Acceptance speech by Hermann Bujard

[Check against delivery]

Dear Mrs Widmann-Mauz, dear Mrs Hengge, dear Mr Erlen, dear Colleagues and Guests!

Your message, dear Mr Hacker, that the Robert Koch Foundation has chosen to present me with this year's Robert Koch Medal greatly surprised and delighted me, and naturally, I felt highly honoured. At the same time, I must admit that I felt a certain sense of unease at the thought that my contributions to the field of infectiology, together with those of my laboratory, should be associated with the name Robert Koch, a giant in his capacity as a researcher and doctor. While I am very aware of the distance between myself and Robert Koch, I gratefully accept the award, which also honours the work of many of my engaged co-workers – and not least as an incentive for our malaria research, in the hope that even at my age, one can still be open to incentive!

It was only late in life that I made the decision to work in an area of infection biology that was of relevance to the medical field. After studying chemistry, I had the good fortune to work at the University of Göttingen as a doctoral student of Hans Brockmann, one of the great natural compound chemists, in an environment in which "precise questions addressed to nature" – in my case, the structure and function of actinomycines – were asked, and in which students were imbued with enthusiasm and trained to work independently. Ideas and the results from experiments were rigorously checked, which occasionally caused enthusiasm to turn to disenchantment – a formative, classic school! The second turn of good fortune, my contacts with the Göttingen working groups headed by Manfred Eigen and Fritz Cramer, opened the door to another world for me. At the "nucleic acid tea" meetings in Eigen's institute, issues relating to prebiological evolution and the emergence of life along physical principles were discussed. It quickly became clear to me that here, in molecular biology, was where I belonged. My time in "small" Göttingen with its 3,500 students was a particularly happy one. I worked in an environment inspired by great scientific role models - Werner Heisenberg, Friedrich Hund and Otto Hahn were "visible" - and I found my wonderful wife, who played a key role in everything that has succeeded in my life.

My move to molecular biology in 1964 could hardly have turned out better. As a postdoc under Charles Heidelberger, who died so young, I investigated the mechanism of action of 5-Fluorouracil, which "Charlie" had developed shortly before, and which is still used today as a highly effective cytostatic treatment in cancer therapy. For me, this project, in which,

however, we disproved our hypothesis, was a stroke of good luck, since it gave me the opportunity to work with the later Nobel laureate Gobind Khorana, in whose laboratory I spent part of my time. His group worked on one of the core problems in molecular biology, the deciphering of the genetic code. It was an incredibly exciting period, and not only for us on site; Khorana's laboratory in Madison, Wisconsin, was the focal point of interest among the scientific community of molecular biologists. Francis Crick was a regular, inquisitive visitor, and it was no coincidence that it was in Madison where he presented in 1965 his "wobble hypothesis" on the genetic code for the first time. In the McArdle Laboratory, my main place of work, the young Howard Temin was researching next door. He had already developed ideas about a "reverse transcriptase", which at that time hardly anyone believed, but which would later be honoured with the Nobel prize. Madison, with its large number of outstanding researchers, was a fantastic place for starting out in molecular biology. Also – and for a German postdoc at that time, this was at first almost shocking, then a relief – there was the Anglo-Saxon academic culture of "flat hierarchies" and the relaxed manner in which colleagues treated each other.

In my enthusiasm for the "new world", I accepted quite quickly an Assistant Professorship at the Southwest Center for Advanced Studies in Dallas, Texas, - in retrospect almost rashly – and focused on my first "own" research programme, aside from some issues relating to the conformation of DNA in solution, on the infection strategy of bacteriophage T5. It was the time of the memorable Cold Spring Harbor Symposia of the 1960s, at which the insights were compiled which Jaques Monod had summarised in 1966 by claiming that "for the first time, life can be explained on the basis of physical and chemical laws". Alongside the work of the "Cambridge School" on the structure of nucleic acids and proteins, most of the relevant new information was obtained on the bacterial model system *Escherichia coli* and its viruses, the "phages". Molecular biology was "prokaryotic", exciting and competitive! During the course of our T5 studies, we stumbled upon promoters with unusual properties, and for two decades or more investigated these signals, which control the first level of information transmission from DNA. How rapidly can promoters be recognised by the information transmitting system (RNA polymerase)? How does a promoter sequence program the function of RNA polymerase at the beginning of a gene? And, finally, how is activity of promoters regulated, either negatively (repressors) or positively (activators)? A later spin-off of this work was the development of our "Tet switch", but I will come back to that shortly.

