



RESEARCH ACTIVITY

at the
Department of Otorhinolaryngology

April 2014



**Karolinska
Institutet**

KAROLINSKA
Universitetssjukhuset

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Eva Munck Wikland, Professor
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Wolf-Dieter Baumgartner, Guest Professor
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Dan Bagger-Sjöbäck, Professor Emeritus
Ulf Rosenhall, Professor Emeritus

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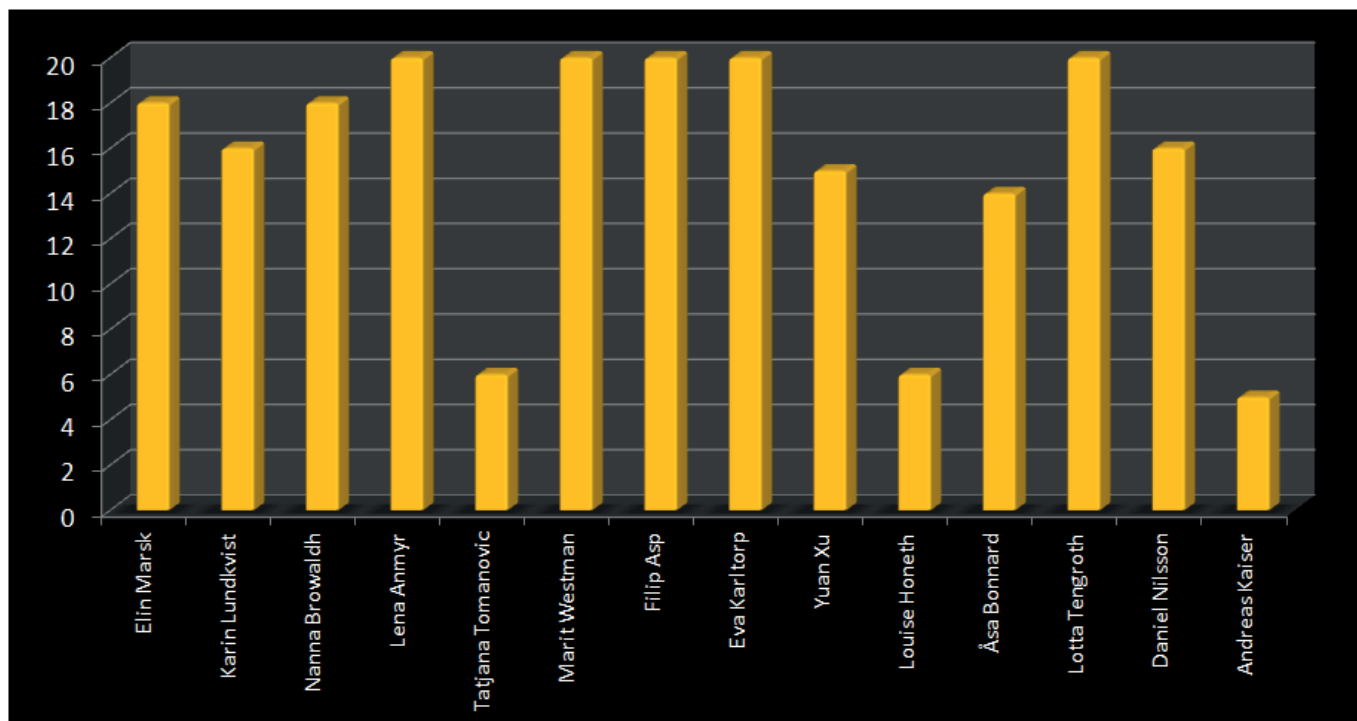
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Per-Åke Lindestad
Riitta Möller
Britt Nordlander

Dissertations / Halftime seminars 2012-2014



Date		Name	Title
2012-01-20	Dissertation	Bengt Svensson	Restoration of Scarred Vocal Folds with Stem Cell Implantation – Analyses in a Xenograft Model
2012-02-03	Halftime	Marit Westman	Rhinitis and rhinosinusitis in the BAMSE birth cohort, followed up to 16 years of age
2012-05-15	Halftime	Filip Asp	Bilateral Cochlear Implants in Children- Clinical and Experimental Studies
2012-05-16	Dissertation	Per Attner	Clinical Implications of Human Papilloma Virus (HPV) in oropharyngeal cancer
2012-06-11	Halftime	Eva Karltorp	Cochlear implantation in early childhood
2012-09-07	Dissertation	Karin Lundkvist	Pharyngeal surgery and epidemiology in sleep apnea
2012-09-18	Halftime	Yuan Xu	Nicotine and endotoxin in asthma pathogenesis
2012-12-07	Dissertation	Elin Marsk	Bell's palsy - study design, prognosis and quality of life
2012-12-12	Halftime	Louise Honeth	Hörsel hos svenska jägare
2013-04-05	Dissertation	Terese Hylander	Novel Potential Targets for Treatment of Airway Inflammation
2013-04-12	Halftime	Åsa Bonnard	Estrogen and hearing
2013-05-16	Halftime	Lotta Tengroth	Pathogen-recognition receptors (PRRs) and inflammation in human upper airway disease
2013-06-10	Halftime	Daniel Nilsson	Identification of risk factors in allergic rhinitis using association studies
2013-11-15	Halftime	Andreas Kaiser	The use of organotypic culture and in vivo-studies to investigate implantation of progenitor neuronal cells to the auditory nervous system.
2013-11-22	Dissertation	Nanna Browaldh	Upper airway surgery in obstructive sleep apnoea - descriptive, observational and randomised controlled studies
2013-12-13	Dissertation	Eva Karltorp	Congenital cytomegalovirus infection and connexin 26 mutations in childhood deafness. Intervention with early cochlear implantation
2014			
2014-01-24	Dissertation	Camilla Rydberg	ÖNH:s föreläsningssal, Solna Pattern-Recognition Receptors and Neutrophils in Cancer Inflammation
2014-02-28	Dissertation	Tatjana Tomanovic	ÖNH:s föreläsningssal, Solna Persistent geotropic nystagmus. A different kind of cupula pathology
2014-04-07	Dissertation	Lena Anmyr	Life circumstances of children and adolescents after cochlear implantation

Participation at halftime seminars during 2010-10 to 2013-11-15



Senior Researchers

Bachert, Claus	11.
Bark, Rusana	12.
Baumgartner, Wolf-Dieter	13.
Berninger, Erik.....	14.
Brantberg, Krister	15.
Browaldh, Nanna.....	16.
Cardell, Lars Olaf	17.
Duan, Maoli.....	19.
Engmér Berglin, Cecilia	20.
Friberg, Danielle	21.
Hammarstedt Nordenvall, Lalle.....	22.
Hederstierna, Christina	23.
Hellström, Sten.....	24.
Henriksson, Gert	25.
Hertegård, Stellan	26.
Hessén Söderman, Anne-Charlotte	27.
Holmström, Mats	28.
Hultcrantz, Malou	29.
Idrizbegovic, Esma.....	30.
Jungebluth,Philipp.....	31.
Karltorp, Eva	33.
Kumlien Georén, Susanna	34.
Larsson, Olivia	35.
Lindestad,Per-Åke	36.
Lundkvist, Karin.....	37.
Macchiarini, Paolo.....	38.
Marklund, Linda	40.
Marsk, Elin.....	41.
Munck-Wikland, Eva.....	42.
Möller, Riitta.....	44.
Nerfeldt, Pia	45.
Olsson, Petter.....	46.
Palmgren, Björn.....	47.
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Chronic rhinosinusitis: Endotypes and genetic determinants

Chronic rhinosinusitis (CRS) is an inflammatory disorder of the sinuses with a large phenotypic variability. The mechanisms of the disease are largely unknown, but are believed to result from a combination of environmental factors and the genetic background of affected individuals. CRS is subclassified into CRS with and without nasal polyposis (CRSwNP, CRSsNP), but recent work identified about 4 different endotypes (based on single major patho-mechanisms). Such pathomechanisms include IL-5 as a major Th2-cytokine, polyclonal IgE based on the impact of Staphylococcal superantigens, TNF-alpha and IL-22 related to bacterial stimuli, and others. Those endotypes may not only guide us to a new understanding of CRS, but also guides the selection of therapeutic targets such as anti-IgE, anti-IL5 etc for individual patients. Furthermore, those endotypes should help to sharpen genetic studies on CRS.

Previous studies of CRS have defined 53 single nucleotide polymorphisms (SNPs) as associated with the CRSwNP or CRSsNP phenotypes. In a first step, we have investigated the reproducibility of previous SNP associations with CRS with and without NP. The study population consisted of 613 patients (248 females and 365 males), with 275 patients having CRS with NP and 338 patients having CRS without NP, and a set of 1588 background population controls (1042 females and 546 males) from the publicly available Illumina iControl database. In this study, we replicated associations between genetic variants in 7 genes and the CRS phenotype. With P values of less than .01 and Q values of less than 0.1, the SNPs in PARS2, TGF-beta1, and NOS1 are all good candidates for further analysis, in particular because they are also plausible candidates from a functional biological perspective. These studies will be continued using the endotypes defined by tissue markers, and finally pooled genome-wide association study (pGWAS) approaches based on endotypes.

2012, 2013, 2014 (publications with KI – för complete list please see med line).

1. Bachert C, K van Steen, N Zhang, G Holtappels, T Cattaert, B Maus, R Buhl, C Taube, S Korn, M Kowalski, J Bousquet, P Howarth. Specific IgE against *Staphylococcus aureus* enterotoxins: an independent risk factor for asthma. *J Allergy Clin Immunol*. 2012 Aug;130(2):376-381. e8. Epub 2012 Jun 26.
2. Akdis CA, Bachert C, Cingi C, Dykewicz M, Hellings P, Naclerio RM, Schleimer RP, Ledford D. Endotypes and phenotypes of chronic rhinosinusitis: A PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2013;131:1479-90
3. Katotomichelakis M, Tantilipikorn P, Holtappels G, De Ruyck N, Feng L, Van Zele T, Muangsomboon P, Jareonchasri P, Bunnag C, Danielides V, Hellings PW, Bachert C, Zhang N. Inflammatory patterns in upper airway disease in the same geographical area may change over time. *Am J Rhinol Allergy* 2013;27:354-60
4. Katotomichelakis M, Simopoulos E, Zhang N, Tripsianis G, Danielides G, Livaditis M, Bachert C, Danielides V. Olfactory dysfunction and asthma as risk factors for poor quality of life in upper airway diseases. *Am J Rhinol Allergy* 2013;27:293-8
5. Henmyr V, G Vandeplas, C Halldén, T Säll, H Olze, C Bachert, LO Cardell. Replication study of genetic variants associated with chronic rhinosinusitis and nasal polyposis. *J Allergy Clin Immunol* 2013 Sep 26. doi:pil: S0091-6749(13)01293-1. 10.1016/j.jaci.2013.08.011, Letter
6. Meng J, Zhou P, Liu Y, Liu F, Yi X, Liu S, Holtappels G, Bachert C, Zhang N. The development of nasal polyp disease involves early nasal mucosal inflammation and remodeling. *PLoS One* 2013;8(12):e82373
7. Feng L, Zhang N, Zhang J, Krysko O, Zhang Q, Xian J, Derycke L, Qi Y, Li K, Liu S, Lin P, Bachert C. Forkhead box protein 3 in human nasal polyp regulatory T cells is regulated by the protein suppressor of cytokine signaling 3. *J Allergy Clin Immunol*. 2013;132(6):1314-1321
8. Yang Y, Nan Zhang, Feng Lan, Van Crombruggen K, Fanga L, Hua G, Hong S, Bachert C. Transforming growth factor-beta 1 pathways in inflammatory airway diseases. *Allergy* 2014 Apr 18. doi: 10.1111/all.12403
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10. Derycke L, Eyerich S, Van Crombruggen K, Pérez-Novo C, Holtappels G, Deruyck N, Gevaert P, Bachert C. Mixed T helper cell signatures in chronic rhinosinusitis with and without polyps. *PLoS One* 2014, accepted



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Publications 2012, 2013, 2014

1. Bark R, Hammarstedt-Nordenvall L. Risk of cervical metastasis in NO gingival cancer. In manuscript 2013.
2. Bark R, Mercke C, Munck-Wikland E, Wisniewski NA, Hammarstedt-Nordenvall L. Cancer of the Gingiva. Oral Oncology. Submitted nov 2013.
3. Bonnard Å, Sahlin L, Hultcrantz M, Simonoska R. No direct nuclear effect of Progesterone in the inner ear: other possible pathways. Acta Otolaryngol. In press 2013.

