronos Bio.]

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