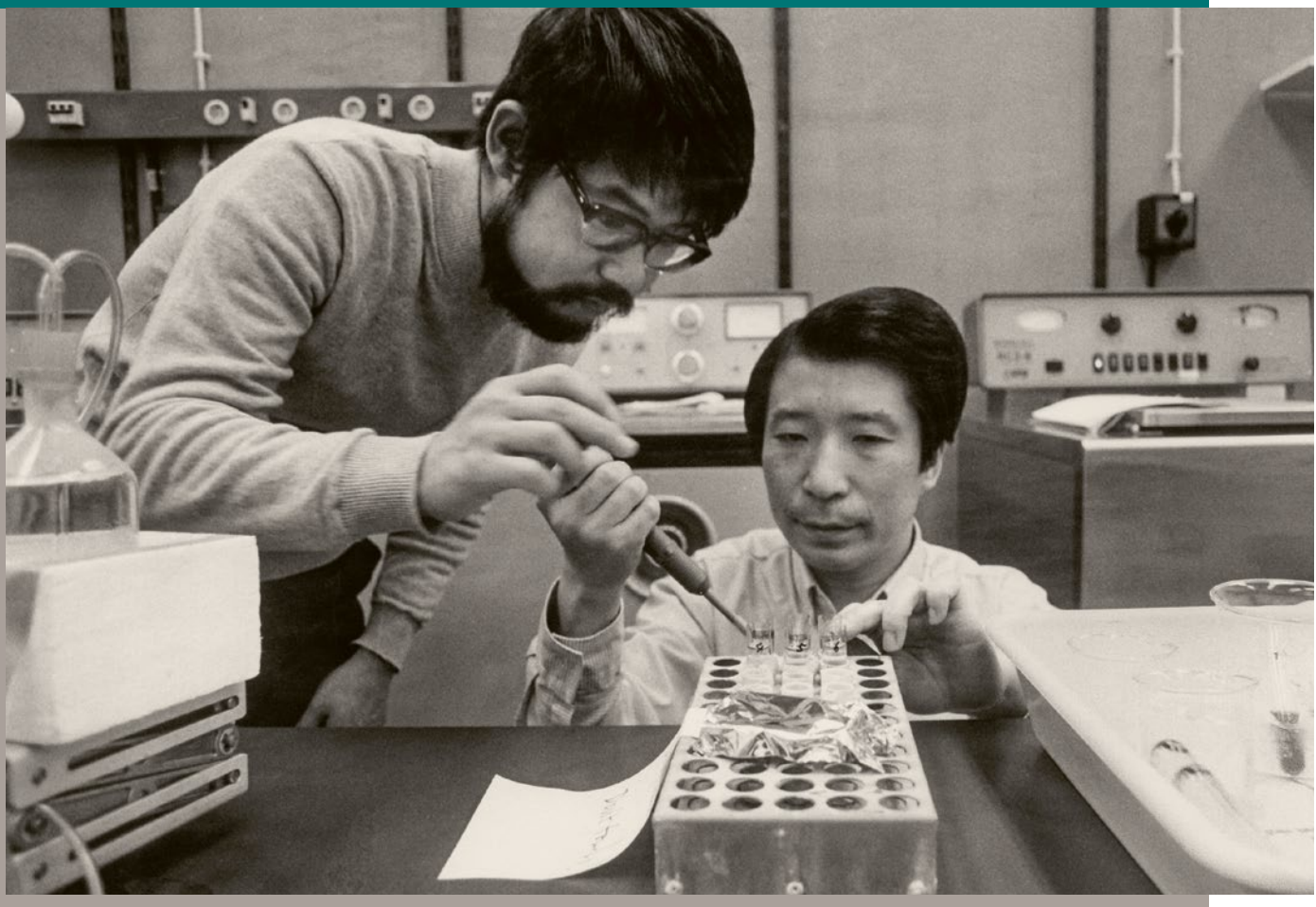
Genes and Men

50 Years of Research at the Max Planck Institute for Molecular Genetics



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PREFACE

RESEARCH IN MOLECULAR BIOLOGY AND GENETICS has undergone a tremendous development since the middle of the last century, marked in particular by the discovery of the structure of DNA by Watson and Crick and the interpretation of the genetic code by Holley, Khorana and Nirenberg. As more efficient methods to study DNA developed and highly automated, parallelised and miniaturised techniques to conduct these studies were established, research shifted to the analysis of complete genomes, in particular on the analysis of the human genome itself. Today, we are not only capable of determining the genome sequence of individual organisms in days, or even hours, at a reasonable cost, but even that of single cells. Currently, many scientists have moved from DNA sequencing studies to the exploration of the regulatory mechanisms, through which genetic information is provided or withheld in various situations.

Since its foundation fifty years ago, the Max Planck Institute for Molecular Genetics (MPIMG) has accompanied and advanced many of these developments. This is an occasion for us to look back and attempt to consider the development of the institute in the scientific context of the times. Only two of the following articles are written by science historians. While much has happened over the past 50 years, there are many who still vividly remember the institute's early days and who are able to share their memories of those times. Some of them, who know the MPIMG and its work well, gave interviews or wrote reviews of their recollections of the people who worked here and the research that was conducted back then. What finally emerged is a portrait of the institute and the people who shaped it from a highly subjective and, in some cases, very personal perspective. We very soon realised that life at the MPIMG was not only influenced by scientific events, but also by social and political upheavals. The result is not a historical review; it simply offers a collection of views by the individual authors and hopefully provides a lively glimpse at research under the impact of local events and global developments.

Naturally, the memories of past events are as manifold as the people who experienced them. Unfortunately, we were not able to include all the recollections

and pictures we received in this anniversary publication, especially those about the early years of the institute. We nevertheless wish to thank all those who have supported and inspired us with suggestions, stories, and pictures and apologise for cuts and omissions we were forced to make due to lack of space.

Today the MPIMG is once again in a situation resembling a “new beginning”. With the retirement of Hans Lehrach und Hans-Hilger Ropers in late autumn of 2014, two major departments were closed and the remaining staff – and with them surely many colleagues and supporters – are eagerly awaiting the arrival of the new generation of directors. Once again, the institute is facing major changes. I am confident, however, that this change holds great opportunities and exciting scientific developments. With this in mind, I would greatly appreciate your continued support and interest in the work of the MPIMG.

Berlin, September 2014

Martin Vingron

Molecular biology in Germany in the founding period of the Max Planck Institute for Molecular Genetics

HANS-JÖRG RHEINBERGER
Max Planck Institute for the History of Science, Berlin

IN THE 1930S AND THROUGH THE 1940S, a new biology began to evolve, primarily in the United States and Great Britain. By the 1950s, this hybrid science that had established itself somewhere between biochemistry, biophysics and genetics, gradually came to be known as molecular biology. The development was characterised by experimentation with and utilisation of a whole range of new biophysical, biochemical and microbiological techniques, the use of simple and rapidly proliferating model organisms such as lower fungi, bacteria and viruses or bacteriophages, the creation of cooperative scientific structures that defied conventional disciplinary boundaries, and the promotion of a new view of the fundamental processes of life that was inspired by cybernetics, information theory and linguistics.

In the 1930s, the potential to contribute decisively to these developments was concentrated on the campus of the Kaiser Wilhelm Society in Berlin-Dahlem. As Robert Olby, the first comprehensive chronicler of the history of molecular biology, commented in his book *The Path to the Double Helix:* "The right ingredients for the development of molecular biology were, it seems, in Dahlem."[1] But things were destined to turn out differently. Many of the promising young scientists working there at the time, among others Max Delbrück, Erwin Chargaff and Fritz Lipmann, to name a few, emigrated from Germany after 1933 to become pioneers of molecular biology, above all in the USA. Only the research on the tobacco mosaic virus, taken up in Dahlem by Hans Friedrich-Freksa, Georg Melchers, and Gerhard Schramm at the Kaiser Wilhelm Institute (KWI) for Biology and at the KWI for Biochemistry in the mid-1930s and later evacuated to Tübingen, was continued uninterrupted at the end of the war at the Max Planck Institutes (MPI) for Biology and for Virus Research in Tübingen. As a result, the two Tübingen-based MPIs were to become the major nucleus for the development of molecular

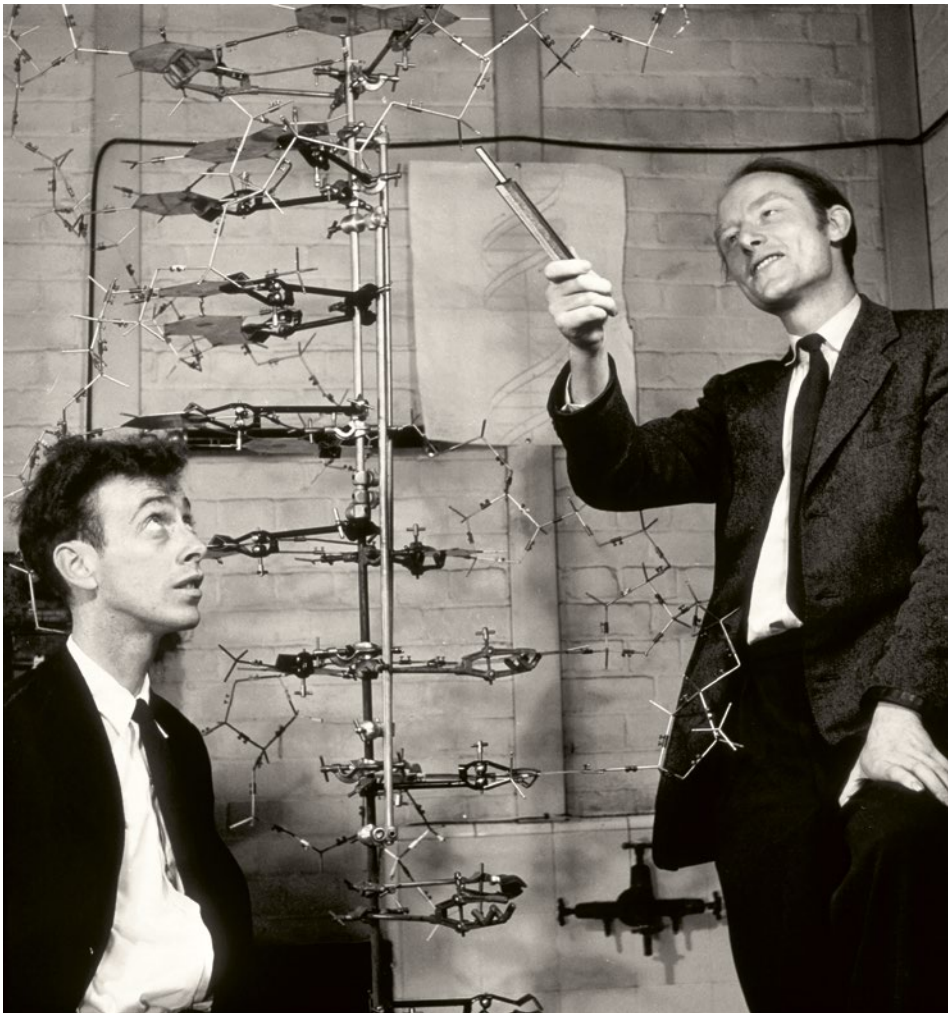
◂ **New building of the Max Planck Institute for Molecular Genetics** at Ihnestraße 73, in Berlin-Dahlem, 1971

Transmission electron microscopy image of an alkaline-stained Tobacco Mosaic Virus after oblique sputtering with platinum; image by Gerhard Schramm, MPI for Virus Research, 1954

biology in Germany after World War II. In the 1950s, they were the only institutes that had not fallen behind the world leaders in the field of molecular genetics. Yet even here, a small air-driven ultracentrifuge built before the war was still in use in the mid-fifties. It resembled the one that Schramm had conceived in the mid-1930s with Physikalische Werkstätten (physical workshops) in Göttingen.

Most of the talented young scientists, who could have picked up and continued the developments in the Anglo-Saxon world after 1945 in Germany, had either emigrated or been killed in the war. The next generation of researchers needed to be educated first. In the decade after the collapse of the "Third Reich" there was neither money for expensive equipment nor were systematic efforts made by the Max Planck Society in Germany to persuade the scientists who had left Germany to return. Until the mid-1950s, the number of young postdocs, who spent one or two years at British or American Universities to catch up with this new world of science could be counted on the fingers of one hand. Among them were the biochemist and physician Wolfhard Weidel in 1949/50 (later Director of the MPI for Biology in Tübingen), in 1953 the chemist Friedrich Cramer (later Director of the MPI for Experimental Medicine in Göttingen), the physicist Alfred Gierer (later Director of the MPI for Virus Research then Developmental Biology in Tübingen) and the microbiologist Thomas Trautner (later Director of the MPI for Molecular Genetics in Berlin). This was the year when Francis Crick, a physicist, and James Watson, a biologist, both working at the Cavendish Laboratory in Cambridge, discovered the structure of the DNA double helix, not only propelling molecular biology into its golden decade but also giving it its emblem – the now omnipresent molecular double spiral. Friedrich Cramer recollects the situation in Germany in the early 1950s: "We had chemistry and we had botany, zoology in the classical sense, but nothing in this field [molecular biology]. On the contrary, the hostility towards these modern fields of science created an environment under which I suffered more than a little as a repatriate."[2]

The discovery of the DNA double helix established the molecular basis of genetics definitively. In 1958, Crick announced his dogma of molecular biology:



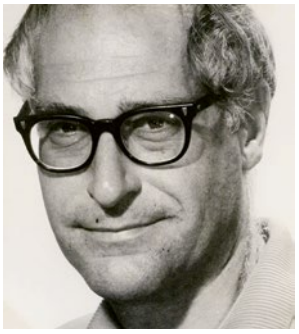
James Watson (left) and **Francis Crick** with their original model of the DNA double helix, 1953

DNA makes RNA and RNA makes protein. All the decisive findings about the molecular basis of inheritance of this decade were based on microorganisms – bacteria, viruses and phages – and the two key macromolecule classes involved in the process were nucleic acids on the one hand and proteins on the other. Around 1960, the experimental and conceptual core of molecular genetics with its central processes of replication (duplication of genetic information), transcription (transfer of information from DNA to RNA) and translation (conversion of the genetic information into protein) were broadly elucidated. The deciphering of the genetic code was within reach.

In 1958, a "Memoir on the Condition of Biology" ("Denkschrift zur Lage der Biologie"), written on behalf of the German Research Foundation (DFG), created quite a stir in Germany. Five, or one third, of the fifteen signatories expressly supporting the proposal came from one small university town, Tübingen. All of them but one were based at the Max Planck Institutes for Biology and Virus Research that were located there since the end of World War II. The memorandum stated that the field of biology, like no other area of the natural sciences, was currently going through a "far-reaching evolutionary change". The devel-

opment of new physical and chemical methods above all had pointed to a new direction in fundamental research for biology.[3] In any case, as the memorandum stated, it was not just about making up "lost ground" due to the war – to avoid mentioning the real issues directly – it was also about catching up with the modern research of other highly developed countries. The gap between the current and the ideal situation outlined by the petitioners of the memorandum – among them the biologist and virologist Hans Friedrich-Freksa from Tübingen, the biochemist Feodor Lynen from Munich and the botanist Josef Straub from Cologne – was nevertheless very wide. According to these pioneers, the biology department of a well-resourced university should include at least one tenured professorship in genetics, one in microbiology and one in biochemistry, in addition to the traditional departmental chairs of zoology and botany. The only location featuring this combination in the first half of the 1950s was Tübingen, and that was only thanks to the three Max Planck Institutes for Biology, Biochemistry and Virus Research.

In 1961, Max Delbrück took a two-year leave from the California Institute of Technology to found a new genetics institute with a molecular focus at the University of Cologne, based on an initiative from Straub. It was to be a compact and exemplary epitome of molecular genetics at one university in Germany. Delbrück's opinion was that the new biology absolutely must reach the universities, not just the MPIs. However, a commission was also established at the biological-medical division of the Max Planck Society (MPG) shortly afterwards in November 1962 to set up a Max Planck Institute for Molecular Genetics in Berlin. The MPI directors from Tübingen had pushed for this re-orientation of the Berlin Institute for Comparative Hereditary Biology and Hereditary Pathology (Vergleichende Erbbiologie und Erbpathologie). It became the first research institute in Germany to include the term "molecular genetics" in its name. Work at the institute was to concentrate entirely on viruses and bacteria and the research focus was on nucleic acids and proteins. However, attempts to attract phage geneticist Gunther Stent (1924–2008), who had emigrated from Berlin to the United States



Gunther S. Stent External scientific member of the Max Planck Institute for Molecular Genetics from 1967–2008

in 1938, to return from the University of California in Berkeley as the founding director were unsuccessful. But Stent, who had learned phage work with Delbrück, agreed to help to set it up and was appointed as an external scientific member of the institute.[4]

In 1964, the institute began its work with two directors. Chemist Heinz Schuster (1927–1997) had been working on the structure, function and modification of nucleic acids since the mid-1950s. Together with Gerhard Schramm and Wolfram Zillig at the MPI for Virus Research, he had developed a technique based on the use of phenol to extract ribonucleic acids from cellular homogenates. It soon belonged to the arsenal of methods used worldwide for working with nucleic acids of high molecular weight. At the time of his appointment, he was on a research stay with Robert Sinsheimer in Pasadena. Heinz-Günter Wittmann (1927–1990) had studied agriculture, biology and chemistry and had been a visiting postdoc in Berkeley (1956/57). In the late 1950s, he had tried to decipher the genetic code by mutating TMV-RNA and identifying the corresponding amino acid substitutions in the coat protein of the virus in Georg Melchers' group in Tübingen. Wittmann had identified the first code words in parallel to the efforts of Heinrich Matthaei and Marshall Nirenberg. Thomas Trautner (*1932) followed in 1965 as the third director. He had studied microbiology and gained an insight into phage research as one of the first Fulbright scholars in America (1953/54) – like Wolfhard Weidel before him. In the late 1950s, he had established phage genetics at the MPI for Physical Chemistry in Göttingen and subsequently had accepted the post of Assistant Professor in Berkeley in 1964.

The institute soon also made a name for itself outside Germany as a leading research centre for molecular genetics. Wittmann had turned to research on ribosomes. One focus of Trautner's work was DNA methylation, and Schuster was investigating DNA replication. The work in the three departments of the institute will be explained in more detail on the following pages. As a graduate student in Knud Nierhaus' group in Wittmann's department, I came to know the institute in 1978 as a hub of international and interdisciplinary exchanges. Guests came to

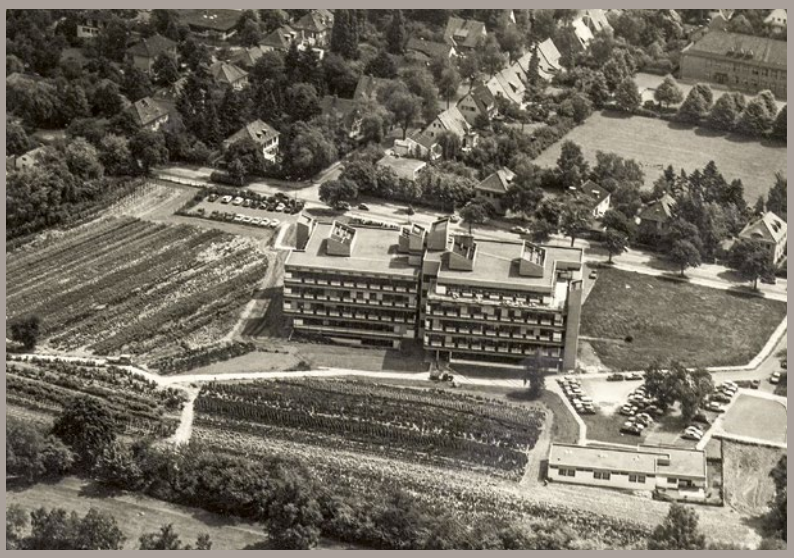
Wednesday colloquium at the private apartment of Thomas Trautner, around 1973

the MPIMG from all over the world. The institute's electron microscope facility was a place where scientists from the different departments got to know one another. The Wednesday colloquia organized by Thomas Trautner were open to everyone. I still vividly remember reporting the first results of my doctoral thesis there.

1 Olby, R., *The Path to the Double Helix: The Discovery of DNA*. Dover Publication, New York, p. 40 (1994). The book was first published in 1974.
2 Interview of the author with Friedrich Cramer, Göttingen, 22 September 2000.
3 Meyl, A. H., "Denkschrift zur Lage der Biologie." On behalf of the German Science Foundation. *Denkschriften zur Lage der Deutschen Wissenschaft* 4. Franz Steiner Verlag, Wiesbaden (1958).
4 Archive of the Max Planck Society, II. Abt, Rep. 1A, BMS, Kommission Molekulare Genetik.

↑ Former main entrance of the MPIMG at Ihnestraße 73, 1993

↓ Low building of the MPIMG at Harnackstraße 21–23, 1993



↖ New institute building of the MPIMG, view from south-west, 1971

↙ Building shell of the MPIMG from south-east, partial view with workshop building in the foreground, 1970

↑ Aerial photograph of the MPIMG, 1975

↓ Aerial photograph of the MPIMG with the newly constructed tower 4, 1986

SOME QUESTIONS TO:

OLAF PONGS

When did you stay at the MPIMG? From 1970 until 1975.
What was your scientific work focused on? I have been interested in how proteins recognize specific RNA sequences.
Do you still have any contacts from this time? Personally yes; scientifically no.
Thinking of your time at the MPIMG, what is the first thing that comes to your mind? The positive, science-friendly atmosphere.
What did you like most? The regular evening seminars usually organized by the Trautner department and held at private homes.
What annoyed you? That I could not stay longer.
What have you done since leaving the MPIMG? I went to Cambridge, UK, to the lab of Francis Crick with a fellowship of the Royal Society and was appointed as Full Professor of Biochemistry at the Faculty of Chemistry at the Ruhr-University of Bochum eleven months later. Subsequently, in 1991, I became Director of the Institute of Neural Signal Transduction at the Center for Molecular Neurobiology (ZMNH) and finally Director of the ZMNH itself. I retired in 2011 and since that time, I am Visiting Professor at the Institute of Physiology at Saarland University.

OLAF PONGS
Former Head of an Independent Research Group
(Selbständiger Arbeitsgruppenleiter, SAG)
at the Otto Warburg Laboratory

VOLKMAR BRAUN

When did you stay at the MPIMG? From November 1st, 1970 until March 31st, 1974.
What was your scientific work focused on? Discovery and determination of structure, function and local distribution of the first lipoprotein with a covalent-bound lipid. Molecular identification of the first cellular protein receptor for bacterial viruses (phages) and of a bacterial protein toxin.
Do you still have any contacts from this time? I am regularly in touch with Professor Klaus Hantke and occasionally with Professor Valerie Bosch and Helga Wolff.
Thinking of your time at the MPIMG, what is the first thing that comes to your mind? It has been an excellent organized institute with a stimulating scientific atmosphere and its members being on familiar terms with each other.
What did you like most? The scientific contact to the directors and heads of departments, which expressed itself especially in joint lectures and spontaneous seminars in private homes.
What annoyed you? The unequal space allocation between the four independent research groups.
What have you done since leaving the MPIMG? From my position at the MPIMG, I was appointed as Chair of Microbiology at the University of Tübingen. I stayed in Tübingen until my retirement in 2007. I was a continuous member and later also Speaker of three Collaborative Research Centres (Sonderforschungsbereiche) and a priority program of the DFG (German Research Foundation). After my retirement, I have been appointed as Max Planck Fellow at the Max Planck Institute for Developmental Biology for six years. I published 335 scientific papers with my PhD students and scientific assistants.

VOLKMAR BRAUN
Former Head of an Independent Research Group
(Selbständiger Arbeitsgruppenleiter, SAG)
at the Otto Warburg Laboratory

From the Kaiser Wilhelm Institute of Anthropology, Human Heredity and Eugenics to the Max Planck Institute for Molecular Genetics*

CAROLA SACHSE
Institute of Contemporary History, University of Vienna

WHEN THE MAX PLANCK INSTITUTE for Molecular Genetics (MPIMG) moved into its new building on Ihnestrasse in Berlin-Dahlem in 1971, the president of the Max Planck Society (MPG) at the time, Adolf Butenandt (1903–1995), used his speech at the opening ceremony to make an unmistakable break with the past, which started with the founding of the Kaiser Wilhelm Institute for Anthropology, Human Heredity and Eugenics (KWIA) in 1927. Butenandt saw the 1963 decision of the MPG Senate to reestablish the research institute known since 1953 under the name MPI for Comparative Hereditary Biology and Hereditary Pathology (MPIVEE) in a new building under new management with a focus on molecular genetics as a "new foundation".[1] His speech was yet another turn in the long post-war narrative of the KWIA, in which declarations of continuity contrasted with opportunistic claims of breaks with the past and new starts and which purposefully obscured any recollection of the genetic and racial research conducted there between 1933 and 1945 that was complicit in the Nazi regime's ideologies of population, race and murder.

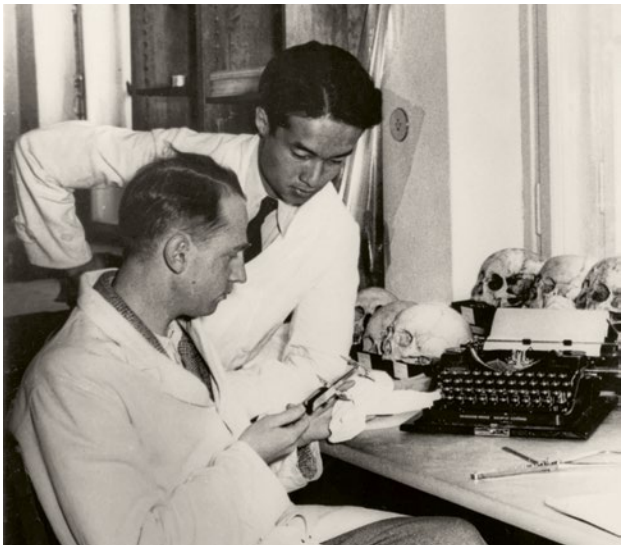
The first director, Eugen Fischer (1874–1967), initiated a human genetics programme that went well beyond the established scientific disciplines of the time. He attempted to combine various anthropological research approaches with "human heredity", with the idea of also integrating Mendelian genetics and the relatively new drosophila research. But Fischer's plans proved to be too broad to establish coherent research practice. Together with his student and close confidant Otmar Freiherr von Verschuer (1896–1969), who had headed the department of human heredity until 1935 and succeeded him as institute head in 1942, Fischer searched for a new paradigm to unite the diverging research areas in a uniform direction. The field of modified phenogenetics, which examined the expression of the genome in the phenotype and the interaction between genes

◂ **Back side of the Kaiser Wilhelm Institute** for Anthropology, Human Heredity and Eugenics, 1928

X-ray photographs of the hand and finger bones of identical (monozygotic) twins at the Kaiser Wilhelm Institute for Anthropology, Human Heredity and Eugenics, 1938

seemed ideal for this purpose. It made interdisciplinary work at the KWIA possible and had potential connections to the physiological and developmental biological heredity research being conducted in the neighboring Kaiser Wilhelm Institutes (KWI) of Biology and Biochemistry. In this way, the KWIA distanced itself from the international mainstream of genetics, which approached molecular genetics through mutation research, but was active in a field that is of current interest again today in the form of epigenetics.

Meanwhile, day-to-day scientific life at the KWIA was dominated by the virulent eugenic question of the time in many industrialized countries of how to biopolitically counteract the assumed "degeneration" of the population. KWIA scientists assisted the Nazi regime's hereditary health and racial agenda in a number of ways after 1933. They served as advisors to the Nazi administration or as hereditary health judges in forced sterilization cases, provided expert opinions on persons classified as "Jewish" or "inferior" and promoted the propaganda of Nazi "race hygiene". This was certainly true of the two institute directors Eugen Fischer and Otmar von Verschuer, but also of Fritz Lenz (1887–1976), who following the forced departure of Catholic theologian and zoologist Hermann



Two staff members of the Kaiser Wilhelm Institute for Anthropology, Human Heredity and Eugenics measuring human skulls and plaster casts, around 1938

Muckermann (1877–1962) in 1933 took over the eugenics department, and especially of longstanding staff member Wolfgang Abel (1905–1997), who advanced to head of the racial science department in 1942. Invasive human experiments were not the norm at KWIA; they typically worked with animal models instead, in addition to surveying, examining, externally measuring and at most taking blood samples from volunteer twin test persons. Procedures resulting in injuries and at least five murders nonetheless took place in Auschwitz, in particular in cooperation with Verschuer's student and concentration camp physician Joseph Mengele (1911–1979); they were directly related to research projects of his PhD advisor and of institute staff member Karin Magnussen (1908–1997).

Even Hans Nachtsheim (1890–1979), who was appointed the new head of Fischer's central phenogenetics department for experimental hereditary pathology in 1940, but was considerably more distanced from Nazi racial policy, did not shy away from exposing children to high if not deadly risks as test subjects. Despite his explicit preference for rabbit models, he conducted vacuum experiments on six children with epilepsy from the Brandenburg-Görden "Euthanasia Center" to demonstrate that lack of oxygen triggered the same seizures in children as in his young epileptic rabbits. The experiment, which was intended to verify the validity of his animal model for humans, failed. The children did not suffer any seizures and survived the experiments; whether they survived the Nazi period is not known.

The KWIA was not the only KWI entangled in Nazi racial ideologies, persecution and murder. However, the direct connection to the Auschwitz-Birkenau extermination camp was so compromising that the decision-makers in the Kaiser Wilhelm Society (KWG)/MPG agreed post-war that it was both inopportune for Verschuer to continue to head the institute and infeasible, considering the occupational ban imposed on him by the American occupying powers. But the cooperation between the KWIA and Mengele in Auschwitz made public in 1946 did not lead them to close the institute. The KWG management decided instead to wait things out, which was facilitated by the particular political circumstances in

Hans Nachtsheim Head of the department for experimental hereditary pathology since 1940 and director of the MPI for Comparative Hereditary Biology and Hereditary Pathology (MPIVEE) from 1953–1960, around 1956

Berlin, the strong reservations of the American military government about continuing the KWG/MPG and the unresolved question of succession of the KWIA department heads remaining in Berlin.

Whereas Verschuer, Lenz and Abel left Berlin after the war and Verschuer was ultimately relocated to the University of Münster in 1951, not least thanks to a "whitewashing certificate" issued by prominent KWG/MPG scientists, a power struggle emerged between Nachtsheim and Muckermann for the directorship of the KWIA. Nachtsheim quickly found his way in the city ruled by the four occupational forces and soon took over direction of three institutes, at least on paper: one at the Humboldt University, where he was quickly appointed professor, one at the German Academy of Sciences (DAW), the East-Berlin successor to the Prussian Academy of Sciences, and his Dahlem KWIA department of experimental genetic pathology, which was located in the American sector and initially operated under the most austere of conditions. In 1949, he accepted a position at the newly founded Freie Universität Berlin and set up his KWIA department at the temporary premises in Dahlem. Once the MPG was approved to operate in Berlin again, this department was upgraded to an independent MPI in 1953.