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Cochlear Implants and implantable hearing aids

Pediatric Cochlear Implant surgery is standard since many years. Based on neonatal hearing screening and genetic analysis of new born cochlear implant candidates a very early implantation is useful and possible. Bilateral cochlear implantation in children six months old is safe and successful.

In children and adults suffering from partial deafness, so called Electric Acoustic Stimulation Cochlear Implantation is needed. This is a combination of natural acoustic hearing together with electric stimulation via cochlear implant on the same ear. Pediatric and adult patients profit from the synergy of two simultaneous stimulation modes.

Cochlear implantation in single sided deafness in children and adults has shown to be successful to reestablish directional hearing and enhanced speech understanding in noise.

Since 1996 fully and semiimplantable hearing aids are available. Classic Vibrant Soundbridge Surgery (crimping onto the long process of incus) is helpful in sensorineural hearing loss. In mixed hearing loss and malformations Vibroplasty surgery with fixation onto the round window, oval window, ossicular remnants, stapes-suprastructure or fenestration is indicated. These surgical procedure is possible in children and adults.

This year a new device, Vibrant Bonebridge, came up. This is an implantable boneconduction stimulator. Like a BAHA, bone conduction is used, but there is no screw through the skin. So far the very first implants have been performed very successfully in adults.

The international pediatric study is right now in conduction and coordinated by myself.

Keywords: Cochlear Implantation, children, bilateral, Electric Acoustic Stimulation, Vibrant Soundbridge, Vibroplasty, Vibrant Bonebridge

Publications 2012, 2013, 2014

1. Laback B, Zimmermann I, Majdak P, Baumgartner WD, Pok SM. Effects of envelope shape on interaural envelope delay sensitivity in acoustic and electric hearing. *J Acoust Soc Am*. 2011 Sep;130(3):1515-29.
2. Arnoldner C, Gstoettner W, Riss D, Wagenblast J, Honeder C, Blineder M, Hamzavi JS, Jappel A, Baumgartner WD. Residual hearing preservation using the suprameatal approach for cochlear implantation. *Wien Klin Wochenschr*. 2011 Oct;123(19-20):599-602. Epub 2011 Aug 25.
3. Mueller J, Baumgartner WD, Godey B, Freijd A, Harris S, Helbig S, Quevedo MS, Mann W, Anderson I, Gstoettner W. The MED-EL SONATATI 100 cochlear implant: an evaluation of its safety in adults and children. *Acta Otolaryngol*. 2011 May;131(5):504-11. Epub 2011 Mar 23.
4. Riss D, Hamzavi JS, Katzinger M, Baumgartner WD, Kaider A, Gstoettner W, Arnoldner C. Effects of fine structure and extended low frequencies in pediatric cochlear implant recipients. *Int J Pediatr Otorhinolaryngol*. 2011 Apr;75(4):573-8. Epub 2011 Feb 15.



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Hearing in young infants - early diagnosing and intervention

The introduction of universal newborn hearing-screening brings identification of hearing loss and intervention forward, thereby enhancing subsequent impressive and expressive language capacity. This rapidly evolving field — hearing aid fitting in very young infants, and bilateral cochlear implantation in infants — requires rapid, objective, and highly reliable methods for diagnosing hearing impairment and validation of intervention programmes. Moreover, the normal maturation processes during the first six months of life remain unclear. In clinical and experimental studies, rapid, objective, acoustical and neurophysiological methods/algorithms are developed for the characterization of the normal and pathophysiological processes of the middle ear, inner ear, and auditory pathways in very young infants. This characterization will then form the basis for, e.g., intervention with hearing aids, fitted in a way that enables audibility for soft sounds without introducing any risk for hearing loss induced by too high sound levels. Identification of bio-markers for late onset hearing loss and evaluation of fine-tuned algorithms in cochlear implants are examples of clinically-oriented studies. Twin studies are used for the study of the mechanisms behind the large inter-individual variability in inner ear cochlear mechanics, at birth.

Supervision of PhD-student:

Filip Asp Main Supervisor

Publications 2012, 2013, 2014

1. Israelsson, K.-E., R. Bogo, and E. Berninger, Reliability in hearing threshold prediction in normal hearing and hearing impaired subjects using mixed multiple ASSR. *Journal of the American Academy of Audiology*, 2014: in review.
2. Berninger, E., A. Olofsson, and A. Leijon, Analysis of click-evoked auditory brainstem responses using time domain cross-correlations between interleaved responses. *Ear Hear*, 2014. 35(3): p. 318-29.
3. Berninger E. Report from 2012 MidWinter Research Meeting, Association for Research in Otolaryngology, San Diego, California, USA. *Audio Nytt* 2012;39(3):28-31.
4. Filip Asp, Gunnar Eskilsson, Erik Berninger. Early cochlear implantation promotes faster sound localization development, 2011 MidWinter Research Meeting, Association for Research in Otolaryngology, Baltimore, Maryland, USA, February 19-23, 2011.
5. Erik Berninger, Åke Olofsson, Arne Leijon. Analysis of click-evoked auditory brainstem responses using time domain cross-correlations between interleaved responses, 2012 MidWinter Research Meeting, Association for Research in Otolaryngology, San Diego, California, USA, February 25-29, 2012.
6. Filip Asp, Åke Olofsson, Erik Berninger. Infants' auditory localization accuracy measured by corneal eye-tracking: A pilot study, Modern techniques in auditory and communication sciences, Karolinska Institutet, Swedish Institute for Disability Research, Linnaeus Centre HEAD Graduate School, Lidingö, Sweden, October 16-18, 2013.
7. Filip Asp, Åke Olofsson, Erik Berninger. Infants' auditory localization accuracy measured by corneal eye-tracking: A pilot study, 2014 MidWinter Research Meeting, Association for Research in Otolaryngology, San Diego, California, USA, February 22-26, 2014.
8. Anne-Marie Jakobsson, Filip Asp, Erik Berninger. Effects of induced lateral asymmetry on speech recognition and sound localization accuracy — a pilot study, 2014 MidWinter Research Meeting, Association for Research in Otolaryngology, San Diego, California, USA, February 22-26, 2014.

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Ocular vestibular evoked myogenic potentials (oVEMP) in response to bone conducted vibration

Aim

- To test whether oVEMP constitute a means of evaluating utricular function
- To test which stimulus parameters that are optimal for testing oVEMP in response to bone conducted vibration

Background

The labyrinth has five parts, three semicircular canals and two otolith organs (sacculae and utricle). The canals sense angular head accelerations. The otoliths sense linear head accelerations and gravity. For canals, there are both reliable tests and good understanding of the effect of lesions (“spinning” vertigo). Lesions to the otoliths cause other balance problems of less known character. During the last ten years, testing “cervical VEMP” has established itself as a clinical test for saccular function. For the utricle, there is, at present, no available non-perceptual and easily applicable clinical test. Based on both animal and human studies, it seems that utricular function can be quantified by testing oVEMP in response to bone conducted vibration.

Project

Test of oVEMP in controls as well as in patients with well defined lesions to the labyrinth/vestibular nerve.

Importance

A clinical test for utricular function is of importance to distinguish, and thus, for understanding the effect of vestibular lesions. Testing oVEMP in response to bone conducted vibration might, potentially, constitute a means of evaluating utricular function. This possibility is significant, considering that, at present, there is no available non-perceptual and easily applicable clinical test for utricular function.

Supervision of PhD-student:

Luca Verrecchia Co-supervisor

Publications 2012, 2013, 2014

1. Taylor RL, Blaivie C, Bom AP, Holmeslet B, Pansell T, Brantberg K, Welgampola MS. Ocular vestibular-evoked myogenic potentials (oVEMP) to skull taps in normal and dehiscent ears: mechanisms and markers of superior canal dehiscence. *Exp Brain Res*. 2014 Jan 25.
2. Westin M, Brantberg K. Mastoid and vertex low-frequency vibration-induced oVEMP in relation to medially directed acceleration of the labyrinth. *Clin Neurophysiol*. 2013 Sep 26. doi:pii: S1388-2457(13)01009-2. 10.1016/j.clinph.2013.08.019. [Epub ahead of print] PubMed PMID: 24076134.
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5. Brantberg K, Duan M, Falahat B. Ménière’s disease in children aged 4-7 years. *Acta Otolaryngol*. 2012 May;132(5):505-9. doi: 10.3109/00016489.2011.643240. Epub 2012 Jan 4. PubMed PMID: 22217217.



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Upper Airway Surgery in Obstructive Sleep Apnoea, a randomised controlled trial

A prospective RCT called Sleep apnoea Karolinska UPPP (SKUP3), with two parallel arms and stratification by Friedman stage (by tonsil size and palate position) and BMI. Sixty-five consecutively included patients with moderate to severe obstructive sleep apnoea syndrome (OSAS), BMI < 36 kg/m² and excessive daytime sleepiness were randomised to intervention (uvulopalatopharyngoplasty, UPPP) or control. Evaluation of respiratory parameters measured by polysomnography and daytime sleepiness and quality of life by questionnaires. Also a vigilance test was performed. There were significant differences between the groups in favour of UPPP.

Further evaluations of metabolic parameters, blood pressure as well as sleep related quality of life are planned.

Publications 2012, 2013, 2014

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The Role of Inflammation in; 1) Rhinitis and Asthma. 2) Head and Neck cancer

Inflammation is a key feature of both allergic and none-allergic rhinitis, nasal polyposis, asthma and epithelial derived cancer in the head and neck region. The mediators involved appear to be the same even though their profile varies depending on the diseases involved.

In rhinitis and asthma our focus is presently on pattern recognition receptors (PRRs) and their interaction with various microbes in causing and/or deteriorating disease. We have also recently demonstrated that a series of three intralymphatic injections, with four weeks in between, can have a very positive effect on seasonal allergic rhinitis symptoms. The intralymphatic therapy decreases the nasal inflammatory response and enhances activation of peripheral T lymphocytes. We are currently working to optimize the intralymphatic route as a way to further develop and improve allergen-specific immunotherapy. Great effort is also spent on investigating the antigen-presenting role of the nasal epithelial cells in allergic rhinitis as well as on evaluating the importance of MHC class II in the development of chronic rhinosinusitis with polyposis. Murine animal models and their response to microbes are used to show that the two cardinal signs of asthma, airway hyperactivity and local inflammation might be the result of two parallel events, rather than one leading to another. In cancer we suggest that PRRs might provide a link between microbial infection and the development of head and neck squamous cell carcinomas (HNSCC). Aberrations in the epithelial PRR expression might therefore increase the risk for the development of HNSCC. We also postulate that changes in a previously normal epithelial PRR profile reflect ongoing changes in the immune response, and can provide information on tumor prognosis.

