STIFTUNG
PROFESSOR DR. MAX CLOËTTA

Achtunddreissigste Preisverleihung

9. Dezember 2011
Genf

Heft Nr. 39 der Schriftenreihe
Stiftung Professor Dr. Max Cloëtta
Schaffhauserstrasse 43, Postfach, 8042 Zürich
Telefon 044 350 44 35
Telefax 044 350 44 32
E-Mail cloetta@stiftung.ch
www.cloetta-stiftung.ch

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

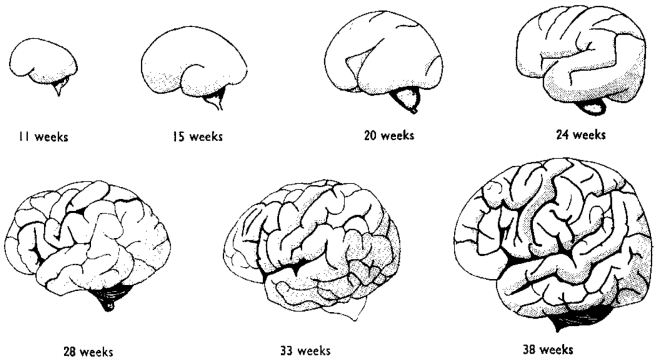

Figure 1: *Drawing of brain cortical development from Sir Peter Tizard, Neonatologist 1966 Br Med Bull 1966 22(1):49–55.*

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.

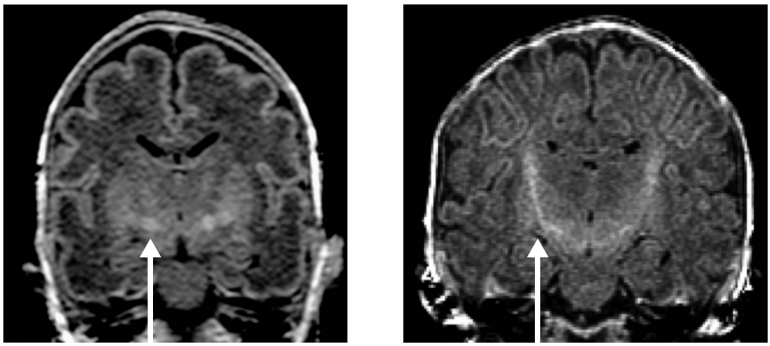

Figure 2: *T1-weighted MR Images of a preterm infant at 30wks and a fullterm newborn illustrating difference in myelin déposition. Arrows indicate areas of ongoing myelination.*

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].

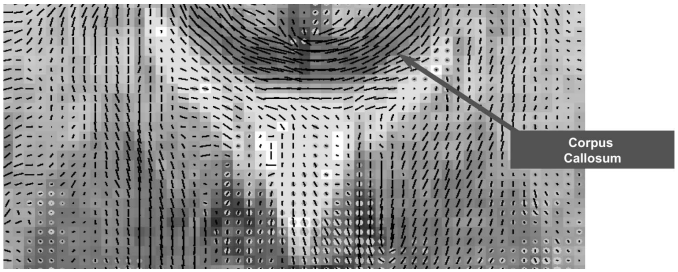

Figure 3: *Illustration of DTI eigenvector maps in the corpus callosum of a preterm brain at 28 wks gestation. Eigenvectors depict unmyelinated white matter fibertracts in the corpus callosum.*

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].

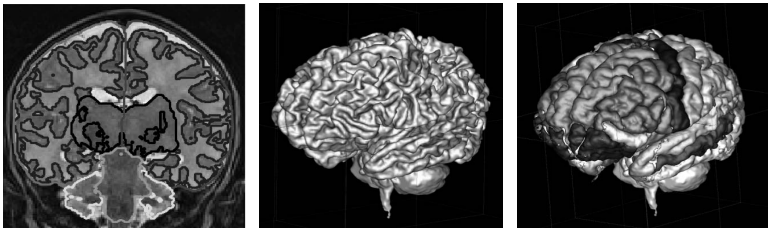

Figure 5: *Fig. 5 Newly developed segmentation technique using mathematical morphology approach (L Gui et al 2011). Surface extraction and manual labelling allows definition of cortical regions in the newborn brain[4].*

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].

