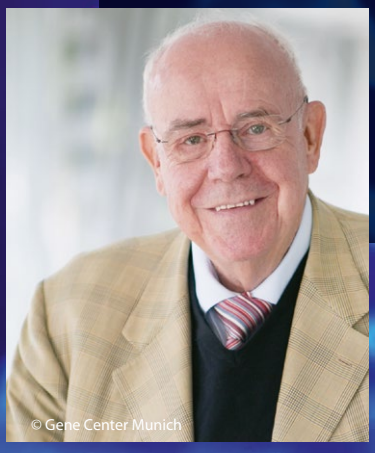
WE ARE IN THE CENTURY OF BIOLOGY

He is considered the father of German biotechnology: Ernst-Ludwig Winnacker is a professor of biochemistry and has been instrumental in countless discoveries in genetic research. He has left his mark on German genetic research like no other. On establishing the Gene Center Munich, he laid the foundation for the "Biotech Valley" in Martinsried and thus for the most successful German biotech cluster.



PROF. DR. ERNST-LUDWIG WINNACKER
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Bio^{M}: Professor Winnacker, you studied chemistry at the ETH Zurich and, after obtaining your doctorate, conducted research in Berkeley and at the Karolinska Institute in Sweden. From 1977, you worked as a professor of biochemistry at the Ludwig-Maximilians-Universität München. In 1984, you founded the Gene Center in Munich, a leading interdisciplinary and internationally visible institute. You are thus considered a pioneer of the successful Munich biotech scene with its university facilities, research institutes and biotech companies. As we sit here now at Bio^{M} with a view of Martinsried, what feeling do you get seeing this center for life sciences, which in a way is also part of your life's work?

Prof. Dr. Winnacker: It's a good feeling of course when I drive here and look around. At the time, in 1984, this was not expected at all. The hospital and the Max Planck Institute were here. Nothing else existed at that point. Even the Gene Center, the building that was being planned and built at that time, was initially supposed to be located in the city center, where the Pinakothek der Moderne is now. Then the state government suddenly decided, especially the then Minister Zehetmair, that it made no sense to place such a tall building in the middle of the city, even if it were close to the LMU and the old chemistry buildings. However, he then promised me that it would be built quickly out here. The fact that so much else has been added here was not apparent at the time. You couldn't really imagine it. We then inaugurated the building in 1994 with a party in a large marquee where the chemical buildings now stand but did not exist back then. It is wonderful of course that it has all turned out so well. Overall, it also fits in with the concept that you need a critical mass in science and interdisciplinarity. That's all here now. It's wonderful.

With the founding of the Gene Center and the establishment of the first biotech companies around Großhadern Hospital and the Max Planck Institutes for Biochemistry and Neurobiology in Martinsried, a special biotech center has developed in the south of Munich over the years. You just mentioned it. You have attracted excellent researchers from all over the world to settle near the Isar river. How did you manage to create this unique atmosphere and gather so many top international researchers here at the site?

I was in fact very fortunate to have worked at Berkeley between 1968 and 1970 with Professor Baker as a tutor. He had discovered and worked on vitamin B12 but was also responsible for many appointments in the area, including at Stanford. Every other Saturday we would drive to Stanford to visit his acquaintances: Professor Kornberg or Paul Berg, both of whom subsequently received the Nobel Prize, also for the development of genetic engineering. That's where you were taught what scientific excellence means and, above all, where you can find it. I kind of internalized that. Then there was the matter of the junior research groups: that was part of the concept, to look for young scientists who could work here independently. I called that early independence – I always went to wherever the people were, including Stanford, and watched how they worked, where they worked, and what the setting was like. Was this really an environment that creates quality and allows scientific independence? Because that was the idea behind this. I tried that and indeed found the first generation of eight scientists in this way.

At that time, you were already acting as a scientific talent scout, so to speak.

Yes, as a talent scout. I wasn't looking for projects so much. We didn't want to appoint classical philologists or art historians and so on. That's a perfectly good thing, too, but we wanted it to be centered around modern technology. So, I started searching: Where are the people with interesting publications who are also interesting in some other way? I didn't know any of them beforehand, but then I visited them, had dinner with them, and talked to their teachers. In this way, I got to know the scientific elite in this field in the US at that time.

You were President of the German Research Foundation (DFG) for nine years, and in this role you decisively improved the framework conditions in research. You once said, "I didn't just want to manage excellence, I wanted to generate it," and you are regarded as the mastermind, if you like, behind the Excellence Initiative. What do you think is needed to sustainably cultivate young talent in research?