Supervision of PhD-student:

Magnus Starkhammar	Main Supervisor
Daniel Nilsson	Main Supervisor
Åsa Kågedal	Main Supervisor
Lotta Tengroth	Main Supervisor
Julia Arebro	Main Supervisor
Laila Hellkvist	Main Supervisor
Sandra Ekstedt	Main Supervisor
Yuan Xu	Main supervisor

Publications 2012, 2013, 2014

1. Bogefors J, Kvarnhammar A, Cardell LO. LEAP-2, LL-37 and RNase7 in tonsillar tissue: downregulated expression in seasonal allergic rhinitis. *FEMS Immunol Med Microbiol* (IF: 2.3). accepted 140422
2. Henmyr V, Vandeplas G, Halldén C, Säll T, Olze H, Bachert C, Cardell LO. Replication study of genetic variants associated with chronic rhinosinusitis and nasal polyposis. *J. Allergy Clin. Immunol.* (IF: 12.0), 2014;133:273-5.
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4. Rydberg Millrud C, Hylander T, Kumlien Georen S, Kågedal Å, MD; Winqvist O, Cardell LO. Inverse immunological responses induced by allergic rhinitis and head and neck squamous cell carcinoma. *PLoS One* (IF: 4.1), 2014;9(1):e86796.
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6. Tengroth L, Rydberg-Millrud C, Månsson-Kvarnhammar A, Kumlien-Georén S, Latif L, Cardell LO. Functional effects of Toll-like receptor (TLR)3, 7, 9, RIG-I and MDA-5 stimulation in nasal epithelial cells. *PLOS One*, accept 140430
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12. Ekman AK, Cardell LO. The expression and function of Nod-like receptors (NLRs) in neutrophils. *Immunology* (IF: 3.4) 2013: accepted
13. Hylander T, Latif L, Peterson-Westin U, Cardell LO. Intralymphatic allergen-specific immunotherapy: an effective and safe alternative treatment route for pollen-induced allergic rhinitis. *J Allergy Clin Immunol.* (IF:12.0) 2013;131:412-20.
14. Månsson Kvarnhammar A, Tengroth L, Adner M, Cardell LO. Innate Immune Receptors in Human Airway Smooth Muscle Cells: Activation by TLR1/2, TLR3, TLR4, TLR7 and NOD1 Agonists. *PLoS One* (IF: 4.1), 2013;8:e68701.
15. Nopp A, Cardell LO, Johansson SG. CD-sens can be a reliable and easy-to-use complement in the diagnosis of allergic rhinitis. *Int Arch Allergy Immunol.* (IF: 2,2) 2013;161:87-90.
16. Nilsson D, Kumar Andiappan A, Halldén C, Tim C-W, Säll T, De Yun W, Cardell LO. Poor reproducibility of allergic rhinitis candidate associations, *PLoS One* (IF: 4.1), 2013;8:e53975.
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Inner ear gene therapy

We take for granted the ability to hear and communicate with each other. Hearing loss, of a degree sufficient to interfere with social and job-related communication, is the most common chronic neural impairment in the modern society. Life becomes exceptionally difficult when disease affects these basic functions. The total number of the people suffering from different hearing disorders tends to increase when health care measures are poor. In Sweden, approximately 10% of the population has some degree of hearing impairment and the number of this impairment is increasing. In addition, more than 50% of the population above 70 years of age have a measurable hearing impaired hearing disorders.

Specific Aims

1. To test the combination of cell- and gene-based techniques on hair cells and spiral ganglion neurons survival.
2. To develop gene therapy models for treatment and prevention of acquired hearing loss in animal model.
3. To develop gene therapy models for treatment of hereditary inner ear disorders, in particular, monogenic hearing loss.
4. To develop gene modified stem cell therapy models and tissue engineering methods for curing hereditary and acquired hearing loss.

Supervision of PhD-student:

Anna-Karin Strömberg	Main Supervisor
Luca Verrecchia	Main Supervisor
Qiang Wang (Kina)	Main Supervisor
Wei Ku (Kina)	Main Supervisor

Publications 2012, 2013, 2014

1. Duan M***, Anders Fridberger, Dongguang Wei, Cecilia Lundberg. Efficient gene transfer to cochlear hair cells using lentiviral vectors. 2012. Submitted
2. Yin HM., Stromberg AK., Duan M. Evaluation of the noise generated by neurotological electrical drills and suction during neurotological surgery. *Acta Otolaryngol.* 2011; 131(11):1132-5.
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Pharmacological treatment and prevention of exogenous inner ear damage

Publications 2012, 2013, 2014

1. Berglin CE, Laurell G, Bramer T, Edsman K, Counter SA, Klason T, Ekborn A. MR imaging of the middle and inner ear following intratympanic injection of a gadolinium-containing gel. *Otol Neurotol*. 2013 Nov 21. (Epub ahead of print)
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Centre of excellence for obstructive sleep apnea in adults and children; RCT of surgical treatments and the complications of pregnancy, evaluated with polysomnography

Obstructive sleep apnea (OSA) is common, 3% of the population, and may be dangerous. OSA is caused by narrow upper airways leading to snoring, apneas and impaired sleep. Serious complications are cardio-vascular disease and a 4-times increased mortality rate. Also, excessive daytime sleepiness and reduced quality of life is common.

To evaluate surgical treatment with randomised controlled trials (RCT) in adults and children with OSAS, and also to investigate pregnant women with toxicos and diabetes, we have started a "Centre of excellence for OSA".

RCT in surgical studies are rare and our studies are requested. We have created Scandinavias largest "Sleep and breathing lab" for adults and children from 8 months, investigated with polysomnography (PSG). Our group consists of several students for doctoral degree and "postdocs" involved in following projects: A. Results from 65 adults who underwent RCT of uvulopalatopharyngoplasty (UPPP). Published results showed that UPPP reduced 60% of the apneas-hypopneas, a significant difference from the control group with 11%. Daytime sleepiness, quality of life and vigilance were also significantly improved compared to controls. Data are collected for blood samples, blood pressures and sleep questionnaires, also from 2 year follow-ups. B. RCT of children with OSA between 2 and 6 years; 35 has now undergone adenotonsillectomy (ATE) and 35 adenotonsillotomy with coblation. The study is blinded where we evaluate postop pain and respiration with PSG. During 2015 all data are completed and manuscripts will be written. C. Plans to start other surgical RCT:s in children during 2014: 1) 35 children with mild to moderate OSA undergo ATE and 35 children undergo 6 month expectancy; 2) 30 children with severe OSA undergo ATE and 30 undergo ATE + rafi of the palatal pillars. Ethical permission is to be submitted. D. Tonsils from OSA children will be investigated for Innate Lymphoid cells (ILC), a cooperation with CIM-lab at KI. E. Investigations of pregnant women with riskfactors toxicos, hypertension or diabetes, with PSG. Evaluations if there is OSA and need for CPAP, as well as the health status of mothers and their children.

Supervision of PhD-students:

Anna Borgström Main supervisor
Ann Abrahamsson Co-supervisor

Publications 2012, 2013, 2014

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2. Browaldh N, Nerfeldt P, Lysdahl M, Bring J, Friberg D. SKUP3 a randomised controlled trial; polysomnographic results after uvulopalatopharyngoplasty in obstructive sleep apnoea patients. *Thorax*, Sep;68(9):846-53. doi: 10.1136/thoraxjnl-2012-202610. Epub 2013 .
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Supervision of PhD-students:

Alexandra Elliot Co-supervisor
Mattias Jangard Co-supervisor
Clara Svenberg-Lind Co-supervisor

Publications 2012, 2013, 2014

1. Anders Näsman, Mircea Romanitan, Hemming Johansson, Lalle Hammarstedt, Linda Marklund, Eva Munck-Wikland, Tina Dalianis and Torbjörn Ramqvist. Tumour infiltrating CD8+ and Foxp3+ lymphocytes correlate to treatment response and HPV-status in tonsillar cancer. PLoS One. 2012;7(6):e38711. doi: 10.1371/journal.pone.0038711. Epub 2012 Jun 12.
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4. Wendt, Malin.A Romanitan, Mircea Näsman, Anders Dalianis, Tina Hammarstedt-Nordenvall, Lalle Marklund, Linda Ramqvist, Torbjörn Munck af Rosenschöld Wikland, Eva Presence of human papillomaviruses and p16 expression in hypopharyngeal cancer. Accepted Head & Neck Jan 2013
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6. Marklund L, Lundberg B, Hammarstedt-Nordenvall L. Mangement of the neck in node positive tonsillar cancer. Accepted ACTA otolaryngologica, april 2014.
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8. Alexandra Elliot, Mattias Jangard, Linda Marklund, Niclas Håkansson, Paul Dickman, Lalle Hammarstedt-Nordenvall, Pär Stjärne. Sinonasal malignancies in Sweden 1960-2010; a nationwide study of the Swedish population. Submitted Rhinology

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I am involved in several clinical or clinically related projects concerning hearing function as follows:

- Hearing and estrogen – a continuation of the work in my doctoral thesis, where the potential protective effect of estrogen on hearing function is further studied in peri-menopausal women and in women with Turner syndrome. Collaborators: Professor Malou Hultcrantz, Rusana Bark, and PhD student Åsa Bonnard.
- Hearing in the elderly and noise, diet and cognition. Epidemiological studies where the influence of various factors on hearing function is assessed in patients, and in population databases such as H70 and LifeGene. Collaborators: Professor Ulf Rosenhall, Assoc. professor Esmā Idrizbegovic and others.
- Otosclerosis and hydrops. A temporalbone study performed during a six month post-doc fellowship (spring 2012) at the Otopathology Laboratory, Department of ENT at the University of Minnesota, with Prof Paparella och Dr Cureoglu.
- Hearing in vestibular schwannoma - Gamma knife surgery vs initial conservative treatment for vestibular schwannoma patients with preserved hearing, a prospective randomized study. Collaborator Dr Förander and others, Department of Neurosurgery.
- TACO- thiosulfate and Cisplatin ototoxicity, a clinical study aiming at testing whether the ototoxic effect of Cisplatin in chemotherapy can be reduced by administering a protective substance – thiosulphate-containing gel – in the middle ear. Primary investigator Professor Göran Laurell, Uppsala.

Supervision of PhD-students:

Åsa Bonnard Co-supervisor

Publications 2012, 2013, 2014

1. Rosenhall, U., C. Moller, and C. Hederstierna, Hearing of 75-year old persons over three decades: has hearing changed? *Int J Audiol*, 2013. 52(11): p. 731-9.
2. Idrizbegovic, E., et al., Short-term longitudinal study of central auditory function in Alzheimer's disease and mild cognitive impairment. *Dement Geriatr Cogn Dis Extra*, 2013. 3(1): p. 468-71.
3. Hederstierna, C., S. Cureoglu, and M.M. Paparella, Undiagnosed severe cochlear otosclerosis as a cause of profound hearing loss. *Otol Neurotol*, 2013. 34(3): p. e14-5.



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Plasminogen and healing of chronic ulcers, in particular chronic tympanic membrane perforations

My research has focused on two avenues; supervising the ALF-project “Early Diagnosis and Intervention in Newborn Children with Hearing Impairment” and as a member of the research group focusing on plasminogen and healing of tympanic membrane perforations and other chronic wounds. In collaboration with professor Tor Ny, Dept of Medical Chemistry, Umeå University, Hellström has been able to show that chronic perforations in the tympanic membrane can be healed by topical application of plasminogen. This has opened a completely new field of research – plasminogen (plg) in wound healing. This project is now mainly performed inside a company named Omniohealer. The experimental studies on plg in wound healing show very promising results in ulcers of diabetic mice/rats. A clinical trial on plg in patients with diabetic ulcers is planned to start in autumn 2014. The next clinical trial in 2015 will focus on chronic tympanic membrane perforations.

Supervision PhD-students:

Torbjörn Lundberg (Umeå) Co-supervisor

Publications 2012, 2013, 2014

1. Shen Y, Guo Y, Wilczynska M, Li J, Hellström S, Ny T. Plasminogen initiates and potentiates the healing of acute and chronic tympanic membrane perforations in mice. *J Transl Med* 2014, Jan 7;12:5. doi 10.1186/1479-5876-12-5.
2. Stenfeldt K, Johansson C, Eriksson PO, Hellström S. Collagen Type II is produced in healing pars tensa of perforated tympanic membranes: an experimental study in the rat. *Otol Neurotol*. 2013 34:e88-92.
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4. Jung TT, Alper CM, Hellstrom SO, Hunter LL, Casselbrant ML, Groth A, Kemaloglu YK, Kim SG, Lim D, Nittrouer S, Park KH, Sabo D, Spratley J. Panel 8: Complications and sequelae. *Otolaryngol Head Neck Surg*. 2013;148(4 Suppl):E122-43.
5. Lundberg T, Hellström S, Sandström H. Development and validation of a new grading scale for otitis media. *Pediatr Infect Dis J*. 2013; 32:341-5.
6. Shen Y, Guo Y, Du C, Wilczynska M, Hellström S, Ny T. Mice deficient in urokinase-type plasminogen activator have delayed healing of tympanic membrane perforations. *PLoS One*. 2012;7(12):e51303.
7. Karltorp E, Hellström S, Lewensohn-Fuchs I, Carlsson-Hansén E, Carlsson PI, Engman ML. Congenital cytomegalovirus infection – a common cause of hearing loss of unknown aetiology. *Acta Paediatr*. 2012;101:e357-62.
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Airway stent treatment of malignant obstructions & a new submucos endoscopic surgical method of subglottic laryngotracheal stenosis

Airway stent is today an established treatment for malign and benign obstructions in tracheal and proximal bronchial region. Airway stents can also be an important treatment when the tracheal and bronchial walls are injured by nearby infections or surgery. In our first study we will carry out box spirometric analysis and an oscillometric pulse wave analysis before and after airway stenting in the patients with a malignant obstruction. The patients will also evaluate their quality of life before and after surgery with a validated enquiry mainly used for chronic airway diseases (CAT™, COPD Assesment Test).

