Preisverleihung 2011

# STIFTUNG PROFESSOR DR. MAX CLOËTTA

Heft Nr. 39

Prof. Dr. Petra S. Hüppi
«From Contex to Classroom»

# STIFTUNG
# PROFESSOR DR. MAX CLOËTTA

## *Achtunddreissigste Preisverleihung*

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INHALT


Vorwort des Präsidenten des Stiftungsrates und der Geschäftsführerin der Stiftung Prof. Dr. Max Cloëtta 5

Urkunde für Prof. Dr. Petra Hüppi 11

Kurzbiographie von Prof. Dr. Petra Hüppi 13

Festvortrag von Prof. Dr. Petra Hüppi «From Cortex to Classroom» 22

Informationen über die Stiftung Prof. Dr. Max Cloëtta 41

Übersicht über die bisher erschienenen Publikationen der Schriftenreihe Stiftung Professor Dr. Max Cloëtta 42

Ehrentafel der Preisträger 50

# VORWORT

*Professor Adriano Fontana*
*President of the Board of Foundation*

The Professor Dr. Max Cloëtta Foundation is proud to have nominated Prof. Dr. Petra Hüppi for the award 2011. Prof. Hüppi is a clinician and a clinical scientist who has devoted her professional life to medicine with a strong clinical focus on aspects of brain development.

A recent survey in the US has reported only 11 % of medical graduates to plan careers that are exclusively or significantly devoted to research. However, patient oriented science and translational medicine do require clinical scientists to study the understanding of disease mechanisms and development of new treatments. The Swiss National Science Foundation (SNF) has put much effort in supporting clinical trials, and in promoting cooperative projects between basic science and clinical science. Moreover, the SNF also supports applications from young medical doctors to do research in well-established laboratories all over the world. Likewise, universities in Switzerland promote clinical studies and research projects in university hospitals. This strongly contrasts with funding of clinical research by the industry and various disease orientated societies in that their funding of comparable projects has decreased in recent years.

Unfortunately it is my personal experience over the years, that clinical science in university hospitals in Switzerland has become a more and more difficult task. The working hours restrictions for medical doctors and the introduction of diagnoses related groups (DRG) puts more and more pressure on hospitals to guarantee their patients excellent medicine in a competitive surrounding with the financial resources available. Despite of health costs having increased over the years, the financial resources provided to the hospitals do not increase accordingly. Until recently, part of the university money aimed at fostering clinical science has even been used by the hospitals to pay clinical routine work rather then clinical science. The administrative directors in university hospitals

have to put all their efforts in clinical medicine. Confronted with this uncomfortable financial situation, clinical science can no longer be rated as a top priority in university medical centers.

Both science and clinical medicine have reached a considerable degree of complexity due to tremendous technical achievements. This has made it more difficult for clinicians to cope with the needs of both science as well as medicine. Thus, it may not be surprising that many young clinicians and even many of their mentors in the clinics have become discouraged to perform clinical trials or to perform more fundamental studies. Regulatory aspects of clinical research have reached a level which, in terms of workload, is very difficult to fulfill by clinicians who are involved in clinical medicine. Furthermore, there is still a low esteem of clinical science by many basic scientists. In some hospitals, the focus of research is given rather in a "top down" than a "bottom up" approach. However, only the latter is the best guarantee to do justice to scientists' interests and fantasy. The late Steve Jobs has called on students at Stanford University to "stay hungry, stay foolish". Rather than limiting by means of overruling and restricting creativity by strict top down approaches, science management needs to have an open mind for the curiosity of young and gifted clinical scientists and a supporting hand to help realizing visionary ideas. However, there is a strong tendency that in University Hospitals the decision making authority in research management very rarely is a senior scientist who can look back onto a career of own excellent science.

It is my strong hope that, despite the difficulties mentioned, young gifted clinical scientists will still have the chance to grow and become leaders in experimental and clinical medicine in the future. To them, Prof. Petra Hüppi, our Cloëtta prize winner 2011, will serve as an excellent role model.

*Brigitt Küttel*
*Geschäftsführerin*

*Stiftungsrat*

Nach 16 Jahren im Stiftungsrat und im Medizinischen Ausschuss, davon 3 als deren Präsident, ist Prof. Marco Baggiolini mit Erreichen seines 75. Altersjahres aus dem Stiftungsrat zurückgetreten. Gewählt wurde er in diesen als Vertreter der Universität Bern, wo er dem Theodor Kocher-Institut vorstand. 1996 wurde er erster Präsident der neu gegründeten Università della Svizzera italiana, ein Amt, das er zehn Jahre, bis am 31. August 2006, innehatte. Die Zusammenarbeit mit Herrn Prof. Baggiolini war stets geprägt von immensem fachlichem Wissen, Weitsicht und einer grossen persönlichen Wertschätzung.

Seit Mitte 2011 präsidiert Prof. Adriano Fontana den Stiftungsrat und den Medizinischen Ausschuss. Er war 2008 als Vertreter der Universität Zürich und Nachfolger von Prof. Jürgen Zapf in den Stiftungsrat gewählt worden. Bis er 2009 die erste Hertie-Senior-Forschungsprofessur in der Schweiz antrat, war er Direktor der Klinik für Immunologie des Universitätsspitals Zürich.

Mitte 2011 trat Prof. Bernard Rossier, seit 1998 Vertreter der Université de Lausanne, aus dem Stiftungsrat zurück.

Es ist eine besondere Freude, dass der neue Vertreter der Université de Lausanne ein ehemaliger Träger des Cloëtta-Preises ist: Prof. Bernhard Thorens, Biochemiker und Professor für Physiologie, erhielt die Auszeichnung 2002.

Die Stiftung wird den beiden verdienten Wissenschaftern freundschaftlich verbunden bleiben und dankt ihnen auch auf diesem Weg herzlich für ihren langjährigen intensiven Einsatz.

*Cloëtta-Preis*

Im Bestreben, die Stiftung Prof. Dr. Max Cloëtta näher an die Universitäten und damit an die Forschenden zu bringen, hat der Stiftungsrat im Sommer 2011 entschieden, statt zwei jährlich nur noch einen Preis auszurichten und die Feier an der jeweiligen Universität des Preisträgers resp. der Preisträgerin durchzuführen. Dass mit **Frau Prof. Petra Hüppi** nun eine Frau erstmals an ihrer Heimuniversität ausgezeichnet wird, freut mich ganz besonders. Unser grosser Dank gilt Frau Prof. Susanne Suter, der Vertreterin der Université de Genève in unserem Stiftungsrat, und den Vertretern der Universität für die tatkräftige Unterstützung bei der Organisation der Feier.