The general management of the MPG had originally planned to consolidate all bioscience "institute fragments" remaining in Dahlem after the war into a newly founded KWI/MPI for Biology. Otto Warburg (1883–1970), prominent director of the largely intact and uncontroversial KWI/MPI for Cell Physiology, however considered it sufficient for the remaining bioscience groups including Nachtsheim's department to continue to operate as research units of inferior rank. Following considerable debate and intrigue, Nachtsheim was the only one to receive his own MPI. In exchange, he had to grant an independent department in his institute to Herbert Lüers (1910–1978), who had worked at the KWI for Brain Research under Nikolai Timoféeff-Ressovsky (1900–1981) and was considered an expert in German drosophila research. Only "at the request of all commission members and on special request of the president" did Nachtsheim

Otto Heinrich Warburg
in his office, 1960s

finally also agree to admit Else Knake (1901–1973) with her Institute for Tissue Culture, which had been associated with the KWI for Biochemistry until the end of the war.[2] In contrast to Lüers however, he never applied for her to be named a Scientific Member of the MPG. The discrimination that Nachtsheim's only female employee at the rank of department head had experienced in the final war years at Butenandt's KWI for Biochemistry thus continued anew in this old boys' network. It was not until 1962 after Nachtsheim's departure that her department was transformed into an independent research unit of the MPG. Her appointment as a scientific member however was blocked to the very end by Nachtsheim and Warburg.

In the upheaval of the frontline city of Berlin, history was repeating itself in more areas than just gender policy. The new name of the MPI "for Comparative Hereditary Biology and Hereditary Pathology" communicated more proximity than distance to the old research program "Anthropology, Human Heredity and Eugenics". Although "Anthropology" had been "outsourced" to Muckermann's research unit, "human heredity" recurred in the term "comparative". In the May 1953 issue of the MPG newsletter, Nachtsheim explained the relevance of his research approach to his colleagues, stating that human genetics must do without the most important method of genetic research, namely breeding experiments, but since "all life created according to the same blueprint" shared "a certain foundation of common genes," animal experiments represented an acceptable alternative. To underscore this aspect, he established a "Working Group for Human Genetics" for his student Friedrich Vogel (1925–2006), who still worked primarily with classic methods of twin and family research at the time.

The old "eugenics" that had characterized scientific practice at the former KWIA was now obscured in the "Hereditary Pathology" part of the title, which likewise took a comparative human genetics approach. Such controversial biopolitical questions as the differentiation and interaction of genetic predispositions, exogenous causation and teratogenic influences on embryonic development could only be explored in animal experiments, in particular by "inbreeding"

Premises of the former German Entomological Museum of the Kaiser Wilhelm Society at Ehrenbergstraße, around 1935 Since 1950, the department for experimental hereditary pathology and future MPI for Comparative Hereditary Biology and Hereditary Pathology had been housed here, as well as the MPI for Molecular Genetics from 1964 until 1970

"any number of animals" with a uniform "gene community".[3] And until the restructuring of the institute in 1963, it was in fact common practice to list "eugenic problems," specifically "selection and counterselection, sterilization, atomic energy and genetic material," as working areas of the MPIVEE in the MPG's annual reports.

In order to save his research program, Nachtsheim actively addressed the Nazi past very early on. He was the first to distance himself from Verschuer and publicly attacked him, while also criticizing the Lysenkoism that had been exalted to the level of a state doctrine in the Soviet Union, thereby distinguishing himself from the recent "abuse of genetics by the totalitarian state" to stylize himself as an early champion of "scientific freedom".[4] In the name of this freedom, he defended eugenics against its critics all the more vehemently as time passed and justified the "unpolitical", at its core "Nazi ideology-free" forced sterilization law, which according to his expert report had at no point ever been misused.[5] Nachtsheim still wanted to see the "will to eugenics" strengthened in the population, along with the cultivation not only of "individual hygiene" but of "hereditary hygiene" as well.[6] Thus, eugenics in the form of applied human genetics remained at the core of the research program pursued at the MPIVEE even beyond Nachtsheim's retirement in 1960. Also with the findings of research in radiation genetics that became relevant once Germany entered the nuclear era, Nachtsheim remained true to his methodological approach of comparative hereditary pathology.

As a result, it took a handover between generations at the MPIVEE before molecular genetics replaced eugenics-focused hereditary biology. Although Nachtsheim initially attempted to establish as his successor Hans Grüneberg (1907–1982), his former student who had emigrated to London in 1933 due to the antisemitic laws of the Nazi regime and in the meantime achieved considerable renown as a mammalian geneticist, he was once again opposed by Warburg, who considered his entire approach to be "outdated". Instead of making amends, the MPG should at long last open itself up to "modern genetics," which is "nothing

Fritz Kaudewitz Director at the Max Planck Institute for Comparative Hereditary Biology and Hereditary Pathology from 1960 until 1964, around 1960

other than the chemistry or physics of nucleic acids," explained Warburg to MPG President Otto Hahn: "No further progress can be made in this area with breeding methods alone".[7]

But since no one besides Warburg was willing to offend the outgoing institute head, a "double solution" was agreed upon and long-overdue decisions were once again postponed. Fritz Kaudewitz (*1921), a microbial geneticist who had been trained at the MPIs for Biochemistry and Virus Research and in the US, was appointed as one of the directors. At the same time, negotiations were conducted with mammalian and human geneticist Grüneberg, who declined as expected. Nachtsheim's hope to see his student Vogel appointed as the second director for the human genetics division was likewise not fulfilled. Vogel's internal conflict with Kaudewitz about resources and decision-making authority instead caused ongoing turmoil in the institute that was apparent even to outsiders and led to Vogel accepting an appointment at the new Institute for Anthropology and Human Genetics at the University of Heidelberg, taking his deeply disappointed and depressed advisor Nachtsheim with him.[8]

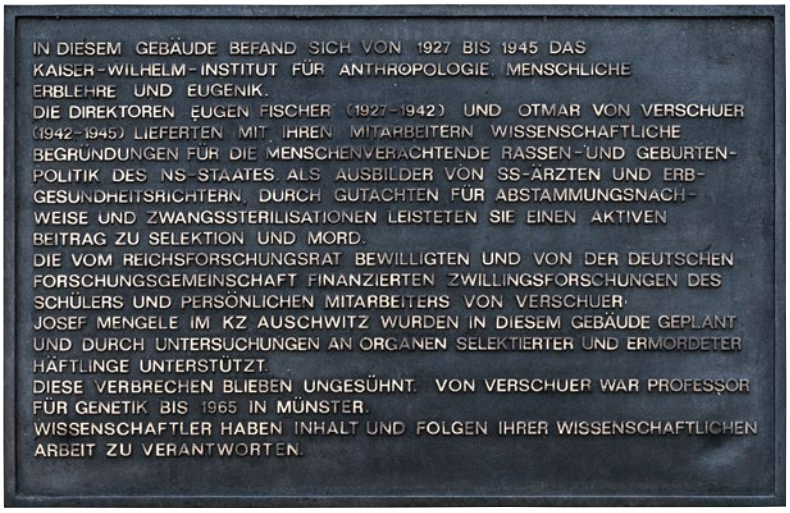
Kaudewitz likewise did not stay in Berlin. He had hardly arrived before accepting a position at the University of Munich and only stayed in Berlin long enough for his successors Heinz Schuster (*1927–1997) and Heinz-Günter Wittmann (1927–1990) to take over from him in 1964/65. These two scientists from virus research circles in Tübingen took over management along with bacteriophage geneticist Thomas Trautner (*1932) and expanded the area of molecular genetics. "Fundamental research is the main task of the Max Planck Institutes," commented Emeritus Director of the Medical Research Institute of the MPG in Göttingen Karl Thomas (1883–1969) on the trend, adding: "Is this possible with human genetics? Would it not be more likely to be classified as applied research, if the two fields were to be differentiated at all?" Thomas tried to mediate between the two opposing fronts that arose in the search for Nachtsheim's successor and promoted the future distinction between fundamental molecular research, with its preferred location at the MPG, and ap-

Main entrance of the Otto Suhr Institute of the Freie Universität Berlin in the former building of the Kaiser Wilhelm Institute for Anthropology, Human Heredity and Eugenics, 2004

plied research in human genetics, which he felt was better suited to universities. Ample funds were made available thereafter to establish professorships in human genetics, not least by the German Ministry for Atomic Research. But during the Cold War, the purpose of these professorships according to Thomas was distinctly population policy-related: to ascertain "the current state of genetic disease in the population, the zero line so to speak". But in light of the "anticipated increase (…) in radiation damage from bombs and the growing peaceful use of atomic energy" combined with the undesired side effects of the "welfare state," he felt "timely eradication or at least reduction of genetically undesirable offspring" was lacking.[9]

The infighting at the Berlin institute thus served as a welcome opportunity to relocate human genetics with all its controversial associations to the universities, while concentrating "fundamental research" in cells, viruses and microbes at the Max Planck Institutes so that they could catch up once again internationally. For the genetics-oriented biosciences in the MPG overall, this meant less a paradigm shift than an opportunistic rectification of their research traditions: Nachtsheim's type of human genetics research, which continued to involve eugenics to the very end, was conveniently "spirited away" in the form of applied research, while genetics-oriented molecular biology, which had continued to develop in the bioscience institutes relocated to West Germany after 1945, was reinforced at the old Berlin site.

In his appointment speech for Kaudewitz in autumn 1960, Butenandt attempted to make a conciliatory connection between Nachtsheim's "brave" resistance against the "undertow of politics in the 1930s and 40s" and the very inceptions of the KWIA – however in vain, since Nachtsheim declined to attend.[10] The general management [of the MPG] proclaimed a "new beginning" three years later. The institute's name change agreed upon in December 1963 was postponed until the new management was in place. Implementing the resolution of 1963 did in fact amount to the "new foundation", which Butenandt had invoked during the inauguration of the newly constructed institute building in 1971. It meant one



Memorial plaque of the Freie Universität Berlin at the building of the former Kaiser Wilhelm Institute for Anthropology, Human Heredity and Eugenics, 2013
Inscription: "The Kaiser Wilhelm Institute for Anthropology, Human Heredity and Eugenics has been located in this building from 1927–1945. The directors Eugen Fischer (1927–1942) and Otmar von Verschuer (1942–1945) and their staff provided the scientific justification for the inhuman racial and population policy of the Nazi state. As instructors of SS physicians and of hereditary health judges, by providing expert opinions for certificates of ancestry and forced sterilization, they actively contributed to selection and murder. Approved by the "Reichsforschungsrat" (Research council of the German Reich) and financed by the German Research Foundation, the twin research of Josef Mengele at the KZ Auschwitz, student and personal cooperator of Verschuer, was planned and supported by examination of organs of selected and murdered prisoners in this building. These crimes remained unatoned. Von Verschuer was Professor of Genetics in Münster until 1965. Scientists have to take responsibility for the contents and the consequences of their scientific work."

thing in particular: A clean break was made without dealing with the past that, as Nachtsheim shrewdly observed upon his departure, seemed to lay as "a curse on German genetics".[11]

* This text is based upon my article: "Ein als Neugründung zu deutender Beschluß … Vom Kaiser-Wilhelm-Institut für Anthropologie, menschliche Erblehre und Eugenik zum Max-Planck-Institut für molekulare Genetik", in: *Medizinhistorisches Journal* 46 (2011), H. 1, S. 24–50. The article traces in detail the development of the institute between 1927 and 1963. All sources and research literature the present text is based upon are specified there at full length. Below, only verbatim citations are documented, for the rest refer to the further reading at the end. Thank you to Ulrike Baureithel for competent shortening and lectorate of this text.

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2 Archives of the Max Planck Society: Abt. II, Rep. 1A–IB, MPIVEE, Bd. 2, Vol. 2, Protocol of the meeting of the Berlin commission on 8.1.1953 (in German).

3 Nachtsheim, H. "Vergleichende Erbpathologie." *Mitteilungen aus der Max-Planck-Gesellschaft zur Förderung der Wissenschaften* 6, 24–26, see 25 (1953).

4 Nachtsheim, H. "Der Mißbrauch der Genetik durch den totalitären Staat." *Kontakte. Mitteilungen vom Kongreß für die Freiheit der Kultur* 3, 12–13 (1953).

5 Nachtsheim, H. "Das Gesetz zur Verhütung erbkranken Nachwuchses aus dem Jahr 1933 in heutiger Sicht." *Ärztliche Mitteilungen* 33, 1640–1644, see 1641, 1644 (1962).

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8 Archives of the Max Planck Society: Abt. II, Rep. 1A–IB, MPIVEE, Kaudewitz, Vol. 1, Thomas to Ballreich on 12.5.1961 (in German).

9 Archives of the Max Planck Society: Abt. II, Rep. 1A–IB, MPIVEE, Kaudewitz, Vol. 1, Thomas to Ballreich on 12.5.1961 (in German).

10 Archives of the Max Planck Society: Abt. II, Rep. 1A–IB, MPIVEE, Kaudewitz, Vol. 1, draft speech from 10.10.1960, comment from 18.10.1960 (in German).

11 Archives of the Max Planck Society: Abt. II, Rep. 1A–IB, MPIVEE, Kaudewitz, Vol. 1, Nachtsheim to Butenandt on 14.10.1960 (in German).

▸

Further reading

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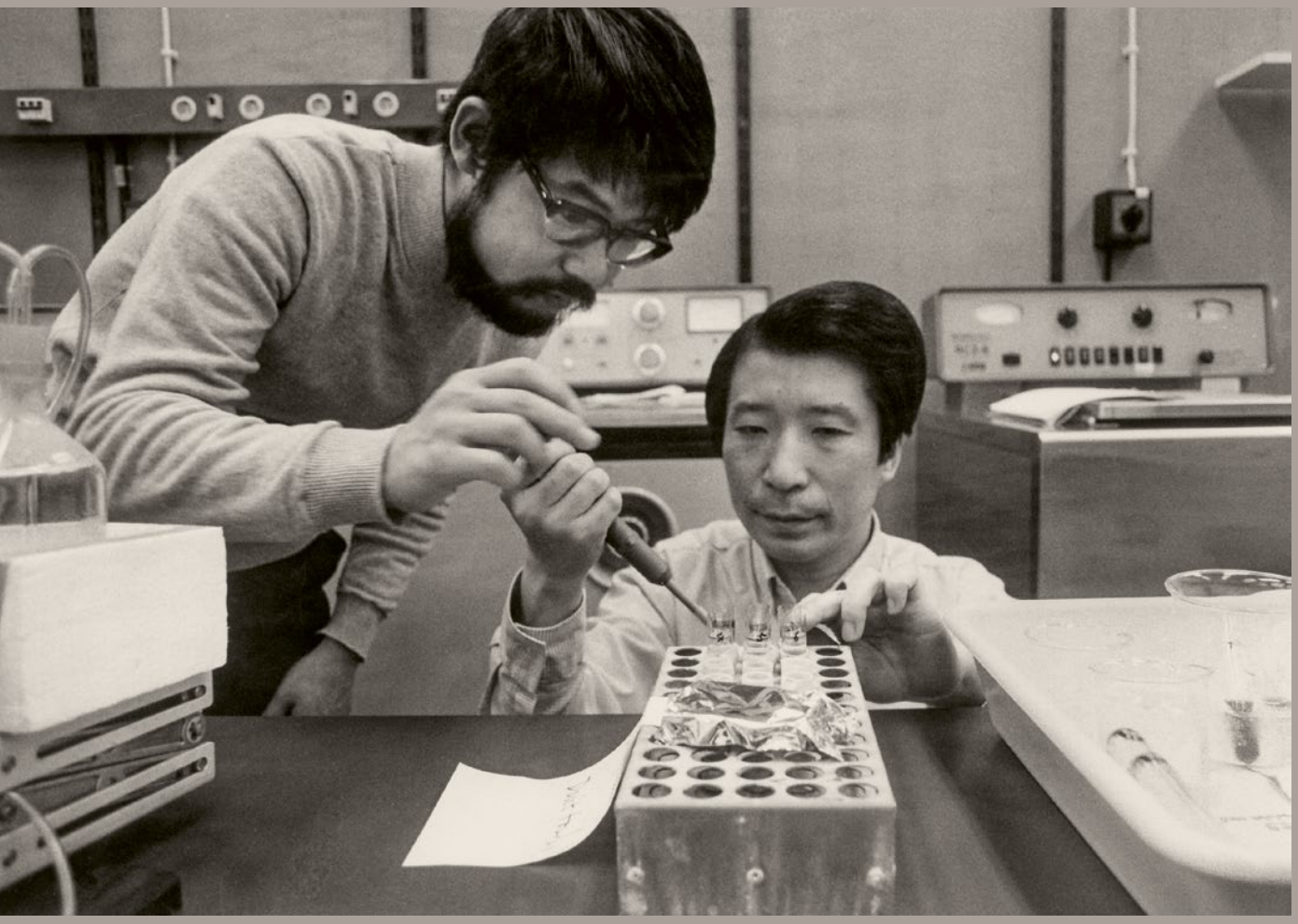
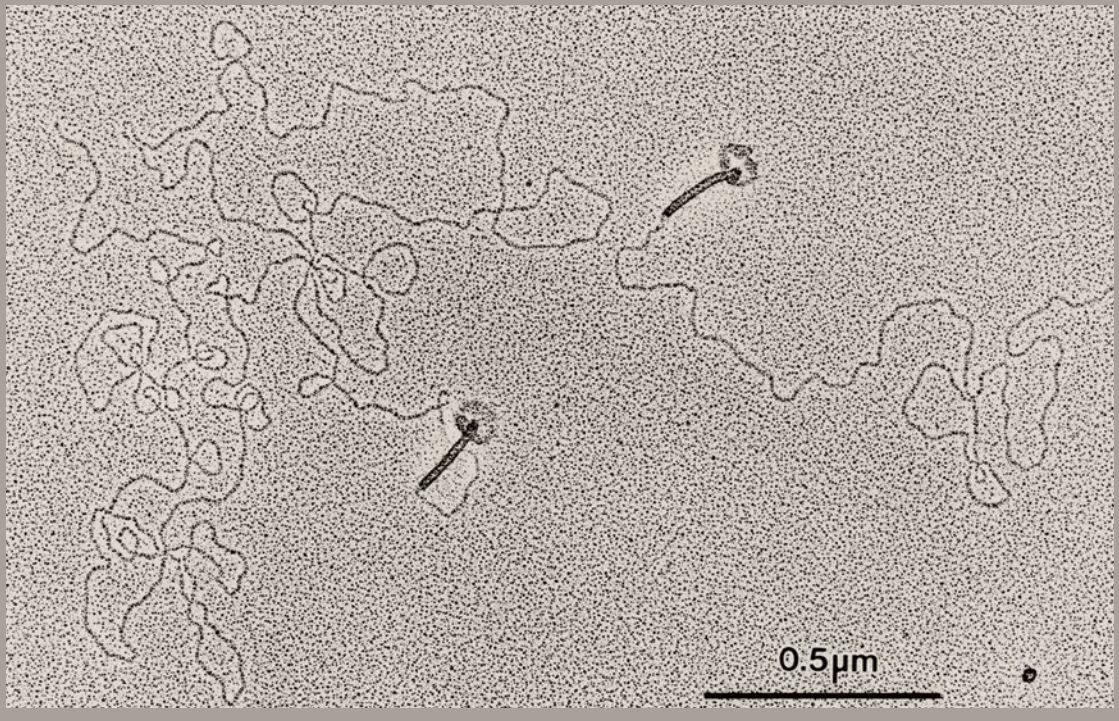
↑ Heinz-Günter Wittmann discussing with colleagues from the Freie Universität Berlin, 1980s

↓ Members of the Scientific Advisory Board of the MPIMG, early 1990s



Two Japanese biologists at work in the lab, 1974



↑ Staff members of the Trautner department, Achtman group, in the lab, around 1983

↓ Electron micrograph of phage SPP1 after ejection of DNA, around 2002

SOME QUESTIONS TO:

KENNETH TIMMIS

When did you stay at the MPIMG? From 1976 until 1981.
What was your scientific work focused on? My group focused on the regulation of plasmid DNA replication; microbial pathogenesis; microbial degradation of aromatic compounds and gene manipulation systems.
Do you still have any contacts from this time? I have contact with Paul Manning and members of my own group, and occasionally with Günther Schütz, Albrecht Sippel, Bernd Groner, Peter Herrlich, Karin Mölling, Ulla Bonas, Regine Kahmann, Hans Lehrach and Trinad Chakraborty.
Thinking of your time at the MPIMG, what is the first thing that comes to your mind? My first two postdocs, Isabel Andres and Hirofumi Danbara, absolutely wonderful and fun people, and extreme contrasts, who set me on a lifelong trajectory of admiration of and recruiting to my group Spanish and Japanese researchers.
What did you like most? The wonderfully stimulating intellectual environment of the Independent Research Groups.
What annoyed you? The awful housing situation in Berlin at that time, which cost me so much time (every weekend for nine months) and energy before we finally found an apartment
What have you done since leaving the MPIMG? From 1981 to 1988, I was Professor at the Medical School of the University of Geneva and, from 1988 to 2011, Head of the Division of Microbiology (Bereichsleiter) at the German Research Centre for Biotechnology (GBF; now Helmholtz Centre for Infection Research, HZI) and Professor of Microbiology at the Technical University of Braunschweig, where I am still Emeritus Professor.

KENNETH TIMMIS
Former Head of an Independent Research Group
(Selbständiger Arbeitsgruppenleiter, SAG)
at the Otto Warburg Laboratory

REINHARD LÜHRMANN

When did you work at the MPIMG? I was a post-doc in the Wittmann department from 1976 to 1980 and then head of an Independent Research Group from 1981 until 1988.

What was your scientific work focused on? During my time as a post-doc, I worked on the structure of *E. coli* ribosomes and studied the specificity of the codon-anticodon interaction on the ribosome. My SAG group worked on the isolation and characterization of pre-mRNA splicing factors.

Do you still have any contacts from that time? Yes, many. What's more, there are still people from the Berlin days working with me at the MPIBPC in Göttingen.

Thinking of your time at the MPIMG, what is the first thing that comes to your mind? It was a great, almost magical time. Even as a post-doc, I was able to pursue my own research interests and thus gained independence. Thanks to the confidence of the former directors and the appointment committee, I then received the unique opportunity to start the hunt for splicing factors with my own SAG group – so to speak at point zero of the beginning of a new research area, one that was just emerging. In the early 1980s it was completely unknown how introns are spliced out of protein-coding pre-mRNAs and which factors are involved. Today we know that spliceosomes are among the most complex molecular machines of the cell.

What did you like most? To start with: the ability to do my own research. In addition: the excellent support from the MPIMG, which included the provision of administrative and technical services. One had a feeling of "unlimited opportunities". I also loved the special working atmosphere of the SAG years because of our accommodation at the Harnackstraße site; we even had our own soccer field at the front door, where we used to hold barbecue seminars in the summer.

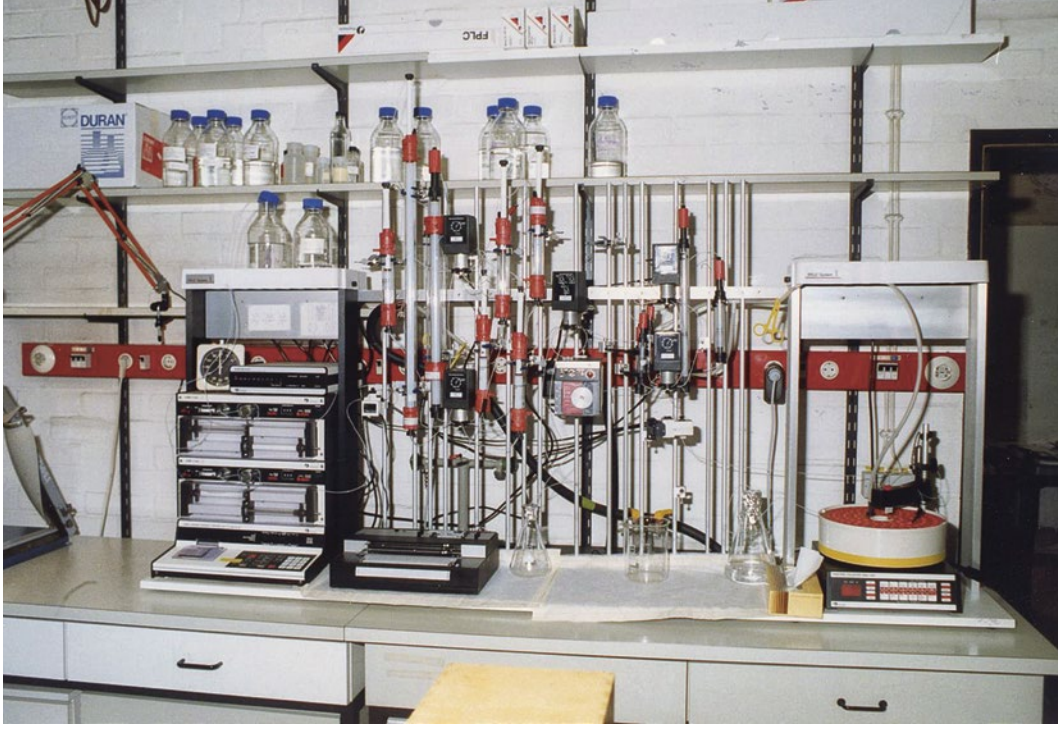
What annoyed you? At that time, the SAG period was strictly limited to five years. An extension period was only ever granted if one had already been accepted for a subsequent position. The pressure for short-term success was correspondingly great.

What have you done since leaving the MPIMG? In 1988 I accepted an appointment at the University of Marburg. Since 1999 I have been Director at the Max Planck Institute for Biophysical Chemistry in Göttingen.

REINHARD LÜHRMANN
Former Head of an Independent Research Group
(Selbständiger Arbeitsgruppenleiter, SAG)
at the Otto Warburg Laboratory

Remembering Heinz Schuster and 30 years of the Max Planck Institute for Molecular Genetics

KARIN MOELLING
University of Zurich, Switzerland
1971 until 1993 Max Planck Institute for Molecular Genetics, Berlin



Foundation of the Max Planck Institute for Molecular Genetics and the Establishment of Independent Junior Research Groups

AT THE END OF 1963, the Senate of the Max Planck Society (MPG) decided to rename the Max Planck Institute for Comparative Hereditary Biology and Hereditary Pathology to Max Planck Institute for Molecular Genetics (MPIMG).[1] The new Institute's scientific goal was the study of hereditary processes and of the molecules underlying these processes such as nucleic acids and proteins at a molecular level, primarily by using biochemical and genetic methods – not hereditary human biology. Thanks to the boom in the development of genetic research at Tübingen and Munich, Germany had managed to catch up a little to the huge head start of other countries in this area. It was also expected that the new Institute for Molecular Genetics in Berlin would make up further ground. In 1964, two of the three directors were appointed. Heinz Schuster (1927–1997), at the time in California, USA, and earlier at the Max Planck Institute for Virus Research in Tübingen, and Heinz-Günter Wittmann (1927–1990), from the Max Planck Institute for Biology in Tübingen accepted appointments as department heads and directors. Schuster and Wittmann had published work together on the tobacco mosaic virus[2,3], but did not continue this work in Berlin. The Berlin-born Gunther Stent (1924–2008), who was working at the University of California in Berkeley, turned down the offer. He nevertheless agreed to give his advice and help with the reorganisation of the institute and was appointed as an External Scientific Member of the institute in 1967. He came regularly and always visited Schuster. Thomas A. Trautner (*1932) was appointed as the third department head in 1965.

Research at the new institute was originally planned to focus on bacteria and viruses. Already then, there existed concerns about this new field of research, which was attacked in the press.[4] Genetic research was regarded as dangerous

◂ **Columns for protein purification** A lab of the department Schuster in the 1980s

Klaus Thies (left), **Heinz Schuster** (middle) und **Thomas A. Trautner** (right) discussing the plans for the new building of the Max Planck Institute for Molecular Genetics, around 1967

and the directors were accused as not outspoken enough. The past still occupied people's minds, but Trautner faced up to the journalists and tried to destroy the worries.

The new departments were first set up in the rooms of the former Max Planck Institute for Comparative Hereditary Biology and Hereditary Pathology at Ehrenbergstrasse 26. But it was clear from the start that the institute would relocate to a new building in Ihnestrasse. Rolf Gutbrod, a student of Hans Scharoun (who had built the Berlin Philharmonic Concert Hall), won the competition to build the new institute. Gutbrod like Scharoun was an anthroposophist and disliked right angles – the institute might have become a small philharmonic hall with curved staircases and portholes in the walls, a bit like a cruise ship, if not for Schuster, who was involved in the construction of the MPIMG building. He probably had to straighten out some walls; after all, the rooms had to accommodate rectangular machines, refrigerators, incubators and furniture. The paths to the institute remained non-geometrical. The modular design of the building was an innovation at the time. Even the furniture and the power supply units were constructed to be variable, which proved useful when new colleagues arrived, who had different needs. From then on, Schuster calculated not in meters, but in spatial axes and window units.

Due to protest from local residents, the building complex in the Ihnestrasse had to be scaled down in size. People argued that it would overshadow their gardens and feared for the future of their idyllic garden atmosphere in Dahlem and the villa district, even threatening lawsuits. Yet Friedrich Althoff (1838–1908), the Director General of the Prussian Ministry of Church, Education and Medical Affairs had originally proposed the idea of establishing a "German Oxford" in Dahlem in the days of the German Empire, with a mix of mansions and functional buildings in the area. The owners of the villas seemed to have forgotten this after the war. Due to the confrontations, the institute had to be set back from the street, reduced in height by one storey and the start of construction was delayed. The institute was supposed to have a wing for visiting scientists, because there

was concern about the isolation of Berlin and lack of international interactions. But this plan was abandoned due to the smaller dimensions of the institute and for financial reasons.

The President of the Max Planck Society at the time, Adolf Butenandt, officially inaugurated the new building in 1971 and asked Schuster where to find the entrance and waiting rooms for the guards and chauffeurs. They had been abolished in Berlin as not timely any more, nor was there an official car with a driver. These days, one would ask where the childcare room is. Such a room was actually added a few months ago near the entrance to the new tower. In his introductory speech, Schuster explained the work at the institute, including, besides research on ribosomes, topics on replication of bacteria and phages, and predicted that the latter had already passed their peak in novelty and interest. That was why it was so important to him to attract junior scientists to join the institute and tackle more complex problems at the level of higher organisms. From the very beginning, Schuster also planned opportunities for technical staff to further qualify, and proposed tests for directors for continued qualifications, just like pilots of aircrafts have to pass, to keep up their standards or bring them down to earth, if necessary. This was unheard of then, but later on the Scientific Advisory Boards came for regular evaluations.

