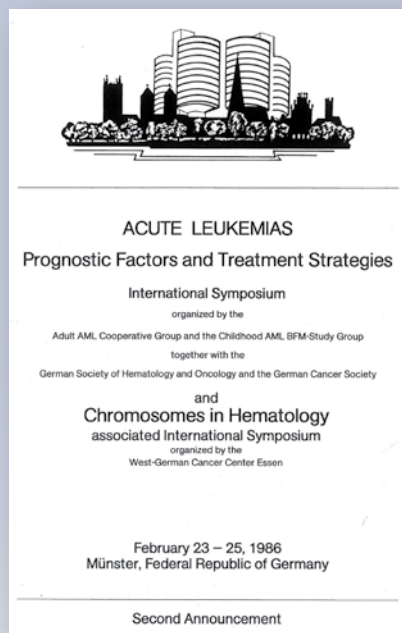
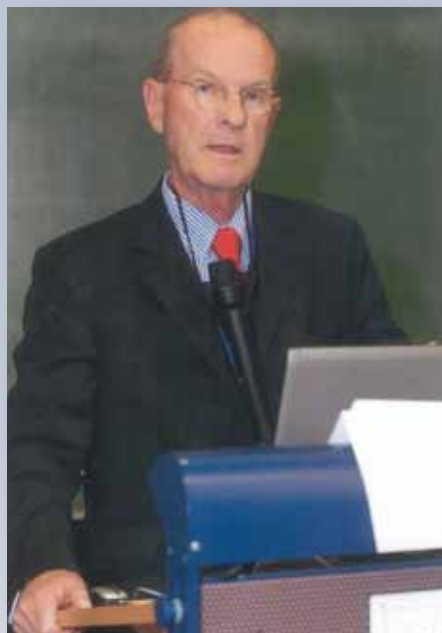


# International Symposium ACUTE LEUKEMIAS XVI Biology and Treatment Strategies

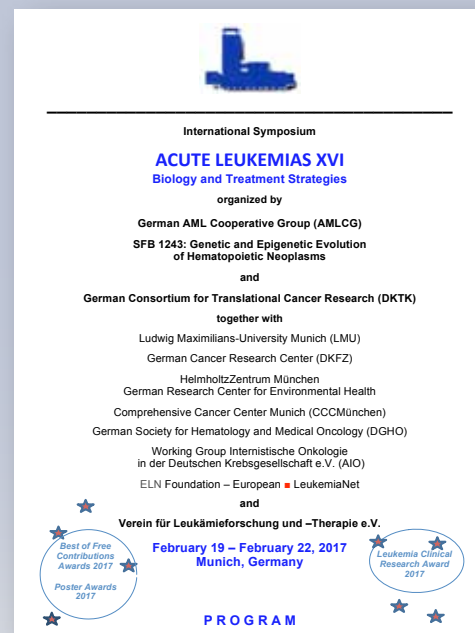
February 19 – February 22, 2017  
Munich, Germany



1986



Prof. Thomas Büchner



2017

## Prof. Thomas Büchner

(22 September 1934 – 5 August 2016)

### A leading European hematologist and AML trialist

*Leukemia* (2016) 30, 2131–2132; doi:10.1038/leu.2016.241; published online 9 September 2016

Dr. med. Thomas Büchner, Professor Emeritus of the Westfalian Wilhelms-University in Muenster, Germany, died suddenly gardening in his home in Muenster on August 5, 2016. Until his last day Thomas was active as a scientist and teacher in Muenster's University and in the international leukemia community.

Thomas was born on 22 September 1934 in Berlin. He moved with his family to Freiburg and grew up in this university town in the south-west of Germany. In 1955 Thomas began to study Medicine at the University of Freiburg and completed his exams and his MD degree in 1961. The title of his experimental MD thesis was: 'Autoradiographic studies concerning cell kinetics in the mouse'. This was the basis of his life-long interest in experimental and clinical research in hematology. In 1962 Thomas Büchner moved to the University of Muenster and was active in the Faculty of Medicine until recently. He joined the Department of Medicine, fulfilled the requirements for a university professor (Habilitation) in 1970 and became consultant physician and Professor of Medicine in 1972. His thesis for obtaining the professorship was again a study on cell kinetics, this time blood cell kinetics in humans. His work was honored

