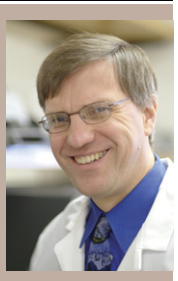
interview

Jochen Salfeld talks about HUMIRA® and the development of biological therapies at Abbott

Interviewed by **Steve Carney**

Jochen Salfeld

Divisional Vice President of Biologics Research at the Abbott Bioresearch Center in Worcester, Massachusetts, and is responsible for the oversight and strategic development of Abbott's human therapeutic antibody generation efforts.



Jochen Salfeld had an instrumental role in the development of HUMIRA®, the first fully human monoclonal antibody approved for the treatment of rheumatoid arthritis, leading his team from concept and discovery to the marketing stage. In addition, he has extensive expertise in the areas of biotechnology, antibody engineering, cytokine biology, virology, formal preclinical and clinical development of biological therapeutics and project management. His work has been published in numerous books and journals, such as *Arthritis & Rheumatism* and the *Journal of Hepatology*, and he has contributed to several symposia.

How did you become involved in the development of biological therapies at Abbott?

I was part of the BASF Bioresearch Corporation that was acquired by Abbott in 2002. We had been doing research around TNF-α itself and TNF-α antibodies, focusing on acute diseases, including sepsis. We realised very early that TNF-α plays a critical role in a number of different diseases, including chronic autoimmune diseases like rheumatoid arthritis.

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The initial work, which focused around mouse antibodies, appeared to be inappropriate for targeting human cytokines in chronic settings. So, we investigated where the field would be going in therapeutic areas and found there was an evolution away from mouse antibodies towards chimeric and humanised antibodies. We felt that fully human antibodies would be the gold standard in the future; however, there were not any fully human antibodies against human proteins anywhere in development. This was in the early nineties and to some extent it was a leap of faith that fully human antibodies would be the way to go. The data we have today proved that the risk to investigate and develop fully human antibodies was worth taking.

What do you see as the major problems that will be encountered in making biological therapies more mainstream and commonplace over the next five to ten years?

If you compare today's landscape with that from a few years ago, therapeutic antibodies have become very widely used. Today, they are used in a number of different indications and are typically given by specialists or by people trained by specialists for self-administration. At Abbott we look at the indication in which treatment will be used but we also look at using biologics from a patient perspective. For example, if you're accustomed to taking pills, then an injectable may be a different experience and some patients may not be comfortable injecting themselves. The devices that Abbott has developed make the process much easier and perhaps possibly less scary for some patients. At Abbott, we are trying diligently to remove these barriers to allow patients to use these antibodies on their own, in the privacy and convenience of their home.

Obviously you're moving HUMIRA® into different indications; what do you see as its future?

HUMIRA® is currently approved for rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. It's doing very well in those indications and provides great benefit to patients. HUMIRA® is also approved for Crohn's disease in the USA, and is expected to receive approval in Europe the first half of this year. We see HUMIRA® in Crohn's disease as a major advance for Crohn's patients to have an alternative to the

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few existing therapies available to them. We're quite excited about the future opportunities in the gastroenterology market*.

'HUMIRA® is a pipeline within a drug'

We also have very promising data in other indications, including psoriasis. HUMIRA® is a pipeline within a drug and Abbott systematically explores the best fit of this drug for indications where TNF-α plays a role in the underlying biology.

Is delivery less of an issue when you are looking at skin?

I have spoken to a number of patients around the world, patients who have been suffering from diseases for many years. Plus, I've talked to young people who have suffered from debilitating diseases, like ankylosing spondylitis. They are so excited because they see biologics as an opportunity to regain control of their lives. Patients and their physicians tell me dramatic stories about life before and after HUMIRA® and the incredible change the TNF agent has had on their lives. The impact is so amazing that patients are very happy to take this drug and inject themselves every other week.

What about all the other conditions like Lupus or Sjögren's; are you going to go after individual indications such as these or a more general label for chronic inflammatory disease?

We're looking very systematically at new indications to see whether there are possible benefits to using a TNF-α antagonist. We focus on areas where HUMIRA® can really do the greatest good for patients who have few treatment options. This is why it is extremely important to provide alternatives for patients with severe forms of diseases such as psoriasis and Crohn's disease., where there are very limited treatments available.

Do you think that an anti TNF-α approach alone is going to get you all the way there or are you considering other molecules that you can put into the portfolio that might address other cytokines?

