Hans Küpper discusses science and venture capital

Interview by Joanna Pinto

Hans Küpper, Partner, Global Life Science Ventures

Hans Küpper has over 30 years of experience in the biotechnology industry in areas from research to R&D management, technology assessment and business acquisitions. He received his PhD in 1974 from the University of Heidelberg. After additional academic research at the Massachusetts Institute of Technology in the USA and at the University of Heidelberg, Germany, he joined Biogen in 1980. Here, he held various R&D positions, the last of which was Assistant Research Director. In 1985, he joined Behringwerke AG, Marburg, to build up and head the company's Molecular Biology Department and thereafter became Head of R&D of the Immunology/Oncology Business Unit. In 1999 he joined Global Life Science Ventures at their Munich office. Dr Küpper is the author of numerous publications and patents/applications and has also served as a consultant to the Pharmaceutical Industry and the European Commission. He is a board member of several early stage companies in the life sciences.

Can you briefly describe to me your career to date?
I started off studying organic and inorganic chemistry at the University of Mainz and Heidelberg, and received my degree in 1971. At that time, I changed from chemistry to molecular genetics and completed my PhD thesis at the University of Heidelberg in 1974. The next step was a two-year postdoc with Har Gobind Khorana's lab at the Massachusetts Institute of Technology, who had then received the Nobel Prize for the discovery of the genetic code. Upon my return to Europe, I took up a position as a faculty member at the University in Heidelberg teaching biology and medical students. In 1980 I left academia to join Biogen in Geneva as the seventh or eighth employee, starting as senior scientist and being promoted to Assistant Research Director two years later. In 1985, I accepted a job offer from Behringwerke in Marburg, which was then part of Hoechst. It was around this time that German companies started to invest heavily in biotechnology and I was asked to establish a Department of Molecular Biology. After three years, I became Head of Immunology/Oncology Research with around 200 people. In the early 1990s, Behringwerke restructured and I assumed more corporate responsibilities as Head of Business Development/Technology Transfer. I was heading projects such as the spin-off of the company's vaccine business, which was sold to Chiron and became Chiron Behring, and the divesture through a merger of the diagnostic department, which became Dade Behring. Eventually, I was offered a position as Partner at Global Life Science Ventures in their German office in Munich.

How does the venture capital industry work?
Basically, you look for investments that offer high potential returns and you try to identify companies that have considerable growth potential, enterprises that will use the funds and other support you provide to generate value. We are not a strategic investor, by that I mean we are only invested in a company for a certain time. A venture capital fund typically runs over ten years, and you may be an active investor in a company for anything from two to six years depending on the stage of development of the company. Over that time period, a company needs to be successful.

Can you tell us more about Global Life Science Ventures (GLSV) and what makes it unique in the venture capital industry?
At present, there are two main areas for high technology investments: one is information technology and the other is biotechnology. Today, if you want to be involved in high technology development, you have more or less to invest in either of these technologies. We at GLSV are an independent venture capital fund that is based on the very attractive investment opportunities offered by the life sciences. The sector encompasses many prominent technologies having a large impact on healthcare in general and consequently there is a big demand for products coming from the biotech industry. We have many pressing challenges such as chronic and degenerative diseases associated with older age, infectious diseases as well as non-communicable diseases such as cancer, and increasing morbidity... What you clearly need is better diagnostics, approaches to prevent disease onset, and new therapeutics. GLSV supports early stage companies that often come from universities or other institutions and which offer innovative approaches in their area. The unique selling points of these companies should in some way allow them to eventually become dominant players in their markets worldwide. So far we have invested in 29 life science companies. Our investment focus is Europe. However, we also support companies in the USA. We do lead investments in Europe and consider co-investments through syndicates — with a strong local lead investor – in the USA. Some companies in our portfolio who have already gone public include Sequenom, Exelixis and Memory Pharmaceuticals in the USA, as well as Cytos Biotechnology in Switzerland. We have also made investments in a range of companies that are still private, like Coley Pharmaceuticals, CombinatoRx and Intercell.