with the Theodor-Frerichs Award of the German Society of Internal Medicine in 1971. In 1997 Thomas Büchner was one of the founding members of the competence network 'Acute and Chronic Leukemias', which he supported for the rest of his life. His saying was: This call is for us. If we don't win, it is our own fault. In 2002 he became also one of the key promoters of the European LeukemiaNet (ELN). His last contribution to the spread of excellence of this competence network was a lecture at the German Cancer Congress in Berlin in February of this year. When Thomas became Professor Emeritus in 1999, he continued his active work as a highly engaged scientist, teacher and clinician. He remained active in the department and beyond. For his ongoing enormous scientific and clinical contribution to the field of leukemia, Thomas Büchner was elected Honorary Member of the German Society of Hematology and Oncology (DGHO) in 2008.

The focus of Thomas Büchner's clinical and scientific interest was acute myeloid leukemia (AML). When he started working in this field in the 1960s, median survival of persons with AML was 05 months and the disease killed almost everyone. At that time hematologists had only few drugs in their hands such as thioguanine and cytarabine and supportive care was unavailable. In 1978 the Federal Government in Germany launched a pro-

gram to support nation-wide multicenter trials for persons with several cancers and Thomas Büchner took over the task of coordinating the German national AML trials. This led to the foundation of the 'German AML Cooperative Group' (AMLCG) and to a successful series of multicenter trials throughout Germany. In the first of this series of AMLCG trials under the charismatic leadership of Thomas, the TAD-9 protocol for remission induction was established consisting of cytarabine, daunorubicin and thioguanine. This concept was based on Thomas' extensive preclinical research and took advantage of the so-called synchronizing effect of cytarabine.

In parallel, systematic supportive care was optimized by platelet transfusions, effective antibiotics and treatment in a protected environment. Under this regimen the AMLCG observed the first long-term survivors. Thomas was very serious, but he had also a deep sense for humor. In his first AML trial after few patients were accrued the survival curve dropped sharply and Thomas declared it as a 'plateau destroyer we have to avoid in the future!' Study generations followed, in which the AMLCG concentrated on adding maintenance therapy for up to 3 years and on intensifying remission induction by introducing double induction and dose intensification of single components such as high-dose cytarabine and mitoxantrone (HAM).

The AMLCG 1999 randomized trial addressed several open questions for induction and postremission therapy in 43000 subjects. This trial showed the limits of further dose escalation of chemotherapy in induction and consolidation/maintenance. It also showed the enormous prognostic impact of age. Whereas with the intensive treatment approach of double induction, consolidation plus maintenance and modern supportive care approximately half of the patients 060 years survived, progress in older patients was substantially worse with 030% long-term survivors. From the beginning the AMLCG trials were complemented by highly sophisticated central diagnostics allowing identification of biologic and prognostic subgroups, which paved the way for translational research projects.

However, as Thomas kept teaching us: we still are not able to really understand and explain the molecular basis of the 'age factor'—as he named it. He hypothesized the 'age factor' as a result of accumulating genetic changes with increasing age. Besides novel anti-leukemia treatment strategies Thomas with his group improved systematic supportive care in cooperation with the Paul-Ehrlich Society within the AMLCG studies. This approach resulted in a close cooperation of hematologists and microbiologists and the establishment of a DGHO working group that developed national and

international guidelines for to manage infections in hematology and oncology. For the statistical design of the AMLCG 1999 trial Thomas introduced the principle of ‘up-front’ randomization into different treatment algorithms, a principle widely discussed in the leukemia community. Some felt it not so helpful in guiding care in distinct situations where specified randomization might give a more precise answer. However, in the Intergroup trial of the German Network for Leukemia Thomas and many others used the powerful instrument of up-front randomization to compare the different therapies specifically designed by the five multi-center trial groups for AML, which evolved in Germany in the meantime—and found no significant differences in outcome. Thomas always explained this to us—with his typical deep but subtle sense of humor—and by this gave further impulse to many of us to seek completely new ways of AML treatment.

Science needs communication and also in this field Thomas Büchner was a driving force. Together with the pediatrician Günther Schellong from Muenster, who was one of the pioneers of the BFM group for studies on children’s leukemia and lymphoma, Thomas Büchner and others founded the series of symposia on ‘Acute Leukemias’, which is attracting international scientists and clinicians every 2 years and is an important forum for the exchange of ideas and results in the field. All this made Thomas Büchner an internationally respected leukemia specialist, which also led to the request by Michael Gorbachev to treat his wife Raissa Gorbacheva in Muenster.

