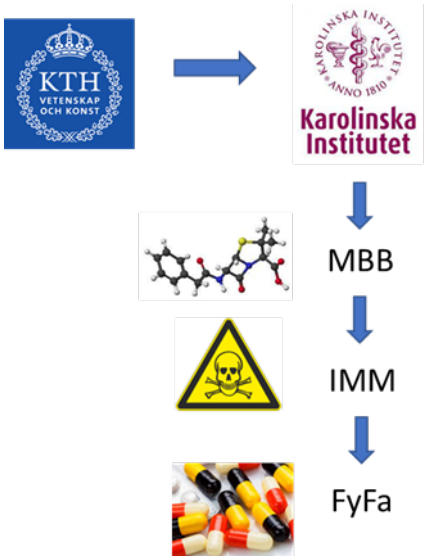
For WikiKi August 15, 2022

Magnus Ingelman-Sundberg, thoughts about a life at KI

Content



1 Introduction

I have been employed at KI since 1971, for 51 years. I have liked this a lot and most appreciated the freedom in the research and the opportunity to get involved in various projects in research, teaching and administration. The most fun has always been finding something completely new in research. Just a small find that is not immediately understandable can engage my thoughts for hours or many days after this. Of the findings we have made, many have not been "planned" but came about very much by chance, and the importance here has been to interpret the findings as they came in a completely objective way. The research must be hypothesis-driven in its initial phase, but the interpretation of the data independently of the hypothesis that has been put forward is of crucial importance. In relation to other researchers, I have spent a higher percentage of time on teaching, research training in developing countries and administration, and appreciated this too.
The time at KI has been very stimulating and contained lots of interesting interactions with other researchers, researchers within the group, research students, undergraduate students and administrative staff.

Accumulated during my 51 years, all the organizations around the business have expanded, the need for control and administration has increased enormously, largely initiated by, among other things, the control need of leading people in universities and ministries, individual mistakes or disregard of rules by individual researchers that lead to a large increase in regulations and a growing concern among many people in society that through their actions sometimes lead to demands for a greatly increased number of rules and increased degree of control. This change has in specific cases been necessary, but often less productive and necessary. When controlling bodies reject an animal ethics application, among other things, because it is not specified that the mice should be dried with a towel after they have swum in the so-called force swim test and that lawyers delay the transfer of uncontroversial gene sequence data between two laboratories that have collaborated for 10 years, by 6 months because not sufficiently guarded against, according to them, possible consequences but which for the project and the collaboration are completely irrelevant, one feels quite tired as a researcher. A very important aspect in this is that, while researchers are continuously evaluated in many instances, no actual evaluation of the usefulness and cost-effectiveness of new administrative rules ever takes place unless they directly cause, for example, increased costs. The increased administration is not only due to an increased degree of administration, but also to the fact that the quantity of research increases exponentially. If you have "disease" as a search term on PubMed, the number of publications per year since 1951 is clearly illustrated.

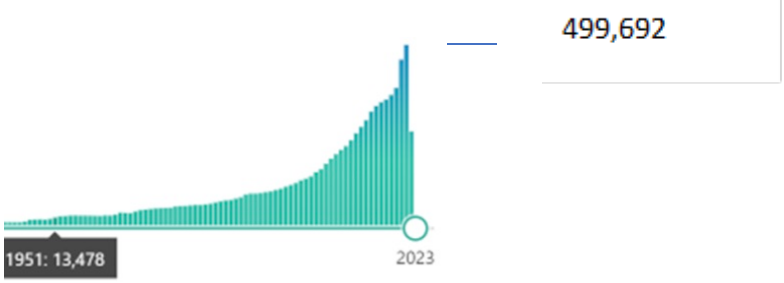


Figure 1. The number of publications per year that, according to PubMed, have been produced in my lifetime based on the search term "disease". From the year of my birth in 1951, the number per year has increased 37-fold.

2. Studies

After matriculation in 1969, I started almost immediately at the Chemistry Department at KTH. There was a lot of mathematics, physics and thermodynamics in the curriculum and I did not enjoy this. I had misunderstood the degree of chemistry and biochemistry taught at KTH and therefore applied to KI to work on more medically related chemical questions. I walked up to Chemistry I at KI on a Friday afternoon in March 1970 and bumped into Jan and Agneta Sjövall. I asked if I could do a chemistry internship at the department as part of my education at KTH. Jan looked at me for a long time and said after a while, uhh I don't know. I gave my name and phone number and the following Tuesday a quick man called my phone and said yes you can work in my lab. The man in question was Jan-Åke Gustafsson, who was building a research group in parallel with the final phase of his medical studies. After general work the first summer, I returned the following summer. The lab hypothesized that in addition to unconjugated steroids, sulfated steroids could also be substrates for liver enzymes as a step in the elimination process. However, it had not been possible to synthesize such steroid conjugates to validate the hypothesis. When I got there I went to the library to find a good recipe for such a synthesis. I also realized that they had not distilled the solvents used in the synthesis experiments and since I had taken the course in organic chemistry, I immediately started distilling these, after which the synthesis went well. I was then able to verify that the hypothesis was correct and identified an enzyme that did such reactions. This finding formed the basis of my thesis.
I started full-time on the thesis work in the spring of 1973, received very good research supervision and was basically finished in March 1975. I worked day in and day out and on weekends my girlfriend Cecilia (later wife) gave an ultimatum that either I reduced my working hours or so it had to be. I supported myself during my PhD with a part-time job as an instructor for the labass school and was also a study counselor at KTH and did some final courses there.

In March 1975, Jan-Åke and I decided on the bacteriologist's stairs that I would do my dissertation in May of the same year, although I was not yet a registered doctoral student. To do this, I must first read the last course at KTH, the continuation course in organic chemistry. The exam was conducted orally with Jan Bergman as the examiner, I got my civil degree, registered as a doctoral student in April, wrote the thesis and defended my dissertation as planned in May 1975. When you think back on this, you get the impression that things can go well even without a huge regulatory framework.

3. The defense

The defense was held on May 30, 1975 when I was 23 years old. I think I may be one of the youngest at KI to have a PhD. It was a chilly spring day with about 10 C. My opponent was Sven Lindstedt, a clinical chemist from Sahlgrenska. The night before I washed the dirty walls in the chemistry lecture hall, where brown liquid had run down them perhaps a couple of years before. At 9 o'clock the opponent entered with a basket of various things. He had taken the night train from Gothenburg and said that he opened the thesis when he woke up in Södertälje. At that time, the opponent would start the show by summarizing the thesis but he ignored that. Instead, his first question was if I was interested in stamp collecting. Then he wanted to mock me as a technologist and projected slides on the freshly washed white wall of various sick patients and asked me to diagnose. I was able to give back a little and answered his question about not showing a figure of a steroid variant in the thesis by saying that we had one but the editors at the scientific journal J Biol Chem thought it was unnecessary for those familiar with the research field. The kind of arrogant behavior I have never

experienced before. My supervisor and I had some intense discussions the next day about why he was taken as an opponent.

My dissertation party was held at a café in Frihamnen, Skeppet, and chicken salad was served as the main and only course. This was in stark contrast to the custom at the time when the party would be at the Medical Society, Kevinge Golf Club or something similar. During the defense party, my supervisor's supervisor Bengt Gustafsson gave me a speech where he urged me to also complete a basic medical education that would be of value in my research career. This advice was, in retrospect, great. It has been very important to have an understanding of the interplay and structure of the organs and the endocrine and physiological processes. With a bachelor's degree, the studies were done in parallel with the fact that I had a job and did research at the chemistry department, and was probably not conducted very intensively. During the chemistry semester, I had an exemption and then, to the horror of my course mates, changed my place from being a student to standing at the chair and lecturing to them. During the physiology semester, I don't think I covered many lectures. After my studies, I first got a research assistant position and then a lecturer's position and taught quite a lot for ten years until Bengt Samuelsson became rector, when in 1986-1996 I substituted for his professorship until I got my own professorship in 1996.

4. Teaching

The teaching was initially fun. I was responsible for the first 5 weeks of the chemistry semester of the medicine course. At best, I was probably in the second semester as a lecturer. One day I went to Håkan Eriksson, director of studies for chemistry teaching at the medical school, and said that we must change the teaching methods and make the whole semester problem-oriented. I came in to see him one day in February, the window was open and his shoes were on the table and the radio was reporting Stenmark's slalom race. In this environment I swooped in and announced this. All said and done and we did this to the students' great delight and received their award "Master" in 1988. However, easy-to-read compendiums with answers to all study questions soon circulated and we had to discontinue the problem-oriented teaching after a couple of years. In 2000, I also received KI's educational award for my efforts in the basic training of doctors.

Figure 2. In the class room teaching in a white coat around 1974 and my writing room around 1992.

Håkan was a fantastically nice and enthusiastic person to work with. He was easy to make decisions and understood the big problems. He offered me premises for research in the Berzelius laboratory when I wanted to separate from my supervisor's laboratory premises in 1978 and greatly supported the initiation of the research activity with, among other things, the purchase of equipment.