Is there such a thing as a typical day for you, and if so could you describe it?
Every day is different and this clearly contrasts with some of the jobs I had before. The venture capital industry is actually a peoples industry and you have to have the right contacts, the right networks and the right access to information, therefore, most of the time you are involved in networking. Keeping up with the latest developments in science, either by going to meetings and conferences,

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through your network of experts, or publications and the Internet, is crucial. You have an intense travel schedule – sometimes you travel to attend board meetings of one of your companies. Then there are the many business proposals that you have to look through and reach opinions as to whether they are interesting propositions or not. If a project is potentially interesting, you will meet with representatives of the companies and discuss the proposition from the science side, or from the business, marketing or financial perspectives; this is all quite time consuming. Once you have invested in a company, it's almost like a marriage; for the following years, you are committed. Because you want them to be successful, you provide your network of contacts to the companies and you discuss upcoming issues and try to work things out. Most importantly, you must be able to understand from the technology side what they are doing, which makes it very important to keep up with the latest science.

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How do you think biotech companies view venture capital companies?
One element biotech companies look for is to establish a long-term relationship. I think biotech companies are interested in smart money. By this I mean they also want access to the networks and experience of the venture capitalist. At GLSV, we believe that one of the ways we differentiate ourselves from other funds is through the people that work here. I have told you about my background but all members of our team have a high level of industry knowledge and complementary skills.

What was it like working for Biogen in the early days, and how did the company develop in the years you were there?
It was very exciting – like myself, most of the early employees came from academia and the biotech industry was still very academic in its approach at that stage. It was exciting because Biogen had very high scientific standards. Several high calibre scientists like Wally Gilbert and Philip Sharp, who both received the Nobel Prize, were directly involved in shaping the

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company as founders of Biogen. The fundamental technology platform of Biogen at that time was the gene transfer technology. We tried to look for applications for this technology, which were really broad. We were looking at every field – not only healthcare but also agriculture and industrial enzymes. One of the first undertakings I was involved in was the development of a foot-and-mouth vaccine. We were also looking at vaccines for other animal diseases as well as improving industrial microbes and plants through genetic engineering. However, the major undertakings at that time were interferon alpha, a hepatitis B vaccine, and then interferons beta and gamma, as well as other cytokines, which at that time were thought to be the most important biologicals. We were also trying to clone erythropoietin and the coagulation factor FVIII. Unlike at the university, we also had direct contact with patent law firms and we were travelling a lot to visit different companies in the USA, Japan, everywhere… It was a gold rush!

Do you ever miss anything about being in R&D or being in the lab?
No, although it's an interesting question. A researcher wants to be creative, which is something very human, and for the most part as a scientist you think that you can only be creative by designing an experiment and then looking at the result, interpreting it, maybe doing more experiments and – ultimately – by discovering something. But during a long career, you realise that you can also be creative by building up teams, hiring the right people, putting them together, strategically guiding what they're doing, which eventually leads to results and success. As a venture capitalist, you can be creative by building companies, providing networks, making the right contacts and setting the right strategic directions. You should be able to discuss science in detail but also be in a position to take a much broader view and look at the bigger picture. At the end of the day, I have to say I'm not really missing anything because you can be extremely creative as a venture capitalist, and you have to be creative otherwise you have a problem!

Over the many years that you have been involved in science, you must have seen considerable advances in the biotech industry. What advances have surprised you the most?
There are always new surprises, and I hope the best ones are still to come! But some of the important discoveries were the early breakthroughs of restriction enzymes and the transfer of genetic material in the 1970s; these were groundbreaking changes. The early DNA sequencing methods developed in the 1970s also come to mind, as well as monoclonal antibodies, hybridomas, PCR and, eventually, the completion of total genome sequences, first of drosophila and mouse but then also of humans. I think these were watershed discoveries with huge implications. The implications were so tremendous that recommendations and laws had to be introduced to regulate their use.

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What do you think are the major challenges facing the biotech industry today, and are they similar challenges to those faced, say, 25 years ago?
The landscape in the industry is always changing, as is the demand from patients, medical professionals and customers, which include among others the pharma companies. Some of the first companies founded included Amgen, Biogen, Chiron and Genentech. At that time – about 25 years ago – there were about 20–30 companies. Now you have about 5000, which is quite a difference! The companies specialized, expanded and diversified… 25 years ago there were many more pharma companies, which disappeared due to mergers and acquisitions. The picture today is an enormous increase in the number of biotech companies, but a parallel decrease in the number of big pharma companies, which results in a tough competitive landscape! What also needs to be borne in mind is that many biotech companies today can only demonstrate marginal improvements to already existing technologies in specific areas – with a marginal competitive edge. For example, take vectors for gene therapy; perhaps 20 companies or so have worked on this approach and each has

used a different vector, which makes it very difficult to differentiate the best company or approach from the rest. This is something I think has really changed. In the beginning we had groundbreaking technologies, but now there are perhaps not enough companies with truly outstanding approaches or novel technologies. For the biotechnology industry, we will probably see consolidation as we have experienced in the pharma industry. Some companies will merge, others will be acquired and some will disappear.

