

FORSKNINGENS DAG

Välkommen till Forskningens dag den 17 april 2015

Tema Forskning - en del av det dagliga arbetet för alla på en universitetsklinik

En ny inriktning för integration - forskning vid kliniken

Program

- 8.00-8.30 Fika
- 8.30-8.40 Professorn hälsar välkommen
- 8.40-8.55 Professorn och verksamhetschefen diskuterar dagens tema
- 8.55-9.00 Blankett för stöd för klinikintegrerad forskning/kvalitetsprojekt
- 9.00-9.15 Tonsillinsamling på Huddinge - vad kan vi lära av det?
- 9.15-11.00 Grupparbeten
- Hur kan vi utveckla och beforska verksamheten på:
- På mottagningen
- På avdelningen
- På operation
- Instruktioner till grupparbete:
- Samtliga deltagare med aktiv forskning berättar kort om sin profil. Därefter
 grupparbete kring frågeställningen.
- Redovisas i plenum.
- 11.00-12.00 Redovisning
- 12.00-13.00 Lunch
- 13.00-13.30 Bästa ST projekt eller delarbete i en avhandling. 5 min presentation
- Vinnaren får en forskningsmånad. Jury är auditoriet
- 13.30-14.00 Senaste årets avhandlingar - 10 min per respondent
- 14.00-14.15 Sammanfattning av dagen - Lars Olaf

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Management Division



Head of the Division, Professor,
Vice Prefect
Lars Olaf Cardell
lars-olaf.cardell@ki.se
+46 8 585 81453



Vice Head of the Division, Professor
Sten Hellström
sten.hellstrom@ki.se
+46 73 626 1861



Vice Head of the Division, Professor
Malou Hultcrantz
malou.hultcrantz@karolinska.se
+46 8 517 75653



Secretary/
LADOK-administrator
Agneta Wittlock
agneta.wittlock@ki.se
+46 8 585 87353

Management Institution



Head of Department
Li Tsai
li.tsai@ki.se
+46 8 585 87191



Head of Administration
Pille Ann Härmat
pilleann.harmat@ki.se
+46 8 524 87741



Head of Finances
Britt-Louise Gothnier
britt-louise.gothnier@ki.se
08-524 87749



Director of postgraduate
studies
Mats Blennow
mats.blennow@ki.se
+46 8 585 81428

Members of the FoU Council at the Clinic

Lars Olaf Cardell, chairman
Åsa Bonnard
Stellan Hertegård
Mats Holmström
Roberg Huhn
Malou Hultcrantz
Eva Munck-Wikland
Pia Nerfeldt
Pär Stjärne
Bo Tideholm

Professors and Docents

Professor and Senior Professors

Lars Olaf Cardell, Professor
Stellan Hertegård, Adjunct Professor
Mats Holmström, Adjunct Professor
Malou Hultcrantz, Adjunct Professor
Eva Munck Wikland, Adjunct Professor
Pär Stjärne, Adjunct Professor
Claus Bachert, Affiliated Professor
Stefano Berritini, Affiliated Professor
Sten Hellström, Senior Professor
Dan Bagger-Sjöbäck, Professor Emeritus
Ulf Rosenhall, Professor Emeritus

Docents

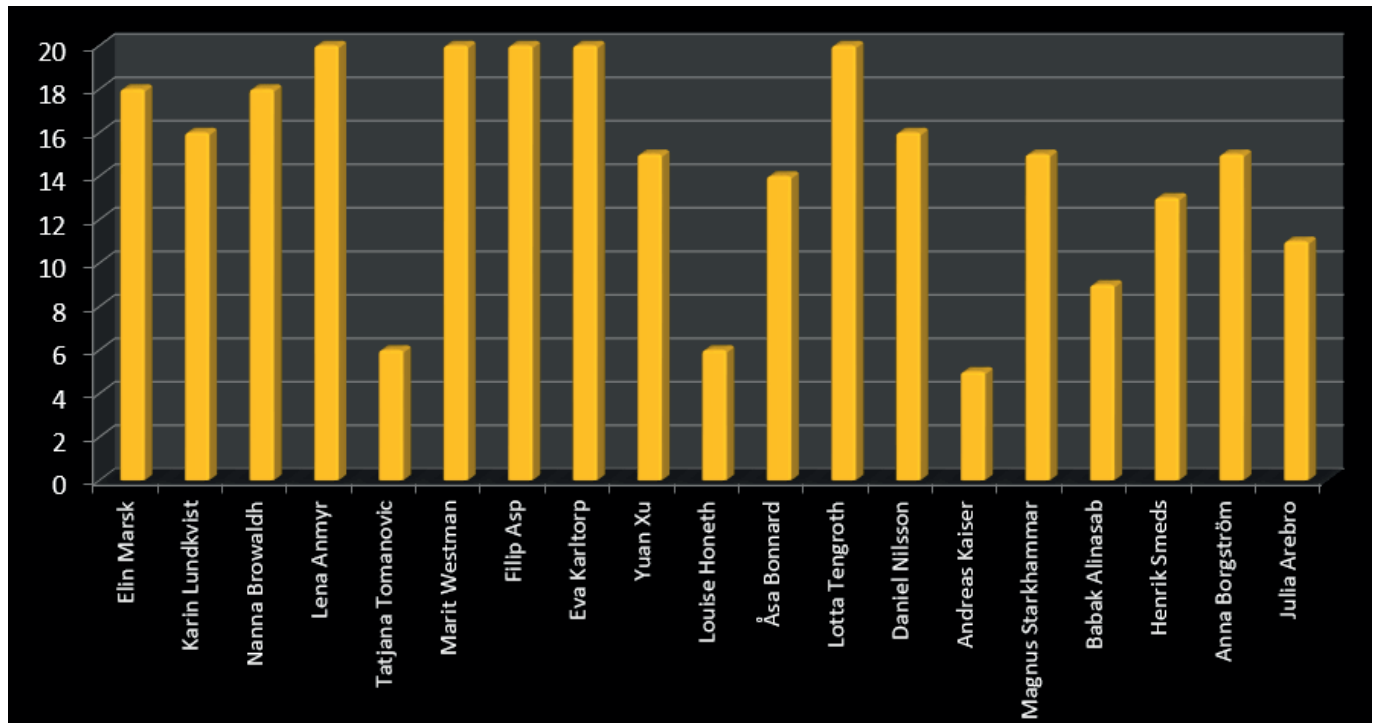
Erik Berninger
Maoli Duan
Anders Freijd
Danielle Friberg
Esma Idrizbegovic
Jan-Erik Juto
Richard Kuylenstierna
Per-Åke Lindestad
Riitta Möller
Britt Nordlander

Dissertations / Halftime seminars 2014-2015



Date		Name	Title
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
2014-10-24	Half-time	Babak Alinasab	Zygomaticomaxillary complex and orbital floor fractures – aspects of diagnostic methods, treatment and seguqlae.
2014-11-28	Dissertation	Mattias Jangard	Malignant melanoma and other malignancies of the nasal cavity and the paranasal sinuses in Sweden
2014-12-11	Dissertation	Daniel Nilsson	Genetic association studies in allergic rhinitis
2014-12-12	Dissertation	Marit Westman	"Hay fever" in children
2015			
2015-03-12	Half-time	Henrik Smeds	Cochlear implantation, surgical trauma and malformed cochleas.
2015-03-27	Dissertation	Victoria Hellberg	Pharmacokinetics and inner ear transport of cisplatin
2015-03-27	Half-time	Alexandra Elliot	Inverted Papilloma: Incidence, ethiology and prognosis
2015-04-16	Half-time	Anna Borgström	Pediatric Obstructive Sleep Apnea - evaluation of questionnaire and surgical treatment
2015-05-28	Half-time	Julia Arebro	Innate immunity in nasal inflammation

Participation at halftime seminars during 2010-10 to 2015-05-28



Senior Researchers

Bachert, Claus	10.
Bark, Rusana	13.
Berninger, Erik	14.
Stefano Berritini	15.
Browaldh, Nanna.....	16.
Cardell, Lars Olaf	17.
Duan, Maoli.....	19.
Engmér Berglin, Cecilia	21.
Friberg, Danielle	22.
Gahm, Caroline	23.
Hammarstedt Nordenvall, Lalle.....	24.
Hederstierna, Christina	25.
Hellström, Sten.....	26.
Henriksson, Gert	27.
Hertegård, Stellan	28.
Hessén Söderman, Anne-Charlotte.....	29.
Holmström, Mats	30.
Hultcrantz, Malou	31.
Häyry, Valtteri.....	33.
Idrizbegovic, Esma.....	34.
Karltorp, Eva.....	35.
Kumlien Georén, Susanna	36.
Larsson, Olivia	37.
Lindestad, Per-Åke	39.
Lundkvist, Karin	40.
Marklund, Linda	41.
Marsk, Elin.....	42.
Munck-Wikland, Eva.....	43.
Mäkitie Antti	44.
Möller, Riitta.....	45.
Nerfeldt, Pia	46.
Olsson, Petter.....	47.
Palmgren, Björn.....	48.
Stjärne, Pär.....	49.
Tideholm, Bo	50.
Tomanovic, Tatjana	51.
Uhlén, Inger	52.
Westman, Marit	53.



Claus Bachert
 Affiliated Professor from Ghent
 +32 473310902
 claus.bachert@ki.se

Chronic rhinosinusitis endotypes and treatment approaches

Pappers made in conjunction with the ENT division, CLINTEC, KI

Chronic rhinosinusitis may be clinically differentiated into phenotypes, but also - with the help of biomarkers - into endotypes. These endotypes are based on a pathophysiological principal and thus clarify possible targets for intervention, but they also are suitable to predict the course of disease, such as recurrence or comorbid asthma.

Within the GALEN sinusitis cohort project, we collected several hundreds of patient data and about 300 mucosal tissues, which allowed us to perform a bias-free cluster analysis. The analysis resulted in 10 distinguishable clusters, 6 of which are characterized by the expression of the interleukin-5 and tissue eosinophilia. In parallel, Th2-type cytokines and IgE formation are significantly increased. In two clusters, IgE antibodies against Staphylococcus aureus enterotoxins (SE-IgE) can be found, associated with the highest severity of local inflammation; 60-70% of patients in these clusters suffer from comorbid asthma.

In those patients, standard treatment consisting of topical corticosteroids and antibiotics, but also sinus surgery, is insufficient. Novel approaches, based on humanized monoclonal antibodies, have been introduced and also tested in patients with nasal polyps with or without asthma. Anti-IL5, anti-IgE and anti-IL4 receptor alpha have all been shown to be efficacious on top of standard treatment (I was principal investigator of all studies). Omalizumab, the only approach currently available, has been introduced already into the clinic at our department for a few highly selected patients with great success. Future approaches might include silencing techniques such as DNAzyme; a first proof-of-concept trial in asthma has been successful. The mode of action has been confirmed in nasal polyp tissue in our lab.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
Karin Jonstam	

Publications 2012, 2013, 2014

- IF 5.883 Jarvis D, Newson R, Lotval J, Hastan D, Tomassen P, Bousquet PJ, Bousquet J, Zuberbier T, Bachert C, Fokkens W, Burney P. Asthma in adults and its association with chronic rhinosinusitis: The GA2LEN survey in Europe. *Allergy* 2012;67:91-98
- IF 2.873 Derycke L, Zhang N, Holtappels G, Dutré T, Bachert C. IL-17A as a regulator of neutrophil survival in nasal polyp disease of patients with and without cystic fibrosis. *J Cyst Fibros.* 2012;11:193-200
- Sejima T, Holtappels G, Kikuchi H, Imayoshi S, Ichimura K, Bachert C. Cytokine profiles in Japanese patients with chronic rhinosinusitis. *Allergol Int.* 2012;61:115-22.
- IF 12.047 Van Crombruggen K, Holtappels G, De Ruyck N, Derycke L, Tomassen P, Bachert C. RAGE- processing in chronic airway conditions: involvement of Staphylococcus aureus and ECP. *J Allergy Clin Immunol* 2012;129:1515-1521
- IF 1.321 Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, Cohen N, Cervin A, Douglas R, Gevaerts P, Georgalas C, Goossens H, Harvey R, Hellings P, Hopkins C, Jones N, Joos G, Kalogjera L, Kern B, Kowalski M, Price D, Riechelmann H, Schlosser R, Senior B, Thomas M, Toskala E, Voegels R, Wang DY, Wormald PJ. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 2012;50:1-12
- IF 5.883 Pace E, Scafidi V, Di Bona D, Siena L, Chiappara G, Ferraro M, La Grutta S, Gallina S, Speciale R, Ballacchino A, Bachert C, Bousquet J, Gjomarkaj M. Increased expression of IL-19 in the epithelium of patients with chronic rhinosinusitis and nasal polyps. *Allergy* 2012;67:878-86
- IF 12.047 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.
- IF 3.376 Bachert C, Zhang N, van Zele T, Gevaert P. From one disease to different phenotypes. *Pediatric Allergy Immunol* 2012;23:S22, 2-4
- IF 4.789 Van Bruaene N, C Perez Novo, N Deruyck, G Holtappels, P Van Cauwenberge, C Bachert. Inflammation and remodeling patterns in early-stage chronic rhinosinusitis. *Clin Exp Allergy* 2012;42:883-90