In 1979, a majority came to the chemistry semester who had no prior knowledge of mathematics, physics and chemistry after the government's reform that work experience would be meritorious to enter university. This was very worrying as no extra funds had been added for more teaching and no directives had been given as to how the colleges should deal with this problem. Suddenly we were left with groups of 185 students of which 70-80% had no prior knowledge to absorb the teaching of chemistry. This led to about 50% of the students failing the exams in chemistry as I basically refused to reduce the requirements. On the basis of this, one did not become popular. Before the second semester's students were due to arrive, I completed a diagnostic test on tasks in mathematics and chemistry called dust zero. Many people's level in these subjects was poor and many could not solve the problem of what is 1/7 + 1/3. I went to the bottom of this and contacted and had meetings with people in charge at various adult high schools where supplementary courses were given for older students who did not have high school qualifications in these. It appeared that the pace of the courses was fast and it was difficult to catch up with everything in the much shortened time that was available. Likewise, these topics require a longer period of reading to be able to understand them on a more thorough level. In addition, unlike the junior high school, there were no central tests or any external evaluation of weight. I got the impression that both students and teachers were most satisfied if the student got the highest grade and could thereby enter the desired higher education. An adult high school teacher who is the sister of one of my friends was still pissed off at me for this when we met once 30 years later and said I made their situation much more difficult.

The rector at KI at the time, Björn Pernow, asked me to participate in a symposium about the upper secondary school where I presented the results. A book was printed as a result of the meeting and I released my chapter to SvD, which the next day filled the entire leaflet with rambling headlines about this. Once at work, SVT report came and interviewed me, that very day the students had outdoor day so they could not get their version. Some students were very provoked by this and reported me to UHÄ. At a meeting there with administrators and the critical students, it was established that it was probably a formal error to introduce an extra examination in the course without the syllabus being formally approved. Eventually the students adapted to the requirements and over the years fewer and fewer took the chemistry exams.

5. Teaching materials.

During my 10-year period as a lecturer and responsible for general chemistry teaching for the medical students, I had as a goal to collect the information given to the students in order to then publish a textbook, Chemistry of the Human Body. The first versions of the book were more like a compendium, but the book gradually grew. Different teachers took responsibility for the different chapters and I did exercises based on those that were given during the course. The data in the book had been fabricated for the examination and sometimes had political aspects such as calculating Lennart Hyland's BAC when he drove into the ditch based on various data on his osmosis and electrolyte balance. At the end of 1986, the book was ready for publication at Natur och Kultur after great help from Bengt Persson in 1986 and ran out of publishing around 2005. It was highly

appreciated but at the same time too advanced for it to pay off with a reprint in the 2000s. However, the book lives on as a basis for repetition of high school chemistry knowledge and basic chemical concepts in electronic form at the medical school administered by MBB.

Another teaching aid I made was a computer program that simulated intermediate metabolism that would complement the animal experiments done in the metabolism lab. I got the idea in the course lab in 1978 when a student told me how he wrote music with the help of the computer. I received funds from the Animal Protection Association and a contact with Rolf Bergin, head of the IT department at KI at the time, who recruited a KTH student who wrote the program in C++ in windows format. The user would, with the help of labeled intermediates, study the metabolism of eg glucose, lipids, amino acids and determine what disease or hormone, alcohol the patient was suffering from. or diet disorder. The person who did the programming was called Roger Skagervall and since he didn't know the subject he wanted me to give him the key to what disease was being simulated in the window he was working with. He therefore introduced a code after the initials of his name, RS, which provided the solution. At one point, a group of students worked on this, all of whom have now become professors or clinical managers, and assumed that there was such a code called the correct answer with the abbreviation RS... The program was used for almost 20 years in medical education at KI and was also exported to a couple other universities.

6. Administration at KI

6.1 Administration within basic training for doctors

During my time at KI, I was always involved in administrative responsibilities and tasks. It started with me being the chairman of the study board of a section at KTH when I went there. Håkan Eriksson, to which neighbouring lab in the Berzelius laboratory we moved in 1979, thought I should be on the line committee for medical education even though I only completed 2 more years with a bachelor's degree. The work started as a member, but soon I became chairman of the curriculum committee and was involved in implementing reforms. I met a lot of conservative teachers and introducing renewal was enormously difficult. In part, this was connected with the close link between funds for teaching and its location. Institutions with a lot of teaching received more funds and did not want to release parts of the courses to other institutions. It started with a new preclinical study plan and the noise level of the discussions in the Session Hall in the administration building was extremely loud, with some teachers shouting their criticism.

One initiative that Håkan and I had was to do an integrated course in endocrinology. This took resources from some institutions because teaching was rationalized through the integration. The course was a success among the students but not among the departments. When the physiology lecturer called up the students for the physiology term that followed the one in chemistry, he told all the students that there were two teachers he wanted to see hanged: MIS and Håkan.
In this vein, I was also responsible for the preparation of an integrated preclinical exam in collaboration with constructive teachers at various institutions.

The work in the line committee led to many contacts at KI and throughout my activity I enjoyed the contacts that were made. Chairman of the Linjenämnden in the 80s was Folke Sjöqvist. We liked working with each other and he suggested that we also do research together. This was realized through a joint grant from MFR for bridging activities between clinic and pre-clinical that we received

and had during a decade a fantastic collaboration that resulted in many original findings as shown below.

Håkan came to do a lot of administrative work at MFR and KI and worked quite closely with the rector Bengt Samuelsson. Håkan had an idea for a total renewal of KI called the KI-90 reform with much fewer institutions and a new management system. In this reform, he also thought that the medical education should be drastically modernized and gave me the task of chairing this reorganization with Ewa Ställdal as administrative responsible and Ernst Brodin, Staffan Ewerth, Sten Grillner, Bengt Fagrell, Agneta Philipson, Birger Winbladh, Tobias Wirén and Andreas Wladis as members. Ewa and I worked well together and a new proposal KI-90 GUL was presented in February 1990. This reform proposal was drastic and involved major changes and funds such as distributions between institutions, but gave medical education a much more modern profile and more integration and better governance. But was very controversial. Bengt Samuelsson contacted me and said ….. MIS this is a very good proposal I will support you when you present this to the faculty". About 60 upset teachers came to the faculty meeting and the Session Hall at KI was boiling right from the start. I presented the proposal, after which a barrage of criticism was delivered in outraged voices. Bengt Samuelsson was not happy and without uttering a single word he walked out of the room in his white lab coat. After the meeting, about 60 letters of protest were received, but thanks to solid work by Kerstin Hagenfeldt with the support of Bengt, most of the presented study plan was introduced.
In 1991, the proposal also included a new Medical Education Center at KI called KI-Lyceum, which, however, was never sufficiently prioritized by KI's management.

The work in the Curriculum Committee provided an enormous amount of input. Contacts with teachers, researchers and clinicians. And experiences of meeting procedures and socializing. Among the memories is a strange farewell dinner for Arne Ljungquist, where the appreciation of all the women shone like a glittering shimmer over the entire event, and a budget meeting with Thomas Ihre and the budget manager Sune Reinhold, which included, among other things, a 30-minute loud argument where both Sune and Thomas were screaming and were red in the the face, whereupon Thomas says now it's coffee and we go out into the corridor and Thomas acts like it was any coffee rope. I was impressed by this distinction between thing and person. The group made various excursions, including with Silja's large ship and Per Lundbergh, who was an infectious disease doctor, later an infection prevention doctor and very interested in shipping and boats, took us up to the captain's cabin where the captain showed us all the subtleties, whereupon suddenly the computer beeps and the boat turns sharply to the left and everyone frantically trying to understand what went wrong.

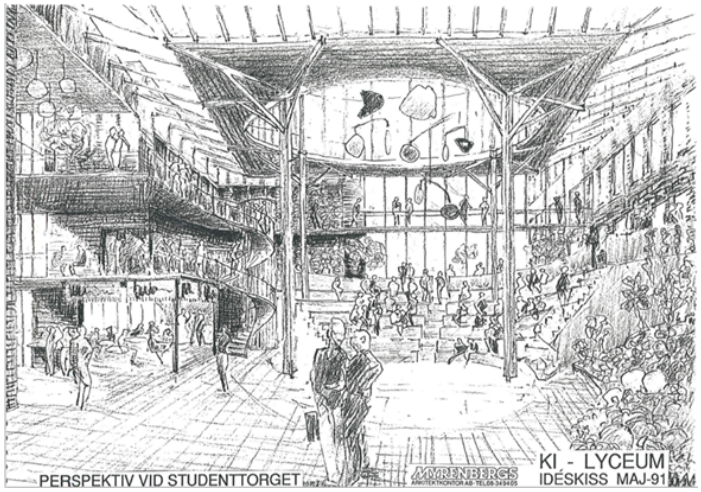


Figure 3. Sketch of an intended training center at KI that would be adapted to the new study plan in KI 90-GUL. However, the project was not prioritized by KI's management.
On one occasion I had called Per Lundbergh and Ragnar Thunell to a meeting. I remember how Ragnar and I waited and waited in my office, but Per never showed up as HIV had just broken out and he had many urgent meetings that were high priority. During this wait, I thought that the world would never be the same.