*MD-PhD-Programm der SAMW*

Seit zwei Jahren wurde die Stiftung Prof. Dr. Max Cloëtta im Auswahlgremium des MD-PhD-Programms der Schweizerischen Akademie der Medizinischen Wissenschaften (SAMW) durch Prof. Dr. Hugues Abriel vertreten. Die SAMW vergibt gemeinsam mit dem Schweizerischen Nationalfonds und unter Mithilfe privater Stiftungen MD-PhD-Stipendien an forschungsinteressierte Ärztinnen und Ärzte für ein naturwissenschaftliches Zweitstudium. Prof. Abriel übergibt das Mandat per 2012 an Prof. Fontana. Beiden sei ein spezieller Dank ausgesprochen, dass sie bereit sind, dieses wichtige Zusatzmandat im Namen der Stiftung zu übernehmen.

*Forschungsstellen*

Im Jahr 2011 finanzierte die Stiftung Professor Dr. Max Cloëtta folgende vier Forscher an Schweizer Universitäten mit fünf- resp. zweijährigen Grants:
**Dr. Rajesh Jayachandran:** Biozentrum der Universität Basel. Projekt: Role for Coronin 1 signaling in the development of autoimmunity and T cell mediated disorders. Unterstützungsdauer 1.7.2011 bis 30.6.2016.

**Dr. Daniel Fuster.** Universität Bern, Institut für Biochemie und Molekulare Medizin. Projekt: Novel mammalian sodium/hydrogen exchanger family NHA – a quest for biological function. Unterstützungsdauer 1.6.2008 bis 31.5.2014.
**Dr. Benjamin Marsland.** Centre Hospitalier Universitaire Vaudois, Service de pneumologie. Projekt: Innate and adaptive immune responses in the lung: implications for protective immunity. Unterstützungsdauer 1.7.2009 bis 30.6.2014.
**Dr. Jean Marc Waldburger.** Laboratoire de Rhumatologie, Département de Pathologie et Immunologie, Centre Médical Universitaire Genève. Projekt: The role of store operated calcium entry in arthritis. Unterstützungsdauer 1.12.2011 bis 30.11.2013.

*Klinische Medizin Plus*

Seit 2010 vergibt die Stiftung Prof. Dr. Max Cloëtta in Zusammenarbeit mit der Uniscientia-Stiftung, Vaduz, Stipendien «Klinische Medizin Plus». Medizinerinnen und Medizinern während oder unmittelbar nach Abschluss der Facharztausbildung werden Stipendien von drei bis max. zwölf Monaten für die Absolvierung einer Spezialausbildung an einer renommierten, vornehmlich ausländischen Institution ausgerichtet.
Aus der ersten Ausschreibung werden unterstützt:
**Dr. Michael Liebrenz,** 1978. Oberarzt. Psychiatrische Universitätsklinik Zürich, für einen Research Fellowship in Forensic Psychiatry am Dept of Psychiatry, Columbia University, New York, USA, 7.2012–6.2013.
**Dr. Tobias Reichlin,** 1979, Assistenzarzt, Universitätsspital Basel, Abt. für Kardiologie, für sein Projekt ‚Characterization of the epicardial substrate for ventricular arrhythmias' an der Harvard Medical School, Brigham and Woman Hospital Boston, USA , 1.7.2011–30.6.2012.
**Dr. Mira Katan,** 1977, Research Fellow an der Division of Stroke, Neurological Institute der Columbia University, New York, USA, 6.2011–5.2012, für ihr Projekt ‚Neuroendokrine und inflammatorische Serum Biomarker für die Risikostratifizierung beim ischämischen Schlaganfall in verschiedenen Schlaganfall Cohorten' und einen Master of Science in Epidemiologie und Biostatistik, 6.2011–5.2012.

**Dr. Isabelle Schmitt-Opitz,** 1974, Oberärztin. Universitätsspital Zürich, Klinik für Thoraxchirurgie, für ihr Projekt ‚Malignant Pleural Meosthelioma – Identification of Predictive and Prognostic Marker' an den Latner Thoracic Surgery Research Laboratories, Toronto, Canada, 1.2011–6.2011.
**Dr. Philipp Schütz,** 1977 Research Fellow. Beth Israel Deaconess Medical Center, Boston und Harvard School of Public Health für einen Master of Public Health mit Konzentration auf quantitativen Methoden, 9.2010–9.2011.

Zusammen mit dem ganzen Team der Geschäftsstelle freue ich mich, die Stiftung Prof. Dr. Max Cloëtta in eine aktive Zukunft für die Förderung der medizinischen Forschung in der Schweiz begleiten zu dürfen!

LE PRIX CLOËTTA 2011
EST DÉCERNÉ À

MADAME LA PROFESSEURE

# PETRA SUSAN HÜPPI

NÉE EN 1960, DE GOMMISWALD SG ET ENTLEBUCH LU,
PROFESSEURE À LA FACULTÉ DE MÉDECINE DE
L'UNIVERSITÉ DE GENÈVE,
CHEFFE DE LA DIVISION DU DÉVELOPPEMENT ET DE LA
CROISSANCE DE L'HÔPITAL DES ENFANTS,
POUR SES REMARQUABLES TRAVAUX
DANS LE DOMAINE DU DÉVELOPPEMENT CÉRÉBRAL
DES NOUVEAU-NÉS.

GENÈVE, LE 9 DÉCEMBRE 2011

AU NOM DU CONSEIL DE FONDATION:

LE PRÉSIDENT

LE VICE-PRÉSIDENT

UN MEMBRE

Prof. Dr. Petra Susan Hüppi

# CURRICULUM VITAE

| | |
|---|---|
| Name: | Hüppi |
| Firstname: | Petra Susan |
| Date of Birth: | 26 October, 1960 |
| Place of Birth: | Lucerne, Switzerland |

*Education and Training:*

| | |
|---|---|
| 1986 | Graduation and MD thesis "Serum antibodies to central nervous system antigens: an analysis of their relation in different human neurological disorders", (Prof. Dr. med. N. Herschkowitz, University of Berne) |
| 1987 | US medical graduation for Foreign Medical Graduates |