10. IF 3.730 Wang XD, N Zhang, S Glorieux, G Holtappels, M Vaneechoutte, O Krysko, L

Papers med in conjunction with the ENT-division, CLINTEC, KI

11. Zhang, DM Han, HJ Nauwynck, C Bachert. Herpes simplex virus type 1 infection facilitates invasion of Staphylococcus aureus into the nasal mucosa and nasal polyp tissues. *PLoS One* 2012;7(6):e39875. Epub 2012 Jun 29.
12. IF 6.455 Bachert C, Zhang N. Chronic rhinosinusitis and asthma: novel understanding of the role of IgE "above atopy". *J Intern Med*. 2012;272:133-43
13. IF 5.883 Yang YC, Zhang N, Van Crombruggen K, Hu GU, Hong SL, Bachert C. Transforming growth factor beta1 in inflammatory airway disease: A key for understanding inflammation and remodeling. *Allergy* 2012;67:1193-202
14. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, Cohen N, Cervin A, Douglas R, Gevaert P, Georgalas C, Goossens H, Harvey R, Hellings P, Hopkins C, Jones N, Joos G, Kalogjera L, Kern B, Kowalski M, Price D, Riechelmann H, Schlosser R, Senior B, Thomas M, Toskala E, Voegels R, Wang de Y, Wormald PJ. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl.* 2012;23:3, 1-298
15. IF 5.883 Pezato R, Świerczyńska M, Nizankowska-Mogilnicka E, Derycke L, Bachert C, Pérez-Novo CA. Role of imbalance of eicosanoids pathways and staphylococcal superantigens in chronic rhinosinusitis. *Allergy* 2012;67:1347-56
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17. IF 12.047 Gevaert P, L Calus, T Van Zele, K Blomme, N De Ruyck, W Bauters, P Hellings, G Brusselle, D De Bacquer, P van Cauwenberge, C Bachert. Omalizumab is effective in allergic and non-allergic patients with nasal polyposis and co-morbid asthma. *J Allergy Clin Immunol* 2013;131:110-116
18. IF 5.883 Krysko O, Maes T, Plantinga M, Holtappels G, Imiru R, Vandenabeele P, Joos G, Krysko DV, Bachert C. et al. The adjuvant-like activity of Staphylococcal enterotoxin B in a murine asthma model is independent of IL-1R signaling. *Allergy* 2013; 68:446-53
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20. IF 5.883 Gevaert P, K T Nouri-Aria, H Wu, C E Harper, P Takhar, D J Fear, F Acke, N Deruyck, G Banfield, HH Kariyawasam, C Bachert, SR Durham, HJ Gould. Local Receptor Revision and Class Switching to IgE in Chronic Rhinosinusitis with Nasal Polyps. *Allergy* 2013; 68: 55-63
21. IF 3.730 Manise M, Holtappels G, van Crombruggen K, Schleich F, Bachert C, Louis R. Sputum IgE and cytokines in asthma: relationship with sputum cellular profile. *PlosOne* 2013, 8(3): e58388
22. IF 2.837 Zhang Y, Wang X, Zhang W, Han D, Zhang L, Bachert C. Polymorphisms in thymic stromal lymphopoietin gene demonstrate a gender and nasal polyposis-dependent association with chronic rhinosinusitis. *Hum Immunol* 2013;74:241-8
23. IF 12.047 Akdis CA, Bachert C, Cingi C, Dykewicz M, Hellings P, Naclerio RM, Schleimer RP, Ledfordh 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
24. IF 12.047 Dutre T, Al Dousary S, Zhang N, Bachert C. Allergic fungal rhinosinusitis (AFRS)- a bacterial presence coexisting with fungal disease? *J Allergy Clin Immunol* 2013;132:487-9
25. IF 4.789 Wang M, Zhang W, Shang J, Yang J, Zhang L, Bachert C. Immunomodulatory effects of IL-23 and IL-17 in a mouse model of allergic rhinitis. *Clin Exp Allergy* 2013;43:956-66
26. 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
27. IF 5.883 Tomassen P, Jarvis D, Newson R, Van Ree R, Forsberg R, Howarth P, Janson C, Kowalski ML, Krämer U, Matricardi PM, Middelveld RJM, Todo-Bom A, Toskala E, Thilsing T, Brożek G, Van Drunen C, Burney P, Bachert C. Staphylococcus aureus enterotoxin specific IgE and its association with asthma in the general population: a GA²LEN. *Allergy* 2013;68:1289-97
28. Balsalobre L, Pezato R, Perez-Novo C, Alves MT, Santos RP, Bachert C, Weckx LL. Epithelium and stroma from nasal polyp mucosa exhibits inverse expression of TGF-β1 as compared with healthy nasal mucosa. *J Otolaryngol Head Neck Surg.* 2013;42:29
29. IF 6.57 Van Crombruggen K, F Jakob, Nan Zhang, C Bachert. Damage Associated Molecular Patterns and their receptors in upper airway pathologies. *Cell Mol Life Science* 2013;70:4307-21
30. IF 6.044 Krysko O, Løve Aaes T, Bachert C, Vandenabeele P, Krysko DV. Many faces of DAMPs in cancer therapy. *Cell Death Dis.* 2013;16;4:e631
31. IF 12.047 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
32. IF 2.755 Lenoir J, Bachert C, Remon JP, Adriaens E. The Slug Mucosal Irritation (SMI) Assay: A tool for the Evaluation of Nasal Discomfort. *Toxicol In Vitro.* 2013;27:1954-1961
33. 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
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35. IF 3.730 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
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37. IF 6.0 Kaczmarek A, Krysko O, Heyndrickx L, Løve Aaes T, Delvaeye T, Bachert C, Leybaert L, Vandenabeele P, Krysko DV. TNF/TNF-R1 pathway is involved in doxorubicin-induced acute sterile inflammation. *Cell Death Dis.* 2013;12;4:e961
38. IF 12.047 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* 2014; 133:273-53, Letter
39. IF 4.789 Newson R, Jones M, Forsberg B, Janson C, Dahlén SE, Bossios A, Toskala E, Al-Kalemji A, Kowalski M, Rymarczyk B, Salagean E, van Drunen C, Bachert C, Wehrend T, Krämer U, Mota-Pinto A, Burney P, Leynaert B, Jarvis D. The association of asthma, nasal allergies and positive skin prick tests with obesity, leptin and adiponectin. *Clin Exp Allergy.* 2014; 44:250-60

40. Bobic S, Hox V, Callebaut I, Vinckier S, Jonckx B, Stassen JM, Jorissen M, Gevaert P, Carmeliet P, Bachert C, Ceuppens J, Helings P. Vascular Endothelial Growth Factor Receptor 1 Expression in Nasal Polyp Tissue. *Allergy* 2014; 69:237-45
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42. IF 4.789 Song WJ, Chang YS, Lim MK, Yun EH, Kim SH, Kang HR, Park HW, Tomassen P, Choi MH, Min KU, Cho SH, Bachert C. Staphylococcal enterotoxin sensitization in a community-based population: a potential role in adult-onset asthma. *CEA* 2014;44: 553-562
43. IF 2.302 Van Zele T, Holtappels G, Gevaert P, Bachert C. Differences in initial immunoprofiles between recurrent and nonrecurrent chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy*. 2014;28:192-8
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49. IF 3.730 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;9:e97581
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64. IF 3.730 Yang Y, Zhang N, Van Crombruggen K, Lan F, Hu G, Hong S, Bachert C. Differential expression and release of activin A and follistatin in chronic rhinosinusitis with and without nasal polyps. *PONE-D-14-50806R2*

Rusana Bark
M.D., Ph.D.
+46 8 517 76020
rusana.bark@karolinska.se



ÖNH-cancer

Pågående:

- Risken för regional metastas hos patienter (n=162) med gingivalcancer i förhållande till tumörstorlek, lokalisering(överkäke/underkäke), T-klass och histopatologi.
- Retrospektiv studie där det studeras förekomst av cystisk metastas i patientmaterial från 2003-2013 opererade för lateral halscysta på Karolinska.

Planerade:

- Prospektiv studie: Är HPV en användbar markör för att skilja cystisk metastas från lateral halscysta?

Könshormoner & hörsel

Pågående studier som del av min doktorands avhandlingsprojekt:

- Longitudinell prospektiv studie av hörseln hos kvinnor med bröstcancer som behandlas med anti-östrogener .
- Uppföljning av hörselutvecklingen hos kvinnor med Turner syndrom som fått östrogen substitution under uppväxten.
- Effekten av östrogen substitution på hörseln hos Turnermöss.

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
Åsa Bonnard	

Publications 2012, 2013, 2014

1. Bark R, Hammarstedt-Nordenvall L. Risk of cervical metastasis in N0 gingival cancer. In manuscript 2015.
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4. Bonnard Å, Sahlin L, Hultcrantz M, Simonoska R. No direct nuclear effect of Progesterone in the inner ear: other possible pathways. Acta Otolaryngol. 2013 Dec;133(12):1250-7.



Erik Berninger
 M.Sc.E.E., Docent
 +73 699 41 01
 erik.berninger@karolinska.se

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 pathophysiological processes of the middle ear, inner ear, and auditory pathways in very young infants. This characterization along with MRI and next-generation sequencing will then form the basis for, e.g., very early 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-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
Filip Asp	

Supervision of PhD-student:

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 participants using mixed multiple ASSR. *Journal of the American Academy of Audiology*, 2015: 26(3): p. 299-310.
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3. 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.
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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.
9. Filip Asp, Åke Olofsson, Erik Berninger. A rapid and objective sound localization test for infants and young children, 2015 MidWinter Research Meeting, Association for Research in Otolaryngology, Baltimore, Maryland, USA, February 21-25, 2015.

Stefano Berrettini
 Affiliated professor from Pisa
 +39050997500
 stefano.berrettini.1@ki.se



Cochlear implant research in children

The research activity involves mainly Otolaryngology. The joint projects with the Cochlear Implant (CI) section at KI focus on CI:s in children with malformed inner ears, evaluation of language development, evaluation of results in multi-impaired children and surgery of CI:s in difficult cases.

Other projects of major interest of professor Berrettini's research concern:

- Etiological studies of the deafness and in particular of childhood progressive neurosensorial hearing loss
- Immunological disorders in audio-vestibular diseases
- Tissue engineering of the middle ear
- Novel implantable middle ear hearing devices
- Imaging studies of the ear

Supervision of PhD-students:

Main Supervisor	Co-supervisor

Publications 2012, 2013, 2014

For complete list please see PubMed

1. Bernabei R, Bonuccelli U, Maggi S, Marengoni A, Martini A, Memo M, Pecorelli S, Peracino AP, Quaranta N, Stella R, Lin FR; participants in the Workshop on Hearing Loss and Cognitive Decline in Older Adults. Hearing loss and cognitive decline in older adults: questions and answers. *Aging Clin Exp Res*. 2014 Dec;26(6):567-73. doi: 10.1007/s40520-014-0266-3. Epub 2014 Oct 4.
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Nanna Browaldh
MD., Ph.D.
+46 8 585 80000
nanna.browaldh@karolinska.se

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 sleep related quality of life are in manuscript. Further evaluation of metabolic parameters and blood pressure are planned.

Publications 2012, 2013, 2014

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2. Browaldh N, Friberg D. Authors' response to letter to the editor concerning our SKUP3 trial. *Thorax* doi:10.1136/thoraxjnl-2013-204622
3. Browaldh N, Bring J, Friberg D. SKUP3 RCT continuous study; changes in sleepiness and quality of life after modified UPPP in obstructive sleep apnea. Submitted
4. Browaldh N, Bautista T, Dutschmann M, Berkowitz R. The Kölliker-Fuse Nucleus: A Review of Animal Studies and the Implications for Cranial Nerve Function in Humans. Submitted

Lars Olaf Cardell
 Professor, Head of the Division
 +46 70 770 99 26
 lars-olaf.cardell@ki.se



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-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
Magnus Starkhammar	
Åsa Kågedal	
Lotta Tengroth	
Julia Arebro	
Laila Hellkvist	
Sandra Ekstedt	
Yuan Xu	

Publications 2012, 2013, 2014

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- Westman M, Stjärne P, Bergström A, Kull I, Toskala E, Cardell LO, Wickman M, Holmström M. Chronic rhinosinusitis is rare but bothersome in adolescents from a Swedish population-based cohort. *J Allergy Clin Immunol.* (IF: 12.0), 2015;S0091-6749(15)00268-7.
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33. Papadopoulos NG, Agache I, Bavbek S, Biló BM, Braido F, Cardona V, Custovic A, Demonchy J, Demoly P, Eigenmann P ... Cardell LO.... and others. Research needs in allergy: an EAACI position paper, in collaboration with EFA. *Clin Transl Allergy* (IF: 2.6), 2012;2(1):21.
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Maoli Duan
 Docent, M.D.
 +46 73 982 6888
 maoli.duan@ki.se



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-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
Luca Verrecchia	Pedro Marques
Qiang Wang (Kina)	
Dan Zhao (Kina)	

Publications 2012, 2013, 2014

1. Yao W, Li B, Huang X, Guo C, Luo X, Zhou W, Duan M. Restoring hearing using total ossicular replacement prostheses-analysis of 3D finite element model. *Acta Otolaryngol.* 2012; 132(2):152-9
2. Brantberg K, Duan M, Falahat B. Ménière's disease in children aged 4-7 years. *Acta Otolaryngol.* 2012 Jan 4. [Epub ahead of print]
3. Wu JF, Jin Z, Yang JM, Liu YH, Duan M. Extracranial and intracranial complications of otitis media: 22-year clinical experience and analysis. *Acta Otolaryngol.* 2012 Mar;132(3):261-5.
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Cecilia Engmér Berglin
M.D., PhD
+46 8 5177 9817
cecilia.engmer-berglin@karolinska.se



Development of central auditory systems in experimental monaural canal atresia

Local pharmacological treatment of the inner ear

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
	Malin Siegbahn
	Emelie Kullring

Publications 2012, 2013, 2014

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Danielle Friberg
 Docent, Consultant
 +46 709 388 880
 danielle.friberg@karolinska.se

Centre of excellence for obstructive sleep apnea in adults and children; RCT of surgical treatments and the complications, evaluated with polysomnography

Obstructive sleep apnea (OSA) is common, 15% males, 4% females and children of the population, and may be health-dangerous. Complications are cardio-vascular disease and a 4-times increased mortality rate. Also, excessive daytime sleepiness and reduced quality of life. The etiology is reduced upper airway lumen during sleep, causing obstructive apneas. To evaluate surgical treatment with randomised controlled trials (RCT) in adults and children, "Centre of excellence for OSA" started 2007.