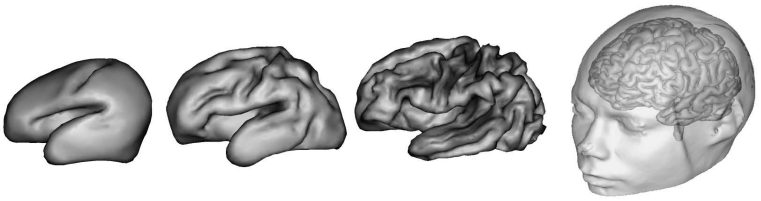

Figure 6: *Examples of the 3D interface between the developing cortex and white matter zone for newborns of different gestational age and adult brain. The colors outline the surface curvature. The surfaces are not displayed with the same spatial scale*[37].

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.

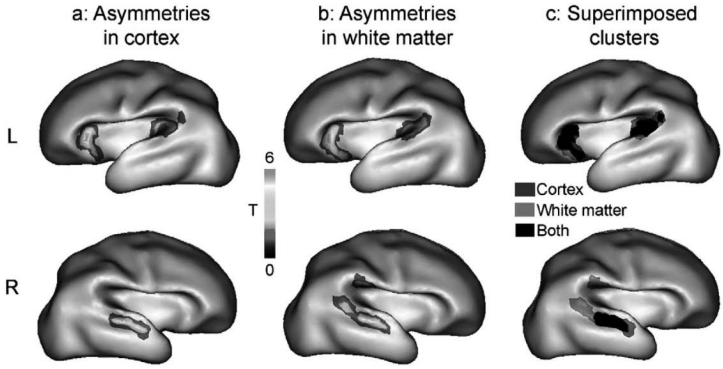

Figure 7: *Inter-hemispherical asymmetries in preterm infants[46] Asymmetries are illustrated in three areas: deeper STS on the right side and larger posterior region of the sylvian fissure on the left side, close to planum temporale and larger anterior region of the sylvian fissure on the left side,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

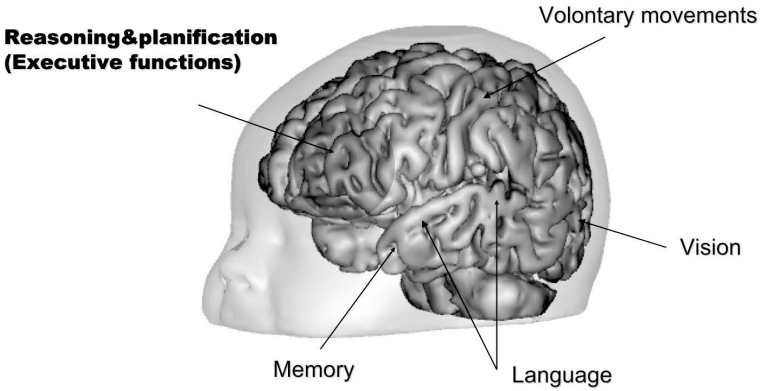

Figure 8: *Structural basis of brain functions in childhood.*

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.

REFERENCE LIST

1. Ramon y Cajal S. Textura del Sistema nervioso del Hombre y los vertebrados. 1899. Madrid, Tomo I Moya.

2. Little, W. J. The influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum on the mental and physicial condition of the child, especially in relation to deformities. Trans Obstet Soc London 3, 293–344. 1861.

3. Robinson R. J., Tizard J. P. 1966. The central nervous system in the new-born. Br Med Bull 22:49–55.

4. Virchow R. «Über das ausgebreitete Vorkommen einer dem Nervenmark analogen Substanz in den tierischen Geweben». Virchows Arch. Pathol. Anat 6, 562–572. 1854.

5. 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.

6. Kostovic I., Vasung L. 2009. Insights from in vitro fetal magnetic resonance imaging of cerebral development. Semin Perinatol 33:220–233.

7. 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.

8. 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.

9. Counsell S. J., Allsop J. M., Harrison M. C., Larkman D. J., Kennea N. L., Kapellou O., Cowan F. M., Hajnal J. V., Edwards A. D., Rutherford M. A. 2003. Diffusion-weighted imaging of the brain in preterm infants with focal and diffuse white matter abnormality. Pediatrics 112:1–7.