*Postdoctoral Training:*

| | |
|---|---|
| 1987–88 | Resident, Department for Anesthesiology, University Hospital, Berne |
| 1988–90 | Resident and Senior Fellow in Neonatology, Division of Neonatology, Department of Obstetrics and Gynecology, University Hospital, Berne |
| 1990 | Neonatal/Behavioral Research Fellow, Children's Hospital, Boston (2 months) |
| 1990–94 | Senior Pediatric Resident and Fellow, Children's Hospital, Berne |
| 1994–96 | Clinical Fellow in Neonatology and Research Fellow (Reynolds-Rich Smith Fellowship), Joint Program in Neonatology, Harvard Medical School, Boston |

| | |
|---|---|
| 1996–97 | Charles A. Janeway Scholar of the Child Health Research Center, Joint Program in Neonatology/ Department of Neurology, Harvard Medical School, Children's Hospital, Boston |
| 1997 | Recipient of the Hans Sigrist Foundation Scholarship, University of Berne, Switzerland |

*Professional qualifications:*

| | |
|---|---|
| 1986 | Swiss Medical Diploma (Swiss National Board of Medical Examinations) |
| 1986 | Medical Thesis Certificate, University of Berne, Switzerland |
| 1987 | ECFMG Certificate for United States Medical Examination |
| 1990 | Harvard Certificate for the Assessment of Preterm Infant Behavior |
| 1993 | Specialization in Pediatrics Diploma, Swiss Medical Society (FMH), Switzerland |
| 1997 | Harvard Certificate of completion of neonatal fellowship |
| 1997 | Swiss Board of Neonatology (FMH) (Diploma) |

*Academic Appointments:*

| | |
|---|---|
| 1998–2003 | Head (Privat-docent), Child Development Unit, Department of Pediatrics, Children's Hospital, University of Geneva, Switzerland |
| 1999 | Habilitation Thesis (Privat-docent), University of Geneva, Switzerland<br>*"Brain development in the newborn: in vivo studies by magnetic resonance techniques"* |
| 2003 | Full Professor of Pediatrics, University of Geneva School of Medecine |

*Hospital or Affiliated Institution Appointments:*

| | |
|---|---|
| 1997 | Head, Child Development Unit, University Children's Hospital, Geneva |
| 1997 | Staff Member, Neonatal & Pediatric Intensive Care Unit, University Children's Hospital, Geneva |
| 2005 | Head, Division of Child Development and Growth, University Children's Hospital, Geneva |

*Other Professional Positions and Major Visiting Appointments:*

| | |
|---|---|
| 1997– | Visiting Scientist, Department of Neurology, Children's Hospital, Harvard University, Boston |
| 1995–1998 | Council Member, European Society for Pediatric Research (ESPR) |
| 1999–2002 | Treasurer, European Society for Pediatric Research (ESPR) |
| 2003–2006 | Member of Board of Trustees, International Pediatric Research Foundation (IPRF) |
| 2008 | Visiting Professor Dept of Pediatrics UCSF San Francisco USA |
| 2006–2010 | European Chief Editor, Pediatric Research |
| 2005– | Head, Division of Child Development and Growth comprising the Child Development Unit and the Pediatric Endocrinology Unit |

*Major Committee Assignments:*

| | |
|---|---|
| 2000– | Member, Committee on Mental Deficiency, Bureau of Internal Affairs, Canton of Geneva |
| 2002– | Women's Advisory Board, NCCR *"CO–ME",* Swiss National Foundation |
| 2002–2004 | Expert, Committee of the Swiss Academy of Medical Sciences and the Swiss Faculties of Medicine: *"The future of medicine in Switzerland"* |

| | |
|---|---|
| 2003–2006 | Committee Member, Ethics Committee, Department of Pediatrics, University Hospitals, Geneva |
| 2003 | Member, Scientific Committee «Réseau Mère–Enfant de la Francophonie» (Mother and Child Network in French-speaking Countries) – Belgium, Canada, France, Switzerland |
| *2001–2004* | Member, Educational Committee of the International Society for Magnetic Resonance in Medicine |
| 2001–2004 | Member, Coordination Committee, European Science Foundation (ESF) Scientific Network: *"Research on early developmental care for extremely premature babies in neonatal intensive care units"* |
| 2004–2006 | Member, Scientific Program Committee of the International Society for Magnetic Resonance in Medicine |
| 2006– | Member, Scientific Program Committee of the European Society for Pediatric Research (ESPR) and Europediatrics |
| 2006– | Scientific Committee Member, *Fondation Motrice,* Paris, France |
| 2007– | Founding Member, *Primenfance,* Geneva, Switzerland |
| 2009– | Member, Scientific Program Committee of Human Brain Mapping (HBM) |

*Awards and Honors:*

| | |
|---|---|
| 1994–1997 | Swiss Academy of Medical Science Research Grant |
| 1994–1996 | Reynolds-Rich Smith Fellowship, Joint Program in Neonatology, Harvard Medical School, Boston |
| 1996–1997 | Charles A. Janeway Scholar of the Child Health Research Center, Joint Program in Neonatology/Dept. of Neurology, Harvard Medical School, Children's Hospital, Boston |
| 1997 | Hans-Sigrist Grant, University of Berne, awarded by Hans Sigrist Stiftung (Hans Sigrist Foundation) |
| 2005 | Honorary Election to Full Membership of Swiss Academy of Medical Sciences |
| 2007 | Leenaards Prize, research award made by the Leenaards Foundation, Lausanne, Switzerland |

*Grants*

| | |
|---|---|
| 1994–1996 | Grant from the Swiss Foundation for medical-biological sciences (under the auspice of the Swiss Academy of Medical Sciences): *Newborn Brain Imaging* |
| 1994–1995 | Reynolds-Rich-Smith research fellowship, Harvard University |
| 1995–1998 | Swiss National Science Foundation (SNF), Grant Nr 32-43426.95, for the project *"Postnatal brain development: The neonatal period"* (E. Bossi, P. Hüppi (Co-PI), C. Boesch, G. Schroth) |
| 1996–1997 | Charles A Janeway scholarship in child health research, National Institute of Health, Children's Hospital, Harvard University |
| 1999–2003 | Swiss National Science Foundation (SNF), Grant Nr 32-56927.99, for the project *"Intrauterine growth restriction"* (PI: P. Hüppi) |
| 2000–2003 | OERI CFDA 84.035T: Consultant for the project *"From cortex to classroom"* (PI: H. Als) (co-investigator: P. Hüppi) |