A new submucosal endoscopic surgical method for treating subglottal stenosis have been carried out at the clinic since 2003². Over 50 patients have been treated successfully so far. In this second study we will measure the improvement of breathing with a box spirometric analysis and an oscillometric pulse wave analysis. The patient will also evaluate the improvement in breathing with a validated quality of life enquiry mainly used for chronic airway diseases (CAT™, COPD Assesment Test).

Publications 2012, 2013, 2014

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2. Arebro J, Henriksson G, Macchiarini P, Juto JE. New treatment of subglottic stenosis due to Wegener's granulomatosis. *Acta Otolaryngol (Stockh)* [Internet]. 2012 [cited 2012 Sep];132(9):995-1001



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Reconstruction of the damaged vocal fold scar with mesenchymal stem cells

Publications 2012, 2013, 2014

1. Svensson B, Nord C, Nagubothu RS, Hultman I, M.S, Cedervall J, Ährlund-Richter L, Tolf A, Hertegård S. Transplantation of human embryonic stem cells improves healing of scarred rabbit vocal folds – a three months xenograft analysis. Submitted for publication to Tissue Engineering 2013
2. Hertegård S., Lindestad PÅ. Hyaluronan combined with dissection used in phonosurgical treatment of sulcus vocalis and vocal fold scarring. Submitted to Otolaryngology: Open Access
3. Hertegård S. Larsson H. A portable high speed camera system for vocal fold examinations .Accepted for publication in Journal of Voice . 2014
4. Granqvist S, Simberg S, Hertegård S, Holmqvist S, Larsson H, Lindestad P-Å, Södersten M and Hammarberg B. Resonance tube phonation in water: high-speed imaging, electroglottographic and oral pressure observations of vocal fold vibrations. Accepted for publication in Logoped Phoniatr Vocol.2013
5. Nygren U, Isberg B, Södersten M, Hertegård S, Nordenskjöld A. Effects of increased level of androgens in the larynx in women with congenital adrenal hyperplasia using magnetic resonance imaging- Submitted to The Journal of Clinical Endocrinology & Metabolism. 2014

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Posttonsillectomy haemorrhage rates related to technique for dissection and for haemostasis

Objectives To detect posttonsillectomy haemorrhage (PTH) and to analyse whether the bleeding rate was related to surgical technique or technique for haemostasis.

Methods Register study from the New Tonsil Surgery Register in Sweden 090301-130426. All patients that had been subjected to tonsillectomy without adenoidectomy (TE) were included in the study. The surgeon answers a postoperative questionnaire concerning data about surgery, including possible early PTH, in this study defined as PTH that occurs during hospital stay. Late PTH is reported by the patient/parent in a questionnaire answered 30 days after surgery.

Results 17216 patients fulfilling the criteria were identified in the database. The by far most commonly used technique for dissection was cold steel (71.4%), followed by diathermy scissors (15%), coblation (8.6%) and ultrascission (2.4%). Haemostasis had been obtained by using some kind of hot technique in 90% of the cold steel cases.

Early bleedings were reported in 3.2% and late in 9.5% of the cases. Return to theatre was necessary in 2.8%. Compared with cold dissection and cold haemostasis, late PTH rate was 2.8 times higher after cold dissection with diathermy haemostasis, 4.3 times higher after using diathermy scissors, 3.2 times higher after coblation and 5.6 times higher after ultrascission.

Conclusions The over all rate for late post tonsillectomy haemorrhage (9.5%) is higher than in most other studies. All “hot” techniques, including cold dissection combined with diathermy haemostasis, resulted in a significant higher risk for late PTH compared with cold steel and cold haemostasis.

Publications 2012, 2013, 2014

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2. Hultcrantz E, Ericsson E, Hemlin C, Hessén-Söderman A-C, Roos K, Sunnergren O, Stalfors J : Paradigm shift in Sweden from tonsillectomy to tonsillotomy for children with upper airway obstructive symptoms due to tonsillar hypertrophy *Eur Arch Otorhinolaryngol.* 2013 Feb 6
3. Sunnergren, O, Hemlin C, Ericsson E , Hessén-Söderman A-C. Hultcrantz E, Odhagen E, Stalfors J : Radiofrequency tonsillotomy in Sweden 2009-2012. Submitted



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Nasal aspects on Unilateral Cleft-, Lip- and Palate and Obstructive Sleep Apnea

Cleft lip and palate has functional and aesthetical impact on the face and upper airways. In this study patients were examined operated 20-40 years ago. A control group was examined in the same way. Objective evaluation was performed of nasal form and function as well as studies of QoL and voice functions with blinded evaluation.

In another study 200 patients ordinated CPAP treatment are evaluated concerning correlation between compliance and nasal function.

In a third project the benefit of adenoidectomy is evaluated in correlation to effect on asthma.

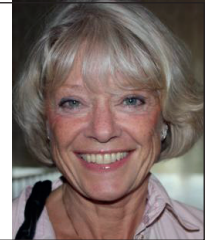
Supervision of PhD-students:

Staffan Morén Main supervisor
Caroline Bengtsson Co-supervisor
Marit Westman Co-supervisor

Publications 2012, 2013, 2014

1. Cardell LO, Wickman M, Hellgren J, Cervin A, Stjärne P, Holmström M, Dahlén B, Bjermer L, Dahlén SE. Internationella riktlinjer för allergisk rinit har uppdaterats. *Läkartidningen* 2012; 109; 622-4
2. Hellgren J, Sandén I, Holmström M. Framtidens utbildningsform är här för att stanna - erfarenheter av ÖNHföreningens web-baserade föreläsningsplattform. *Läkartidningen* 42; 1897-8; 2012
3. Morén S, Mani M, Lundberg K, Holmström M. Nasal symptoms and clinical findings in adult patients treated for unilateral cleft lip and palate. *J Plastic Surg Hand Surg*; 383-9; 2013.
4. Mani MR, Reiser E, Andlin-Sobocki A, Skoog V, Holmstrom M. Cleft Factors Related to Quality of Life and Satisfaction with Nasal Appearance in Patients Treated for Unilateral Cleft Lip and Palate. *The Cleft Palate-Craniofac J*. 50(4); 432-9, 2013
5. Bengtsson C, Jonsson L, Svensson M, Holmström M, Theorell-Haglöf J, Lindberg E. Impact of nasal obstruction on sleep Quality - a community-based study in women. Accepted for publication 2014, *European Archives of Otorhinolaryngology*

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Peripheral and central auditory pathways and Bell's Palsy

Supervision of PhD-students:

Åsa Bonnard Main supervisor
Malin Siegbahn Main supervisor
Emelie Kullring Main supervisor
Johan Svedbrant Co-supervisor

Publications 2012, 2013, 2014

1. Marsk E, Hammarstedt L, Nina , Berg T, Hadziosmanovic N, Engström M, Jonsson L, Hultcrantz M. Prediction of nonrecovery in Bell's palsy using Sunnybrook grading. *Laryngoscope*. 2012 Apr;122(4):901-6. PMID: 22374870
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Hearing - Cognition - Dementia - Aging

During the last years the area of the research interest has been about Hearing and dementia, more specifically to study a central auditory function and cognitive development of the persons with Mild Cognitive Impairment (MCI) and with Alzheimer's disease (AD).

A baseline study (Idrizbegovic et al., 2011) has been performed to investigate the central and peripheral hearing in patients with MCI and AD in early stage and in controls with subjective memory complaints, but normal cognition (SMC) The first follow up has been performed after 1.5 years (Idrizbegovic et al., 2013) and the second follow up after 5-6 years has been recently completed. The Psychoacoustical and Neuropsychological hearing function have been studied in all three groups. A screening procedure combining pure tone audiometry (detecting peripheral auditory dysfunction), speech in noise performance, and a central auditory test (the Dichotic Digit Test, DDT), have been performed as well as a component of event-related potentials (ERPs), the Mismatch Negativity (MMN). Our results have showed that Central Auditory Processing dysfunction is present especially in early dementia, as well as in MCI group.

Collaborators: Professor Emeritus Ulf Rosenhall, MD, PhD Christina Hederstierna, MD, PhD Vesna Jelic. This project will continue and expand in collaborations with Associate Professor Per Östberg, and MD, PhD student Jenny Häggström and above mentioned collaborators.

I am also involved in project regarding Hearing in the elderly and diet: an epidemiological study where the influence of diet on hearing function is assessed in population databases H70.

Collaborators: Professor Emeritus Ulf Rosenhall, MD, PhD Christina Hederstierna and PhD Elisabet Rothenberg.

Publications 2012, 2013, 2014

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Development of tracheal graft with clinical implications

Our early successful results and clinical experiences demonstrate that our strategy, based on optimally bioengineered materials combined with autologous cells and pharmacological therapy can help to boost progenitor cell, recruitment and commitment and thereby promoting tissue regeneration. However, a limitation of our current technology is the time it takes to re-populate the entire implanted decellularized trachea with differentiated cells. The shortage of adequate donor organs still represents a major issue in the entire transplantation field. Furthermore, we anticipate that the size of the transplant may be limited since the transplanted tissue needs to be efficiently and rapidly vascularised to prevent necrosis *in vivo*. Therefore, important questions remain before a full Clinical Trials Accreditation may be obtained. We aim to: i) improve, scale-up and commercialize a socially acceptable tracheal tissue engineering biomaterial, ii) label and *in vivo* track cells in small animal model (rat) to reveal their contribution to trachea regeneration, iii) develop pharmacological approaches to activate and mobilize endogenous stem cells to stimulate tissue regeneration and vascularisation *in situ*, iv) develop a novel tracheal nanocomposite polymeric scaffold, particularly suitable for newborns and children, v) transfer findings to our clinical protocol. Achieving each scientific milestone is fundamental because it allow us to translate our proof-of-concept observations and early clinical experiences of regenerative technology into a commercially viable, routine clinical procedure for a cohort of patients without suitable therapy in current practice. The trachea is a relatively simple, hollow organ. It is therefore an ideal starting point for resolving many of the technical problems associated with whole organ engineering. The experience obtained with trachea could be used as a 'baseline' for establishing a way forward for the engineering of more complex hollow organs.

Supervision of PhD-students:

Linda Helen Friedrich	Main supervisor
Ylva Gustafsson	Co-supervisor
Xuan Li	Co-supervisor
Alina Popova	Co-supervisor
Irina Gilevich	Co-supervisor

Publications 2012, 2013, 2014

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Congenital CMV infection and connexin 26 mutations in childhood deafness : intervention with early cochlear implantation

Hearing impairment (HI) is a common disability, which affects a significant proportion of the population. Early in life, however, the risk of acquiring a HI is low, with 0.2 % of all newborns having a permanent HI, and of these, 0.04 % have a severe or profound HI. Even if there are only a few children born with a permanent HI, the consequences can be devastating for their speech perception and spoken language development. Normal hearing children, start to hear and differentiate sounds already in the fifth month of pregnancy, and thereafter, their speech and language acquisition is intensive during the first years of life. If, however, a child with a HI is to have a chance to catch up with normal hearing children, in terms of spoken language acquisition, it is important to provide the child with the best possible auditory input at the earliest opportunity.

The two most common reasons for permanent childhood HI are congenital cytomegalovirus (cCMV) infection and Connexin 26 (Cx26) mutations. cCMV infection might give the child other disabilities, such as cognitive delay, cerebral palsy and visual impairment, in addition to the HI. For children with Cx26 mutations, additional disabilities are less common.

The aim of this thesis was to study the results after CI intervention in children with permanent HI, and especially, to examine the effect of implantation in infants. Moreover, the aim was to study children with cCMV infection and Cx26 mutations and to describe the additionally disabilities arising from a cCMV infection.

In the first study, 90 children with a variety of HIs, which were of unknown etiology and non-syndromic, were tested for cCMV infection. The dried blood spot (DBS) sample, taken in the newborn period, was analysed for CVM DNA. Of the 90 children, 18 (20%) tested positive for cCMV infection.