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 where also significantly improved compared to controls. Data are collected for blood samples, blood pressures and sleep questionnaires, also from 2 year follow-ups. B. Data collection of RCT of children between 2 and 6 years is finished; 34 have undergone adenotonsillectomy (ATE) and 34 adenotonsillotomy with coblation. The study is blinded, and we evaluate postop pain and with PSG. C. Start of another RCT in children 2-5 years in January 2015; a) children with mild to moderate OSA are randomized to ATE or watchful waiting for 6 months, b) children with severe OSA are randomized to ATE or ATE+ raphi of palatal pillars, blinded study. Postop PSG and questionnaires. D. Start of new RCT in adults september 2015. New PhD student planned Joar Sundman. Ethic permission will soon be submitted.

The group received 2013 a two years project ALF. Three PhD-dissertations from this group between 2008-2013.

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
Anna Borgström	Ann Abrahamsson
Johan Fehrm	
Joar Sundman, planned Sept 2015	

Publications 2012, 2013, 2014

1. Nerfeldt P, Aoki F, Friberg D. Polygraphy vs. Polysomnography: Missing OSAS in Symptomatic Snorers - A reminder for clinician. *Sleep and Breathing*;18(2):297-303, 2014.
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5. Lundkvist K, Sundquist K, Li XJ, Friberg D. Familial risk of sleep-disordered breathing. *Sleep Medicine*; 13 (6): 668-673, 2012.

Caroline Gahm
M.D., Ph.D.
+46 8 51770404
caroline.gahm@karolinska.se

Radiotherapy induced tissue inflammation in patients treated for head and neck cancer

The project is in collaboration with Dr. Martin Halle (PhD) at the Department of Reconstructive Plastic Surgery.

Clinical epidemiological studies have shown that radiotherapy increases the risk of cardiovascular disease such as heart attack or stroke at irradiated sites years after exposure.

Since 2004, we include paired biopsies from all previously irradiated patients who undergo cancer surgery followed by reconstruction with free autologous tissue at the Karolinska University Hospital in a biobank, Biobank of Radiated tissues at Karolinska (BiRKA). By taking biopsies from previously irradiated carotid arteries (branches of A.Carotis) and non-irradiated arteries from grafts, we can compare the difference in gene expression between irradiated and non-irradiated arteries from the same patient at the same time and thereby exclude the effect of inter-individual differences.

The group studies the effects of irradiation, seen as acute and long-term changes in human blood vessels, and the underlying mechanisms using an interventional experimental mouse model. The purpose of the project is to answer the following specific questions:

- I. How does gene and protein expression differ in human irradiated blood vessels compared to unirradiated controls and how do they change over time after administration of radiation therapy? Are there differences in the handling of oxidative stress in radiosensitive patients?
- II. Can treatment with an IL-1-antagonist (anakinra; Kineret[®]) after radiotherapy contribute to decreased vascular and tissue inflammation? Is the NF-kappaB-mediated inflammatory response in irradiated tissue mediated through IL-1beta?

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
	Mattias Gunter

Publications 2012, 2013, 2014

1. Hellberg V, Gahm C, Wei L, Ehresson H, Rask-Andersen H, Laurell G. Immunohistochemical localization of OCT-2 in the cochlea of various species. In print, Laryngoscope 2015.
2. Gunter M, Plantman S, Gahm C, Sonden A, Risling M, Mathiesen T. Shock wave trauma leads to inflammatory response and morphological activation in macrophage cell lines, but does not induce iNOS och NO synthesis. Acta Neurochir (Wien). 2014 Oct 12.
3. Christersdottir Björklund T, Reilly SJ, Gahm C, Bottazzi B, Mantovani A, Tornvall P, Halle M. Increased long-term expression of pentraxin 3 in irradiated human arteries and veins compared to internal controls from free tissue transfers. Journal of Translational Medicine 2013 Sep 23;11:223.
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Lalle Hammarstedt-Nordenvall
M.D., Ph.D.
+46 8 51771554
lalle.hammarstedt-nordenvall@karolinska.se

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
	Alexandra Elliot
	Clara Svenberg Lind

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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3. Elin Marsk, MD; Nina Bylund, MD; Lars Jonsson, MD, PhD; Lalle Hammarstedt, MD, PhD; Mats Engström, MD, PhD; Nermin Hadziosmanovic, MSc; Thomas Berg, MD, PhD; Malou Hultcrantz, MD, PhD Prediction of non-recovery in Bell's palsy using Sunnybrook grading. Laryngoscope. 2012 Apr;122(4):901-6. doi: 10.1002/lary.23210. Epub 2012 Feb 28.
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
5. 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. Accepted ACTA Otolaryngologica jan 2013.
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

Christina Hederstierna
M.D., Ph.D.
+46 8 51776964
christina.forsshell-hederstierna@karolinska.se

I am involved in several 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.
- 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.

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
	Åsa Bonnard

Publications 2012, 2013, 2014

1. Hederstierna C, Cureoglu S, Paparella MM. Undiagnosed severe cochlear otosclerosis as a cause of profound hearing loss. *Otology & neurotology* : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology. 2013;34(3):e14-5.
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Sten Hellström
Senior Professor
+46 70 496 2432
sten.hellstrom@karolinska.se

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 of PhD-students:

Main Supervisor	Co-supervisor
Satu Turunen-Taheri	

Publications 2012, 2013, 2014

1. Hellström S, Shen Y, Ny T. A reply to the commentary on “Animal models of chronic tympanic membrane perforation: in response to plasminogen initiates and potentiates the healing of acute and chronic tympanic membrane perforations in mice” by Wang AY, Shen Y, Wang JT, Eikelboom RH, Dilley RJ. Clin Translat Med 2014;3:5 Clin Transl Med 2015 Feb 26;4:8 doi: 10.1186/s40169-14-0044-z. eCollection 2015.
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6. Cayé-Thomasen P, Hermansson A, Bakaletz L, Hellström S, Kanzaki S, Kerschner J, Lim D, Lin J, Mason K, Spratley J. Panel 3: Recent advances in anatomy, pathology, and cell biology in relation to otitis media pathogenesis. Otolaryngol Head Neck Surg. 2013;148(4 Suppl):E37-51.
7. 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.
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Gert Henriksson
Consultant, Ph.D.
+46 876 116 3561
gert.henriksson@karolinska.se



Airway stent treatment of malignant obstructions & a new submucosal endoscopic surgical method of subglottic laryngotracheal stenosis

Airway stenting is today an established treatment for malign and benign obstructions in tracheal and proximal bronchial region. Airway stens can also be an important treatment when tracheal and bronchial wall have been injured by nearby infections or surgery. In the study that was initiated autumn 2014 we aim to combine airway measuring before and after stent surgery because of obstructing malign lesions in the region of the trachea and the proximal bronchus. Box spirometry and oscillometric pulse wave analysis will be carried out in cooperation with a research facility at the pulmonary clinic. The included patients will also evaluate their quality of life before and after this surgical procedure with a validated enquiry mainly used for chronic airway diseases (CAT™, COPD Assessment Test).

A new endoscopic submucosal surgical method for treating subglottal stenosis has been carried out at the clinic since 2003 (2). Over 50 patients have been treated successfully until now. In our second study we will measure the improvement in breathing with box spirometry and oscillometric pulse wave analysis. The patient will also evaluate the change in quality of life after this surgery. We will also include patients with recurrences where the pre-operative intraluminal reductions are at least 50%. The validated enquiry used is also used in chronic airway diseases (CAT™, COPD Assessment 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).* 2012;132(9):995-1001.



Stellan Hertegård
Adjunct Professor in Phoniatics
+46 8 585 80000 vx
stellan.hertegard@ki.se

Reconstruction of vocal fold scarring with mesenchymal stem cells

This projects aims to find a treatment for severe voice disorders caused by vocal fold scar. This may be the result of surgery cancer treatment severe inflammation of congenital disorders affecting voice. At present effective treatment is lacking. In a series of animal experiments since 2004 we have shown positive effects, regeneration and prevention of scar formation after injection of human mesenchymal stem cells, MSC (and embryonic stem cells).

From 2012 an ongoing study in cooperation with Professor Katarina LeBlanc at KI is including and treating patients with severe hoarseness and scarring of the vocal folds. The patients are recruited from Karolinska and other parts of Sweden. Vocal folds are dissected and scar tissue is reduced/removed followed by a local injection of autologous MSCs. At present 14 patients are treated. Preliminary results at 1 year follow up for the first 5 patients shown clearly improved vocal fold function in 4 without side effects. Evaluation and recruitment of patients is ongoing.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
Emma Malmström	Srinivasa Rou Nagubothu

Publications 2012, 2013, 2014

1. Hertegård S, Larsson H. A portable high speed camera system for vocal fold examinations . Journal of Voice . 2014. Jul 5. pii: S0892-1997(14)00070-8. doi: 10.1016/j.jvoice.2014.04.002. [Epub ahead of print]
2. 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 – a pilot study. Logoped Phoniatr Vocol. 2014 May 28:1-9. [Epub ahead of print]
3. 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- Accepted for publication in The Journal of Speech and Hearing Research 2014
4. Svensson B, Nord C, Nagubothu RS, Hultman I, M.S, Cedervall J, Ährlund-Richter L, Tolf A, Hertegård S. Stem cell therapy in injured vocal folds – a three months analysis of human embryonic stem cells. Accepted for publication to Biomed Research International 2015
5. Södersten, M, Nygren, U, Hertegård, S. Dhejne, C. Interdisciplinary program in Sweden related to transgender voice. 2015. Accepted for publication in Perspectives on Voice and Voice Disorders SIG3

Anne-Charlotte Hessén Söderman
Docent
+46 70 721 4308
lotta.hessen.soderman@gmail.com



Randomiserad prospektiv studie av olika transmyringeala rör.

Bakgrund: Att operera in ventilationsrör i trumhinnan är ett mycket vanligt ingrepp på barn. Cirka 10 000 barn får rör varje år i Sverige, dels på grund av återkommande akuta öroninflammationer, dels på grund av långvarig öronkatarr med hörselnedsättning. Rören gör att man får klart färre akuta öroninflammationer samt hörselförbättring.

Det finns ett stort antal olika typer av rör att välja på. Skillnaderna mellan rörtyperna ligger i rörens längd, diameter, material och eventuell förekomst av yttre fläns

De komplikationer som kan uppstå är igensättning av röret, infektion uppkommen genom röret, kvarstående trumhinneperforation och kalkinlagring i trumhinnan (myringoskleros).

Trots att det är en så vanlig behandling är det alltså oklart om det föreligger skillnader i komplikationsfrekvens mellan de olika rörtyperna.

Metod: Prospektiv randomiserad studie av långa respektive korta rör av fluoroplastic samt silikon.

Kontroll var tredje månad hos öronläkare.

Primär slutpunkt:

Röret har fullständigt lämnat trumhinnan

Sekundära slutpunkter:

Smärta, infektion, rör-ocklusion, behov av att dra bort röret, kvarstående perforation samt förekomst av myringoskleros.

Betydelse: I nuläget väljs rörtyp vanligtvis beroende på tradition på kliniken och inte baserat på objektiv kunskap. Det finns ett stort behov att utvärdera om material eller längd av rör är av betydelse för hur länge rören sitter och komplikationsfrekvens. Resultaten av en stor randomiserad studie kan bli av avgörande betydelse för rörbehandling i framtiden.

Publications 2012, 2013, 2014

1. Stalfors J, Ericsson E, Hemlin C, Hultcrantz E, Månsson I, Roos K, Hessén Söderman A-C, Tonsil surgery efficiently relieves symptoms, Analysis of 54 696 patients in The National Tonsil Surgery Register in Sweden Acta Otolaryngol. 2012; Early Online, 1–7
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. Eur Arch Otorhinolaryngol. 2014 Jun;271(6):1823-7
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Mats Holmström
 Adjunct Professor, Consultant, Senior Lecturer
 Tel. 0734 414 466
 mats.holmstrom@karolinska.se

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 after 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.

A fourth project is an analysis of skeletal demineralization after systemic treatment with corticosteroids for nasal polyposis.

A fifth ongoing project is studying of nasal oscillations in treatment of idiopathic rhinitis.

