Opening speech by the President of the
Max Planck Society for the Advancement of Science

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Ladies and gentlemen, dear guests,

As a student at Maximilian High School here in Munich, Max Planck had two great passions: music and the sciences. When he completed school at the age of 17 with top grades, the question came up of whether he should study music or physics. The advice he received from his family was very plain: he should by all means be sensible and study music. One was certain that three hundred years after Newton there was nothing new to discover in physics. But Max Planck chose - as we all know - to study physics. Although I can't judge his qualities as a pianist, I am nevertheless certain he made the right decision.

Together with another passionate music lover, Albert Einstein, he succeeded in overturning decade-old theories in physics and putting forth a completely new understanding of the world. Albert Einstein devoted his attention to the large elements, the cosmos, and developed the theory of relativity while Max Planck focused on the very small elements, the atoms, and developed quantum mechanics.

Both not only shared a love of music and an appreciation of its exceptional historical contribution to our understanding of our world. They were also in complete agreement on another matter: never would anybody ever be able to practically apply their discovery. They performed basic research in its purest form or, rather, science for science's sake.

Today, nearly a century after their groundbreaking findings we have to differ with Planck and Einstein at least in this respect. It took many decades, but without quantum mechanics there would be no transistors, for example, that have become the heart of our society. Computers would still operate with tubes, fill complete factory buildings, and not even have the capacity of a modern calculator. Mobile phones would be just as unthinkable as ABS or airbags. And without Einstein's equations, the now ubiquitous GPS system would have difficulties distinguishing between Munich and Stuttgart. The list can be extended at random: whether lasers, computer tomography, optical data transmission, or satellite technology, without the basic research performed back then our life today would be hardly imaginable.

A glance at the past however reveals that basic research cannot only trigger widespread industrial and social revolutions. History also reveals that idealists and visionaries are needed to implement the results. In Europe prominent scientists such as the Italians, Volta and Galvani; the Frenchman, Ampere; or the Germans, Lichtenberg, Gauss, and

Ohm advanced research into electricity. But it was an American, Thomas Alva Edison, who identified the economical importance of electricity. Today, the most significant of his many companies, General Electric, employs over 300,000 people and has a turnover of roughly *134 billion US dollars*.

Just how essential the social climate is for these visionaries becomes evident in another example: Karl Pfizer *(Deutsch aussprechen)* and Karl Erhart both originated from the Swabian town of Ludwigsburg. They dreamed of building up their own factory for fine chemicals and pharmaceutical products, but in small town Germany of the 19th century there was no room for their ideas. On a whim they emigrated to the US in 1848 and founded a company in New York, which is now the global leader of the "**Big Pharma**" with over 120,000 employees and *45 billion US dollars* in revenues: Pfizer Incorporated.

The course of the most recent "industrial" revolution involving red biotechnology reveals that the problems experienced back in 1848 are regrettably still very present today. While Germany was painting the bleakest picture of the risks and politicians were seriously considering banning restriction enzymes, an indispensable tool in biotechnology, Genentech was established in the US in 1976 and Amgen shortly thereafter. Today both companies combined employ around 15,000 staff, and the turnover amounts to *8.1 billion US dollars*.

But despite getting off to a bad start, the situation in Germany has undergone changes. There are more biotech companies here than in any other European country thanks to the investor friendly climate that has prevailed since the middle of the nineties. Of course in the early stages some over did it, and not all of the original company concepts turned out to be viable in the long-term. Nevertheless even since the onset of more difficult times following the big stock market bubble almost four years ago hardly anybody has questioned the fact that new technologies such as biotechnology will drastically impact our life in the decades to come.

Allow me to go into more detail on the opportunities and problems of red biotechnology:

Red biotechnology is regarded as one of the **key** technologies of the 21st century with an enormous growth potential. Last year, Genentech and Roche made about *2 billion euros* with their cancer drug MabThera® or Rituxan®. On the whole, the potential for the antibody-based drug market is estimated to exceed *50 billion euros*. What's more the "classic" pharmaceutical industry is increasingly using biotech methods in product development. In recent years over 70 percent of Pfizer's research and development investments have been made in new biotech methods. Thus, the distinctions between searches for agents with a biotechnological and chemical basis are diminishing more and more. As a result, biotechnology is increasingly lurking its way into the health markets of western industrialized countries - averaging 10 to 14 percent of the gross domestic product - via the pharmaceutical industry. In the US alone this corresponds to an annual turnover of *1,000 billion US dollars*.