We certainly feel that HUMIRA® and anti TNF-α in general is a major step forward in these indications. I talked to many physicians in the early nineties and they clearly were concerned with their limited treatment options - only having methotrexate and a few other drugs. Then, we saw the tremendous revolution that anti TNF-α drugs had in the arthritis field. Now we see the same game-changing impact of these agents in dermatology and gastroenterology. TNF-α drugs have tremendous value for patients, and that's the first thing Abbott looks at. The work we do is to create the best value for patients and maximize the impact these drugs have on their lives.

Do you see any potential impact of biosimilars in the near future for HUMIRA®, or is that the reason for your multiple indication approach to the drug?

How biosimilars might be developed is a question people are discussing from many different perspectives. Right now, biosimilars are not a major issue on the horizon for us. The skill that it takes to develop these medicines makes biosimilars quite different from typical generics, especially when you take into consideration the complexity of developing and manufacturing biologics.

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Even with biosimilars, you have to take drugs all the way through preclinical, manufacturing and clinical studies, amongst many other things.

Do you have any follow on strategies for HUMIRA®, for example, a pegylated form to improve half life or availability or is that something you're not pursuing?

HUMIRA® is an incredible drug; its efficacy to date already provides a major advantage for patients. But we do continue to look at additional areas for creating more convenience for patients. The pre-filled syringe and the pen device are two examples of how Abbott delivers greater convenience to patients.

At Abbott, how do the biologics and small molecules sit together within a portfolio?

Biologics and small molecules complement each other within Abbott's portfolio. When looking at new disease areas, the first thing we have to do is to perform extensive biologic studies, a process we call 'target validation', for any pathway that we assume to be involved in a human disease. It can take quite some time to really be certain that the pathway that you've selected is appropriate or relevant for human disease.

'biologics and small molecules are really complementary to each other within Abbott's portfolio'

After the target validation, we look at this particular pathway and determine whether it is amenable to a small molecule or biologic approach, either singly or in combination. Next we develop an internal strategy around that target, possibly with both small molecules and biologics.

It is a tremendous benefit and strength of Abbott to be able to conduct, within one company, small molecule drug discovery and development along side biologics drug discovery and development. This kind of portfolio-based, complementary approach to drug discovery spreads the overall risk in the discovery and development phases.

So, then, they are effectively dealt with in the same way. You don't have the different paths for one or the other but it's a decision that's made on therapeutic needs and on that basis alone.

Exactly. Over the last 15 years, the discovery and development of biologics has really changed. Today, we can think about developing a biologic much more like a small molecule. Today, you can sit down at the beginning of the discovery programme and carefully lay out specific rules and expectations of the programme, both pre-clinically and clinically. Next, you can match that programme with the science that you understand about your target. You can then work diligently towards these goals using biologics that fit exactly into your clinical expectations and, ultimately, your commercial expectations.

'Over the last 15 years, the discovery and development of biologics has really changed.'

In the old days, people had to select a number of mouse monoclonal antibodies, choose the ones that looked the best and then move them

* On 27th February 2007, Abbott announced that it had received US Food and Drug Administration approval to market HUMIRA® (adalimumab) as a treatment for the signs and symptoms of and for inducing and maintaining clinical remission in adults with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

forward. Today we are able to screen intensely for the best molecule, identify the best half-life, the best potency and so on. This is how our approach to biologic discovery development today is very similar to the way people approach small molecules. Of course, there are significant differences in those processes as well and managing them both is something I believe Abbott does very well.

Can antibody discovery be made to be more akin to small molecule discovery by using particular platform approaches and molecular engineering? Is that an approach that you have or plan to introduce at Abbott?

We use a number of different platforms and, again, which platform is best begins with what is the best fit for the specific biology. Abbott uses a number of different platforms and the way we carry out biological discovery today is a very sophisticated discovery and selection process of identifying the best molecule with the best characteristics that we can envision for that particular disease. This is very different from the way scientists worked biologics on even ten or 15 years ago.

'the way we do biological discovery today is a very sophisticated discovery and selection process'

If you were looking for a molecule to do what HUMIRA® does and you started looking today, how different do you think it would be?

Surprisingly, not all that different. The molecule on which HUMIRA® is based is a very good molecule, and we've spent a lot of time getting it just right. It took us about two years to create the product for development. We actually used very similar strategies for developing HUMIRA® to those I have discussed with you. Even back then, we approached this with a very specific goal and had a very specific potency, affinity and half-life in mind.

'I wouldn't really change this molecule as it really delivers great value for patients'

We really thought about the best characteristics that we wanted to impart on this molecule. It took us quite some time to get there and a lot of diligence, stamina, patience, and funds. That's why I wouldn't really change this molecule as it really delivers great value for patients.