Sune Reinhold was easy to get along with and the budgets for the training were done quickly and creatively. His manager for a long time was Margareta Almling as head of administration and university director at KI 1965–1985. Margareta ruled KI with a firm hand when Sune Bergström was rector. Sune Reinhold expressed concerns about many things within KI's financial management and then moved on to become financial manager at Solna city.

Figure 4. The curriculum committee (Linjenämnden) at KI in 1984, from the KI magazine.

6.2 Administration at the Departments.
My administrative department career began at MBB with Bengt Samuelsson as head of department. Bengt I appreciated a lot. He had a nice sense of humour and said very important things in a tone that was not pretentious. I arranged MBB's lunch seminars for a long time and many of the lecturers had a great deal of respect for Bengt as an audience. I borrowed Bengt's advanced spectrophotometer as often for measuring the P450 spectrum. In the end it was almost only our group that used it. One day in the early 1980's he humbly came to me and said, ...MIS, can we use

the machine a bit now, we have some important spectra to run. These were the UV triplet absorption of the leukotrienes that won him the Nobel Prize in Medicine or Physiology in 1982. I was missing in my library a couple of volumes of J Biol Chem. When Bengt received the award, he ordered a container and cleaned the entire writing room, including the volumes of J Biol Chem I wanted. So easily I fished these out of the container for space in our library.

At IMM, I was mostly deputy head of department and collaborated well with Göran Pershagen as head of department. He was responsible for the overall and policy and I for budget and logistics. When I came to the department, all groups were allocated 1.6 million each per year, but I found it necessary to have an activity-related control instrument where the funds were distributed in accordance with the activity carried out in research, administration, applied investigation and teaching. This model was gratefully received and I never heard any strong criticism. I think that the administrative part of my work was at its greatest during my time at IMM. Budget and personnel problems lined up. At FyFa I was deputy head of department for many years with a stimulating collaboration with Stefan Eriksson. Stefan did an enormously good job with, among other things, new recruitments. Sometimes during the journey we sometimes had to deal with quite difficult financial and personnel issues. After Stefan left, the administration within FyFa consisted mostly of work with professor recruitments, while Stefan and I spent time as friends with, among other things, golf and tennis.

6.3 Chairman of the recruitment committee

One day in 2004, the dean for research Jan-Carlstedt Duke contacted me and thought I should get involved in KI's teacher and professor recruitment. I started as a deputy for a few years in the Recruitment Committee, then vice-chairman for 3 years and then chairman for a little more than six years when it was thought that the dean for research duties as responsible for recruitment should be separated from other duties that the dean had. I liked the recruiting job. Each case was often like a soap opera in itself with many different aspects such as fraud, financial management and attempts to circumvent regulations from the institutions. At the same time, there was always one person whose life was sometimes decided by the decision of the recruitment committee. It was exciting to dig into the background of various cases and often get a different background than the original presentation had. The interviews were usually extremely informative and it was nice to get to know the people behind the applications. Jan was succeeded by Karl Tryggvason, who wanted the deanship to continue not to include the recruitment part, but asked me to continue. One justification he had was that I was so good about frills… I really enjoyed the interactions with Karl which were very open and pleasant but which came to an abrupt end in March 2010.

A controversial reform at KI was Carl Tham's proposal that all lecturers who were formally academically competent for a professorship should also receive such employment. No extra funds were given for the reform, but it meant that all lecturers who thought they were competent as professors could apply for promotion from lecturer to professor. In total, about 140 applications were received over a few years for which I was responsible. Of these promotion cases, I thought that the candidates in about 30-40% of the cases had a quality in line with the open recruitment standard. The least cited promoted professor who converted had at the time of professor conversion at age 62 a total of 64 citations.

Sometimes the applicant was disgruntled and assertive and fought for their cause, resulting in many less pleasant interactions and conversations as a result. Subject bias sometimes occurred by experts in a small subject supporting their colleague to a professorship to strengthen the subject in question. In many cases when the application for promotion did not go through, the candidates became very angry with me and stopped greeting me. But in other cases, it was of course very competent researchers who were converted. This work with promotion professorships was perceived as quite burdensome both by me and by the recruitment unit. The funniest recruitment cases were, of course, those of the top researchers coming from outside. I did a larger survey for the background for the recruitment of professors who were rated outstanding in KI's research evaluation ERA 2010 and found that internal contacts at KI as a driving force for the recruitment process and as help for the establishment at KI were very important in this process.

One recruitment received a lot of mass media coverage, i.e. that of Paolo Macchiarini. Much has been written about this case in the last 10 years and I have in other contexts, among others, given my detailed view on this to the author of the report, Sten Heckscher. Heckscher concludes the case in https://nyheter.ki.se/heckscher-mycket-forvanade-under-utredningens-gang :
One can thus only conclude that this case was unsuccessful due to several different interacting factors, including:

• No one at KI knew him. He made contact himself in a stubborn way.
• Within regenerative medicine there were large amounts of unused research funds for which no plan for their use had been created.
• Paolo had an enormous charm that in a psychopathic way hid many of the negative sides.
• Those from KI who acted to recruit him kept secret many of the very negative references given.
• For a long time, the information about wrongdoing in his business was rejected by KI's and KS' management. I personally think that these people, the "whistle-blowers" who de facto spoke about what was going on, should receive an expression of gratitude from KI.

In total, during my time as recruitment chairman, I had been involved in hiring approx. 180-200 professors and 3-400 other teachers and researchers. In addition to assessing applications for employment, I have assessed applications for docents in the docenturnämden for 6 years and for the most part always sat in some research council that assessed national research applications or in Brussels for EU applications or for UK-MRC and NWO.

7. Work in research councils
I started at the Natural Sciences Research Council relatively young in 1985. Several hundred applications were reviewed in everything from inorganic chemistry to cell biology. I worked well with Chairman Charles Kurland. For three years I was chairman of one of the three review groups when we processed a large number of applications, about 100, in one day. This required efficiency and one member gave me the epithet steamroller, maybe I moved too quickly... The collaboration with Bertil Andersson, later rector of Linköping University, then head of ESF, and now president of Nanyang Technological University (NTU) in Singapore, appeared to be rewarding and the philosophical and more theoretical discussions with Svante Wold were extremely rewarding. Within the group, we did different study visits every year. Among other things in November 1989 in Heidelberg. I came from a conference at Yalta and landed on November 11 at Schönefeldt. The taxi driver I went with said the

city was so different now. I slept over at Kurfürstendamm and on the morning of November 13, 1989, I wandered the street and saw all the soup kitchens for the East Germans and how they stood in groups looking at the offerings in the various shops. Every East German visitor was given 100 DMarks to trade for at the border. Perhaps the most historic moment I've been a part of.

After 7 years in the Natural Sciences Research Council, I sat for six years in the Medical Research Council. And after that 7 are in the Norwegian Research Council. This was special because, despite all the oil money, they did not want to distribute more than approx. 25 million Norwegian kroner to all research in biology and life sciences. A large part of the funds went to the later Nobel laureates in 2014, the couple Edvard Moser, and his wife May-Britt Moser. After this, I returned to the Swedish Research Council for a few years. You learn a lot through this work and get a good insight into the research dynamics. You meet colleagues and have a relatively good relationship, even though it usually did not manifest itself in a particularly large way.

8. Work in EMA

At a meeting in London in 2004, a manager at the European Medicines Agency EMA asked if I could not be part of an expert group focused on personalized medicine. The task for the group would be to establish and review pharmacogenetic documentation in the medicinal product information (SmPC) but also to assist the EMA regarding general advice regarding the development of the research area. Over the years, this mission became quite extensive with meetings in London about 3-4 times a year and the organization of meetings and symposia. A number of research colleagues in Europe joined the group, many who have become friends over the years, such as George Patrinos, Ron von Schaik and Julia Stingl. The group functioned fairly unengraved until 2018 when the organization changed as EMA moved from London to Amsterdam. Somehow this group became a family where it was always the joy of recognition to meet and every meeting of 2 days included many nice dinners and nice collegial socializing. By creating rules of conduct for how and when prescribers must take into account inter-individual genetic differences in metabolizing drugs and experiencing side effects from drugs, the work was very meaningful, if not very effective. Some meetings felt long and de facto we from my research group wrote an overview recently about how big the differences in the assessment of the genetic contribution to inter-individual drug response were between academic institutions such as CPIC and DPGW, and regulatory entities such as the FDA (United States Agency for Medicines) and the EMA. But participating in the explicit clinical use of pharmacogenomics in drug development and clinic based on the application of the research fund that was made was in its entirety important, I thought.

Internationally, for 20 years from 2002 I have been the chairman of the organization Microsomes and Drug Oxidations, which organizes the most important meetings globally in the research field, next in Seattle in September and next year in Prague https://mdoprague2023.cz/ . The meetings serve a lot as a home stay and many productive contacts were made, among others, with Minor Coon, Mike Waterman, David Waxman and not least with Nico Vermeulen.

9. The work of the Nobel Assembly

In 2008 I was elected as a member of the Karolinska Institute's Nobel Assembly. I retired from there on December 31, 2018. I think this work has been the most enjoyable I have done. The discussions were only about research, evaluation of research and its significance for humanity. A lot of discussion

takes place and of course different people have different opinions, but in most cases these have led to the reward of an important discovery. The surrounding events with symposia, lectures, dinners and Nobel parties have been very much appreciated.