10. Counsell S. J., Shen Y., Boardman J. P., Larkman D. J., Kapellou O., Ward P., Allsop J. M., Cowan F. M., Hajnal J. V., Edwards A. D., Rutherford M. A. 2006. Axial and radial diffusivity in preterm infants who have diffuse white matter changes on magnetic resonance imaging at term-equivalent age. Pediatrics 117:376–386.

11. Rutherford M., Counsell S., Allsop J., Boardman J., Kapellou O., Larkman D., Hajnal J., Edwards D., Cowan F. 2004. Diffusion-weighted magnetic resonance imaging in term perinatal brain injury: a comparison with site of lesion and time from birth. Pediatrics 114:1004–1014.

12. Anjari M., Srinivasan L., Allsop J. M., Hajnal J.V., Rutherford M.A., Edwards A.D., Counsell S. J. 2007. Diffusion tensor imaging with tract-based spatial statistics reveals local white matter abnormalities in preterm infants. Neuroimage 35:1021–1027.

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. Zheng D., Purves D. 1995. Effects of increased neural activity on brain growth 1. Proc Natl Acad Sci U.S.A. 92:1802–1806.

15. Als H., Duffy F. H., McAnulty G. B., Rivkin M. J., Vajapeyam S., Mulkern R.V., Warfield S. K., Hüppi P. S., Butler S. C., Conneman N., Fischer C., Eichenwald E.C. 2004. Early experience alters brain function and structure.
2. Pediatrics 113:846–857.

16. Van Essen D. 1997. A tension-based theory of morphogenesis and compact wiring in the central nervous system. Nature 385:313–318.

17. Richman D. P., Stewart R. M., Hutchinson J.W., and Caviness V. S. Mechanical model of brain convolutional development. Science 189, 18–21.

18. Toro R., Perron M., Pike B., Richer L., Veillette S., Pausova Z., Paus T. 2008. Brain size and folding of the human cerebral cortex. Cereb Cortex 18:2352–2357.

19. Mangin J. F., Riviere D., Cachia A., Duchesnay E., Cointepas Y., Papadopoulos-Orfanos D., Scifo P., Ochiai T., Brunelle F., Regis J. 2004. A framework to study the cortical folding patterns. Neuroimage 23 Suppl. 1:S129–S138.

20. Lefevre J., Mangin J. F. 2010. A reaction-diffusion model of human brain development. PLoS Comput Biol 6:e1000749.

21. 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.

22. Kroenke C. D., Taber E. N., Leigland L. A., Knutsen A. K., Bayly P. V. 2009. Regional patterns of cerebral cortical differentiation determined by diffusion tensor MRI. Cereb Cortex 19:2916–2929.

23. 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.

24. L. Gui, R. Lisowski, T. Faundez, P. S. Hüppi, F. Lazeyras, and M. Kocher. Automatic segmentation of newborn brain MRI using mathematical morphology. submitted to the 8th IEEE International Symposium on Biomedical Imaging. 2011. Chicago.

25. Weisenfeld N. I., Warfield S. K. 2009. Automatic segmentation of newborn brain MRI. Neuroimage 47:564–572.

26. Habas P. A., Kim K., Corbett-Detig J. M., Rousseau F., Glenn O.A., Barkovich A. J., Studholme C. 2010. A spatiotemporal atlas of MR intensity, tissue probability and shape of the fetal brain with application to segmentation. Neuroimage 53:460–470.

27. 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.

28. Inder T. E., Warfield S. K., Wang H., Hüppi P. S., Volpe J. J. 2005. Abnormal cerebral structure is present at term in premature infants. Pediatrics 115:286–294.

29. Mewes A. U., Hüppi P. S., Als H., Rybicki F. J., Inder T. E., McAnulty G. B., Mulkern R. V., Robertson R. L., Rivkin M. J., Warfield S. K. 2006. Regional brain development in serial magnetic resonance imaging of low-risk preterm infants. Pediatrics 118: 23–33.

30. Zacharia A., Zimine S., Lovblad K. O., Warfield S., Thoeny H., Ozdoba C., Bossi E., Kreis R., Boesch C., Schroth G., Hüppi P. S. 2006. Early assessment of brain maturation by MR imaging segmentation in neonates and premature infants. AJNR Am J Neuroradiol 27:972–977.