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What are the current biggest trends in pharma and biotech investments; where is the smart money going?

A clear trend in past years has been to invest in later stage companies, with more advanced technologies or products, in part because the industry had experienced too many unfulfilled promises about technologies and products that were supposed to accelerate drug discovery and development! Obviously the biotech industry has to react to these trends. One consequence is that companies will not only have to provide a technology platform, but will also have to develop this technology into Phase I and II products. Investors are always looking to reduce risk and one approach is to invest in later stage products. I personally believe that there are excellent technologies around. At the same time, I have 400–500 business plans per year, and 20 of these might be compelling. Eventually, you might invest in no more than 3–5 companies a year. In earlier years, you had fewer business plans but the strengths of the companies were more immediately apparent. You have to be very, very selective as an investor.

What do you think are the emerging trends?

Some of the recent trends – which look extremely promising – are RNAi technologies (RNA interference approaches), perhaps more at the R&D stage initially, but in time there should also be advances in therapeutic applications. Stem cells clearly have considerable potential. You might also think about organ remodelling, which includes, for example, growing pancreatic beta and islet cells for diabetics, or even parts of a liver. The more we understand about the immune system, the better is our approach to developing more promising vaccines. Another important trend includes personalized medicine. The more information we know about the genetic background and its influence on disease, the better we can define the pathways involved in disease. This should allow us not only to slow disease processes but also, in time, to prevent the onset of disease in the first place. There will be a clear move towards preventive medicine. You can only do this if you know what certain modifications or changes in the genome really mean. Other trends concern therapeutics for the CNS, which is an extremely complex organ. We are now starting to understand certain pathways and companies like Memory Pharmaceuticals in the USA are working to improve cognitive function in diseased and even non-diseased states; developing an effective treatment for Alzheimer's disease remains one of the major challenges for the future.

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How do you think the elucidation of the human genome sequence has affected the biotech industry?

In my opinion, the elucidation of the genome sequence can be compared with the establishment of the periodic table of elements in the 19th century because we now have a real basis for understanding disease at the molecular level. We can now start to unravel and understand different diseases in a systematic way. It gives us a real basis for the development of diagnostics, defining new pathways and identifying new drug targets. The benefits also relate to personalized medicine and predisposition to disease and ultimately to prevention of disease onset. If you think about it, medicine to date has been largely trial-and-error. You went to the doctor and he or she said: 'Okay, you probably have this or that disease, why don't you try this medicine and come back in a week?' If it worked, the doctor said 'Okay, carry on taking it', if it didn't work, 'Oh, try something else!' Therefore, one can compare today's standard of medicine with the field of chemistry before the periodic table of elements was established, an event which transformed alchemy into the science of chemistry we know today.

How do you think recent progress in areas such as pharmacogenomics, systems biology, immunotherapies and the like have impacted the biotech industry?

The progress in these areas has had a huge impact. We have several companies in our portfolio who work in these fields. For example, take immunotherapies and a company like Cytos Biotechnology, which was founded in 1995. The initial technologies that support the patient's own immune system to fight disease originated from the work of Dr Renner and others at the Swiss Federal Institute of Technology in Zurich. We were the first venture capital company to invest in Cytos. They have since had a successful public listing and have been able to develop a broad pipeline of immunodrugs offering new treatment options across several disease areas. They have also secured two big agreements with Novartis and are quite successful. Another company is Agendia in The Netherlands who has developed an interesting prognostic test based on gene expression profiles in breast cancer. What the company and its collaborators demonstrated is that a certain expression profile in cancer can predict whether this cancer will metastasize in a short time or not. That provides the doctor with additional help to initiate the right therapy. I think these are extremely important areas of endeavour and some of them are still in an early development phase. Many big pharmaceutical companies are already prepared to implement pharmacogenomics. The FDA is starting to request the genetic background of patients involved in clinical trials. This will change the whole pharma industry because you will have drugs associated with genetic tests. Big pharma is not ready for this yet but this will eventually be the only way to take advantage of personalized medicine. Pharmacogenomics offers the possibility of selecting drug treatments that maximize

therapeutic effects and minimize or even eliminate drug side effects. This will in time be the optimal approach for the individual patient in a population.

