Professor Margareta Hammarlund-Udenaes: humbled scientist shaping modern neuropharmacokinetics

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EDITORIAL

Professor Margareta Hammarlund-Udenaes - A Humble Scientist Shaping Modern Neuropharmacokinetics

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Margareta Hammarlund-Udenaes is Professor Emerita and Former Dean of the Faculty of Pharmacy at the Uppsala University, Department of Pharmacy. Professor Margareta has had a profound impact on the development of fundamental concepts in neuropharmacokinetics, and the application of these principles in CNS drug discovery and development. This theme issue is dedicated to Professor Margareta in tribute to her substantial contributions to the pharmaceutical sciences.

Dr. Hammarlund-Udenaes started as a pharmacy student in 1973 at Uppsala University in Sweden, convinced that she wanted to become a "bedside pharmacist". However, nothing of that was at the time present in the curriculum. She became very interested in pharmacokinetics, so much that she pursued a PhD where she studied the PKPD of furosemide, including its tolerance development. Her supervisor was Lennart Paalzow who became a professor in 1980 and they, together with colleagues, could develop the subject area further. When the curriculum of the pharmacists expanded it was a golden opportunity to introduce pharmacotherapy into the program, and Margareta Hammarlund-Udenaes became a devoted teacher responsible for its development, including introducing problem-based learning at the University. The development continued and since many years, Uppsala has a specific Master program in Clinical Pharmacy, inspired by both UC San Francisco and Strathclyde, Glasgow. She is very proud that she was able to be part of the development of the area that engaged her early on.

The development of Clinical Pharmacy teaching was in parallel to Margareta's scientific focus on preclinical PKPD research. She spent 1,5 years as a post-doc at UCSF under the leadership of Dr. Les Benet in 1985–87, a six-month visiting professorship with Dr. Lewis Sheiner also at UCSF in 1996–97, and six months with Professor Tetsuya Terasaki at Tohoku University in Sendai in 2004. Her research successively moved from PKPD relationships of opioids to blood-brain barrier (BBB) transport and how to interpret brain concentrations in relation to plasma concentrations of drugs. The inspiration came from Professor Paalzow and Dr. Gerhard Levy, emphasizing the unbound drug concentrations as the driver of effect. Together with the use of microdialysis as a method to measure the unbound concentrations in brain, the concepts of the unbound drug transport and partitioning across the BBB was developed, now termed Kp,uu. The concept has had a tremendous progress within the drug industry, and Dr. Hammarlund-Udenaes hopes this will improve the development of new important drugs for diseases within the CNS by investing in the drugs that actually cross the BBB to a high enough degree.

In 1999, she succeeded Lennart Paalzow as a full professor, and in 2017–2020 she was the Dean of the Faculty of Pharmacy in Uppsala. During her career she received several awards, among them becoming Fellow of AAPS in 2005, receiving the Academy of Pharmaceutical Science and Technology Nagai International Woman Scientist Award and becoming

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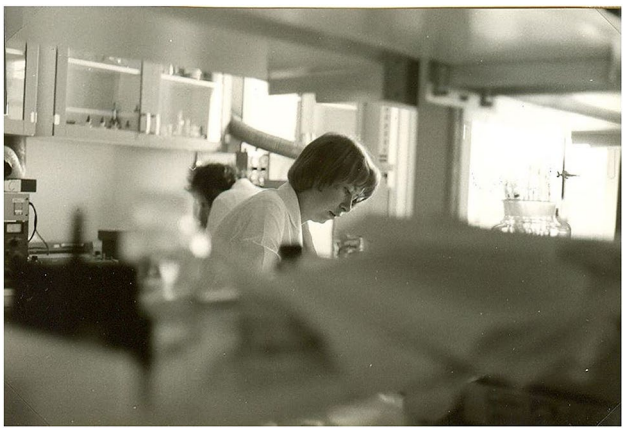
an International fellow of the Academy in Japan in 2015, an Honorary member of the Swedish Pharmaceutical Society in 2016, and the Arïens Award in the Netherlands in 2021. She also received the Rune Lönngren Award from the Swedish Pharmaceutical Society in 2021 for her development of Clinical Pharmacy.



Margareta's first experiments in the lab, Uppsala 1967.