31. Limperopoulos C., Soul J. S., Gauvreau K., Hüppi P. S., Warfield S. K., Bassan H., Robertson R. L., Volpe J. J., du Plessis A. J. 2005. Late gestation cerebellar growth is rapid and impeded by premature birth Pediatrics 115:688–695.

32. Limperopoulos C., Soul J. S., Haidar H., Hüppi P. S., Bassan H., Warfield S. K., Robertson R. L., Moore M., Akins P., Volpe J. J., du Plessis A. J. 2005. Impaired trophic interactions between the cerebellum and the cerebrum among preterm infants. Pediatrics 116:844–850.

33. 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.

34. Murphy B., Inder T., Hüppi P., Zientara G., Warfield S., Kikinis R., Jolesz F., Volpe J. 2001. Impaired cerebral cortical gray matter growth following treatment with dexamethasone for neonatal chronic lung disease. Pediatrics 107:217–221.

35. Lodygensky G.A., Seghier M.L., Warfield S.K., Tolsa C.B., Sizonenko S., Lazeyras F., Hüppi P.S. 2008. Intrauterine growth restriction affects the preterm infant's hippocampus. Pediatr Res 63:438–443.

36. Ment L.R., Kesler S., Vohr B., Katz K.H., Baumgartner H., Schneider K.C., Delancy S., Silbereis J., Duncan C.C., Constable R.T., Makuch R.W., Reiss A.L. 2009. Longitudinal brain volume changes in preterm and term control subjects during late childhood and adolescence. Pediatrics 123:503–511.

37. 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.

38. Hill J., Dierker D., Neil J., Inder T., Knutsen A., Harwell J., Coalson T., Van E.D. 2010. A surface-based analysis of hemispheric asymmetries and folding of cerebral cortex in term-born human infants. J Neurosci 30:2268–2276.

39. Habas P.A., Scott J.A., Roosta A., Rajagopalan V., Kim K., Rousseau F., Barkovich A.J., Glenn O.A., Studholme C. 2011. Early Folding Patterns and Asymmetries of the Normal Human Brain Detected from in Utero MRI. Cereb Cortex.

40. 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.

41. Biagioni E., Frisone M.F., Laroche S., Kapetanakis B.A., Ricci D., yi-Obe M., Lewis H., Kennea N., Cioni G., Cowan F., Rutherford M., Azzopardi D., Mercuri E. 2007. Maturation of cerebral electrical activity and development of cortical folding in young very preterm infants. Clin Neurophysiol 118:53–59.

42. Kapellou O., Counsell S.J., Kennea N., Dyet L., Saeed N., Stark J., Maalouf E., Duggan P., jayi-Obe M., Hajnal J., Allsop J.M., Boardman J., Rutherford M.A., Cowan F., Edwards A.D. 2006. Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth. PLoS Med 3:e265.

43. Kesler S.R., Vohr B., Schneider K.C., Katz K.H., Makuch R.W., Reiss A.L., Ment L.R. 2006. Increased temporal lobe gyrification in preterm children. Neuropsychologia 44(3):445–5.

44. Inder T. E., Hüppi P. S., Zientara G. P., Jolesz F. A., Holling E. E., Robertson R., Barnes P. D., Volpe J. J. 1999. The postmigrational development of polymicrogyria documented by magnetic resonance imaging from 31 weeks› postconceptional age. Ann Neurol 45:798–801.

45. Ramenghi L. A., Fumagalli M., Righini A., Bassi L., Groppo M., Parazzini C., Bianchini E., Triulzi F., Mosca F. 2007. Magnetic resonance imaging assessment of brain maturation in preterm neonates with punctate white matter lesions. Neuroradiology 49:161–167.

46. 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.

47. Lefevre J., Leroy F., Khan S., Dubois J., Hüppi P. S., Baillet S., Mangin J. F. 2009. Identification of growth seeds in the neonate brain through surfacic Helmholtz decomposition. Inf Process Med Imaging 21:252–263.