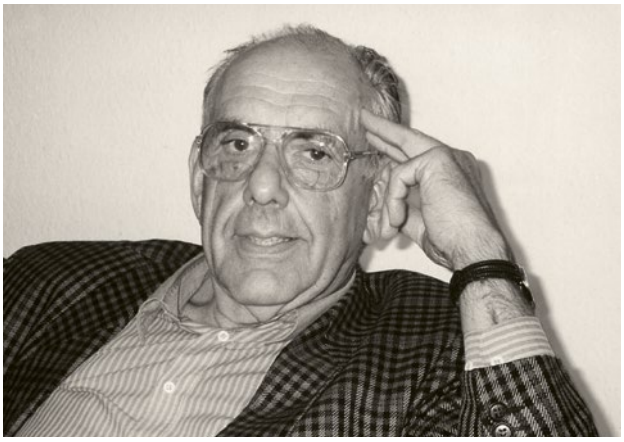
Already in 1970, instead of the planned but unbuilt guest wing, four independent research groups (Selbständige Arbeitsgruppen, SAGs) were established, today's Otto Warburg Laboratory (OWL). This was only possible, because Schuster generously offered to reduce his department by half – not only in terms of space but also financially. He gave away 50 per cent of his budget and half his storey – much to Butenandt's surprise. Schuster had experienced this concept in California and got to know the independent junior research groups established in 1969 in Tübingen (Friedrich Miescher Laboratory). Later, similar groups were also set up outside Berlin, for example in Cologne (Max Delbrück Laboratories, since 1989) and in Munich. Schuster regarded support of junior research groups as one of the major obligations of his generation, which is why he actively spon-

Staff members of the Schuster department with "their" proteins From left to right: Mathias Velleman, Martina Heirich, Thorsten Heinzel, Jochen Heinrich, Hans-Dieter Riedel, Anke Heisig, Martin Citron

sored them, nobly reducing his own resources and facilities. Fourteen independent research group leaders worked at the institute over the years while he was in charge. At least twelve of them were offered professorships in Germany and abroad later. Two of them, Reinhard Lührmann in Göttingen and Regine Kahmann in Marburg, became Max Planck Directors themselves. Additionally, five scientists from Schuster's own department went on to become professors. In Switzerland, Department Heads are evaluated by their output of younger professors; none had as many as Schuster.

The SAG/OWL group leaders were selected after public advertisements for applications by a search committee. The sole criterion for selection was scientific excellence – based on relevant publications, as well as the impact and novelty of the research projects and their putative eligibility for subsequent high research positions. The age was also important, only young people qualified. Schuster retained his right to veto the appointment of the group leader, only to avoid political interests, but beyond that, he did not exert any influence on the selection. The contracts were strictly limited to five years and start-up conditions were the same for everyone: two scientists, two PhD students and one technical assistant. Additionally, there was one secretary for all groups, and at that time all applications and publications had to be typed on paper! When equipment was ordered, we had to provide room plans to prove we had enough space for the huge radioactivity counters, the numerous deep freezers and ultracentrifuges. We also had to avoid heat build-ups on hot summer days in the inner zones, where the machines were installed. Schuster had a generous attitude towards keeping the budget even at the end of the year, more than once he stocked up our finances with his own funds.

On Sunday evenings Schuster loved to go to the laboratory to set up cultures, but also to drop by the adjacent corridor, where the independent research groups were located, to see what was going on – this was a great pleasure for him. The SAGs were important to him, and he loved the informal atmosphere and looked forward to the exciting new topics and results, the enthusiasm and



Heinz Schuster, around 1990

the speed. He not only asked the group leaders about their results, but also gave young co-workers a chance to speak up. Besides that, he was always there for us and saved many situations. For example, I once had a dispute with the union members of the institute about some safety regulations for an EMBO laboratory course. The participants had already arrived and the situation was more than critical. Schuster negotiated and saved the situation and made it possible for the course to take place.

A personal remembrance of Heinz Schuster

Heinz Schuster (1927–1997) grew up near the River Rhine; his father was the director of a School of Agriculture and Whine in Eltville. In keeping with this tradition, Schuster was an excellent wine connoisseur. The poles for the vineyards almost killed him, when he and his brother played with fire. It got out of control and put hundreds of poles on fire and trapped the children inside a hollow. The two brothers used the laundry room at home as a chemical laboratory. They jumped into the river Rhine to catch up with the heavily loaded freight boats and climbed on board, just for fun. Schuster was an enthusiastic and skilled model aircraft builder. His brother died at the very beginning of the Second World War under mysterious circumstances, having just graduated from high school. Schuster himself was drafted in 1944 at the age of 17 to the paratroopers at the Eastern Front, where he was captured by American soldiers. When they took away his watch, he fiercely objected, believing Germany would win the war. He never forgot about the hunger he had to suffer from during captivity in the camp, and later, he never left home for a trip without some emergency food. After the war, Schuster started studying chemistry in Mainz. He had to finance his studies himself. He patched the bomb holes in the walls of his room with newspapers. In 1954, he finished his doctorate with a dissertation entitled “The enzymatic synthesis of C14-traced adenosintriphosphoric acid” and started working under Gerhard Schramm at the Max Planck Institute for Virus Research in Tübingen in 1955. There, they explored, whether RNA or proteins of the Tobacco Mosaic Virus

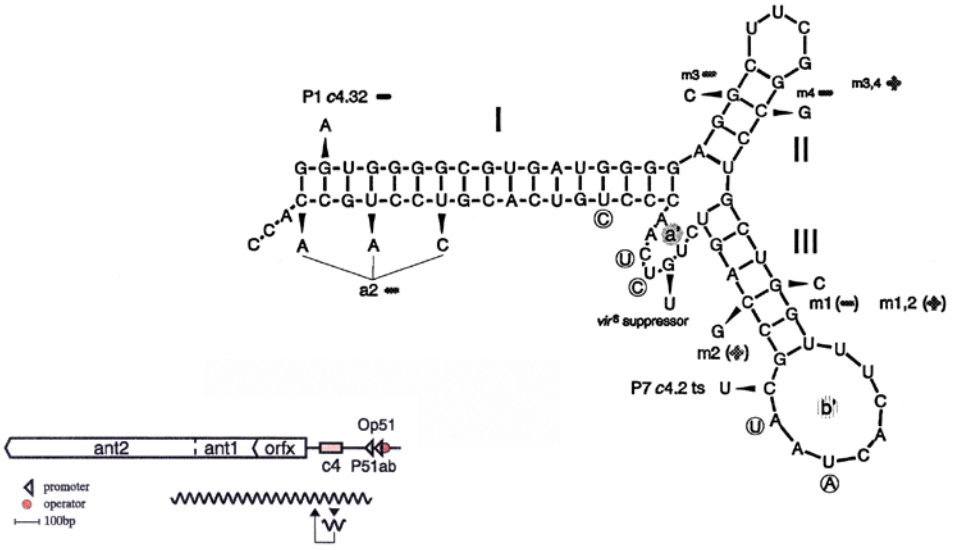
Heinz Schuster, Mary and Max Delbrück (from left to right) during a visit of the Delbrücks in Berlin

(TMV) were the carriers of genetic information. Schuster, Schramm and Zillig applied a new technique of mild RNA extraction by phenol and succeeded in isolating the TMV RNA in 1956. Based on this separation Schuster and Schramm defined the RNA of TMV as the biologically important component.[5] Schuster mutagenized the DNA of phages and described mutations by defined chemical changes to the bases of the DNA for the first time.[6] Maybe, he mutagenized his own genetic material by these experiments, which later caused his brain tumor leading to his early death.

Tübingen played a major role in Schuster's life. There he built lifelong friendships with Friedrich Bonhoeffer, Alfred Gierer, Uli Schwarz and later also with Christiane Nüsslein-Volhard. The independent research group leader Volkmar Braun changed from Berlin to Tübingen, Heinz Schaller moved from there to Heidelberg. They got together for skiing and hiking trips or met in Corsica for a barbeque. In Switzerland, Barbara and Thomas Hohn from Basel were also frequently included. Schuster's reaction vessels marked with "HS" in Tübingen as well as the apartment were taken over by "HS" (Heinz Schaller) later. As all scientists from Tübingen, Schuster welcomed the hospitality of Ursula Day, a previous co-worker of Schramm in New York – as I still do today.

From 1963 to 1965 Schuster worked as a post-doc at Caltech in Pasadena with Jean Weigle and Robert Sinsheimer. The latter had some years ago discovered Phage ΦX174, a single-stranded DNA phage; this was Schuster's introduction to DNA replication. Here also a lifelong friendship with Max and Mary ("Manny") Delbrück started, who later were frequent visitors in Berlin. Delbrück's son Tobi, a scientist at ETH in Zurich, today still shows photographs of Schuster doing a headstand in the California desert, his frequent Yoga exercise.

From Pasadena, Schuster was called to Berlin to the MPIMG as founding director in 1964, where he continued his work on the underlying molecular mechanisms of DNA replication and gene regulation. The fundamental principles of DNA replication in microorganisms seemed to have been understood rather well, so research focused more on the regulation of plasmids and bacteriophages,



Structural model of the c4 repressor RNA (top right), which loops are auto inhibitory for the own transcript, thus inhibiting protein synthesis. The encircled nucleotides mark mutations inhibitory for phage P7

Immunity region with RNA transcript (zigzag line) (bottom left) and c4 regulatory RNA (w), which retroacts to the own transcript (arrow)

transfer replication during the conjugation of bacteria and the host range of plasmids. Other important topics included a primase and horizontal gene transfer.

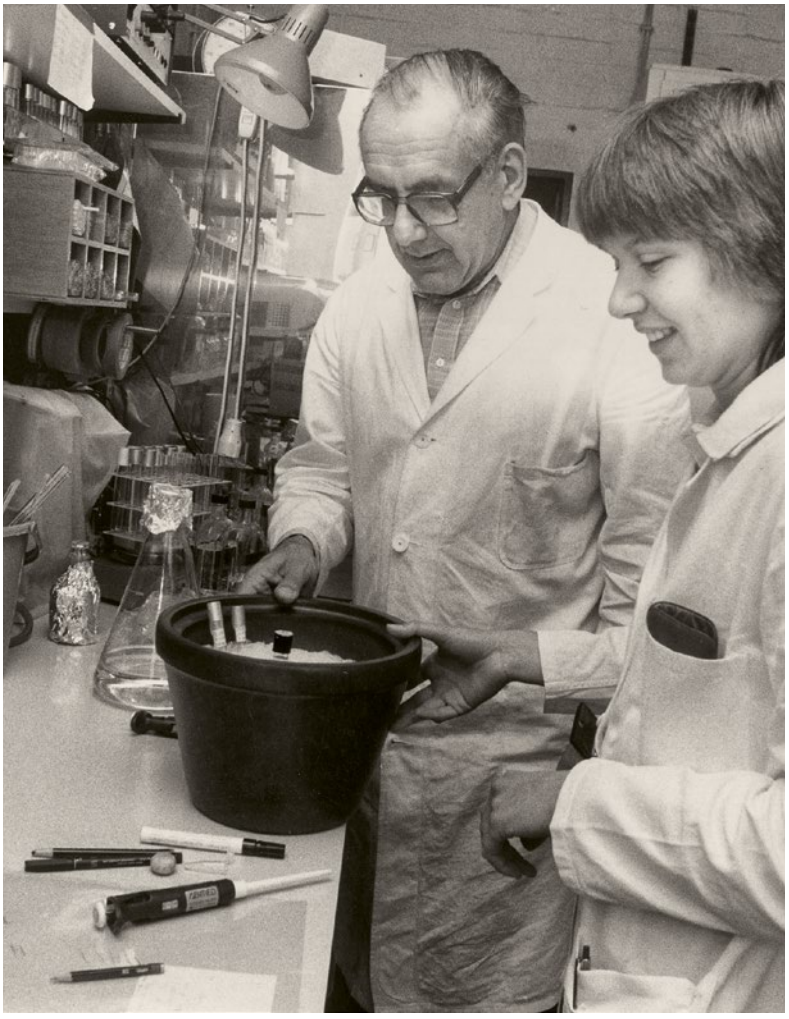
Gene regulation was investigated using the temperate bacteriophage P1 as an example. P1 possesses complex regulation and replication systems. The relevant proteins such as the C1 repressor, bof, coi, ant1/ant2 and c4 were expressed and purified using recombinant DNA technology and characterised using *in vivo* and *in vitro* systems.

The unusual immunity region of P1 that is responsible for the lysogenic state of the host cell was a mystery. A repressor was sought that inhibited the synthesis of the anti-repressor. Instead, during the last years of his research time, Schuster and his colleague Martin Citron discovered a new regulation principle, a regulatory RNA that functioned as a repressor.[7,8] They themselves for a long time had believed it to be a protein, but actually it was a processed antisense RNA that originated from the same promoter as the repressor RNA and through autoinhibition blocked its transcription and thus also its translation. The proof that the repressor molecules are not necessarily proteins, but can also be regulatory RNAs, was a great surprise and novelty. The antisense nucleic acid is first processed, before it generates the phage's immunity through a feed-back mechanism. It became clear that nature uses this mechanism often for maintenance of the latent state in the absence of replication. Even today, former colleagues of Schuster talk about these results. Moreover, it seems phage research is experiencing an unexpected comeback as potential therapy against bacteria – except that today there are hardly any phage researchers left. In the meantime, research on gene regulation through single- and double-stranded RNA has boomed as RNA interference and gene silencing. Today, the regulation mechanisms of RNA molecules are among the most important areas of research for understanding gene regulation especially in tumours, epigenetics and paragenetics. And phage research is revitalized with the hope to fight bacteria.

At work, Schuster loved to be near the laboratory. He hurried over no later than eight o'clock in the morning, because Astrid would be waiting. For her part, she

usually arrived without having breakfast to be there on time. In fact, we only ever saw Schuster in his white lab coat, and more often he could be found picking or counting clones than sitting at his desk. His door was always open, there was no hierarchy. In a birthday speech he despised ties and striped suits as requisites of an establishment he did not belong to. As the boss, he had no interest in superiority, unlike the typical German professor at that time, but he nonetheless attracted respect and attention by the way he spoke and acted. Schuster was convinced that a department should have no more than 15 staff members and to this he adhered. Frequently, departmental breakfasts were organised, with more than enough food, and the word spread. Then in the evenings, the ever-hungry young folk sneaked into the cooling rooms to pilfer meatballs and eat up the leftovers. He kept warning us about ether, because it had been the cause of a spectacular fire, at a time when there were no spark-proof fridges. A huge dangerous acid spill then finally resulted in safety metal closets. Other activities included baking Christmas fruit cake (Stollen) with special ingredients from the food department of the KaDeWe store. Curd cheese dumplings (Quarkknödel) were another speciality, with Irene Wilke supplying baby diapers to squeeze the water out of the cheese. On another occasion Schuster surprised his guests with "Pauvre Homme" from Maier-Leibnitz' cookbook, which describes the preparation time as a countdown and the dish is served at time zero. In Schuster's fridge, the eggs were marked with the date by a felt pen, just like the samples in the lab – this is common now in Germany. There were evenings when Schuster cleared one of his rooms to show his slides of Mexico. He gave lectures at the University in Mexico, which he knew well from his time in the USA. He particularly enjoyed its nature, flowers, and climate with so much sun in winter in contrast to the darkness at home. He almost even settled there, as the sun had a beneficial effect on his health condition. This effect has now been confirmed as light therapy.

Schuster loved numbers and regularly calculated the mean age of colleagues at the time of their appointments, which increased steadily. He felt his generation was extremely privileged, because they had been appointed at a very young



Heinz Schuster with a technician in the lab

age. He calculated that a paper costs 200,000 deutschmarks in 1970, less than a third of a modern paper. He also amused his audience with unexpected comparisons, for example with the cost of Albert Speer's new candelabrums lining the Bismarckallee or the budget of Berlin's police force – showing that the annual cost of the MPIMG was exactly the same as Berlin's police force spent in three days. He compared the number of women in the MPG with those of the Catholic Church or the Berlin Philharmonic Orchestra, which only required the ability to count to one. Gender issues did not exist yet, but he was already supporting female scientists. The 1970s were the time of student riots. Schuster was very interested in politics; he had an antiauthoritarian view and joined protests on the street himself. During one demonstration against the Shah of Persia, he only just managed to avoid arrest.

He was actively in contact with East Berlin and Berlin-Buch. Erhard Geissler invited Schuster to speak at the Kühlungsborn Symposia, which he organised every two years from 1970 until the mid-1990s. Schuster came at short notice as a replacement for a Russian speaker, which led to a GDR decree prohibiting replacement speakers from the West with immediate effect. The title of the speech

Heinz Schuster as "Mauerspecht" (people, who hacked small pieces/souvenirs out of the Berlin wall after the border crossings were opened) after the fall of the Berlin wall, 1989

was *"The properties of an E. coli mutant with thermosensitive DNA synthesis and host cell reactivation in UV-irradiated phage lambda in this mutant"*, a phenomenon still highly appreciated today by phage researchers: the phage is healed by the host cell. Virology continued to attract his interest and Schuster arranged lecture series with retrovirologists from the Robert Koch Institute, including myself, comparing phages and viruses with their striking smimilarities.

Schuster visited Geissler at the University of Rostock and later regularly at Berlin-Buch. I received a dry ice package with biological samples from Cold Spring Harbor, which I was supposed to transfer to Geissler at Berlin-Buch. Expecting extensive customs formalities at the border, Schuster took advantage of the situation to hide a copy of *The Gulag Archipelago* under the bonnet of his Renault. The book was secretly widely circulated around the GDR and fortunately, Schuster was not caught in the act. This saved him from becoming an unofficial informant for peace. Besides jeans and coffee, Schuster also transferred a big saw for Geissler to cut trees. Because it was a West German brand, it was confiscated by the Stasi the first time he used it. A gel electrophoresis chamber led to a disciplinary action against Geissler despite an import permit. Even the nitrocellulose centrifuge tubes I transferred for the Beckmann rotor of the ultra-centrifuge SW50.1 were confiscated by the border guards in Berlin-Buch. Schuster enjoyed meeting Christa Wolf and her husband at Geissler's home and attending theatre performances at the Berliner Ensemble or the Volksbühne am Rosa-Luxemburg-Platz. Heiner Müller's play "Zement" was performed there. The completely empty restaurants always smelt of sausages, but there were never any left to eat. In Prague, too, Schuster not only worked in a scientific collaboration, but also mailed Burda fashion magazines to the wives regularly.

His craftsmanship impressed the workers at the institute's workshop. It led to the renovation of a floor of a country home in the Lüneburger Heide and he was also involved in the refurbishment of his new home in Berlin after he had to leave his apartment. He worked particularly hard to learn to use computers. Afterwards he never again mistook the television menu in hotel rooms for a restaurant menu!

He never sailed his Pirate-class boat in less than force four winds, and even survived a collision with a ferry on the Wannsee with his colleague Walter Messer on board. His love of art and nature motivated Schuster to cycle over the Alps to Rome right after graduating high school, without any money in his pocket. Later he gradually became a connoisseur and collector of art and researched works of art in libraries with scientific meticulousness. With his knowledge of the provenance of ceramics and pewter objects he could keep up with many a specialist auctioneer. He even approached his hobbies scientifically. He never left home without a camera and his pictures were as carefully organised as the eggs in the fridge were labelled. I had the privilege to accompany Heinz Schuster for many years. He shaped and enriched my life and influenced my attitude and thinking. His modesty and humor and concern about the younger generation of scientists were unique among his scientific peers.

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1 Compare with Sachse, C., *From the Kaiser Wilhelm Institute of Anthropology, Human Heredity and Eugenics to the Max Planck Institute for Molecular Genetics,* article in this anniversary publication.

2 Schuster, H., Wittmann, H. G. "The inactivating and mutagenic action of hydroxylamine on tobacco mosaic virus ribonucleic acid." *Virology* 19, 421–430 (1963).

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4 *Berliner Morgenpost* and *Süddeutsche Zeitung,* 19.12.1970

5 Schuster, H., Schramm, G. "Bestimmung der biologisch wirksamen Einheit in der Ribonucleinsäure des Tabakmosaikvirus auf chemischem Wege." *Z. Naturforschg.* 13 B, 697–704 (1958).

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↑ A staff member of the Schuster department working in the lab

↓ Karin Moelling and a colleague in her office

Staff members of the Schuster department at work in the lab

SOME QUESTIONS TO:

REGINE KAHMANN

When did you stay at the MPIMG? I worked on my PhD in the department of T. A. Trautner between 1972 and 1974. From July 1st, 1982 until December 31, 1986, I headed an Independent Research Group at the Otto Warburg Laboratory.
What was your scientific work focused on? Sequence-specific recombination of phage Mu, detection of an enhancer for recombination and identification of the FIS protein, which binds to the enhancer. Regulation of the DNA modification gene mom by a secondary structure element of the RNA and the protein COM that binds to it. The start of my work on the phytopathogenic fungus *Ustilago maydis,* which laid the foundation of the system that I am engaged in and fascinated by ever since that time.
Do you still have any contacts from this time? Yes, to the heads of some other OWL groups and to members of the former Trautner department.
Thinking of your time at the MPIMG, what is the first thing that comes to your mind? It has been the most easygoing time of my scientific career, still standing at the bench myself and for the first time being able to decide about which way to go on my own – and the first generation of wonderful co-workers: Gabi Mertens, Anke Klippel, Marlis Dahl, Andrea Seiler, Burkard Schulz, Christian Koch, Gregory Wulczyn, Peter Heisig and Michael Bölker.
What did you like most? To have friends and partners for discussion across the boundaries of the departments.
What annoyed you? The end of this time and the move to the adjacent Institut für Genbiologische Forschung (IGF Berlin GmbH) with a different structure and increasingly other duties.
What have you done since leaving the MPIMG? Between January 1st, 1987 and March 31st, 1992, I headed an independent research group at the IGF Berlin GmbH. I was appointed as Chair of Genetics at the Ludwig-Maximilians University of Munich on April 1st, 1992. On January 1st, 2000, I was appointed as Scientific Member of the Max Planck Society and started to establish the department of Organismic Interactions at the Max Planck Institute for Terrestrial Microbiology in Marburg. Since April 1st, 2001, I was also appointed as Professor of Genetics at the Philipps University of Marburg.

REGINE KAHMANN
Former Head of an Independent Research Group
(Selbständige Arbeitsgruppenleiterin, SAG)
at the Otto Warburg Laboratory

KLAUS BISTER

When did you stay at the MPIMG? From January 1982 until December 1987.
What was your scientific work focused on? Structure and function of oncogenes (amongst others Myc and Mil/Raf, which are meanwhile established as important drivers of human tumours) // regulation of cell proliferation and molecular mechanisms of oncogenesis // intracellular signal transduction // regulation of eukaryotic gene expression.
Do you still have any contacts from this time? Yes, to former colleagues of my own research group and to some heads of other OWL groups.
Thinking of your time at the MPIMG, what is the first thing that comes to your mind? The formidable dynamic and motivation of the scientists at the MPIMG, especially the spirit amongst the young people at the Otto Warburg Laboratory.
What did you like most? The conditions at the MPIMG that allowed me to focus completely on research without any distraction by bureaucracy and so on.
What annoyed you? There is nothing I could name.
What have you done since leaving the MPIMG? 01/1988 until 12/1993 Associate Professor at the Institute of Biochemistry at the Medical Faculty of the University of Cologne // 01/1994 until 09/2014 Full Professor and Chair of the Institute of Biochemistry at the Faculty of Natural Sciences, University of Innsbruck // 06/2004 until 12/2007 Director of the Center for Molecular Biosciences Innsbruck CMBI) // 07 until 09/2001 Guest Scientist at The Scripps Research Institute, La Jolla, California, USA // 07 until 09/2003 Guest Scientist at The Scripps Research Institute, La Jolla, California, USA // since 10/2014 Professor Emeritus of Biochemistry, University of Innsbruck // since 12/2014 Adjunct Professor in the Department of Molecular and Experimental Medicine at the Scripps Research Institute, La Jolla, California, USA.

KLAUS BISTER
Former Head of an Independent Research Group
(Selbständiger Arbeitsgruppenleiter, SAG)
at the Otto Warburg Laboratory

Ribosome research at the Max Planck Institute for Molecular Genetics in Berlin-Dahlem – the Wittmann era

KNUD H. NIERHAUS
Institute for Medical Physics and Biophysics, Charité – Universitätsmedizin Berlin
1968 until 2013 Max Planck Institute for Molecular Genetics, Berlin

DECIPHERING THE DNA STRUCTURE on one and a half pages in Nature 1953 by Watson and Crick is a central pillar of the history of molecular genetics.[1] The work that was awarded a Nobel Prize in 1962 explained to us immediately, how the genetic information mainly about the protein structure was copied from the mother to the daughter cell. The missing link carrying the information of the protein structure to the protein-synthesizing ribosomes was identified by Jacob and Monod[2] 1961 and named messenger RNA (mRNA). This discovery was soon confirmed by many groups and also awarded with a Nobel Prize in 1965. Ribosomes were seen in the electron microscope as "microsomes" 1955 and called "ribosomes" by Hubert Dintzis; ribosomes were known as the loci of protein synthesis since the end of the 50's.[3,4] When the Max Planck Institute for Molecular Genetics (MPIMG) was founded in 1964, it seemed to be logic from the retrospective that one of the Founding Directors, Heinz-Günter Wittmann, decided to study structure and function of the ribosome. Was the expectation of a third Nobel Prize a possible motivation along the line DNA structure → existence of mRNA → ribosome structure? A clear "no" is the answer, the goal to understand structure and function of the ribosome was not in the horizon of feasibilities of those days. In fact, a number of his colleagues strictly warned him against taking on a project of this magnitude, for instance Alfred Kühn, a leading expert of comparative zoology and genetics in Tübingen at those days. But this kind of negative appraisal was precisely the challenge, Wittmann was looking for.

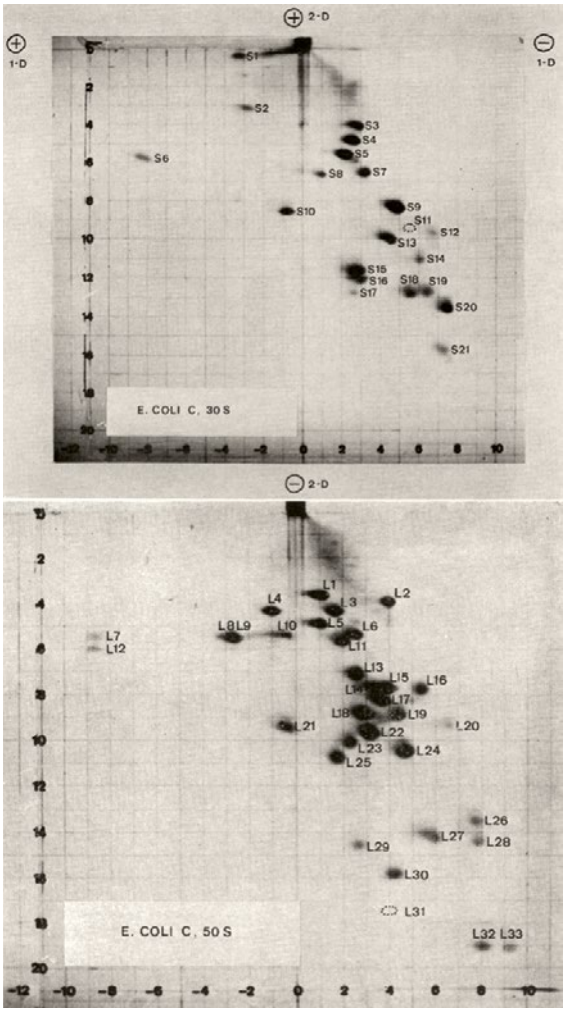
Wittmann was born in 1927 on a family estate in Stürlack in East Prussia. At the age of sixteen he was enlisted into the armed forces, and when the war ended two years later, he began to study agriculture at the Landwirtschaftliche Hochschule Hohenheim (now University of Hohenheim) near Stuttgart. He

◂ **Rotating evaporator** for vaporization of solvents in a lab of the Wittmann department, 1971

Heinz-Günter Wittmann, 1985

chose this course of education in order to be prepared for directing and managing the family farm, but by the time finishing his studies in 1951, it had become clear to him that the farm was lost and his plan could not be realized. Therefore, he went to the Universities of Stuttgart and later to Tübingen and continued his studies in biology and chemistry. In 1956, he received his doctorate under the direction of Georg Melchers and Wolfhard Weidel at the Max Planck Institute (MPI) for Biology in Tübingen. The thesis focused on the mutability of bacteriophages, which he extended with studies of the tobacco mosaic virus (TMC) as post-doctoral fellow at the University of California in Berkeley, working with C. A. Knight. After one year, he returned to the MPI for Biology in Tübingen and began to build up his own research group in the Department Melchers. His ambitious goal was to contribute to the deciphering of the genetic code by analyzing mutations induced in the coat protein of TMV. His first codon assignments[5,6] were achieved at the same time as those of the groups of Nirenberg and Ochoa[7,8] with *in vitro E. coli* systems. The results of all three groups were in agreement concerning (i) the conclusion that codons are non-overlapping triplets, and (ii) the nucleotide composition (not so much the sequence!) of many codons. Wittmann's results with the plant virus TMV documented the universality of the genetic code, and represented an *in vivo* verification of the *in vitro E. coli* results. His brave and very laborious enterprise led to his appointment as director at the new Max Planck Institute for Molecular Genetics (MPIMG) in Berlin-Dahlem.

