Blazing a trail in a new type of research

➜ Simon Crompton

When confronted with the novel gene technology of the early '70s, molecular biologist **Axel Ullrich** posed the question: what use can this be to medicine? In doing so, he opened the door on the era of translational research and a personal career which went on to encompass lead roles in the development of two of the first intelligently designed cancer drugs.

He's the man behind the first monoclonal antibody drug Herceptin (trastuzumab), and the innovative kidney cancer treatment Sutent (sunitinib). He has come as close as anyone to finding a 'magic bullet' for cancer, but Axel Ullrich still feels a sense of failure. At the age of 66, with four years to go until compulsory retirement, there's a deadline for making the really big breakthrough, the one that will change cancer treatment forever. The clock is ticking, and the prospect that he won't be able to achieve it makes him sad.

"I feel this responsibility…" he says, "Having to retire now, I feel a little bit of a defeat, even though there is no one else who has brought two cancer drugs to the market from bench to bedside. I hope there will be one or two more. But with cancer, it's only a partial victory."

It's a battle that started as an intellectually intriguing skirmish, and has grown into an increasingly personal war over the years. For all his dissatisfaction, Ullrich stands as one of the living giants in cancer research, for 25 years a leader in translating discoveries in molecular cloning into usable therapies. Last year he was awarded the prestigious Dr Paul Janssen Award for Biomedical Research, cited as "one of few basic scientists whose work not only has influenced academic research, but also has helped millions of patients suffering from major chronic diseases." He is among the top 10 most cited biologists in the world.

How does it feel to have such an influence on people's lives? Ullrich deflects the question. "Well, there are many stories to be told…" he says, and continues with the tale he has begun about the problems he had making drug companies understand the concept of monoclonal antibodies as a targeted cancer therapy. It's not modesty that makes him change the subject. Ullrich sticks to an agenda for what he wants to talk about.

The Ullrich agenda

The reason that Ullrich still thinks a magic bullet for cancer might be achievable (and many would disagree with him) is that he has already pioneered a different direction of cancer treatment from anyone else in the face of reluctance and disbelief. He did

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it, by his own admission, through a dogged refusal to go in directions people told him to. He doesn't like being told where to go if he believes another way is better – whether that be in academia, within the pharma industry or in an interview.

Ullrich knows that very few people operate like this. He directs my attention to a picture on his office wall of some of the 100 research students at the Institute under his supervision over the past 20 years. "There are a few of them," he says, "just very few who spot what the most important thing is, and go for it straight away."

The difference between those few, he explains, and the remainder, is partly that they refuse to be "book-keeper scientists who just add one stone to another." Some simply have a creativity of approach that inevitably puts them at odds with others.

"The essence of creativity is to see connections where other people don't see them. You can only make breakthroughs if you don't go the most logical common track."

He provides an example of his counterintuitive creativity in his current research at the Max Planck Institute. Examining gene structures in a cancer tumour, one of his students stumbled on an abnormal variant in a gene. Was it relevant to why the tumour formed? Research revealed that the aberration was not restricted to the cancer. It was what is known as a single nucleotide polymorphism (SNP) – a type of variant that also occurs in non-cancerous genes, and which is responsible for the variety and individuality of humans. The SNP that the student had found, it transpired, was one of the more common of around 10 million in the human genome.

A dead-end then. Most colleagues believed so. But Ullrich thought it looked interesting, so continued with experiments. They revealed that though the SNP didn't cause cancer, it did appear to make breast cancer more aggressive. Reports of his research, published in 2002, were met with scepticism: the influence of such SNPs was hard to prove, and was likely to be marginal, he was told.

So Ullrich devised a new experiment to prove the

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critics wrong, breeding mice with his newly discovered SNP with others with a gene variant known to make mice more susceptible to cancer. The way cancers developed, progressed and metastasised in the mice clearly indicated that the new SNP influenced how aggressive tumours were. The results were published in *Cancer Research* in January.

"Even my students said, 'Why are you continuing to look at this?' Now we are translating the results back into humans, and are making even more exciting discoveries, because the people we can identify as having a bad prognosis through this SNP may respond much better to some types of treatment than those who do not have the allele."

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So what was it that made him go on? "I had this feeling that there's something important, and that made me fascinated by the beauty of this experiment – of changing one single nucleotide in a mouse and seeing what the effect was on a major disease."

It has been the same story through his career. Ullrich says he's never had a rational approach to his work – he has been led by his 'inner compass', his instinctive sense that some leads need to be followed because they are interesting or important.

He was born in Lauban, Silesia, in 1943. His parents had fled from the Northern Czech Republic – formerly known as the Sudetenland – and lost everything in the process, so they set up a grocery store to make a living. He was good at biology and chemistry at school, but no one told him he could become a scientist. All he really knew was that he didn't want to be a teacher – which is interesting for a man who has spent much of his professional life supervising students. "I hated teachers. I'd seen how they could set out to destroy the life of a young child."

