

WORK EXPERIENCE

May 1996–Present

Professor of Molecular Toxicology
Karolinska Institutet
Department of Physiology and Pharmacology
SE-171 77 Stockholm, Sweden

EDUCATION AND TRAINING

September 1969–May 1975

Masters of Science Technology
Royal Institute of Technology, KTH, Stockholm
(Sweden) Chemistry, molecular biology,
biochemistry

September 1975–May 1978

Bachelor of Science in Medicine
Karolinska Institutet, Stockholm (Sweden)

March 1973–May 1977

Histology, Anatomy, Embryology, Medical Chemistry, Physiology, Immunology
PhD and Docent in Physiological Chemistry
Karolinska Institutet, Stockholm
(Sweden) PhD and Docent

Positions

All at Karolinska Institutet, Stockholm, Sweden

- Research Assistant in Physiological Chemistry 1976-1977; Lecturer in Physiological Chemistry 1977-1987 Acting Professor of Physiological Chemistry 1987-1996. Professor of Molecular Toxicology 1996-

Academic honors, awards and prizes

- More than 420 original papers, 24,626 citations (32,238 in Google Scholar) and an h-factor of 85 (ISI) or 104 (Google Scholar).
- Ranked as the **3rd "highest impact" researcher** of 4,000 in the field of drug metabolism (cytochrome.net) and **one of the world's most cited authors** within the category Pharmacology (<http://isihighlycited.com/>).
- Categorized by Thomson Reuters as one of the **World's Most Influential Scientific Minds** (<http://sciencewatch.com/sites/sw/files/sw-article/media/worlds-most-influential-scientific-minds-2014.pdf>) based on recent (2002-2012) citations from highly ranked papers. (Top 1 % cited in the field of pharmacology)
- Honorary Member of *The American Society for Biochemistry and Molecular Biology* (ASBMB) since 1982.
- Selected by Thomson Reuters and Clarivate Analytics as Highly Cited Researcher for 2015, 2016 & 2017. (www.highlycited.com)
- **Awards** include The Svedberg Price, The Swedish Society for Biochemistry and Molecular Biology 1989; Honorary member of The American Society for Biochemistry and Molecular Biology 1990; The Gerhard B Zbinden Lecture Award, EUROTOX 1996; The ISSX European Scientific Achievement Award 2003; The Bengt Danielsson Prize, The Swedish Academy of Pharmaceutical Sciences 2008; The John G Warner Pfizer Lectureship in Pharmaceutical Sciences, University of Michigan, USA 2011.
- Selected as Nauta Chair, Vrije University of Amsterdam, April, 2012.
- Teaching awards: Master from The Student Union at Karolinska Institutet 1978; The Karolinska Institutet Pedagogical Award 2000.

Recognitions

- Ranked as outstanding by the external evaluation of Karolinska Institutet (ERA2010) 2010
- Ranked as outstanding by The Swedish Research Council 2015
- Ranked as outstanding 2015, 2016 and 2017 by the European Research Council (ERC) LS7 panel
- Obtained ERC Advanced Grant (AdG) 2017-2022.

Supervision of graduate students and postdoctoral fellows

Main supervisor to a PhD degree for 30 postgraduate students, postdoctoral training for 25 PhDs.

Commissions of trust

- Member of **The Nobel Assembly** at Karolinska Institutet since 2008
- Member of *Faculty of 1000 Biology* since 2006.
- Member of **Editorial Advisory Boards** of e.g. *Trends in Pharmacological Sciences* (Board member), *Pharmacogenetics and Genomics*, *Pharmacogenomics*, *Drug Metabolism Reviews*, *Drug Metabolism and Disposition*.
- Responsible for the International allele nomenclature in the field of cytochrome P450 polymorphism (www.cypalleles.ki.se)
- Chairman of the international Scientific Advisory Committee of "Microsomes and Drug Oxidations" (MDO) since 2005 (www.mdo.ki.se), the major congress series in the field of drug metabolism and related areas.
- Programme committee of the MD curriculum: Head of curriculum committee 3 years, responsible for the new 1990 study plan for the MD curriculum.
- Docentnämnden, Karolinska Institutet, member for 6 years,
- Chairman of Karolinska Institutet Research Training Programme KIRT 6 years,
- Chairman of the Committee for Elective Periods in the MD curriculum 6 years.
- Chairman of The Recruitment Committee at Karolinska Institutet for 6 years and vice dean for recruitment at Karolinska Institutet for 2 years.
- Chairman of study section, The Swedish Natural Science Research Council 3 years.
- Member of study sections at The Swedish Natural Science Research Council (6 years), The Swedish Medical Research Council, 6 years, The Norwegian Research Council for 6 years.