| | |
|---|---|
| 2000–2005 | PPG National Institute of Health (Nr P30HD18655): Consultant for the project *"Pathogenesis of Periventricular leukomalacia"* (PI: J. J. Volpe) |
| 2001–2004 | Swiss National Science Foundation (SNF), Grant Nr 3200-063135, co-investigator for the project *"Neurobehavioral Phenotype and Brain Development in Velocardiofacial Syndrome"* (PI: S. Eliez; Co-PI: P. Hüppi) |
| 2002–2005 | Whitaker Foundation grant, collaborator for the project *"Characterization of newborn brain development"* (PI: Simon Warfield; Co-investigator: P. Hüppi) |
| 2004–2007 | NICHD *"Preterm Foetal Growth Restriction and Developmental Care"* (PI: Heidelise Als; Co-investigator: P. Hüppi) |
| 2004–2007 | Swiss National Science Foundation (SNF), Grant Nr 32-102127, for the project *"Hypoxia-ischemia in the developing brain. Correlations between electrophysiological activity, biomarkers of brain injury, advanced Magnetic Resonance Imaging and neurodevelopmental outcome"* (PI: P. Hüppi) |
| 2004–2005 | Grant of the University Hospitals of Geneva (HUG) called "Fonds de péréquation" for the project *"Hypoxia-Ischemia in the developing brain. Correlations between electrophysiological activity, biomarkers of brain injury, advanced Magnetic Resonance Imaging and neurodevelopmental outcome"* (PI: P. Hüppi) |
| 2005–2006 | Grant from the Gertrude Von Meissner Foundation for the project *"The role of spontaneous general movements assessment in the follow-up of high risk preterm infants: Comparison with Bayley scales of infant development and advanced magnetic resonance imaging"* (Datta A. N., Hüppi P., Menache-Starobinski C.) |
| 2005–2007 | Swiss National Science Foundation (SNF), Grant Nr PNR 405040-108713/1, co-investigator for the project *"Role of environmental endocrine disruptors in the aetiology of intrauterine growth retardation and its later consequences such as disorders in brain development and adult-onset obesity"* (PIs: M. Aubert, P. Hüppi) |

| | |
|---|---|
| 2005–2006 | Grant from Novartis Foundation, *Endocrine disruptors in development* (PI: P. Hüppi) |
| 2005–2008 | Swiss National Science Foundation (SNF), Grant Nr 3200-108176, co-investigator for the project *"Effect of Erythropoietin on the developing brain in very preterm infants"* (PI: H. Bucher; Co-PI: P. Hüppi) |
| 2006–2008 | Grant from the "Fonds de péréquation" (Realignment Fund), University Hospitals of Geneva (HUG) for the project *«Recherche d'endophénotypes par l'étude électroencéphalopraphique et neuroanatomique du trouble hyperactivité avec déficit d'attention»* (PI: C. Menache-Starobinski; Co-investigators: E. Sforza & P. Hüppi, C.A. Haenggeli, A. Malafosse, F. Lazeyras) |
| 2007–2010 | Leenaards Prize for the project *"Development of Executive Functions in children born prematurely in relation to neurostructural brain development"* (PI: P. Hüppi) (Funds). |
| 2007–2010 | Swiss National Science Foundation (SNF), Grant Nr 3200BO/113632/1, for the project *"Development of Executive Functions in children born prematurely in relation to neurostructural brain development"* (PI: P. Hüppi) |
| 2006–2009 | European Project Framework VI: NEOBRAIN *Neonatal estimation of brain damage risk and identification of neuroprotectants* LSHM-CT-2006-036534, contract Nr 036534 (Co-PI: P. Hüppi) |
| 2007– | Nestlé Research contract: *Nutrition for the brain:* Experimental studies (rat model of IUGR) on effects of maternal and perinatal nutrition on brain development (PI: P. Hüppi) |
| 2009–2012 | SPUM (Swiss Program University Medecine): *From Cortex to Classroom: enhancing brain development for premature infants* (PI: P. Hüppi) |
| 2010–2012 | European Project Framework VII: CONNECT contract Nr 238292 (Co-PI: P. Hüppi) |

## SELECTED PUBLICATIONS:


1. Hüppi P. S., Posse S., Lazeyras F., Burri R., Bossi E., Herschkowitz N. **Magnetic** resonance in preterm and term newborns: 1H-spectroscopy in developing human brain. Pediatr Res. 1991 Dec; 30(6):574–8

2. Hüppi P. S., Schuknecht B., Boesch C., Bossi E., Felblinger J., Fusch C., Herschkowitz N. 1996 Structural and neurobehavioral delay in postnatal brain development of preterm infants Pediatr Res. 1996 May; 39(5):895–901

3. Hüppi P., Maier S., Peled S., Zientara G., Barnes P., Jolesz F., Volpe J. 1998. Microstructural development of human newborns cerebral white matter assessed in vivo by diffusion tensor MRI. Pediatr Res 44:584–590

4. Hüppi P., Warfield S., Kikinis R., Barnes P., Zientara G., Jolesz F., Tsuji M., Volpe J. 1998. Quantitative magnetic resonance imaging of brain development in premature and mature newborns. Ann Neurol 43(2):224–235

5. Inder T., Hüppi P., Warfield S., Kikinis R., Zientara G., Barnes P., Jolesz F., Volpe J. 1999. Periventricular white matter injury in the premature infant is associated with a reduction in cerebral cortical gray matter volume at term. Ann Neurol 46:755–760

6. Hüppi P., Murphy B., Maier S., Zientara G., Inder T., Barnes P., Kikinis R., Jolesz F., Volpe J. 2001. Microstructural brain development after perinatal cerebral white matter injury assessed by diffusion tensor magnetic resonance imaging. Pediatrics 107:455–460

7. Kreis R., Hofmann L., Kuhlmann B., Boesch C., Bossi E., Hüppi P.S. 2002. Brain metabolite composition during early human brain development as measured by quantitative in vivo 1H magnetic resonance spectroscopy. Magn Reson Med. 2002 Dec; 48(6):949–58

8. Tolsa C. B., Zimine S., Warfield S. K., Freschi M., Sancho R. A., Lazeyras F., Hanquinet S., Pfizenmaier M., Hüppi P. S. 2004. Early alteration of structural and functional brain development in premature infants born with intrauterine growth restriction. Pediatr Res 56:132–138

9. Seghier M. L., Lazeyras F., Zimine S., Saudan-Frei S., Safran A. B., Hüppi P. S. 2005. Visual recovery after perinatal stroke evidenced by functional and diffusion MRI: case report. BMC 26;5:17