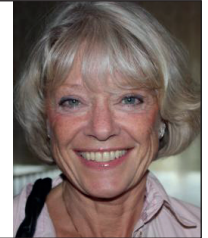
Supervision of PhD-students:

Main Supervisor	Co-supervisor
Staffan Morén	Caroline Bengtsson
	Joar Sundman

Publications 2012, 2013, 2014

1. 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.
2. 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
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5. Westman M, Stjärne P, Bergström A, Kull I, Toskala E, Cardell LO, Wickman M, Holmström M. Chronic rhinosinusitis is rare but bothersome in adolescents from a Swedish population-based cohort. *J Allergy Clin Immunol*. 2015

Malou Hultcrantz
Adjunct Professor
+46 8 517 75653
malou.hultcrantz@karolinska.se



Estrogen and hearing

Estrogen seems to have a protective effect on hearing in women since mapping their hearing longitudinally show good hearing up to menopause, but thereafter a decrease is triggered. Males have a deterioration starting already from 20-30 years of age. Translational research is performed clinically with our huge samples of patients (women in menopause, women with Turner syndrome, women suffering from breastcancer treated with anti estrogen) together with basic animal research where the influence of estrogen and other sex hormones on hearing and balance is performed (genetically manipulated strains of mice and rats) with hearing tests, immunohistochemically, PCR etc . New basic physiology research is produced which can be important for rehabilitation and future guidelines for better care of patients suffering from low levels of estrogen during life and to make the receptors available for treatment.

Bells palsy

1 month after onset of Bells palsy seems to be a critical period. A risk analysis can be performed and patients having a bad prognosis are randomised prospectively to either surgery (cross facial) or conservative treatment. The outcome is analysed 1 year after onset. Research and surgery are performed together with reconstructive surgeons. National research concerning Quality of life has been set up as well as studies on facial palsy in children in Sweden.

Bone anchored hearing implants

Implantable hearing aids are evaluated after new surgical techniques and skinreactions are tested histochemically and bacteriologically to try to reduce side effects . A new implant is under development together with Sahlgrenska Akademin and Chalmers Technical University.

Functional MRI studies have started in humans and in a rat model in order to investigate central hearing pathways in patients suffering from single sided hearing loss (atresia). Eye reflex test is implemented in order to test binaural hearing.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
Åsa Bonnard	
Malin Siegbahn	
Emelie Kullring	

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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Valtteri Häyry
MD, PhD, Postdoctoral Fellow
+46 72 7223358
valtteri.hayry@ki.se



How Tumor Heterogeneity and Immunomodulation Influence Metastasis of Head & Neck Cancer

Head and neck cancer frequently involves metastases to lymph nodes of the neck. Undetected metastases lead to local recurrence after treatment and significantly influence both patient treatment and survival. Cancer cell metastasis to lymph nodes requires evasion of the immune response and the recruitment of non-cancerous stromal cells to facilitate cancer cell growth. My postdoctoral research project aims at producing novel information of tumor heterogeneity in relation to the interaction between the tumor microenvironment and cancer cells in lymph nodes. We hypothesize that, due to frequent chronic inflammation and the abundance of tumor infiltrating lymphocytes usually seen in head and neck tumors, the immune response regulates metastasis possibly through a dual role of anti-tumor and protumor effects.

To date we have extracted eight samples comprising of primary tumor, metastatic or sentinel lymph node and distant (healthy) lymph node from oral squamous cell patients and characterized the immune cell signature in these samples. Also, we have developed a highly sensitive method of detecting tumor cells in lymph nodes and extracted metastatic squamous cell carcinoma cells from HNSCC patients. Detailed analysis of metastatic SCC cells is currently performed.

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Esmá Idrizbegovic
Docent, Consultant
+46 73 6996286
esma.idrizbegovic@karolinska.se

Aging and central auditory dysfunction: the relation to cognitive abilities in 60-80-year-old adults

Project description: Persons with central auditory dysfunction (CAD) have difficulties perceiving speech in a noisy environment or a multi-speaker situation. They also gain little benefit from standard hearing aids; despite the amplification, patients still complain they cannot hear what people say in ordinary conversational settings. The result is frequent conversational breakdowns and, as a consequence, reduced participation in speech-based social activities.

Our hypothesis is that combined measures of CAD and cognitive function will accurately identify persons with both hearing impairment and cognitive deficits. This group exists but is still underdiagnosed and undertreated. Our goal is to establish an assessment method by which CAD can be verified in patients with cognitive impairment, thereby allowing for prevention of accelerated cognitive decline and hearing rehabilitation adapted to cognitive level. The aim is to establish whether dichotic listening with digits (DDT) will show satisfactory diagnostic accuracy in identifying CAD and associated cognitive disorders. Study design, subjects and methods : 60-80 years, men and women being fluent in Swedish will be included. Audiometric assessment will be conducted primarily at the Hearing & Balance clinic. Cognitive measures will be taken via self-report The Sahlgrenska Academy Self-reported Cognitive Impairment Questionnaire (SASCI-Q), Mini-Mental State Examination (MMSE), The 7 Minute Screen (7MS), A Quick Test of Cognitive Speed (AQT).

Relevance of the project: This project represents a substantial effort to validate new methods to identify persons with CAD among the large group of older adults with different degrees of cognitive impairment. Collaboration: Per Östberg is associate professor of speech-language pathology. Professor emeritus Ulf Rosenhall; MD, PhD Christina Hederstierna; MD, PhD student Jenny Häggström, Leg Audiologist Jeannette Hägerström

Publications 2012, 2013, 2014

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Eva Karltorp
Consultant, Ph.D.
+46 8 58580000
eva.karltorp@karolinska.se



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.

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Susanna Kumlien Georén
 Senior Lab. Manager, Ph.D.
 +46 704 225 908
 susanna.georen@ki.se

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:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
	Lotta Tengroth
	Julia Arebro
	Sandra Ekstedt

Publications 2012, 2013, 2014

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Olivia Larsson
Post doc
+46 703 864 355
olivia.larsson@ki.se



The interplay between the innate immune system and peripheral nervous system in upper and lower airway inflammation and hyperresponsiveness

The overall goal of this research project is to characterise the involvement of both the innate immune system and the peripheral nervous system (PNS) in both inflammatory and functional changes in the upper and lower airway. The project focuses on disease models, including airway allergy, chronic rhinosinusitis and viral infection.

Bacterial and viral pathogens have been shown to play a role in both the development of allergic inflammation, as well as exacerbation of the disease, promoting both heightened inflammation and airway hyperresponsiveness (AHR). Toll-like receptors (TLRs), which have been shown to be expressed on neuronal, smooth muscle, inflammatory and epithelial cells in the lung, are vital to the recognition of bacterial and viral particles. Interestingly, TLR ligands are also currently being investigated for their use as a treatment for allergic inflammation in the upper and lower airways, with some success in dampening inflammation and AHR. The mechanism by which bacteria and viruses, as well as other TLR ligands, alter inflammation and AHR is not fully understood.

The PNS is known to play a role in both lower allergic airway inflammation and AHR. In particular, changes in neuropeptide production and neuronal signalling are known to be associated with lower airway allergy and asthma. However, the role of the PNS in respiratory infections, upper airway disease, and inflammation-induced structural changes has not been well-studied. In particular, the role of neuronal mediators in TLR-mediated innate inflammation is unknown.

Our current research looks into investigating how TLR agonists impact on upper and lower allergic airway inflammation, AHR, and inflammation following respiratory infection, while simultaneously looking at how neuronally-derived mediators shape this process

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Per-Åke Lindestad
Docent, Consultant
+46 70 677 1294
per-ake.lindestad@karolinska.se



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:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
Kristina Nyberg	

Publications 2012, 2013, 2014

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Karin Lundkvist
M.D., Ph.D.
+46 8 585 80000
karin.lundkvist@karolinska.se

Pharyngeal Surgery and Epidemiology in sleep apnea Intralymphatic allergen-specific immunotherapy ILIT in allergic rhinitis

The overall aim of my theses evaluates two aspects of Obstructive sleep apnea (OSAS); firstly Pharyngeal surgery, uvulopatopharyngoplasty (UPPP) in adult OSAS patients failing CPAP and mandibular retaining device treatment regarding efficacy, safety satisfaction and side effects. Secondly, the relationship between sleep disordered breathing (SDB) in children and adolescents, and parental diagnoses of OSAS, occupation and family socioeconomic status.

In summary UPPP reduces the nightly respiratory disturbances to a mean of 60%, halved the daytime sleepiness, did not change the median scores of pharyngeal disturbances, and may be a safe alternative in selected OSAS patients. Swedish children with a parent affected by OSAS had a significantly higher risk of hospitalization for OSAS and SDB. Children with low family SES and in some occupational groups were associated with an increased OR for hospitalization for OSAS and SDB.

Allergic rhinitis is a major health problem and allergy vaccination (SIT) is the only treatment that acts disease modifying. SIT is time consuming and expensive. Previous studies has shown that only three low doses of allergen injections direct into the lymph node, Intralymphatic immunotherapy (ILIT), could induce symptom relief comparable to that after conventional ASIT. Our group evaluates an ILIT combination of grass and Birch allergen according to allergic reactions, symptom score and specific antibody reactions. To achieve improved symptom relief both the number and the dose of injections will be increased. The aim is to increase the opportunity for rhinitis patients to receive SIT, to improve the symptom relief and to gain insight in the mechanisms behind tolerance development in allergic disease.

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
	Laila Hellkvist

Publications 2012, 2013, 2014

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Linda Marklund
M.D., Ph.D.
+46 8 51770000
linda.marklund@karolinska.se



Predictive and prognostic biomarkers for Head Neck cancer

Head and neck cancer is the 6th leading cause of cancer mortality worldwide accounting for nearly 300,000 deaths each year. Despite advances in treatment, the 5 year survival rate has vastly remained unchanged for many of the diagnosis over the last few decades. Recently human papilloma virus had been established as an etiological and prognostic factor for oropharyngeal cancer. Delineating the underlying mechanism of cancer development, and identifying genetic and molecular alterations are indispensable in personalized medicine.

In addition, dependable diagnostic and prognostic biomarkers are needed for improved cancer care. Although cancer cure is the aim of most treatment plans, treatment-related morbidities often limit attainment of the goal and reduce a patients quality of life. Medicines that avert head and neck cancer therapy-related complications without compromising cancer cure are a necessity.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
	Malin Wendt
	Alexandra Elliot
	David Landin

Publications 2012, 2013, 2014

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Elin Marsk
M.D., Ph.D.
+46 8 517 70000
elin.marsk@karolinska.se

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

Bell's palsy is acute peripheral facial nerve dysfunction with unknown etiology. The disease can cause severe disfigurement of the face, impair the ability to eat, drink and speak, and seriously affect the patient's quality of life. There are no tests or clinical signs that can predict the outcome of Bell's palsy in the initial state. The palsy's impact on the patient's quality of life has not fully been evaluated.

In our work, we study different aspects of Bell's palsy to find prognostic clinical signs for non-recovery (using the Sunnybrook facial grading scale). We also measure alterations in the patient's quality of life using the Swedish versions of the Facial Disability Index (FDI) questionnaire and Facial Clinimetric Evaluation (FaCE) scale.

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
	Kristina Nyberg
	Stefan Toth

Publications 2012, 2013, 2014

1. Marsk E, Bylund, Jonsson L, Hammarstedt L, Engström M, Hadziosmanovic N, Berg T, Hultcrantz M. Prediction of nonrecovery in Bell's palsy using Sunnybrook grading. *Laryngoscope*. 2012 Apr;122:901-6
2. Berg T, Bylund N, Marsk E, Jonsson L, Kanerva M, Hultcrantz M, Engström M. The effect of prednisolone on sequelae in Bell's palsy. *Arch Otolaryngol Head Neck Surg*. 2012 May;138(5):445-9
3. 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.

Eva Munck-Wikland
 Adjunct Professor, Consultant
 +46 730 379 684
 eva.munck-afrosenschold-wikland@karolinska.se



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 mantlecell 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:

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

Publications 2012, 2013, 2014

- Näsman A, Andersson E, Nordfors C, Grün N, Johansson H, Munck-Wikland E, Massucci G, Dalianis T, Ramqvist T. MHC class I expression in HPVpositive and negative tonsillar squamous cell carcinoma in correlation to clinical outcome. *Int J Cancer* 132: 72-81, 2013.
- Nordfors C, Grün N, Tertipis N, Ahrlund-Richter A, Haegglblom L, Sivars L, Du J, Nyberg T, Marklund L, Munck-Wikland E, Näsman A, Ramqvist T, Dalianis T. CD8+ and CD4+ tumour infiltrating lymphocytes in relation to human papillomavirus status and clinical outcome in tonsillar and base of tongue squamous cell carcinoma. *Eur J Cancer* 49(11) :2522-30, 2013.
- Romanitan M, Näsman A, Munck-Wikland E, Dalianis T, Ramqvist T. EGFR and Phosphorylated EGFR in Relation to HPV and Clinical Outcome in Tonsillar Cancer. *Anticancer Res.* 2013 Apr;33(4):1575-83.
- Näsman A, Nordfors C, Grün N, Munck-Wikland E, Ramqvist T, Marklund L, Lindquist D, Dalianis T. Absent/low CD44 intensity and positive HPV status in oropharyngeal squamous cell carcinoma indicates a very high survival. *Cancer Medicine* Aug;2(4):507-18, 2013.
- Näsman A, Andersson E, Marklund L, Tertipis N, Hammarstedt-Nordenwall L, Attner P, Nyberg T, Masucci GV, Munck-Wikland E, Ramqvist T, Dalianis T. HLA class I and II expression in oropharyngeal squamous cell carcinoma in relation to tumor HPV status and clinical outcome. *PlosOne* Oct 10;8(10):e77025. Doi:10137/journal.pone.0077025.2013
- Millrud CR, Kvarnhammar AM, Tajti J, Munck-Wikland E, Uddman R, Cardell LO. Nod-like receptors in head and neck squamous cell carcinoma. *Acta Otolaryngol* 133(12): 1333-1344, 2013.
- Wendt M, Romanitan M, Näsman A, Dalianis T, Hammarstedt L, Marklund L, Ramqvist T, Munck-Wikland E. Presence of human papillomaviruses and p16 expression in hypopharyngeal cancer. *Head and Neck* Jan;36(1):107-12, 2014.
- Sivars L, Näsman A, Tertipis N, Vlastos A, Ramqvist T, Dalianis T, Munck-Wikland E, Nordemar S.: Human papillomavirus (HPV) and p53 expression in metastasis from unknown primary head and neck cancer in relation to clinical outcome. *Cancer Medicine* 3(2): 376-384, 2014.
- Nordfors C, Vlastos, A, Du J, Ahrlund-Richter A, Tertipis N, Grün N, Romanitan M, Haegglblom L, Roosaar A, Dahllof G, Dona Mg, Benevolo M, Ramqvist T, Munck-Wikland E Dalianis T. Human papillomavirus prevalence is high in oral samples of patients with tonsillar and base of tongue cancer. *Oral Oncology* 50(5): 491-497, 2014.
- Danielsson D, Brehwens K, Halle M, Marczyk M, Sollazzo A, Polanska J, Munck-Wikland E, Wojcik A, Haghdoost S. Influence of genetic background and stress response on risk of mandibular osteoradionecrosis after radiotherapy of head and neck cancer. *Head&Neck* Oct 28. Doi:10.1002/hed.23903, 2014.
- Näsman A, Nordfors C, Holzhauser S, Vlastos A, Tertipis N, Hammar U, Hammarstedt-Nordenwall L, Marklund L. Munck-Wikland E, Ramqvist T, Bottai M, Dalianis T. Incidence of human papillomavirus positive tonsillar and base of tongue carcinoma: a stabilization of an epidemic of viral induced carcinoma? *Eur J Cancer* 51(1): 55-61, 2015.
- Bark R, Mercke C, Munck-Wikland E, Wisniewski NA, Hammarstedt-Nordenwall L Cancer of the gingival. *Eur Arch Otorhinolaryngol.* 2015 Epub ahead of print PMID:2564283

Abstracts:

- Eva Munck-Wikland, Martin Halle, Karl Brehwens, Andrzej Wojcik, Siamak Haghdoost, Michal Marczyk, Joanna Polanska. Mandibular osteoradionecrosis Scandinavian Society Head and Neck Oncology, Stockholm 140320-140321.
- E Munck-Wikland, A Näsman, T Ramqvist, L Hammarstedt, L Marklund, T Dalianis. HPV concordance between neck metastases and primary tonsillar cancer. *EUROGIN Sevilla* 150204-150207.



Antti Mäkitie
Affiliated Professor from Helsinki
+358-50 428 6847
antti.makitie@ki.se

Treatment Outcome, Prognostic Markers, and New Reconstruction Modalities in Head and Neck Cancer

1. Identification of biomarkers that predict HNSCC treatment sensitivity.
This collaborative project aims to identify markers that predict treatment response and can be analyzed in a biopsy from a suspected tumor and/or in a patient's blood sample. The ultimate goal is to find combinations of markers which could guide clinicians to provide cancer patients with a more adequate, individualized, and effective treatment.
2. The nordic nasopharyngeal cancer study: management and outcome of nasopharyngeal cancer in the nordic countries during 2005 – 2009.
Our aim is to evaluate current treatment outcome of NPC in the Nordic countries and to form a recommendation for a unified NPC treatment protocol to be used in this area. The secondary aim is to find prognostic markers for clinical use.
3. Additive manufactured applications for tissue-engineered constructs in HNSCC management - new materials and processing methods.
We aim at investigating various novel materials that can be additive manufactured (i.e. 3D printed) for their potential use in the clinical setting of different upper airway tissue transplants. Various in vitro and in vivo methodologies will be used to analyze the mechanical, biocompatible and immunological characteristics of the materials.

Publications 2012, 2013, 2014

Selected KI-publications for 2014-2015

(for complete list of publications - see Pubmed: Makitie A)

1. Tuomi J, Paloheimo KS, Vehvilainen J, Bjorkstrand R, Salmi M, Huutilainen E, Kontio R, Rouse S, Gibson I, Mäkitie AA. A novel classification and online platform for planning and documentation of medical applications of additive manufacturing. *Surg Innov.* 2014;21:553-9.
2. Perheentupa U, Mäkitie AA, Kinnunen I. Subcranial craniotomy approach for frontobasal fracture correction. *J Craniomaxillofac Surg.* 2014;42:1371-7.
3. Renkonen S, Cardell LO, Mattila P, Lundberg M, Haglund C, Hagstrom C, Mäkitie AA. Toll-like receptors 3, 7, and 9 in juvenile nasopharyngeal angiofibroma. *APMIS* 2015 [Epub ahead of print]
4. Hirvonen K, Bäck L, Saarilahti K, Leivo I, Hagström J, Mäkitie AA. Pattern of recurrent disease in major salivary gland adenocystic carcinoma. *Virchows Arch.* 2015 Apr 3. [Epub ahead of print]
5. Ruohoalho J, Mäkitie AA, Atula T, Takala A, Keski-Säntti H, Aro K, Haapaniemi A, Markkanen-Leppänen M, Westman M, Bäck LJ. Developing a prospective registry for complications in otorhinolaryngologic surgery: experiences from a pilot tonsil surgery registry. *Laryngoscope* 2015 (in press)
6. Renkonen S, Sayed F, Keski-Säntti H, Ylä-Kotola T, Bäck L, Suominen S, Kanerva M, Mäkitie A. Reconstruction of facial nerve after radical parotidectomy. *Acta Otolaryngol* 2015 (in press)

Riitta Möller
Consultant, Ph.D.
+46 73 326 1296
riitta.moller@ki.se



I've ongoing research in two areas: oropharyngeal dysphagia and science education in medical education. Oropharyngeal dysphagia is an increasing problem because we live longer, and dysphagia is more common among elderly people. The validation study of Eat Assessment Tool (EAT)-10 questionnaire is ongoing and will be continued by identification of dysphagia and possible malnutrition in these patients. Research in science education focuses on students' learning during research project course; learning environment and scientific outcome (publications and presentations) after research project course.

Publications 2012, 2013, 2014

1. Möller R, Shoshan M, Ponzer S. Handledaren har avgörande roll för läkarstudentens examensarbete. KI:s erfarenheter från de sju första terminerna. Läkartidningen 2014;111:C43E
2. Möller R, Shoshan M, Heikkilä K. What is the reward? Medical students' learning and personal development during a research project course. Accepted for publication. Medical Education 2015.



Pia Nerfeldt
M.D., Ph.D.
+46 709 770 207
pia.nerfeldt@karolinska.se

OSAS in children

My thesis in 2008 dealt with obstructive sleep apnea syndrome (OSAS) in adults, with a focus on treatment with weight reduction.

My continuous commitment to research is now in children with OSAS:

1. RCT ATT / ATE in children with OSAS: Analysis phase .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 (ATT= partial tonsillectomy) or adeno-tonsillectomy (ATE= complete tonsillectomy). 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. Intervention study on the treatment effect of anti-apnea dental splint for Upper Airway Resistance Syndrome: Submitted.
3. 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.
4. RCT ATE / watchful waiting for mild to moderate OSAS in children 2-5 years old: Inclusion phase.
5. RCT ATE / ATE+pharyngoplasty for severe OSAS in children 2-5 years old: Inclusion phase
6. National registry for tonsillar surgery: start up phase

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
	Anna Borgström
	Johan Fehrm

Publications 2012, 2013, 2014

1. P. Nerfeldt, F. Aoki, D. Friberg. Polygraphy vs. Polysomnography: missing OSAS diagnosis in symptomatic snorers - a wake-up call for clinicians. Karolinska Institutet, Sweden. Sleep Breath. 2013 Aug 14.
2. Borgström A, Nerfeldt P, Friberg D. Questionnaire OSA-18 has poor validity compared to polysomnography in pediatric obstructive sleep apnea. Int J Pediatr Otorhinolaryngol. 2013 Sep 5. doi: S0165-5876(13)00417-5.
3. Browaldh N, Nerfeldt P, Lysdahl M, Bring J, Friberg D. SKUP3 randomised controlled trial: polysomnographic results after uvulopalatopharyngoplasty in selected patients with obstructive sleep apnoea. Thorax. 2013 Sep;68(9):846-53.

Petter Olsson
M.D., Ph.D.
+41 795 432 885
petter.olsson@ki.se



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

1. Svensson J, Lundberg J, Olsson P, Stjärne P, Tennvall GR. Cost-effectiveness of mometasone furoate nasal spray in the treatment of acute rhinosinusitis *Prim Care Respir J*. 2012 Sep 21. pii: pcrj-2012-05-0082. doi: 10.4104/pcrj.2012.00085.
2. Stjärne P, Odebäck P, Ställberg B, Lundberg J, Olsson P. High costs and burden of illness in acute rhinosinusitis: real-life treatment patterns and outcomes in Swedish primary care. *Prim Care Respir J*. 2012 Feb 20. doi: 10.4104/pcrj.2012.00011.
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.



Björn Palmgren
M.D., Ph.D.
+46 8 517 75048
bjorn.palmgren@karolinska.se

The value of analysis of genetic instability and specific biomarkers in prediction of sensitivity to radiation in patients with T2/T3 laryngeal cancer.

Background

This is a multicenter study is a collaboration between Karolinska University Hospital, Linköpings University hospital and Helsinki University Hospital. The aim is to identify markers in laryngeal cancer that can predict sensitivity to chemo radiation. In the future we hope that these markers will help us in planning adequate and individualized treatment for patients with laryngeal cancer.

Questions:

1. Can the expression of the protein Survivin be used to predict response to chemo radiation in T2/T3 laryngeal cancer?
2. Can the expression/localization of WRAP53 be used to predict response to chemo radiation in T2/T3 laryngeal cancer?
3. Can single nucleotide polymorphism (SNP) in genes involved in DNA-growth and repair be used to predict response to chemo radiation in T2/T3 laryngeal cancer?

Methods:

Paraffin embedded tumor biopsies from around 150 patients diagnosed with T2/T3 laryngeal cancer are sectioned and immunohistochemical controlled for the different protein markers. The biopsies also undergo DNA-analysis. The results will be matched with outcome of treatment.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
	Andreas Kaiser

Publications 2012, 2013, 2014

1. 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
2. Jiao Y, Palmgren B, Novozhilova E, Englund Johansson U, Spieles-Engemann AL, Kale A, Stupp SI, Olivius P. BDNF increases survival and neuronal differentiation of human neural precursor cells cotransplanted with a nano-fiber gel to the auditory nerve in a rat model of neuronal damage. *Biomed Res Int.* 2014;2014:356415. doi: 10.1155/2014/356415. Epub 2014 Aug 26
3. Ajay Kale¹, Ekaterina Novozhilova, Ulrica Englund-Johansson, Samuel I. Stupp, Björn Palmgren, Petri Olivius. Exogenous BDNF and Chondroitinase ABC consisted biomimetic microenvironment regulates survival, migration and differentiation of human neural progenitor cells transplanted into a rat auditory nerve. *Neuroscience & Medicine*, 2014, 5, 86-100

Pär Stjärne
Adjunct Professor, Consultant
+46 70 725 0749
par.stjarne@karolinska.se



Clinical studies on upper airway inflammation, skullbase and sinonasal tumors and treatment of facial fractures

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:

Main Supervisor	Co-supervisor
Babak Alinasab	Magnus Starkhammar
Ola Fridman Bengtsson	Karin Jonstam
Ann Abrahamsson	
Alexandra Elliot	

Publications 2012, 2013, 2014

1. Westman M, Stjärne P, Bergström A, Kull I, Toskala E, Cardell LO, Wickman M, Holmström M. Chronic rhinosinusitis is rare but bothersome in adolescents from a Swedish population-based cohort. *J Allergy Clin Immunol*. 2015 Apr 1. pii: S0091-6749(15)00268-7.
2. Elliot A, Jangard M, Marklund L, Hakansson N, Dickman P, Hammarstedt-Nordenvall L, Stjärne P. Sinonasal malignancies in Sweden 1960-2010; a nationwide study of the Swedish population. *Rhinology*. 2015 Mar;53(1):75-80.
3. Westman M, Lupinek C, Bousquet J, Andersson N, Pahr S, Baar A, Bergström A, Holmström M, Stjärne P, Lødrup Carlsen KC, Carlsen KH, Antó JM, Valenta R, vanHage M, Wickman M; Mechanisms for the Development of Allergies (MeDALL) consortium. Early childhood IgE reactivity to pathogenesis-related class 10 proteins predicts allergic rhinitis in adolescence. *J Allergy Clin Immunol*. 2015 May;135(5):1199-1206.e11.
4. Westman M, Kull I, Lind T, Melén E, Stjärne P, Toskala E, Wickman M, Bergström A. The link between parental allergy and offspring allergic and nonallergic rhinitis. *Allergy*. 2013 Dec;68(12):1571-8.
5. Ek A, Middelveld RJ, Bertilsson H, Bjerg A, Ekerljung L, Malinowski A, Stjärne P, Larsson K, Dahlén SE, Janson C. Chronic rhinosinusitis in asthma is a negative predictor of quality of life: results from the Swedish GA(2)LEN survey. *Allergy*. 2013 Oct;68(10):1314-21.
6. 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.
7. Alinasab B, Ryott M, Stjärne P. Still no reliable consensus in management of blow-out fracture. *Injury*. 2014 Jan;45(1):197-202.
8. Svensson J, Lundberg J, Olsson P, Stjärne P, Tennvall GR. Cost-effectiveness of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. *Prim Care Respir J*. 2012 Dec;21(4):412-8.
9. Cardell LO, Wickman M, Hellgren J, Cervin A, Stjärne P, Holmström M, Dahlén B, Bjermer L, Dahlén SE. [International guidelines for allergic rhinitis have been updated]. *Lakartidningen*. 2012 Mar 21-27;109(12):622-4. Swedish.
10. Stjärne P, Odebäck P, Stållberg B, Lundberg J, Olsson P. High costs and burden of illness in acute rhinosinusitis: real-life treatment patterns and outcomes in Swedish primary care. *Prim Care Respir J*. 2012 Jun;21(2):174-9;
11. Ehnhage A, Olsson P, Kölbl KG, Skedinger M, Stjärne P; NAFS 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.
12. Westman M, Stjärne P, Asarjoo A, Kull I, van Hage M, Wickman M, Toskala E. Natural course and comorbidities of allergic and nonallergic rhinitis in children. *J Allergy Clin Immunol*. 2012 Feb;129(2):403-8.