Invited presentations to peer reviewed internationally established conferences

Invited during the last 10 years to about 60-70 different international meetings. Some highlights are:

2006: World Congress of Pharmacology Beijing, China (July); International Congress of Toxicology, Rome (July); Pharmacogenomics Symposium Changsa, China (June), Microsomes and Drug Oxidations Budapest (Aug); EUROTOX Dubrovnik (Sep) North American ISSX, Puerto Rico (Oct);

2007: American Association of Cancer (AACR); Los Angeles, USA (April); European Science Foundation (ESF) Pharmacogenomics, Barcelona, (June); International Congress on P450, Bled Slovenia (June); Cold Spring Harbor Pharmacogenomics Hinxton, UK (Sep); Pharmacogenomics Congress Cochin, India (Dec);

2008: Microsomes and Drug oxidation, Saratoga USA (July); IUPHAR pharmacogenomics congress, Sao Paulo (Sep); North American ISSX, San Diego (Oct);

2009: British Atherosclerosis Society Cambridge, UK ((Sep); Cold Spring Harbor, Hinxton, UK (Sep); Cold Spring Harbor, Hinxton UK (Sep); Pharmacogenomics Symposium Volos, Greece (Sep);

2010: The ISSX meeting, Indianapolis USA, (April), Microsomes and Drug Oxidations, Beijing, China, (May); Rutgers pharmacogenomics meeting, New Jersey, USA, (May); World Congress of Pharmacology, Copenhagen (July); International ISSX meeting Istanbul, (September), Eur Assoc Clin Pharm, Dresden, (October); American Association of Pharmaceutical Science (AAPS) , New Orleans, (November);

2011: American Association of Pharmaceutical Sciences (AAPS), Washington, USA (October), EAACI Istanbul (June); European Perspectives in Personalized Medicine, Brussels May); 17th International conference on P450, Manchester, UK (June) 2nd world Summit on Pharmacogenomics, Munich (October); Personalized medicine in Europe (EPEMED) Luxembourg (Dec);

2012: Microsomes and Drug Oxidations together with ISSX meeting, Noordwijk Holland (June); IUPHAR Section of Pharmacogenetics, Rio De Janeiro (June); CDSS meeting Liverpool May; and Sep;
2013: Pharmacogenomics conference, Bilbao July; ECPT meeting, Lisbon (September), Experimental Biology, ASPET Boston, USA (March);
2014: World Congress of Pharmacology, Johannesburg (July); Gordon Conference on Adverse Drug Reactions, Boston (June); European Society for Pharmacogenomics and Theranostics (ESPT) Santorini, (September); American Association of Pharmaceutical Sciences, San Diego (November);
2015: European ISSX, Glasgow (June), Pharmacogenomic Latine American Congress, Vina, Chile (May); Eurotox, Porto, Portugal (September); BTS congress, Liverpool (October); 9th European Meeting on Molecular Diagnostics, Noordwijk an See (October), ESPT Budapest (October); IVTS meeting, Birmingham (November);
2016: BTS congress Manchester (April) ECPN congress Vienna (September); Eu_PIC Meeting Rotterdam (May); SSX Bangalore (September), MDO plenary lecturer, Davis, CA (October). AAPS Denver, USA (November);
2017 SOT congress Baltimore (March), ISSX Europe (Bonn) June