10. Work with Astra

For a long time I have been a consultant for Astra but also for other companies. Over the years, Astra has contributed research funds, but in total the funding of research from industry never amounted to more than 10% of the total budget. Astra has recruited quite a few doctors who were trained with us. I was invited by Claes Wilhelmsson and Jan Lundberg to the head office on Birger Jarlsgatan in about 1988 for lunch and discussion and they offered a four-year grant of good scope as a kind of support that could be used freely in research.

As a consultant, you often join the project groups and contribute with advice. During the 1980s at Astra, this was very stimulating with creative work in small groups. The reception at Astra in Gothenburg knew who you were and the atmosphere was quite familiar. But after the merger with Zeneca, the administration and bureaucracy increased manifold.

During the 30 years we have had research collaboration with AstraZeneca, Tommy B Andersson has been the contact person and he was also an adjunct professor at KI for 8 years. Together, we have published 16 works and solved many problems discovered during the development of various drugs and, among other things, identified a new enzyme system in the mitochondria (MOSC) that reduces amidoximes, including Exanta, and identified two completely new mechanisms for drug-induced metabolism that have caused confusion for including omeprazole and a drug candidate in oncology. Overall, this collaboration has been extremely stimulating and academically rewarding.

11. Research training in developing countries (KIRT)

My doctoral student Göran Skoglund got involved a lot in postgraduate education in developing countries. Researchers who were interested in intensifying the exchange between KI and developing countries pushed through the formation of the Karolinska Institutet Research and Training Committee (KIRT). KIRT had a board with Sune Bergström, Hans Wigzell, Marc Bygdeman and others who gave charter and experience to the business. Göran Sterky, who was a pediatrician for many years in Ethiopia at Addis Ababa's pediatric clinic, was one of the driving forces. One day Göran Skoglund came and announced that they thought I would become chairman of this committee. Actually, I had no experience whatsoever of working in developing countries, but I found the idea attractive. I had a feeling that they chose me to get a better impact and recognition of the activity if a theoretical researcher led the activity. Göran Sterky had received funds to build a laboratory and research training center in Ethiopia, Addis Ababa. In April 1988, my first trip together with Göran Sterky was to Addis and I was driven to many different places for visits in different parts of Addis, including to Sven Britton's infection laboratory and clinic. We were accommodated at the Ghion Hotel which was surrounded by a beautiful garden but outside this the slum was complete. For me, the strong sun from the zenith and the hikes in this new environment were quite special. The war came closer and every year the number of roadblocks and soldiers in the city increased until the guerrillas took over in 1993. Politically, the situation was very strained and the government rather weak. During the period, the Eritrean guerrilla mobilized more and more activities and every year

they came closer to the capital. When I arrived one year, the entire Ghion hotel had been blown up and we switched to staying at the Hilton Hotel.

I had the idea that with the Sarec/Sida money allocated, a top laboratory would be built in premises between the different departments, biochemistry, physiology, pharmacology, microbiology and pathology. So it happened and many people were engaged from KI for the transport and installation of top equipment for the diagnosis of diseases and for mechanistic analyzes for the emergence of these. The work was done in collaboration with some preclinical institutions at KI and from the Ethiopian side a man named Legesse Zerihun was the coordinator of the project. The laboratory was to be the center of the master's education that we built in Addis and the idea was that students and teachers from different institutions would come together in this laboratory. However, it did not turn out as I had imagined. The willingness to cooperate between many of the Ethiopian teachers was not the best. When I visited the laboratory one year, I was approached by a horde of students who were very unhappy that they could no longer enter the laboratory. One of the prefects had arbitrarily decided that the lab should be his and changed the lock with a key that only he had. A lot of work had to be put into solving this problem. Another year, the prefects had completely sonically started entering the laboratory and tampering with devices for their own department, which again led to the students not being able to complete their projects. In retrospect, perhaps my experience of developing countries in general and Ethiopia in particular was not sufficient. I got the impression that many of the Ethiopian teachers were very stubborn by nature and they were simply not used to collaborating in a way that occurs in European laboratories, for example.

The recruitment of students for the Master's program was often an adventure and took place in collaboration between the medical faculty in Addis and KI. I had been involved in education to some extent and as a lecturer had meetings with two educational consultants that the then government/UKÄ placed at KI in the 70s to ensure that the educational level was raised. This educational activity was not viewed kindly by the researchers and was at the time in the dark. The consultants did their best to implement pedagogical innovation but had a very difficult time getting a response. I was called to lunch meetings with them held in a basement room in the Berzelius laboratory at KI. One of them, Dick Mårtenson, or Mårten Dickinson as he was called by some Americans, was a nice and very enthusiastic person with whom I discussed a lot. For the recruitment of students in Addis, I thought that instruments would be used here that were not considered suitable in Sweden and which I thought could also be useful in the recruitment of Swedish students later. With the help of Dick, I ordered all the intelligence and comprehension tests etc. that he could come up with. Before I wanted to bring them to Addis, I thought I would test them on my own research group. Thus, we all sat one afternoon and solved the tests. The result for us was that the worst researcher from a production point of view had the best overall score on the tests.
In Addis, they were quite well implemented and they formed part of the basis for the recruitment.

In Addis, they were quite well implemented and they formed part of the basis for the recruitment.
Otherwise, interviews with the candidates were conducted in a rather unpleasant atmosphere where the Ethiopian teacher often had a very boring and condescending attitude. One of the students I recruited was Eleni Aklillu, a pharmacist who did very well in the tests. She became my Master's student and PhD student and she brought 160 blood samples from Ethiopia for genetic analysis,

which enabled the conclusion that the genetic variability in the P450 genes had to some extent originated in dietary selection.

During these processes, the war between the Eritrean guerrillas and the Ethiopian state continued. I worked for the government side. My father Axel, who was a surgeon and later a gynecologist, had been a field doctor on two occasions, partly during the Finnish Winter War and the subsequent war. He volunteered in this, repairing soldiers injured in war. At the age of 82 in 1992, he realized that he would repeat this type of activity but then for the Eritrean guerrillas. He was stationed in southern Sudan where troops advanced during the night to avoid detection and hid in the valleys during the day under cover, allowing time for operations that he carried out. He spent a long time there, longer than relatives in Sweden expected and without contacting them. I myself did not know about this activity at the time but realize that we were active in the war on opposite sides of the conflict and that the side my father was on won the war.

In the end, the Eritrean guerrillas won in 1993 and the government was replaced by a very left-wing radical government. My main counterpart in Ethiopia, Legesse Zerihun was imprisoned for a year. When he came out, the new government had taken a stand against our Masters program and research center, mostly for political reasons because the previous government had supported this. We found this at KI and at SIDA/Sarec to be very unfortunate with so much money invested. I went down on a rescue operation in 1993 and met Legesse Zerihun who told me details. He had arranged for me to meet their new minister Asrat Woldeyes to try to persuade him to continue. The meeting was arranged one afternoon. Legesse Zerihun was allowed to attend but forbidden to speak. Asrat was a very intelligent and intense person. The meeting was probably the most demanding I have ever been a part of. It started with Asrat having a 20 min monologue with political and health based arguments why we should not continue. During those 20 minutes I took notes, after which I gave a 15 minute monologue about all the benefits and opportunities that could emerge if we continued. Asrat then spoke again for 15 min and the meeting continued in this style. After many hours, we were able to agree on still having a symposium with the government and SIDA representatives and KI representatives. Asrat suggested that we have the meeting in the government's summer residence Wondo Genet located in southern Ethiopia.

So on the next trip we had a Swedish delegation of 4 people and were assigned a bus with other participants that would take us to Wondo Genet during a 6 hour journey. The roads were bad and the traffic out of control. We drove past a recently stripped minibus that collided with a truck that removed everything in the bus except the bottom plate. Dead people lay scattered in the ditches. In Wondo Genet it is rainforest and I was accommodated in a hut/bungalow with a hole in the roof so the rain filled the floor. The monkeys darted about on the roof and gave the whole thing a strange atmosphere.

The meeting was held in a room without windows and with about 15 people from the government side and the university. The meeting was attended by Mikael Holst who was coordinator for the Ethiopia program, Irene Persson and representatives of SIDA/Sarec. The discussions were loud and the hosts had a lot of political arguments. We tried our best for a long time but failed to find a solution before my 6-year term as chairman of KIRT ended

The program has continued with a PhD education program directed by Mikael Holst, but unfortunately all the trained doctors have moved to other countries. The project was probably a bit naive and I myself, as a leader, probably did not have the right training regarding developing country issues and conditions in Ethiopia to be able to smoothly facilitate the development of the program. However, the end result was 25 educated Masters students and 8 PhDs.

