



# Rudolf Magnus Institute of Neuroscience

Rudolf Magnus Bulletin 16  
October 2005

## interview

### Decreased SMN protein associated with ALS

**ALS (amyotrophic lateral sclerosis) is a fatal and incurable disease of the motor neurons. In order to understand the contribution of genetic make-up to the development of ALS, Jan Veldink determined the contribution of the Survival Motor Neuron (SMN) genes on ALS. Veldink found that SMN genotypes producing less SMN protein increase both susceptibility to and severity of sporadic ALS. This indicates that increasing the SMN protein production may be a future lever to slow down ALS progression.**

ALS is a progressive disease of the motor neurons, which is one of the diseases studied in the Section Neuromuscular Disease of our Institute. The muscle cells no longer under control of the motor neurons gradually weaken and waste away. Sometimes the strength in hands, arms and legs is lost first or sometimes speech or swallowing problems are the first indications. Death occurs when the respiratory muscles become paralysed - on average about three years after onset of symptoms. ALS develops in adulthood with its incidence peaking between the ages of forty and sixty. In approximately 10-20% of patients ALS is familial with clear indications of genetic involvement. Inheritance is usually autosomal dominant, but autosomal recessive modes of inheritance have been reported also. In 80-90% of cases however its cause is unknown and referred to as sporadic.



Veldink explains the rationale of his study, "There is another, related motor neuron disease, Spinal Muscular Atro-

phy (SMA), which may shed light on the effects of genetic background on sporadic ALS. SMA is an autosomal recessive disorder, caused by mutations in the *SMN* genes. There are two highly homologous *SMN* genes, *SMN1*, mutation of which causes SMA and which produces relative high amount of SMN protein, and *SMN2* producing only 20% of the SMN protein compared to *SMN1*. Both *SMN1* and 2 may occur in up to 4 copies, whereas in some patients the *SMN2* gene is absent. Since SMA and ALS are both motor neuron diseases it seemed plausible that the *SMN* genes are somehow involved in ALS."

The large span of possible *SMN* genotypes was determined within a well characterized patient population of 242 sporadic ALS patients and 175 controls. Veldink found, that having only one copy of *SMN1* was associated with an increased risk of developing ALS (odds ratio 4.1,  $p = 0.02$ ). Also ALS patients were shown to carry fewer *SMN2* copy numbers ( $p = 0.001$ ). As ALS patients had generally a smaller number of *SMN* gene copies the calculated total amount of SMN protein was significantly lower in ALS patients. Lower *SMN2* copy numbers as well as lower estimated SMN protein levels were associated with increased mortality rate of sporadic ALS patients. These data will soon be published in *Neurology* (epub, August 2005).

As Veldink speculates on the clinical use of his data: "The function of the SMN protein is as yet unknown. It seems however that higher SMN protein levels protect against ALS and slow down the disease progress. Although actual protein expression measurements are needed to confirm our results, clinical trials with agents that activate the *SMN* promoter could extend survival of patients with ALS. Several agents are known to up-regulate SMN protein synthesis *in vitro*, in particular valproic acid, which is an attractive candidate for a clinical trial in patients since this is a safe FDA-approved compound with a well-known pharmacokinetic profile."

Jan H. Veldink (MD, Utrecht University, 1998) is a resident in Neurology in the Department of Neurology. On May 25<sup>th</sup>, 2004, he earned his PhD degree on a thesis entitled 'Factors determining risk and outcome in Amyotrophic Lateral Sclerosis', which included the work as described in the present interview (supervisors, John Wokke, Dop Bär, and Leonard Van den Berg). Despite his extensive clinical duties, he is still actively involved in the ongoing ALS research.

## PhD theses

2005-30

### Management of brain trauma under pressure

October 5, 2005

Olaf L. Cremer

#### Goal-directed intensive care of traumatic brain injury: pathophysiological and clinical studies

C.J. Kalkman, K.G.M. Moons, G.W. Van Dijk  
supervisors

The main goal of neurosurgical intensive care in comatose patients with head injuries is to prevent secondary neuronal damage resulting from ischemia and tissue hypoxia. Olaf Cremer examined the rationale and risk-to-benefit ratio of aggressive manipulation of blood pressure, intracranial pressure, cerebral perfusion pressure, and temperature in head trauma patients. He concludes that there is little evidence to manage these variables at strictly controlled values in each patient, and stresses the necessity to individualise treatment in the future, so that optimal therapy can be offered with a reduced risk of complications.