Thomas Büchner had a major impact on the international progress in AML therapy and gained substantial honors and awards. His sudden death leaves us with the challenge and obligation to continue his work and to follow his outstanding example as a highly engaged researcher and clinician. Thomas is survived by his three sons and grandchildren. His beloved wife Edith predeceased him in 2013. The field of hematology and leukemia research has lost a pioneer, a wonderful person, a good friend, a mentor, an eminent colleague and first of all an intellectual human who will smile forever with friendly humor about what we do and what we try. Thomas Büchner’s favored song was ‘Imagine’ by John Lennon; there is nothing to add.

W.E. Berdel<sup>1</sup>, R. Hehlmann<sup>2</sup>, D Hoelzer<sup>3</sup>, and W Hiddemann<sup>4</sup>

<sup>1</sup> Department of Medicine A (Hematology/Oncology), University Hospital WWU Muenster, Muenster, Germany

<sup>2</sup> Medizinische Fakultät Mannheim, Universität Heidelberg, Heidelberg, Germany;

<sup>3</sup> Onkologikum Frankfurt, Frankfurt, Germany and

<sup>4</sup> University Hospital LMU Munich, Munich, Germany

E-mail: berdel@uni-muenster.de

### Clara Bloomfield

Thomas was one of the early initiators of international collaborations in acute myeloid leukemia. He first came to see me when I was on the faculty at the University of Minnesota in the late 1970s. We had met before at international meetings, but his visit to Minnesota was the beginning of a long friendship that lasted until his unfortunate recent death. Over the many years that we knew each other he hosted me multiple times in Germany where he always took incredibly good care of me and saw that my visit was perfect. We interacted several times a year at professional meetings, by visits at my University or his or by phone or mail. It is a great loss for me that he is gone.

### Michael Andreeff

We go back to 1971, 46 years ago. We met over our passion for leukemias and the new field of Impulsphotometrie = Flow Cytometry. I invited Thomas to Heidelberg where I organized, in my first year of residency, the First German Flow Cytometry meeting. We measured DNA in single cells at a rate of 1,000 per second!!! It had taken me 3 years to measure DNA and RNA in 900 cells as part of my thesis, so a light went on when Wolfgang Goehde developed the first European flow cytometer. This was unbelievable and irresistible to both of us. We both recognized immediately the paradigm-changing power of this technique. And we had the tumor cells that we could get by simply drawing blood, while the solid tumor folks had to liberate them from tumor biopsies.

This professional bond developed into a true friendship. Thomas was incredibly supportive, kind and inspirational. I was just at the beginning of my career and he was already „Herr Professor“, the scion of a family famous for its medicine professors.

We had an early meeting in Munich where we all bonded over „fluidics“ of another sort. Later, Thomas send me his best young doctor to Sloan Kettering where I had landed, Wolfgang Hiddemann, and a second life-long friendship developed.

In the meantime and over more than 25 years, Thomas invited me to each of the wonderful Muenster meetings on Acute Leukemias, which later moved to Muenchen under the tutelage of Wolfgang. I remember one Muenster meeting where a suckling pig was paraded through the dining room in complete darkness, with sparklers blazing away. Thomas had this very cool, understated sense of humor, which I relished. He and „Kiepenkerl“, the Muenster original, could tell the best stories.

We had many meetings in the US, first on flow cytometry, later on leukemias. Asilomar stood out as special. Thomas, the quiet German professor, was always renting typical American muscle cars when in the US and hugely enjoyed the freedom that they symbolized.

Thomas was, to the end, the most driven hematologist I met: quiet but persistent over a life time, driven by the urge to cure more, if not all of his patients. He presented highly innovative protocols,



never afraid to break with „standards of care“. The results were the envy of the leukemia world; his persistence paid off, but he was never complacent.