Within KIRT, we also started postgraduate programs in Vietnam, Estonia and Latvia, and maintained the established program in South America. As KIRT chairman, I worked closely with the coordinator/director of studies for KIRT, who was first Göran Skoglund and then Johan Carlson for a few years, former head of the public health authority. A clear memory I have from a trip to Vietnam with Johan Carlson and Ingeborg van der Ploeg was our stay in Hanoi by bicycle taxi. One day we were going to visit an institute outside of Hanoi and a car came to pick us up at the hotel.
It stopped on the road and the driver said that the reason was that another person would arrive. His name is Henry Strobel, do you know him? I answered, of course I know him. When he got into the taxi it seemed natural to say "Henry Strobel I presume". Henry was a colleague I met often at conferences in Stockholm on occasion, who worked in Houston with P450 enzymes but was a priest on the weekends.

I was also scouting in Pakistan from the Aga Khan University in the capital Karachi but also up in the countryside north of Lahore. I was driven there because the politicians wanted support for the activities there and was met with enormous poverty. The villages consisted of houses in ruins, cows walking around in the middle of the villages and extremely thin and poor people around. I was wearing a suit and they flocked around me thinking I was a medicine man who was going to cure them. Their pharmacy consisted of a bowl with lots of different pills in many different colors. They could inject various antibiotics and tranquilizers without permission. In 2005, an agreement was signed between KI and Aga Kahn University in Karachi for a collaborative program.

In the Baltics there were formal meetings, but organized people and good exchange programs were started both in Tartu and Riga, largely organized by the paediatrician Tommy Linné.

In South America there was a large turnout. SIDA and Sarec were invited to a gathering in Buenos Aires to go over KIRT's research training project. This had been going on for a few years and had been very successful. Ernest Arenas and Carlos Ibanez were a couple of researchers from this program who established elite research at KI and built large successful groups and participated in the Nobel work. Many projects dealt with different parasites and how these could be treated. One evening we were invited to President Menez, but just before that the Israeli embassy was blown up and the president cancelled the event. The South America project was perhaps KIRT's best.

Hans Rosling, who succeeded me in 1994 as chairman of KIRT, was perhaps not so active on the administrative side, but he exuded a lot of enthusiasm and brought an agreement with Leningrad and Belarus to port together with Tommy Linné.

12. The research

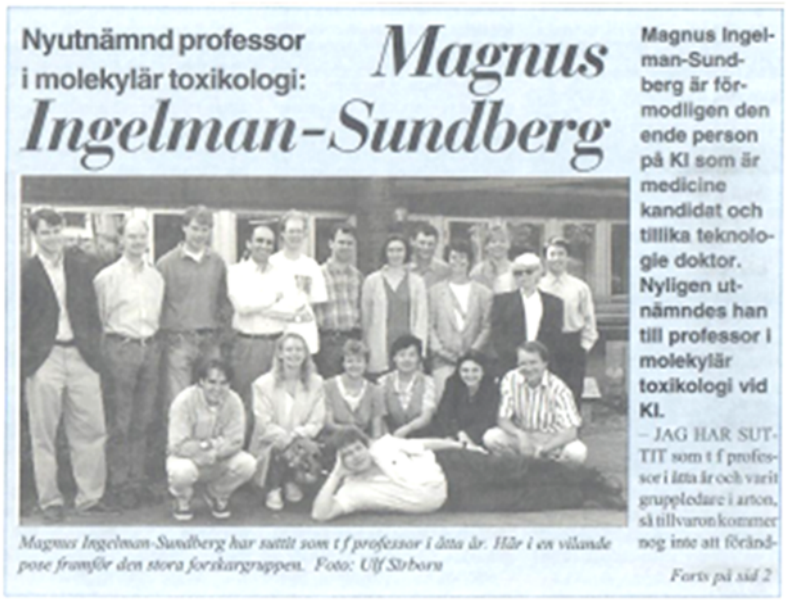
Research has been central to professional activities. A summary of the research up to 2015 appears in an interview with me in the journal Trends in Pharmacological Sciences https://pubmed.ncbi.nlm.nih.gov/25542077/ .

12.1 Research logistics

I formed my own research group in 1979 after a separation from my supervisor and was supported by Håkan Eriksson to move from Gamla Kemikum to the Berzelius Laboratory. The biggest problem for a young researcher is to become self-sufficient, and for that external support is of course important. Furthermore, to have colleagues who can inform about the problems of research logistics and be important for the recruitment of research funds. In the beginning, I collaborated a bit with Hans Glaumann concerning a new way of making membrane vesicles that contained the components of the microsomal electron transport chain. And his early support via, among other things, the Cancer Foundation was a springboard for the research to get started.

During the course of research, support and scientific interactions are essential for me, who function worse without social contacts that often provide energy and stimulation. In this context, Hans Jörnvall has been a great enthusiast at chemistry, both as a collaboration partner for one of the most cited publications, but also as head of the department. After a meeting with him, one felt uplifted.

In 1996, Sven-Erik Dahlen, the physiologist, and I moved from MBB to IMM for professorships announced by Sten Orrenius. The group of about 18 people came along and KI bladet made a report:



Nyutnämnd professor i molekylär toxikologi:

Magnus Ingelman-Sundberg

Magnus Ingelman-Sundberg är förmodligen den ende person på KI som är medicine kandidat och tillika teknologie doktor. Nyligen utnämndes han till professor i molekylär toxikologi vid KI.

– JAG HAR SUTTIT som t f professor i åtta år och varit gruppledare i arton, så tillvaron kommer nog inte att förändMagnus Ingelman-Sundberg har suttit som t f professor i åtta år. Här i en vilande pose framför den stora forskargruppen. Foto: Ulf Ströbom

Forts på sid 2

Figure 5. The research group in KI-bladet in connection with the move from MBB to IMM in 1986.

We arrived at new custom-made premises in the Scheele laboratory on the ground floor. The research was extremely intensive and the lab was in full activity from 9 in the morning until 10-11 pm in the evenings. At the same time, I had 13 registered doctoral students. Everyone did their dissertation and thought it was good. Today this would be an impossibility as according to the rules a

researcher cannot have more than a couple of registered PhD students. In my opinion, some researchers cannot supervise one PhD student while others can supervise dozens. As in many other contexts today, individual considerations are not taken into account, but the regulations provide the framework. Some people who have been important for and during the research work.

I met Pierluigi Nicotera as a member of the grading committee at his defense in 1986. We came to have very creative gatherings which included dinner at Capri Due every to every two weeks but also meetings in Leicester, Konstanz and Bonn where he moved after the KI period. We talked a lot about different types of research projects and a lot about our own excellence, but no direct collaboration emerged.

Around that time, I had an ambition to start a new research focus on intracellular signaling. Among the first PhD students were Anders Hansson and Göran Skoglund who started with this and to gain perspective the so-called Pizza Group was formed with Bertil Fredholm's and Per Olof Berggren's research groups. The pizza meetings that lasted until late at night for a couple of years were extremely creative and stimulating and sometimes involved external guests such as Yasutomi Nishizuka, the discoverer of protein kinase C. In this vein, I applied to the Research Council for two grants, one for drug research and one for the action of protein kinase C. The council took a strong position that I should stick to the pharmaceutical project and not enter new territory, after which the activity in signal transduction ceased.

After Folke Sjöqvist's and my work in the Linjenämnden, we started research collaboration initially because we expressed that it was fun to work together. I liked Folke very well, a visionary and enthusiast, regarded by some as arrogant. Perhaps his attitude meant that some did not appreciate him as much as he really deserved. His twin studies in the 1960s concerning the inheritance of nortriptyline metabolism and thus the identification of genetic factors responsible for interindividual variations in drug metabolism were groundbreaking but never received the status they deserved. Instead, Michel Eichelbaum (who was in Folke's laboratory when he did the sparteine metabolism experiments with input from Leif Bertilsson) and Bob Smith, who measured the metabolism on himself and was defective for the CYP2D6 gene, are the ones most associated with this discovery. The collaboration with Folke lasted for about 10 years with regular meetings between the research groups where the atmosphere was always at its best, sometimes maybe a little too much. Creative discussions were held a lot between Folke, me, Inger Johansson, Leif Bertilsson, Lars Gustafsson, Marja-Liisa Dahl and others and the collaboration was enormously fruitful largely due to the fact that the research groups, one genetic basic science and one clinical pharmacological worked so synergistically together. Inger Johansson was responsible for the molecular biology part and her efforts were of enormous importance for the identification of various clinically important variants of P450 genes, specific duplication and amplification of CYP2D6. A talent that she has applied in the lab over several decades. The research was financed, among other things, by the NIH without the involvement of American researchers.

Börje Uvnäs started KI's master's course in toxicology in 1976 and I was asked to take responsibility for a 5-year course in molecular methods in toxicology, which we arranged every two years for 20 years. In the first group there were many talented students such as Marie Vahter, Rune Toftgård and Jim Halpert, all of whom received professorships relatively soon after this training. One of the more

provocative students was Jim Halpert who, perhaps rightly, complained that they had to use substandard equipment to purify protein until 10 pm in the evenings. He later became a Masters student with me and we had really creative discussions and research projects together. Over time, he became one of my best friends and I have followed his personal and professional development as a professor, including visits to the universities of Tucson, Galveston, San Diego and Connecticut until today.