When the first groups started their work in the Wittmann department ("Abteilung Wittmann"), the problem was still discussed, whether or not a ribosome looks like a virus with an RNA core and many identical proteins at the surface, and whether or not the long ribosomal RNA (rRNA) was the template coding for the ribosomal protein(s). It soon became clear to Wittmann and his co-workers that both assumptions were wrong: The ribosome is a huge complex of more than three million dalton and comprises more than 50 different ribosomal proteins (r-proteins), which – as shown by others – were all present in exactly one

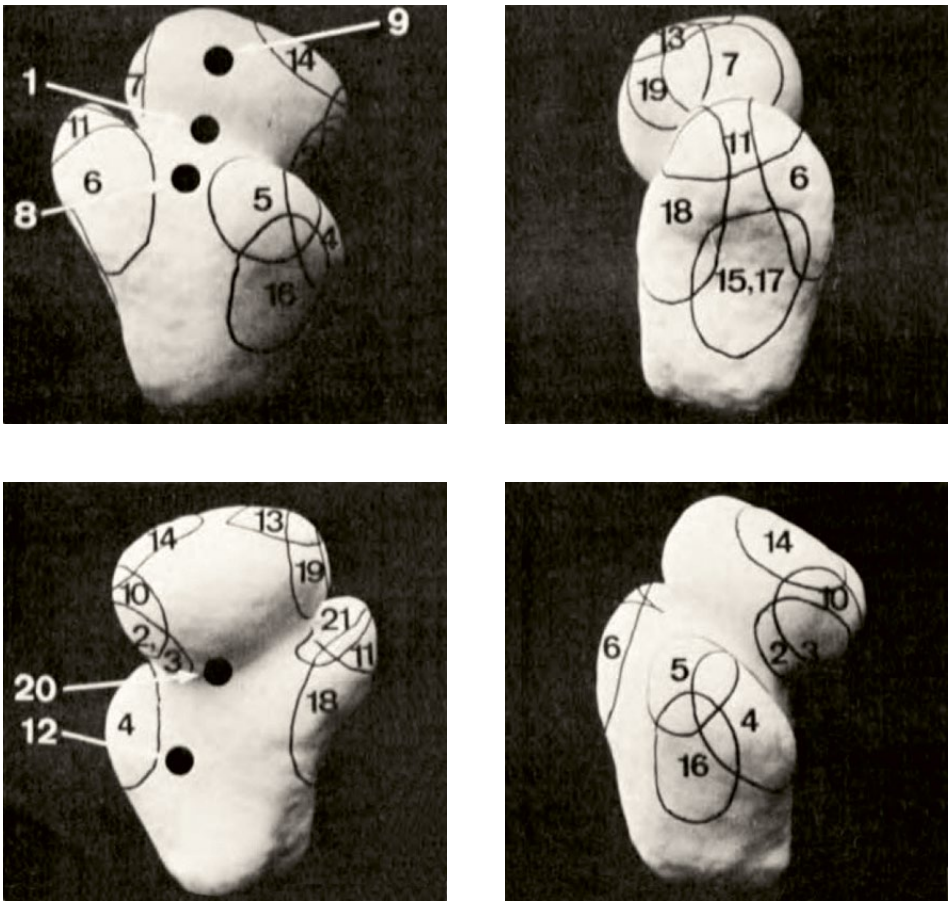


Two-dimensional electrophoresis of the r-proteins
The proteins of the small subunit are shown on the left, and those of the large subunit on the right, carrying the prefix S or L, respectively. Figure according to [15], modified

copy per ribosome except L12, which is present in four or six copies. The three rRNA molecules in bacterial ribosomes do not code for r-proteins, but, in spite of their small number, represent the majority of the molecular weight.

In the seventies and eighties, Wittmann developed his department to a Mecca for ribosome research. In the late eighties, he and Masayasu Nomura, another leading figure in ribosome research in Madison, Wisconsin, USA, were considered to be prime candidates for the Nobel Prize. In Nomura's laboratory, the procedure for the reconstitution of the small ribosomal subunit from its components was developed,[9] which indicated that the ribosomal components contained the necessary information for both assembly and adopting the correct ribosomal quaternary structure ("the wonder of Masayasu"). Nomura's work in Madison founded our understanding of translational control of the synthesis of r-proteins.[10] After a move to the University of Irvine, he continued with groundbreaking research concerning ribosome biogenesis in eukaryotes and the organization of the nucleoli.[11]

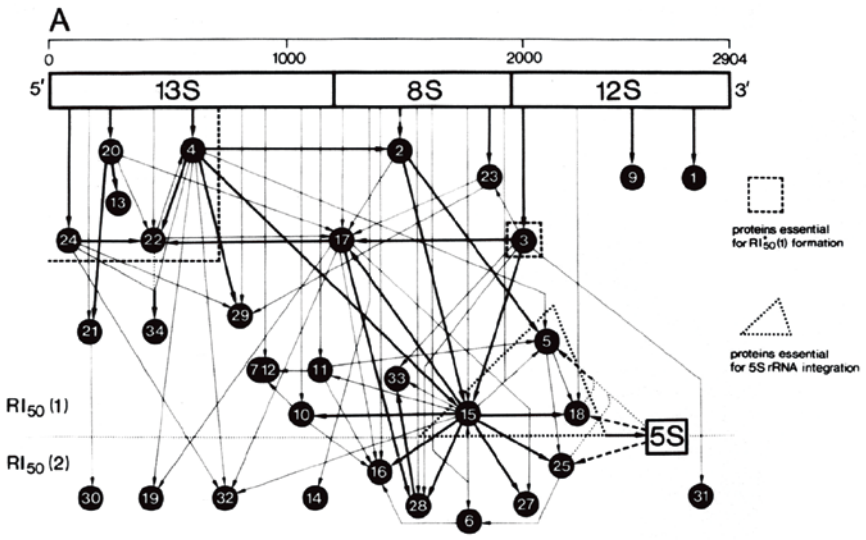
The achievements of the Wittmann department were not less important. Partially, this was due to the excellent group leaders, Wittmann was able to select



Location of epitopes of some S-proteins on the small 30S subunit, determined by immune-electron-microscopy. Upper row: solvent side; lower row: interface side. Similar data were also collected for the large 50S subunit. Figure according to [31], modified

and hire. Many of them received excellent research positions all over the world later. Here is not the space to acknowledge all the scientific achievements properly; so I will just mention a few highlights with the involved groups given in brackets.

One of the first decisions that Wittmann made, was to isolate all r-proteins and sequence them (Brigitte Wittmann-Liebold, Viktor Rudloff, Makoto Kimura);[12,13,14] practically all r-proteins were sequenced in his department. A two-dimensional electrophoresis was developed by Eberhard Kaltschmidt to separate all r-proteins on one plate. This was used to define the nomenclature for the r-proteins.[15] The proteins of the small ribosomal subunit got the prefix "S" and a number roughly according to their molecular weight, with S1 as the largest and S21 as the smallest protein. Accordingly, the proteins of the large subunit of the ribosome are named L1 to L36, with "L" for large. This scheme finished the Babylonian confusion of naming of r-proteins in the various laboratories, and is still the obligatory nomenclature today.[16] The purified proteins were used to raise antibodies, with which the distribution of epitopes of the r-proteins on the ribosome surface was determined by immune-electron-microscopy (Georg Stöffler).[17]

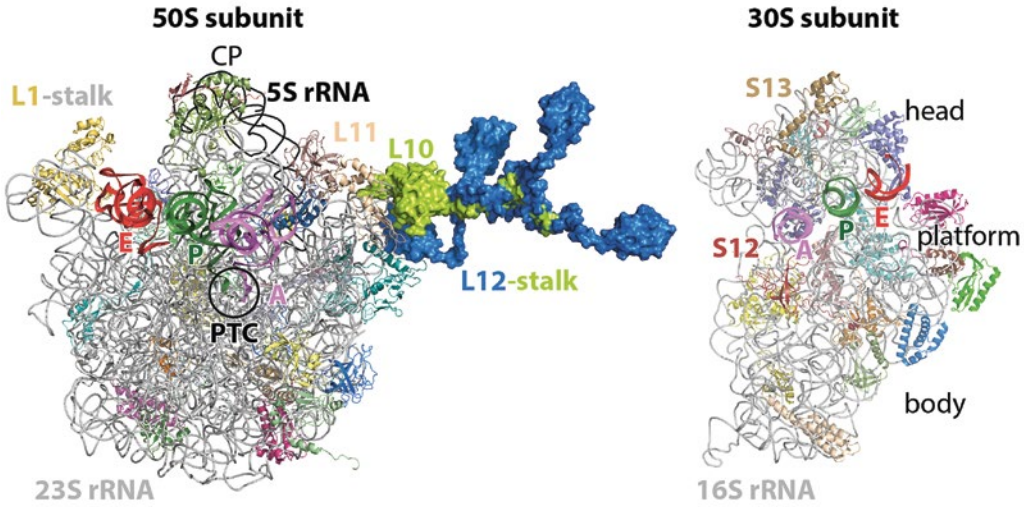


Assembly map of the large 50S subunit The map indicates the assembly dependencies, for example, L20 binds directly to the 23S rRNA, whereas L13 depends on the pre-binding of L20. Thick arrows indicate strong and thin arrows weak dependencies. The main fragments of 23S rRNA (13S, 8S and 12S) are indicated. RI50(1) and RI50(2) indicate the first and second assembly intermediates formed during the 50S formation. Figure according to [23], modified

These epitope maps together with the calculated three-dimensional map of the whole ribosome (Richard Brimacombe)[18] and the neutron-scattering analyses of the distribution of the ribosomal L-proteins inside the ribosome (Knud Nierhaus) were the central information about the ribosomal structure before the advent of the atomic X-ray structure of the ribosome after 2000.[19] Genes of the r-proteins could be localized on the *E. coli* chromosome by the groups of Katsumi Isono and Eric Dabbs, who developed selection systems, in which mutants could be isolated with mutations in almost all r-proteins.[20,21]

As mentioned already, the total reconstitution of the small 30S subunit of *E. coli* ribosomes from its isolated components was achieved in the Nomura group. Volker Erdmann accomplished the reconstitution of the large 50S subunit of *Bacillus stearothermophilus,* when he was in the Nomura group before joining the Wittmann department. But the central goal was the total reconstitution of the *E. coli* large subunit comprising 36 different components, a topic of strong competition involving many laboratories at those days, because a vast genetic and biochemical knowledge had accumulated around the *E. coli* ribosome. This was achieved in 1974 by Knud Nierhaus, and in the following decade essential features of the self-assembly of this 50S subunit were unraveled culminating in the 50S assembly map.[22,23] In addition to bacterial ribosomes, Alap Subramanian studied genetics and structure of chloroplasts intensively, too.[24]

Not only structural, but also functional breakthroughs happened in the department. The group of Claudio Gualerzi elucidated many mechanistic questions around the initiation of translation, which is driven by three initiation factors and the small ribosomal subunit recognizing the start signals for protein synthesis on the mRNA.[25] The discovery of a third tRNA binding site besides the canonical A- and P-sites, the Exit- or E-site, had a large impact on our understanding of ribosomal functions (Knud Nierhaus).[26] The E-site is universal and is important for maintaining the reading frame and the accuracy of protein synthesis. It is specific for deacylated tRNA, which leaves the ribosome from this site after having delivered its peptidyl residue from the P-site.[27]



Three-dimensional structures of the two ribosomal subunits from bacteria shown from the interface side The 50S subunit contains the 23S rRNA and 5S rRNA (light grey and black, respectively) and the 30S subunit is the 16S rRNA (light grey). Ribosomal proteins are represented as colored ribbons; the acceptor-ends of A- and P-site tRNAs within the peptidyltransferase center on the 50S subunit are highlighted by surface representation. The A-, P- and E-tRNAs are shown in violet, green and red, respectively. For clarity, only the anticodon stem-loops of the tRNAs are shown on the 30S subunit. Structural landmarks of the ribosome indicated (50S: L1 stalk; L12 stalk; CP, central protuberance; 30S: head, platform and body). Figure according to [32], modified

During his last years, Wittmann's interest focused on the crystallization of ribosomes and the analysis of the crystal structure – a task of unprecedented challenge and difficulty due to the enormous complexity of the ribosome. He invited the experienced crystallographer Ada Yonath, and together they made significant progress in this area. Some surprising findings emerged, such as the evidence for a tunnel through the large ribosomal subunit harboring the growing peptide chain before entering the cytosol. The tunnel could be seen in three-dimensional reconstructions from electron micrographs of crystalline sheets of ribosomes.[28]

In an early cooperation with Volker Erdmann, Yonath was the first to demonstrate that it was indeed possible to crystallize ribosomal particles, in this case the large subunit isolated from the extremophile *Bacillus stearothermophilus*, which was published in 1980.[29]

However, the ribosomal crystal data were not yet amenable to data processing without technical breakthroughs. Such a breakthrough included the introduction of cryogenic conditions for the ribosome crystals by Ada Yonath, without which the crystals would be fried by the enormous luminosity of the synchrotron beam before diffraction data could be collected. She became one of the heads of the Max Planck Research Unit for Structural Molecular Biology at DESY, Hamburg, from 1986 to 2004, where the crystal data were processed, whereas all the crystals were prepared in the Wittmann crystallography group in Berlin. After 1990 the group was taken over by Francois Franceschi, now at the NIH in Bethesda, USA.

From the first ribosome crystal in 1980 it still took 15 years until good and well-diffracting crystals were obtained, and significant technological improvements paved the way to collecting satisfactory diffraction patterns, five years after the premature death of Wittmann in 1990 felled by an insidious disease. He would have seen with pride that Ada Yonath together with Venki Ramakrishnan and Tom Steitz received the Nobel Prize for reaching the fantastic goal of unraveling the atomic structure of ribosomes.[30] Wittmann's work was characterized by two main features, namely his courage in tackling problems and defining goals,

which at the time were deemed to be virtually impossible to achieve, and his extraordinary talent for organizing a scientific unit and optimizing its scientific output along the line of ribosome research. The ribosome era at the Max Planck Institute for Molecular Genetics ended in 2013, when the Nierhaus group as the last Mohicans of the Wittmann era left the institute and found a new home at the Charité in Berlin.

Acknowledgments

I thank Drs. Brigitte Wittmann and John Achenbach, Noxxon Berlin, for helpful discussions.

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↑ Crystals of the 50S subunit of ribosomes of the bacterium *Deinococcus radiodurans*

↓ Centrifuge parade at the MPIMG around 1980, at that time the biggest accumulation of zonal centrifuges for isolation of ribosomes in Europe

SOME QUESTIONS TO:

TOMAS PIELER

When did you stay at the MPIMG? I was a Diploma student in the department Wittmann, Erdmann group, in 1980 and Head of an Independent Research Group from 1988 until 1992.
What was your scientific work focused on? During my diploma time, I worked on the secondary and tertiary structure of 5S ribosomal RNA. Being head of an independent group, I was interested in the regulation of the gene transcription of 5S ribosomal RNA, in the correlation of structure and function of the RNA- and DNA-binding Zink finger protein TFIIIA, the nucleus to cytoplasm transport of 5S ribosomal RNA in *Xenopus* oocytes and the function of other Zink finger proteins during the embryonic development of *Xenopus laevis*.
Do you still have any contacts from this time? Apart from former members of my own group, I keep rather loose contact to the heads of other Independent Research Groups, who had stayed at the MPIMG at the same time and to former members of the Wittmann department, arising more or less incidentally from our scientific activities, and to Reinhard Lührmann, who also works in Göttingen now.
Thinking of your time at the MPIMG, what is the first thing that comes to your mind? The summer party of the Independent Research Groups in 1988!
What did you like most? The five years with an Independent Research Group were a particularly privileged time: an excellent scientific environment, perfect support by the administration and absolute concentration on research. The everyday routine at university is something different yet.
What annoyed you? The five privileged years of independent research at the MPIMG were over so fast.
What have you done since leaving the MPIMG? Since 1992 Professor and Head of the Department of Developmental Biochemistry at the University of Göttingen // 2003 until 2009 Managing Director of the Göttingen Center for Molecular Biosciences (GZMB) // 2004 until 2011 Managing Director of the Center of Biochemistry at the Medical Faculty // since 2009 Dean for Scientific Affairs at the Medical Faculty.

TOMAS PIELER
Former Head of an Independent Research Group
(Selbständiger Arbeitsgruppenleiter, SAG)
at the Otto Warburg Laboratory

ALBRECHT BINDEREIF

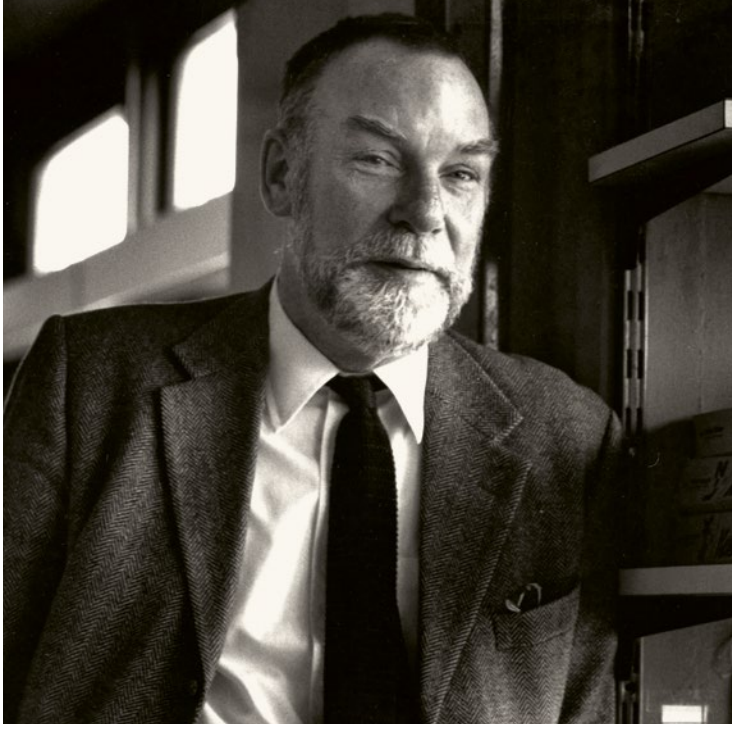
When did you stay at the MPIMG? From September 1988 until August 1994.
What was your scientific work focused on? Splicing of mRNA: mechanisms, factors and regulation in the human system and in trypanosomes.
Do you still have any contacts from this time? Yes, with former colleagues and co-workers.
Thinking of your time at the MPIMG, what is the first thing that comes to your mind? Laboratories at Harnackstraße; administration and workshop; my colleague and lab neighbor Claus Scheidereit; Professor Schuster, who has been in administrative charge of the OWL groups.
What did you like most? Scientific freedom; enough time to reflect on projects; generosity of equipment, budget, and personnel; no teaching obligations – all points, I only learned to appreciate later in comparison to working at the university.
What annoyed you? Comparatively little interaction and scientific contacts within the institute; no flexibility of the Max Planck Society, regarding the maximum contract period of six years at that time.
What have you done since leaving the MPIMG? Heisenberg fellowship at the Institute of Biochemistry at Humboldt University/Charité Berlin until April 1999. In May 1999, I have been appointed as Professor (C3) of Biochemistry at the Faculty of Biology and Chemistry at Justus Liebig University of Gießen.

ALBRECHT BINDEREIF
Former Head of an Independent Research Group
(Selbständiger Arbeitsgruppenleiter, SAG)
at the Otto Warburg Laboratory

“I couldn’t imagine anything better.”

THOMAS A. TRAUTNER
Director emer. at the Max Planck Institute for Molecular Genetics, Berlin

interviewed by RALF HAHN



You were born in Göttingen, Germany in 1932; can you tell me something about your early years with your parents?

I was raised as an only child in Göttingen, Hannover and Osterode am Harz, in a liberal, strictly anti-national socialist family, with a large international circle of friends. My father was drafted into the German army in 1939. He returned to Germany in 1954 after the war and nine years in Soviet war captivity. Due to the war, my mother and I moved from Hannover to Osterode in 1942. I passed my Abitur, the German higher education entrance qualification, there in 1950, and started studying biology in Münster in the same year.

How did your interest in science evolve?

Not so much by school. Our school classes in biology were very conservative and dominated by "natural history". It was literature that piqued my interest. At the time, there were a few books in Germany that sought to bridge the divide between biology and physics, for example by physicist Pascual Jordan or [Ludwig von] Bertalanffy. I also used to read a modern scientific journal, ORION, which was published at the time. My interest was intensified through my cousin and later PhD supervisor, Carsten Bresch, who took over the Genetics Chair at the University of Freiburg later.

You started studying in Münster in 1950 and transferred to Göttingen in 1951?

In Göttingen, zoology was particularly interesting, as Alfred Kühn and Karl Henke gave it a genetic focus. Another unique aspect was that Göttingen had the only Microbiology Chair in Germany back then.

In 1953, you went to the USA with one of the first Fulbright scholarships. How did you choose your destination in the USA?

It was chosen for me. When applying for the Fulbright scholarship, you had to provide a profile of scientific interests, and mine were: biochemistry, microbiology, virology. So they sent me to the University of Illinois at Urbana. The university started as an agricultural university, then grew rapidly and had really fantastic biochemistry, microbiology and genetics departments with I. C. Gunsalus, Rose, Carter and Sol Spiegelman. My most important mentor was Salvador Luria [1912–1991, Nobel Prize winner in 1969], an Italian Jew who had been persecuted by the fascists.

When you returned to Göttingen …

◂ Thomas A. Trautner, 1985

… I continued my studies and then took up a position as PhD student with Bresch at the Max Planck Institute for Biophysical Chemistry headed by [Karl-Friedrich] Bonhoeffer.

What exactly was your doctoral thesis?

When I started my doctoral thesis, the genetic concepts from classical genetics were well known. In contrast, the understanding of the biochemistry of genetic material, which had just been identified as DNA, was still in its infancy. This led to the approach of using the genetic behaviour of microorganisms such as bacteriophages to gain insights into the molecular behaviour and potential of the genetic material.

As a contribution to this, I crossed bacteriophages in certain configurations to obtain information on the molecular mechanism of genetic recombination for my PhD thesis. After crossing, phages with both parent alleles from a gene used in the crossing occasionally occurred (“heterozygotes”). Genetic analysis of these phages led to the conclusion that DNA molecules, in which complementary strands of different parental origin are paired with one another must occur as an intermediate product of genetic recombination. This genetic interpretation was later verified by biochemical analysis.

That sounds like a challenging subject.

Yes, it was. The thesis was based on the knowledge that DNA has a double helix structure, which had just been published at the time.

After your PhD, you worked in the Microbiology Department of the Botanics Institute in Cologne for two years, and then joined Arthur Kornberg in the USA as a postdoc. How did that come about?

I had been working on DNA in Cologne, but had only seen it through the lens of bacteriophage genetics. Now I wanted to get “hands-on” with DNA. To me,

Kornberg's lab seemed to be the best place for this. So I wrote to ask him whether he would take me on. At the time, Kornberg was in St. Louis and had not won the Nobel Prize yet.

And he just said yes?

It wasn't that easy. He answered that he had never had anyone with my background as a biologist in his institute, and it would be new to him. But he would accept me, if I got a scholarship. And the German Research Foundation actually did approve my scholarship application to go and work with him as a postdoc for a year.

At the time, I was the first German at all to work in Kornberg's laboratory. One of the biggest impressions to me was how I was welcomed at Kornberg's institute. Most of the scientists who worked there were Jewish. They included Morton Swartz, with whom I worked for an entire year. Mort was an American postdoc. He was infectiologist at the Massachusetts General Hospital and spent his sabbatical in Stanford. My publications from the Stanford time resulted from our combined work. The Swartzes often invited me to their home. Mort's wife, Cesia, was from Poland and had survived the persecution there. She still had the number that was tattooed on her arm as a child in a concentration camp. We spoke very frankly about the Nazi era. Bear in mind that at the time the catastrophe Germany had caused had only ended a few years before. For me, the welcome to the Kornberg group, whose tolerance was exemplified by Kornberg himself, was one of the most important impressions in my life.

We all worked very hard. That was expected. I learned all DNA-specific biochemical knowledge and methods I used later during my time with Kornberg. Added to this were the enriching discussions with other colleagues at Kornberg's institute like Paul Berg, Dale Kaiser or Buzz Baldwin. The Genetics Institute was next to our Biochemistry Institute. There, Josh and Esther Lederberg and their colleagues were my contacts, to whom I also developed a scientific and cordial relationship.

There's one more thing I should mention about Kornberg's institute. Besides the human and scientific quality, I have never seen another institute organised that well. It was simply fantastic. I also benefited from this experience in Berlin. The scientists had generous grants and the rule was that all money was pooled. And then there was another strength of Kornberg's laboratory, that each working group produced certain items for all the other working groups, respectively, such as technical equipment, or chemicals that everybody needed.

After this time in California, you returned to Cologne to the new Institute for Genetics, which had grown from the Botanics Department, with Max Delbrück as a director. What memories do you have of your years there?

Good memories. It was my first opportunity to have my own students and lead my own group. I had postdocs, and I started working on transformation and transfection building on my experience in Stanford. I used the *Bacillus subtilis* organism, which was unusual at the time, to cause infections with isolated phage DNA for the first time, and coined the term “transfection” for this process. That was a very, very effective and very good time. It was then that I developed very close scientific and friendly relationships with Peter Starlinger, Rudolf Hausmann and Rainer Hertel.

You qualified as a professor in 1963.

Yes, under Delbrück with a cumulative state doctorate [“Habilitation”] on DNA biochemistry.

Immediately after that, you went back to the USA. How did you get your assistant professorship in Berkeley?

While I was at Stanford, we had of course produced really exciting results, and I had received many invitations to give talks during that time. And I did so in Berkeley, too. In addition, a German emigrant, Gunther Stent, whom we had also appointed to this institute, was living and working in Berkeley. Stent was a full professor there and I believe it was due to him, combined with my background in genetics and biochemistry with Kornberg that I got an appointment as assistant professor at Berkeley.

Now you were back in California, where, I suppose, you probably didn’t feel bad about?

No, but then, my naïveté had harmed me, as I had simply extrapolated my entirely positive experience at the Kornberg Institute to America as a whole. And I thought the institute in Berkeley would be just like the institute in Stanford.

However, the problem was that the financial generosity at Stanford in no way applied to Berkeley as a state university. Also, the personnel structure of the institute was not as pleasant as in Stanford. But it was California after all, and personally, we had a really good time. During my Stanford scholarship, my wife had stayed in Germany to take her final state examination in medicine, and we were all together again in Berkeley. Unfortunately, it was an unsatisfactory, unproductive period scientifically. But that can happen.

"Temporary premises do not necessarily prevent good scientific work. They require proximity, contact, and consideration, which have a positive effect."

So I presume you were delighted to receive an appointment from Germany?

Yes, especially because Peter Starlinger and I were both appointed to the Max Planck Institute for Molecular Genetics in Berlin. The opportunity of working for the Max Planck Society and the fact that the society was so accommodating to me encouraged us to return. There was also the problem that my wife could not work as physician in the USA without retaking all the exams and finals she had already passed in Germany. The fact that she was not allowed to work in the US was a negative aspect of living there. We also had good friends in Berlin. I always wanted to move to Berlin – I would only return to Germany if I could go to Berlin … I would have liked to come to Berlin together with Starlinger, but he was focused on the institute in Cologne.

The president of the Max Planck Society at the time, Adolf Butenandt, also seemed to value this institute particularly highly, as evidenced in the unique personnel resources. Did you have direct personal contact with him?

Of course, though it was not with the same intensity as with the succeeding presidents. A key aspect for Butenandt was surely the fact that our institute's subject was very close to his own scientific interests.

When you moved to Berlin, you were not yet able to move into the beautiful new building. You had to use temporary premises first, and I was wondering how terrible that must have been?

It wasn't terrible at all. Temporary premises are almost always home to productive scientific work. We started working in the former Entomological Institute in Ehrenbergstrasse, Wittman started in the former villa of the Secretary General [Friedrich Glum], and Schuster also started in the Entomology

building. I had great co-workers, and we had quite a productive and pleasant time in the temporary premises. Temporary premises do not necessarily prevent good scientific work. They require proximity, contact, and consideration, which have a positive effect.

What were your main areas of research in this time?

In Cologne, we had proved that isolated DNA from bacteriophages can be inserted into transformation-competent *Bacillus subtilis* cells. This DNA is manifested by production in such cells of intact bacteriophages. At the time, we called this phenomenon “transfection”. Using transfection, we studied a genetic phenomenon initially known from fungal genetics: gene conversion. It is a molecular process, which eliminates regions of different genetic information in the two strands of a DNA molecule, as can occur in recombination. Christof Spatz and I used DNA, whose strands could be separated, and created DNA molecules with genetic differences in multiple regions in the two strands, using mutations. Transfection with these molecules and studying the resulting phage offspring showed that gene conversion occurred in this system and permitted analysis of the process.

You were then also appointed honorary professor at FU Berlin. Did you hold many lectures?

No, not many in Berlin. But I did supervise numerous graduate and doctoral theses. In Berkeley, I had to do a lot of teaching. And while in Cologne and as part of the EMBO course programme, I was also involved in courses for postgraduate scientists.

You moved into the new building in 1971. What came next there?

The move to the new institute allowed us to increase the number of scientific and technical staff. When it was established, the institute received incredible personnel resources. That allowed me to attract colleagues to Berlin I could never have had otherwise in a temporary building, even if they didn’t really suit the main focus defined by my research. The new building allowed me to set up working groups in subject areas close to mine. That led to the formation of a whole range of working groups, which were all enormously successful. In the meantime, they have all been appointed to professorships or equivalent positions elsewhere.

My philosophy for my department differed from Wittmann’s – whom I greatly admire. He focused consistently on one area, and established a large department, which exclusively studied the structure and functions of ribosomes, after moving into the new building. My own scientific focus would have been far too restrictive to devote a whole “army” of scientists to the question.

In 1990, you were appointed Vice President of the Max Planck Society. How did that come about?

I had actually always been interested in science policy. This is evidenced by my work in many commissions, in Berlin and within the MPG as well as within the scientific community in Germany and overseas. The Vice Presidency only arose when Hans Zacher took over as President from Heinz Staab. The other two Vice Presidents, Hans Zacher appointed with me, Professor [Herbert] Walther and Professor [Franz E.] Weinert, were from Munich. Maybe that is why they also wanted someone from another region. When it came to working together, the relationship between the President and Vice Presidents soon proved very harmonious. Today, Hans Zacher* and I are good friends and time has shown that the regional aspect was definitely not the main reason for the choice.

When you took up the office, did you set yourself a goal you wanted to achieve?

No, the main policy of the MPG is determined by its President, but it was clear to me that pending the retirement of directors within the MPG would mean many decisions, which required my expertise. Of course, we could not have anticipated the problems associated with the [German] Reunification at that time.

When you look back on these six years as Vice President, which of your achievements makes you happiest?

The new institutes established by our section as part of the Reunification, which were important to me. One of those was the MPI for Infection Biology, which was based on my idea. Then the new foundation of the Institute for Evolutionary Anthropology in Leipzig. For this [Svante] Pääbo was the connection for me, whom I had already suggested as possible candidate in an upcoming succession for Seewiesen. And finally, arranging the successors to the first generation in this institute, oriented to work in the field of molecular human genetics.

There seemed to have been major discussions on your institute's move in this direction. I presume at the end of the 80's, am I right?

As usual, commissions were formed to govern this succession. For example, there was an idea to establish cell biology as second generation successors. I wanted to establish infection biology as our succession, but those involved did not agree.

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* Deceased in 2015

It was not until the Reunification that the establishment of the Institute for Infection Biology in (Eastern) Berlin was possible as a new institute in the New Federal States. The solution finally chosen, “molecular human genetics” here in our institute, was a difficult process, as the field of human genetics has extremely negative connotations in Germany.

There also seemed to be quite a lot of resistance against human genetics/ genome research as a subject. Where did this resistance come from?