10. Sizonenko S.V., Camm E.J., Garbow J.R., Maier S.E., Inder T.E., Williams C.E., Neil J.J., Hüppi P.S. 2007. Developmental changes and injury induced disruption of the radial organization of the cortex in the immature rat brain revealed by in vivo diffusion tensor MRI Cereb Cortex Nov; 17(11):2609–17

11. Dubois J., Benders M., Cachia A., Lazeyras F., Ha-Vinh L.R., Sizonenko S.V., Borradori-Tolsa C., Mangin J.F., Hüppi P.S. 2008. Mapping the Early Cortical Folding Process in the Preterm Newborn Brain. Cereb Cortex 18(6):1444–54

12. Dubois J., Benders M., Borradori-Tolsa C., Cachia A., Lazeyras F., Ha-Vinh L.R., Sizonenko S.V., Warfield S.K., Mangin J.F., Hüppi P.S. 2008. Primary cortical folding in the human newborn: an early marker of later functional development. Brain 131:2028–2041

13. Ment L.R., Hirtz D., Hüppi P.S. 2009. Imaging biomarkers of outcome in the developing preterm brain. Lancet Neurol 8:1042–1055

14. Dubois J., Benders M., Lazeyras F., Borradori-Tolsa C., Leuchter R.H., Mangin J.F., Hüppi P.S. 2010. Structural asymmetries of perisylvian regions in the preterm newborn. Neuroimage 52:32–42

# FROM CORTEX TO CLASSROOM

*Petra S. Hüppi*

The Brain is a fascinating organ and in evolution even our ancestors some 200 millions years ago had a small neocortex – extra layers of neural tissue on the surface of the brain responsible for the complexity and flexibility of mammalian behaviour, but overall their brain was very small. Today we can only speculate about why their brains began to grow bigger, factors that certainly contributed were diet, culture, technology, social relationships and genes – all together led to the modern human brain. This modern human brain in turn in every individuum starts out from a few cells to become an extremely complex structure, a process we call brain development. Ramon y Cajal beautifully described the importance of the developmental processes in the brain and their importance for the structure and function of every cell.

**"The innumerable processes and intercellular connections offered by the adult nervous system can be interpreted as the morphological expression of the infinite routes traced in space by currents of inducing or positive chemotropic substances during the entire developmental period. Thus, the total arborisation of a neuron represents the graphic history of conflicts suffered during its developmental life" (Ramón y Cajal, 1899).[1]**

Neuroanatomists and Neuropathologists have for centuries studied the brain both in development and in disease through autopsy tissue. Relevant for neonatologists, Virchow 1867 described a disease in newborns who demonstrated pale softened zones of degeneration within the periventricular white matter at autopsy.and called it congential encephalomyelitis, Clinically he suggested that these lesions might be related to a disease described earlier by Little[2], in which the patients suffered from spasmodic limb contractures, diplegia, and mental retardation. But there was no way to look for these lesions in the brain prior to autopsy.

For pediatricians and neonatologists understanding the brain and its vulnerabilities during development are of utmost importance and early research in the field was led by many European pediatricians, neurologists and neonatologists such as Sir Peter Tizard who wrote about the central nervous system in the newborn[3], illustrating the dramatic changes in brain development occurring throughout gestation

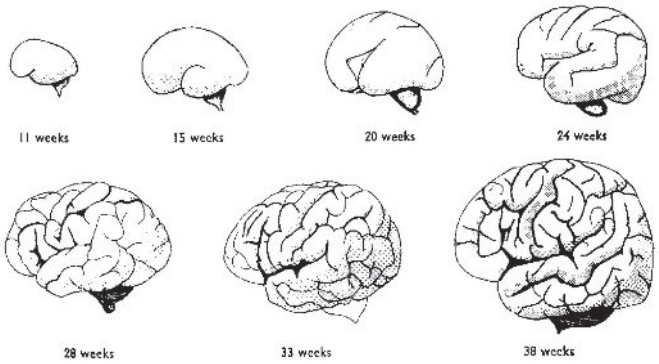


***Figure 1:*** *Drawing of brain cortical development from Sir Peter Tizard, Neonatologist 1966 Br Med Bull 1966 22(1):49–55.*

With the advent of ultrasound technology introduced to neonatology in the late 1970's and the introduction of magnetic resonance imaging to the human brain in the 1980's for the first time the in vivo assessment of the developing brain became possible.

Magnetic resonance (MR) techniques are attractive for use in the developing brain because of their resolving power and their relative noninvasiveness. Their ability to provide detailed structural as well as metabolic and functional information without the use of ionizing radiation is unique. For the first time such important processes such as myelination first described by Virchow in 1854[4] were now possible to study in vivo.

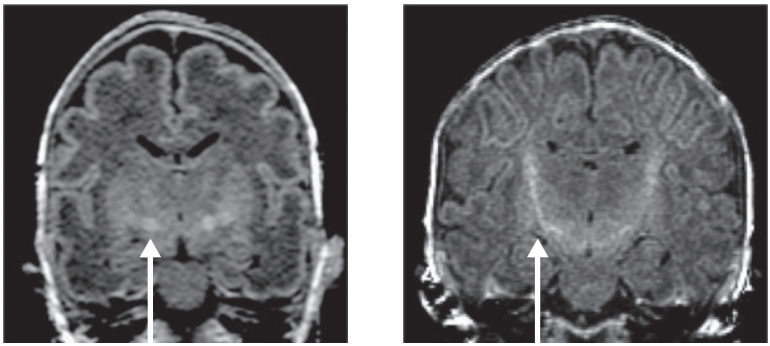

***Figure 2:*** *T1-weighted MR Images of a preterm infant at 30wks and a fullterm newborn illustrating difference in myelin déposition. Arrows indicate areas of ongoing myelination.*

Conventional MR imaging techniques, including mainly T1- and T2-weighted images, allow the assessment of brain development in-vivo with the highly sensitive assessment of gray and white matter changes, as well as the differentiation of unmyelinated and myelinated white matter[5].
The subplate zone a transitory area of the cerebral mantle during development can be clearly distinguished in ex-vivo T1 MRI images after 13 weeks of gestation as an area of hypointensity and on in vivo T2 MRI as an area of hyperintensity[6] due to the higher water content of the extracellular matrix (ECM) between the bordering cortical plate and the intermediate zone. The presence of this transient subplate zone is one of the main signs of cortical immaturity. This structure localized underneath the neocortical plate reaches its maximal thickness between 22 and 36 gestational weeks. The sub-plate is present in pre-term neonates but has disappeared in full-term neonates.
When neurons are reaching their final destination, they start to produce axons and dendrites, allowing connecting distant cerebral structures and by that forming functional networks. This ontogenic step is occurring largely but not exclusively during the second half of gestation and extends during the postnatal period. For example, evoked visual potentials can be produced as early as 24–27 gestational weeks in human neonates, confirming the existence of an established wiring at this early developmental stage.