Around 1990, more and more of the human genome sequence became clear and my doctoral student Mikael Oscarsson used this information to identify new cytochrome P450 genes. These were cloned and the functions investigated. In total, we published 28 publications together and he was an exemplary research supervisor in the lab before becoming a clinical geneticist at KS via a post doc in Basel with Urs Meyer. Urs is an incredibly enthusiastic and visionary researcher and in the years since 1992 we have continuously socialized in different contexts in different parts of the world, although we have never directly collaborated to a significant extent.

One day in May 1985, a medical student came up to my room and wanted to start research. It was Erik Eliasson who, among other things, was interested in mechanisms in diabetes. We did 20 works together concerning, among other things, findings of CYP2E1 for the gluconeogenetic action of acetone and identified mechanisms behind substrate stabilization of P450 via specific phosphorylations, an important mechanism in the regulation of P450 levels in the liver. In total, we produced 20 articles together. We became close friends, this even after 37 years and activities include golf, bowling and tennis.

I was sitting at home watching the Wimbledon final between Stefan Edberg and Boris Becker in July 1988 when the phone rang. Moderately amused, I went to answer and the handset said "Hi I am Martin Ronis, I want to make a post doc with you". Aha I said and continued to watch the tennis and was not interested. He called again at a later date and completed a successful post doc which continued with a long-term collaboration with his supervisor at the University of Arkansas, USA Tom Badger and over the years developed strong friendships with both. Together we did 25 works that showed, among other things, the importance of oxygen radicals from ethanol-inducible CYP2E1 for the development of liver cirrhosis and for the metabolism of ethanol and substrate-mediated control of degradation mechanisms for the P450 enzymes. We received a joint US grant from the NIH and visited frequently. Martin Ronis first received a professorship at the University of Arkansas and is now a professor at the University of New Orleans. Also participating in the program was Kai O Lindros from Helsinki, whom I met at a disco in Finse in the Norwegian mountains at 01:30 at a conference, who became a very good friend and co-author of about 15 publications.

A stong PhD student was Collen M Masimirembwa. He was sent to the lab by his supervisor Julia Hasler and arrived on a dark and cold January day in 1993. He brought blood samples from Zimbabwe and was to identify African-specific mutations in the CYP2D6 gene. He was very unhappy at first and became a little happier when he acquired a tape player that played African music. After a year of work, we were able to identify CYP2D6*17, which causes defective drug metabolism of clinical value for, among other things, malaria treatment. Collen is a great visionary and man of action. After his defense, he was a post doc at Uppsala University and then principal scientist at Astra Zeneca in Gothenburg for 10 years, after which he moved back to Africa and built up a large research

organization, the African Institute of Biomedical Science and Technology (AiBST), of which he is the director and develops personalized medicine with a focus on Africa (described in the book Masimirembwa C, The AiBST Story (2022)). He is also Professor of Health Sciences at the University of the Witwaterstand in Johannesburg, South Africa.

Another very talented person is Volker Lauschke, who came as a post doc from EMBL in 2015. His bioinformatics skills allowed us to solve the question of the quality of our liver spheroids in 2015, and we have since had a very fruitful and stimulating collaboration concerning toxicology, 3D liver - spheroids and pharmacogenetics and together wrote about 40 works which are generally highly cited. Volker, who has become a very good friend, now has his own research group in Biomedicum and is about to become a professor. We also started a company together in 2016, HepaPredict AB.

Sarah Sim was an employee for about 20 years. During her thesis work, she was the project leader for a study that resulted in the discovery of genetically controlled ultra-fast metabolism of CYP2C19 substrates, e.g. antidepressants and cardiovascular active drugs. She worked in parallel as responsible for the nomenclature of P450 gene variants, a website started by Mikael Oscarson. With gusto, she held worldwide nomenclature issues until 2017 and later it was transferred to the USA with NIH support to The Pharmacogene Variation (PharmVar) Consortium (https://www.pharmvar.org/. Our collaboration, where she was often responsible for various project, resulted in 27 joint publications and developed into a good friendship. She now holds a senior management position at SIS.

Another important person in the research has been Cristina Rodriguez-Antona. She did her doctorate under tough conditions in Valencia before she came as a post doc and in the years 2003-2018 we published 19 important works with a focus on oncological pharmacogenetics. Cristina's good analytical skills and high work capacity were very stimulating for the business.
Hans Jörnvall and Hans Wigzell have been stimulatingly optimistic people. Hans J as a mentor and stimulus during the establishment phase of the research group at MBB and Hans W for countless witty and stimulating lunches that all had great creativity. On one occasion where Rune Fransson was also present, Hans W characterized the event in a class with Gökboet. Hans W and I had a couple of projects going on, one concerning P450 humanization of mice and one concerning the use of tumor-specific CYP2W1 enzyme for targeted cancer treatment.

Peter Reichard became very interested in the P450-dependent mechanism for the production of oxygen radicals that we described in 1984. We had long discussions after which he himself began to study the radical formation in the enzyme ribonucleotide reductase that he had identified. He would often turn up unannounced to my lab wearing a white coat and rummage through one of our lab freezers for chemicals I had used in the radical research he was interested in. For the radical studies he lent his EPR machine and was happy until a couple of Italian researchers in my lab came over one evening to run their experiment but in order to do so they dismantled his entire experimental set up to be equilibrated during the night. The following morning he called and shouted something that sounded like "damn bandits". The anger passed and after a few months he said I would have the EPR machine transported to my lab. But after another year or so he called and said he regretted it and the machine was transported back to Biokemihuset.

12.3 The move to the FyFa department

The research went well and the research group expanded to 30 people. After 6 years at IMM, there would be a new prefect election. The staff voted and I received a large majority (75%) of the votes. However, the applied part of IMM's activities, governed by the environmental medicine board, did not like me as being too critical of environmental medicine thinking and working methods, and vetoed it. However, I thought I was invited and felt that I had the staff's trust, but perhaps I should still look elsewhere where there was research more in line with what we were doing. The research area closest to us was actually pharmacology. Stefan Eriksson was the newly elected prefect there. Stefan and I had worked together in the Ethiopia project, among other things, together down in Addis Ababa and I knew him quite a bit. He and I had a special jargon of mutual arrogance under the guise of humor. One day I called him on the mobile and heard about the situation of moving the research group. We decided to meet at a restaurant to discuss. I was lucky, because the pharmacologist had just been emptied of a research group whose leader had retired and there were premises that, however, had to be rebuilt. We met in secret another dark night in November 2005 at Capri Due and began to negotiate. It went well and around eleven o'clock he wrote on a napkin 2.5 k, which was the base grant he offered plus remodeled premises and other things. Stefan started project MIS which was successful as we were able to work in an integrated manner with the architect and get the premises as we wanted. The project lasted a few months and in March 2006 we moved and celebrated with the inauguration. At IMM, they had organized a farewell function where it felt strange to shake hands with all the colleagues you had worked with a lot who lined up for a personal farewell before leaving the room and who you then largely never saw again. It took 8 years before I physically visited IMM again. For us, it was stimulating to come to FyFa with many research-hungry people with the same interest as us.

On May 4, 2018, we moved from Farmakologen to Biomedicum. The advantages of Biomedicum were many: very large opportunities for interactions and utilization of the core lab and equipment. The disadvantages were that the rental prices to begin with were much higher than what we had in the old premises and the house as such was oversized in relation to the possibilities that were believed in 2013. It was assumed that when the house was designed, many strong groups would be recruited from outside that would contribute to the premises costs, but conditions changed in the meantime and this did not become the case to the extent desired. Me, Mats Wahlgren and Jesper Haeggström convened several meetings in Eva and Georg Klein's lecture hall for discussions between Biomedicum's researchers and Ki's management, from the rector and the director of administration, concerning the situation that had arisen and how this could be resolved. Over time, the situation has stabilized.

Figure 6. On May 4th 2018, we moved from the pharmacologist to Biomedicum block 5B. My writing room in the foreground and Aula Medica in the background.

13. Research results

To summarize the discoveries we made in our lab, I provide below the basis that was given for the nomination for the R. T. Williams Distinguished Scientific Achievement Award, which I received in July 2022.