He remains the most admired clinical hematologist of his generation, in Germany and beyond. His presence is palpable, even if he can not be with us today.“

### Robert Peter Gale

I first met Thomas in 1977 shortly after Prof. Martin J. Cline and I published a typescript in the LANCET reporting a high rate of complete remissions in adults with acute myeloid leukaemia (AML) treated with TAD (6-thioguanine, cytarabine and daunorubicin). Thomas, ever curious, was impressed by our report and invited me to visit Munster. On arriving I noticed a rather formal professorial delegation awaiting the arrival of a small plane from Frankfurt with only 8 or 10 passengers and presumably bringing Prof. Gale. I was 32, a very junior academic and had flown overnight from Los Angeles in economy class. Thomas and his distinguished colleagues, in 3-piece suits waited anxiously outside the baggage claim area. I was the last person out. They seemed incredulous but somehow resigned. Perhaps they hoped Prof. Gale had missed his connection (easily done at FRK). I greeted Thomas saying: Regrettably, I am probably the person you are here to greet. Anyone who knows Thomas well will appreciate his extraordinary good manners and formality. He welcomed me warmly, made a

kind comment on my UCLA sweatshirt and thus began a lovely and productive visit.

Thomas' made many important contributions to AML therapy. In his later career he became interested in the role of age in AML which he termed the age factor. After adjusting for other prognostic variables such as cytogenetics, mutations, prior myelodysplastic syndrome (MDS) etc, age per se remained strongly-correlated with AML outcomes in the AMLCG trials. Also, because he and his colleagues had thousands of subjects in their trials they could compare therapy outcomes in subjects 57-60 years receiving intensive therapy and those 61-63 years receiving less intensive therapy. Again they found similar outcomes suggesting we are not going to make much progress treating older subjects with increasingly intensive therapy.

A last curious bond between Thomas and me was his fondness for red Hermes ties, often with an animal motif. These were always selected by Edith. I now have one of his to wear on special occasions recalling our deep friendship.

### Rüdiger Hehlmann

Thomas Büchner was the central figure of two international conferences: the International Symposium on Acute Leukemias in Münster, now Munich, which he chaired and co-chaired for almost 30 years, and the Raisa Gorbacheva Symposium in St. Petersburg organized by Boris Afanasiev which he introduced since its inception in 2007 with the Memorial Lecture named after his most prominent patient Raisa Gorbacheva. I remember well a steering committee session of the Kompetenznetz Leukämien at Frankfurt Airport in 1999 which he left unexpectedly early to reach a plane to Moscow. I only learned later that he left to see Raisa Gorbacheva.

Thomas and I became friends in 1985, when we waited, actually as competitors, for our interviews for a professorship in Mainz. Thomas was very nervous. He had a dry mouth and could hardly speak. I got a glass of water for Thomas which helped. He did not forget.

In 2012, Thomas, Bengt Simonsson and I travelled together to Brussels on behalf of ELN and visited Commissioner Dalli and tried to convince him to alleviate the clinical trial directive 2001. Thomas and I believed that this visit contributed to the new clinical trial regulation which acknowledges treatment optimization studies by defining minimal risk interventional clinical trials.

Since Thomas died only a few weeks before he was supposed to give the Raisa Gorbacheva Memorial Lecture 2016, I had to step in on request of Boris Afanasiev and also give his obituary.

On suggestion of Wolfgang Hiddemann I include this obituary and introduction to the Raisa Gorbacheva Memorial Lecture which used to be given by Thomas for the participants of the XVI Symposium on Acute Leukemias in Munich as a homage to Thomas.







### Wolfgang Hiddemann

When I knocked at a door in the upper office floor of the University hospital in Münster in early 1972 I didn't know that my life was just given a direction which determined my future career substantially. I entered Professor Thomas Büchner's room searching for a doctoral thesis. Under Thomas' guidance I started to work on cell kinetics in acute leukemias with the intent to develop a more rational basis for the treatment of this disease. The cell kinetically designed so called TAD-9 regimen became the backbone for all our subsequent clinical studies in AML. With the foundation of the German AML Cooperative Group (AML-CG) in 1978 a series of multicenter phase III studies was initiated and guided by Thomas Büchner investigating major elements of AML therapy. New approaches were developed and evaluated such as monthly maintenance therapy or double induction treatment. Thomas was a pioneer in performing controlled and well designed multicenter trials in AML which were recognized world wide for their scientific value and accuracy.



Thomas was highly dedicated to his fight against AML. He once told me that he would give a couple of years of his life if he could beat this disease. Until his very last moments Thomas continued his efforts and concentrated in his later years on the so called „age factor“ in AML which describes the still unresolved problem of poor outcome in patients beyond 60 years of age .

Over the many years that I had the privilege to work with Thomas our personal relation changed and after having been a mentor in the beginning Thomas became a colleague and finally close friend. Thomas' strong belief in his ideas and his dedicated efforts to understand the biology of AML and to improve the prognosis of patients suffering from this disease made him an internationally recognized leader in this field. With his charming personality and his special sense of humor Thomas has not only gained scientific recognition but will furthermore and maybe more importantly remain in our memories and hearts.