Increasingly, biotechnology companies are becoming bigger than pharmaceutical companies. How do you think this will affect their relationship in the future?
I think there are still only a few companies, such as Amgen, Genentech and Biogen, that can compete with the big pharma companies – most are still in some way largely dependent. The reality is that it takes more than 15 years to really be in that position – most biotech companies are much younger. What is particularly interesting is that until 1975 – before most of the first biotech companies had been established – there was a strong relationship between pharma companies and universities. The pharma industry was traditionally the acceptor of scientific discoveries, and developed these discoveries into products. However, with the advent of gene discovery and gene transfer technologies in the 1970s, big pharma was not flexible enough at the outset to create a sufficiently innovative environment for these new technologies. This is where biotech came in, as an acceptor and incubator for these novel technologies. Biotech develops technologies and products up to a certain stage and passes them on primarily to the pharma industry. This is a very central role in the link between science in academia and the pharma industry. I think with large biotech companies you also have a 'grey zone'; some might forward integrate and become fully independent; however, in general, the Genentech's and Amgen's mainly focus on biologicals, and big pharma has focused on small molecules so far. Biotech therefore has an established role and there is a strong dependence on big pharma, and vice versa.

If you personally were investing in an area of biotech or drug discovery, what would it be?
As a VC company, we're always looking for the one technology to invest in! As an investor, you try to have a very balanced portfolio. You look for balance in terms of maturity – that is, some early stage companies and some at a later stage. It is important not to put all your eggs in one basket, which means you should not exclusively focus on CNS or cancer or cardiovascular. The most important thing is that you believe in the company as well as in its technology or products, which must be developed, and which might take 5–10 years before they reach the market. This needs strong intellectual property protection and you have to have the right team driving it. The management team, the intellectual property protection, and the potential market are key. If you look at a company, you also need to look at the exit possibilities, which means looking for the preferred route for returning value to investors. Interesting areas are CNS research, like Alzheimer's, cancer and new approaches in immunology. However, it is difficult to classify by therapeutic area because each project has to be considered on its individual merit.

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During your career you worked with such people as Nobel Prize winners Har Gobind Khorana at MIT and Wally Gilbert at Biogen – who has been a significant influence on your career so far?
One was a professor in Heidelberg with whom I did my PhD. Professor Bautz, who was a young professor at the time, had just returned from the United States in 1970. He held the first chair of molecular genetics in Germany, and I had just finished my diploma and was looking for a PhD. I hesitated about going into organic chemistry because I did not wish to work in the chemical industry. As I was very interested in the biological sciences, I talked to him, and this started my career as a molecular biologist. Khorana at the MIT, who is just a very impressive person, also had a large impact. He is a model scientist and is absolutely dedicated to the highest possible standards of science. He must be nearly 85 now and he's still at the Institute. At MIT, I also came into contact with the likes of Phil Sharp, Bob Weinberg, David Baltimore and Wally Gilbert, each of whom received the Nobel Prize. This had quite some influence on a young scientist, so these were very important times. When I think of Bautz, who converted me from a chemist to a biologist, and then Khorana with his dedication to science, they have certainly had a significant influence on my career.

What would you consider to be the biggest scientific highlight of your career so far?
One was in 1975 when Khorana finished the synthesis of the first synthetic gene. It was a tRNA, and represented really pure, basic science. It was a bacterial gene, and I was probably the first one to put a synthetic gene into a bacterium – and it worked! At that time, when Khorana finished the synthesis, it made the headlines of the *New York Times* – it was really quite exciting! At Biogen, I would have to mention the first sequencing of the epitope of a vaccine- relevant antigen, which was for a foot-and-mouth vaccine. Another achievement was to establish a successful molecular biology department at Behringwerke, which was personally very fulfilling. I have also published about 50 articles. But the biggest highlight could still be to come!

What do you hope to achieve by the end of your career?
Probably two things: the first is really to pass on the experience that I have gained during my relatively broad exposure to biotechnology. I would like to pass on my knowledge acquired from academia, biotech, pharma and now venture capital, to the next generation, namely early-stage biotech companies. The second thing is to improve public opinion of the industry as a whole, especially in Germany. This is something I have been involved with in the past and which I think is crucial to the future development of the industry. Biotechnology has made tremendous progress but for some reason this message is not influencing the public at large. There is still a lot to come – but you have to communicate the achievements and the challenges.

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