In two clinical experiments, Cremer sought to determine the effects of varying temperature and blood pressure on the regulation of cerebral blood flow and brain tissue oxygenation in patients. He found that hyperthermia caused transient cerebral vasoparalysis, but did not impair brain oxygenation. The effects of blood pressure augmentation by vasopressors varied between patients and from day to day. However, intervention generally seemed to be beneficial only when intracranial hypertension was present. In a large cohort study Cremer subsequently found that aggressive management of intracranial pressure and cerebral perfusion pressure at strictly controlled values resulted in increased levels of therapy intensity and a much-prolonged stay in the intensive care unit, but not in improved neurological outcome. Furthermore, aggressive therapy that included the use of both vasopressors and high-dose propofol infusions to suppress cerebral metabolic demand for oxygen proved to be associated with a rare, but lethal cardiac complication.



Cremer concludes that, due to a large heterogeneity within the head trauma population, clinical algorithms to retain certain physiological parameters within rigid and arbitrary limits at all times are likely unnecessary or unrealistic for some patients. Therefore randomised, controlled manage-

ment trials are needed that are targeted at specific subgroups of head-injured patients with a certain cerebral pathology and an intermediate prognosis. To assist in patient selection for such trials, Cremer developed (and validated) a prediction rule to estimate the prognosis of patients who remain comatose for more than 24 hours after severe blunt head trauma.

**Olaf Cremer** (March 23, 1971, Rotterdam). Secondary education (Bisschoppelijk College Schöndeln, Roermond), 1989; Medical School at Utrecht University, MD in 1997; MSc in Clinical Epidemiology (Netherlands Institute for Health Sciences, Rotterdam), 2001. From 1999 until 2005 he has worked as a resident in Anaesthesiology (UMC Utrecht), during which period he performed the research described in the thesis.

2005-31

October 6, 2005

P.J. Stienen

#### Development of a rat model to assess analgesic efficacy using somatosensory-evoked potentials

L.J. Hellebrekers, A.J. Venker-Van Haagen,  
W.E. Van den Brom  
supervisors

2005-32

October 7, 2005

P.J.E.C. Wijchers

#### Forkhead transcription factors in brain development. 'Fox chasing in midbrain dopaminergic neurons'

J.P.H. Burbach, M.F.M. Hoekman, M.P. Smid  
supervisors

2005-33

October 11, 2005

W. Opstelten

#### Herpes zoster and postherpetic neuralgia in general practice

Th.J.M. Verheij, C.J. Kalkman, K.G.M. Moons,  
G.A. Van Essen  
supervisors

2005-34

### ELANA comes of age

October 25, 2005

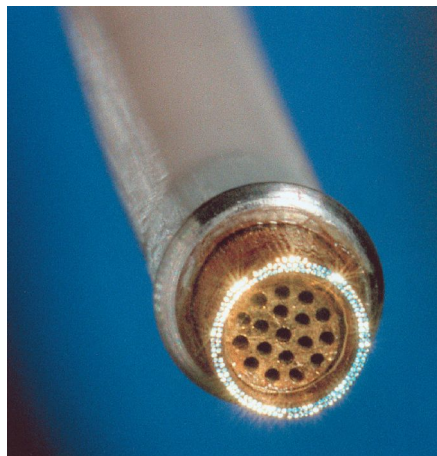
Henk Johan N. Streefkerk

#### The ELANA technique: application in experimental and clinical settings

C.A.F. Tulleken, B. Hillen, R.M. Verdaasdonk,  
A. Van der Zwan  
supervisors

High flow revascularization of the brain is hampered by the fact that temporary occlusion of a major cerebral artery is necessary to create the distal anastomosis, which may result in brain ischemia. Henk Johan Streefkerk contributed to the development of

the excimer laser-assisted non-occlusive anastomosis (ELANA) technique to make anastomoses to the major cerebral arteries. He evaluated use of this technique and studied the re-endothelialization of the anastomosis in animals. In clinical practice the ELANA technique met all the safety criteria and appeared the technique of choice for difficult to reach areas in the brain and in cases that are notoriously difficult to operate, such as giant aneurysms.