### Dieter Hoelzer

In the 80ies, the first Leukemia Meetings were organized in Vienna by Prof. Stacher. Thomas Büchner gave an evening lecture. Kinetic Synchronization of High Dose ARA C. In the discussion his presentation was completely “destroyed”. Thomas was very much depressed. Thus, we about 7/8 national and international hematologists tried to find a place for a dinner with him. All restaurants were closed. Finally we found a bar at the Wiener Ring. Also nearly closing, but the keeper gave us 2 bottles of Whiskey and we had good entertainment and discussion until the early morning. When we left, Thomas was reasonable happy. Later it turned out, that all the statements he gave in his presentations became true.

In the 80ies the German government installed a great research program to initiate prospective multi-center-clinical-trials. These trials were Investigators initiated (a Term not existing at that time). Thomas Büchner started a huge prospective trial on Acute Myeloblastic Leukemia particularly based on his and Wolfgang Hiddemanns research work of the Universities of New York and Münster. Thomas was very serious, but also a strong sense for humor. When he had his first interim analysis, the relapse free survival curve dropped sharply to zero Thomas declared this is a “plateau destroyers” and that we have to avoid it. The terminus became international known, associated with him. To honor Thomas, we all should avoid this “plateau destroyers” in our studies.





### Utz Krug

After I entered the Department of Medicine A of the University of Münster, my first encounter with Thomas took place when I attended the weekly hematology grand round for the first time in May 2006. Already retired since 1999, Thomas still examined every bone marrow cytology in person and taught us the most interesting findings.

Shortly afterwards in autumn 2006, a knee injury gave me enough time to start collecting clinical data on monthly maintenance therapy as postremission therapy, a rather cumbersome exercise. However, this paved the way for a very close and fruitful collaboration. Thomas, together with the biostatisticians Cristina Sauerland and Achim Heinecke, helped me to enter the arena of clinical research. Over the following 10 years, a lot of fruitful discussions, calculations and publications evolved.

Thomas was dedicated to his will to understand the biology of AML and to find ways to target this deadly disease. Until his last days, Thomas pursued his efforts to fight AML. One of our last efforts were to understand the biology behind the „age factor“, the age-dependent worse outcome of older patients.

Despite differences in age and diametral interests in either a bavarian red or a royal blue football team, over the years a friendship evolved. I appreciated his brilliant ideas, his decent modesty, his seek for agreement and his deep sense of humor he opened to close friends.

I'm deeply honoured for the common path I had the chance to share with Thomas for 10 years, and for having a mentor and friend like him. The hematology society will miss him as a scientist with international reputation. I will also miss him as a mentor and a friend.

### Jörg Ritter

I met Thomas Buechner for the first time in the late 1970s when he arrived at the Clinic for Paediatric Haematology/ Oncology in Münster, then headed by Günther Schellong, from the Department of Paediatrics, Braunschweig Community Hospital. On his arrival we discussed the clinical significance of the DNA content, as measured by flow cytometry, of leukaemic blasts in children and adolescents with acute leukaemias. This discussion engendered a fruitful cooperation also including Wolfgang Hiddemann and Bernhard Wörmann.

At that time we launched the paediatric AML-BFM (Berlin-Frankfurt-Münster) multi-center study together with Schellong und Ursula Creutzig of the Department of Paediatric Haematology/ Oncology Muenster. It was a stroke of luck that at the same time Thomas initiated the AML Cooperative Group (AMLCG) for adults at Muenster University Hospital. This allowed us paediatricians to learn a lot about AML, which we then thought to be an ugly form of ALL, from Thomas' group. We found out about the importance of early intensive polychemotherapy, especially in the form of "double induction", and learned that the combination of

high dose ARA-C with Mitoxantrone (HAM) is especially effective. We introduced HAM first in children and adolescents with relapsed AML and then in all children with AML. Furthermore we learned from the adult studies that severe opportunistic infections, especially invasive fungal ones, are a major obstacle against the cure of AML. We also gained a lot of knowledge about risk factors in AML, the most important being response of the individual patient to the treatment administered.

In 1986 we started a symposia series on Acute Leukemias in Muenster, the first chairmen were Büchner from Medical Oncology and Schellong from Paediatric Haematology/Oncology. These symposia were then worldwide the only ones dealing with all forms of acute leukaemias in both adults and children.