In the second study, 79 children, of whom the majority had severe to profound, non-syndromic HI, were tested for Cx26 mutations. Twenty-four of the 79 children (30%) had two pathological Cx26 mutations.

In the third study, 26 children with a HI caused by cCMV infection and 13 children with a HI caused by Cx26 mutations were examined by a multidisciplinary team, with the intention of investigating how frequently additional disabilities were present. Among the children with cCMV infection, there were a high number of children with disturbed balance and in addition neurodevelopmental disabilities and feeding problems were also found. Many of these additional disabilities have not previously been associated with a cCMV infection. In the Cx26 group, such additional problems were not found.

In the fourth study, a cohort of 137 children with CIs, operated between 2002 and 2011 was described. When children were operated on before nine months of age, no language delay was apparent when compared with data for normal hearing children. Additionally, their speech intelligibility was rated high sooner than for children who received their implants at a later age. The children who received implants between 9 and 11 months of age, caught up with the children operated on before they were nine months old, within two to three years. When their vocabulary was tested, the children with implants introduced at 12-17 months of age, caught up at early school-age. Those implanted later, when 18 months old or more, did not, however, catch up with the children who had received implants when younger.

In conclusion, early CI intervention is of great importance for children born with profound HI, if the aim is to acquire age-equivalent spoken language development. In addition, knowledge about the child's etiology is important for an appropriate early and correct HI diagnosis, and to identify possible additional disabilities. Based on this broader knowledge about the child with a HI, it will be possible to give the child and family tailored support.

Publications 2012, 2013, 2014

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Innate immune system, toll-like receptors and inflammation in the airways.

The overall goal of the research is to enhance our understanding of the innate immune system, its interaction with adaptive immune responses and its effects on airway inflammations. Our interest is presently focused on toll and NOD-like receptors (TLRs and NLRs) and their role in allergy, rhinitis and asthma.

- Respiratory infections are known to promote airway hyperresponsiveness (AHR) in asthmatic patients. Toll-like receptors (TLRs) are parts of the innate immune system that recognize viral and bacterial components. One of our focuses is to explore the relation between activation of these virus/bacterial related TLRs and AHR in models of allergic airway inflammation.
- Chronic rhinosinusitis and nasal polyps has lately been thought to have underlying infectious basis, and the innate immunity is thought to have a great importance. We aim to outline the TLRs and NLRs role of the pathogenesis in the development of chronic rhinosinusitis and nasal polyps. We hope to discover new information that will contribute to new treatment strategies.
- Chronic inflammation is considered to play an important role in the development of squamous cell carcinoma of the head and neck (HNSCC). Moreover, the degree of the inflammatory response seen in these tumors has reported to have prognostic value in different histopathological malignancy grading systems . The overall goal of this research is to gain a better understanding of innate immunity and inflammation in head and neck cancers and to stress the possibility for using inflammatory markers as base for novel approaches to prediction.

Supervision of PhD-students:

Lotta Tengroth	Co-supervisor
Julia Arebro	Co-supervisor
Sandra Ekstedt	Co-supervisor

Publications 2012, 2013, 2014

1. Starkhammar M, Kumlien Georén S, Swedin L, Dahlén SE, Adner M, Cardell LO. Intranasal administration of poly(I:C) and LPS in BALB/c mice induces airway hyperresponsiveness and inflammation via different pathways. PLoS One. 2012;7(2):e32110.
2. Swedin L, Arrhigi R, Andersson-Willman B, Murray A, Chen Y, Karlsson MC, Kumlien Georén S, Tkach AV, Shvedova AA, Fadeel B, Barragan A, Scheynius A. Pulmonary exposure to single-walled carbon nanotubes does not affect the early immune response against *Toxoplasma gondii*. Part Fibre Toxicol. 2012 May 23;9(1):16
3. Adner M, Starkhammar M, Georén SK, Dahlén SE, Cardell LO. Toll-like receptor (TLR) 7 decreases and TLR9 increases the airway responses in mice with established allergic inflammation. Eur J Pharmacol. 2013 Oct 15;718(1-3):544-51

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The Role of Toll-like Receptors in Allergic Inflammation and Airway Hyperresponsiveness

The overall goal of this research project is to understand the role of pathogen-recognition receptors (PRRs), including Toll-like Receptors (TLRs) and NOD-like Receptors (NLRs) in allergic inflammation in the lung and in airway hyperresponsiveness (AHR). AHR is a characteristic trait of asthma, in which lungs are hyper-responsive to contractile stimuli, resulting in heightened bronchoconstriction.

Bacterial and viral pathogens have been shown to play a role in both the development of allergic lung inflammation, as well as exacerbation of the disease, promoting both heightened inflammation and AHR. Interestingly, bacterial and viral mimetics are also currently being investigated for their use as treatment for allergic inflammation in the upper and lower airways, with some success in dampening inflammation and AHR. However, the mechanism by which bacterial and viral pathogens, and their mimetics, alter AHR is currently not fully understood.

TLRs and NLRs, which have been shown to be expressed in neuronal, smooth muscle, inflammatory and epithelial cells in the lung, are vital to recognition of bacterial and viral particles. We have found that different agonists of TLRs and NLRs (e.g. LPS, poly I:C, R-837, CpG ODNs) have varying and sometimes opposing effects on AHR in the normal and allergic lung. For example, TLR7 is currently the only TLR to relax airways and therefore actively reduce AHR. Our current research looks into investigating the mechanisms by which these agonists alter AHR and inflammation in the healthy and allergic lung, in order to understand how TLR and NLR agonists can simultaneously exacerbate and treat AHR.



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Studies of normal and pathological voice function with special reference to singing and to neurological disorder.

Studies of vocal fold function in normal subjects and especially in high performance artists may provide knowledge that can give benefits for health care. At present we are looking at vocal fold vibrations during pressed, consciously hoarse pop singing, so called dist. A few concluding recordings are missing for publication. The work is done in cooperation with a research group in Vienna. A retrospective and a follow up study of patients with bilateral vocal fold paresis is currently under progress together with dr Fatima Denanto, but is not yet formed to a doctoral project. Similarly we have started a follow up of youngsters with VCD, vocal cord dysfunction, paradoxical vocal fold movements during physical exercise. Dr Kia Nyberg performs this work in which also speech pathology students are active. Together with a group from Dept of Speech Pathology at HS and a group från The Åbo University in Finland, me and Stellan Hertegård have been studying the effects of tube phonation on the voice source. This method has become very popular recently throughout the world. The work has been accepted for publication.

Supervision of PhD-students:

Staffan Morén Co-supervisor

Publications 2012, 2013, 2014

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Throat Surgery and Epidemiology at the apnea + Is intralymphatic allergen-specific immunotherapy against birch and grass effective and safe?

Publications 2012, 2013, 2014

1. Lundkvist K, Li X, Sundquist K, Friberg D Familial risk of sleep-disordered breathing Sleep Medicine Sleep Med. 2012 Jun;13:668-73.
3. Lundkvist K, Li X, Sundquist K, Friberg D Family Socioeconomic Status and Parental Occupation as Risk Factors for Sleep-Disordered Breathing in Swedish Children and Adolescents Submitted.



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Tissue engineering of different organs and/or tissues in the thorax

Regenerative medicine (RM) is a promising and growing field for the treatment of several incurable diseases. It is focused on the repair, replacement or regeneration of cells, tissues or organs dysfunctioning as a result of many causes, including congenital defects, disease, trauma and aging. The ability to combine several approaches such as cell therapy and/or natural or synthetic scaffolds to replace organs and tissues (tissue engineering) has the potential to move traditional transplantation to a new era of medicine. To further enhance tissue engineering, mathematical modeling approaches can be used to produce better clinical and experimental outcomes. My research team investigates tissue engineering of different organs and/or tissues in the thorax (i.e. esophagus, trachea, heart valve, heart, diaphragm, lung). These studies are carried by utilizing a multi-disciplinary approach such as stem cells, scaffolds and signalling molecules. We aim to mimic the target organs/tissues structurally and mechanically when engineering biomedical scaffolds for different applications. Cell therapy is an alternative treatment approach for highly complex and multifunctional organ. We aim to use the cell therapy approach for various acute and chronic respiratory (such as pulmonary hypertension, ARDS) by local or systemic administration of stem cells in combination with bioactive molecules.

Supervision of PhD-students:

Sebastian Sjöqvist Main supervisor
Ylva Gustafsson Main supervisor

Publications 2012, 2013, 2014

1. "Experimental orthotopic transplantation of a tissue-engineered oesophagus in rats". Sjöqvist S, Jungebluth P, Ling Lim M, Haag JC, Gustafsson Y, Lemon G, Baiguera S, Angel Burguillos M, Del Gaudio C, Rodríguez AB, Sotnichenko A, Kublickiene K, Ullman H, Kielstein H, Damberg P, Bianco A, Heuchel R, Zhao Y, Ribatti D, Ibarra C, Joseph B, Taylor DA, Macchiarini P *Nat Commun.* 2014 Apr 15;5:3562.
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Tumour markers in head neck cancer

Publications 2012, 2013, 2014

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3. Malin Wendt, Mircea Romanitan, Anders Näsman, Tina Dalianis, Lalle Hammarstedt, Linda Marklund, Torbjörn Ramqvist, and Eva Munck-Wikland. Presence of human Papilloma Viruses and P16 expression in hypopharyngeal. Submitted *Head&Neck* Juni 2012

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Bell's palsy- study design, prognosis and quality-of-life

Background: Bell's palsy is acute peripheral facial nerve dysfunction with unknown etiology. The disease can cause disfigurement of the face, impair the ability to eat, drink and speak, and seriously affect the patient's quality of life. There have not been any tests or clinical signs that can predict the outcome of Bell's palsy. Studies also show several methodological differences and interpretation of results is difficult. Validated instruments measuring quality of life aspects in these patients in Swedish have not been available.

Aims: To examine the effect of different analysis methods on a Bell's palsy study, to find prognostic clinical signs for non-recovery in Bell's palsy using the Sunnybrook facial grading scale, and to translate and validate the Facial Disability Index (FDI) and Facial Clinimetric Evaluation (FaCE) scale questionnaires in Swedish.

Data: Data were extracted from a prospective, controlled multicenter study including 829 patients with Bell's palsy. Patients were randomized to treatment with prednisolone and/or valacyclovir or placebo. 93 patients with peripheral facial palsy had their facial function assessed with House-Brackmann and Sunnybrook scales and answered FDI and FaCE-scale questionnaires twice with a 2-week interval.

Results: The choice of statistical method and definition of complete recovery substantially influence the rate of recovery. Early deterioration in Sunnybrook scores between baseline and first follow-up at days 11-17 is found to be a negative prognostic factor for complete recovery at 12 months. Early prednisolone treatment reduces this deterioration and improves outcome. Sunnybrook grading at 1 month can accurately predict non-recovery at 12 months in Bell's palsy. A prediction model and a simple-to-use risk curve for identifying patients at risk for sequelae based on the Sunnybrook score at 1 month are presented. The Swedish versions of the FDI and FaCE-scale show high reliability and validity.

Publications 2012, 2013, 2014

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2. Marsk E, Hammarstedt-Nordenvall L, Engström M, Jonsson L, Hultcrantz M. Validation of a Swedish version of the Facial Disability Index (FDI) and the Facial Clinimetric Evaluation (FaCE) scale. *Acta Otolaryngol*. 2013 Jun;133(6):662-9.



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Head and neck cancer

We study predictive and prognostic markers in head and neck cancer. HPV is a very important prognostic marker for tonsillar and base of tongue cancer and possibly also for hypopharyngeal cancer. This research continues in close collaboration with professor Tina Dalianis at Cancer Centrum Karolinska.

Åsa studies immunological aspects and significance in head and neck cancer patients.

Daniel studies osteoradionecrosis after radiotherapy and whether it can be predicted.

Lina studies mantle cell lymphoma, predictive markers, the role of microenvironment for the course of the disease and therapy targets.

Malin studies the effect of OK 432 therapy for branchial cleft cysts and ranulae.