Contribution to Science

1. The mechanisms behind alcoholic liver disease (ALD) was essentially unknown. We purified and characterized CYP2E1 (Cytochrome P450 2E1) and found the enzyme to produce a major amount of reactive oxygen species in the absence of substrates. After gaining this knowledge, we established contacts with Samuel W French (UCLA). Utilizing his *in vivo* rat model of ALD, we could show, in a series of 26 papers, that inhibition of CYP2E1 protected from ALD and that CYP2E1 dependent radical formation causes an autoimmune response. This forms a basis for the development of new drugs against ALD.
 - a. Ekström and Ingelman-Sundberg *Biochem Pharmacol*: 38:1313-1319, 1989; Cited 415 times.
 - b. Butura et al., *J Hepatol*. 2009;50:572-83;
 - c. Bardag-Gorce et al., *Gastroenterology*. 2002 123:325-35;
 - d. Morimoto et al., *Hepatology*. 1995;21:1610-7,
2. In 1993 we identified the first example of a stable gene duplication, as well as stable gene amplification, in the human genome. The background was that besides poor metabolism of many drugs like antipsychotics and antidepressants, also some individuals show rapid metabolism. By screening of gDNA from such individuals, we were able to make this identification in the *CYP2D6* locus and couple to the ultrarapid metabolizer phenotype. This is of clinical importance, since individuals carrying multiple *CYP2D6* gene copies metabolize certain drug too rapidly, with reduced drug efficiency as a consequence. E.g. in individuals taking codeine that is metabolized to morphine by *CYP2D6*, the ultrarapid metabolism can cause CNS depression and even death. This phenotype is now taken into consideration in many clinical trials and during treatment with drugs having a pharmacogenomic label for this phenotype (See <http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>). The finding also permitted to conclude on a dietary dependent selection of *CYP2D6* genotypes, based on the ability of *CYP2D6* to metabolize plant toxins. Those with an ultrarapid phenotype had higher probability to survive starvation periods in Africa due to higher capacity to detoxify plant toxins.
 - a. Johansson et al., *Proc. Acad Natl Sci (USA)* 90: 24, 11825-11829; Cited 508 times
 - b. Ingelman-Sundberg, M, *Pharmacogenomics J*. 5: 6-13, 2005; Cited 406 times
3. In the *CYP2C19* locus we identified the first ultrarapid metabolizer phenotype by examining gDNA from people with rapid in *S*-mephenytoin metabolism. This was found to be due to a mutation in the upstream 5'-untranslated region, causing higher expression of the enzyme. This finding is of importance for several large patient groups, since the mutation causes much too low plasma concentrations of SSRIs and other *CYP2C19* drugs, and for increased activation of Plavix to its active metabolite, causing increased risk for bleeding.
 - a. Sim et al., *Clin Pharm Ther* 79; 103-113; 2006; Cited 328 times

4. When screening 1740 twins, we found that individuals lacking functional CYP2C19 enzyme exhibited a much less depressed mode. We developed a transgenic mouse CYP2C19 model, and found that overexpression of CYP2C19 caused decreased hippocampal volume and increased stress and anxiety, as well as less immature neurons in hippocampus. It was found that these changes were induced in fetal life when the CYP2C19 enzyme is expressed in brain. In a large multicenter study we have recently found that also in humans the size of the hippocampus relates to the CYP2C19 phenotype. These findings are of importance for understanding mechanisms in depression, with possibilities for novel types of pharmacological interventions.
 - 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 Apr 18. doi: 10.1038/mp.2017.93
5. Discovered the crucial importance of miRNAs in the de-differentiation of hepatocytes (Lauschke et al *Hepatology*, 64:1743-1756. 2016)
6. Developed a novel *in vitro* system for analyses of drug toxicity, liver function and liver disease
 - a. Bell et al, *Sci Rep*. 2016 May 4;6:25187; 32 citations (Highly Cited)
 - b. Hendriks et al, *Sci Rep*. 2016 Oct 19;6:35434.
 - c. Bell et al., *Drug Metab Dispos*. 2017;45:419-429.
 - d. Vorriink et al., *FASEB J*. 2017;31:2696-2708

A list of all 455 PubMed indexed publications can be found at:

<http://www.ncbi.nlm.nih.gov/pubmed/?term=ingelman-sundberg+m>

Research Support

Ongoing Research support

K2015-02760 Swedish Research Council Ingelman-Sundberg (PI) 01/01/16-12/31/19
Pharmacogenomic and epigenomic regulation of hepatocyte function, drug metabolism and drug response