1. CYP2E1 in ALD. The mechanisms underlying alcohol-induced liver disease (ALD) were largely unknown. The background was that we found a P450-dependent hydroxy radical-mediated oxidation of ethanol in our in vitro systems. In August 1981 at a conference in Tokyo, MJ Coon presented evidence that there was an ethanol-induced P450 enzyme. I found that We purified and characterized CYP2E1 (Cytochrome P450 2E1) and found that the enzyme produced a large amount of reactive oxygen species in the absence of substrate (a) and Gunilla Ekström's work showed that the enzyme through its production of ROS induces lipid peroxide oxidation (b). After gaining this knowledge, we established contacts with Samuel W French (UCLA). Using his in vivo rat model of ALD, we were able to show, in a series of 26 papers, that inhibition of CYP2E1 protected from ALD (c) and that CYP2E1-dependent radical formation causes an autoimmune response (d) and that ALD was strongly induced in transgenic Cyp2e1 mice (e). This forms a basis for the development of new drugs against ALD as described in Harjumäki et al., 2022. CYP2E1 was also found to be important in NASH (f).

a. Ingelman-Sundberg and Johansson J. Biol. Chem 259 (10) 6447-6458. (251 citations)
b. Ekström and Ingelman-Sundberg Biochem Pharmacol: 38:1313-1319, 1989; (461 citations).
c. Morimoto et al., Hepatology. 1995;21:1610-7. (152 citations).
d. Bardag-Gorce et al., Gastroenterology. 2002 123:325-335;
e. Butura et al., J Hepatol. 2009;50:572-83;
f. Weltman et al., Hepatology. 1998 Jan;27(1):128-33. (469 citations)

2. First example of duplication and amplification of active human genes. In 1993, we identified the first example of a stable gene duplication, as well as stable gene amplification, in the human genome (a). The background was that in addition to poor metabolism of many drugs such as antipsychotics and antidepressants, some individuals also exhibit rapid metabolism. By screening gDNA from such individuals, we were able to make this identification in the CYP2D6 locus and link it to the ultrarapid metabolizer phenotype (a, b). This is of clinical importance, as individuals carrying multiple CYP2D6

gene copies metabolize some drugs too rapidly, with reduced drug efficacy as a result. For example. in individuals taking codeine that is metabolized to morphine by CYP2D6, the ultra-rapid metabolism can cause CNS depression and even death. This ultrarapid metabolizer phenotype is now being taken into account in many clinical trials and under treatment with drugs that have a pharmacogenomic label for this phenotype (see http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm). The finding also made it possible to infer a diet-dependent selection of CYP2D6 genotypes, based on the ability of CYP2D6 to metabolize plant toxins. Those with an ultrafast phenotype were more likely to survive famine periods in Africa due to higher capacity to detoxify plant toxins (b). We also described the plausible mechanisms for the gene amplification in Gene (c).

This was a result of the extremely successful collaboration between Folke Sjöqvist's clinical pharmacology group and our more molecular genetics-oriented group, and our collaboration extended to the identification of a variety of clinically important genetic variants in genes encoding drug-metabolizing enzymes (see also below). This time between 1990 and 2000 can probably be considered as perhaps the most stimulating in research. In the mid-2010s I was interviewed by TiPS regarding my research career and Folke Sjöqvist wrote about his character in BCPT in connection with a Nordic award he received. Unaware of each other, in these summary writings we had mentioned only one name each, which was each other's.

a. Johansson et al., Proc. Acad Natl Sci (US) 90:24, 11825-11829; 1993 (565 citations)
b. Ingelman-Sundberg, M, Pharmacogenomics J. 5: 6-13, 2005; (744 citations)
c. Lundqvist E, et al., Gene. 1999 Jan 21;226(2):327-38

3. Identification of two common ultrarapid CYP2C19 alleles (CYP2C19*17 and CYP2C:TG). In the CYP2C19 locus, we identified the first ultra-rapid metabolizer phenotype by examining gDNA from subjects with rapid S-mephenytoin metabolism identified by Leif Bertilsson. This was found to be due to a mutation in the upstream 5´-untranslated region, causing higher expression of the enzyme (CYP2C19*17). This finding is of importance for several large patient groups, as the mutation causes far too low plasma concentrations of SSRIs and other CYP2C19 drugs, and for increased activation of Plavix to its active metabolite, leading to an increased risk of bleeding. Recently, together with Espen Molden's group, we identified a novel ultrarapid CYP2C haplotype (CYP2C:TG) (allele frequency 17%) (b, c) that causes higher rates of drug metabolism than CYP2C19*17. For preventive genotyping of CYP2C19 activity, it is very important to include this variant.

a. Sim et al., Clin Pharm Ther 79; 103-113; 2006; (519 citations)
b. Bråten et al., Clin Pharm Ther. 2021;110:786-793.
c. Bråten et al., Clin Transl Sci. 6 June 2022. doi: 10.1111/cts.13347.

4. Identification of several frequent defective CYP2D6 alleles such as CYP2D6*2, CYP2D6*9, *10, (a) CYP2D6*17 (b), CYP2D6*29. (d)
The collaboration with Folke Sjöqvist's group led to the identification of many new common variants of CYP2D6 with regional accumulation in certain areas that are now of great importance for prediction of CYP2D6 activity in vivo.

a. Johansson et al., Mol Pharmacol. 1994;46(3):452-9. (407 citations)
b. Masimirembwa et al., Pharmacogenetics. 1993 3(6):275-80
c. Johansson and Ingelman-Sundberg Toxicol Sci. 2011;120(1):1-13.
d. Wennerholm et al., Pharmacogenetics. 2001;11(5):417-27.
e. Oscarson et al., Mol Pharmacol 1997 52 (6), 1034-1040 (118 citations)

5. Cloning of many new human cytochrome P450 genes including CYP2W1, tumor-specific enzyme that catalyzes activation of procancer drugs.
After the first draft of human genome sequences, we cloned and characterized new P450 genes such as CYP2U1, CYPS1, CYP2W1, CYP3A43 largely driven by Mikael Oscarson. Of particular interest was CYP2W1 which was cloned and characterized by Maria Karlgren was found to be specifically expressed in human tumor tissue and where we, in collaboration with Laurence Patterson, developed drugs that are activated by the enzyme that kills the tumors (f). CYP2W1 was also found to be a prognostic factor for colon cancer (g).

a. Westlind et al., Biochem Biophys Res Commun. 2001 Mar;281(5):1349-55 (246 citations)
b. Rylander et al., Biochem Biophys Res Commun. 2001 Feb 23;281(2):529-35
c. Karlgren M, et al., Biochem Biophys Res Commun. 2004 Mar 12;315(3):679-85.
d. Karlgren et al., Biochem Biophys Res Commun. 2006 Mar 10;341(2):451-458
e. Sheldrake et al., J Med Chem. 2013;56(15):6273-7.
f. Travica et al., Clin Cancer Res. 2013 19(11):2952-61.
g. Edler et al., Eur J Cancer. 2009 45(4):705-12.

6. Higher CYP2C19 expression in the fetal brain causes anxiety and depression in adulthood. When screening 1,740 twins in collaboration with Nancy Pedersen, we found that individuals who lacked functional CYP2C19 enzyme showed a much less depressed state (a). We used a transgenic mouse CYP2C19 model developed by AstraZeneca for pharmacokinetic studies and found that overexpression of CYP2C19 caused reduced hippocampal volume and increased stress and anxiety, as well as less immature neurons in the hippocampus (b). It was found that these changes were induced in the fetus when the CYP2C19 enzyme is expressed in the brain. In a large multicenter study, we have found that also in humans, the size of the hippocampus relates to the CYP2C19 phenotype (c). These findings are important for understanding mechanisms in depression, with possibilities for new types of pharmacological interventions. Within this project, Marin Jukic has been of enormous importance. He came to the lab as a post doc from Israel with one publication in his bag and has since developed into a fantastic researcher over a period of 6 years. We have written 17 works together, many published in journals with very high impact factors.

a. Sim et al., Am J Med Genet B Neuropsychiatr Genet. 2010;153B:1160-6
b. Persson et al., Mol Psychiatry. 2014;19:733-41
c. Jukic et al., Mol Psychiatry. 2017 April 18. doi: 10.1038/mp.2017.93

7. The role of CYP2D6 and CYP2C19 polymorphism in the metabolism of antipsychotics and antidepressants. Using very large cohorts of patients, we were able to present drug dose dependence for optimal treatment and a higher incidence of drug switching among carriers of poor

and ultrafast phenotypes of the enzymes, a work driven largely by Marin Jukic in close collaboration with Espen Molden. This applies e.g. escitalopram (d) and risperidone (c). We also found that the phenotype is stable in specific patients regardless of the type of drug they are given (a). We identified 5 different psychoactive drugs where applications of preventive genotyping in the psychiatric clinic are clear (b).

a. Jukic et al., Clin Pharmacol Ther. 2021;110(3):750-758
b. Milosavljevic et al., JAMA Psychiatry. 2021 78(3):270-280.
c. Jukic et al., Lancet Psychiatry. 2019;6(5):418-426.
d. Jukic et al., Am J Psychiatry. 2018;175(5):463-470.

8. Discovery of the importance of the polymorphic nuclear protein NFIB in the regulation of CYP2D6 and metabolism of antipsychotics. A variant of NFIB TC with 5% allele frequency was found to cause increased CYP2D6 activity in psychiatric patients, causing an ultrarapid phenotype among normal metabolizers. The mechanism was found to involve less expression of the NFIB protein in hepatocyte nuclei in carriers of NFIB TC, which in turn causes less inhibition of NFIB in the expression of CYP2D6.

a. Lenk et al, Clin Pharmacol Ther. 2022;111:1165-1174.

9. Identification of the importance of rare genetic variants causing interindividual variations in drug metabolism. Extensive bioinformatic analyzes showed that approximately 4-5% of interindividual variation in drug metabolism is caused by rare mutations in the P450 genes. This has been reproduced using the UK Biobank.

a. Westlind-Johnson et al., Clin Pharmacol Ther. 2006;79(4):339-49.
b. Fujukura et al., Pharmacogenet Genomics. 2015;25(12):584-94.
c. Kozyra et al.. Genet Med. 2017;19(1):20-29.
d. Ingelman-Sundberg et al., Hum Genomics. 2018 25;12(1):26.
e. Lauschke VM & Ingelman-Sundberg M. NPJ Through Med. 2020 5;5:9 and Clin Pharmacol Ther. 2018;103(5):745-748.