Studying white matter development with in vivo imaging was largely impossible prior to the use of advanced magnetic resonance techniques, diffusion imaging being of particular interest in the assessment of the white matter microstructure[7]. Apparent diffusion coefficient is called 'apparent' to take into account that what we are measuring in vivo in the brain is not intrinsic diffusion, which would be determined by molecular weight, intermolecular interactions (viscosity) and temperature, but rather the interactions of the diffusing molecule with the cellular structures over a given diffusion time. During typical diffusion times of about 50–100 ms, water molecules move in the brain on average over distances around 10–15 μm, bouncing into, crossing or interacting with many tissue components within individual compartments (e.g. intracellular, extracellular, neurons, glial cells and axons). Diffusion weighted imaging now helps to diagnose the entity periventricular white matter injury first described by Virchow, in vivo[44].

The distance that a molecule diffuses in one direction in space may or may not be the same as in some other direction, we measure these differences by measuring the diffusion anisotropy. As evidenced in many experimental studies axonal membranes play the primary role for anisotropic diffusion in the brain white matter. The use of Diffusion tensor Imaging (DTI) has allowed to visualize early white matter connectivity with demonstration of interhemispheric callosal fibers in non myelinated stage at 28 weeks of gestation and has further allowed to characterize for the first time differences in white matter connectivity in preterm vs fullterm infants[7] and the effects of injury to the white matter in prematurity[8].

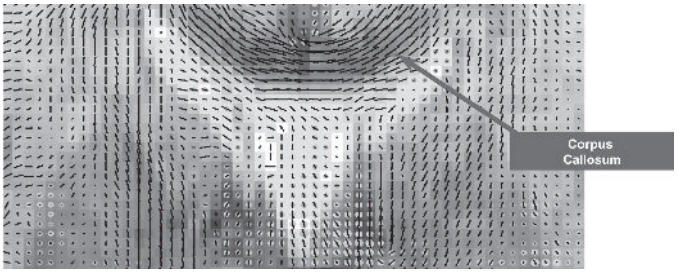


***Figure 3:*** *Illustration of DTI eigenvector maps in the corpus callosum of a preterm brain at 28 wks gestation. Eigenvectors depict unmyelinated white matter fibertracts in the corpus callosum.*

Many studies using DTI have since been able to characterize the forms of white matter injury occurring in the context of prematurity[9–13].

As for neuronal production, some axonal projections are produced in excess, connecting too many structures or neurons. This initial phase is followed by a regressive phase where redundant or misconnected axons are eliminated or retracted, allowing the emergence of adequate and functional connections. Electrical activity among others is a key determinant for the maintenance of axons. Accordingly, in utero and especially postnatal stimuli and experiences significantly shape the developing brain by modulating the maintenance or elimination of some axons[14], an observation highly relevant to the premature infant and its early life experiences.
Developmental care, such as NIDCAP (neonatal individualized developmental care) aims at reducing stress during NICU care and stimulate preterm newborns through interactions with parents and care personnel according to individualized behavioral observations. A comparison of NIDCAP cared preterm infants and a standard care group revealed significantly more mature white matter connectivity as assessed by DTI[15].

***Figure 4:*** *Illustration of a developmental care approach.*

Making proper connections through white matter structures is probably one of the determining factors for further cortical organization. One major hypothesis for the morphogenetic mechanism of cortical folding is based on mechanical tension along axons in the white matter[16], the other being that differential growth of the cortex leads to folding[17, 18].
MRI has in recent years helped researchers to tackle this unsolved question of brain development through evolution[19, 20]. In animal models the combination of conventional MRI and diffusion tensor imaging (DTI has further allowed to depict the relationship of changes in intra-cortical layering and cortical folding[21, 22]. The basis for these MRI based measures are image processing techniques that allow fine quantification of specific brain tissues such as white matter, cortex, subplate, cerebrospinal fluid and the exact definition of their borders.

*MR Image analysis: Automated computational techniques*

High-resolution T1- and T2-weighted images are the basis for the application of mathematically-based segmentation techniques that allow volume measurement of total cortical grey matter, white matter, basal ganglia and cerebrospinal fluid. Segmentation techniques for the developing brain are challenging due to: 1) an inversion of the contrast between gray and white matter and changes during development prohibiting the use adult segmentation toolkits; 2) a strong signal heterogeneity secondary to myelination affecting both cortical structures and white matter regions; 3) the small size of the brain requiring high resolution MRI, which leads to low signal-to-noise; 4) thin structures in particular the cortex, prone to partial volume effects complicating further any automated segmentation tool based on signal intensity. Volumetric analysis of MRI data sets is achieved by segmentation of the imaged volume into tissue types depending on their difference in signal intensity, contour and anatomical knowledge followed by three-dimensional renderings[23]. The combination of a signal-based k-means classification with a mathematical morphology approach for shape recognition is currently the preferred method for fetal and neonatal brain segmentation [24, 25, 26].

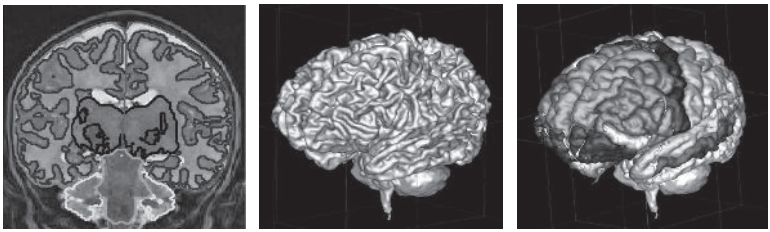

***Figure 5:*** *Fig. 5 Newly developed segmentation technique using mathematical morphology approach (L Gui et al 2011). Surface extraction and manual labelling allows definition of cortical regions in the newborn brain[4].*

A striking increase in cerebral cortical volume accompanies the axonal and dendritic growth described previously. That this growth is particularly rapid between approximately 28 and 40 weeks' gestational age has been shown by these quantitative three-dimensional MRI techniques with use of postacquisition image analysis. Overall brain volume more than doubles between 28 and 40 weeks' gestation, and cortical gray matter volume increases fourfold in the same period[23]. This increase is thought to relate primarily to neuronal differentiation rather than to an increase in the total number of neurons.