With his parents giving him total freedom on career choice, he decided to study biochemistry at the University of Tübingen, and then went on to earn a PhD in molecular genetics at Heidelberg in 1975. Realising that if he was to stay in science, he would have to learn its international language, English, he decided his next step should be to go to the US – preferably somewhere where the quality of life was good. California for example. So he applied for a fellowship, and a postdoctoral tenure in biochemistry at the University of California, San Francisco. He got them.

A first for gene technology

It was a time when the first reports about the potential of gene technology were beginning to circulate. He decided to see whether he could do anything 'medically relevant' with the new technology. In the mid '70s, DNA sequencing was still not possible, but Ullrich thought insulin looked a promising

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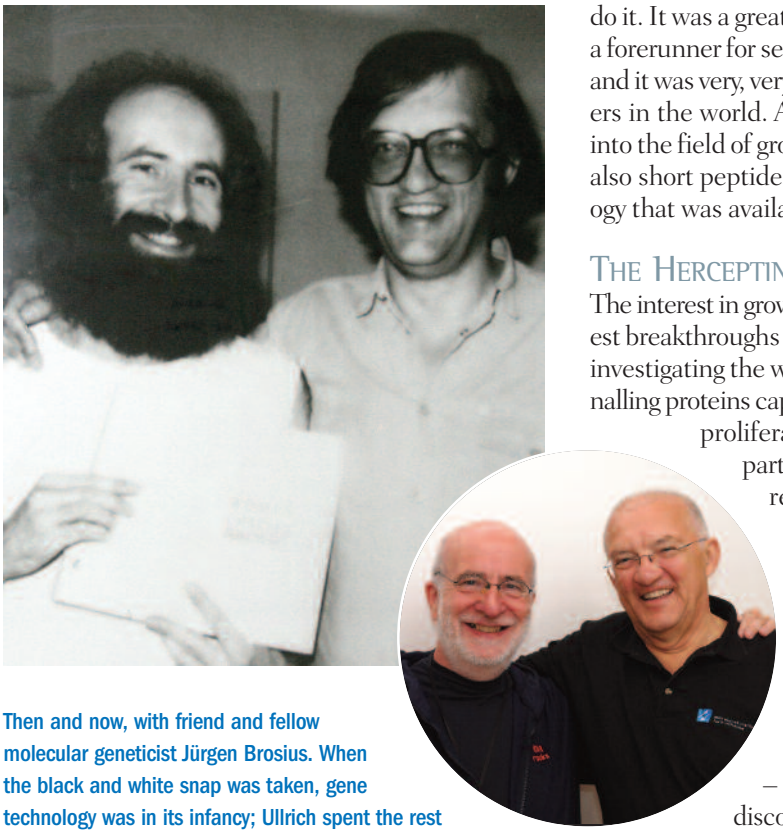

Then and now, with friend and fellow molecular geneticist Jürgen Brosius. When the black and white snap was taken, gene technology was in its infancy; Ullrich spent the rest of his career putting it to work to treat disease

area for investigation – it was a small polypeptide with probably a small, manageable gene.

It was a long fight to convince colleagues that this was a good route for research, but by 1977 he had come up with the molecular cloning process that could produce synthetic insulin. The breakthrough occurred just before his fellowship was due to expire, and allowed him to stay on in America to work with the pioneer biotechnology company, Genentech, to develop human insulin, or Humulin – the first treatment developed through gene-based technology.

"I told the founder of the company, Bob Swanson, that I wanted to explore my own ideas. I was probably a pain in the neck for him, but he let me do it. It was a great time for Genentech, which was a forerunner for semi-academic industrial research, and it was very, very exciting. We were the best cloners in the world. And so I got through insulin and into the field of growth factors – because they were also short peptides, and accessible to the technology that was available at the time."

The Herceptin story

The interest in growth factors was to lead to his greatest breakthroughs in cancer therapy. Ullrich started investigating the way in which growth factors – signalling proteins capable of stimulating cell growth or proliferation – function. He looked in particular at how they interact with receptors – molecules that take their messages into cells. He and colleagues from the UK and Israel cloned receptors, and found a new type of receptor for a growth factor called epidermal growth factor (EGF). They called it HER2.

There was, he says, excitement – but not at the implications of the discovery for countering a disease. "It was the technical challenge," he says.

Its major implications became clearer when they found its peptide sequences were related to an oncogene. In 1987, Ullrich, working in collaboration with Dennis Slamon and others, discovered that the gene for HER2 was overamplified or overexpressed in at least 25% of invasive breast cancers. "The end of the story was Herceptin – the first targeted drug against the product of a gene that was abnormally amplified in about a quarter of all mammary carcinomas. We made an antibody that blocked the function of this oncogene. So this was a first, first, first…"

But Ullrich also felt disappointment, especially when initial trials showed that just 15% of HER2-positive patients responded to Herceptin alone (later trials showed it helped many more in

combination with other drugs). "As a biologist, it had to be all or nothing. I had much higher expectations, whereas for oncologists who work with these patients every day, it was a huge breakthrough."