Supervision of PhD-students:

Malin Wendt	Main supervisor
Daniel Danielsson	Main supervisor
Åsa Kågedal	Co-supervisor
Lina Nygren	Co-supervisor
Cecilia Nordfors	Co-supervisor
Lars Sivars	Co-supervisor

Publications 2012, 2013, 2014

1. Attner P, Näsman A, Du J, Hammarstedt L, Ramqvist T, Lindholm J, Munck-Wikland E, Dalianis T, Marklund L. Survival in patients with human papillomavirus positive tonsillar cancer in relation to treatment. *Int J Cancer* 131: 1124-30, 2012.
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19. Romanitan M, Näsman A, Munck-Wikland E, Dalianis T, Ramqvist T. Epidermal growth factor receptor (EGFR) and phosphorylated EGFR in relation to human papilloma virus (HPV) status and clinical outcome in tonsillar squamous cell carcinoma. Accepted *Head and Neck*.



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Science degree in the medical program; prospective long-term follow-up of results and students' attitudes to research

Publications 2012, 2013, 2014

1. Möller R, Shoshan M, Ponzer S. EXAMENSARBETE PÅ LÄKARUTBILDNINGEN. Handledaren har en central roll för studentens framgång. Läkartidningen 2012 (submitted).
2. Möller R, Shoshan M, Bolander-laksov K. Medical students' expectations and learning experiences; first findings from a long-term study on a degree project course. Högre Utbildning 2012 (submitted).

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OSAS in adults and children, focusing on surgical treatment

My thesis in 2008 dealt with obstructive sleep apnea syndrome (OSAS) in adults with a focus on treatment with weight reduction, and the prevalence of drug abuse (alcohol and sleeping pills) .

My continued commitment to research is now in the following main points:

1. RCT ATT / ATE on child OSAS : Inclusionsfase .Children 2-6 years with OSAS who are enrolled for operation of the tonsils and adenoid : does it matter which surgical method we use? We randomize children to either adeno-tonsillotomy (= partial tonsillectomi) or adeno-tonsillectomi (= complete tonsillectomi). Our first outcome parameter is the apnea hypopnea - index (AHI) measured by polysomnography , but we also evaluated quality of life questionnaires, postoperative pain, complications , inflammation , etc.
2. RCT UPPP / Watchful waiting in adult OSAS : Partly published results and manuscript, monitoring and analysis phase partly. Adult OSAS patients (mostly untreated because they do not accept treatment with CPAP or anti-apnea dental splint) are enrolled to be UPPP - operated (throat surgery including tonsillectomi) and followed regarding AHI, sleepiness, quality of life , blood tests, etc.
3. Intervention study on the treatment effect of anti-apnea dental splint for Upper Airway Resistance Syndrome : Analysis phase .
4. Treatment with Rapid Maxillary Expansion for Child OSAS : Start up phase. I am starting a project to treat children with OSAS and crossbite, with an orthodontic method of maxillary widening. This maxillary expansion has shown to result in an improvement in nasal breathing and also reduced OSAS degree, but the method is not used in Sweden yet for this indication.

Supervision of PhD-student:

Anna Borgström Co-supervisor

Publications 2012, 2013, 2014

1. A two-year weight reduction program in obese sleep apnoea patients. Pia Nerfeldt, Bengt Y Nilsson, Liliana Mayor, Joanna Uddén, Danielle Friberg, Karolinska Institutet, Sweden. JCSM 2010; 6: 479-86.
2. 15-year efficacy of uvulopalatopharyngoplasty based on objective and subjective data N. Browaldh, D. Friberg, E. Svanborg, P. Nerfeldt, Karolinska Institutet, Sweden. Acta Otolaryngol 2011; 131: 1303–1310.
3. Polygraphy vs. Polysomnography: missing OSAS diagnosis in symptomatic snorers - a wake-up call for clinicians. P. Nerfeldt, F. Aoki, D. Friberg. Karolinska Institutet, Sweden. Sleep Breath. 2013 Aug 14.
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Register-based epidemiologic studies of patients with chronic rhinosinusitis treated with endoscopic surgery in Sweden

BACKGROUND

Chronic rhinosinusitis (CRS) is a significant health problem, resulting in a great financial burden to society and a significant loss of quality of life for the patient. There is need for large cohort studies aimed at identifying risk factors as well as studies of the natural course of CRS. All previous epidemiological data have been based on interviews or questionnaires. A register-based nationwide study on CRS has not previously been conducted.

QUESTIONS

1. The distribution of age, gender and socio-economic status of patients with CRS treated with surgery?
2. A study of medical treatment, the risk of recurrence and postoperative complications in patients with CRS.
3. A study of the possible link between the risk of developing CRS requiring surgery and degree of exposure to air pollution.
4. Comorbidity in patients with CRS treated with surgery.

METHODS

From the Patient Registry at the The National Board of Health and Welfare, we will extract a cohort of approximately 80% of all patients (cases) in Sweden which were subject of endoscopic sinus surgery from 1997 to 2011. The number of cases will amount to approximately 11 000. As a reference cohort, we aim to study patients who underwent nasal septal surgery during the same time period. Matched for age and gender, we also extract a background population from Statistics Sweden. Connections will be made between these cohorts and e.g. the drug registry and the cause of death registry.

Publications 2012, 2013, 2014

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3. Ehnhage A, Olsson P, Kölbeck KG, Skedinger M, Stjärne P for the NAF2S2 Study Group. One Year after Endoscopic Sinus Surgery in Polyposis: Asthma, Olfaction, and Quality-of-Life Outcomes. *Otolaryngol Head Neck Surg*. 2012 May;146(5):834-41. doi: 10.1177/0194599811435638. Epub 2012 Jan 27.
4. Nordin S, Olsson P, Hedén Blomqvist E, Stjärne P, Ehnhage A; NAF2S2 Study Group†. Effects of FESS and additional fluticasone propionate nasal drops on psychological well-being in nasal polyposis with asthma. *Acta Otolaryngol*. 2013 Sep;133(9):939-43. doi: 10.3109/00016489.2013.783715.

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The value of genetic instability and TGF-alpha analysis as predictive markers of radiation sensitivity in T3 laryngeal cancer.

Publications 2012, 2013, 2014

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3. Palmgren B*, Jiao Y*, Novozhilova E, Stupp S, Olivius P. Survival, migration and differentiation of mouse tau-GFP embryonic stem cells transplanted into the rat auditory nerve. Experimental Neurology 235 (2012) 599–609



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Inflammation of the upper respiratory tract; mechanistic mapping and evaluation of medical and surgical intervention

Inflammation in the upper respiratory tract ; mechanistic mapping and evaluation of medical and surgical intervention. The project contains two parts:

- Studies of mechanisms in pregnancy rhinitis and its effect on the pregnant woman's quality of life.
- The epidemiology of allergic rhinitis studied in a birth cohort (Bamse) .

The overall objective is to understand the basic epidemiology and mechanisms and but also to improve the treatment of these patient groups.

Zygomatic and orbitabotten fractures ; diagnosis and evaluation of treatment

The project includes both retrospective studies as prospective randomized trials and aims to improve the management of patients with facial fractures .

Some questions that we want to highlight :

- To what extent does the change in orbital volume upon an orbital fracture influence patient's symptoms and what other factors are important for the development of sequelae
- What is the significance of fixation of facial fractures in relation to adequate fracture reduction

Studies of sinonasal tumors and pituitary adenomas

We have created an interdisciplinary network that aims to study sinonasal tumors and pituitary adenomas . The network, which covers most aspects from "bench to bedside ", has all prerequisites to get powerful synergies both in terms of basic knowledge about the tumor pathophysiology and epidemiology as well as the implementation of new discoveries in clinical work.

Supervision of PhD-students:

Babak Alinasab	Main supervisor
Ola Bengtsson	Main supervisor
Marit Westman	Co-supervisor

Publications 2012, 2013, 2014

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**Binaural hearing with cochlear
Long-term measurement of middle ear pressure**

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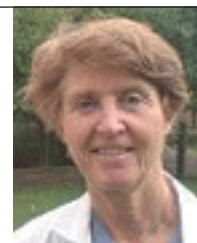
Persistent geotropic nystagmus - a different kind of cupula pathology

We have described a geotropic persistent nystagmus (g-PCDN) in patients during vestibular crisis. In addition, when the patient is in the supine position and the head is turned slowly from one side to the other it is possible to discern a zero zone where the geotropic nystagmus is absent. Theoretically this occurs when the longitudinal axis of the affected cupula is aligned with the gravitational vertical. We have called this new diagnostic entity "light cupula". In order to reproduce a clinical condition where the density of the cupula was lower than the surrounding endolymph we examined the nystagmus pattern in different head positions in unilaterally deafferented patients during the stage one of alcohol nystagmus (PAN 1). This nystagmus pattern permitting a lateralization of the affected side was tested on 20 patients with g-PCDN during acute vestibular disability. Nystagmus patterns in different head positions were recorded, both caloric and otolith tests were carried out. The slow phase velocity of geotropic nystagmus was low and of equal intensity and did not present an indication of the affected side according to Ewald's second law. We did not find an applicable pattern for simple determination of the affected side by analysing nystagmus direction in different head positions. There was a high prevalence of migraine (40%) and the patients also had problems with recurrent vertigo (80%). The vestibular tests were pathologic in 60% of the patients.

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Neurophysiological preconditions for the hearing, cognitive abilities and reading development in hearing-impaired and deaf children with hearing aids and cochlear implants.

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Publications 2012, 2013, 2014

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Local inflammatory parameters in women with Pregnancy Rhinitis



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Zygomaticomaxillary complex & orbital floor fractures - aspects of diagnostic methods, treatment & sequelae

Publications / manus

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Innate immunity receptors and the role of local infections in development of chronic rhinosinusitis with polyps

Background

Chronic rhinosinusitis (CRS) is a disease defined as chronic inflammation of the nose and paranasal sinuses. It has a considerable impact on morbidity.

During the last decade the opinion has shifted from considering CRS to have an underlying infectious basis to view it as a primarily disorder of persistent inflammation. Lately the discovery of pattern-recognition receptors (PRR) as part of the innate immune system has opened new possibilities for exploration of the underlying mechanisms.

Patients with CRS with polyps can often be successfully treated with steroids. However, the clinical impression is that the therapeutic effect gradually weakens over time leaving a minor patient group insensitive to local steroid treatment. There may be several mechanisms accounting for the resistance to the anti-inflammatory effects of glucocorticoids, including changes in the receptor expression.

Aim

The over-all aim is to chart the potential role for infectious inflammation in relation to innate immunity as a part of the pathogenesis of NP.

Material and Method

A large number of studies have analysed polyp tissue from patients with NP. In this project we will focus on changes in the adjacent “healthy” nasal mucosa. The idea is to understand how a local infection, through interaction with various innate immunity receptors could affect the onset and growth of polyps. Nasal polyps, nasal mucosal biopsy specimens, lavage fluid and blood will be obtained from patients undergoing surgery and from healthy subjects. They will be characterized using flow cytometry, immunohistochemistry, PCR and ELISA based techniques. Procedures for analysing cellular proliferation and migration will also be used and epithelial cells will be isolated and cultured in vitro. Special attention will be given to the role of glucocorticoid receptors and the development of steroid resistance.

Importance

We aim to discover new information that can contribute to new treatment strategies.



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Bilateral cochlear implants in children - Clinical and experimental studies

A growing number of children receive bilateral cochlear implants (BiCIs), based on the assumption that speech recognition in the presence of background noise and sound localization will be improved. The purpose of this project is to quantify the effects of bilateral cochlear implants in children. Specifically, we studied the effects of age at first implantation, age at second implantation, and the auditory experience on absolute and relative (bilateral versus unilateral) speech recognition in noise and sound localization performance. In addition, the project aims at developing objective and precise methods for the assessment of sound localization accuracy in infants from 6 months of age.

The main findings from the project so far are that BiCIs results in a bilateral benefit for speech recognition in noise and horizontal sound localization, and that sound localization performance improves with increasing auditory experience after bilateral implantation. The bilateral benefit is, on average, stable over time. Further findings suggest that early bilateral implantation is associated with a larger bilateral sound localization benefit and a faster improvement of sound localization abilities after activation of the second implant.

Currently, an method for precise and objective sound localization measurements is under development. Preliminary data suggest that sound localization may be assessed from 7 months of age and that the method has high reliability.