MRI volumetric techniques were used to evaluate the effect on subsequent brain development of early white matter injury in premature infants. In the premature infants with preceding white matter injury, the volume of myelinated white matter at term was significantly lower than in the premature infants without prior white matter injury and the infants born at term. Furthermore this study showed a marked decrease in cortical gray matter volume in the preterm infants with prior periventricular white matter injury indicating impaired cerebral cortical development after early white matter injury[27]. In a population based study similar volumetric changes of overall brain development in preterm infants was confirmed with significant reduction of myelinated white matter and cortical gray matter in preterm infants compared to fullterm infants, with a reduction also of deep nuclear gray matter (basal ganglia) most pronounced in the lowest gestational ages[28] zand being associated with neurodevelopmental delay at 2 years of age. Regional assessment of white

matter myelination in preterm infants further revealed particular delay in myelination in the central and posterior part of the brain[29]. Assessing moderately preterm infants without signs of white matter injury cortical development could be confirmed to be similar to fullterm infants[30]. When assessing cerebellar volume at term there was a significant reduction of cerebellar volume of preterm infants when compared to term infants[31]. Unilateral cerebral white matter lesions resulted in contralateral reduction of cerebellar volume indicating the trophic interplay due to loss of cerebro-cerebellar connectivity[32]. Prematurity associated conditions such as poor growth and chronic lung disease with corticosteroid treatment led to up to 30 % reduction in cortical volume in preterm infants[33, 34].
Longterm follow-up studies of preterm infants have confirmed the permanent character of these disruptive/adaptive changes in brain development. Recent evaluations of 8 year old preterm infants with volumetric brain assessment showed persistence of cortical gray matter reduction in preterm infants accompanied with a reduction in the volume of hippocampus, which correlated with cognitive scores indicating longterm functional consequences[35]. Cerebral white matter was shown to be equally affected by preterm birth. Overall white matter volume was reduced in former preterm infants with a significant impact in males born prematurely predominantly in the cingulum, the corpus callosum and the corticospinal tracts[36].

*Cortical folding in the fetus&preterm infants*

The emergence of the cortical foldings in the preterm newborn brain was recently studied by applying dedicated post-processing tools to high quality MR images acquired shortly after birth over a developmental period critical for the human cortex development[37, 38].

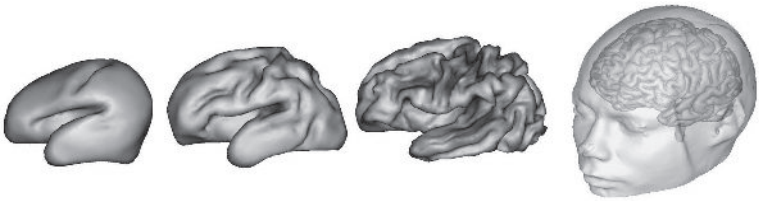

***Figure 6:*** *Examples of the 3D interface between the developing cortex and white matter zone for newborns of different gestational age and adult brain. The colors outline the surface curvature. The surfaces are not displayed with the same spatial scale*[37].

For the first time, the interface between the developing cortex and white matter zone was reconstructed coherently in 3D using an original approach, which enabled a quantitative and in vivo mapping of the individual sulci appearance. A sulcation index was derived and allowed measurement of variations with age, gender and presence of brain lesions and highlighted early inter-hemispherical structural asymmetries that may be related to the cortical functional specialisation of the brain.
Females have lower cortical surface, and smaller volumes of cortex and white matter than males, but equivalent sulcation. The highest sulcal index is found in the central region, followed by the temporo-parieto-occipital region, with the lowest sulcation index in the frontal region, which confirms that the medial surface folds before the lateral surface, and that the morphological differentiation of sulci begins in the central region, and progresses in an occipito-rostral direction. Recent applications of similar image analysis tools to MR images from the fetal brain confirm the timescale of appearance of sulci and gyri, to be similar to the results from postnatal preterm infants brain folding[39].

Changes in the intrauterine environmental conditions such as twinning and poor intrauterine growth have been shown to alter sulcation and decrease the sulcation index[37]. This finding indicates that intrinsic (genetic), as well as extrinsic (environmental), factors affect cortical folding. Size and cortical morphology has further been shown to reflect abnormal functioning or vice versa, as indicated in correlations between surface, gyrification index at birth and the neurobehavioral assessment at term equivalent age which correlates with later neurodevelopmental deficits[40].

Preterm birth, a modulator of developmentally expected environment, may be responsible for the delay that was observed in sulci appearance in comparison with post-mortem and foetal studies, as both cortical volume[28] and surface area[41] of extremely preterm infants imaged at term equivalent age are decreased and less complex than in normal infants, and this impairment seems to increase with decreasing gestational age at birth[42].
That these early changes persist into childhood and potentially adulthood has been shown. Kesler noted abnormalities in sulcation in the temporal lobes of prematurely born children when compared to term control subjects at school age[43].
Infants with early white matter lesions showed a trend to increased gyrification in overlaying cortex[44] and abnormalities in primary cortical folding have been associated with both functional development in preterm infants at term equivalent and school age[37]. Ramenghi et al had similar findings comparing infants with MRI-diagnosed white matter injury and matched PT controls with a normal MR appearance at term equivalent age with both myelination and cortical folding being significantly delayed in infants with white matter injury[(45)].

*Asymmetries in cortical folding during development*

Specific early brain asymmetries have been described in post-mortem brains but in order to study their relation to functional development in vivo assessment of these asymmetries are required. With the studies in the preterm population we were able to show that the right hemisphere presents gyral complexity earlier than the left, which is particularly evident at the level of the superior temporal sulcus (STS), which parallels early functional competence in response to auditive stimuli in preterm newborns. Inter-individual variations associated with increasing age were first detected in large cerebral regions, with a prevalence of the right hemisphere in comparison with the left. Asymmetries were further highlighted in three specific regions over the external cortical surface[46]. The authors observed deeper STS on the right side, and larger posterior region of the sylvian fissure on the left side, close to planum temporale. For the first time, this rater independent approach also detected larger anterior region of the sylvian fissure on the left side, close to Broca's region.