The project aims to evaluate the basis for de-differentiation of hepatocytes to progenitor cells in 2D cultures and the mechanisms behind re-differentiation during spheroid formation, evaluate the roles of microRNAs (miRNAs) and non-coding RNAs (ncRNAs) in the processes of liver de- and re-differentiation and hepatic gene expression and liver function, develop novel *in vitro* systems for prediction of chronic drug hepatotoxicity, including the identification of novel biomarkers. investigate epigenomic regulation in diseased livers

Role: PI, Research lead

Swedish Cancer Fund 140697 Ingelman-Sundberg (PI) 01/01/15-12/31/17
CYP2W1 as a prognostic marker and target for treatment of colorectal cancer;
This project aims to develop prodrugs bioactivated by cytochrome P450 2W1 specifically expressed in colorectal tumors and investigate function of CYP2W1.
Role: PI, Research lead.

European Research Council (ERC) Ingelman-Sundberg (PI) (HEPASHER) 01/09/17-08/31/22
Mimicking liver disease and regeneration *in vitro* for drug development and liver transplantation
The project aims to study diseased liver *in vitro* with identification of mechanisms, biomarkers and novel drug candidates for treatment of NAFLD and fibrosis, evaluate drug toxicity sensitivity and mechanisms in diseased liver systems and further develop methods for hepatocyte proliferation and regeneration *in vitro* for transplantation purposes, including genetic editing in cases of hepatocytes obtained from patients with genetically inherited liver diseases.

EU H202: Guchelaar HJ (PI) 1/01/16-12/31/20
Ubiquitous Pharmacogenomics (UPGx).
The project aims to implement pharmacogenomics testing in European health care.
Our responsibility is to identify genetic reasons for outliers where geno- and phenotype does not comply.
Role: partner (In total 15 partners)

The Swedish Brain Foundation Ingelman-Sundberg (PI) 05/01/17--06/30/19
CYP2C19 and depression;

This project aims at elucidating the mechanisms behind the hippocampal shrinkage and increase anxiety and stress in mice overexpressing CYP2C19, as well as analyzing human subjects for their CYP2C19 genotype in relation to hippocampal volume and depressive mode.

Role: PI;

Completed Research Support

The Swedish Brain Foundation Ingelman-Sundberg (PI) 07/01/11--06/30/12
CYP2C19 and depression;

This project aims at elucidating the mechanisms behind the hippocampal shrinkage and increase anxiety and stress in mice overexpressing CYP2C19, as well as analyzing human subjects for their CYP2C19 genotype in relation to hippocampal volume and depressive mode.

Role: PI;

IMI SafeSciMET Vermeulen (PI) 01/01/11--12/31/14
European Modular education and training programme in safety sciences for medicines.
Role : Course leader

ERA-Net NEURON E0005001 Stingl (PI) 01/01/14-12/31/16

Cytochrome P450s in brain

This project aims to study the role of cytochrome P450 2C19 (CYP2C19) for brain development and risk for depression. Transgenic animal models and human specimens are used.

Role: Partner, Scientist

IMI-JU (EU FP7 and EFPIA): Park BK (PI) 02/01/12-01/31/17
Mechanism-based integrated systems for the prediction of drug-induced liver injury (MIP-DILI).
The project aims to find novel *in vitro* systems for prediction of drug hepatotoxicity and consists of a big collaboration with different academic labs and with large pharmaceutical companies.
Role: Work package leader and partner (in total 25 partners).

EU FP7 NOTOX Heinzle (PI) 01/01/11-12/31/15

System toxicology

The project aimed at taking a systems approach for a more comprehensive understanding and better prediction of repeated dose toxicity of test compounds.

Role: WP leader

EU-FP7 SCR&Tox Peschanski (PI) 01/01/11-12/31/15

Stem cells for relevant efficient extended and normalized toxicology

SCR&Tox aimed at making use of these two attributes to provide in vitro assays for predicting toxicity of pharmaceutical compounds and cosmetic ingredients.

Role: Partner