48. Gibbons A. 2010. Paleoanthropology. Neandertal brain growth shows a head start for moderns. Science 330:900–901.

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

Cloëtta-Preises

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

Stiftungsrat

Im Jahr 2011 setzt sich der Stiftungsrat wie folgt zusammen:

Prof. Dr. Adriano Fontana *	Universität Zürich Hertie-Senior Forschungsprofessor	Präsident des Stiftungsrates und des Medizinischen Ausschusses
Dr. Hans Bollmann	Rechtsanwalt, Zürich	Vizepräsident des Stiftungsrates
Prof. Dr. Hugues Abriel*	Universität Bern Departement Klinische Forschung	Mitglied des Stiftungsrates
Prof. Dr. Martin Janssen	Universität Zürich Institut für Banking und Finance, Präsident der Ecofin-Gruppe	Mitglied des Stiftungsrates
Prof. Dr. Peter Meier-Abt*	Universität Basel Vizerektorat Forschung	Mitglied des Stiftungsrates
Prof. Dr. Susanne Suter *	Hôpital Universitaire de Genève Département de Pédiatrie	Mitglied des Stiftungsrates
Prof. Dr. Bernard Thorens *	Université Lausanne Centre intégratif de génomique	Mitglied des Stiftungsrates

*Mitglieder des Medizinischen Ausschusses

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

Heft Nr. 1 (6. Auflage 2000):
Vorwort von Bundesrätin Ruth Dreifuss
Biographie von Professor Dr. Max Cloëtta
Biographie von Dr. Antoine Cloëtta
Übersicht über die Stiftung Professor Dr. Max Cloëtta
Ehrentafel der Preisträger
Organe der Stiftung

Heft Nr. 2:
Preisverleihung 1974
Festvortrag des Preisträgers Dr. med. Urs A. Meyer:
«Klinische Pharmakologie – eine Herausforderung für interdisziplinäre Zusammenarbeit»

Heft Nr. 3:
Preisverleihung 1975
Festvortrag des Preisträgers Dr. med. Hans Bürgi:
«Die Bekämpfung des Kropfes in der Schweiz. Ein Beispiel der Zusammenarbeit zwischen Grundlagenwissenschaftern, Kliniken und Behörden»

Heft Nr. 4:
Cérémonie de remise du prix 1976
Exposé du Dr. Rui C. de Sousa, sur le thème:
«La membrane cellulaire: une frontière entre deux mondes»

Heft Nr. 5:
Preisverleihung 1977
Festvortrag des Preisträgers Professor Dr. Franz Oesch:
«Chemisch ausgelöste Krebsentstehung»

Heft Nr. 6:
Preisverleihung 1978
Festvortrag des Preisträgers Dr. Susumu Tonegawa:
«Cloning of Immunoglobulin Genes»

Heft Nr. 7:
Preisverleihung 1979
Festvorträge der beiden Preisträger
Professor Dr. Theodor Koller:
«Die strukturelle Organisation des genetischen Apparates höherer Organismen»
Professor Dr. Jean-Pierre Kraehenbuehl:
«Hormonal Control of the Differentiation of the Mammary Gland»

Heft Nr. 8:
Preisverleihung 1980
Festvorträge der beiden Preisträger
Professor Dr. Edward W. Flückiger:
«Neue Aspekte der Mutterkorn-Pharmakologie»
PD Dr. Albert Burger:
«Ein Vierteljahrhundert nach Entdeckung des aktivsten Schilddrüsenhormons (Trijodothyronin)»

Heft Nr. 9:
Preisverleihung 1981
Festvorträge der beiden Preisträger
Professor Dr. Rolf Zinkernagel:
«‹Selbst›-Erkennung in der Immunologie»
Professor Dr. Peter A. Cerutti:
«A role for active oxygen species in human carcinogenesis?»

Heft Nr. 10:
Preisverleihung 1982
Festvorträge der beiden Preisträger
PD Dr. Jürgen Zapf:
«Wachstum und Wachstumsstörungen: ein gemeinsames Forschungsziel der klinischen und experimentellen Endokrinologie»
PD Dr. Jean-Michel Dayer:
«Le monocyte-macrophage: un pivot entre le système immun et le tissu conjonctif dans le processus inflammatoire de l'arthrite rhumatoïde»

Heft Nr. 11:
Preisverleihung 1983
Festvorträge der beiden Preisträger
Professor Dr. Peter Böhlen:
«Peptides and Proteins as messengers in the communication between cells and organs»
PD Dr. Claes B. Wollheim:
«Regulation of insulin release by intracellular calcium»