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Estrogen and hearing

It's known that women have better hearing than men until menopause; therefore estrogen is suggested to have a protective effect on hearing. Estrogen acts via two nuclear receptors, ERalpha and ER beta, both found in the inner ear and in the central pathways in the brain of mice, rats and humans. The localization and expression of the receptors varies during development and pregnancy mirroring the fluctuating estrogen levels in blood. In Turner syndrome (loss of one X-chromosome, lack of ovaries and low estrogen levels) a rapid decline in hearing is seen at the age of 30 (resembling presbycusis). Studies suggest that progesterone in hormone replacement therapy has a negative effect on hearing thresholds and otoacoustic emissions, progesterone acts via nuclear progesterone receptor A and B as well as via membranebound receptors.

Aims: To investigate

1. The effect on hearing of Estrogen substitution in Turner women
2. The effect on hearing and estrogen receptors after Estrogen substitution in Turner mice
3. The presence of progesterone receptors in the inner ear (in press)
4. The effect of anti-estrogen therapy on hearing in women treated for estrogen-positive breast cancer.

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Childhood obstructive sleep apnea; evaluation of questionnaire and RCT of surgical treatment

Pediatric obstructive sleep apnea (OSA) has a prevalence of 1-4% with a peak incidence at 2-5 years of age. The main cause is adenotonsillar hypertrophy. If left untreated OSA can cause severe complications (e.g. failure to thrive, neurocognitive complications, hypertonia and in severe cases cor pulmonale and heart failure).

Gold Standard to diagnose OSA in children is polysomnography (PSG). However, this is a costly method, not widely available. In most cases diagnosis is based on patient history, clinical examination and questionnaire. In Sweden the questionnaire mostly used is OSA-18. This questionnaire has not before been evaluated against objective PSG data, but this has now been done in the first part of this project. The results show poor validity when comparing OSA-18 to PSG-parameters.

Treatment of OSA in children is surgical with adenotonsillectomy (ATE) and adenotonsillotomy (ATT). These both methods have however not yet been compared concerning the effect in treating OSA and randomised controlled studies are asked for. The main part of this research project aims to compare ATE vs ATT and their effect in treating OSA. 70 children aged 2-6 years with tonsilhypertrophy and OSA verified by PSG are randomised to either ATE or ATT and are followed up with a new PSG one year postoperatively. Besides PSG-parameters, the study patients will be evaluated concerning bloodpressure, postop bleeding and pain and their parents will answer two questionnaires pre- and postop.

Publications / manus

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Osteoradionecrosis, markers for individual radiosensitivity, evaluation of reconstructive treatment modalities for osteoradionecrosis and quality of life for patients before and after reconstruction

Irradiation, surgery and chemotherapy are the three main treatment modalities for head and neck cancer patients. Irradiation, especially in combination with chemotherapy, is associated with considerable side effects.

Osteoradionecrosis, ORN, is a late and often severe side effect to irradiation. It is defined as necrotic bone exposed through a mucosal and/or skin defect without tumor recurrence and with a duration of more than three months.

There is no exact definition of the pathophysiology of ORN but the current thesis include:

1. Direct damage to local micro vessels causing vascular necrosis in the irradiated area.
2. Production of ROS(reactive oxygen species) that gives an irreversible damage to osteoblasts, -cytes, -clasts.
3. Cytokine mediated dysregulation of fibroblasts and collagen metabolism leading to fibrotic tissue.

ORN is for the individual patient a severe condition affecting daily life. Symptoms include trismus, pain, impaired nutritional capacity and infection not seldom associated with oro-cutaneous fistula. ORN is seldom reversible and will progress over time leading to pathological fractures and need for extensive reconstructive surgical intervention including free tissue transfer. This treatment is costly to both patient and society.

Radiation therapy is dose dependant but individual differences exists. The incidence of ORN in the head and neck ara is reported to 3-8%.

Aim of our studies:

1. Possible markers for individual radiosensitivity, DNA-repair, oxidative stress and inflammation.
2. Evaluation of possible advantages in surgical planning utilizing CT-angiograms.
3. Quality of life comparative study for ORN patients before and after extensive reconstructive surgery with free tissue transfer.

Publications / manus

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Inverted Papilloma, incidence, ethiology and prognosis

OBJECTIVES

The true incidence of Inverted Papilloma (IP) is not yet known. From hospital based studies its incidence has been estimated to approximately 1/100000 personyears. IP and squamous cell carcinomas (SCC) have been reported to exist concomitantly in 3-13% but the frequency of its synchrone and metachrone malignant transformation is to much extent unknown. This study aims to investigate incidences and changes in incidence in the Swedish population 1960-2010 for IP and malignant sinonasal tumours as well as the relation between IP and SCC. It also aims to establish the survival- trends of sinonasal malignancies (SNM) in the same population during the same time period.

Furthermore we intend to analyse any possible viral ethiology, mainly HPV, for IP or its eventual malignant transformation.

METHODS

Using data from the Swedish Cancer Registry (SCR) we have identified 3221 patients with SNM, of these 1570 had SCC, 823 patients with IP and 83 with cancer in situ. All diagnosed between 1960 and 2010. From Statistics Sweden we have the date of death among these patients. Statistical analysis has been performed to acquire our wanted epidemiological data, described above.

We will use PCR as a method to analyse the presence of HPV on parafin-embedded biopsies from patients in Stockholm with IP.

RESULTS

IP seem to be less frequent than expected and tend to malignify less seldom, although at a higher rate than the normal population.

SNM have rather decreased over the time period except for sinonasal malignant melanomas (SNMM) and adenoidcystic cancers (although a small group).

SNMM and undifferentiated carcinomas had the poorest prognosis.



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The role of neutrophils in airway smooth muscle contraction

Asthma is a highly complex disease which is characterized by chronic inflammation and airway hyper-responsiveness, which causes airway obstruction. The project focuses on airway hyper-responsiveness and the role of the neutrophil. Neutrophils are known to be one of the first lines of defense against invading microbes, playing a pivotal role in the antimicrobial host defense by recognizing microorganisms through various receptor systems. To fulfill this function, they are the first leukocytes to be recruited toward areas of inflammation. The known functionality of neutrophils in the inflammatory process has changed over time from initially being a cell limited to phagocytosis and the release of enzymes and other cytotoxic agents to a cell releasing mediators with a more specific role for asthma development.

Several studies have documented that asthma dominated by a local pulmonary neutrophil influx is over-represented among patients that respond poorly to traditional treatment. Information about the role of neutrophils in airway smooth muscle contraction is limited.

The aim is to see if the neutrophil alone can affect the airway smooth muscle by organ culture and measuring of the smooth muscle contraction in a myograf, *in vitro*. Various receptor-specific antagonists will be used to understand how the neutrophils affect the airway smooth muscle and through which pathway. The ligands for these receptors will be measured from neutrophils as a secreted product, using ELISA, or with various kits and flow cytometry. By studying the neutrophils various activation states, sensitivity and apoptosis outside their usual environment, will we be able to develop a stable method for studying the effect of airway resistance *in vitro*.



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Pathophysiology and treatment of rhinitis medicamentosa

Publications / manus

1. Enerdal J, Edman G, Stjärne P. Rhinitis Medicamentosa - Personality profile and symptomatology of nasal decongestant abstinence. Rhinology, submitted.



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Neurophysiological conditions for hearing, cognitive capabilities and reading development in hearing-impaired and deaf children using hearing aids or cochlear implants

The aim of this study is to examine the neurophysiological conditions for auditory function as well as the development of cognitive and reading abilities of hearing impaired and deaf children using hearing aids or cochlear implants. It has been shown that these children perform more poorly in school as compared with non-hearing impaired children, despite equal learning aptitude. The children who participate in the study are between five and seven years of age. It is a longitudinal study and we have followed them up after three years and will examine how an internet-based phonological training program impacts the cognitive development.

By measuring different event-related brain potentials (ERP) one can follow how the acoustic information of a tone or a word travels along the brainstem auditory pathway to the primary hearing centre in the cerebral cortex, where the acoustic information can be detected on a conscious level. The acoustic information can be processed only when it reaches the secondary auditory centre. The P1-N1 complex provides a measure of the auditory system's ability to detect sound, and is impacted primarily by external stimulus. Later components (P300 and N400) reflect a more complex processing of sound which impacts the secondary auditory centre. Mismatch negativity (MMN) provides a measure for detecting minor differences in sound which are important for the ability to understand speech. It is regarded as a subconscious process not requiring active listening.

The ERP technique is non-invasive and safe. The training program is expected to have positive effect on hearing-impaired and deaf children's ability to hear and develop a language.

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Pituitary tumors; clinical aspects of treatment and expression of galanin and PRR receptors.



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Mesenchymal stromal cell therapy in rat models of pulmonary hypertension

Pulmonary hypertension is a heterogeneous group of diseases with different etiologies, resulting in an elevated blood pressure in the pulmonary circulation. Based on etiology and differences in pathology, pulmonary hypertension is subdivided into five different categories. This project is focused on animal models in rat of two of these subcategories, namely Pulmonary Arterial Hypertension (PAH) and Chronic Thromboembolic Pulmonary Hypertension (CTEPH).

Cell therapy is an emerging treatment in the fast-growing field of regenerative medicine. The aim is to use stem cells to repair damaged organs, preventing the onset of end-stage organ failure and the need for organ transplantation. In the case of pulmonary hypertension, cell therapy using mesenchymal stromal cells has been shown to relieve PAH and CTEPH in animal models. The mechanism for this effect is however largely unknown.

One possibility is that the cells engraft to injured tissue in the pulmonary vascular bed and directly repair it by differentiation and replacing injured cells. Another possibility is that the cells engraft for a shorter time and exert the effect through local factor secretion, paracrine signaling and cell homing. It is also possible that the engraftment isn't so important, and that the cells give mostly systemic effects.

Understanding these dynamics is crucial to optimizing the cell therapy treatment, including cell administration way, dosage and treatment timing. We intend to investigate this through in vivo cell tracking, as well as cell detection in histological sections of lungs. We will also utilize physiological measurements to determine treatment effect, and mathematical modeling, analysis of gene and protein expression, signaling pathway blockade and additional factor treatments to further investigate the mechanisms of mesenchymal stromal cell therapy for pulmonary hypertension.

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Ototoxicity of cisplatin – pharmacokinetic and pharmacodynamic aspects

Publications / manus

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Intralymphatic allergen specific immunotherapy (ILIT) in allergic rhinitis

Allergic rhinitis is a major health problem. Allergy vaccination, or allergen specific immunotherapy (SIT) is the only treatment that not only gives symptom relief but also acts disease-modifying. Few patients undergo SIT mainly due to the time-consuming process with up to 50 doctor appointments with subcutaneous injections over 3 years. An alternative to conventional SIT is sublingual immunotherapy in which the patient takes a tablet under the tongue every day for three years without the need of medical supervision. However, there is a problem with long-term patient adherence. It is natural to look for a better way to administer SIT.

A previous study showed that only three low dose allergen injections direct into the lymph node, intralymphatic immunotherapy (ILIT), could induce symptom relief comparable to that after conventional ASIT. Our research group has recently reproduced these results. Only mild allergic reactions were registered.

Presently, an ILIT-combination of grass- and birch allergen is evaluated with focus on symptom score and specific antibody production. To achieve improved symptom relief both the dose and the number of injections will be increased.

Samples from vaccinated lymph nodes will be collected through fine needle aspiration. Tonsil tissue will also be obtained from patients undergoing elective tonsillectomy after receiving ILIT and the tonsils and lymph node aspirates will be analyzed regarding immunologic activation.

The proposal is aimed to increase the opportunity for rhinitis patients to receive SIT, and maybe even to improve the induced symptom relief. We also hope to gain new insights in the mechanisms behind tolerance development in allergic disease.



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2014

Hearing ability among Swedish hunters

Questions: Is it possible to accurately measure hearing ability with a PC and the Internet? How is the hearing ability among Swedish hunters and how do they protect their hearing? How important is the choice of gun for the hearing ability? Does hypertension, CVD, and /or the use of smokeless tobacco affect the vulnerability for hearing loss?

The project aims at developing an Internet-based hearing test for screening, aswell as a questionnaire and to measure and investigate hearing ability among Swedish hunters, and possible risk factors for hearing loss.