In the decades to come this market will grow in size and importance for a number of reasons:

- The increase in the average age of the population
- The "ailments of our time" brought on by non-conducive habits
- The growing number of treatable sicknesses
- Increasing affluence and the means to cover costly treatments of sicknesses that were simply accepted in the past
- The rising demand for "life style drugs"

Despite this apparent importance of biotechnology for society, surprisingly little is known about its function and possibilities. This is not because people lack interest but rather because wrong conclusions are drawn and sheer misconceptions develop as a result of the complexity of fundamental questions such as how does life function in general and, more specifically, in our bodies?

Although we are intuitively aware of life and the human body, modern scientific analysis has to go far beyond intuition and rely on exact qualitative and quantitative descriptions of all molecular processes in our bodies. Most people only really begin to understand this task once they put on "molecular glasses" that enable them to see our bodies in a different light. An average person weighing 70 kg suddenly turns into a gigantic amount of atoms, or, to be more exact, 6.5 × 10 to the 27th power of atoms. For scale think of it as approximately one million times more than the stars in the known universe or all the sand grains on all the beaches on our planet.

Even more impressing – if it is at all possible to present a more impressive figure – is the complexity with which these atoms can be joined to molecules. If you take a molecule with an average size of 500 grams per mole, there are around 10 to the 62nd power ways of joining the atoms in a meaningful way chemically speaking. For scale think of the same number of sand grains in the shape of a ball having a radius of 6.5 light years and weighing more than the entire known universe.

The differences between molecules don't necessarily have to be big in order to have a biological or medical effect. For instance, let's take the very closely related molecules, chemically speaking, testosterone and progesterone. While testosterone is the most important male sex hormone and is responsible for one for the development of the male reproductive organs, progesterone is produced in the ovaries and placenta and is essential for the preparation and course of pregnancy as well as for lactation after birth.

These examples clearly depict the dual dilemma that biotechnology faces today. The apparent simplicity of biology and the great successes achieved in biotechnology lead to enormous expectations of this key technology, which cannot always be met in the short-term since our present knowledge on biochemical and genetic processes is really only the tip of the iceberg.

This does not mean that a deeper understanding of these processes goes hand in hand with a greater variety of possibilities. However, seeing as numerous successful developments in the past were made possible with an elementary understanding, more basic research will certainly open the door to tremendous potential for biotechnology over the mid and long-term.

Unfortunately we obviously lack the patience to commit ourselves over the inevitable long-term. Of course it is prudent and indeed necessary to make those usable results available to mankind as quickly as possible. When it comes to treating sicknesses we have a moral obligation to make use of all possibilities to develop new medication on the basis of today's knowledge. At this same time this does not mean that our society produce medication and other products **at the expense of** basic research. In doing so we would deprive ourselves of the opportunity to produce effective drugs in the future based on as yet unknown findings.

With the future in mind the mantra of science cannot be to invest all of our resources in pure application, but, rather, by using good judgment **to engage in one aspect without neglecting the other**. Of course neither one is free. The US has demonstrated that the funds employed here are sensible investments in the future. The American biotech industry, which surpasses ours by leaps and bounds, is based on just as much public funding. The US government, for instance, has increased the budget of the National Institutes of Health, the foremost research funding organization in biomedical research, by an average of 15 percent per year from *13.6 billion US dollars* in 1998 to *27.2 billion US dollars* 2003. In Germany by comparison the **entire** annual sum for public research funding amounts to a little less than *16 billion euros*, and only a fraction of this goes to basic biomedical research.

Now and then we hear that in today's *global village* knowledge, more than anything else, is common property. A German founder can, of course, like his or her American colleague take the latest edition of *Science* or *Nature* and read up on what researchers have discovered and based on this establish a new company. At the same time no attention is given to the fact that knowledge is linked to specific scientists or individuals something that becomes apparent in a study conducted by Francis Narin, Kimberly Hamilton, and Dominic Olivastro. They explored the connection that exists between the high tech industry and publicly funded basic research by analyzing the cited sources in patents. Their findings show for one that in the last twenty years basic research has gained dramatically in significance in this sector. In the US the relation between citations of public research compared to other patents increased over ten years from 0.4 in 1985 to 1.5 in 1995. In other words at the start of the eighties less than one third of the citations came from publicly funded research, but, by the middle of the nineties, the majority of citations stemmed from publicly funded research.