Much of the resistance was political. Can and should the MPG, the successor organisation to the Kaiser Wilhelm Society [Kaiser-Wilhelm-Gesellschaft, KWG], which provided the theory to support the National-Socialist race policy through its “KWI for Anthropology, Human Genetics and Eugenics”, ever work on human genetics again? I was always vehemently of the opinion that it MUST! The shame brought on the Kaiser Wilhelm Society by this cannot be rectified by steering clear of the subject area. We also had to offer our young and upcoming scientists opportunities in human genetics again. It is an immense and incredibly important field. Human genetics has been very successful in the area of diagnosis. Hospitals and institutes in Germany working on human genetics have done great work. But that was not the molecular human genetics we wanted here. I must mention the great support I received from the Berlin-based human geneticist Professor Karl Sperling from Humboldt University, who has just retired. He contributed a lot to the conception of this plan and I am happy that it went that way.

What was the position of the MPG top management on this?

I had the full support of Hans Zacher. And also from his successor [Hubert] Markl, who supported this initiative and viewed it positively in particular for Berlin as a location. Markl impressed me greatly when he, as the president of the former Kaiser Wilhelm Society and the MPG, invited the few Jewish survivors from the Nazi twin “research” to Berlin and apologised officially for the barbaric treatment from the Kaiser Wilhelm Society. You can’t undo what has happened, but I have always viewed the establishment of molecular human genetics in its present form as a duty to inform the public about the injustice genetics can create. An injustice, which can never be surpassed in its scope.

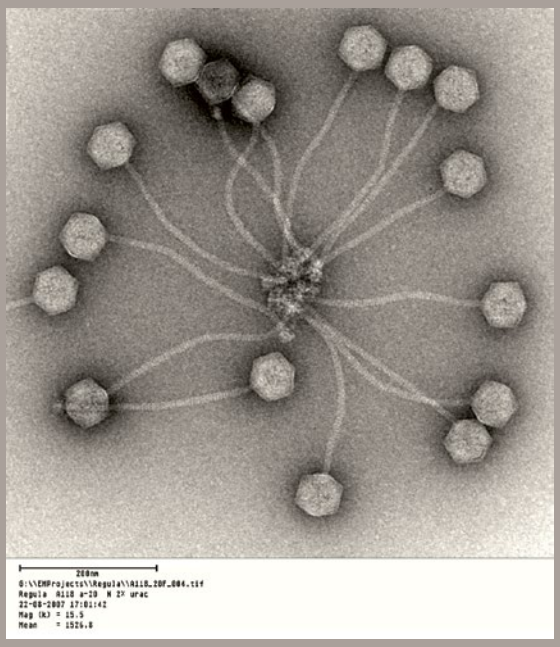
Was there ever an attractive offer, which would have tempted you to actually leave the institute?

No, never. My best years, both in scientific and personal terms, have been here. I couldn’t imagine anything better.

If I were to ask you for your most important scientific achievements, which would you mention?

I don't know if it counts as a scientific achievement. On one hand, I would say that I had many students, doctoral candidates and postdocs, most of whom have found leading positions in the field of science and are doing excellent work. In a way, that speaks to the effect of my department on science as a whole. And where my own work is concerned, I believe that the combination of DNA and genetics, as started in my doctoral thesis on heterozygotes, is an aspect of this scientific achievement. The second, as the final part of my work, is definitely the discovery of structures of DNA methyltransferases. DNA methylation by such enzymes went on to become an entirely new field in genetics, named epigenetics. That is not to say that it came from here, but the understanding of the importance of methylation and the documentation of how it starts with the enzymes we studied certainly was good work. The existence of methylation has been known since the first chemical analyses of DNA. There was always a base whose function was not understood, methylcytosine. After I retired, epigenetic work continued at many research institutes. They were able to prove that DNA methylation plays a key role in regulating the expression of genes, for example in embryogenesis.

Thank you very much for this interview.

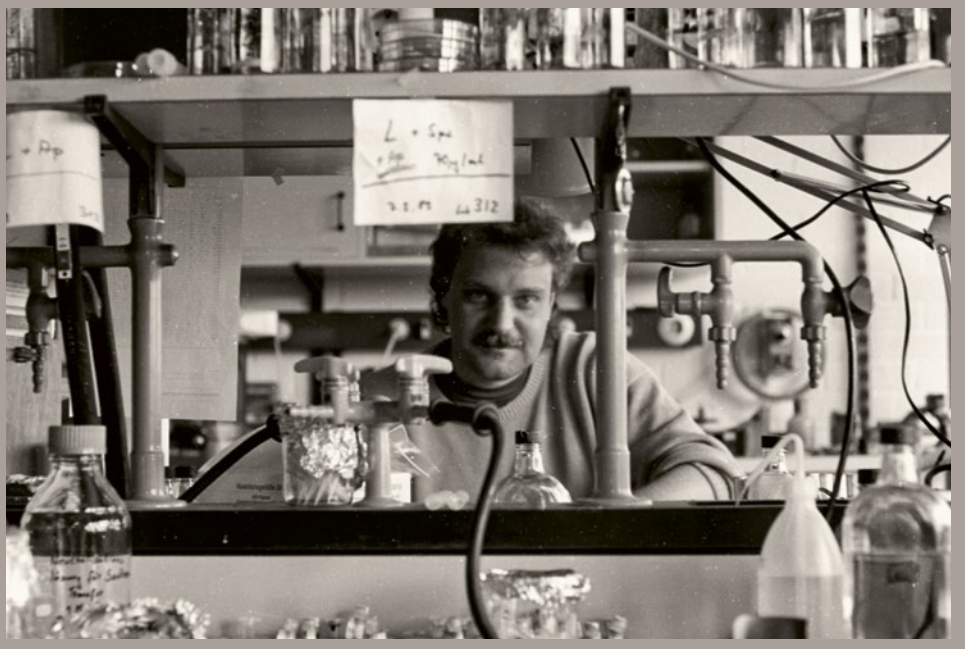


← Electron micrograph of bacteriophage A118, phage tails are attached to one another *via* an antibody against the receptor binding protein.

↓ Members of the Trautner department, Messer group, in their lab, around 1980

↗ A staff member of the Trautner department at his workplace

↘ Thomas A. Trautner with a technician in the lab, around 1980



SOME QUESTIONS TO:

CLAUS SCHEIDEREIT

When did you stay at the MPIMG? I started at the MPIMG in November 1988, coming from Rockefeller University, New York, and officially stayed until November 1994, when I left for the Max Delbrück Center for Molecular Medicine in Berlin-Buch. However, the actual lab move was in springtime 1995.

What was your scientific work focused on? A main focus of our lab was the purification of [the transcription factor] NF-κB, the molecular cloning of NF-κB subunits and the biochemical analysis of structure-function relationships in NF-κB and IκB molecules. Other projects focused on the characterization of further gene specific transcription factors, using *in vitro* transcription systems.

Do you still have any contacts from this time? There are rather sporadic meetings with various previous MPIMG colleagues.

What did you like most? Altogether, the working conditions and support provided by the institute were excellent. Professor Heinz Schuster was actively involved in the recruitment process for the heads of the junior research groups. Later, he supported us as well as he could, when we had to solve any budgetary or institutional issues. Most of my time at the MPIMG overlapped with Albrecht Bindereif and Tomas Pieler and I greatly enjoyed all the scientific and personal interactions we had. The research fields of our three groups were very complementary, covering transcription, mRNA processing and developmental molecular genetics. Thus, there were ample interactions between the people in our groups. Albrecht and I had common weekly lab group seminars for a couple of years and we shared a bungalow as laboratory building at Harnackstraße.

What have you done since leaving the MPIMG? After I left the MPIMG, I continued my research at the Max Delbrück Center in Berlin. Furthermore, I have been appointed as Adjunct [außerplanmäßiger] Professor at the Institute for Biochemistry at Freie Universität Berlin.

CLAUS SCHEIDEREIT
Former Head of an Independent Research Group
(Selbständiger Arbeitsgruppenleiter, SAG)
at the Otto Warburg Laboratory

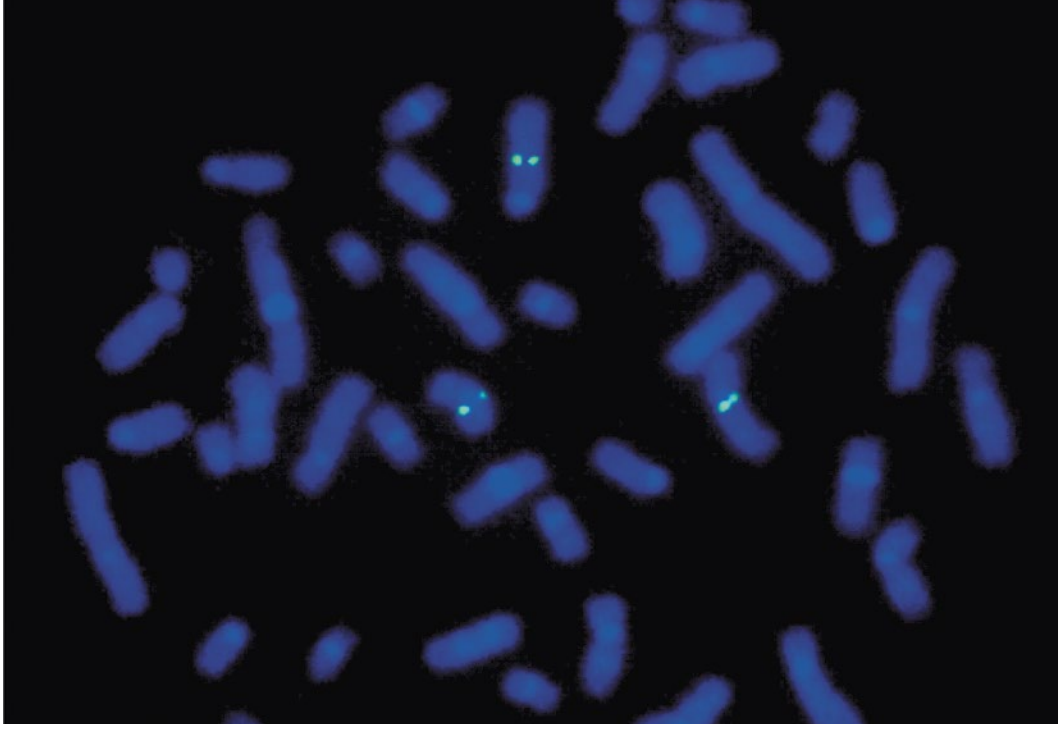
ADAM ANTEBI

When did you stay at the MPIMG? From November 1997 to June 2004.
What was your scientific work focused on? Regulation of developmental timing and longevity in *C. elegans*.
Do you still have any contacts from this time? Yes, I still keep in contact with many of my students, fellow OWL group leaders and directors.
Thinking of your time at the MPIMG, what is the first thing that comes to your mind? Great science, awesome Christmas parties, true friends. It was one of the best and exciting times of my life.
What did you like most? Developing my own science and ideas, being with the people in my lab and in the Otto Warburg Laboratory, raising my family (my two boys are original Berliners), and living in the exciting city of Berlin.
What annoyed you? The architecture was not ideal and did not provide a good opportunity for communication.
What have you done since leaving the MPIMG? I am one of the Founding Directors at the Max Planck Institute for Biology of Ageing in Cologne.

ADAM ANTEBI
Former Head of an Independent Research Group
(Selbständiger Arbeitsgruppenleiter, SAG)
at the Otto Warburg Laboratory

50 years of research at the Max Planck Institute for Molecular Genetics – the transition towards human genetics

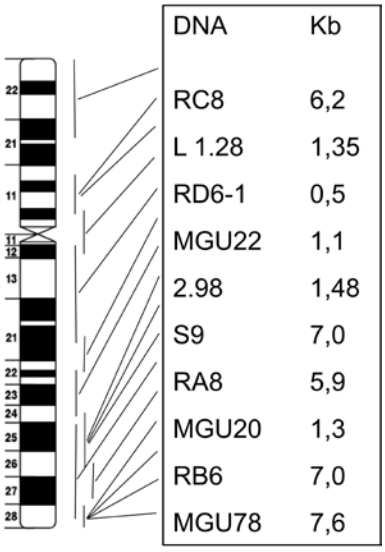
KARL SPERLING
Institute for Medical Genetics and Human Genetics,
Charité – Universitätsmedizin Berlin



The time before the transition: the situation of human genetics in post-war Germany

"THE SENATE DECIDES TO CHANGE the name of the Max Planck Institute for Comparative Hereditary Biology and Hereditary Pathology to Max Planck Institute for Molecular Genetics (MPIMG)." This decision of the Max Planck Society of 6 December 1963 was obviously intended to avoid antagonising the previous director of the institute, the nationally and internationally acclaimed Hans Nachtsheim, who was also professor ordinarius for General Biology and Genetics at the Freie Universität Berlin, by closing his department. In fact, the MPIMG was a scientifically well-justified new foundation.[1] At the same time, this was a clear break with the Kaiser Wilhelm Institute of Anthropology, Human Heredity and Eugenics in Berlin-Dahlem.[2] Nachtsheim had taken over its department for experimental hereditary pathology in 1941, and it was the only department, where work was continued after the war. The Kaiser Wilhelm Institute had provided the so-called scientific justification of Nazi eugenics and racial hygiene during an era, in which fundamental ethical guidelines were violated, as H. A. Staab, President of the Max Planck Society, stated in 1986.[3] Not least, it was this dark "heritage", which precluded the Max Planck Society's engagement in the field of human genetics for over three decades after the War.

Nachtsheim, who received two honorary doctorates and was awarded the Knight Commander's Cross of the Order of Merit [Großes Verdienstkreuz mit Stern] of the Federal Republic of Germany, had shaped the development of genetics and human genetics in Germany significantly. After the war he vehemently made every effort to keep German genetics on the map. "Considering the large scientific and practical significance of genetics it must be our goal to ensure that the subject is offered at every German university, namely general genetics at the



◂ **Chromosomes (blue) of a patient** with a balanced chromosome translocation and a breakpoint spanning genomic clone (green), chromosomes are shown during metaphase

Map of the human X chromosome, generated out of cloned DNA sequences of X chromosomes in somatic cell hybrids. Data from [6]

faculties of natural sciences and human genetics at medical faculties."[4] In this sense, the German Council of Science and Humanities [Wissenschaftsrat] recommended in 1960 that each medical faculty in the Federal Republic of Germany should establish a chair in human genetics. This was decisive for the establishment of human genetics as profession in medicine. Following the recommendation of the German Council of Science and Humanities, the majority of chairs in human genetics were established in West Germany in the 1960s and 1970s, and in East Germany in the late 1970s and 1980s.[5] They were relatively small institutes with minimal equipment compared to the established medical fields such as anatomy, physiology or biochemistry. However, they had to fulfil important tasks in the fields of genetic diagnostics and consultation.

In the late 1970s, the first efficient methods of DNA sequencing emerged, followed by linkage analyses for the localisation of genes. Exemplary for this was the human X chromosome due to its special mode of inheritance. Based on soma cell hybrids with fragments of the X chromosome, a map of cloned sequences[6] was created for the first time in 1984, and in 1986, the first disease-causing gene was identified by a German geneticist who however was working in the U.S.[7] As a consequence of these fundamental achievements, the analysis of the human genome moved into the focus of molecular biological research. Already in 1985, the complete sequencing of the human genome was subject of a serious debate. At this time, the public opinion in Germany was extraordinarily negative towards so-called gene technology. This attitude was strongly influenced by the memory of eugenics of the Nazi era. Among others, this manifested in the resolution of a highly restrictive law on genetic engineering in 1990. Many institutes for human genetics found themselves under major attack.

In order to keep pace with the scientific advancements, representatives of the field successfully applied for a priority programme "Analysis of the human genome with methods of molecular biology" at the German Research Foundation in August 1984.[8] From abroad, Hans Lehrach, Head of the Department of Genome Analysis at the Imperial Cancer Research Fund (ICRF), London, and

Hans-Hilger Ropers, Director of the Department of Human Genetics at the University of Nijmegen, The Netherlands, collaborated in the project, and later Svante Pääbo joined with studies on "old DNA." Not less important was that Thomas A. Trautner, Director at the Max Planck Institute for Molecular Genetics and until 1983 chairman of the review committee for "General Biology" at the German Research Foundation, agreed to peer review the new priority programme. Along with its first funding period, the "Human Genome Organisation" (HUGO) was founded in 1988, and in 1990 the American human genome project was launched. Most of the other major industrialised nations, especially the United Kingdom and France, recognised these challenges and started their own genome projects.

The MPIMG's transition to human genetics

The International Human Genome Project initially took place without any German participation. In 1991, the Society for Human Genetics demanded from the Federal Minister for Research and Technology with regard to the analysis of the human genome, "to give priority to the funding of projects, in which local cooperations or cooperations between universities and other research institutions are formed that can tackle more complex challenges at an international level."[9] Along the same line, Friedrich Vogel had already approached the Max Planck Society in the 1980s and requested the foundation of a department of human genetics at the Max Planck Institute for Medical Research in Heidelberg. However, he was unsuccessful.[10] The transition was initiated by Thomas A. Trautner, who has been appointed as Director at the Max Planck Institute for Molecular Genetics in Berlin-Dahlem in 1965, and later elected as Vice-Chairman at the Biological Medical Section and, in 1990, as Vice-President of the Max Planck Society. It is thanks to his initiative that the Max Planck Society took up research in human genetics, which completely had been avoided before.

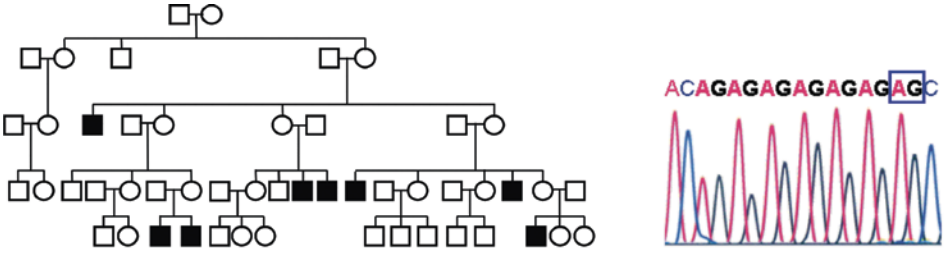
In 1992, Trautner sent a "Proposal for founding a Max Planck Institute for Human Genetics" to Hans F. Zacher, President of the Max Planck Society at that time. In this proposal, he explained that by introducing gene technologi-

cal methods, human genetics had become equal to other genetic disciplines. "Furthermore, the accumulated knowledge on normal and pathological development of humans gained over centuries represents a plenitude of information for the general understanding of the entire field of biology, which has been unsurpassed by any other species. This is now accessible to genetic analysis." He added that most of the results were largely gained in Anglo-Saxon countries. "A reason for this is the fact that there is no Institute for Human Genetics primarily dedicated to research in Germany that can compete internationally due to a lack of structural diversity." This letter was discussed for the first time during a meeting in Hannover on 7 September 1992, where the future direction of the Max Planck Institute for Experimental Endocrinology in Hannover was to be laid out after the retirement of its director. On this occasion, Trautner did also mention the Kaiser Wilhelm Institute in Berlin, which had been rightly discredited. But now the times had changed and with an awareness of the past it was possible again to conduct responsible, important and highly topical research. The committee gave it a positive assessment and agreed to further discuss the subject.

During a meeting of the committee in Heidelberg on 3 February 1993, however, it turned out that neither the resources nor the room situation at the institute were adequate for establishing an institute with the necessary equipment in Hannover. On the other hand, two appointments could be realised at short notice at the MPIMG in Berlin, especially since Berlin offered an extremely attractive environment with regard to its demography and science for the field of human genetics. Following an initiative of the committee for the "succession of Schuster and Wittmann", a Max Planck Society Symposium on Human Genetics was held in May 1993 in preparation of the transition. The opening lecture on "The human genome project and clinical medicine" was held by V.A. McKusick, Baltimore. Among the 17 outstanding speakers were Hans-Hilger Ropers from Nijmegen, with his presentation on "Genome mapping, positional cloning and the elucidation of hereditary diseases", and Hans Lehrach from London, who talked about "Strategies and progress in the molecular analysis of mammalian genomes".

Participants of the "Max Planck Society Symposium on Human Genetics", Berlin 1993
Amongst others are H.-H. Ropers (4th from the left) and H. Lehrach (3rd from the left in squatted row); in the background also with Thomas A. Trautner (8th from the right) and Karl Sperling (7th from the right), 1993

After the symposium the committee swiftly agreed to suggest the appointments of Ropers and Lehrach. Following the usual procedure of the Max Planck Society, the President appointed both as directors of the MPIMG in 1994. This concluded a transition of so to say historical dimension. Once again, Germany had a Max Planck Institute, which focused exclusively on human genetics. It was a good decision to abstain from a name change. As expected the new direction also attracted heavy criticism. An example of this can be found in an article from the Frankfurter Allgemeinen Zeitung (FAZ) of 30 March 1994, written by Benno Müller-Hill, a renowned molecular geneticist, on "Humangenetik der Gewalttätigkeit – 'Aggressions-Gen' als Testfall für den Umgang mit der Menschenwürde" [Human Genetics of Violence – The 'aggression gene' as a test case for handling human dignity]. The author referred to a talk Ropers had given in Cologne about X-linked learning disabilities and an article in "Science", describing the analysis of an enzyme defect, which causes the affected male members of a Dutch family to respond aggressive to mild frustrations. Ropers had just been appointed as Director of the MPIMG in Berlin and was now placed in the line of tradition of the KWIA by Müller-Hill. "Will these restless researchers examine if



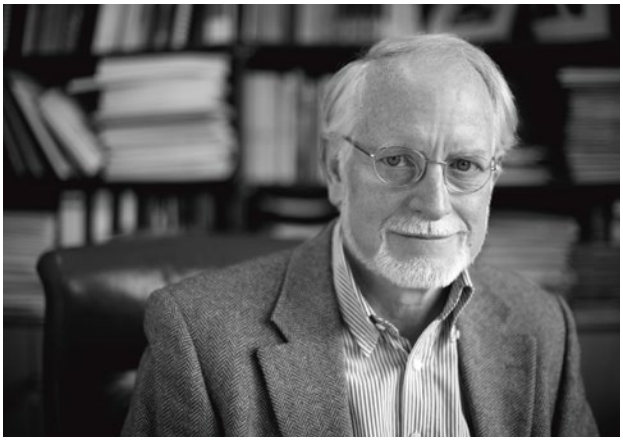
Pedigree of a family with congenital X-linked intellectual disability and a disease-causing insertion of two nucleotides (AG) in the responsible gene

these mutations occur more frequently in certain ethnic groups?", he requested and explained that such research "attempts to explain violence as something natural destroyed traditional morals, law and religion" and inevitably led "as a substitute for religion to evil." Müller-Hill's article garnered strong, public objections.[11] In his impressive response Ropers declared, for example, that "the knowledge of a genetic predisposition can contribute to making the application of the law more equitable" and rejected any assumption of an "affinity to Nazi eugenics."[12]

Post transition: from the Human Genome Project to molecular human genetics

The following shall provide a brief look at the beginning of the Human Genome Project in Germany and the integration of the MPIMG, before we take a closer look at the more medically oriented research at the MPIMG.

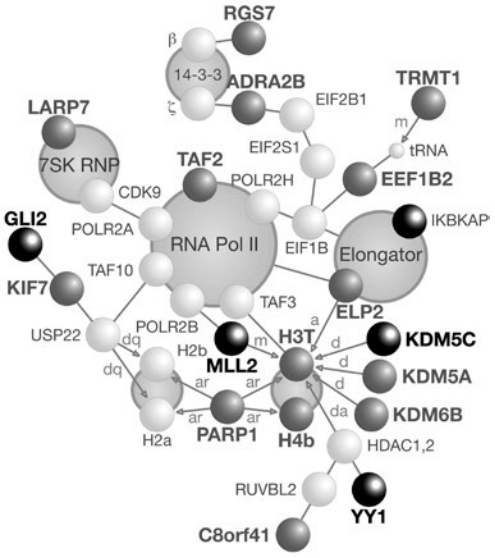
On 5 February 1993, the German Research Centre for Biotechnology (today the Helmholtz Centre for Infection Research) held a workshop in Brunswick on the development of the Human Genome Project in Germany, where Lehrach and Ropers participated among others. The organisers warned that "if targeted funding is not initiated in Germany for human genetics soon, especially with regard to the Human Genome Program, German scientists will only be able to play a secondary role in this field despite their enormous potential."[13] In the same year an ad hoc committee of the German Research Foundation, which also saw Ropers and Trautner as their members, suggested a "Proposal for a programme for funding of genome research in the Federal Republic of Germany". This was the basis for a research concept on human genome research of the Federal Ministry of Education and Research, which was developed in 1995[14] and launched in 1996. At its core was the German Resource Centre for Genome Research, which was based on the "Reference Library/Primary Database" at the ICRF in London. It was transferred by Lehrach and his co-worker Günther Zehetner to the MPIMG. In addition, Annemarie Poustka, a former co-worker of Lehrach and also a member of the priority programme of the German Research Foundation, transferred it to the



Hans-Hilger Ropers, 2008

German Cancer Research Centre in Heidelberg. André Reis of the Berlin Institute of Human Genetics established a microsatellite centre at the Max Delbrück Center (MDC) for Molecular Medicine in Berlin-Buch. Headed by Marie-Laure Yaspo, also from the MPIMG, the human chromosome 21 was the second human chromosome in history to be completely sequenced, in collaboration with scientists from England, France and Japan – an event, which received attention worldwide. Also in terms of the number of funded workgroups, Berlin became a centre of human genome research in Germany.

Whereas Lehrach focused on genome research and his work is recognised in another article of this anniversary publication,[15] Ropers' work targeted on the identification of disease-causing genes. More than anyone else in the German-speaking world Ropers used the new methodological repertoire to identify a large number of medically relevant genes. His work provided the basis for elucidation of their pathogenesis and simultaneously provided the basis for consultation and diagnostics of affected families. Since 1985, Ropers has been the chairman in various chromosome committees of the International Workshop on Human Gene Mapping, member of the "Human Genome Organization" (HUGO) and member of the HUGO Council since 2003. Emphatically he stood up for including the examination of single gene disorders during the discussion about the second phase of the German Human Genome Project. The planned competence centres and competence networks, however, only targeted the analysis of complex diseases, i.e. widespread diseases, to which Ropers fervently objected. He was then asked to develop a network concept to analyse single gene disorders for the core area, which was supported by the German Society for Human Genetics without any objections. Still, the steering committee rejected it without any comments. In this situation and after thorough consultation with representatives of science and science policy, Ropers decided to address the public through the FAZ as a last resort to stand up for his convictions.[16] In his article he emphasised and supported the necessity to determine the genetic basics of complex diseases, but he equally made it clear



Network of known and new genes for intellectual disability Systematic elucidation of Mendelian diseases allows insights into the function of the respective genes. Figure modified according to [19]

that the intended methods are no longer capable of achieving this goal. However, it would be possible through the analysis of single gene disorders. Even though he knew that his public criticism would result in massive opposition (and more), he stood up for it and could not do otherwise.

Not least his experiences in the Netherlands, where six university centres for clinical genetics focus on the healthcare of patients with "rare diseases" made Ropers publicly speak out for a more centralised organisation of genetic healthcare also in Germany. In his role as secretary to the Biological and Medical Sciences class at the Berlin-Brandenburg Academy of Sciences and Humanities he was primarily responsible for the publication "Statement on new sequencing techniques and their consequences for genetic healthcare" published in 2013.[17] Looking at future healthcare, research and data protection it is a plea for establishing such centres also in Germany, which would permit interdisciplinary consultations.

Additionally, Ropers made a vital contribution to the development of human genetics within the medical community of Berlin. In 1998, the Charlottenburg Hospital in West Berlin moved with its Institute of Human Genetics to Humboldt University in East Berlin effectually uniting it with the university hospital Charité. There, the Institute for Medical Genetics was located, whose director Regine Witkowski retired in 1999. The structural plans of the Medical Faculty intended for the head of Human Genetics and author of this essay to take up responsibility for both institutes afterwards, the consequences of this were fairly obvious. In light of the increasing significance of this medical field the head emphatically pushed to keep both academic chairs. It is thanks to Ropers that this in the end actually happened. He convinced the Max Planck Society to set up a joint appointment with the Charité and to fund the position for five years. In autumn 1998 at an excellent Italian restaurant in Northern Berlin Wolfgang Eckey, the responsible official from the Berlin Senate, Ropers, and the author of this essay came together by invitation of the Medical Head of the Charité at the time, Eckart Köttgen, which led to a revision of the existing structural plans of the Charité.

As a consequence, Stefan Mundlos was appointed as C_4-S professor for Medical Genetics at the Charité and as head of a research group at the MPIMG – an almost unheard of procedure at the time. Together we were able to establish a German Research Foundation collaborative research centre for "Molecular principles of the clinical variability of monogenic diseases (SFB 577)" in Berlin for the first time in three decades with an exclusive focus on human genetics, which took up its work in 2001.[18]

The ground-breaking concept of a joint appointment has certainly proven itself in the world of academia and has led to a particular close relationship between the Max Planck Society and the Charité in Berlin. Particularly, this can be seen in the impressive list of publications of Stefan Mundlos, which almost completely demonstrates the successful correlation of basic research at the MPIMG with the clinical research and healthcare of patients at the Charité. At the same time, the successful appointment is testament to Trautner's vision of 1992, where owe to the unique conditions in Berlin the genetic analyses of and for humans have improved applied and basic research alike.

From the scientific perspective Ropers faced a special challenge, the identification of genes, which cause unspecific cognitive disorders: The degree of genetic heterogeneity is large, and the lack of clinical specificity makes it difficult, if not impossible, to merge independent families. For understandable reasons, mouse models that would permit conclusions with regard to humans are not available. For this reason he initially focused on cases with X-linked inheritance. Within the framework of a European consortium, which he co-founded with others, the molecular causes of many forms of X-linked mental disabilities known today were revealed. At the same time, together with Niels Tommerup, he originated the international register for disease-associated balanced chromosome translocations, thus also making crucial contributions to explaining single gene disorders. In an exemplary analysis in Iran with its high number of intermarriages, several hundred families with autosomal-recessive mental retardation could be recruited, which resulted in the identification of a large number of new genes

for non-syndromic autosomal-recessive mental retardation. Surprisingly, these works demonstrated that there are much more cases of non-syndromic mental disabilities with a monogenic cause, i.e. not of a multifactorial nature, than originally assumed, which simultaneously opens a direct access to the "pathways" involved. In 2009, in recognition of his fundamental achievements, the German Society for Human Genetics awarded Ropers the medal of honour and made him an honorary member. The European Organisation for Rare Diseases also awarded him the EURORDIS Scientific Award 2014.