Then there were disputes with Genentech, which, he says, was initially reluctant to develop and produce an antibody as a therapy. In the end, clinical development didn't begin until 1992 and Herceptin was only approved in 1998. "The story of my life includes many discoveries that were made too early and not understood." Partly as a result of his frustrations with the company, Ullrich took up an offer to become director of the Department of Molecular Biology at the Max Planck Institute of Biochemistry in 1988.

On a personal level, it wasn't an easy time. He had left a house and a wife in California. Each month he spent three weeks in Munich, one week in California. "That lasted about five years and ended in a divorce."

But on a research level, things were moving on. Ullrich, who throughout his career has straddled the academic and commercial spheres, convinced the Max Planck Institute that the best way to translate basic scientific discoveries into treatments was to link an academic lab to a company. They allowed him to start a company to develop the products of research – it was based in the US and called Sugen.

The Sutent story

It was here that Sutent was developed – the first multikinase inhibitor drug, now a standard for treating renal cell carcinoma and gastrointestinal stromal tumours. It came into being after a new receptor cloned by a research student at Max Planck was found to be critical to the formation of blood vessels (angiogenesis). Angiogenesis is a key process in tumour development, and Ullrich and his colleagues believed they could develop an angiogenesis inhibitor. Initial trials of a Sugen-developed drug based on the discovery were disappointing – they revealed that it also inhibited other receptors.

But again, Ullrich turned defeat into triumph. "So we rationalised," he says. "We said, okay, maybe this is good. Maybe other oncogenes are also inhibited by the drug, and therefore this drug will be effective against cancer in many ways. This is what happened." Sutent, it turned out, was what Ullrich calls a "broadband antibiotic against cancer" – a new type of multi-targeted drug. Research continues into possible new applications.

Ullrich, who in 2001 set up his third biotech company, U3 Pharma, continues to work on developing similar multikinase inhibitors, which are effective against a broad range of cancers. His work continually demonstrates the importance of translational research, yet it worries him how slowly the translation from bench into clinical practice generally occurs – the result, he says, of simple lack of nerve.

"When I look at how much money and time pharma companies say it takes to develop a new drug, I think this is not necessary. All this could be done in half the time quite easily." How? "By hiring better people and giving them responsibility. You need people who are passionate, who don't just see it as a job, and you need to give them the power to take risks."

It's an opinion clearly born of the frictions that have arisen as his confident approach has been viewed as too risky. But he's not a risk-taker in his personal life. He lives with his partner, a medical doctor, and they enjoy the relatively sedate occupations of travelling and cooking. Most of his kicks, he confesses, come from his work, and there are no children to distract him.

It isn't surprising, then, that retirement holds no allure. Ullrich wants to be in the thick of it, pushing forward translational research and encouraging interaction between academics and medical scientists, so that access to biopsies and patient data is easy, and basic science can be put into practice as quickly as possible. It's here, he believes, that the future of cancer research should lie. Stem cell therapies, he emphasises, are unlikely to lead to novel cancer therapies. Focusing on immunology, he believes, on harnessing the body's own ability to fight disease, provides the best chance of defeating cancer.

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Speaking at an ESO meeting at the World Conference of Science Journalists. One of most frequently cited biologists in the world, Ullrich argued that increasing pressures on academic scientists to get coverage in the wider media can lead to them exaggerating the significance of their findings, which may undermine their credibility

JASON HARRIS

"Only the immune system is so clever that it can track down a cancer cell wherever it is in the body"

The magic immune system

Ullrich believes that immunology holds out the tantalising prospect that, somewhere out there, a magic bullet for cancer still awaits discovery. Even though cancer is hundreds of diseases, they all have a single common denominator. "The biggest problem is the instability of the genome. It's not important whether you have stem cells or not, but it's important that the cancer cells that have stem cell characteristics have an unstable genome. This is the biggest problem. But you will never defeat cancer without the immune system. It is your ally. Only the immune system is so clever that it can track down a cancer cell wherever it is in the body."

It's the end of the interview and Ullrich, candid but pragmatic throughout, is just beginning to reveal some of the passion that he advocates so strongly in researchers. In a career where he was led to investigate cancer by instinct and curiosity rather than by a sense of mission, in latter years his work seems to have accumulated meaning. He has seen more and more people die of cancer – his father and friends, one of them young, and just a few days ago.

"I only began to appreciate the incredible complexity of cancer after the clinical phase I Herceptin results. I've felt it as an incredible challenge – you know, to take up the War on Cancer that Richard Nixon declared in 1971. I have to say, it has become really, a sort of a calling. I sometimes feel a little depressed that I have to go without having made a really strong impact. But it's a realisation that cancer is just an incredible, formidable enemy."