First of all, we need the will to give young scientists and researchers the necessary independence. We had and still have the habilitation procedure, which works well in some ways, but in my opinion has become almost a coercive instrument with which older professors restrict younger ones. Later on, I experienced that myself. I also have my habilitation, but my concept was this early autonomy. In other words, people who already had their doctorate for a few years, had postdocs, and were then able to work independently. I am convinced to this day that you can be hugely creative, especially at this age. Not everyone, of course, and there are older people too who are creative. Galileo wrote his famous book about the two systems at the age of 68! It was a miracle in those days to live so long. But in short: early independence. At the DFG, we developed the Emmy-Noether concept, which still exists today. This later became the Starting Grants of the European Research Council, which I also established. You need an environment where scientists can truly work in peace. That's not just early independence, but also critical mass: they must have access to tools that they can use to answer their questions. That's why I always had a mixture of young people, junior scientists and researchers, and older colleagues my age. It created a very pleasant interactive environment.

Was it also necessary to break old habits?

Yes, it was necessary to break a lot of old habits. Even the fact that suddenly people who are not habilitated are writing their own publications and applications. Regardless of the money that we later received from the Gene Center, they also wrote applications themselves, including international ones, and above all publications. Some people certainly had to get used to the fact that they were not named first, but rather that only these young scientists were credited on the paper. That was the important thing: they didn't have to name someone on the paper simply because

there was an institute director somewhere. No, these were their own papers. That was quite rare in Germany at the time, but it had long been accepted abroad, of course, so that they could publish. If you submit a paper to Nature or Science and American journals, nobody asks whether there is an institute director anywhere, but the relationships must be clear.

They helped break down barriers.

We tried to tear them down, and we succeeded. Of course, like many others I also realized that you need a critical mass for science. At the time, you could send individual proposals to the DFG, but also to the collaborative research centers. But even that was still not enough. Then we founded the first DFG research centers. I remember the very first one was in Berlin for mathematics. I think it was Mr. Grötschel. And then we founded one in Würzburg. Lohse, Professor Lohse. He had previously been group leader in 1984 or 1985 and then moved to Würzburg. All these fellows were appointed and went everywhere over the course of time.

What prompted you to enter the BioRegio competition with the Munich-Martinsried site in 1995? The idea was to leave the field of basic research and transform research into innovation. What were your reasons for expanding research to encompass innovation, leading you to also introduce the term "Munich innovation culture" at the time?

What lies behind the culture of innovation is that as a scientist you must also be open to applications. Not that someone must necessarily make use of what they are doing. But if projects, which you often don't even know beforehand, lead in certain directions, to projects, the researcher must be able to follow them. So, if you can start a biotech company, you must have the capacity to do it. That was the idea behind participating in this competition. To be fair, I had also learned that in America. After all, it all started back in the seventies with genetic engineering: that's when the first biotech companies were founded. I'm thinking of Genentech and Biogen, which are still around today. And the Biogen people were often the founders here in Munich back then. One colleague, Professor Hofschneider, who unfortunately has since passed away, was even part of their start-up team at that time.

In this way, it was quite clear to me that we had to create a framework so that people who wanted to – nobody had to – would have this opportunity. Of course, this requires a lot of effort. And naturally it's mainly about money. Innovation culture also means venture capital, and that didn't exist at the time. But by founding this center, perhaps also by using the term "innovation culture," some of the potential investors woke up, came to me and said: Can you really found companies there?

Does science, in some way, also have a kind of obligation to society, so that through the findings of science, products should be launched for the benefit of society?

Yes, it very much does. I think that if the situation demands or requires it, then as a scientist you must also follow this direction. The BioNTech founders in Mainz are the most recent example. I know them from the time when they were working in a DFG collaborative research center and they were already working with RNA molecules, but at that time their goal was cancer research. That is still their goal today. But then the coronavirus pandemic suddenly started and, fortunately, they were quick off the mark, and that's great I must say: they put all their resources into the development of a vaccine against the coronavirus. Technically, it's not tremendously different to developing a drug for cancer. Conceptually, however, it's much more complex and much more difficult. But they did it, which is admirable. And that was also the idea back then.

You set new standards in biochemistry and molecular biology, researched the differentiation of cells, the multiplication of genetic material, prions and associated diseases such as BSE, as well as the big world of viruses. Most people have only been interested in viruses for a good two years. This topic has now accompanied you for almost your entire life. As a researcher as well as in your private life. As a child, you yourself fell seriously ill after an unsuccessful smallpox vaccination. Your wife suffered from the life-threatening Hong Kong flu. Viruses thus became your area of expertise. And you recently published a new book, My Life with Viruses. What fascinates you so much about viruses?