Material and methods: We have developed a website, <http://jagarhorsel.ki.se>, with a questionnaire with questions on riskbehaviour, weapon type, shooting habits, previous/present diseases, drug use, heredity on hearing, previous noise experience etc. The questionnaire is followed by two screening hearing tests performed on the internet with a PC. One of the tests, speech-in-noise, measures "social hearing ability", the other one, developed and validated within the study, resembles an ordinary clinical audiometry.

Results: A pilot test of the website with 560 hunters has been done, and resulted in a published article. The pilot proves that the method is valid. The Internet-based hearing test has been validated against clinical audiometry and this has lead to another published article.

In august 2013 the main study was closed. It has been running since february 2012. We have 1771 participants. Data analysis is currently proceeding.

Publications / manus

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The use of organotypic culture and in vivo-studies to investigate implantation of progenitor cells to the auditory nervous system

Modern hearing aids, like cochlear implants (CI), have made more patients accessible to modern hearing rehabilitation. There are still many patients with damage to their hearing nervous system that are too adverse to be suitable for these new techniques. The overall objective of our project is to make more patients suitable for modern hearing aids.

The health of the auditory nervous system, how we possibly can modulate repair of a damaged system and possibilities to improve receptability to hearing aids are the main themes of our project.

Presence of an intact auditory system is a prerequisite for a successful auditory rehabilitation. We are studying ways to affect the damaged hearing system on a cellular- as well as functional level.

We are utilizing both cell culture settings as well as in vivo models to investigate cell survival, differentiation, migration and the ability to establish new functional contacts with other cells.

In our in vitro settings we primarily use mouse and rat donor cells, but also human cells. Different cell types are utilized, as brain stem, dorsal root ganglion, organ of Corti and spiral ganglion cells. Embryonic and young adult cells with varying stem and progenitor characteristics are transplanted to an auditory nervous system model.

Results from our in vitro studies are transferred to in vivo models. Deafened animals are treated and their damaged auditory systems are studied. We transplant cells locally, apply of bio active gels and growth factors to study survival, migration and effects on glial scarring.

We also do functional evaluations.

Publications / manus

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Innate immunactivity in head and neck cancer

What is the influence of the immune system in the development of head and neck cancer?

Chronic inflammation caused by cigarette smoke or viral infections are associated with different types of squamous cell carcinomas. In these cases, the inflammatory response is characterized by increased level of free radicals and inflammatory mediators. Instability in the epithelial cells occurs and contributes to tumor development. Recognition of these microbes is mediated by the so-called pathogen recognition receptors (PRRs).

The immune system of cancer patients exhibit an altered immune defense pattern compared with healthy controls. Tumors of the head neck area metastasize primarily to regional lymph nodes of the neck. Sometimes a small primary cancer can be found after the lump at the neck, the metastases. This gives interest to the lymph node from a tumor immunological perspective. A high infiltration of leukocytes into the tumor has indicated a favorable prognosis, but how, the leukocytes affect the prognosis is unknown. We are studying how the leucocytes in the lymph nodes are affected by tumors and metastasis.

Our long term goal is to find ways to predict the prognosis of head and neck cancer patients by studying the immune system's role in cancer development.

More specifically, we want:

- Characterize leukocytes level, examine neutrophil / lymphocytes ratios relation to cancer development
- Learn about the importance of PRRs in cancer inflammation
- Study how the level of different leucocytes in the lymph nodes is associated with cancer.



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**Treatment of scar damage the vocal cords with mesenchymal stem cell transplantation.
Effects and mechanisms.**



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Identification of genetic risk factors in allergic rhinitis using association studies

This project aims to identify, validate and characterize genetic risk factors for allergic rhinitis (AR). The project analyzes a total of 1,800 AR patients and 2,100 healthy individuals from a number of different materials: one collected in Malmö, one Chinese population from Singapore, but also individuals from the BAMSE cohort. Both "single nucleotide polymorphisms" (SNPs) and copy number variants (CNVs) are analyzed using a candidate gene approach.

In a first study, previous AR-associated risk factors described in the literature has been investigated. The study summarizes all previous AR associations and emphasizes the difficulties in replicating associations and the need for large, well characterized case/control materials to successfully identify and replicate candidate genes and SNPs in AR.

Since AR and asthma have many similarities, genes with known risk factors for asthma has also been investigated for association with AR. The study indicates that asthma and AR have fewer genetic risk factors in common than previously anticipated, but some of the investigated risk factors could be common to both phenotypes.

In a third study, SNPs in all ten Toll-like receptor genes were examined for association with AR. SNPs in the TLR7-TLR8 gene region was found to be associated with disease in both the Swedish Malmö population and the Chinese population.

Three additional studies are ongoing. In these studies, focus has been on replication in the BAMSE material of previous associations, and the detection and analysis of rare variants in the form of SNPs and CNVs in the TLR genes.

Publications / manus

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- 5.



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Hearing conservation inner ear surgery

Publications / manus

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The direct influence of Toll-like receptors during airway virus infections

Respiratory infections, both viral and bacterial, are known to promote exacerbation and airway hyper-responsiveness (AHR) in asthmatic patients. The AHR development is often considered as a result of the inflammatory response, but the mechanisms behind this are poorly understood. It has become increasingly clear that activation of the innate immune system constitutes a critical element in the process. Toll-like receptors (TLRs) are, as a part of the innate immune system, key elements in recognizing viral and bacterial components

In this project we study effects of TLR activation on airway reactivity and inflammation in an animal in vivo model. By this model we mimic a respiratory infection. We register the AHR and the local inflammation picture in the airway.

Our studies can demonstrate that activation of TLRs cause AHR. The AHR does not seem to depend on the local inflammatory profiles characterized by inflammatory cell recruitment and cytokine release. This challenges the idea that inflammation is a prerequisite for AHR development and suggests that at least part of the effect might be due to a direct microbial interaction with the smooth airway musculature.

Publications / manus

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Estrogen substitution & hearing in humans and estrogen receptor knock-out mice

Publications / manus

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Pattern-recognition receptors (PRRs) in human upper airway diseases.

The aim of this project is to characterize the roles of pattern-recognition receptors (PRR)s in airway inflammation.

The nasal mucosa constitutes the first line of defense against foreign airborne and initiates the first immun response. This tissue are of importance and involved in many different disease developments. PRRs, including Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs) and the recently discovered retinoic acid-inducible gene 1 (RIG-I)-like receptors (RLRs), are all known to play important roles in pathogen recognition, cell activation and regulation of immune responses. The nasal epithelium has the ability to recognize viral intrusion through TLR and RLR receptors, and the subsequent response might have a role in exacerbation of inflammatory diseases like allergic rhinitis and chronic rhinosinusitis (1).

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory disease in the nose and the paranasal sinusitis and the remodeling and inflammatory pattern are important in the development of the polyps. It is unknown why the mucosal immune function in CRSwNP patients is ineffective in eliminating microorganisms. We study the role of TLR9 in CRSwNP patients and how the inflammatory response, proliferation and angiogenesis is changed after nasal administration of CpG (TLR9 agonist).

Activation of PRRs has also been implicated in the pathobiology of asthma. Infections of the respiratory tract by bacteria or viruses may act via these receptors to either prevent or exacerbate the clinical presentation of the disease. Human airway smooth muscle cells (HASMCs) are major effector cells in asthma by affecting airway hyperresponsiveness, remodeling and inflammation. They express TLRs, suggesting that they might have a role in mediating microbe-induced disease exacerbations. We have shown the function of TLRs, NLRs and RLRs in HASMC and that manipulation of the PRR system might be of therapeutic use in the management of asthma (2).

Publications / manus

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2. Innate immune receptors in human airway smooth muscle cells: activation by TLR1/2, TLR3, TLR4, TLR7 and NOD1 agonists. PLoS One. 2013



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Injection Treatment of benign neck cysts and ranula with OK 432 - a prospective, randomized, double-blind, placebo-controlled study



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Vestibular evoked myogenic potentials in the clinical neurotology

This research plan is designed for widen the clinical application of the vestibular evoked myogenic potentials (VEMPs). VEMP is a myogenic potential that can be evoked through stimulation of the vestibular apparatus of the inner ear, mainly by activation of the otolith organs (sacculus and utricle) in response to sounds or vibration stimuli. VEMPs can be recorded with electromyography from various groups of muscles using skin electrodes. Two methods have been introduced in the clinical field: cervical VEMP (cVEMP), myogenic potential evoked by sound and recorded on the muscle sternocleidomastoideus; ocular VEMP (oVEMP), myogenic potential evoked by skull vibration and recorded beneath the eyes on the inferior oblique muscle. The first is used as a test of saccular function and integrity of the inferior division of the vestibular nerve; the second is used as a test of utricular function and integrity of superior division of the vestibular nerve.

cVEMPs and oVEMPs are nowadays useful for the diagnosis of “third window” syndromes (showing enhanced response) or in case of vestibular loss (showing which vestibular division is affected).

The research plan is based on the actual experimental and clinical research and the aim is to widen the diagnostic role of VEMPs in clinical neurotology. Four areas will be considered:

1. VEMPs & middle ear disorders: can VEMPs add information on both the vestibular function in case of middle ear pathology and also on the alteration of sound transmission in the middle ear?
2. VEMPs & vestibular loss: can VEMPs during the recovery phase following vestibular lesions add information on the prognosis and expected balance function?
3. An alternative way to evoke VEMPs: VEMPs will be studied with a combination of sound and vibration instead of single modality stimuli.
4. Assessment of specific parameters and settings of VEMPs in different vestibular diseases.

Publications / manus

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Rhinitis and rhinosinusitis in the BAMSE birth cohort, followed up to 16 years of age

The overall aim of my PhD project is to study the natural course of and risk factors and predictors for rhinitis and rhinosinusitis in children and young adults.

I use data from the population based BAMSE birth cohort (Barn/Children Allergy Milieu Stockholm Epidemiology). 4089 unselected children were included at birth between 1994 and 1996. The children have been followed up at 1, 2, 4, 8, 12 and 16 years of age with questionnaires. At 4, 8 and 16 years of age everyone with a completed questionnaire was invited to a clinical investigation including blood samples for specific IgE. At 16 years of age we also collected nasal lavage samples in a case-control model among children with severe rhinitis. In a subgroup of children with symptoms of chronic rhinosinusitis we also do nasoscopy, odor threshold test and the symptom specific questionnaire SNOT-22.

In the first study we saw that rhinitis symptoms are more likely to persist if they are allergic than nonallergic. Among children with allergic rhinitis, sensitization seems to precede rhinitis symptoms rather than symptoms of rhinitis preceding sensitization. OAS is common among children with symptoms to birch.

In the second study we saw that parental allergy was associated with allergic as well as nonallergic rhinitis. Maternal and paternal allergy increased the odds similarly. Hay fever seemed to be the most important risk factor for allergic rhinitis. The risk of nonallergic rhinitis increased only if one parent had two or more allergy related diseases.

The aim of the third study is to see whether IgE reactivity to PR-10 components better predict symptoms to birch pollen than IgE to birch alone.

The aim of the fourth study is to estimate the prevalence of chronic rhinosinusitis in adolescence through a clinical follow up and analyze symptom severity..

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Nicotine and endotoxin in asthma pathogenesis, with focus on airway hyperreactivity and G-protein coupled receptors

Cigarette smoke is a well-known risk factor for the development of airway hyperreactivity (AHR) and inflammation, but the mechanisms behind this remain to be characterized. Nicotine and endotoxin (LPS) are two components in cigarette smoke. The latter is also a part of the bacterial cell wall. LPS is known to activate the innate immune system through Toll-like receptor 4.

The project is aimed at exploring the mechanisms behind cigarette smoke-induced AHR. Signal pathways activated by nicotine and LPS will be dissected and the role of their interaction investigated. To this end, various animal models will be used. In vivo, effects on lung mechanism as the result of subcutaneous nicotine pumps and nasal nicotine/LPS application will be evaluated. The contractile capacity of isolated murine airways will be investigated in vitro using tissue baths. Tissue baths will also be used to assess the contractile activity of arteries in human nasal mucosa. Specific pharmacological inhibitors will be employed to dissect the signal pathways involved and the inflammation will be characterized using PCR, immunohistochemistry and ELISA.

The goal is to pinpoint pivot molecules with a central role in the development of cigarette smoke-induced AHR. By using specific inhibitors to target these molecules we hope to contribute, not only to the development of better asthma therapy for the future, but also to novel treatment options in chronic obstructive lung disease and rhinitis.

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