The ELANA technique allows for end-to-side anastomosis to a cerebral artery without occluding that recipient artery. First a graft with a platinum ring in its distal end is stitched onto the wall of the recipient. Then a laser catheter (see photograph) is inserted inside the graft, so that the tip touches the wall of the recipient artery within the platinum ring. Vacuum suction is activated within the laser catheter, ensuring a firm fixation of the laser fibres to the wall of the recipient artery. When the laser is activated, a hole is burned in the wall, effectively creating the anastomosis. Upon retraction of the laser catheter, the punched-out portion of arterial wall is also withdrawn with the catheter because of the continued vacuum suction. Attaching the free end of the graft with another graft will complete the bypass procedure. The sideways anastomosis leaves a rim of medial and adventitial layers of the vessel exposed to the blood-stream. In experimental settings (in a model and in pigs), Streefkerk showed that in long-term experiments ELANA anastomoses will re-endothelialise comparable with conventional end-to-end anastomoses. Re-endothelialisation of the platinum ring starts within 4 days, and completes within 2 weeks, after which the anastomoses are wide open, fully round, and with a continuous layer of endothelium covering the inside of the anastomosis. Streefkerk concludes that the re-endothelialisation of ELANA anastomoses in human is likely to occur, which was confirmed in four patients post-mortem.

The ELANA technique has been used since 1996 in many patients with giant intracranial aneurysms. After evaluating the most complicated applications (intracranial-to-intracranial bypasses surgery) Streefkerk concludes that the techniques is at least as safe as other forms of cerebral revascularisation using bypass surgery. Moreover, its ease of use and non-occlusive nature make it the technique of choice for notoriously difficult bypass operations in the treatment of intracranial giant aneurysms.

**Henk Johan Streefkerk** (October 27, 1974, Malang, Indonesia). Secondary school (Christelijk Lyceum, Zeist), 1992; Medicine at Utrecht University; MD, 2004. From 1999-2005 he worked on the ELANA technique as described in his thesis. Presently he is a resident in Otorhinolaryngology at the Radboud UMC, Nijmegen.

2005-35

## Functioning with Spina Bifida

October 25, 2005

Marjolein Verhoef

**Spina bifida: implications for functioning and health in young adults**

**A.J.H. Prevo, M.W.M. Post, F.W.A. Van Asbeck, R.H.J.M. Gooskens**  
supervisors

Spina bifida is a disabling disorder caused by a developmental lesion in the spinal cord, which is often accompanied by hydrocephalus. Due to improved health care nowadays most patients reach adulthood. There is however little information about health problems of this patient group of young adults. Marjolein Verhoef determined functioning and health in young adults with spina bifida. In particular faecal and urinary incontinence are widespread and severely hamper functioning of these patients. Patients with hydrocephalus suffer more health problems in general than patients without hydrocephalus. She finds that spina bifida patients need continued care by specialised teams to meet their health needs.

Verhoef included 179 patients (16-25 yrs), which were representative for the spina bifida population in the Netherlands, and performed a broad survey of health issues. Many spina bifida patients, especially young adults with hydrocephalus and/or a high level of lesion, suffer from secondary impairments such as urinary and/or faecal incontinence, constipation, foot deformities, scoliosis and needed devices for their mobility. Most young adults with spina bifida are sexually active. Young adults with hydrocephalus are less active in relationships and sexuality than those without hydrocephalus and face more problems concerning these issues.

Most young adults with spina bifida are independent in activities of daily living. Individuals with hydrocephalus and a high level of lesion frequently need support with sphincter control, locomotion and self-care. The perceived health of young adults with spina bifida is poorer than of an age-matched norm population, but differences are small except in the domain of physical functioning.

Spina bifida appears a diagnosis with a variety of manifestations. Verhoef's most important recommendation is that medical care for young adults with spina bifida should be available, preferably by specialized multidisciplinary teams. A core team should, at the very least, consist of a rehabilitation physician and a urologist. Verhoef further suggests starting longitudinal cohort studies to determine the long-term outcome (including psychosocial aspects) of spina bifida patients, in relation to characteristics at birth and ageing. Also further research on incontinence and adequacy of bladder and bowel management should be encouraged.

**Marjolein Verhoef** (September 27, 1970, Maartensdijk). Secondary education (College Blaucapel, Utrecht), 1989; Health Sciences Maastricht University, 1995, Medicine Maastricht University, MD 1998. From 1998-2005 she was resident in Rehabilitation Medicine, while working on the research as described in this thesis. In September 2006 she will be registered as Rehabilitation Specialist.