9. Development of an in vitro spheroid system to study human liver function.

A novel 3D liver spheroid in vitro system was developed (a) and shown to exhibit transcriptomic, proteomic, and metabonomic characteristics highly similar to the liver from which the cells originated. We have used this system in our lab for successful prediction of drug toxicity (a, b), drug cholestasis (d), for regulation of liver regeneration (e), and in Volker's lab for mechanisms of action of liver viruses and Coc-SARS-2 (f).

a. Bell et al., Sci Rep. 2016 6:25187 (336 citations)
b. Hendriks et al., Toxicol Sci. 27 2019:kfz195.
c. Cordero-Herrera et al., Proc Natl Acad Sci U S A. 2019;116(1):217-226.
d. Vorrink et al. Toxicol Sci. 2018;163(2):655-665
e. Oliva-Vilarnau et al. Adv Sci (Weinh). 2020;7(15):2000248.
f. Stebbing et al., Sci Adv. 2021;7(1):eabe4724.

10. Development of an in vivo-like human spheroid system to study drug-induced stress responses and diet-induced steatosis and NASH and its mechanisms and treatment.

Using the novel 3D liver spheroid system, we were able to develop the first versatile in vitro system for the study of fat-inducible steatosis (a) and NASH (b), investigate underlying mechanisms and demonstrate its treatment with specific anti-NASH compounds in a work driven by Tracey Hurrell, a post doc from South Africa. In addition, we identified novel markers of drug-induced ECM stress in the form of tags (c).

a. Kozyra et al., Sci Rep. 2018;8(1):14297.(123 citations)
b. Hurrell et al, Cells. 2020 14;9(4):964.
c. Pridgeon et al. Cells. 2022;11(10):1597.

11. Novel EGF signal transduction mechanism of importance for drug-induced expression of CYP3A4 and previously an indirect induction of CYP1A by omeprazole.

From studies of drug development in oncology, it was found that a certain new anticancer drug failed further development due to autoinduction of CYP3A4, even though animal and cell culture studies did not produce any induction. Using the spheroid system, we were able to identify a new mechanism for CYP3A4 induction that does not involve direct activation of PXR or CAR, a work in which Delilah Hendriks has had a major role (a). A similar kinase-dependent regulatory mechanism has previously been found for CYP1A induction by omeprazole by Maria Backlund (b,c). For CYP2E1, we identified a ligand- and kinase-dependent posttranslational mechanism as the main mode of enzyme regulation (d).

a. Hendriks et al., Clin Pharmacol Ther. 2020;108(4):844-855
b. Backlund et al., J Biol Chem. 1997;272(50):31755-63 (109 citations)
c. Backlund and Ingelman-Sundberg Cell Signaling. 2005;17(1):39-48.
d. Eliasson et al., Proc Natl Acad Sci (USA) 1990 87(8), 3225-322 (134 citations)

Citations and degrees

The research we have done has been well cited. Today 34,888 citations (WoS), and 54,147 in Google Scholar and an h-factor of 94 (WoS) or 121 (Google Scholar). Has received the award Highly Cited Researcher for 2014, 2015, 2016, 2017 and 2021 and is ranked as No. 6 top cited among all Swedish researchers in biochemistry and biology https://research.com/scientists-rankings/biology-and-biochemistry/ see). (No. 434 in the world) and ranked No. 13 in pharmacology and pharmacy in the world with special emphasis on first and last authorship https://journals.plos.org/plosbiology/article/file?id=10.1371/journal.pbio.3000384&type = printable. Received approx. 6 scientific awards, most recently the R. T. Williams Distinguished Scientific Achievement Award in 2022 and received an honorary doctorate at the University of Southern Denmark.

Main supervisor for doctoral students (33):

Anders Hansson, Gunilla Ekström, Inger Johansson, Göran Skoglund, Ylva Terelius, Erik Eliasson, Collen M Masimirembwa, Niclas Tindberg, Irene Persson, Yin Hu, Mikael Oscarson, Roman A.

McLellan, Che Fang, Etienne Neve, Souren Mkrtchian, Mats Hidestrand , Eleni Aklillu, Maria Backlund, Anastasia Simi, Tove-Rylander Rudqvist, Anna Westlind Johnsson, Jue Wang, Maria Karlgren, Sarah Sim, Ylva Edling, Alvin Gomez, Jessica Mwinyi, Louise Sivertsson, Sandra Travica, Anna Persson, Juo Gia, Delilah Hendriks, Mikael Kozyra.

Main supervisor for post docs (35).
Mariá Pitarque, Oliver von Richter, Vessela Nedelcheva, Cristina Rodriguez-Antona, Jukka Hakkola, Vita Dolzan, Seokjoo Yoon, Shin Ichii Miura, Yvonne Hoffman, Martin Ronis, Maria-Louisa Ledesma, Simon D Lytton, Vincenzo Longo, Mike Baldwin, Monica Ek, Rasmus Pedersen, Isa Cavaco, Jana Nekvindova, Irene Loryan, Sarah Sim, Maxim Ivanov, Marina Kacevska, Isabel Barragan, Volker Lauschke, Sabrina Moro, Catherine Bell, Lisa Fredriksson, Marin Jukic, Sabine Vorrink, Tracey Hurrell, Julia Riede, Sander v Riet, Katharina Klöditz, Christopher Pridgeon, Riina Harjumäki.

14. Actions against age discrimination affecting older professors
In recent years, I have been very involved in increasing the status of Karolinska Institutet's (KI's) approx. 100 older professors, professors who, upon application, have been re-employed on their own external research grants for a limited time after retirement. To begin with, the cooperation in these matters has been excellent with fruitful meetings with research dean Anders Gustafsson and rector Ole Petter Ottersen. A steering group was formed in what we called Senior Faculty (SF) which originally emanated on the initiative of professors Vinod Diwan, Anders Ahlbom and Marie Vahter at the head and which was expanded with Sven Cnattingius, Ingemar Ernberg, Jan-Inge Henter, Anders Rane, Annika Scheynius and me. The aim was to represent the older professors and counteract age discrimination. We held hearings with all retired professors and KI's management and participated in discussions about new rules for employment after retirement. Our interactions with KI's management resulted in some changes in the regulations for professors who have reached the age of LAS, but not enough, e.g. a 5-year limit was retained to continue being employed after retirement age and to be able to be a maximum of 50% employed, which many believe is age discriminatory. We did not feel support from specific parts of KI's administrative management and some of KI's 20 department prefects in this. SF has therefore continued its work.

Today, SF's steering group includes professors Ingemar Ernberg, Kristina Alexandersson, Claes Frostell, Anders Rane, Kerstin Brismar, Annika Scheynius and myself. Many creative meetings have been held within the steering group and also with the participation of approx. 50% of the older professors with the support of Barbro Westerholm. A survey was drawn up where the main question was to take stock of how much the professors who have reached retirement age contribute to KI's activity. The survey responses (79% participation) were compiled into a report that shows that the professors' non-profit work effort, in addition to the salary compensation paid from KI based on the professors' own external research grants, corresponds to approximately 50 full-time jobs. When combined with the external funding reported by the professors, it gives the university a financial boost of almost SEK 300 million per year. Retired professors are co-authors on 10% of all KI's scientific articles per year and in 18% of the articles published in journals with an IF (Impact Factor) >10. With this result as a basis, good discussions have been held with KI's management about further improvements in the employment rules and attitude towards older professors within KI. This work will continue and is relevant in a report from the Delegation for senior workforce Older have never been younger - more and more people can and want to work longer (SOU 2020:69). Here it is said

that seniors today are healthier than seniors in the past, they are more well-educated compared to previous generations, they usually enjoy their tasks and wish to continue in working life, but also that the state is the worst at hiring people after the LAS age. One wonders why an end age is needed at all? Åsa Morberg's comment on this "Senior teachers and researchers are stopped with age racism" in the university teacher clearly illustrates this concept https://universitetslararen.se/2022/06/07/seniora-larare-och-forskare-stoppas-med-aldersrasism/. In relation to other Swedish universities, however, KI is now at the forefront of this issue.

15. Final words

During the 51 years I have worked at Karolinska Institutet, I have never once regretted my choice of profession or choice of workplace. The research, collaboration with colleagues and interactions with doctoral students and students have resulted in a continuously stimulating heritage work existence. We have been fortunate to continuously receive good research funds from, in addition to KI, from e.g. NIH, EU, IMI, ERC, the Swedish Research Council, the Brain Foundation, the Cancer Foundation, which usually provide a safe base for continued research. The opportunity to switch between research, postgraduate training, administration and teaching provides a great variety in the work. But the funnest thread throughout the years has been the expected and unexpected research discoveries. With a research orientation that is quite close to the clinic, we have also been able to see the concrete clinical use of many of our discoveries. With this, I would like to finish and thank everyone at KI who helped us in this work, including all the talented TA staff, in our lab especially Åsa Nordling, Sussi Virding, Anita Norström, Ann-Louise Hagbjörk and Margareta Porsmyr.

14. Namnregister