Well, these events that you referred to: The problem with the smallpox vaccination – I was a good year old then, but I can't remember it. I was treated at the time, in the middle of the war in 1942, with Prontosil, a sulfonamide, which is still available today. Back then, it was a blood-red liquid, a dye. It was Paul Ehrlich's idea that dyes could be used to develop drugs. My wife had contracted Hong Kong flu in 1968 when we went to Berkeley and almost died. She was 24 years old at the time. In the Bay Area, in Berkeley, San Francisco, over 16,000 people died in one month. It took a year for the virus to get from the West Coast to Europe. By then, the flu was much weaker, but still severe enough. As a researcher, indeed, you are interested in viruses because they are good model systems. They are very small. The human genome, which was first determined in the early 2000s, has 3 billion building blocks. The viruses we were working with at the time had maybe 5,000 or 6,000 building blocks. Neither the technology nor the data processing was so advanced in the 80s that work with the human genome could start right away. I was still assigning diploma theses to determine the sequence of 50 building blocks in a piece of DNA. 50 building blocks! That was enough for a diploma thesis back then. Today, with these new Oxford Nanopore machines, you can manage 20 human genomes a night. Now we live in a completely different time. But back then, viruses were very important model systems for practicing sequencing, for conducting the first genetic engineering experiments. At that time, we were unable to isolate fragments, pieces of DNA, from the human genome. We didn't even know where to start. But viruses often have only one restriction site or two, so we learned to isolate the pieces of DNA and link them together. That's a wonderful model system. Apart from the fact that they are also pathogens. But you can only fight them if you know what you're talking about and

if you know what you're working on. The major achievement or breakthrough with the coronavirus came when someone published this sequence on January 27, 2020. Then everyone, including the BioNTech founders and many others, could draw appropriate conclusions and start working with it.

This leads us nicely to the next question. The fact that we can currently lead an almost normal life again in this country can be attributed to the effective vaccines against the SARS-CoV-2 virus. Despite genetic engineering in biological production, the novel vaccines are welcomed by the majority of the population. Genetic engineering in agriculture, on the other hand, is widely rejected by society. In a guest article in the Frankfurter Allgemeine Zeitung newspaper at the end of last year, you called for a change of perspective in genetic policy. How could this be achieved?

To date, it has not been achieved. Medical applications have been accepted from the very beginning. Such as the first time insulin was produced by means of genetic engineering. Suddenly, the difficult conditions under which pancreases from cattle all over the world were transported frozen to Europe or the U.S. and from which insulin was then isolated, could be eliminated. That was over in one fell swoop and everyone else was able to produce insulin. Hundreds of these proteins are now on the market. Growth factors, monoclonal antibodies etc. This is accepted because it works. In agriculture, a kind of proxy war is being fought with the help of genetic engineering. Agriculture as it is currently practiced is not sustainable. In Europe and in Germany, it's getting better and better. But these huge fields that you see in Brazil and in Ukraine, where the farms have an average size of 4,000 to 5,000 hectares, there is not a single farm in Bavaria of that size. You can no longer pluck the weeds by hand, you need plants that can either somehow cope with them or you need insecticides. The population is against insecticides and herbicides because they are chemicals, even though they have been tested hundreds of times. But in this way, the whole of agriculture is discredited and, with it, genetic engineering, which is supposedly to blame. In Europe, however, there is no genetic engineering in agriculture at all because it is prohibited. Nevertheless, agriculture is not sustainable and attempts are continually made to limit the areas of land and to achieve sustainability. By banning herbicides etc. Why I have hope now is because a new era has dawned. There is a new technology, I call it genetic engineering 2.0, namely CRISPR/Cas technology, which can be used to edit genomes. So, you no longer have to isolate and transfer whole genes, but can change individual building blocks. Two women – Emmanuelle Charpentier and Jennifer Doudna – were awarded the Nobel Prize in Chemistry two years ago for this technology. This technology has enormous potential because, unlike conventional genetic engineering, it no longer involves genes but individual building blocks.

Does it also depend a little on the communication of this technology, to explain more clearly to the masses what the benefits are?