Bo Tideholm
Head of the Clinic, M.D., Ph.D.
+46 8 585 85719
bo.tideholm@karolinska.se

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

Publications 2012, 2013, 2014

1. A Randomised, Double Blind Trial of N-Acetylcysteine for Hearing Protection during Stapes Surgery. Bagger-Sjöbäck D, Strömbäck K, Hakizimana P, Plue J, Larsson C, Hultcrantz M, Papatziarnos G, Smeds H, Danckwardt-Lillieström N, Hellström S, Johansson A, Tideholm B, Fridberger A. PLoS One. 2015 Mar 12;10(3):e0115657. doi: 10.1371/journal.pone.0115657. eCollection 2015.
2. Swarts JD, Alper CM, Luntz M, Bluestone CD, Doyle WJ, Ghadiali SN, Poe DS, Takahashi H, Tideholm B. Panel 2: Eustachian Tube, Middle Ear, and Mastoid-Anatomy, Physiology, Pathophysiology, and Pathogenesis. OTOLARYNGOLOGY-HEAD AND NECK SURGERY 2013 148; E26-E36 doi:10.1177/0194599812472631
3. Brattmo M, Tideholm B, Carlborg B. Inadequate opening capacity of the eustachian tube in Meniere's disease. ACTA OTO-LARYNGOLOGICA 2012 132;3 255-260 doi:10.3109/00016489.2011.637175

Tatjana Tomanivoc
M.D., Ph.D.
+46 8 517 70635
tatjana.tomanovic@karolinska.se



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-PDCN 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.

Publications 2012, 2013, 2014

1. Tomanovic T, Bergenius J. Is the nystagmus pattern in hemi-labyrinthectomized subjects during positional alcohol nystagmus 2 similar to that found in patients with cupulolithiasis in the lateral semicircular canal? *Acta Otolaryngol.* 2013 Aug;133(8):796-803. doi: 10.3109/00016489.2013.777472. Epub 2013 Apr 8. PubMed PMID: 23565838.
2. Tomanovic T, Bergenius J. Can the nystagmus pattern in patients with a 'light cupula' be reproduced in hemi-labyrinthectomized subjects during positional alcohol nystagmus 1? *Acta Otolaryngol.* 2011 Sep;131(9):929-36. doi: 10.3109/00016489.2011.574645. Epub 2011 May 12. PubMed PMID: 21563872.
3. Tomanovic T, Bergenius J. Different types of dizziness in patients with peripheral vestibular diseases--their prevalence and relation to migraine. *Acta Otolaryngol.* 2010 Sep;130(9):1024-30. doi: 10.3109/00016481003671236. PubMed PMID: 20380548.



Inger Uhlén
 Consultant, Ph.D.
 +46 73 966 1649
 inger.uhlen@karolinska.se

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

The present study is focusing on cognitive development and central auditory processes in children with hearing aids and/or cochlear implants (CI). A specific purpose is to examine how an individually designed phonological intervention programme can affect neurophysiological development and development of cognitive and reading skills. The study is a longitudinal design, where the children are followed over a period of three years. Three groups of children have been included in the study: Deaf children with CI, hearing-impaired children with hearing-aids and normal hearing children. The children wer be between 5 to 7 years old when the study started. The phonological intervention was administrated via internet and the actual traning have been managed by the childrens’ parents. The parents were, during the training phase, supported by a speech pathologist.

The results show training effects regarding language development presented in a thesis 2014. Neurophysiological data are being analysed and are the subject for a second thesis.

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
Elisabet Engström	Emelie Kullring

Publications 2012, 2013, 2014

1. Sloot F, Hoeve H LJ, de Kroon M, Goedegebure A, Carlton J, Griffiths H J and Simonsz H J for the EUS€REEN study group*. Inventory of current EU paediatric vision and hearing screening programmes. J Med Screen (accepted for publication Jan 2015) *Sweden: Uhlén I
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3. Nakeva von Mentzer, C., Lyxell, B., Sahlen, B., Dahlström, O., Lindgren, M., Ors, M., Kallioinen, P., & Uhlén, I. (2014). The Phonics Approach in Swedish Children using Cochlear Implants or Hearing Aids: Inspecting Phonological Gain. Journal of Communication Disorders, Deaf Studies & Hearing Aids 2(3).
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Marit Westman
M.D., Ph.D.
+46 8 585 80000
marit.westman@karolinska.se



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..

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
	Karin Jonstam

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PhD-Student	Registered
Abrahamsson, Ann	2012-01-0156.
Alinsab, Babak	2009-11-0957.
Arebro, Julia	2012-03-1958.
Asp, Filip	2009-05-2559.
Bonnard, Åsa	2010-10-1460.
Borgström, Anna	2011-12-2361.
Danielsson, Daniel	2008-10-0862.
Elliot, Alexandra	2011-03-1763.
Ekstedt, Sandra	2013-09-2664.
Enerdal, Jakob	1996-11-0865.
Engström, Elisabet	2007-02-1266.
Fehrm, Johan	2014-11-1467.
Fridman Bengtsson, Ola	2011-12-2268.
Gustafsson, Ylva	2013-05-2069.
Hellkvist, Laila	2013-05-2070.
Honeth, Louise	2009-06-1871.
Jonstam, Karin	2015-03-2472.
Kaiser, Andreas	2008-10-3073.
Kågedal, Åsa	2011-01-1874.
Malmström, Emma	2012-05-2475.
Nyberg, Kristina	2015-05-0276.
Siegbahn, Malin	2014-10-2777.
Sjöqvist, Sebastian	2011-11-0178.
Smeds, Henrik	2008-05-0679.
Starkhammar, Magnus	2008-02-1280.
Tengroth, Lotta	2011-04-2681.
Turunen-Taheri, Satu	2015-03-2482.
Wendt, Malin	2010-03-1183.
Verrecchia, Luca	2013-04-1684.
Xu, Yuan	2009-07-0185.



Ann Abrahamsson
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned disseration

ann.abrahamsson@karolinska.se

Pär Stjärne

Lars Olaf Cardell, Danielle Friberg, Karin Toll

2012-01-01

Local inflammatory parameters in women with Pregnancy Rhinitis

Publications / manus



Babak Alinasab
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

babak.alinasab@karolinska.se
Pär Stjärne
Michael Ryott
2009-11-09

Zygomaxillary Complex and Isolated Orbital Floor Fractures -aspects of diagnostic methods and , treatment and sequelae

Facial skeleton injuries around the orbit can be divided into 4 different fracture types. Zygomaxillary complex and isolated orbital floor fractures are the two major and most common fractures involving orbit walls. These two types of fractures are the subjects we will study in this project.

Injuries around the orbit as zygomaxillary complex and orbital floor fracture can result in considerable facial deformity and affect both the vision and the nervous system of the face. Failure in early assessment of the significance of the displacement will result in severe sequelae. In fractures of the orbital floor it is important to identify those injuries which have resulted in significant disruption and restore the volume and shape of the orbit. A failure in assessment will result in enophthalmos and ocular mobility problems. To day generally 1.5mL of herniation is considered as an indication for surgery, however, the evidence for this is poor and not based on randomized, controlled studies.

In zygomaxillary complex fractures an obvious displacement could be left in elderly patient. But in a young patient even a minor displacement may need to be elevated to restore contour and minimize late problems like sensibility disorder, cheek asymmetry, enophthalmos, diplopia and malocclusion. Some authors suggest less invasive reduction with a single hook, while other would consider this treatment a compromise with no satisfactory results and claim that open reduction and internal fixation is always necessary. Other author stress that poorly reduced and plated fractures are increasing epidemically, in spite of access to the sophisticated and best fixation tools.

A review of the literature shows that there is still no evidence based medicine or reliable studies in management of patients with these fractures.

We believe that changes in orbital volume has little or no effect on the development of enophthalmos in patients with orbital fractures. We also believe that the degree of reduction and not fixation of the fracture correlates with late symptoms in patients with zygomaxillary complex fractures. In this project we aim to improve the diagnostic methods of orbital floor fracture and zygomaxillary complex fractures and to compare the Swedish and the international treatment traditions in these fracture types. Through prospective controlled randomized studies, we aim to elucidate which treatment benefits the patient best, both in short and long term.

In our first study we could conclude the relative orbital volume change is not a useful criterion for surgery. We also concluded that the importance of the herniation, the location of the fracture in development of posttraumatic enophthalmos and the mechanism of the diplopia requires to be evaluated with prospective controlled studies.

In a second study we could conclude that there are considerable differences in the management of the orbital floor fractures due to lack of a reliable consensus and individual and local traditions. We also concluded that guidelines based on randomized prospective study in BOF are required.

The on going study is a prospective controlled randomized clinical study in management of patients with orbital floor fracture. We aim to evaluate which patient with isolated orbital floor fracture develop enophthalmos and need early surgical intervention to prevent late sequelae.

An other study in progress is a prospective controlled randomized clinical study in management of zygomaxillary complex fractures. We aim to study the effect of open reduction and fixation on late sequelae in patients with zygomaxillary complex fractures.

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Julia Arebro
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

julia.arebro@karolinska.se
Lars Olaf Cardell
Susanna Kumlien Georén
2012-03-19
2015-05-28

Innate immunity in nasal inflammation

Chronic rhinosinusitis (CRS) is a disease defined as chronic inflammation of the nose and paranasal sinuses. 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 as part of the innate immune system has opened new possibilities for exploration of the underlying mechanisms.

Allergic rhinitis (AR) is an inflammatory disease of the nasal mucosa, induced by a reaction to a normally harmless antigen. In the initial sensitization phase, allergen-specific Th2 cells are activated, secreting cytokines thus inducing IgE-production by B cells. The second phase, the effector phase, constitutes of cross-linkage of IgE leading to degranulation and release of inflammatory mediators and recruitment of eosinophils, neutrophils and Th2 cells.

The overall aim of this project is to characterize and analyze potential altered innate immunity factors in CRS and AR as two variants of nasal inflammation.

We have shown that defects in the TLR9 mediated microbial defense in the mucosa adjacent to the anatomic origin of the polyp in CRS with nasal polyps might explain virus induced polyp growth. Moreover, we have established that nasal epithelial cells are important antigen presenting cells in AR by initiating a local adaptive immune response. Finally, we have characterize different neutrophil subsets that tend to displace between the different compartments blood, mucosa and NAL in a schematic pattern in response to allergy exposure. Experiments are now ongoing to find functional properties of these subsets.

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Filip Asp
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned disseration

filip.asp@karolinska.se
Erik Berninger
Stefan Stenfelt, Jan-Erik Juto
2009-07-01
2012-05-15
2015

Bilateral cochlear implants in Children

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 accuracy after activation of the second implant.

Currently, a method for rapid, precise and objective assessment of sound localization accuracy measurements is under development.

Findings suggest that sound localization accuracy may be reliably and rapidly assessed from 6 months of age. The technique may be used as a clinical tool for evaluation of very early intervention in a young, pre-verbal population and throughout the life span.

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Åsa Bonnard
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

asa.bonnard@karolinska.se
Malou Hultcrantz
Rusana Simonoska, Christina Hederstierna
2010-10-14
2012-04-12
Hösten 2015

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.

Publications / manus

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Anna Borgström
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

anna.borgstrom@karolinska.se
Daniell Friberg
Pia Nerfeldt, Göran Elinder
2011-12-12
2017

Pediatric obstructive sleep apnea; evaluation of questionnaire and 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 (eg failure to thrive, neurocognitive complications, cardiovascular complications).

Gold Standard to diagnose OSA in children is polysomnography (PSG). However, this is a costly method, not widely available. In most cases diagnose 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 methods have 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. 79 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 postop complications (bleeding and pain) and frequency of reoperation.

Further the project includes a study of trends in tonsil surgery in children and adolescents in Sweden during the last decades.

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Daniel Danielsson
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

daniel.danielsson@karolinska.se
Eva Munck-Wikland
Siamak Haghdoost
2008-10-08

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 area is reported to 3-8%.

Aim of our studies:

1. Possible markers for individual radiosensitivity; oxidative stress response, genetic and protein level
2. Osteoradionecrosis impact on indications for extensive maxillo-mandibular reconstruction
3. Quality of life comparative study for ORN patients before and after extensive reconstructive surgery with free tissue transfer.