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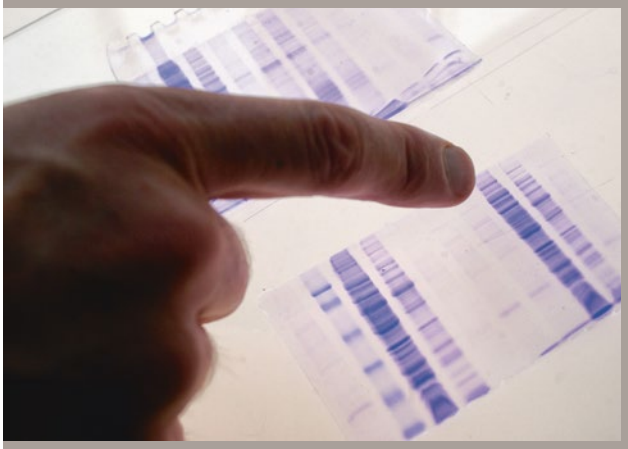
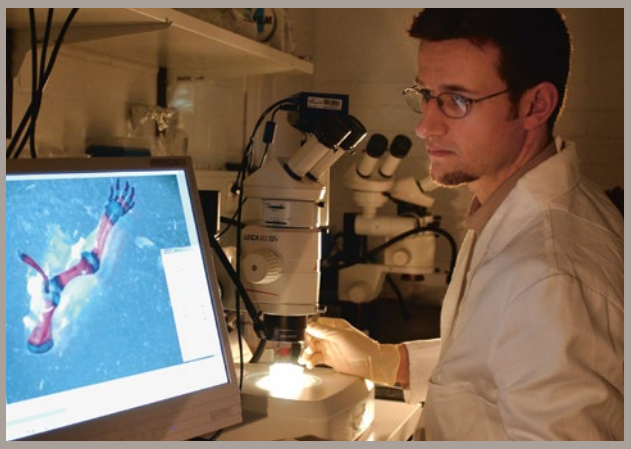
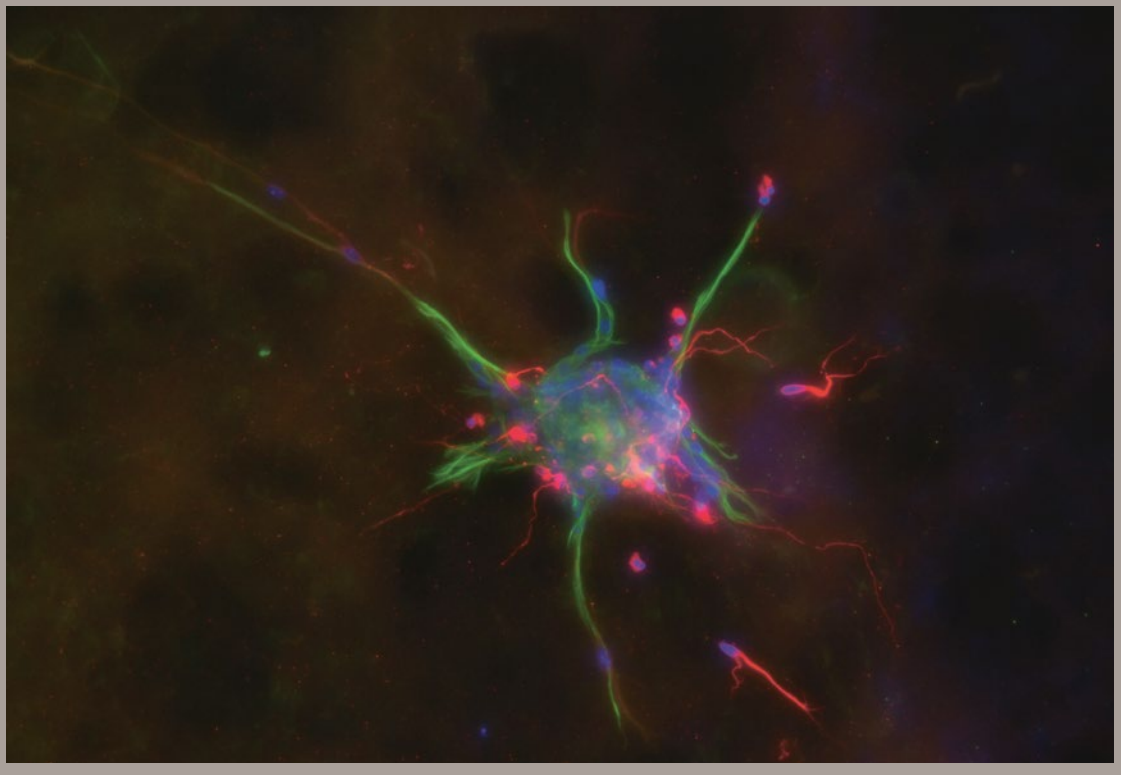




↖ Agarose gels to separate mixtures of nucleic acids according to their size

↓ Staff members of the Lehrach department, Adjaye group, in the lab, 2008

↑ A staff member of the Mundlos research group working at the microscope, 2004



↑ Students of the International Max Planck Research School for Computational Biology and Scientific Computing (IMPRS-CBSC) at the MPIMG, 2004

↓ Differentiation of neural progenitor cells into neurons (red) and astrocytes (green, nuclei in blue), confocal laser scanning microscopy, 2004

SOME QUESTIONS TO:

ANN EHRENHOFER-MURRAY

When did you stay at the MPIMG? From December 1st, 1997 to September 30th, 2004.
What was your scientific work focused on? Epigenetic mechanisms of gene regulation, chromatin structure and function.
Do you still have any contacts from this time? Yes, I am in contact with Jörn Walter [former group leader at the Trautner department], Ho-Ryun Chung [head of Max Planck Research Group], Harald Saumweber from the Humboldt University and many more.
What did you like most? The good working atmosphere among the OWL groups and the strong administrative support.
What annoyed you? The somewhat isolated location of the institute within the city.
What have you done since leaving the MPIMG? I was appointed as a Professor (C3) of Genetics at Justus Liebig University, Giessen, from 2004 to 2005. From 2005 to 2013, I was Professor (W3) of Genetics at the University Duisburg-Essen. Since July 1st, 2013, I hold a Professorship of Molecular Cell Biology (W3, Einstein Professorship) at the Humboldt University in Berlin.

ANN EHRENHOFER-MURRAY
Former Head of an Independent Research Group
(Selbständige Arbeitsgruppenleiterin, SAG)
at the Otto Warburg Laboratory

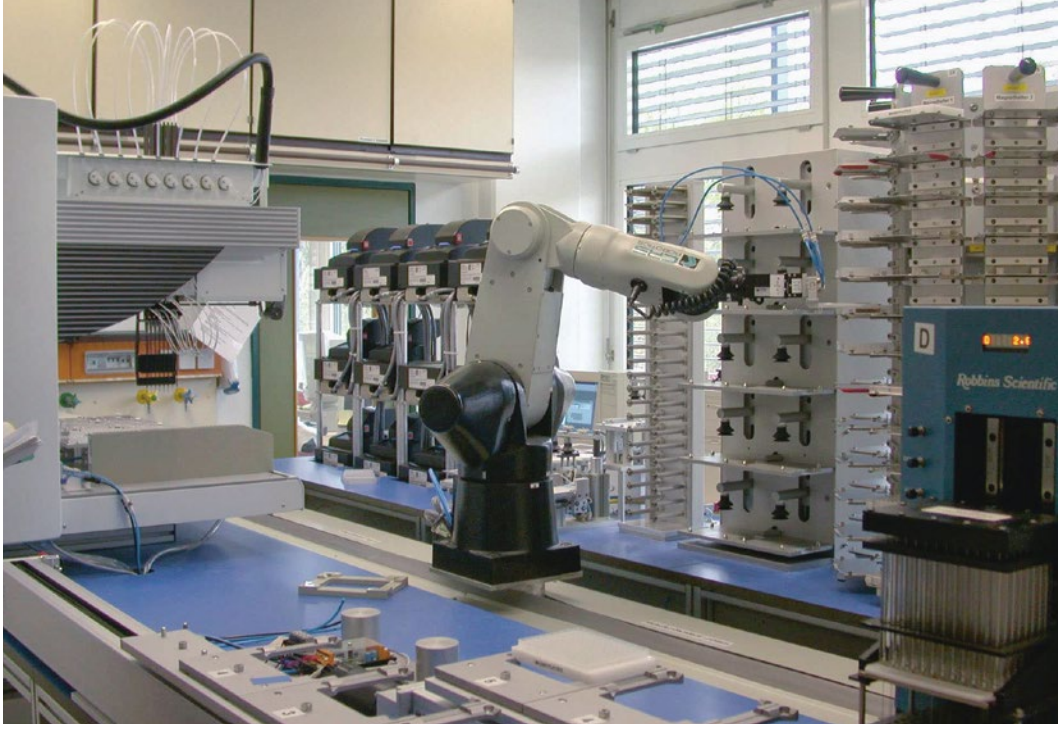
ANDREA VORTKAMP

When did you stay at the MPIMG? From 1998 until September 2004.
What was your scientific work focused on? Molecular control of skeletal development.
Do you still have any contacts from this time? Yes, to Ann Ehrenhofer-Murray [another head of an OWL group] and to Uwe Kornak and several other members of the Mundlos Research Group.
Thinking of your time at the MPIMG, what is the first thing that comes to your mind? I had the freedom to establish my own independent research. The financial and personal situation was excellent and the scientific environment highly stimulating.
What did you like most? I was allowed to spend my time doing mainly research with only little administrative or teaching loads. Nevertheless, limited administrative tasks prepared for the heavier loads as professor. I also enjoyed the fact that the other heads of Independent Research Groups of the OWL were at similar career stages and formed a "sub-department" of the institute. It allowed us to handle things together, to be independent from the large departments and to learn from each other. The fact that the research topics were quite different allowed us to get insight into other fields and to have a broad spectrum of knowledge and methods available.
What annoyed you? Nothing serious.
What have you done since leaving the MPIMG? I have a Professorship (C4) at the Biological Faculty of the University Duisburg-Essen since October 2004. I am member of the Centre for Medical Biotechnology and Head of the Department of Developmental Biology. From October 2008 until September 2010, I was Dean [Dekan] of the Faculty of Biology and Geography and Vice Dean [Prodekan] for the subsequent year.

ANDREA VORTKAMP
Former Head of an Independent Research Group
(Selbständige Arbeitsgruppenleiterin, SAG)
at the Otto Warburg Laboratory

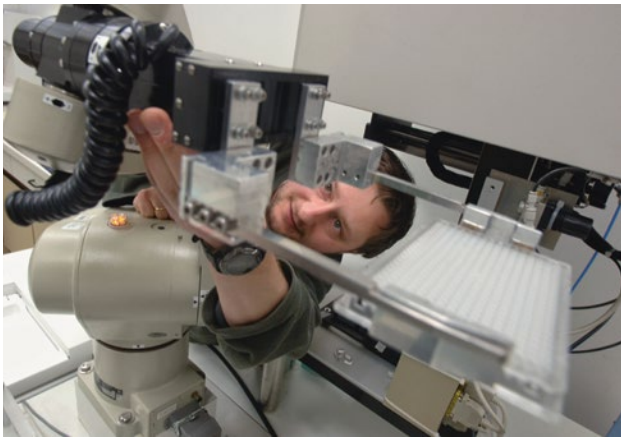
Genome sequencing and the pathway from gene sequences to personalized medicine

RUSS HODGE
Science writer, Berlin



NO SCIENTIFIC INSTITUTE CAN BE AN ISLAND, particularly at a time when answering fundamental questions about life, our health, and diseases requires immense, integrated efforts on the part of scientists across the world. Thus, 50 years of research at the Max Planck Institute for Molecular Genetics (MPIMG) form a tributary in some very large trends in science: the invention of methods to sequence proteins, genes and entire genomes; the rise of automated, high-throughput sequencing, numerous methods to study cellular molecules, and a range of new discoveries and concepts about their behavior and functions in states of health and disease. Even in such large efforts, the MPIMG has gained a significant role in analyzing the contents of genomes and their meaning in the lives of individual organisms, through the creativity and unique approaches taken by its scientists.

The aim of this article is to capture a feeling for the institute, particularly the Department of Vertebrate Genomics, by describing some of the technological developments and projects that it has witnessed over the past 20 years. But it's worth taking a moment to enlarge the context: the initial decision to found the MPIMG was made at about the time Francis Crick, James Watson, and Maurice Wilkins made their way home from Stockholm with the freshly minted gold medals given to winners of the Nobel Prize. That was just a decade after Watson and Crick had drawn on data produced by Wilkins and his colleague Rosalind Franklin to solve a riddle that had occupied biochemists for half a century. Their 1953 paper in *Nature* described the structure of DNA – two strands built of complementary nucleotides, bound together and entwined in a double helix – providing an architecture that could be replicated. This finally solved crucial questions regarding the molecular basis of heredity while delivering entirely new ones, particularly in the form of Crick's "central dogma of molecular biology:" DNA makes RNA



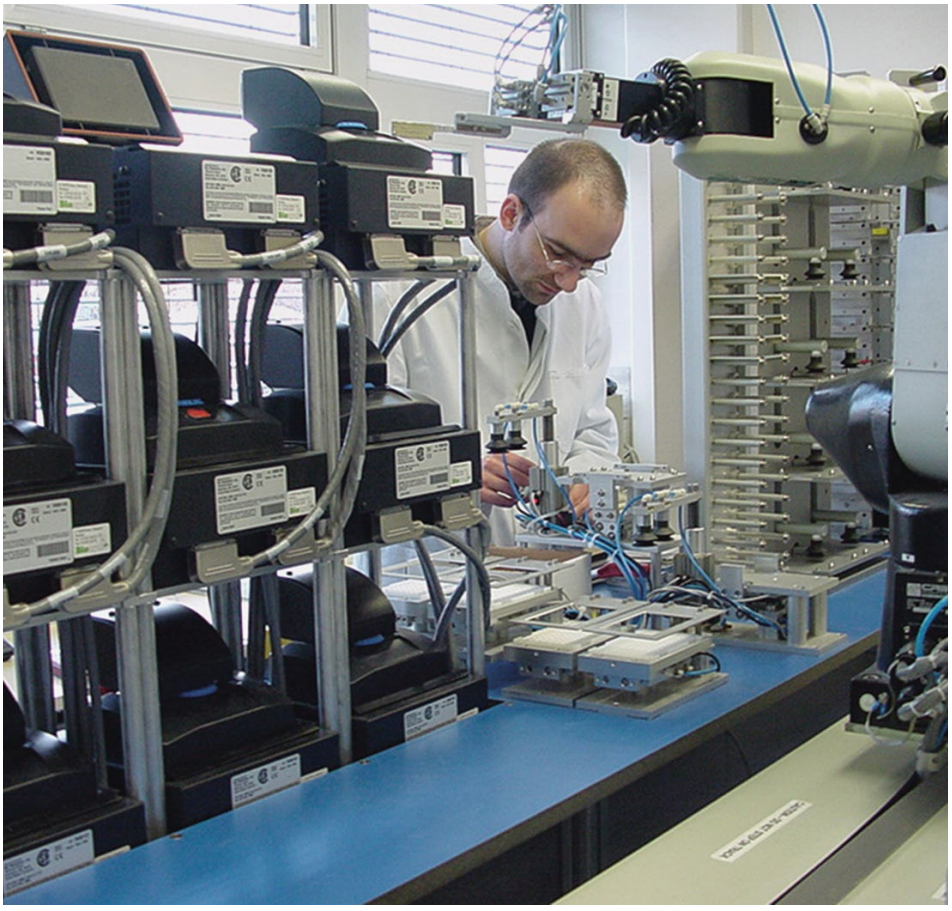
◂ **"Big Robby"** – this automated platform, developed at the MPIMG, has been used for example for sequencing in the framework of the Human Genome Project, around 2002

A staff member of the Analytics service group working at the F3 robot, 2005

makes protein. At the time, the biochemical reactions that produced this transformation of hereditary information were unknown, but new molecular biology institutes were springing up all over the world in hopes of understanding the way they orchestrated the life of huge, complex organisms such as humans. The MPIMG was one way for the Germans to jump into the fray, and the institute and its scientists would go on to make important contributions to our understanding of the biology of many organisms including humans – in states of health and in the context of a variety of diseases.

In the first two decades, most MPIMG research was devoted to unraveling the biochemistry, by which cells replicate their DNA and use the information contained in the synthesis of cellular proteins. Initially, these questions were addressed in simple model organisms such as bacteria and bacteriophages. Another focus of attention was the ribosome. The research projects at the institute helped expose new aspects of the replication process, for which Crick's "dogma" had provided a bare outline. Enlarging the basic scheme to encompass complex organisms such as humans required precise insights into the chemical composition and structure of genes, RNA molecules, and proteins. Here two tremendously important milestones were achieved by the British scientist Frederick Sanger. In 1955, Sanger invented the first method to determine the sequence of proteins – demonstrating that each type of protein contains a precise linear sequence of amino acids. Two decades later, he established a method to sequence DNA, using the new approach to determine the sequence of most of the genetic material in a bacteriophage. These two accomplishments were so fundamentally important that Sanger was awarded two Nobel Prizes; he remains one of only four people to have received the prize twice in a lifetime.

Sanger's work lay the foundations for modern, high-throughput sequencing technologies that have developed at an almost exponential rate. In the mid-1990s, after the retirement of its first generation of directors, the MPIMG undertook a basic reorientation toward the study of whole genomes and human genetics. Hans Lehrach was brought to the institute to establish a department for the anal-



A staff member of the Analytics service group preparing samples, around 2002

ysis of vertebrate genomes, with the result of drawing the MPIMG into the International Human Genome Project. In parallel, Hans-Hilger Ropers was hired to build a department of human molecular genetics with a central focus on mechanisms of monogenic diseases in humans.

Automated sequencing and genome projects

When Hans Lehrach arrived at the MPIMG in 1994, scientists lacked many resources that have now become mainstays in research, particularly the huge collections of biological information – from "consensus" sequences of species' genomes to myriad types of experimental data – now publicly accessible and as close as the nearest computer with Internet access. Today, scientists continually put the results of their work into a larger context, using a wide range of databases and bioinformatic tools. *In silico* experiments are routinely used to develop new hypotheses by comparing pieces of information that have arisen in laboratories across the world and to better recognize the function of single genes or proteins. However, genes and proteins do not exist on their own, but are parts of the complete network of life processes in each cell and the whole

Microarrayer for spotting probes on cDNA arrays (chips), around 2004

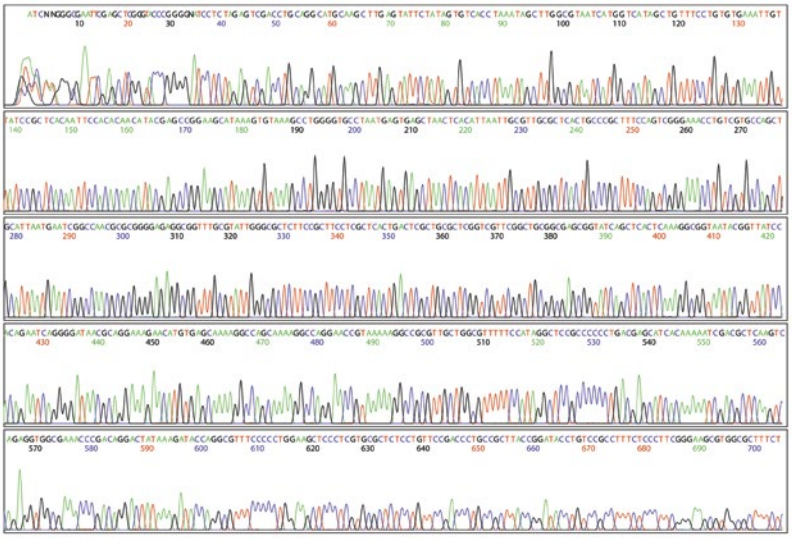
organism. Hence, it is important to understand the function of all components of these networks.

In the mid-1990s, most gene sequences were still the hard-won products of cloning experiments. Hans, who had been involved in some of the very first projects to clone mouse and human genes, was frustrated by a general lack of interest on the part of scientists to develop centralized resources. They typically regarded gene sequences as privileged data, storing them on individual computers that couldn't be accessed by their colleagues. And many sequences existed only in the form of hard copies published in a journal somewhere. In the mid-1990s, the situation was changing through the advent of ever-more efficient and accurate DNA sequencing machines and the launch of large international collaborations such as the Human Genome Project. Around 1979, at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Hans had contributet to the launch of public databases for gene and protein sequences and had suggested the sequencing of the *E. coli* genome as a first genome project. During his time at EMBL and later at the International Cancer Research Fund (ICRF) in London, he had attended the first meeting, where sequencing of the human genome had been discussed (Santa Cruz, 1985) and in 1986, together with Annemarie Frischauf, he had organised one of the first workshops to discuss the new opportunities arising from genome research. Upon arriving at the MPIMG, he was eager to secure an important role for the institute in the large International Human Genome Project. That would involve the development of better, automated sequencing technologies and a massive expansion of the institute's instruments, a move that echoed the establishment of a huge "sequencing farm" established at the Wellcome Trust's Sanger Center in the United Kingdom. These developments were in keeping with a philosophy that Hans Lehrach had long ascribed to: "It seemed that everything you do with single genes, you should be able to do with the entire human genome, in parallel," he says. "If you could sequence one gene, you could sequence the genome – it was simply a matter of organization and technology."

Spotting robot to generate high density filters. On each filter (array) up to 57,000 PCR products can be spotted, around 2004

The new department started to develop approaches suitable for analysing the function not only of one single gene, but preferably of all genes or proteins of an organisms in parallel. This effort required a lot of robotics – machines that could take on the job of "pipetting" rows upon rows of samples, a procedure that had previously required labor-intensive, manual handling by individual scientists. By developing new equipment for the automated construction and manipulation of clone libraries and machines for high-parallel analysis with high-density filters or chips, it was possible to analyze tens of thousands of clones in parallel and to generate a cornucopia of information to each clone. Using such a systematic approach, the researchers targeted at analyzing all aspects of the function of the total set of human genes in parallel (through functional genomics, structural genomics, proteomics etc.). Quite often, this involved trying to combine many different types of data based on individual clones in clone libraries. At that time, the identity of a clone had been the only sensible way to combine data from a specific gene or protein, but maintained from different experiments out of various labs from all over the world. Today, due to the enormous progress in sequencing technologies, this is replaced by sequencing-based approaches, but in those days, it was important to generate as much data as possible on clearly identified clones from "reference libraries", to collect them centrally and make them available. The concept led to the establishment of the Resource Centre/Primary Database, which was initially established at the MPIMG and then transferred into a limited liability company [GmbH] and became the largest data base for genetic clones worldwide.

In addition, Hans played a central role in establishing the German Human Genome Project (DHGP), as well as its successor, the German National Genome Research Network (NGFN). The MPIMG's main contribution, together with other German and Japanese Groups, was to carry out the complete mapping and, in 2000, the sequencing of Chromosome 21, the second human chromosome published as part of the Human Genome Project. Other projects soon followed: the institute joined an international collaboration to completely sequence the 22nd



Chromatogram of a Sanger sequencing

chromosome of chimpanzees. Later it undertook large-scale projects to analyze the DNA sequences of many more members of the ape family, and carried out more work devoted to an in-depth analysis of the human X chromosome.

Under Hans' direction, the Department of Vertebrate Genomics and the institute began a vast expansion of sequencing efforts. With the advent of "next-generation sequencing," an effort shared with the department of Hans-Hilger Ropers, this would ultimately lead to the establishment of one of the largest sequencing centers in Europe today. Most recently, the department became the only center on continental Europe to participate in the 1000 Genomes Project. "Sequencing the first human genome took the research community ten years and cost somewhere between one and three billion dollars," Hans says. "By 2012 we were able to sequence one complete genome per day in the department, and the speed continues to increase and the costs are dropping." Eventually the 1000 Genomes Project would completely sequence the DNA of about 2,500 people across the globe. 150 of those genomes were produced by the MPIMG. As well as providing sharp new insights into the extent of human variation, the information gleaned from these projects is becoming vital in understanding the biology of diseases. Genome-wide association studies are now permitting its use in the detection of new correlations between certain forms of genes that cause diseases or increase an individual's risk of developing them – particularly a range of conditions that have not been extensively studied, because they strike so few individuals. When this data is extended to studies of gene expression, it offers a wealth of information about the way individual genomes develop in response to a wide range of lifestyle and other environmental factors.

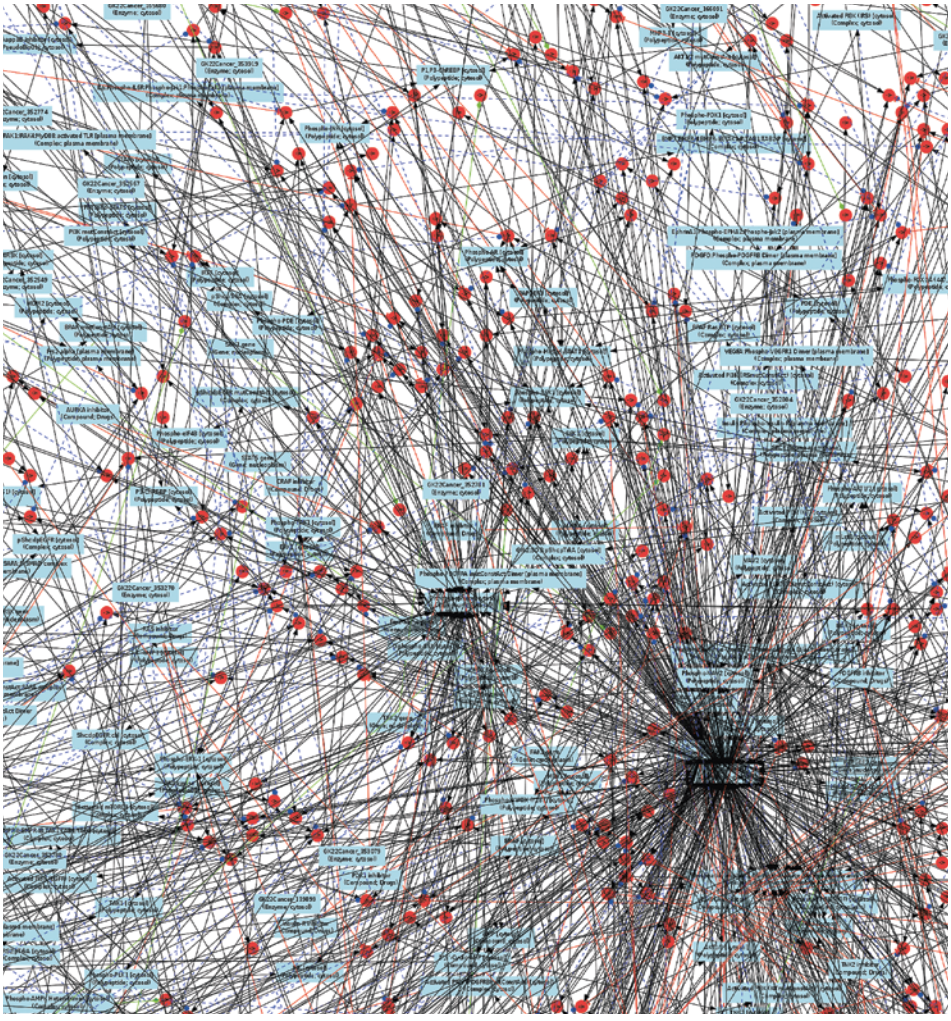
From functional genomics to systems biology

It was clear that the real benefits of genomics would come, when scientists learned to interpret sequence data in terms of the functions of molecules: as they had evolved over immense stretches of evolutionary time, in various tissues as an embryo developed, and in response to the challenges posed by diseases. Ob-

taining such insights would first require new technology platforms to investigate the expression and functions of proteins and RNA molecules. While, with a few exceptions, all of the cells of a complex organism contain the same genomic information, different cell types express specific subsets of genes, and the RNAs and proteins they produce vary depending on the circumstances. Capturing a glimpse of such changes in gene expression was a prerequisite to understanding the interdependencies between molecules. A change in the production of a single type of cellular molecule might ultimately affect patterns of activation among hundreds of genes, which then go on to affect many more. In the process, biochemical signaling pathways influence each other through crosstalk, feedback loops, and other types of interaction to manage cell structure and behavior. A disease might strike these networks anywhere, with rippling effects that spread in all directions.

Capturing this picture in its full complexity would require carrying out a complete "census" of cellular molecules under all sorts of different conditions. Originally based on array or chip hybridization, a technique pioneered by Hans, this is now increasingly based on the use of next-generation sequencers. This work was like the discovery of an entirely new biological continent. The methods revealed that, while only a fraction of the DNA of humans and other organisms encodes genes, a majority of it is used to produce RNA molecules – such as microRNAs and other non-coding RNAs. Still, the functions of many non-coding RNAs is widely unknown.

So it was equally important to assess the populations of proteins in cells, which couldn't simply be calculated by observing gene activity and detecting RNAs. Teams under Hans' direction began inventing or improving methods to study RNAs and cellular proteins (using, for example, yeast two-hybrid arrays). This had to be accompanied by computational tools to analyze protein interactions. These efforts were a manifestation of a new "movement" in the molecular life sciences called "systems biology:" researchers aimed to transcend classical descriptions of the behavior and functions of single molecules by exposing



Interaction network of signalling pathways involved in cancer (section), 2014

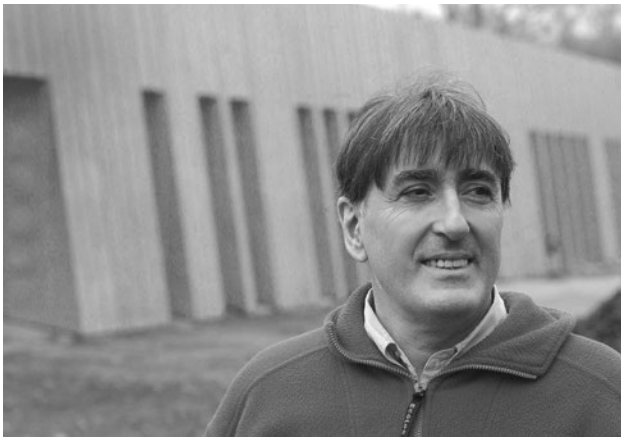
the complex networks, by which they interact in cells, tissues, and organs. Such networks could only be understood through computer models. Take the case of cancer: most types of tumours seem to originate, when a molecule undergoes a mutation that interferes with normal processes of cell division and differentiation. The basic biochemical pathways that govern these processes are robust, with checkpoints and backup systems to ensure that they remain on course, and a tumour has to overcome specific obstacles to survive and grow. Usually, this requires disrupting a handful of pathways, but the original problem may be as unique as the patient.

So an individual case of cancer stands at a crossroads between individual genomes, a mutation, and the ways systems in cells and tissues respond. Here all levels of understanding basic processes of gene regulation come into play. To approach this problem, a number of groups in the department have applied the various technology platforms to the study of cancer – for example, by completely analyzing the genome sequence of a tumour to identify mutations and comparing it to the sequence of healthy tissue from the same patient, then comparing its output in terms of RNA and protein molecules. This work is being carried out in

collaboration with national partners in the National Genome Research Network (NGFN), and beyond in the framework of EU projects. Treat1000, launched about five years ago, is a collaboration with the Charité Comprehensive Cancer Center (CCCC) and the Harvard Medical School. Here, the aim is to use systems biology approaches to develop individualized treatments.