Yes, of course we tried that in the past, too. But with the old technology, to even find the cells that were genetically modified, antibiotic resistance had to be introduced – back then, 40 years ago. Of course, some thought that this would introduce antibiotic resistance into the environment, which was not the case. They are brought into the environment in a different way, essentially through animal breeding. None of that is necessary today. That's now history thanks to the new high-throughput technologies that allow you to sequence the plants. Almost any farmer could do it. He doesn't need to, but he could. But this has not really reached the public yet, although the Leopoldina, the National Academy of Sciences, to which I also belong, had a committee that already completed a paper recommending that the legislation in this area be changed to enable this technology to be applied. Because our opinion is that, without this new technology, agriculture will not become sustainable. Herbicides and insecticides will still be needed. But there is also natural resistance. That's what I've been promoting, and there are model cases for that. There are good examples, which I mentioned in the essay last December, like the 70-plus plant breeders who have joined together to find and cross out natural resistance in wheat. And it seems to be working quite well, too. When the project started a year and a half ago, Ukraine was not yet the focus of all discussions. Today we are glad that there were earlier developments. For example, there is this famous yellow rust, which makes wheat resistant without the need for herbicides.

As a researcher and science manager, you have revolutionized German and European science and undertaken far-reaching, pioneering work. What else would you like to achieve?

Using genetic methods in agriculture, as just discussed, would already be a major achievement. Another major goal is to make progress in cancer research. The idea of using messenger RNA vaccines, which we talked about at the beginning, in cancer therapies, that would be a big target. Almost all of today's cancer therapies are aimed at tumors of the hematopoietic system, lymphomas and leukemias and so on. Single cells that are floating around in the blood and degenerating. The big challenges are solid tumors, i.e. lung cancer, breast cancer, prostate cancer and pancreatic cancer. It's not so easy here. New approaches are needed and are indeed being pursued. But we have not yet reached that stage. So solid tumors, scientifically speaking, would be a great goal.

Do you have the confidence to forecast a time frame?

No, it's difficult to say. But so much is expected because of the success of vaccine development with messenger RNAs. I think we could see something on the market in the next ten years and we will get to the important ones, such as breast cancer or lung cancer, and above all the pancreas, which is almost untreatable. The prospects for this are good. Some are already in the second phase of clinical trials with colleagues from BioNTech and here in the surrounding area. Great care must be taken. It is a delicate question when you think about it because it is certainly more difficult than working with viruses, because you must work with the body's own cells, and you have to find

proteins that exist only and exclusively on the cancer cells and not on the normal cells. That is a really difficult task. That is one of the biggest challenges that I see, apart from the agricultural problem, which has not only been a problem since Ukraine, but is basically a huge problem due to the world population and its growth.

You were and are a great visionary. What is your vision for the future of biotechnology and, in this context, of Munich, Martinsried, and ultimately Bavaria as a location?

The only thing I haven't been able to do when I look around here and see all these buildings is build the subway. The government promised that 40 years ago. Here we are in a district of Munich and the border is just where the Gene Center is, where the road goes down there. Sometimes this border seems to me to be more difficult to cross than the national borders during the Cold War or the borders between South and North Korea. Now that's a bit of an exaggeration, but they haven't been able to come to an agreement. I often see – I almost said hundreds of – students at the bus stop in Großhadern waiting for the bus here, where the bus trailer often isn't big enough to get them to the institutes here. Why they couldn't build the train line to Gräfelfing and so on long ago is a complete mystery to me. But you don't have to succeed on all fronts.

On the occasion of Bio^{M}'s 25th anniversary, what are your your hopes for the next 25 years, for the complete biotech industry and for Bio^{M}.

Bio^{M} has of course been key to this whole story. Mr. Domdey, at that time a dedicated group leader at the Gene Center and one of the first, if not the first young scientist, set up the center envisaged in the BioRegio application, which we subsequently won, when it was clear in the summer of 1997 that I would be leaving as DFG President. Many of the things we see here, especially all the companies, are of course his babies. Achieving this was a mammoth task. Not only did you have to empower young people who wanted to start companies, but you needed money. Then you needed permission to build here. Then you needed the state government. He somehow convinced everyone that this would work. One big wish would be that this continues in the future. It's fair to say that this is the century of biology. The new CRISPR technology, which has since been further developed, has modified, or is opening up, I would almost have said, endless new possibilities, also for company start-ups. Not only for basic research, but also for company start-ups. The concept of interdisciplinarity persists. Back then, we had physicians, biologists, chemists, pharmacists, microbiologists, everyone together. That has not changed at all. On the contrary, because of the new instruments that are now available, it is becoming more and more important. But you must maintain that standard of excellence. You must still try to find young people. I'm now going to say something really mean: I don't think you find young people with committees. Not if you appoint ten people and say: this microbiologist is now the best in the world. It sounds very arrogant, but I was lucky at the time that I was allowed to do it on my own. It could have gone wrong; it could have been a disaster if the wrong people had been appointed. But you must observe the field closely and enjoy these things. I can only hope that there will be people like that in the future. Today, the Gene Center is managed very well. I can only hope that there are people who will continue to do that and especially continue so methodically, also here at Bio^{M}.