Thomas became a good friend of the paediatric AML studies, and we paediatricians were glad that he accepted our invitation to become a member of the paediatric AML – BFM study committee.





### Charles Schiffer

A benefit of the privilege of participating in large scale clinical research is the opportunity to meet and work with colleagues from all over the world, who often become great friends, despite the fact that you see them infrequently. I first met Thomas at what some have called "Leukemia in the Woods" in the hut in Wilsede, when I was young and he was already renowned.

We were somewhat different in nature – he was a quiet, formal and serious gentleman (albeit with the potential for a twinkle in his eyes), always impeccably dressed, and addicted to double induction and maintenance therapy for AML, whereas I was from New York and somewhat irreverent. However, we shared a passion for moving beyond "7 & 3", and looked forward to meeting a few times a year at national meetings and in Munster often focusing on family, friends, and not necessarily leukemia. At one meeting in Phoenix, we played golf together. Edith, his charming and gregarious wife, played well, hitting it short but consistently straight down the middle; I was mediocre, although Thomas was worse and essentially needed an allogeneic swing transplant. Fortunately, golf was not our day job.

More interesting and revealing was a visit to Petra with Edith and my wife, Pamela, during a break from a meeting of the Jordanian Society of Hematology. Our guide was an interesting and knowledgeable older gentleman who was also curious about us and far from shy. He peppered Edith with questions about Thomas and she apparently laid it on pretty thick: famous professor, leader of

German leukemia, worldwide lecturer, wonderful family man, etc. I think the guide was getting bored and abruptly changed tack, asking: "But is he good in bed?" Without breaking stride, Thomas said: "Some say yes, and some say no." This resulted in a quieter guide and convulsions of laughter from the rest of us.

At the last Munich meeting, Thomas and I were chairing a session together (that's what old men get asked to do), and I told him of my plans to introduce him with this story. He, of course, said "no", but I could tell that he didn't really mean it (and it wouldn't have mattered anyway). The audience loved it, gaining some new insights about what lurked beneath his reserved demeanor. It was clear that Thomas was quite touched, in part related to this memory of Edith who had died recently. So, I choose this as my defining memory of my friend Thomas, personally more meaningful and uplifting than the fact that "7 & 3" remains in ascendancy (which he came to belatedly acknowledge).

### Bernhard Wörmann

My first personal encounter with Thomas Büchner occurred in 1977, when I looked for a mentor for my doctoral thesis. He had his office on the top floor of the historic department of Internal Medicine in Münster, even with a terrace. In our first conversation, he checked the seriousness of my intentions and my readiness to work hard. Being satisfied, he directed me to Wolfgang Hiddemann, who was on an outpost at the department of nephrology, but had some exciting ideas for a subject on treatment-induced cell kinetics of acute myeloid leukemia using flow cytometry.

However, part of the laboratory equipment including the microscope was situated in Thomas Büchner's fully cramped, but spatial office. Thus for a substantial part of the following two years, we shared the same room.

Some anecdotes:

- I am sitting at the flow cytometer, and the phone on Thomas Büchner's desk doesn't stop ringing. Finally I lift the receiver, Thomas Büchner is on the phone. He had travelled to Southern Germany for a presentation on acute myeloid leukemia, but had left the invitation with description of the location on his desk.
- Thomas Büchner needed a new car. He started a phone call with a car dealer, and at some time-point he leaned towards me: „Herr Wörmann, this is not for your ears.“
- When he was invited for a major ASH presentation on elderly patients with AML, he meticulously

rehearsed every word. He started as slowly as always: „Our first patient was 86 years old.“ Pause. (I already got nervous,) He continued: „And this patient is now – pause (I almost went crazy) – 88! Big laughter in the audience. The rest of the presentation went smoothly.

In the following years, I got more clinically involved, also in the design of the largely successful AMLCG studies. We started to include not only patients with de novo AML, but also with sAML und tAML. Besides the clinical work, I learned hematologic cytology from Thomas Büchner. For long evening hours, he was sitting at the teaching microscope, slide after slide, focussing on single cells, discussing with me on granularity, nuclear shape, blast vs non-blast, etc.

When I decided in 1992 to leave Münster for Göttingen, moving further to Braunschweig and finally to Berlin, Thomas Büchner was disappointed. We continued the professional exchange within the study group.