The new vision: a "virtual patient" as test subject for individual therapies

Ultimately, biologists hope that their discoveries will lead to a profound understanding of the real underlying causes of diseases – in terms of the way they disrupt networks of interactions in molecules and tissues in individual patients. That will represent a huge step towards addressing illnesses by targeting their specific causes. The view of life provided by systems biology approaches is a crucial step along the way, Hans Lehrach says. But he also believes that another step must be taken before the advent of a truly "molecular medicine," and many of his efforts over the past few years have been devoted to achieving it. They follow directly from his work over the last few decades and are best expressed in his own words. "When a company builds a car," he says, "they don't build a prototype, fill it with living people, and crash it against something to observe the effects of a particular design on passengers in an accident. But in many ways this is comparable to the current situation in cancer treatments. Of course, up until now, the real situation of patients has been so dire, and the methods that are available have been so generic in a way, that this was the only choice you had. Currently, the drugs that we have to treat cancer are tremendously expensive, and you try them knowing that often they will only work in 25 percent of your patients. The other 75 percent will show no benefits and, in many cases, will actually suffer from the treatment. If what you've tried doesn't work, then you move on to the next drug – which, once again, will only benefit a fraction of the cases. What we are trying to develop is a series of computer models that imitate the complete biology of the patient, as best we can, as closely as possible – in a "virtual patient". These models are based

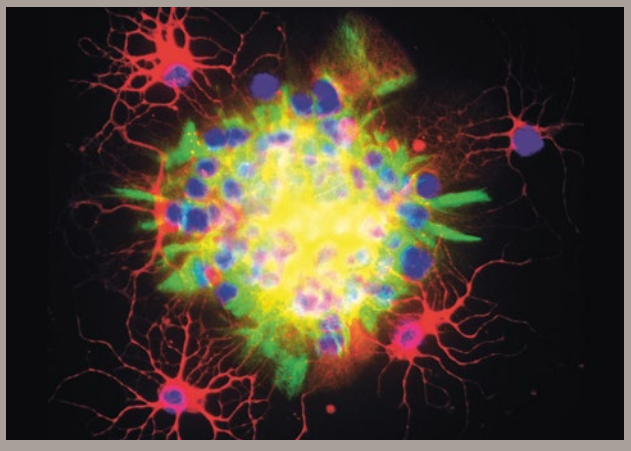


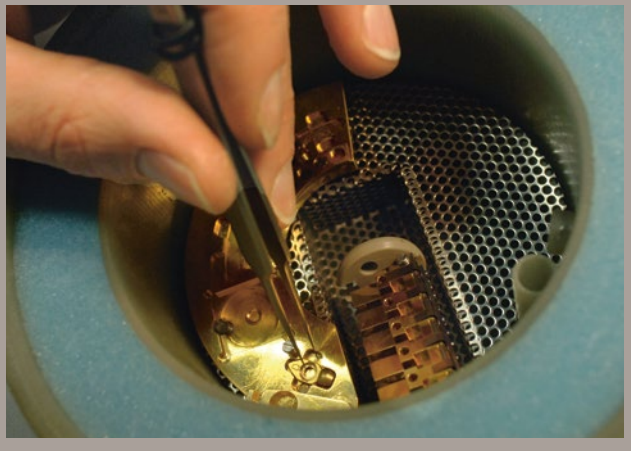
Hans Lehrach, 2004

on our best information about systems of molecular pathways, derived from our own studies of cells and tissues and a vast amount of experimental data from the scientific literature. The networks that are involved have thousands of components. Our models obviously won't be perfect because, first of all, the literature isn't perfect, and even if it were, we don't have nearly enough resources to include information from every publication. Additionally, we're still amassing huge amounts of information about the way, networks operate in unique individuals – a "computation" of the unique genome, as it faces unique and largely unquantified environmental conditions. But what we can do is develop models and test them against reality: to make observations, before, during, and after various types of therapies, and then let the models evolve based on differences between predictions and observations. Eventually what we hope – and as we are currently trying in pilot studies based on real patients and their tumours – is to test virtual therapies on these virtual patients. We should make our mistakes on the computer model of the patient, not on the patient himself, as we are acting in most other fields, too. We must know enough about the factors that contribute to the operation of molecular networks in an individual's cells. We will have to be able to identify the points, at which they are disrupted, and then the specific effects of thousands of substances on molecular networks. At that moment, we should be able to make a much more rational prediction about the type of therapy that will benefit a specific patient. To go back to the analogy of the car – we'll be running simulations in the computer and checking them, before actual human beings are involved."

This is a bold vision that will surely require many more years until its general implementation in medical routine. But collaborations with colleagues at places like the Charité Comprehensive Cancer Center, research labs, and companies are helping to bring it closer to reality. Hans Lehrach is well aware that his concentration on future problems has made him a bit of a maverick. He is acquainted to this from other scientific areas and it reminds him of the early years of genome research, when he was fighting to gain German science a place at the table

in international genome projects. A prerequisite to that accomplishment was the establishment of a new, quickly growing department aimed towards a vision of the human genome. That work helped achieve a complete sequence of human DNA many years before the leading experts in the field would have predicted. Who is to say that this new vision – of a marriage between a profound knowledge of the biology of individuals, computational models, and treatments for human disease – won't follow a similar curve of success?

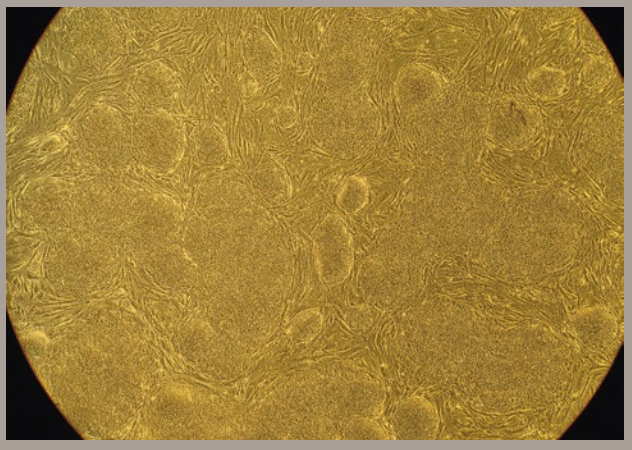


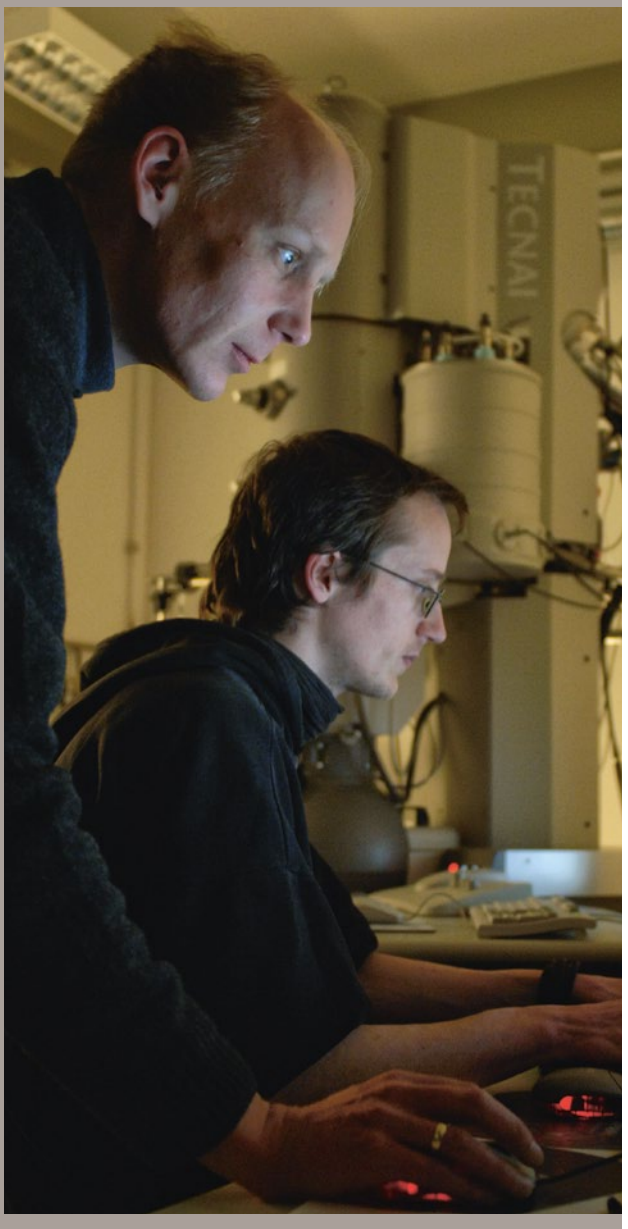


↑ A glance at the library of the MPIMG, 2007

↗ Differentiation of neural progenitor cells into neurons (red) and astrocytes (green, nuclei in blue), confocal laser scanning microscopy, 2004

→The charging station of the cryo electron microscope, 2004





↑ International PhD students at the MPIMG, 2004

↓ Human embryonic stem cells under the microscope, 2007

→ Two scientists of the MPIMG working at the cryo electron microscope, 2004

SOME QUESTIONS TO:

EDDA KLIPP

When did you stay at the MPIMG? From October 1st, 2001 until September 30, 2008 – seven years, right on the day.
What was your scientific work focused on? We were interested in the dynamics of regulatory networks, e. g. MAP kinase signalling pathways, and developed mathematical models for these in close cooperation with experimental (lab) groups. This work has gradually been extended to metabolism, cell cycle and osmotic changes of cells. In addition, we developed mathematical tools, e. g. for parameter estimation out of experimental data, and addressed modelling standards.
Do you still have any contacts from this time? Yes, for instance to M. Vingron and A. Bockmayr, who are active in the Research Training Group [Graduiertenkolleg] 1772 with me, to U. Leser, with whom we share common interests in teaching and research, or to Zhike Zi, who has been PhD student in my group at the MPIMG and came back to Berlin with a BMBF grant for his own junior research group. Together with former MPIMG colleagues and staff from my OWL group, we are currently writing the third version of our textbook on systems biology.
Thinking of your time at the MPIMG, what is the first thing that comes to your mind? I have been able to establish my own research group and develop my own research profile at the MPIMG. In addition, I became acquainted with many experimental techniques and analysing methods, with which I wasn't familiar before. This caused us to look more consciously at the precise conditions of experiments and the informative value of data.
What did you like most? The confrontation with many new biological approaches and experimental techniques has been very stimulating. For this purpose, the department seminars provided many interesting insights.
What annoyed you? The allocation at Boltzmannstraße has been rather generous and romantic, but it lacked the spontaneous contact to other groups.
What have you done since leaving the MPIMG? Since 2008, I am Professor (W3) of Theoretical Biophysics at Humboldt University, Berlin.

EDDA KLIPP
Former Head of an Independent Research Group
(Selbständige Arbeitsgruppenleiterin, SAG)
at the Otto Warburg Laboratory

ULRICH STELZL

When did you come to the MPIMG? In June 2007.
What is your scientific work focused on? The group is focusing on the analysis of molecular interaction networks with the aim to understand the dynamics of molecular networks underlying cellular processes related to human disease. Experimental functional genomics techniques, e. g. high-throughput yeast two hybrid (HTP Y2H) screening, are utilized in combination with biochemical, cell biological and computational methods. Network biology offers a more comprehensive understanding of biology concomitantly improving the practice of medicine.
Do you have any collaboration at the MPIMG?
I collaborate with Sebastiaan Meijsing from the Vingron department, Philip Grote from the Herrmann department, Ralf Herwig from the Lehrach department, and with the service groups sequencing and mass spectrometry.

Thinking of your time at the MPIMG, what is the first thing that comes to your mind? Establishing an independent research group is for sure the most important and challenging step in my career.
What do you like most? The MPIMG provides an environment that allows for and supports 100 per cent research.
Do you already think about what comes after your time at the MPIMG? I am aiming at a seamless continuation of my research in a complementary research environment.

ULRICH STELZL
Head of an Independent Research Group
at the Otto Warburg Laboratory

Transformation of biology to an information science

JENS G. REICH
Max Delbrück Center for Molecular Medicine, Berlin-Buch

Preface

To write a scientific-historical essay on the occasion of the 50th anniversary of the Max Planck Institute for Molecular Genetics is not possible for me without a personal reminiscence to the non-relationship, which I (the author) had, as also almost all my colleagues in East Berlin, to the colleagues in Dahlem for a quarter of a century. I was completely unaware that a MPIMG had been founded in 1964. Dahlem, a region that before and after August 13, 1961, was geographically as far away as the few kilometres it is today, became a white spot on our city maps. All scientific contacts broke off, when the GDR cut back pan-German scientific societies, organisations and projects completely. In the following years, one heard in conversations that certain connections had secretly been taken up again. Heinz Bielka at the Academy institute in Berlin-Buch (once also a Kaiser Wilhelm Institute), where I was working, too, was doing research on ribosomes as was Heinz-Günter Wittmann at the MPIMG – the first on mammalian, the latter on bacterial specimens of these "protein factories". Pretending being tourists visiting relatives, colleagues from Dahlem occasionally came over to East Berlin for an afternoon to meet "conspiratively" in the private home of the person visited or unremarkably (yet of course "registered") in a café. Moreover, the ribosome people in Buch wanted to keep knowledge of all this low among colleagues, for if it had become widely known, the authorities would certainly have put an end to such contacts. For us, who in this regard were completely isolated, a place in Dahlem, if read about in the newspaper, was something similar to a place on the moon, that is just as unreachable. So, when the Wall and the Iron Curtain finally fell after about a quarter of a century, the first years saw a prolonged period of confusion until, at long last, a freely cooperating network of scientists and institutes formed in Berlin again as befits a European metropolis.

◂ **Construction of the Berlin wall** in August 1961

Illustration from the "Universal Technological Dictionary" by British author George Crabb, showing the taxonomy of plants, 1823

Moreover, this reminiscence indeed belongs to the reflections on the development of molecular biology. Max Delbrück at the Kaiser Wilhelm Institute (KWI) for Chemistry in Dahlem (with Otto Hahn and Lise Meitner) and Nikolai Timofeev-Ressovsky at the KWI for Brain Research in Buch (with Oskar Vogt) had worked hard to jointly establish a decisive conceptual basis for the "invention" of molecular genetics in the mid-thirties. Dahlem plus Buch – that is the original source of a field that was to revolutionise biology. The cooperation back then ceased not due to the wall of concrete built up through Berlin, but because one of the co-authors, Delbrück, could no longer endure the mental aberration of the Nazi era in Berlin and in 1937 immigrated to the USA. Timofeev, who could not return to Stalin's cutthroats, remained "inconspicuously" in Buch and continued research "quietly" where the Soviets did not "fetch" him until after the war.

Charles R. Darwin
(1809–1882)

UNTIL THE MIDDLE OF THE 20TH CENTURY, biology on the basis of its methodological principles consisted of two core domains. One, supported by the "Naturalists", was classical biology that was devoted to describing all organisms and phenomena as they are found existing in nature. This domain reached its height with the work of the Swedish scientist Carl Linnaeus (Carl Linné), who in the 18th century developed a "System of Nature", a binary system for classifying all species of living creatures. Back in this time, "bioinformatics" consisted of long lists of animal and plant species in the handbooks of taxonomy. The second main branch, experimental biology, grew in the 19th century from tentative forerunners. It taught that all biological phenomena can be explained as physicochemical processes employing the methods of this "exact" discipline. This is how biophysics and, in particular, modern biochemistry evolved, which was to become the leading discipline in biology by the turn of the 20th century. With its myriads of enzymes, inhibitors, activators and regulatory signals (hormones) it is even today a basic method in biology and all its applied sciences. In this regard, the sources of "bioinformatics" in the shape of systems biology were the metabolic networks and transport pathways that still decorate the walls of biochemical laboratories today.

Charles Darwin, the patriarch of modern biology, still had an impact on the old school of naturalists. He did not undertake any planned laboratory experiments. All his insights were a result of patient observation of nature. With his doctrine of variation and selection, he provided the conceptual basis for both descriptive as well as experimental biology. This course was not on an even keel, as Darwin knew himself. The principle of selection explains, why the old remains or vanishes and why the new prevails or disappears again. Yet, how variations in characteristics come to be and how they are passed on to the next generation – both indispensable principles of every evolution – of this the brilliant naturalist only had vague notions.

But Mendel came to his rescue, without Darwin being aware of this, of course. Mendel developed a plant test system with strictly segregating features. He so

Gregor Mendel
(1822–1884)

to speak experimented with "pure" inheritance without selection. This way he introduced discrete mathematics to biology and with this change also the more profound rationale for today's bioinformatics. Mendel's approach and his interpretations led to the establishment of formal genetics, albeit only after a 40-year slumber, and it took another 50 years to "form out" its molecular shape.

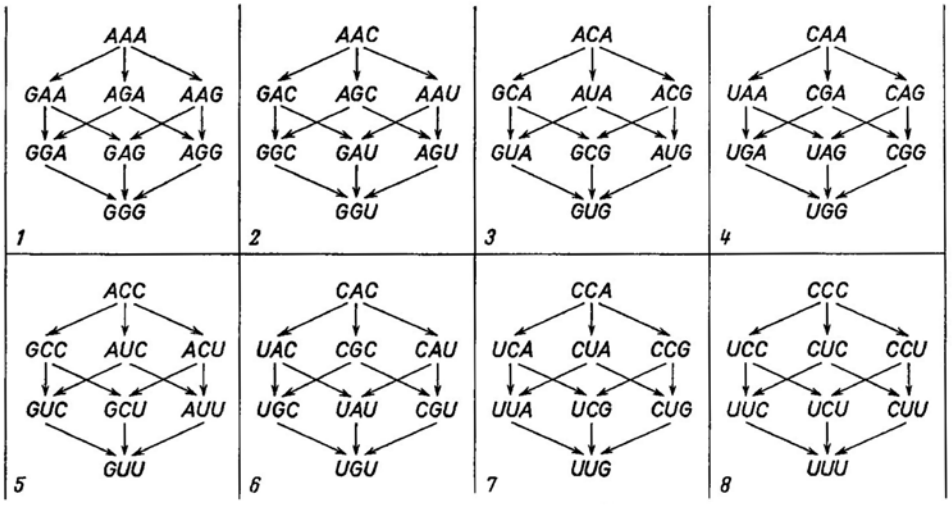
In the first half of the century, genetics played an ancillary role, overshadowed by the queen of disciplines at the time, biochemistry. Genetics was only a side subject with very special concepts and a remote spectrum of methods. As an applied science of experimental nature, it was very successful especially in plant biology. Its use in anthropology, however, made headway for the dark side of human inheritance research, "human heredity", eugenics and racial hygiene, delivering the scientific and methodological instruments for the infamous political repressions and the notorious human experiments and mass murders in the concentration camps during National Socialism.[1] However, for today's bioinformatics, formal genetics has provided an axiomatic system, with which the population genetic models of evolution theory can be explained mathematically.

At the beginning of the second half of the 20th century, there was a fundamental reorientation in the basic concepts of biology. Until then, the concept dominated that living organisms consisted of cells, which one could define in physicochemical terms as finely chambered biochemical reactors. The syntheses of biological substances, substance transformation and substance transport were regulated by specific proteins (enzymes), the functional properties of which had been elucidated in the past decades. That proteins show a specific primary structure, id est an exact arrangement of amino acid building blocks in a chain, was clear by the beginning of the 1950s, when it became possible to isolate cleavage peptides of a specific sequence. Frederick Sanger in 1952 was the first to present the complete amino acid sequence of a small protein, the beta chain of insulin, after a systematic study of his peptide fragments. A few years later, the structural analysis of the biomolecules myoglobin and haemoglobin by Kendrew and Perutz revealed the whole amino acid sequence

of these proteins as a "secondary finding". The success of such sequence elucidations was limited, however, because not all proteins can be crystallised easily. Cleavage peptide analysis also had tight methodological limitations due to the larger yields of pure protein required and because solving the puzzle of the order of the fragments was a very difficult task. Then the DNA molecule in the nucleus stepped into focus. Watson and Crick (1953) interpreted the X-ray diffraction pattern of DNA as a double helix that was stabilised through the base pairing of two complementary strands. "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material", they wrote at the end of their short report. What they did not write, yet what soon became clear to them and others, was that if the bases were not arbitrarily paired along the spiral stairway, but in a meaningful order, the DNA structure formed a letter code. It took another ten years to find out that the specific sequence of amino acids in proteins is encoded in a specific sequence of the DNA chain.

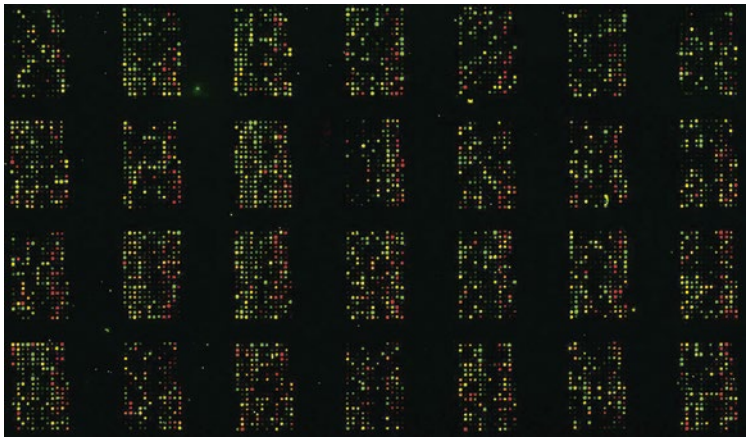
This concept of physicochemically encoded information in both types of information-carrying biomacromolecules (nucleic acids and proteins) marked the "abiogenesis" of bioinformatics and molecular genetics, which were to become the two sub-disciplines determining the advancement of modern biology. However, there was still a long way to go from genesis to maturity. The notion of life as an information carrier and information "processor" was born. Yet for a long time, it seemed a futile task to attempt to read the enormous volume of nucleic acid and protein "texts" from the mountains of data.

With the herald of this phenomenal shift from the material of life to the text of life, the classical fields of biochemistry and biophysics achieved completion of their cell "factory" model of interconnected biochemical reactors. Using electron-optics, the cellular machine's sub-compartments, the cell organelles with their membranous external borders, were made visible. These could then be experimentally separated by ultracentrifugation so that the biochemical make-up of the cells and thus the function of each type of organelle became evident.



Octet diagram to represent possible nitrite mutations of amino acid triplets, Wittmann, 1962

Alongside these novel insights, in the mid-60s, the Max Planck Society decided basically to depart from the traditional paradigm and give the "Max Planck Institute for Comparative Hereditary Biology and Hereditary Pathology" a new name, a new goal, and shortly thereafter, a new building. This then became the Max Planck Institute for Molecular Genetics. In addition, young biologists, who had devoted their work to translating the genetic text of bacteria and viruses, were taken on from Tübingen and Göttingen. They determined the footprint of the institute for the next 25 years, a footprint that depicted the overall development of the new biology. The researcher generation of this "notated" [verschriftete] biology was fascinated by the new guiding paradigm of biology and worked patiently to establish and confirm it with the help of methodically manageable biological systems: viruses, bacteria and fungi. Access to them was difficult enough. The elucidation of the simplest of protein and nucleic acid sequences demanded years of astute and arduous detail work. The tools for a more efficient analysis and manipulation of genetic texts were found only gradually, through worldwide scientific efforts – in methodological terms all copies of the nature's workshop itself. Restriction endonucleases, DNA and RNA polymerases, the DNA polymerase chain reaction and many more – almost all of them tools, microorganisms had invented millions of years ago – were reworked during the last quarter of the 20th century into increasingly refined tools for reading and later also for manipulating the text of genetic systems.[2] Molecular genetics moved, so to speak, from its romantic era of painstaking precision work to the industrial era of mass sequencing of genomes. Where once small sections of text were sagaciously deciphered, now increasingly larger, data-laden genomic text structures were automatically read and collected in computers. Some of the most prominent researchers of the time lamented the end of the romantic era as a loss of fascination and creativity – like for example Gunther Stent in his widely discussed article "That was the molecular biology that was" (Science, 26 April 1968). A similar view of Max Delbrück has been passed down; who together with Niels Bohr had dreamed of a biologi-



cDNA microarray for analysis of differential gene expression (false color representation)
A chip like this can contain up to 20,000 cDNA samples, each representing a single gene

cal complementarity principle and now was disappointed by the putative banality of the discovery that the principle of life was based on a text sequence of four chemically coded letters. He then concentrated on other topics.

From the middle of the 1980s, the biologists "seized" on the analytical and synthetical tools present in microorganisms and began to use the two most important material characteristics of biogenic polymers on a large scale, namely their extraordinary reliable and robust characteristics: hybridisation of complementary oligonucleotides and the precise oligonucleotide synthesis using copy templates (PCR). It succeeded to miniaturise and automatise the sequencing technique and to integrate sensitive detection methods (radioactivity, fluorescence). This development reached its peak at the beginning of the 1990s, when the human genome sequencing project was initiated.

Bioinformatics experienced another boost through the enormous performance increase of integrated circuits (chips), which according to "Moore's law" is exponential or even hyper exponential.[3] Together, both tendencies let the Human Genome Project seem a rehearsal for much wider data projects of molecular genetics and epigenetics in conjunction with bioinformatics.

In the first decades, bioinformatics was rather a sober, pragmatic tool. Its theory based initially on simple heuristic search methods with archetypal algorithms such as the Needleman-Wunsch algorithm or statistical secondary structure prediction by means of the amino acid sequence. The search for text similarities in large data pools (BLAST algorithm, etc.), so to speak the search for a needle in a haystack, was soon put on firm ground by mathematical statistics of extremely rare events in appropriate comparison models of random sequences. Today, bioinformatics has developed into a strategic sub-discipline for biology. It allows the screening and the detailed comparison of extensive biological databases of primary sequences and the network-like connections of their computational interactions.[4] What remained for the earlier generation of biologists an utopian ideal, that is the systematic comparison of the genetic basis of all life across all taxonomical branches and developmental differentiations with the

Server room of the MPIMG with servers and storage disks to store biological data, 2012

pragmatic "tools" of bioinformatics, has become the standard in experimental cell biology and developmental biology. The search and comparison methods of bioinformatics ensure that the conceptual basis of biology, that is evolution theory, is given a solid empirical foundation and will no longer exclusively need to rely on the systematic observation of fossil relicts.

Currently, there is evidence of a trend to further develop bioinformatics together with additional experimental techniques into a more complex discipline, which has been given the somewhat ambiguous name of "systems biology". As soon as this project reaches full maturity, the field of bioinformatics will have fulfilled its conversion from a hypothesis generator to a tool for designing complex organisms and ecosystems.

It is no longer an utopian notion to read the complete genome and epigenome of all individuals of a species with at least a moderate number of individuals, such as the species *Homo sapiens* and to look for variants, mutations and disease-promoting defects. In particular, the field of human genetics and the epidemiology of human diseases with multicausal aetiologies are receiving an inflow of knowledge from this development with diverse potential applications.

For the time being though, the grandiose promise of a grand design of life, which Francis Collins and Craig Venter gave at the turn of the century when presenting the human genome (at the time incomplete), is not even close to being fulfilled. New doors are being opened all the time and give motivation for huge new projects (recently Haplotype mapping, Personal Genome, tissue-specific expression patterns of the whole genome [ENCODE], integration of the new world of RNA regulation …). A complete theory of biological information is still a futuristic project. Even the in-depth approach to understanding the "phenotypes" such as cancer, immune disorders or neurodegenerative diseases is still in an early stage. There is still room for optimistical fantasies, for future projects and utopias, but also for passionate disputes, at the MPIMG as elsewhere in the global world of biology, to which bioinformatics makes a major contribution.

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1 Besides Dahlem with its numerous praiseworthy sites of science, Dahlem, Ihnestrasse 22, is also the place of the Kaiser Wilhelm Institute for Anthropology, Human Heredity and Eugenics, the think tank of racial politics with its directors Eugen Fischer, Otto von Verschuer, as well as Josef Mengele as corresponding "postdoc".

2 Instead of Kary Mullis, the bacterium *Thermus acquaticus* that lives in the hot geysers of the Yellowstone National Park should have received the Nobel Prize for Chemistry in 1993 for the invention of Taq polymerase.

3 In a semi-logarithmic plot the normal curve of quantitative growth is convex (curved upward), that it shows a greater than exponential growth.

4 Comparative Genomics, Functional Genomics, Metagenomics, Personal Genomics, Epigenomics, Lipidomics, Proteomics, Nutrigenomics, Pharmacogenomics, et al.

↖ Herbert Jäckle, vice president of the Max Planck Society, addresses the audience at the roofing ceremony of the newly constructed tower 3, 2011

↑ Central roof light of the newly constructed tower 3, 2013

↑ A glance at the foyer of the newly constructed tower 3 prior to the institute taking possession, 2013

← Guests during the opening ceremony of the newly constructed tower 3, October 2013

SOME QUESTIONS TO:

SYLVIA KROBITSCH

When did you come to the MPIMG? In September 2008 as Head of a Minerva group.
What is your scientific work focused on? The main research interest of my group is to elucidate molecular mechanisms contributing to neurodegenerative processes in the polyglutamine disorder spinocerebellar ataxia type 2 (SCA2) and whether and how these pathways can be correlated to other neurodegenerative disorders, such as spinocerebellar ataxia type 1 (SCA1) and amyotrophic lateral sclerosis (ALS), on different cellular levels by combining yeast genetics, humanized yeast models, and functional genomics approaches. Moreover, we are interested in studying the biology of stress granules and P-bodies, central self-assembling structures regulating mRNA metabolism, and their relevance in age-related human disorders including neurodegenerative disorders and cancer.

Do you have any collaboration at the MPIMG? We currently collaborate with the Lehrach department (Hans Lehrach and Michal Schweiger).
Thinking of your time at the MPIMG, what is the first thing that comes to your mind? I really appreciate that the doors to the Directors are always open and they find time for their staff.

SYLVIA KROBITSCH
Head of an Independent Research Group
at the Otto Warburg Laboratory

SASCHA SAUER

When did you come to the MPIMG? I came to the MPIMG as scientific staff member on December 1st, 2001, and I am Head of my own Independent Research Group since January 1st, 2008.
What is your scientific work focused on? We are working on the influence of nutrition and other environmental factors on gene regulation in order to get a deeper understanding of physiologically relevant processes, e. g. the origin of age-related diabetes (Diabetes type 2) or aging processes in general. In addition, we are developing new products on plant basis for prevention and therapy of age-related diseases.
Do you have any collaboration at the MPIMG? Our research group joins up with several groups of the MPIMG that have complementary expertise – especially from the departments Lehrach and Vingron and the OWL – in order to tackle our complex questions as efficient as possible.
Thinking of your time at the MPIMG, what is the first thing that comes to your mind? I am still here! Thus, such kind of reflection is difficult.
What do you like most? The beautiful, inspiring surrounding in Dahlem, especially in summer.
Do you already think about what comes after your time at the MPIMG? Yes, but I don't want to reveal it yet.