Heft Nr. 12:
Preisverleihung 1984
Festvorträge der beiden Preisträger
Frau Professor Dr. Heidi Diggelmann:
«Beiträge der Retroviren zur Aufklärung grundlegender biologischer Prozesse»
Professor Dr. Jean-François Borel:
«Entwicklung und Bedeutung des Ciclosporins»

Heft Nr. 13
Preisverleihung 1985
Festvorträge der beiden Preisträger
Professor Dr. Hans Thoenen:
«Entwicklungsneurobiologie; von der deskriptiven Analyse zum molekularen Verständnis»
Dr. Roberto Montesano:
«Cell-Extracellular Matrix Interactions in Organogenesis»

Heft Nr. 14:
Preisverleihung 1986
Festvorträge der beiden Preisträger
Professor Dr. Ueli Schibler:
«Mechanismen der gewebespezifischen Regulation von Genen»
Professor Dr. Walter Schaffner:
«Enhancer-Sequenzen und die Regulation der Gen-Transkription»

Heft Nr. 15
Preisverleihung 1987
Festvorträge der beiden Preisträger
Professor Dr. Jacques Louis:
«Rôle des lymphocytes T spécifiques sur l'évolution des lésions induites par leishmania major, un parasite vivant dans les macrophages de leur hôte»
Professor Dr. Joachim H. Seelig:
«Magnetische Resonanz – ein ‹magnetisches Auge› zur Untersuchung der Lebensvorgänge in vivo»

Heft Nr. 16:
Preisverleihung 1988
Festvorträge der beiden Preisträger
Professor Dr. Jean-Dominique Vassalli:
«Protéolyse et migrations cellulaires: Multiples facettes du contrôle d'une cascade enzymatique»
PD Dr. Hans Hengartner:
«Über die immunologische Toleranz»

Heft Nr. 17:
Preisverleihung 1989
Festvorträge der beiden Preisträger
Professor Dr. Heini Murer:
«Parathormon: Auf dem Weg zum Verständnis seiner Wirkung im proximalen Tubulus»
Dr. Hugh Robson MacDonald:
«Selection of the T Cell Antigen Receptor Repertoire during Development»

Heft Nr. 18:
Preisverleihung 1990
Festvorträge der beiden Preisträger
Professor Dr. Martin E. Schwab:
«Entwicklung, Stabilisierung und Regeneration von Faserverbindungen in Gehirn und Rückenmark: Die Rolle von Nervenwachstums-Hemmstoffen»
Professor Dr. Denis Monard:
«Protéases et inhibiteurs extracellulaires dans le système nerveux»

Heft Nr. 19:
Preisverleihung 1991
Festvorträge der beiden Preisträger
PD Dr. Peter J. Meier-Abt:
«Die Ausscheidungsfunktionen der Leber: Rolle von Membrantransport-Systemen»
PD Dr. Jacques Philippe:
«Structure and pancreatic expression of the insulin and glucagon genes»

Heft Nr. 20:
Preisverleihung 1992
Festvorträge der beiden Preisträger
PD Dr. Leena Kaarina Bruckner-Tuderman:
«Molecular Pathology of the Epidermal-Dermal Interface in Skin»
Professor Dr. Jürg Tschopp:
«Das Phänomen der von Lymphozyten vermittelten Zellyse»

Heft Nr. 21:
Preisverleihung 1993
Festvorträge der drei Preisträger
Dr. Paolo Meda:
«Cell-to-cell Communication and Pancreas Secretion»
Professor Dr. Adriano Fontana:
«Transforming Growth Factor Beta 2, ein von Tumorzellen gebildetes Zytokin mit immunparalysierender Wirkung»
Professor Dr. Michel Aguet:
«Neue Erkenntnisse zur Biologie und Molekularbiologie der Interferone»

Heft Nr. 22:
Preisverleihung 1994
Festvorträge der beiden Preisträger
Professor Dr. rer. nat. Hans Rudolf Brenner:
«Die Regulation der Expression synaptischer Transmitter-Rezeptoren während der Synapsenbildung»
Daniel Pablo Lew, Professeur ordinaire de médecine:
«Signal Transduction and Ion Channels Involved in the Activation of Human Neutrophils»

Heft Nr. 23:
Preisverleihung 1995
Festvorträge der beiden Preisträger
Professor Dr. Jürg Reichen:
«Die sinusoidale Endothelzelle und Leberfunktion»
Dr. George Thomas jr.:
The $p70^{s6k}$ Signal Transduction Pathway, S6, Phosphorylation and Translational Control»