From Lennart Paalzow

During 1979 the Swedish Government decided that a new chair in biopharmaceutics and pharmacokinetics should be established in Sweden and placed at the Faculty of Pharmacy, Uppsala university. Premises and laboratory spaces should be arranged at Uppsala Biomedical Center. The professorship for this chair was announced the following year and among the applicants I was selected and I could take up my post during the fall 1980. During the first two years I got the possibility to accept five Ph.D. students and Margareta Hammarlund-Udenaes was the first among them. These initial years were very much devoted by all of us to set up the laboratory spaces and equipment and not least to start the education program for pharmacy students in this new subject of the pharmacy curriculum. The research during coming years was very much concentrated to establish and develop pharmacokinetic principles and characteristics of old as well as new drugs. A desired goal was always to try to investigate possible relationships between drug concentration and elicited pharmacodynamic response. Margareta was immediately engaged and devoted to this research directions and become soon very clever in studying and measuring different pharmacological effects and drug concentrations in animals, which she had good use of in her coming studies on e.g. the blood-brain barrier. In 1984 she was able, as the first PhD student at the new department, with success defend her thesis for a PhD degree with Professor Leslie Benet as opponent.

During the following years, she got an appointment as senior lecturer in of her established subject, pharmacotherapy, of the pharmacy curriculum. She introduced this subject with success by using the new technique ¨problem-based learning¨ at our faculty, inspired by the rapidly growing new discipline clinical pharmacy in USA and England. In her following years, as my successor at our department and as a dean at our faculty, she has further been able to develop clinical pharmacy to be an important part of the pharmaceutical profession. In the year 1999 Margareta was selected to be my successor as professor at the department and as I understand she has through her strong leadership and successful research, especially on the transport of drugs through the blood-brain barrier, been able the further develop pharmacokinetics as one of the most important areas of pharmaceutical sciences and pharmacotherapy.

Margareta with her PhD supervisor Prof. Lennart Paalzow after receiving jubilee doctor diploma, Uppsala 2018. Jubilee doctor title earned by individuals who received their doctoral degrees fifty years earlier at Uppsala University.

From Douwe Breimer

Professor Margareta Hammarlund – Udenaes has made most significant scientific contributions to the pharmaceutical sciences in general and to drug delivery to the brain in particular. Her research has always been based on excellent innovative research methodologies and sound theoretical PK/PD theory. In 2021 she gave the annual Ariëns Lecture of the Dutch Pharmacological

Society in Leiden entitled: "From ligand-receptor interactions to whole body pharmacokinetics and back: on tissue uptake and the importance of unbound concentrations", which represented a splendid review of much of the research that she, with her PhD students, had conducted over the past 40 years. In particular the emphasis on "unbound concentrations" has been a major characteristic of her work, the "Kp,uu-concept" as she often called it herself.

She also took up leadership roles during her career by becoming Dean of the Faculty of Pharmacy at Uppsala University for several years and internationally by becoming a member of the Executive Committee of the European Federation for Pharmaceutical Sciences (EUFEPS). I have personally experienced that she is a wonderful person to interact with, both scientifically and socially. She came to Leiden regularly, in later years to collaborate with Professor Liesbeth de Lange, her "buddy" in BBB-research. It has been fascinatiing to watch the synergy between these two passionate scientists develop over the years in organizing international meetings and courses on the BBB and drug delivery to the brain. Margareta: you can look back on a most successful academic career for which you deserve a lot praise and admiration!

From David E. Smith

I first became aware of Professor Margareta Hammarlund-Udenaes through two excellent papers she published on acute tolerance development to the diuretic effect of furosemide (1,2). These papers were instrumental in helping my laboratory to understand the relationship between hydration status and the development of acute tolerance to another loop diuretic, bumetanide, which we published subsequently (3,4). However, our scientific interests, collaboration and friendship deepened significantly when my own research on peptide transporters was applied to the blood-brain and blood-cerebrospinal fluid barriers, of which Margareta was then an expert in the field. In particular, Margareta had published a seminal paper (5) introducing the concept of $K_{p,uu}$ (or $K_{p,uu,brain}$), a new parameter describing the ratio of unbound drug concentrations in brain interstitial fluid to that of unbound drug concentrations in blood (or plasma). In 2012, Margareta was very generous in inviting my graduate student, Xiaomei Chen, to visit Uppsala University, Sweden, for over one year and in mentoring her on the concepts and technical skills required to perform *in vivo* microdialysis studies. I was extremely pleased with this collaboration in which we co-authored three papers, including one where we adapted the microdialysis technique for mice and studied the role of a peptide transporter on cefadroxil distribution in the brain of wildtype and PepT2 null animals (6). I feel fortunate in knowing Margareta and in sharing our scientific (and other) views at Gordon Research Conferences, Cerebral Vascular Biology meetings, American Association of Pharmaceutical Sciences meetings, and at journal meetings for Pharmaceutical Research, where we both served as Editors. However, I must say my best memory of our friendship is when we went to see the Broadway revival of the play Hair and, to some extent, revived the great energy and music of our youth. Congratulations Margareta on an outstanding career as I look forward to continuing our friendship!