## Rudolf Magnus Graduate School Certificates

The Director and the Research Training Committee of the Graduate School took pleasure in presenting the Rudolf Magnus Graduate School Certificate to the following Doctors:

Judy Veldhuijzen (September 8, 2005)  
Ineke Bos (September 23, 2005)  
Manon Boeschoten (September 29, 2005)

## Frank Van Genderen wins Horoszowski Award

At the 9<sup>th</sup> Musculoskeletal Congress of the World Federation of Haemophilia (11 September 2005, Istanbul, Turkey) Frank Van Genderen (PhD student, section Neuromuscular Diseases) received the Henri Horoszowski Memorial Award for his paper, 'The haemophilia activities list: final development and validation of a haemophilia-specific self-assessment questionnaire on functional abilities', by F.R. Van Genderen, N.L.U. Van Meeteren, L. Heijnen, P. De Kleijn, H.M. Van den Berg, P.J.M. Helders. The Award, a silver plaque, is awarded at each Musculoskeletal Meeting of the World Federation of Haemophilia to the best original paper.

## Rudolf Magnus Gift-box

Still freely available for all guest speakers and PhD graduates: the Rudolf Magnus Gift-box. Contact the Institute's Office, Jan Dekker, Stratum Building, Room 5-135.



## Presenting Rudolf Magnus Posters

The Institute provides model posters which will help anyone who prepares posters for national or international presentations. The posters show correct use of affiliation, logo, and colours, and provide directions for general layout. The model posters can be downloaded from the website, <http://www.rudolfmagnus.nl> (go to 'Training and Education', and 'Making posters'). For questions contact, [j.dekker@med.uu.nl](mailto:j.dekker@med.uu.nl).



## October 20, Rudolf Magnus Seminar

**Guus Smit** (Inst. Neurosciences, Vrije Universiteit, Amsterdam)  
'Acetylcholine Binding Protein (AChBP): A structural and functional model of the ligand binding domain of the nicotinic acetylcholine receptor'.  
9:00-10:00, Room 4.208, Stratum Building UMC Utrecht  
contact, [j.pasterkamp@med.uu.nl](mailto:j.pasterkamp@med.uu.nl)

## October 20, Rudolf Magnus Seminar

**Christian Broberger** (Karolinska Institute, Sweden)  
'Neuropeptides shifting the forebrain between sleep and wakefulness'  
16:00-17:00, Room 4.208, Stratum Building, UMC Utrecht  
Contact, [r.a.h.adan@med.uu.nl](mailto:r.a.h.adan@med.uu.nl)

## October 28, 27<sup>th</sup> 'PUK' Psychiatry symposium

'Which patients, which doctors?' (Programme in Dutch)  
9:45-16:00, Pink Lecture Hall, UMC Utrecht  
Contact, [e.schreurs@azu.nl](mailto:e.schreurs@azu.nl)

## November 24-25, Annual Meeting PhD students

Conference Centre Woudschoten, Zeist  
Information, <http://www.rudolfmagnus.nl>

## November 30, Rudolf Magnus Symposium and Rudolf Magnus Research Award 2005

Speakers are Chantal Kemner, Jaap Kappelle, Herman Westenberg, and Berry Spruijt.  
Keynote, **Michael Gazzaniga** (Hanover NH, USA)  
'Brain Mechanism of Conscious Experience'  
13:30-18:00, Green Lecture Hall, UMC Utrecht  
Programme, <http://www.rudolfmagnus.nl>

## November 30, An Evening with Rudolf Magnus

A unique mixture of social and scientific events is organised following the Rudolf Magnus Symposium. While diner is served, you will be entertained with good science and sparkling acts by some of your artistically talented colleagues.  
18:00-20:30, Foyer of the Stratum Building, UMC Utrecht  
The evening programme is freely accessible for all members of the Rudolf Magnus Institute. Registration however is required.  
Contact Marijke Van de Nadort, [m.vandenadort@med.uu.nl](mailto:m.vandenadort@med.uu.nl)

## November 28 – December 2, Introductory Course for PhD students

Course organised to introduce PhD students of the Rudolf Magnus Graduate School and the Graduate School ONWA (Amsterdam) to the research in both graduate schools.  
Information and registration, <http://www.rudolfmagnus.nl>