Heft Nr. 24:
Preisverleihung 1996
Festvorträge der beiden Preisträger
Dr. Lukas C. Kühn:
«Molekulare Mechanismen zur Steuerung des Eisenstoffwechsels»
Professor Dr. Peter Sonderegger:
«Wegweiser- und Sensormoleküle beim gezielten Wachstum der Nervenzellausläufer»

Heft Nr. 25:
Preisverleihung 1997
Festvorträge der beiden Preisträger
Dr. Gérard Waeber:
«Métabolisme moléculaire de la cellule insulino-sécrétrice»
Professor Dr. Denis Duboule:
«Genetic control of limb morphogenesis and evolution»

Heft Nr. 26:
Preisverleihung 1998
Festvorträge der beiden Preisträger
Professor Dr. Adriano Aguzzi:
«Pathophysiologie der Prionen-Krankheiten»
Professor Dr. Primus E. Mullis:
«Short stature: from the growth hormone axis
to the Development of the pituitary gland»

Heft Nr. 27:
Preisverleihung 1999
Festvorträge der beiden Preisträger
Professor Dr. Clemens A. Dahinden:
«Pathophysiologie der allergischen Entzündung»
Professor Dr. Antonio Lanzavecchia:
«Deciphering the signals that regulate T cell
mediated immunity»

Heft Nr. 28:
Preisverleihung 2000
Festvorträge der beiden Preisträger
Professor Dr. Giuseppe Pantaleo:
«Mechanisms of human immunodeficiency virus (HIV) escape
from the immune response»
Dr. Brian A. Hemmings:
«Protein kinase B (PBK/Akt) – a common element in multiple
signaling pathways involved in insulin signaling, cell survival
and cancer»

Heft Nr. 29:
Preisverleihung 2001
Festbeiträge der beiden Preisträger
Professor Dr. Isabel Roditi:
«The surface coat of african trypanosomes»
Dr. Thierry Calandra:
«Innate immune responses to bacterial infections: a paradigm for exploring the pathogenesis of septic shock»

Heft Nr. 30:
Preisverleihung 2002
Festbeiträge der beiden Preisträger
Professor Dr. Bernard Thorens:
«Impaired Glucose Sensing as Initiator of Metabolic Dysfunctions»
Professor Dr. Andrea Superti-Furga:
«Molecular Pathology of Skeletal Development»

Heft Nr. 31:
Preisverleihung 2003
Festbeiträge der beiden Preisträger
Professor Dr. Michael Nip Hall:
«TOR Signalling: from bench to bedside»
PD Dr. Bernhard Moser:
«Chemokines: role in immune cell traffic»

Heft Nr. 32:
Preisverleihung 2004
Festbeiträge der beiden Preisträger
Professor Dr. Amalio Telenti:
«Adaption, co-evolution, and human susceptibility to HIV-1 infection»
Professor Dr. Radek C. Skoda:
«The control of normal and aberrant megakaryopoiesis by thrombopoietin and its receptor, c-MPL»

Heft Nr. 33:
Preisverleihung 2005
Festbeiträge der beiden Preisträger
Professor Dr. Urs Emanuel Albrecht:
«The circadian clock: orchestrating gene expression and physiology»
Professor Dr. Dominique Muller:
«Functional and structural plasticity of synaptic networks»

Heft Nr. 34:
Preisverleihung 2006
Festbeiträge der beiden Preisträger
Professor Dr. Adrian Merlo:
«Pas de mythe de Sisyphe: Glioma research on the move»
Professor Dr. Michael O. Hengartner:
«Roads to ruin: apoptotic pathways in the nematode Caenorhabditis elegans»

Heft Nr. 35:
Preisverleihung 2007
Festbeiträge der beiden Preisträger
Professor Dr. François Mach:
«Inflammation is a Crucial Feature of Atherosclerosis and a Potential Target to Reduce Cadriovascular Events»
Professor Dr. Nouria Hernandez:
«Mechanisms of RNA Polymerase III Transcriptions in Human Cells»

Heft Nr. 36:
Preisverleihung 2008
Festbeiträge der beiden Preisträger
Professor Dr. Darius Moradpour:
«Hepatitis C: Molecular Virology and Antiviral Targets»
Professor Dr. Sabine Werner:
«Molecular and cellular mechanisms of tissue repair»