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From Elizabeth CM de Lange

Margareta was the referent on my thesis on "the use of intracerebral microdialysis to study blood-brain barrier transport of drugs" that I was to defend in 1993. At that time, microdialysis was the technique that could measure for the first time the concentration time profiles of unbound drugs in animal brain extracellular fluid, while before, at best, concentration time profiles of unbound drugs could be obtained from serial sampling of cerebrospinal fluid from the cisterna magna, or lumbar puncture in human. We started to have discussions on this and it went far more deep into the matter than what I had with others. I was very exited by the profound

and open minded attitude by Margareta. This is what I thought science should be like: not being afraid to reconsider existing paradigms, but always keep on looking for the truth.

From that discussion onwards Margareta and we had regular discussions. At a conference on microdialysis in Tenerife (1996) we were standing in the corner with our posters on CNS pharmacokinetics, while all other posters were on neurotransmitters and how these changed by drugs. After a social outing to the volcano we were sitting next to each other in the bus, and Margareta said: lets start organizing our own conference on quantitative microdialysis of drugs. Supported by the LACDR we had our first Symposium on Microdialysis in Drug Research and Development in Noordwijkerhout (NL) in April 1998.

At the Keukenhof in Lisse, during the social event of the 1st Symposium on Microdialysis in Drug Research and Development (the Netherlands, 1997).

This started a community of colleagues (friends) in this research area and many microdialysis symposia would follow, at different locations. This year, 2022, the 9th version is held in Berlin.

At the 4th Symposium on Microdialysis in Drug Research and Development in Vienna (Austria, 2003).

Margareta has been extremely supportive to me (and many others). She is an always listening, interested and helpful person that likes to interact on science as well as on personal aspects. Specifically she stand up for females and the younger ones. She indicated that it would be good for me to go the American Association of Pharmaceutical Scientists Annual meeting in 1997, where later Prof dr Ron Sawchuk (on the photo second left) had started the microdialysis focus group to promote this research area. That became a scientific home, and also further growth.

At the Cerebrovascular Biology Conference in Sendai (Japan, 2011).

With all the research that we did on CNS drug distribution into the brain, all discussions about that, and all the knowledge and insights that we gained, we thought we should teach these lessons learned and In 2010 we started the Annual Course series on the BBB in Drug Research and Development. This is a very successful series of events that, apart from scientific perspectives, also further deepened our friendship.

I have been always inspired by the research Margareta and her team performed. The explicit distinction between Rate and Extent of transport processes and the Combinatory Mapping Approach are important examples of the high quality. Those have served as real game changer in CNS drug research.

Furthermore, with all that she accomplished and what she has been honoured for, Margareta has always remained humble and has been -and still is- an inspiration for the PhD students and postdocs on CNS pharmacology in (also) the Netherlands.

From Tetsuya Terasaki

In June, 2000, Professor Margareta Hammarlund-Udenaes organized the 2nd International Symposium on Microdialysis in Drug Research and Development in Stockholm, Sweden. She kindly invited me to be a member of the scientific committee, which was the 1st international meeting for me to be a member of scientific committee. During the meeting, I was very much impressed with her outstanding leadership and warm hospitality. This meeting paved my way to the international scientific society and also intrigued the Nordic countries. In 2004, Margareta and her whole family stayed in Sendai, Japan for 6 months. She contributed to the research and education significantly as the Visiting Professor of Tohoku University. I and Professor Yoshiharu Deguchi have enjoyed our collaboration with Margareta, Mother of $K_{p,uu}$, on the active influx transport system across the blood-brain barrier. In 2015, Margareta received the Nagai Women Scientist Award from Academy of Pharmaceutical Science and Technology Japan (APSTJ). She gave a lecture entitled, "*Application of the free drug hypothesis in CNS drug discovery and development, with focus on the role of the BBB and drug binding in brain"* as a recipient of the award at the Annual meeting of APSTJ in Nagasaki, Japan. Taking this opportunity, I would like to express my sincere appreciation to Margareta for her great achievements of the blood-brain barrier drug transport research and her warm encouragement to many young scientists in Japan!

Margareta and Professor T. Nagai at the banquet of Annual meeting of APSTJ, Nagasaki, Japan in 2015, where she received the Nagai Women Scientist Award.