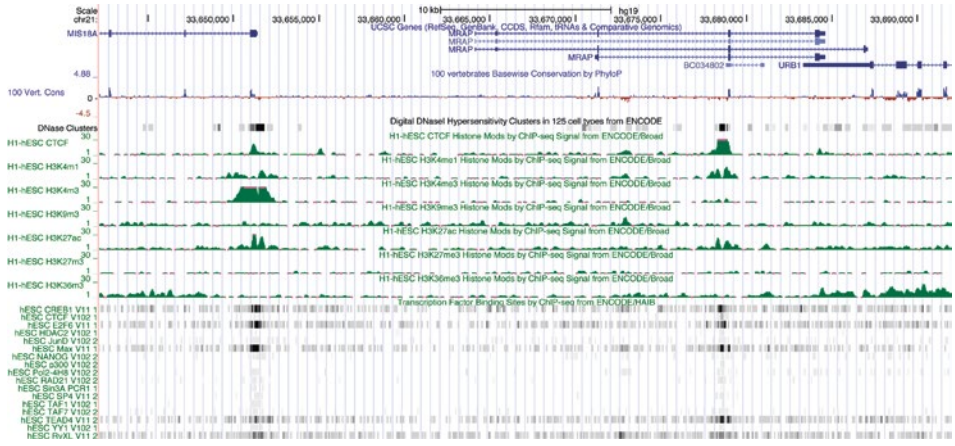
SASCHA SAUER
Head of an Independent Research Group
at the Otto Warburg Laboratory

Understanding the rules behind genes

CATARINA PIETSCHMANN
Science Journalist, Berlin

THOSE ENTERING THE SERVER ROOM FOR THE FIRST TIME are instinctively reminded of Stanley Kubrick's classic "2001: A Space Odyssey". Nearly filling out the room stands a black monolith, the institute's "brain". Countless blue light-emitting diodes behind fine-meshed doors indicate the vast number of hard disks and computers running in a total of 30 server racks. An arrangement called a hot aisle that passes through the steel block takes up the heat from the electronics and the buzzing coolers to keep the sensitive nervous system from overheating. In a second room, there is a further server complex just about one third smaller. Together, they have a storage capacity of six petabyte, one quadrillion bytes, a barely conceivable number with 15 zeros. "We could store about 1,500,000 DVDs here", says Peter Marquardt, head of the IT department, not without pride.

Today, molecular genetics is much more than precision pipetting in ice-cooled Eppendorf tubes, polymerase chain reaction and automated sequencing technology. With the possibility of storing the whole genome of an individual – gene per gene – on a chip and studying its activity by the end of the 1990s, one finally realised that not only a gigantic storage system is necessary to take up the flood of data pouring in, but also that mathematics will henceforth be an indispensable tool. "We did not care about statistical variations, while we were still studying single genes. However, if we screen, for example, 6,000 yeast genes simultaneously for their expression levels, there is not only the process we will want to observe, but also the experimental background noise. Then all questions become inherently statistical", says Martin Vingron and settles back on the leather couch in the library. The Vienna-born mathematician started to establish the Department of Computational Molecular Biology at the Institute in 2000. Using mathematical methods he explores with his team, how genes are regulated. Vingron started his scientific career with differential equations to solve biological



◂ **Server room** of the MPIMG in tower 3, 2013

Summary of so far known regulatory mechanisms in a section of the human genome
The base numbers of the respective region on chromosome 21 can be found in the top line. Thereunder, the different forms of genes are shown as rectangles on the genomic axis. The following lines show the graph of sequence conservation between 100 vertebrates, the accessibility of the DNA for DNA-binding proteins (DNAse clusters), e. g., CTCF (next line); followed by curves for the type of histone modifications (H3K4m1 etc.) in the analyzed cell line (H1-hESC). The lowermost gray "stripe pattern" each show the binding of a specific DNA-binding transcription factor (CREB1 etc.).

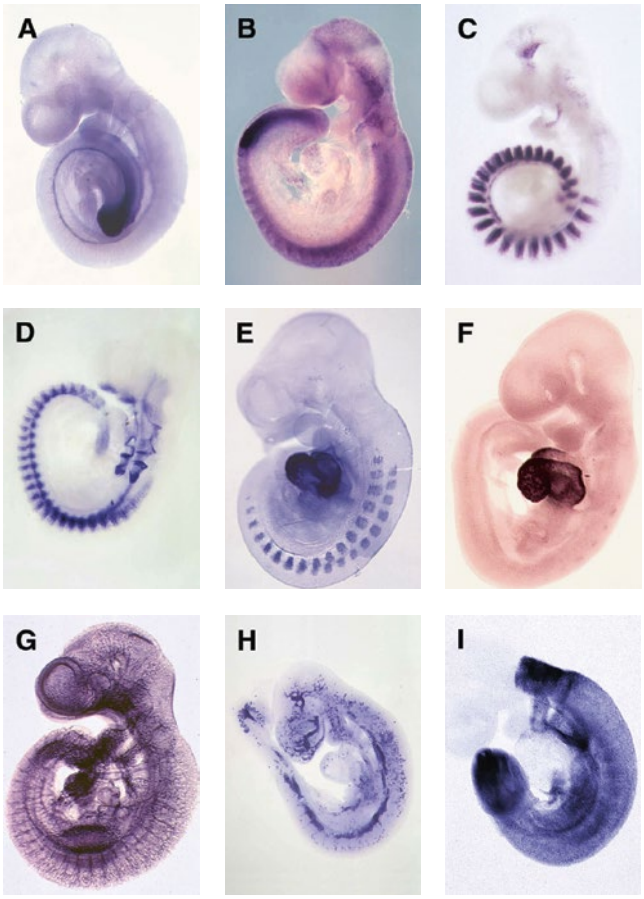
questions – first at the University of Vienna and later at the European Institute for Molecular Biology (EMBL) in Heidelberg. The question how genes are switched on and off has also fascinated him right from the outset. "But, back then, there simply wasn't enough data." However, when he moved from the German Cancer Research Centre to Berlin 14 years ago, the time came. The Human Genome Project had just reached the home stretch, and soon, not even one week passed without the announcement of yet another sequencing of usually a smaller organism's genome. And the world was left marvelling: How could it be that a tiny daphnia has more genes than we have? And brainless cabbages even four times as many as *Homo sapiens?* However, when the grandiose promise "once all genes are identified, we will be able to understand – and heal – all diseases" proved to be as empty as (seemingly) wide sections of the genome, a period of disillusionment set in. "What is frequently forgotten is that the Human Genome Project led to a revolution in technology development", explains Vingron. Novel methods suddenly enabled the exploration of gene activities and differences between individual genomes. This radically changed the view on molecular genetics and gave new impetus to worldwide research. The ENCODE project revealed that the non-coding regions of the genome, making up over 90 per cent of it, were not at all useless. Instead, they contain the regulatory sequences, to which the transcription factors bind to start off the reading of the genes. So much for junk DNA! At long last the control centre of the genome with 24-hour accessibility had been identified.

"More and more landmarks are being set to understand the mechanisms of gene regulation: sequence, expression and for many transcription factors we meanwhile know exactly, where the binding sites are". Adding the data on epigenetic modification, we get increasingly more evidence on the activity status of genes. "From a statistical point of view, this is a terrible situation!" Martin Vingron laughs, "because huge volumes of data exist for few individuals." These data are screened by him and his colleagues with specific algorithms to explore basic questions: Why and when is a gene switched on or off? What other genes

Martin Vingron (2nd from the left) under discussion with students of his department, 2014

are responsible for this? How do they act together? What happens, if one wheel in this network gets stuck or fails completely? And please, what is the genetic difference between healthy and sick? "We strive to gain new insights from our data and our ideas about how such mechanisms work." The workplace of a bioinformatician is a desk and a computer – sure enough. Dull number crunching? Not at all. Some projects are literally about life and death. Recently, Stefan Haas had a staple of hard drives on his desk that had arrived by post from Max Planck colleagues in Cologne. 30 terabyte – and this is only the beginning! They contain genetic information about patients, who are suffering from a non-manageable type of lung cancer. Haas is developing algorithms to identify mutations (SNP's) in tumour tissue characteristic for this extremely aggressive type of cancer. In another cooperative project with human geneticists of the Ropers' department, he is using mathematical tools to discover mutations that cause mental disability. Such mutations could serve as prognostic markers for genetic counselling of affected families, who wish to have children.

Peter Arndt taps the institute's brain rather out of "historical" interest. His aim is to go back to the evolutionary origins of the genome. With historical and statistical analyses, Arndt is trying to extract from today's DNA sequences, how and under which processes the mammalian genome was shaped over millions of years to its present occurrence. Besides the offices, a number of laboratories also belong to the department. How come? "In bioinformatics, we are forced to generalise and have to leave out one detail or another. In the experimental groups, we then take a closer look at the details and try to understand, what can be generalised and what is so specific that we have to ignore it," explains Martin Vingron. "Of course, this leaves room for a lot of scientific conflict and friction, but I need to feel this pain," he adds theatrically. "It is an important corrective". Sebastiaan Meijsing's group, for example, is analysing cell cultures to find out in detail, how transcription factors bind to DNA. He assumes that the spatial structure of such a factor changes depending on the sequence, to which it binds. "Whether causing a difference that is insignificant, such as an attached earlobe, or another that



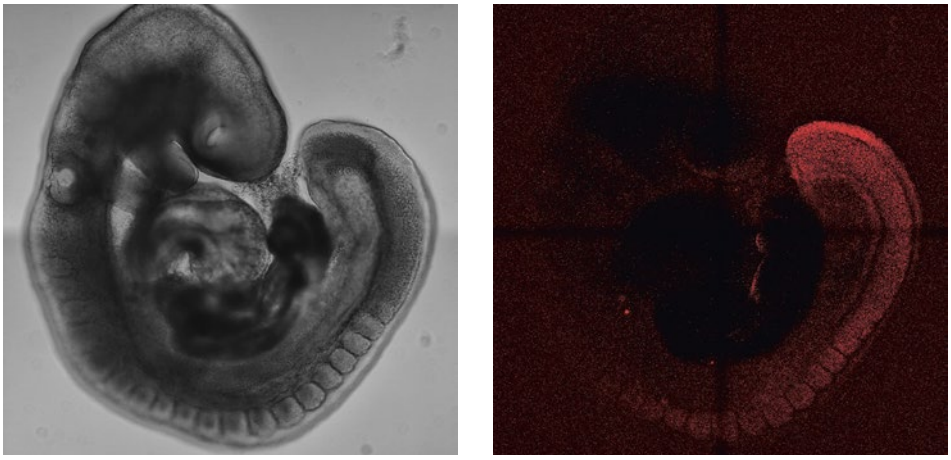
Representation of different gene activities in mouse embryos aged 9.5 days
(RNA *in situ* hybridization).
A Tail bud (growth zone) and Chorda dorsalis
B Paraxial mesoderm and neuronal tissue
C Somites (precursor of spine and skeletal muscles)
D Sclerotome and pharyngeal pouches
E Skeletal and heart muscles
F Heart
G Blood vessels
H Blood cells
I Position information

we define as a disease, phenotypic changes are usually due to a signalling cascade not functioning properly," explains Vingron. Sometimes, the reason can be a binding site with just one single mutated base in a regulatory gene section. Small cause – great effect.

Disease symptoms rarely have such a plausible link to a gene as, for example, in lactose intolerance. The body produces either too little or none of the enzyme that splits milk sugar. In the case of learning disabilities or skeletal abnormalities, the "mistake" can be traced back very far. But what exactly happened back then? To find the answer, it is sometimes helpful to go right back to the beginning; to the point where life starts to take shape – in the first days of embryonic development. Since 2003, Bernhard Herrmann's Department of Developmental Genetics is working with mice to find out, how regulatory networks in stem cells control the formation of organs and tissues in the embryo. More exactly, how pluripotent cells differentiate after division and for this purpose are literally commanded to take certain paths: you shall form neuronal tissue and you mesodermal tissue. The former develops into the brain and spinal cord later, and the latter into the heart, the bones, or the ultra-thin abdominal wall covering the tiny inner organs

of the embryo. The starting point was a developmental disorder in mice, first described in 1927, on which the biologist Herrmann has worked during his whole scientific career. Due to a mutation called Brachyury, the trunk and tail of the mouse is only partially developed or lacks completely. At first, Herrmann cloned the gene region in question, then, in 1990, he identified the responsible gene and found out that it contains the code for a transcription factor. Yet the most interesting question remained unanswered: how and in which network of regulatory genes does this factor act? "The less factor there is, the more pronounced the phenotype was. Mice with only one copy of the responsible gene are viable, but have a stumpy tail." (That explains the name Brachy ury, "short tail".) In the worst case, only the head region is formed and the embryo dies. The approach of Hermann's team is common for many groups working on molecular genetics: going from one gene to many genes, then finally along the whole genome. They feel their way forward, spurred on by novel technologies such as *in situ* hybridisation, microarrays and high-throughput sequencing. At the same time they drive forward the development of newer and more refined methods, propelled by their own scientific curiosity and creativity.

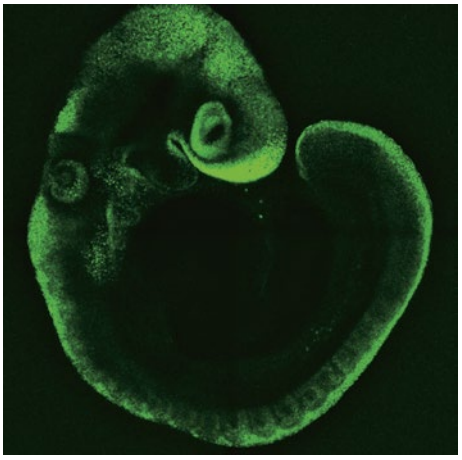
The development of a mouse's trunk takes place between the 9th and 11th day of gestation. Within this timeframe, the team performs expression analyses to study the activity of more than 10,000 genes. Transparent and three dimensional, four mouse embryos lie in the light beam of a stereomicroscope. They are 9.5 days old, about half of the gestation period is over. A layperson cannot distinguish whether it is chicken, mouse or human. The head and the thorax, complete with a heart, are already established. The blue colour indicates gene activity, where neuronal precursor tissue is found: in the head and neural tube, where soon the spinal cord of a healthy mouse would have developed. Only the hind feet are still missing. Over 20,000 embryos from different projects are stored in countless tubes at 4°C in the cooling chambers of the institute. Studies – preserved in formaldehyde for eternity. One could say it is an organic archive of numerous studies and the tangible counterpart of an electronic memory system.

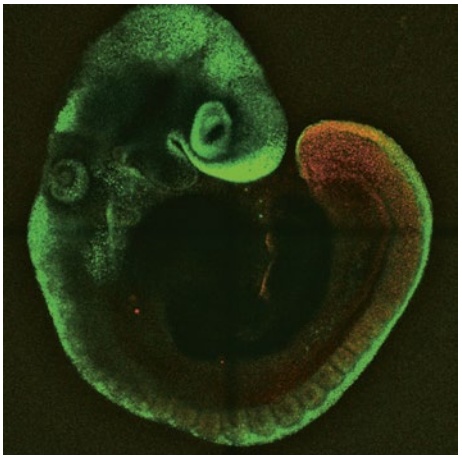


Picture of a mouse embryo at day 9, taken with a two-photon laser scanning microscope
The red fluorescence protein shows gene activity in the precursor cells of skeleton and muscles, the green fluorescent proteins of brain and spinal cord.

A few doors further, the two-photon laser scanning microscope can show the distribution of up to three different tissues marked with different fluorescence dyes in a living embryo. And there are even more sophisticated methods: with FACS, fluorescence-activated cell sorting, these cells are not only counted electronically for presentations in power point, but at the same time, are also sorted according to the marker colour into different sample tubes. Each time, only a few but very clean cells are sorted into one tube, on which the transcriptome, the RNA, or their epigenetic changes can be studied. In Hermann's team this is the task of Frederic Koch. He uses high-throughput sequencing to conduct such studies on sorted cells. This way he screens mouse genomes in search of the regulatory elements (enhancers) that control both neighbouring and remote genes. "Mutations at these sites can have an influence on the whole regulatory network of cells".

The discoveries of the past years have been both exciting and controversial. When searching for triggers of disease, it is not sufficient to just scan the coding regions of the genome. Mutations can also be located in the regulatory elements. "And now the long non-coding RNAs have come along, making the whole regulatory network even more complex", emphasises Herrmann. The sharper the picture of gene regulation at the beginning of life gets outlined; the clearer becomes the similarity to processes that can lead to a premature and painful death. The same signalling cascades, for example, observed in the formation of the mesoderm are also active during the growth and spread of tumours. "Regeneration and maintenance of tissue actually are embryonic processes shifted to the adult," says Herrmann. "Nothing here has been invented anew!" Unlike differentiated cells, stem cells never die. That is why mutations can build up over the years, which also is a plausible explanation for the connection between age and cancer. If mutations cause the stem cells to proliferate too strongly, a benign tumour will grow at first, and then at some point may become malignant. Herrmann and his team studied the regulation of tumour genesis in colon tumours. Both in the mouse and in patient tissue they found mutated chromosome sections that





could serve as early markers for diagnosis. “We were able to identify methylation patterns that say: Attention! A tumour is developing here. This would allow early diagnosis and therapy would be possible, even before metastasis sets in.”

Developmental genetics can provide models for cancer research for a better understanding of tumour genesis. This approach has still not spread widely in cancer research dominated by clinicians. But this will change in the years to come, Herrmann is convinced. By the way, what is the future of developmental genetics? A lot will happen in the area of stem cells. Already now, skin cells can be reprogrammed to develop back into stem cells, from which specific cell types can be cultured. “Even today kidney, liver or thyroid gland tissue can be cultivated in a culture dish, and in a few years it may even be organs. But it will take some time to reach medical application. Of course, there will be a cure for androgenetic hair loss”, he grins stroking his high forehead.

If Bernhard Herrmann were to have a second life as researcher, he would study the communication between body cells more closely. “We see ourselves as an organism with a head, body, arms and legs. But that is not so! We consist of billions of individual cells communicating with each other to ensure the organism functions properly.” What a venture, when it is still unclear, how a single cell works. But of one thing Herrmann is sure: “We will know, how cellular regulation works to maintain stem cells and allows them to repeatedly produce particular cell types, before I retire.”

His retirement is not in sight yet, but two of the four director posts at the institute will be vacant in the near future. With the appointments, the direction of thought of both steel “brains” will be readjusted. What will be the highlights in the coming decades? If Martin Vingron had a say, the research of diseases would take up more room. “What is disease? As a first approximation, it is the difference between two individuals. We are gradually beginning to understand that certain changes in the genome at least make us more susceptible.” Genotype-environment interactions such as nutrition, environmental influences and stress can determine whether such a predisposition takes effect – or not! Many more

Bernhard G. Herrmann, 2008

diseases than supposed could have genetic causes. That is why ever more individual genomes are being sequenced worldwide – of healthy and sick persons – and the vision of a personalised medicine is taking shape. Behind all these efforts, there is yet another central issue. For Martin Vingron it is perhaps the most exciting question of molecular genetics at all. What is the origin of individuality? What is it that makes each individual so unique?

↑ Summer party of the MPIMG on the premises of the institute, 2013

↓ Staff members of the MPIMG during the summer party, 2008

↑ Schoolgirls at the IT group of the institute during Girls' Day 2010

↓ Visitors during the Long Night of Sciences at the foyer of the MPIMG in tower 3, 2014

← A visitor at the Mundlos research group, Long Night of Sciences 2012

↓ Children pipetting at the Long Night of Sciences 2014

SOME QUESTIONS TO:

HO-RYUN CHUNG

When did you come to the MPIMG? I came in June 2005 as postdoc and got my own Independent Research Group in September 2011.
What is your scientific work focused on? I am analyzing the influence of chromatin on transcriptional regulation.
Do you have any collaboration at the MPIMG? I work closely with the department of Martin Vingron. In addition, there are close collaborations with the sequencing unit of Bernd Timmermann and the group of Sebastiaan Meijsing.
Thinking of your time at the MPIMG, what is the first thing that comes to your mind? The first thing coming to my mind is ivory tower, because we are very well appointed, but don't look beyond our own noses very often.
What do you like most? The high density of bioinformaticians. I also want to point out the smooth cooperation with the administration.
What annoys you? The isolation between the different groups.
Do you already think about what comes after your time at the MPIMG? A permanent contract.

HO-RYUN CHUNG
Head of an Independent Research Group
at the Otto Warburg Laboratory

ULF ANDERSSON ØROM

When did you come to the MPIMG? On January 1st, 2012.
What is your scientific work focused on? My research group is working on long non-coding RNA and how they are involved in transcriptional regulation of gene expression.
Thinking of your time at the MPIMG, what is the first thing that comes to your mind? A dynamic start of my research career in a great environment.
What do you like most? The friendly attitude of colleagues both researchers and administrative personnel.
What annoys you? That German efficiency is really just a rumor.

ULF ANDERSSON ØROM
Head of an Independent Research Group
at the Otto Warburg Laboratory

Time line about the development of molecular biology and the Max Planck Institute for Molecular Genetics

1964
- Establishment of the Max Planck Institute for Molecular Genetics
- **Heinz Schuster** appointment as Director and Head of Department (1964–1995)
- **Heinz-Günter Wittmann** appointment as Director and Head of Department (1964–1990)
- **K. Bloch, F. Lynen** *for their discoveries concerning the mechanism and regulation of the cholesterol and fatty acid metabolism*
- **D.C. Hodgkin** *for her determinations by X-ray techniques of the structures of important biochemical substances*

1965
- Departments Schuster and Trautner in the building of the MPI for Comparative Hereditary Biology and Hereditary Pathology, Ehrenbergstraße 26–28 (1965–1969)
- **Thomas Trautner** appointment as Director and Head of Department (1965–2000)
- **F. Jacob, A. Lwoff, J. Monod** *for their discoveries concerning genetic control of enzyme and virus synthesis*

1966
- Planning of new institute building starts
- **F. Peyton Rous** *for his discovery of tumour-inducing viruses*

1967
- Department Wittmann in temporary labs at Harnackstraße 23 (lab prototype for new Institute building) (1967–1969)
- **Gunther S. Stent** appointment as External Scientific Member (1967–2008)

1968
- **W. Arber, S. Linn** isolation of restriction enzymes type I (Eco B and K)
- **R.W. Holley, H.G. Khorana, M.W. Nirenberg** *for their interpretation of the genetic code and its function in protein synthesis*

1969
- **M. Delbrück, A.D. Hershey, S.E. Luria** *for their discoveries concerning the replication mechanism and the genetic structure of viruses*

1970
- Establishment of Independent Research Groups (“SAGs”)
- Move to the new building at Ihnestraße 73 (tower 1 and 2, 80% completed)
- **Manfred Schweiger** (1970–1976)
- **Olaf Pongs** (1970–1975)
- **H.O. Smith, K.W. Wilcox** isolation of restriction enzymes type II (Hind II)

1971
- Official inauguration ceremony of the MPIMG
- **Volkmar Braun** (1971–1974)
- **Akio Miyake** (1971–1974)
- **D. Nathans** first gel with Hind II fragments of SV40 DNA
- **E.W. Sutherland** *for his discoveries concerning the mechanisms of the action of hormones*

1972
- **G. M. Edelmann, R. R. Porter** *for their discoveries concerning the chemical structure of antibodies*
- **C. Anfinsen** *for his work on ribonuclease, especially concerning the connection between the amino acid sequence and the biologically active conformation*
- **S. Moore, W. H. Stein** *for their contribution to the understanding of the connection between chemical structure and catalytic activity of the active centre of the ribonuclease molecule*

1973
- **S.N. Cohen, H.W. Boyer** insertion of recombinant DNA in bacteria and subsequent expression (cloning)

1974
- **A. Claude, C. de Duve, G. E. Palade** *for their discoveries concerning the structural and functional organization of the cell*

1975
- **Günther Schütz** (1975–1980)
- **P. Berg** International Asilomar Conference about the risks of gene technology
- **F. Sanger, A. Coulson** Dideoxy DNA Sequencing (Sanger Sequencing)
- **D. Baltimore, R. Dulbecco, H.M. Temin** *for their discoveries concerning the interaction between tumour viruses and the genetic material of the cell*

1976
- **Karin Mölling** (1976–1981)
- **Adolfo Ruiz-Carrillo** (1976–1981)
- **Kenneth Timmis** (1976–1981)
- **A. Maxam, W. Gilbert,** Maxam-Gilbert Sequencing

1977
- Completion of the new institute building

1978
- **P. Berg** first hybrid DNA, rabbit DNA in monkey cells
- **W. Arber, D. Nathans, H.O. Smith** *for the discovery of restriction enzymes and their application to problems of molecular genetics*

1979
- **R. Staden, S. Anderson** Shotgun Sequencing (1979–1981)

1980
- **B. Benacerraf, J. Dausset, G.D. Snell** *for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions*
- **P. Berg** *for his fundamental studies of the biochemistry of nucleic acids, with particular regard to recombinant-DNA*
- **W. Gilbert, F. Sanger** *for their contributions concerning the determination of base sequences in nucleic acids*

1981
- **Reinhard Lührmann** (1981–1988)
- **N. Bloembergen, A.L. Schawlow** *for their contribution to the development of laser spectroscopy*

1982
- **Regine Kahmann** (1982–1986)
- **Klaus Bister** (1982–1987)
- **S.K. Bergström, B.I. Samuelsson, J. Vane** *for their discoveries concerning prostaglandins and related biologically active substances*
- **A. Klug** *for his development of crystallographic electron microscopy and his structural elucidation of biologically important nucleic acid-protein complexes*

1983
- Renaming of the Independent Research Groups to Otto Warburg Laboratory
- **B. McClintock** *for her discovery of mobile genetic elements*

1984
- **N.K. Jerne, G.J.F. Köhler, C. Milstein** *for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies*
- **R.B. Merrifield** *for his development of methodology for chemical synthesis on a solid matrix*

1985
- Annex of administration building to the institute
- **H.A. Hauptman, J. Karle** *for their outstanding achievements in the development of direct methods for the determination of crystal structures*

1986
- Construction and utilization of tower 4 by the Institut für genbiologische Forschung Berlin GmbH (1986–1996)
- **K. Mullis** Polymerase Chain Reaction (PCR)
- **E. Ruska** *for his fundamental work in electron optics, and for the design of the first electron microscope*

1987
- **T. Susumu** *for his discovery of the genetic principle for generation of antibody diversity*

1988
- **Tomas Pieler** (1988–1992)
- **Albrecht Bindereif** (1988–1994)

Development of the Institute
Scientific Members
Heads of Research Groups (SAG/OWL)
Significant Scientific Developments
Nobel Prizes

1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

Utilization of the 2nd floor of tower 4 by Metagen
Taking over of tower 4 (cellar–1st floor) by the MPIMG
Move-out of Metagen from tower 4
Utilization of the animal house
Start of construction of tower 3
Start of reconstruction of tower 2
Completion and utilization of tower 3
Extension of the guest house
Construction of cellar of tower 3 and building of an underground connection between towers 2 and 4
Extension of the administration building

Claus Scheidereit (1989–1994)
Hans Lehrach appointment as Director and Head of Department (1994–2014)
Hans-Hilger Ropers appointment as Director and Head of Department (1994–2014)
Martin Vingron appointment as Director and Head of Department (since 2000)
Adam Antebi (1997–2004)
Stefan Mundlos (since 2000)
Ann Ehrenhofer-Murray (1997–2004)
Marie-Laure Yaspo (W2, since 1995)
Andrea Vortkamp (1998–2004)
Bernhard Herrmann appointment as Director and Head of Department (since 2003)
Chen Zhu appointment as External Scientific Member (since 2005)
Peter Arndt (W2, since 2003)
Michael Lappe (2004–2010)
Edda Klipp (2006–2008)
Sylvia Krobitsch (since 2008)
Sascha Sauer (since 2008)
Ulrich Stelzl (since 2007)
Ulf Andersson Ørom (since 2012)
Ho-Ryun Chung (since 2011)
Zhike Zi (since 2014)

Start of the Human Genome Project
First complete genome sequence of a plant *(Arabidobsis thaliana)*
Genome sequence of yeast *(Saccharomyces cerevisiae)*
Complete sequencing of the human genome
Sir J. B. Gurdon, S. Yamanaka *for the discovery that mature cells can be reprogrammed to become pluripotent*
F. Zhang development of CRISPR/Cas system for genome editing of mammalian/human cells

E. H. Fischer, E. G. Krebs *for their discoveries concerning reversible protein phosphorylation as a biological regulatory mechanism*
Complete sequencing of chromosome 21
Genome sequence of a nematode *(Cenorhabditis elegans)*
First complete genome sequence of an organism *(Haemophilus influenzae)*
A. Z. Fire, C. Mello *for their discovery of RNA interference - gene silencing by double-stranded RNA*
R. D. Kornberg *for his studies of the molecular basis of eukaryotic transcription*
J. E. Rothmann, R. W. Schekman, T. C. Südhof *for their discoveries of machinery regulating vesicle traffic, a major transport system in our cells*

R. J. Roberts, P. A. Sharp *for their discoveries of split genes*
Complete sequencing of chromosome 22
Development of various next generation sequencing methods (NGS)

K. Mullis *for his invention of the polymerase chain reaction (PCR) method*
G. Blobel *for the discovery that proteins have intrinsic signals that govern their transport and localization in the cell*
First draft of the human genome
M. Capecci, M. Evans, O. Smithies *for their discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells*
O. Shomomura, M. Chalfie, R. Tsien *for the discovery and development of the green fluorescent protein, GFP*

M. Smith *for his fundamental contributions to the establishment of oligonucleotide-based, site-directed mutagenesis and its development for protein studies*
E. B. Lewis, C. Nüsslein-Volhard, E. F. Wieschaus *for their discoveries concerning the genetic control of early embryonic development*

L. H. Hartwell, T. Hunt, P. Nurse *for their discoveries of key regulators of the cell cycle*
S. Brenner, H. R. Horvitz, J. E. Sulston *for their discoveries concerning genetic regulation of organ development and programmed cell death*
E. Blackburn, C. W. Greider, J. Szostak *for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase*

J. M. Bishop, H. E. Varmus *for their discovery of the cellular origin of retroviral oncogenes*
J. B. Fenn, K. Tanaka *for their development of soft desorption ionisation methods for mass spectrometric analyses of biological macromolecules*
V. Ramakrishnan, T. A. Steitz, A. Yonath *for studies of the structure and function of the ribosome*

S. Altman, T. R. Cech *for their discovery of catalytic properties of RNA*

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A CLEAN DESK
IS A SIGN OF A
SICK MIND!

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