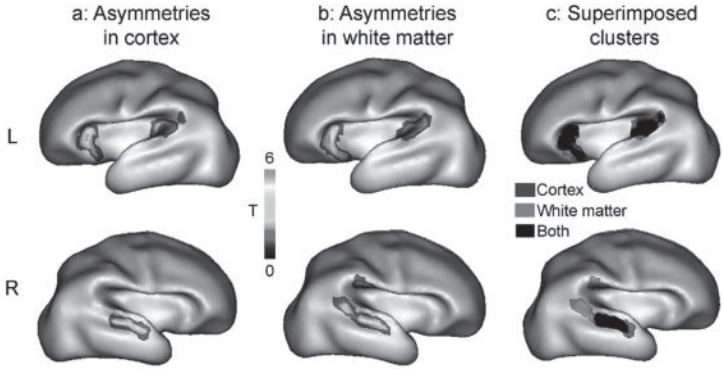


***Figure 7:*** *Inter-hemispherical asymmetries in preterm infants[46] Asymmetries are illustrated in three areas: deeper STS on the right side and larger posterior region of the sylvian fissure on the left side, close to planum temporale and larger anterior region of the sylvian fissure on the left side, close to Broca's region.*

These asymmetries go parallel with functional maturation. Very recent results from functional MRI show that preterm infants as early as term age will activate voice perception cortical areas of the right superior temporal gyrus when listening to the mother's voice (unpublished data).

During the last trimester of human pregnancy or during early weeks of life for preterm babies the macroscopic morphology of the human brain changes greatly and quickly through the formation of sulci and gyri within the cortex as shown above. The high complexity observed in the adult brain is present in the term newborn, and more specifically sulcal patterns become variable across individuals. When comparing appearance of sulci central sulci showed less inter-individual variations than parietal, temporal and frontal sulci.

Regions with the most acute variations over this age range are to be the first cortical places to fold, as well as the most spatially stable regions across individuals. It may represent the "sulcal roots" from where the primary sulci fold[47].

These data have contributed to a new extended framework for modelling cortical folding presented recently[20]. It is based on a system of reaction-

diffusion equations defined on a surface that evolves through the action of morphogens, this model allows introducing noise (just like in biology of situations such as IUGR, brain lesions) that will lead to morphological variability in the brain sulcal pattern. These new ways of studying brain development and cortical folding will finally allow us to evaluate the influence of genes and environment on the structural-functional relationship and its modulation throughout development. One day we will understand what made our brains grow globular and expand our frontal lobe a significant difference between neandertal and human brains and largely responsible for executive function and for children to perform in their classroom[48].

Understanding human brain development is clinically relevant since many neurobiological disorders and disabilities have their origin in early structural, functional development and plasticity.

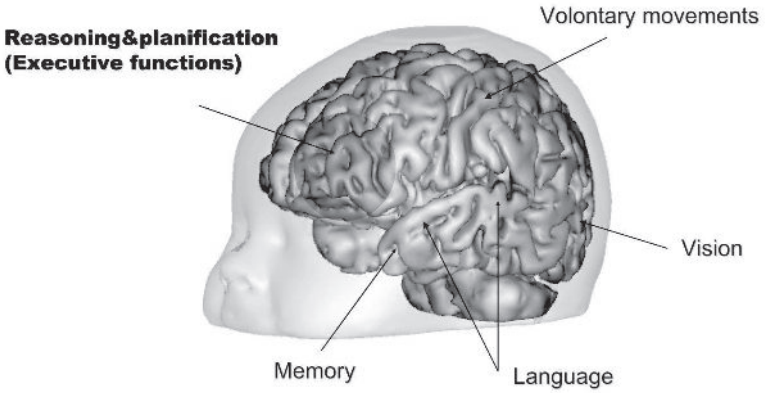


***Figure 8:*** *Structural basis of brain functions in childhood.*

With the advent of magnetic resonance imaging (MRI), it has become possible to address the question of where, when and how adverse conditions in fetal and early postnatal life and prematurity relate to the brain maturation and alteration in brain development[13]. If connectivity can be altered and plasticity understood, specific educational or behavioral therapies may be developed to restore functional connectivity and help pre-

maturely born children to face the cognitive and socio-behavioral challenges at school age.

*Thank you*

I would like to thank the Professor Dr. Max Cloëtta Foundation for honoring me with this prestigious award in Medicine including me in a impressive list of distinguished clinical and basic scientist having received the prize before me.

As most of this work is based on teamwork with many colleagues, pediatricians and neonatologists, outstanding doctoral and postdoctoral fellows I would like to thank them first for their contribution to me as their team-leader being honored today.
Of course this exciting adventure of using magnetic resonance to study the developing brain all started with Prof Norbert Herschkowitz to whom I am very grateful for having introduced me to science in medicine with great enthusiasm and has given me the opportunity to be part of the pioneering time of introducing MR in Bern in 1988. I am equally grateful to my second mentor Professor Joseph J. Volpe, Chief Neurologist at Children's Hospital Boston, who welcomed this young neonatologist from Switzerland into his team to explore the potential of magnetic resonance imaging in the newborn brain at a time when no MRI had been done on a newborn at children's hospital yet. His academic excellence, his dedication to the newborn and the developing brain and his translational approach to research have been a role model for me ever since.
Becoming a clinical scientist is impossible without the support of people and institutions that provide young doctors with the opportunity to ask new questions and have time to go in depth, for me the Swiss Academy of Medical Sciences had given me that opportunity with their stipend support. Funding research today is also a team-effort and I would like to thank the University of Geneva to give me the infrastructure to perform, the Swiss National Science Foundation for their continued support together with the EU Commission, Fondation Leenards and companies like Nestlé dedicated to science-corporate collaborations.

Finally I would like to thank my parents who have given me the strength and the self-confidence to become a woman-scientist and I would like to dedicate this award to my late father, who would be very proud of me to be honored today for my achievements in medicine.

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## Informationen über die Stiftung Prof. Dr. Max Cloëtta

Die Stiftung Prof. Dr. Max Cloëtta wurde am 27. September 1973 in Zürich von Dr. Antoine Cloëtta zu Ehren seines Vaters Prof. Dr. Max Cloëtta errichtet.

Im Absatz 1 von Art. 3 der Stiftungsurkunde wird der Zweck der Stiftung wie folgt umschrieben:

«Die Stiftung bezweckt:
a) die Unterstützung und Förderung der medizinischen Forschung sowie der damit verbundenen naturwissenschaftlichen Hilfsdisziplinen in der Schweiz;
b) die Schaffung und jährliche Verleihung eines

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Zur Auszeichnung schweizerischer und ausländischer Persönlichkeiten, die sich in besonderer Weise um bestimmte Gebiete der medizinischen Forschung verdient gemacht haben.»

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