In 1970, I returned to Germany to work as Professor of Molecular Genetics at the University of Heidelberg. After 12 years, tired by the German university system, I accepted an offer by Hoffmann La Roche in Basel to establish "modern biology" in the company. An important

factor in my decision was the liberal research culture at Roche, which allowed me to bring my entire research group with me and to continue my work. The company's research focus was, understandably, oriented towards the major diseases in wealthy societies. Nevertheless, it was possible to establish a programme towards the development of vaccines against malaria, utilizing the still existing though dwindling research tradition of a company in tropical medicine. Malaria, still today one of the great scourges of mankind and a "poverty causing disease", has been a focus of my research ever since also upon my return to the Zentrum für Molekulare Biologie (ZMBH) of the University of Heidelberg. At the ZMBH, we developed a research focus on infection biology. With Heinz Schaller (Hepatitis B), Christine Clayton (*Trypanosoma brucei*), Richard Herrmann (Mycoplasma), Alexander Schmidt (*Bordetella pertussis*), Dominique Soldati (Toxoplasma) and our malaria group, we did, I believe, make a contribution towards firmly establishing infectiology in Heidelberg, which just a few decades ago was still a rather neglected field, and also set up an outpost in Burkina Faso. It is highly gratifying that we now have several malaria groups in the Campus, with the group leading the way headed by Michael Lanzer, a former doctoral student in my promoter group, who was at that time clearly "infected" by malaria.

The purpose of our work on malaria is to develop a vaccine, first against *Plasmodium falciparum*, the pathogen that causes the most dangerous malarial disease, *Malaria tropica*. We are currently focussing on the surface protein "MSP-1", which on the basis of a large number of results, mainly from our laboratory, has become a highly promising vaccine candidate. In the course of several years of field studies in Mali and Burkina Faso, West Africa, in collaboration with our colleagues Ogobara Doumbo, Yeya Touré and Boubacar Coulibali we found positive correlations between the humoral immune response to MSP-1 and protection against reinfection. We have also identified MSP-1-specific cytotoxic T cells in semi-immune adults, which are very likely directed against the liver stage of the infection. These findings and the results from further studies in animal and *in vitro* infection models permit me to formulate our hypothesis that vaccines based on MSP-1 will trigger immune responses that will act in a multivalent (i.e. against different parasite strains) and multistage way (against the liver and blood stage of the parasites).

In the interim, there is sufficient clinical material available for around 10,000 immunisations. The preclinical characterisation (stability, toxicology, etc.) has been completed to a large degree, so that now, nothing – except for the funding – stands in the way of the next step, a Phase I clinical study.

However, in the absence of these clinical results, please permit me, on the basis of two examples, to explain briefly how the genetic switch that we have developed can be used in infectiology. These switches make it possible to specifically control the activity of individual genes with tetracyclines (particularly with doxycycline), both in cell lines as well as in entire organisms such as yeasts, insects, fishes and mammals.

The medication that is currently most effective against AIDS and Hepatitis B was identified or validated in cell lines, in which the replication for example of the Hepatitis B virus can be tightly controlled by doxycycline. It is not difficult to realize that such cells are exquisitely suited for the identification of replication-inhibiting compounds.

The second example relates to the genetic control of harmful insect populations, such as those widely used in agriculture. With a method (RIDL) developed by a company in Britain, which is based on our Tet switch, it has been possible to breed for example strains of the mosquito *Aedes aegypti*, the transmitters of *dengue* fever, which when released in the open leads to females which are unable to reproduce. In this way, the mosquito populations can be eliminated at a local level. The first field trials on the Cayman Islands and in Brazil have shown that this strategy can be used to achieve effective, sustainable protection against dengue fever.

The decision to work on malaria has influenced my views in many ways. On the one hand, there is the fascinating biology of the parasite-mosquito-human system, which reflects a long co-evolution of three genomes, and which has led to the probably largest genetic “footprint” in the human genome – thalassaemias, sickle-cell anaemia – under which generations of humans will continue to suffer, even if malaria is one day eliminated. On the other, my co-workers and I have experienced the severity of the disease during the course of our field studies in the highly endemic regions in Africa. In “our village” of Safo, in a rural area in Mali, the average life expectancy among the population was 38, and before we set up a rudimentary medical service with our colleagues in Bamako, around 20% of infants and young children died from malaria. And malaria is not the only serious infectious disease that is rampant there. Despite the fact that their lives are so at risk, and are characterised by extremely harsh work in the fields, we met cheerful, courageous and friendly people, with whom it was a joy to work. In our wealthy society, we must act more decisively than we have done in the past to help such people to break out of the cycle of disease and poverty. It remains to be hoped that the current Ebola tragedy in West Africa will be a wake-up call with a long-term effect.

Robert Koch and his co-workers – and the same applies to the Pasteur Group in Paris – travelled regularly to the crisis regions of the world in which epidemics had broken out, and carried out important work there as researchers and physicians under the most difficult and dangerous conditions – some paying with their lives for their humanitarian engagement Against the background of the pusillanimous discussion around Ebola in our country, it is my wish that more people take these pioneers as a role model.

Many thanks to you again for your acknowledgement of our work.