From Yuichi Sugiyama

Margareta's important contributions to pharmacokinetics and central drug transporter research are appreciated worldwide. In particular, Margareta is highly regarded as the researcher who established the pivotal scientific concept of Kp,uu. In 2010, I was happy to play an important role as an opponent for her PhD student Markus Fridén's thesis review. It was a great pleasure not only to be involved in the review, but also to be invited to the party that started that evening and lasted until the next morning, and to get to know the Swedish people's warm-hearted nature, who sang songs and made the party a great success. On another occasion when I visited Uppsala (see photo), I saw the ash clouds from the volcano on Iceland blew in over Europe and all flights were cancelled. I had an engagement in Berlin on next day. Margareta kindly lined up and book my train ticket. That very crowded train ride is burned in my mind as a nostalgic experience. In 2015, Margareta received the Nagai Female Scientist Award from the Pharmaceutical Society of Japan (APSTJ). I still remember our enjoyable conversation at a Nagasaki ryotei (Japanese-style restaurant) after listening to her lecture at the APSTJ annual meeting. I look forward to new and exciting scientific conversations and to discussing non-scientific subjects as well with Margareta.

Margareta and Professors Sugiyama and Artursson at the 3rd Symposium on Pharmaceutical Profiling, Uppsala University, Uppsala 2010. During the meetings the ash clouds from the volcano on Iceland blew in over Europe.

From Yoshiharu Deguchi

Professor Margareta Hammarlund-Udenaes is one of the most influential researchers in my entire research career. The $K_{p,uu}$ theory proposed by Prof. Margareta to evaluate drug transport to the brain is universal and indispensable not only for basic research on the blood-brain barrier (BBB) but also for the development of drugs targeting the central nervous system nowadays. The first time I met her was at the International Symposium Drug Delivery to the Central Nervous System (ISDDC) in 2003 held at the University of Tokyo, Japan. The second time was during the Pharmaceutical Sciences World Congress (PSWC2004) held in Kyoto, Japan, in 2004. Due to our mutual interest in studying the brain microdialysis method, I had the opportunity to extensively discuss the evaluation of drug distribution into the brain using this method, which led to a collaborative study including Prof. Tetsuya Terasaki. As a result, we elucidated that oxycodone (1) and diphenhydramine (2) are actively delivered into the brain through the BBB and that this action is carried out by the proton/cationic antiporter (also known as pyrilamine transporter) present in the BBB. After being inspired by this, I was devoted to the functional analysis of this transporter, the search for substrate drugs, and the elucidation of the molecular entity, and it became a part of my core research. Owing to this, Prof. Margareta is considered one of the unparalleled research leaders who has had a great influence on the researchers on university and corporate researchers around the world. We would like to take this opportunity to thank Professor Margareta for her contribution to the BBB research field and congratulate her on the publication of the Special Issue of *Pharmaceutical Research* Dedicated to Prof. Margareta Hammarlund-Udenaes.

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From per Artursson

While this issue honors Margareta's scientific excellence, as a faculty member, I would also like to emphasize her great contribution to modernize and renew our undergraduate teaching. For instance, she introduced and argued strongly for problem-based teaching at our faculty, an initiative that was met with quite some resistance at the time. Today, it is a natural part of our undergraduate courses. On a personal plane, I was a sceptic initially (I felt it would take too much time), but after listening to Margareta's pedagogic lectures on the subject, I realized that this was worth trying and soon became a supporter. Further, she introduced courses that are relevant for today's pharmacists, such as pharmacotherapeutics. In extension, this contributed greatly to a broader acceptance of clinical pharmacists, that today optimize medication therapy at our hospitals. Finally, I would also like to mention Margareta's altruistic efforts as a Dean in reorganizing our faculty for the future. While international review boards have criticized our organization as fragmented for over a decade, fear of change (and perhaps lack of energy) prohibited any action from our leadership. This did of course not stop Margareta from trying, and with support from a few key faculty, a partial reorganization was completed last year. As a result of this reorganization, I am proud to be at the same department as Margareta, Irena, and their team. Had Margareta had a few more years as Dean, I am convinced that she would have shaped our faculty to be even better prepared for the future.

From Irena Loryan

Already during my PhD I got acquainted with Margareta's research via her publications. In particular I was thrilled by the studies on assessment of the extent of blood-brain barrier transport of drugs by the use of cerebral microdialysis in both preclinical animals and patients. This was eye opening (and honestly still fascinating)! The moment I decided to contact Margareta was turning point for my life and career. Even though the EMBO grant application that she kindly supported at that time was not granted, it was grounding for the everlasting collaboration. Starting from 2011 I have been working with Margareta as a post doc and later as a researcher in the group. This was and is exciting time full of learning and a true freedom for research! Margareta's attention to details and unbiased evaluation of any results is unprecedented, turning a "simple" meeting to though-provoking discussion! A combination of wisdom, experience, knowledge with positive energy and kindness creates a new super power that makes me and many others to follow her! Being the first female Professor in the Faculty of Pharmacy and the first female Dean she metamorphosed the culture making the path for female scientist less bumpy as it could have been otherwise. I am honoured and blessed for the opportunity to work (and not only) with you Margareta – a role model who masters the power of the wandering mind!

Declarations

Competing Interests No competing interests.