This study also brought to light a more important aspect namely, that despite the global village and international publications, the ties between strong basic research and the high-tech industry are now more consolidated than ever in **one** country or, as the authors put it, "**a strong scientific base is necessary for a strong national technology**".

The Max Planck Society recognized the connection between exceptional basic research and resulting industrial application early on, and since 1970 it has been running Garching Innovation GmbH, its own technology transfer company. With its help there have been a total of 65 start-ups, 38 of which have been financed with venture capital. Among the most well known apart from Sugen Inc., which was sold to Pharmacia & Upjohn Inc. (now Pfizer) in 1999 for *650 million US dollars*, are Evotech OAI, GPC Biotech, and DeveloGen. One of the most recent start-ups, which, like Sugen Inc., was also carried out in association with American scientists, is Alnylam Holding Inc. - already regarded as being the most important company in the rapidly growing field of RNA interference technology.

Despite the connection between basic research and application, performing basic research with a view to a specific product will be the exception and not the rule in the near future even though it might be economical and the approach many scientists favor. There are a number of reasons for this. To begin with, the product of science or "Wissenschaft", is, as the German word suggests, "knowledge" or "Wissen" itself. Although this is an important cultural asset, it cannot really be converted into a product. Accordingly, knowledge has to be "translated" to a scientific product in a second or third step and because this product is the result of basic research, scientists who perform basic research have no specific product in mind. As a rule, industrial research takes pre-existing findings or knowledge as the basis for designing a more or less specific product. This is not science, but rather development. The inherent nature of basic research implies the unpredictability of its results.

Another aspect worthy of consideration is the manner in which science or "Wissenschaft" proceeds in creating knowledge (Schaffung von Wissen). This is by no means a slow and continual process of collecting findings from one's own research activities that ultimately leads to new findings. This linear idea connected with the oft-romanticized notion of the "lonely thinker", has fortunately little in common with reality. I say fortunately because such a linear relation would only permit a linear growth of our understanding and knowledge. In actual fact, our knowledge grows exponentially, thus explaining the rapid progress of recent decades. Researchers not only work with their own data, but also incorporate as much information as possible when planning and assessing approaches. Reading, discussing, and interpreting data from other researchers is just as important as their own experiment. As a result feedback networks develop and each and every new finding enables science to advance even faster.

This fact can be clearly illustrated by the publications on the tumor suppressor gene **p53**, described for the first time in 1981. Between 1984 and 1987 some 50 articles were published per year. But by 1995 the number had increased to over 1,600 and reached a maximum of more than 3,000 articles in 2000. These figures show that it took roughly ten years before there was an exponential increase in new findings. All in all there have been more than 27,000 publications on p53 since its discovery.

This knowledge does not necessarily bear a relation to its possible application. p53 is regarded as one of the key proteins in the development of cancer. Research on it has led to valuable insights into the development and progression of cancer, which have indirectly influenced the course of cancer treatment and will be an important basis for future development of the next generation of oncology drugs. Nevertheless p53 itself has not been able to be used as a "target" to develop a new drug.

The situation is completely different in the case of CD20, a surface molecule that is being expressed on a specific type of cancer cell called the non-Hodgkin's lymphoma. Despite the relatively small number of 3,000 publications in total on this molecule, it is the target of one of the most important cancer drugs, namely, Rituxan®. It was the first biotech drug approved in oncology and was developed to target CD20. While other chemotherapy drugs generally target dividing cells and therefore have an array of side effects, and show limited effectiveness against non-Hodgkin's lymphoma, Rituxan® is highly effective and has only limited side effects.

Ultimately the scientific correlation between a gene, in this case CD20, and the sickness was identified and became the key for developing the drug. This approach in biotechnology, that is using knowledge on functional biological correlations to develop drugs, generally termed "the target-based search for and development of agents" has radically impacted the development of drugs and medications. We are only at the outset, and the possibilities for developing agents in this manner will increase with increased awareness of

- biological connections in the development of diseases.
- molecular interactions between identified targets and the agents targeted against them.
- biochemical processes of agents and resulting physiological effects.

Not only will pure biology have a hand in fighting diseases. The spectrum will also extends to include

- mathematics and quantum physics to describe atomic and molecular interactions.
- computer science and computer development without which knowledge cannot be implemented.
- chemistry, a must to produce agents and finally
- biology to reveal the connections between molecules and diseases.