Heft Nr. 37:
Preisverleihung 2009
Festbeiträge der beiden Preisträger
Professor Dr. Margot Thome-Miazza:
«Molecular mechanisms controlling lymphocyte proliferation and survival»
Professor Dr. Walter Reith:
«Regulation of antigen presentation in the immune system»

Heft Nr. 38:
Preisverleihung 2010
Festbeiträge der beiden Preisträger Professor Dr. Christan Lütscher:
«Sucht: Die dunkle Seite des Lernens»
Professor Dr. Burkhard Becher:
«Cytokine networks: the language of the immune system»

EHRENTAFEL
DER PREISTRÄGER

1974 Dr. Urs A. Meyer

1975 PD Dr. Hans Bürgi

1976 Dr. Rui de Sousa

1977 Prof. Dr. Franz Oesch

1978 Dr. Susumu Tonegawa

1979 Prof. Dr. Theodor Koller
Prof. Dr. Jean-Pierre Kraehenbuehl

1980 Prof. Dr. Edward W. Flückiger
PD Dr. Albert Burger

1981 Prof. Dr. Rolf M. Zinkernagel
Prof. Dr. Peter A. Cerutti

1982 PD Dr. Jürgen Zapf
PD Dr. Jean-Michel Dayer

1983 Prof. Dr. Peter Böhlen
PD Dr. Claes B. Wollheim

1984 Prof. Dr. Heidi Diggelmann
Prof. Dr. Jean-François Borel

1985 Prof. Dr. Hans Thoenen
Dr. Roberto Montesano

1986 Prof. Dr. Walter Schaffner
Prof. Dr. Ueli Schibler

1987 Prof. Dr. Jacques Louis
Prof. Dr. Joachim H. Seelig

1988 Prof. Dr. Jean-Dominique Vassalli
PD Dr. Hans Hengartner

1989 Prof. Dr. Heini Murer
Dr. Hugh Robson MacDonald

EHRENTAFEL
DER PREISTRÄGER

1990 Prof. Dr. Martin E. Schwab
Prof. Dr. Denis Monard

1991 PD Dr. Peter J. Meier-Abt
PD Dr. Jacques Philippe

1992 PD Dr. Leena Kaarina Bruckner-Tuderman
Prof. Dr. Jürg Tschopp

1993 Dr. Paolo Meda
Prof. Dr. Adriano Fontana
Prof. Dr. Michel Aguet
} Jubiläumsjahr

1994 Prof. Dr. Hans Rudolf Brenner
Prof. Dr. Daniel Pablo Lew

1995 Prof. Dr. Jürg Reichen
Dr. George Thomas jr.

1996 Dr. Lukas C. Kühn
Prof. Dr. Peter Sonderegger

1997 Dr. Gérard Waeber
Prof. Dr. Denis Duboule

1998 Prof. Dr. Adriano Aguzzi
Prof. Dr. Primus E. Mullis

1999 Prof. Dr. Clemens A. Dahinden
Prof. Dr. Antonio Lanzavecchia

2000 Prof. Dr. Giuseppe Pantaleo
Dr. Brian A. Hemmings

2001 Prof. Dr. Isabel Roditi
Dr. Thierry Calandra

2002 Prof. Dr. Bernard Thorens
Prof. Dr. Andrea Superti-Furga

EHRENTAFEL
DER PREISTRÄGER

2003 Prof. Dr. Michael Nip Hall
PD Dr. Bernhard Moser

2004 Prof. Dr. Amalio Telenti
Prof. Dr. Radek C. Skoda

2005 Prof. Dr. Urs Emanuel Albrecht
Prof. Dr. Dominique Muller

2006 Prof. Dr. Adrian Merlo
Prof. Dr. Michael O. Hengartner

2007 Prof. Dr. François Mach
Prof. Dr. Nouria Hernandez

2008 Prof. Dr. Darius Moradpour
Prof. Dr. Sabine Werner

2009 Prof. Dr. Margot Thome-Miazza
Prof. Dr. Walter Reith

2010 Prof. Dr. Christian Lüscher
Prof. Dr. Burkhard Becher

2011 Prof. Dr. Petra S. Hüppi