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Alexandra Elliot
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

alexandra.elliott@karolinska.se
Pär Stjärne
Linda Marklund, Lalle Hammarstedt
2011-03-17
2015-03-27
2016

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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Sandra Ekstedt
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

sandra.ekstedt@ki.se
Lars Olaf Cardell
Susanna Kumlien Georén
2013-09-26
2017

The role of neutrophils in airway smooth muscle contraction

Astma är en komplex sjukdom som karakteriseras av kronisk inflammation och en ökad luftvägsreaktivitet som leder till ett minskat luftflöde till lungorna. Projektets fokus ligger på den ökade luftvägsreaktivitet och neutrofilens roll. Neutrofiler är kända för att vara det första försvaret mot invaderande mikrober, spelar en central roll i antimikrobiella försvaret genom att känna igen mikroorganismer genom olika receptorer. För att uppfylla denna funktion, rekryteras denna leukocyt till det inflammerade området först. Neutrofilers funktionalitet i den inflammatoriska processen har förändrats över tiden, från början en cell begränsad till fagocytos, frisättning av enzymer och andra cytotoxiska mediatorer till en cell som frigör mediatorer med en mer specifik roll för astmautveckling.

Flera studier har dokumenterat att astma som domineras av neutrofil tillströmning lokalt i lungan är överrepresenterade bland patienter som svarar dåligt på traditionell behandling. Information om neutrofilens roll i den ökade luftvägsreaktiviteten är begränsad.

Målet är att se om neutrofilen ensam kan påverka den glatta muskeln i luftvägarna genom organkultur och mätningar av den glatta muskels kontraktion i en myograf, In vitro. För att förstå hur neutrofilen påverkar den glatta muskeln och genom vilken signalväg kommer olika receptor-specifika antagonister användas i myografen. Liganderna till dessa receptorer kommer kunna mätas från neutrofilen som en utsöndrad produkt, med ELISA, eller med olika kit och flödescytometri. Genom att studera neutrofilers olika aktiveringsgrad och känslighet utanför sin vanliga miljö kommer vi att kunna bygga upp en stabil metod för att studera Neutrofilers påverkan på hellungans mekanik In vivo.

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 overrepresented 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 vivo.

Publications / manus



Jakob Enerdal
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

jakob.enerdal@karolinska.se
Pär Stjärne
Lars Olaf Cardell
1996-11-08

Pathophysiology and treatment of rhinitis medicamentosa

Overuse of nasal decongestants induces chronic nasal stuffiness and drug dependence. The underlying mechanisms are unclear, but several hypotheses have been stipulated. Some studies on healthy subjects, patients and animals has identified edema, unspecific inflammation, increased amount of goblet cells and inflammatory mediators. Another possibility is that the overuse induces a down regulation of adrenergic receptors in the nasal mucosa.

When the decongestant nasal sprays were introduced there were no dose-response studies made, raising questions whether the drugs, today available OTC, are correctly dosed.

Patients with nasal problems induced by an overuse of nasal decongestants often have severe problems handling the stuffiness. Our hypothesis is that these persons may have an underlying personality predisposing for this intolerance to nasal stuffiness.

Publications / manus

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Elisabet Engström
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

elisabet.engstrom@karolinska.se
Inger Uhlén
Anders Freijd, Magnus Lindgren
2007-02-12
Prel. 2015
Prel. 2016

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.

Publications / manus

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Johan Fehrm
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

johan.fehrm@karolinska.se
Danielle Friberg
Pia Nerfeldt
2014-11-14
2020

Pharyngeal surgery of obstructive sleep apnea (OSA); randomized studies in children and adults.

Sleep disordered breathing (SDB) is a common condition, for both children and adults, characterized by intermittent partial or complete upper airway obstruction. Clinically it contains a spectrum of symptoms, ranging from primary snoring to more severe form obstructive sleep apnea (OSA).

Pediatric OSA

Factors leading to narrowing of the upper airways are usually due to enlarged tonsils and/or adenoid. The traditional treatment of choice is surgical, adenotonsillectomy (ATE), where the tonsils and adenoid are removed. Recent studies have though indicated that a modified version, called adenopharyngoplasty (APP), where the tonsillar pillars are sutured together and lateralized, might improve the result. In less severe cases it has also been clinical practice to wait and see if the symptoms abate. We plan to perform 2 RCTs (80 patients/trial); one comparing APP with ATE in children with severe OSA and one comparing ATE with observation 6 months, in children with mild to moderate OSA.

Adult OSA

OSA is an endemic disease, the incidence is still increasing and untreated OSA leads to increased morbidity and higher risk for cardiovascular mortality. Uvulopalatopharyngoplasty (UPPP) was the predominant surgical treatment for patients with adult OSA before continuous positive airway pressure (CPAP) and mandibular retaining devices (MRD) became available. The role of UPPP has been questioned because of its possible side effects, complications and lack of efficacy in treating patients with OSA. Though, in 2013 a RCT from our research group called SKUP3, proved that UPPP was an efficient way to treat a selected group of patients with OSA.

Concerning the fact that OSA is an endemic disease with increased morbidity and risk for cardiovascular mortality, we find it important to evaluate the health impact of the surgical treatment over time. We plan to do this by analyzing blood pressure, metabolic and inflammatory blood samples collected during SKUP3.

Publications / manus



Ola Fridman Bengtsson

Main supervisor

Co-supervisor

Registered

Halftime seminar

Planned dissertation

ola.fridman-bengtsson@karolinska.se

Pär Stjärne

Jerker Stigare, Anna-Lena Hulting, Charlotte Höybe

2011-12-22

2015

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

Pituitary tumors accounts for approximately 15% of intracranial neoplasms. Cross-sectional, community-based studies reveals a prevalence of 77-94 cases per 100 000. Morbidity of PT is due to hormonal secretion as well as local tumor expansivity.

Clinical management of pituitary tumors is multidisciplinary and includes both surgical, radiation and pharmacological treatment – often combined. Pituitary tumors are classified according to their hormonal activity

The pituitary center at the Karolinska Hospital is one of the major centers in Europe. There has been a lack of clinical evaluation of the surgical outcomes at the center during a time of dramatic change in the surgical approach and procedures. Therefore this research is important, not only for the patients with pituitary adenomas, but also for the Pituitary center at the Karolinska Hospital for benchmarking with other major centers.

Studies:

1. The effect of postoperative corticosteroid treatment is evaluated in a retrospective study. High dose postoperative treatment is compared to low dose treatment in a population of patients admitted for pituitary surgery at the Karolinska University Hospital.
2. The postoperative results of transsphenoidal pituitary surgery at the Karolinska University Hospital are analyzed retrospectively since 2003-2013.
- 3,4 Using immunohistochemistry as well as PCR techniques the expression of galanin and PRR receptors are studied in pituitary tissue from healthy controls as well as from patients with pituitary adenomas who are subjected to surgery at the Karolinska University Hospital.

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Ylva Gustafsson
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

ylva.gustafsson@ki.se
Paolo Macchiarini
Philipp Jungebluth, Ana Teixeira, Ola Hermanson
2013-05-20

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.

Publications / manus

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Laila Hellkvist
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

laila.hellkvist@karolinska.se
Lars Olaf Cardell
Karin Lundkvist, Ulla Peterson Westin
2013-05-20

Intralymfatisk allergenspecifik immunterapi (IL-ASIT) vid allergisk rinit

Allergisk rinit är ett växande folkhälsoproblem. Allergivaccination eller allergenspecifik immunterapi (ASIT) är den enda behandling som ger symptomlindring samtidigt som den allergiska sjukdomsutvecklingen hämmas. Få patienter genomgår ASIT på grund av den tidskrävande proceduren med upp till 50 läkarbesök under 3 års tid. Ett alternativ till traditionell subkutan ASIT är sublingual behandling. Då lägger patienten en tablett under tungan dagligen i 3 år. Detta kan göras i hemmet men den långsiktiga patientfölsamheten är dålig. Det är därför angeläget att hitta ett effektivare behandlingssätt för ASIT.

För ett par år sedan visades att endast tre injektioner av låg dos allergen direkt i en inguinal lymfkörtel hade en symptomlindrande effekt motsvarande konventionell ASIT. Vår egen forskargrupp har nyligen upprepat dessa resultat. Vi har dessutom visat på ett par nya tidigare inte beskrivna mediatorvägar vilka kan vara involverade i toleransutvecklingen. De biverkningar som förekommit har varit få och milda, mestadels i form av lokal svullnad kring injektionsstället.

IL-ASITs effekter utvärderas nu ytterligare och 2015 avslutas en studie med kombinerad vaccination av björk- och gräsallergen. Preliminära resultat har visat på en ökning av allergenspecifika IgG4-nivåer, induktion av T-memory celler och förbättring av livskvaliteten under pollensäsong i den aktiva gruppen jämfört med placebo. I hopp om att ytterligare förbättra den symptomlindrande effekten kommer allergendosen att ökas. Effekten av detta vägs mot ökad risk för biverkningar.

För att studera mekanismerna vid ASIT görs analys av finnålsaspirat från lymfkörtlar och biopsierad vävnad från annan immunologiskt aktiv vävnad som tonsiller och näslemhinna efter behandling.

Med föreliggande studier strävar vi efter att förbättra möjligheterna för fler att genomgå allergivaccination, kanske

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 where preliminary results show an increase in allergen specific IgG4 levels, increase in T-memory cells and improvement of quality of life in the active group compared to placebo. To achieve additional symptom relief both the dose and the number of injections will be increased. Immunological activation will be studied on fine needle aspirations from lymph nodes and biopsies from other parts of the immune system such as the tonsils and nasal mucosa.

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.



Louise Honeth
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

louise.honeth@karolinska.se
Olof Nyrén
Dan Bagger-Sjöbäck, Ulf Rosenhall
2009-06-18
2012-12-12
Spring 2016

Hearing ability among Swedish hunters

The project aims at examining hearing ability, factors that may increase the vulnerability for hearing loss, shotload and ear-protection use among Swedish hunters- a group of about 300 000 individuals in Sweden. The project is a cross-sectional epidemiologic, internet based study. The study may identify important factors for increased hearing-vulnerability among hunters in specific, but also factors that may be important to the general population. We also aim at increasing the knowledge of the risks with not using ear-protection during hunting and training shooting.

We have within the project, developed a survey "instrument" in form of a questionnaire combined with an internet-based hearing test. The hearing test, and also the survey instrument, has been clinically validated and tested as a part the project.

We finished the data-collection of the big survey in august 2013, and have 1771 responders, where 202 also made the hearing test. The large amount of data has partly been analyzed, and has so far resulted in one submitted manuscript and one manuscript in the end of the writing-process. In the submitted manuscript we write about our data pointing at the significant higher adjusted prevalence risk (PR) for susceptible individuals to have high frequency hearing loss after just 1-6 fired unprotected gun shots with a hunting rifle caliber weapon the preceding 5 years, compared to those who have shot no such unprotected shots. We also see, that some hunters seem if not resistant, at least not susceptible at all to this type of shot trauma. In the following and last manuscript of this doctoral thesis, we write about the tobacco use and its dramatic effect modification of the effect of impulse noise on high frequency hearing loss.

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Karin Jonstam
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

karin.jonstam@ki.se
Lars Olaf Cardell
Claus Bachert, Pär Stjärne, Marit Westman
2015-03-24

Chronic Rhinosinusitis with nasal polyps – evolvement of personalized treatment of patients with severe disease

Chronic rhinosinusitis (CRS) is a common disease and is characterized by a chronic mucosal inflammation of the nose and paranasal sinuses and clinically presents with nasal obstruction, anterior/posterior rhinorrhea, facial pain and/or loss or reduction of smell. CRS can clinically be divided into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) defining two different phenotypes.

CRSwNP is associated with a TH2-driven eosinophilic inflammation with high levels of ECP, IL-4, IL-5, IL-9 and IL-13. Patients with high levels of IgE, both specific to staphylococcus aureus and non-specific, in nasal polyps and in serum have a higher prevalence of asthma. Recent years new treatments towards CRSwNP have been investigated, mainly targeting the TH2 response.

Anti-IL4 (Dupilumab) have shown to be effective in patients with moderat-to-severe asthma where first line treatment with high-dose inhaled glucocorticoids and long-acting-beta-agonist did not achieve disease control. Dupilumab binds the IL4R-alfasubunit and inhibits both IL-4 and IL-13 signaling. Unpublished data suggest it to be effective in treating CRSwNP.

Aim:

1. To develop, validate and evaluate new outcome parameters for CRSwNP research.
2. To understand the mechanism of action of Dupilumab and down-stream effects in the local mucosal tissue and systemically in the blood
3. To compare the effect of sinus surgery with treatment with Omalizumab and Dupilumab.

Publications / manus



Andreas Kaiser
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

andreas.kaiser@karolinska.se
Petri Olivius
Ekaterina Novozhilova, Björn Palmgren
2008-10-30
2013-11-15
2015

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.

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Åsa Kågedal
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

asa.kagedal@karolinska.se
Lars Olaf Cardell
Eva Munck-Wikland, Mats Lidegran
2011-01-18
2017

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). We are working on methods to cultivate tumor cells to be able to study the inflammatory patterns into more detail.

The immune system of cancer patients exhibits an altered immune defense pattern compared with healthy controls. Tumors of the head neck area metastasize primarily to regional lymph nodes of the neck. Occasionally the lump at the neck, the metastases, gives symptoms before the primary tumor does. This gives us a specific interest to the lymph nodes from a tumor immunology perspective. A high infiltration of leukocytes into the tumor has indicated a favorable prognosis. We are looking for patterns and receptors in the nodes that help us to explain why metastases will establish in that specific lymph node.