By international comparison Germany is competitive in all of these areas, a fact the numerous biotech companies founded in Germany goes to show. Ten years ago there was only a handful of companies in this branch. Today there are some 350 companies. Germany is the leader in Europe and third worldwide behind Japan and the US a fact that has to be qualified by noting that biotechnology has a longer tradition in the latter two countries and the companies are generally more experienced. The world's largest biotech company, Amgen, for example, employs more staff than all of the 350 companies combined.

Unfortunately, this unfavorable comparison between the US and Germany has not improved any in the last three years. During the new economy bubble, which also impacted the biotech branch, serious mistakes were made that have led to a far-reaching consolidation phase of numerous companies, which initially embarked optimistically only to be shut down. But it would be wrong to over-generalize and write off biotechnology altogether. Many companies will weather the reorientation phase and enter the international arena with renewed fortitude. We have the necessary know-how and highly motivated managers and scientists to apply it lucratively.

The situation on the venture capital markets is proving to be an increasing obstacle with regard to insufficient public support of technology transfer. Figures from the German Venture Capital Association show that in 2002 the member companies were only able to attract a little under *1.0 billion euros* in new risk capital, roughly two thirds less than in 2001. By comparison, the US attracted around *7.7 billion US dollars* from venture capital companies in the same time frame.

More problematic is the situation for new investments. While in the US *21.2 billion US dollars* were invested, of this roughly *2.8 billion US dollars* in biotechnology, only *2.8 billion euros* were invested in Germany and of this merely *240 million euros* in biotechnology. This inadequate flow of capital is further aggravated by the fact that a large number of venture capital lenders are forced to concentrate available funds mainly on pre-existing investments meaning that funds are no longer available for new start-ups. The reasons are coupled with the lack of opportunities for companies to go public. As a result companies have to be financed longer than planned by private investors. At the same time the most important option for an exit of the investors is missing that would make new capital available for investments.

In Germany there is another structural pitfall in the area of biotechnology when it comes to applying basic research findings in industry. Most of the "raw data" derived from universities, Max Planck Institutes, and other research organizations require additional validation to make a marketable product out of scientific findings. A typical example is the so-called "target", or biochemical target structure that can be used for developing drugs. For product development it is essential not only to be able to draw a scientific correlation between the disease and the "target", but also to collect statistics on the frequency in the patient population and in healthy individuals. These statistical aspects have a minimal scientific content meaning that typical public funds are not available from the institutes or the German Research Foundation. At the same time venture capital financing is hardly possible because, as I mentioned earlier, it is not available and, secondly, at this stage the scientific concepts themselves are nowhere near industrial application for a "seed financing".

In the US this problem is much less pronounced. On the one hand, the possibilities for a seed financing are much greater. On the other hand, the scientific concepts at the point of founding a company financed by private funds are considerably more advanced since public funds, especially from the budget of the National Institutes of Health, support studies that explicitly deal with medical application. In most cases American companies are much better off at the point of inception than German ones.

It would be devastating for the future if investments were only made in preexisting know-how and companies and basic research were neglected. Only by focusing on the development in companies and on basic research in science can we ensure over the long-term that the economic prospects of biotechnology in Germany are developed and the products are used for the benefit of the population.

The scientific and economic potential in Germany is just as crucial as the willingness of society to identify the opportunities and not just the risks. Regrettably the past all to clearly shows the consequences of focusing exclusively on the theoretical risks for an entire sector: Germany once had the reputation of being the world's apothecary. Public discussion characterized by an aversion to technology and the ensuing restrictive legislation played a significant role in Germany losing its entire large-scale pharmaceutical industry. Only by creating an "innovation culture" will the germinating biotechnology sector be able to reach the standing it has already achieved in the US. As the former President of Germany, Roman Herzog, put it: “Innovation begins in the mind: it starts with our view towards new technologies, new work and education forms, and ultimately towards change in general.”

Whether it is the revolution in physics thanks to scientists like Planck and Einstein or in biomedicine thanks to Arber, Nathans, and Smith – the discoverers of the restriction enzyme – it was basic research that changed daily life decades later although in the beginning nobody held it for possible. I reckon the next revolution will come about without its practical significance being initially apparent.

Ladies and gentlemen, let us delve into the unknown without any preconceived notions because that is where the true potential for the future lies.