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 to:

- Characterize different leukocytes levels; examine innate immunocells relation to cancer development
- Develop a method to cultivate tumor cells and be able to find tumor immunology patterns
- Study how leucocytes and receptors in the lymph nodes are associated with cancer development and metastases establishment in at specific lymph node.

Publications / manus

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Emma Malmström
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

emma.malmstrom@karolinska.se
Stellan Hertegård
Katarina LeBlanc
2012-05-24

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

Background

Scarring of the vocal chords is a major cause of severe and chronic disorder voice. Scarring may occur after severe inflammatory conditions of the larynx or after radiation treatment and surgery of tumours of the larynx.

The vocal fold scarring reduces viscoelasticity of the vocal cord and the voice function diminishes. The result of these conditions are a strenuous voice (fonastenia) or total voice loss (aphonia). Many causes of voice disorders can be successfully treated with the help of the speech therapy and / or phonosurgery.

It has been attempts to fill in scars with autologous fat and hyaluronic acid. Also surgery and dissection of the mucosa to remove scar tissue has been done. These treatments, however, often shows modest improvement, and at present there is no satisfactory treatment for scarring of the vocal cords.

Recently, research groups have studied the effect of stem cells, after injection into the scar tissue on the vocal cords. Results showed that stem cells have the potential to specific regional differentiation, ie is converted to the cartilage, muscle tissue or mucosa where such tissue is needed. Also the content of collagen and the degree of fibrosis, decreased in the tissue. The studies also showed improved viscoelasticity of the vocal cords resulting in improved vibration capability in the vocal fold mucosa. However, there is no certain explanation of the mechanisms behind this, although other research suggests that mesenchymal stem cells can improve wound healing via paracrine effects.

Aim

The overall aim of the research project is to continue to develop the method using autologous mesenchymal stem cells in the prevention of scarring of the vocal folds. The research project also aims to investigate the underlying mechanisms of stem cells in the healing power of scarring and underlying factors of people who develop it. The overall goal of this project is to give people with scar on the vocal folds an opportunity to get a better and more functional voice.

Publications / manus



Kristina Nyberg
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

kristina.nyberg@karolinska.se
Per-Åke Lindestad
Elin Marsk
2015-05-02

Exercise-induced laryngeal obstruction - outcome of treatment and relation to laryngomalacia

Patients with exercise-induced laryngeal obstruction (EILO) are adolescents who get inspiratory stridor at maximal effort while performing sports. The stridor is caused by adduction of vocal folds and/or collapse of supraglottic structures.

We will perform an observational study of patients diagnosed with EILO 2005-2012 and we will also perform a retrospective follow-up of the effect of treatment of these patients.

In a prospective treatment study, patients with a medical history of EILO will be examined by continuous laryngoscope exercise test (CLE-test) and those with EILO will be randomized to treatment by speech and language pathologist or information about the condition. In a 6 month follow-up we will evaluate the effect of treatment.

Laryngomalacia, a condition causing stridor in infants, have anatomical features in the larynx which are similar to those of EILO, the kind where supraglottic structures cause the obstruction. Is laryngomalacia in infancy linked to EILO later in life? In a third study we will investigate this by a 12-year follow-up of patients with laryngomalacia as infants. Do they still have anatomically characteristics of laryngomalacia at 12 years of age and do they suffer from EILO?

In a fourth study we will investigate if infants with laryngomalacia have obstructive sleep apnea by performing polysomnography on patients with laryngomalacia.

Importance:

EILO is common and causes considerable problems and anxiety for the patients and their parents. It is often misdiagnosed for asthma. Increased knowledge about examination and treatment will improve management of this group of patients.

EILO is similar to laryngomalacia but the relationship is unknown. Our study will help understanding long-term development of the condition.

Laryngomalacia can cause obstructive sleep apnea in children. More knowledge in this field will help small children with breathing disorders to get better diagnosis and treatment.

Publications / manus



Malin Siegbahn
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

malin.siegbahn@karolinska.se
Malou Hultcrantz
Claudia Priwin, Cecilia Engmér Berglin, Martin Ingvar
2014-10-27

Aural canal atresia and development of central auditory pathways

Unilateral hearing loss was previously not considered a condition requiring rehabilitation. Several studies (Cho Lieu JE 2004 , 2010 , Brookhouser PE 1991) have shown that major problems in social situations (22-59 %) and school education (12-41 %) may occur. Adult patients with unilateral aural canal atresia, who have not received rehabilitation had significantly poorer perception of speech in noise in the atresic ear compared to the normal hearing ear (Priwin et al 2007). This could mean that an under-development of central auditory pathways are present, possibly due to lack of stimulation during critical phases of development in childhood.

Every year 20-30 children in Sweden are born with aural canal atresia. This condition gives a maximum conductive hearing loss on the affected ear. Habilitation is available from infancy through bone anchored hearing aid on headband, from two years of age in the form of implanted bone anchored hearing aid or reconstructive hearing enhancement surgery . The knowledge of how early habilitation affect auditory perception in the long run is limited.

The purpose of this project is to identify the central auditory pathways in adults with congenital unilateral aural canal atresia, both using functional MRI and functional hearing tests. An animal model will also be used to examine whether, and if so, how central auditory pathways affected by an untreated unilateral conductive hearing loss (eg atresia). A new method to measure directional hearing, called the Eye- reflex movement , will also be evaluated.pathophysiology of preterm birth. Moreover, these studies will generate hypotheses for subsequent projects and form the basis for future intervention studies. This may pave the way for treatment to women with threatened preterm delivery by AF induction and a simple therapy to enhance breast milk composition in order to prevent inflammatory complications and improve growth of preterm infants. Strategies that reduce the prevalence or severity of these morbidities could have a substantial impact on both health outcomes and health care costs.

Publications / manus



Sebastian Sjöqvist
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

sebastian.sjoqvist@ki.se
Paolo Macchiarini
Matthias Löhr, Katarina LeBlanc, Magnus Nilsson
2011-11-01
2014-03-06
Autumn 2014 hopefully

Tissue Engineering of the Esophagus

A tissue-engineered oesophageal scaffold could be very useful for the treatment of pediatric and adult patients with benign or malignant diseases such as carcinomas, trauma or congenital malformations. Here we decellularize rat oesophagi inside a perfusion bioreactor to create biocompatible biological rat scaffolds that mimic native architecture, resist mechanical stress and induce angiogenesis. Seeded allogeneic mesenchymal stromal cells spontaneously differentiate (proven by gene-, protein and functional evaluations) into epithelial- and muscle-like cells. The reseeded scaffolds are used to orthotopically replace the entire cervical oesophagus in immunocompetent rats. All animals survive the 14-day study period, with patent and functional grafts, and gain significantly more weight than sham-operated animals. Explanted grafts show regeneration of all the major cell and tissue components of the oesophagus including functional epithelium, muscle fibres, nerves and vasculature.

We have now made progress in the field and successfully decellularized porcine and human oesophagus. In both species we could retain important properties of the organ while removing the majority of cells.

Publications / manus

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Henrik Smeds
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

henrik.smeds@karolinska.se
Anders Fridberger
Mats Ulfendahl, Stephen O'leary
2008-05-06
2015-03-12

Cochlear implantation, surgical trauma and malformed cochleas

1) Cochlear implants are today widely used in the treatment of deaf patients. However, all patients with a severe hearing disability do not have a completely eliminated inner ear function but a residual hearing in the apical parts of the cochlea resulting in a useful low frequency hearing. If the residual hearing can be preserved during cochlear implant surgery there is a possibility of a combined electric and acoustic stimulation of the cochlear nerve resulting in a better speech perception.

2) One to three in 1000 newborns are affected by hearing loss. 50% of these are of genetic causes, the majority being non-syndromic (70%). 18% of the children in the cochlear implant program at The Karolinska University Hospital present with a cochlear malformation on radiology as the reason for deafness. Within this group children with x-linked deafness relating to a mutation to the gene POU3F4 will be further examined.

The project aims at;

1) investigating the mechanisms responsible for inner ear trauma during surgery and possible otoprotective strategies. Vibrations and hydrodynamic forces from surgery and electrode insertion can cause a direct trauma to the apical part of the cochlea but there can also be a delayed hearing loss by activation of inflammation and cell death pathways as well as development of intracochlear fibrosis.

2) a comprehensive study of children with x-linked malformation including genetics (we will sequence and identify the genotype for each child), radiological and clinical diagnoses, surgical considerations (summarise our experiences with cochlear implantation procedures pre-, intra- and post-operatively), complications post procedure, audiological/speech outcomes and balance. The assessment also includes examination of executive functions and possible neurodevelopmental psychiatric disorders.

Publications / manus

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Magnus Starkhammar
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

magnus.starkhammar@karolinska.se
Lars Olaf Cardell
Sven-Erik Dahlén, Pär Stjärne, Michael Adner
2008-02-18
2014

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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Lotta Tengroth
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

lotta.tengroth@ki.se
Lars Olaf Cardell
Susanne Kumlien Georén
2011-04-26
2013-05-16
VT 2016

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 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. Our study have shown that defects in the TLR9 mediated microbial defense in the mucosa adjacent to the polyp might explain virus induced polyp growth (2).

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 (3).

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Satu Turunen-Taheri
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

satu.turunen-taheri@ki.se
Sten Hellström
Per-Inge Carlsson
2015-03-24

Adult patients with severe to profound hearing loss. A register-based and interview study

Background

The Quality Register for severe to profound hearing loss have estimated the number of patients in Sweden with a severe to profound hearing impairment to be 10000 to 15000. There are 2000 adults with cochlear implants in Sweden (2014). There are approximately 1200 deaf-blind people in Sweden (2014). Patient with hearing loss experience fatigue due to mental strain in various hearing situations, in particular with surrounding disturbing noise. Extended audiological rehabilitation requires input from multiple professional. Patients defined as having received extended audiological rehabilitation have participated in group rehabilitation or having been subjected to at least three individual efforts of various hearing care professionals such as audiologists, technicians, welfare officers, hearing pedagogues, psychologists and doctors.

Aim

The overall aim of this study is to present the quality and the usefulness of audiological rehabilitation for patients with severe to profound hearing loss.

Materials and Methods

The study is a descriptive register study with a quantitative approach. Study 3 has also a qualitative approach with interviews.

Four areas will be investigated:

1. Which kind of extended audiological rehabilitation had patients with severe to profound hearing loss received and how did they experience the benefits of the rehabilitation?
2. Patients with cochlear implant and extended audiological rehabilitation.
3. Patients with severe to profound hearing impairment with severe vision impairment: A quality of life study.
4. Mental fatigue in patients with severe to profound hearing loss.

Publications / manus



Malin Wendt
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

malin.a.wendt@karolinska.se
Eva Munck Wikland
Linda Marklind, Georgios Papatziarnos
2010-03-11

Sclerotherapy of benign cysts in the head and neck with OK 432 - a prospective, randomized, double-blinded, placebo-controlled study

Benign cysts in the head- and neck area such as thyroglossal duct cysts, branchial cleft cysts and ranulas are traditionally treated with surgical excision. Since over 30 years sclerotherapy with OK 432, a lyophilized streptococcal preparation, has been used for the treatment of lymphatic malformations, with very good results. Studies indicates that this type of sclerotherapy is effective also in other benign cystic lesions in the head- and neck. A pilot study in our clinic supports this theory with 50-80 % of patients cured after 1-3 injections.

To confirm these results we have started a prospective, randomized, double-blinded placebo- controlled study of this new treatment. This study is a unique possibility to evaluate the effect of OK 432 on these conditions but also to look further into the mechanism behind this effect.

The study is approved by the Swedish Medical Products Agency and monitored by Karolinska Trial Alliance.

Publications / manus

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Luca Verrecchia
Main supervisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

luca.verrecchia@karolinska.se
Maoli Duan
Krister Brantberg
2013-04-16
2016
2018

Vestibular evoked myogenic potentials in clinical neurotology

This research plan is designed for assessment of the clinical application of the vestibular myogenic potentials (VEMPs) in clinical neurotology. VEMP is a myogenic potential evoked through activation of the otolith organs of the inner ear (sacculle and utricule) in response to sounds or vibration stimuli. VEMPs can be recorded with electromyography from various groups of muscles using skin electrodes. The two methods for VEMP testing that have reached a sufficient reliability to be introduced in the clinical research are cervical VEMP (cVEMP), in which the recorded potential represents the modulation of muscle sternocleidomastoideus activity and ocular VEMP (oVEMP), in which the potential is recorded beneath the eyes and represents the activation of the inferior oblique muscle.

The two methods (cVEMP and oVEMP) have shown different response patterns in different vestibular disorders: an enhancement in case for “third window” syndromes or reduction in case of vestibular loss. The research plan explores the possibility to widen the application of VEMP testing in the clinical practice.

Four areas will be considered:

1. VEMP & middle ear disorders: the roll of VEMP testing in the analysis of the vestibular function and of the transmission failure in case of middle ear pathology.
2. VEMP & vestibular loss: the roll of VEMP testing in the recovery phase after vestibular paresis.
3. VEMP evoked by combined stimuli: analysis the VEMP pattern evoked by different stimulus modalities.
4. VEMP and vestibular asymmetries: analysis of VEMP response pattern with current or alternative settings in different vestibular disorders.

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Yuan Xu	yuan.xu@ki.se
Main supervisor	Lars Olaf Cardell
Co-supervisor	Lars Edvinsson
Registered	2009-07-01
Halftime seminar	2012-09-18
Planned dissertation	2015

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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