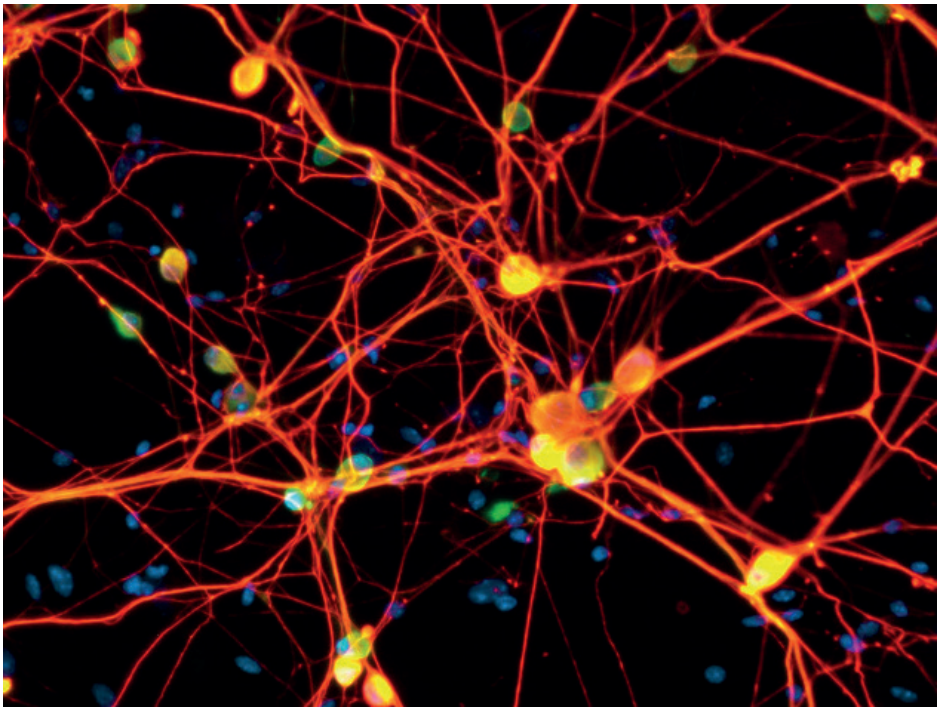

RESEARCH ACTIVITY

at the Division of
Ear, Nose and Throat Diseases

2020

Karolinska Institutet

KAROLINSKA Universitetssjukhuset

Cover: Photo of nasal mucosa demonstrating the co-localization of nerves (red) and innate receptors (TLR7, yellow) demonstrating the possible role of nerve signaling in the activation of our microbial defense.
Photo: Staffan Larsson

CONTENT

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Head of Department
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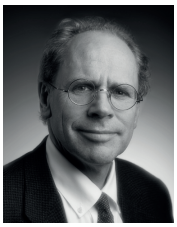
Management

Members of the FoUU Council



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Stellan Hertegård, Adjunct Professor
Eva Munck Wikland, Adjunct Professor
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Claus Bachert, Affiliated Professor
Wolf-Dieter Baumgartner, Affiliated Professor
Stefano Berritini, Affiliated Professor
Antti Mäkitie, Affiliated Professor
Sten Hellström, Senior Professor
Dan Bagger-Sjöbäck, Professor Emeritus
Ulf Rosenhall, Professor Emeritus
Bengt Carlsöö, Professor Emeritus

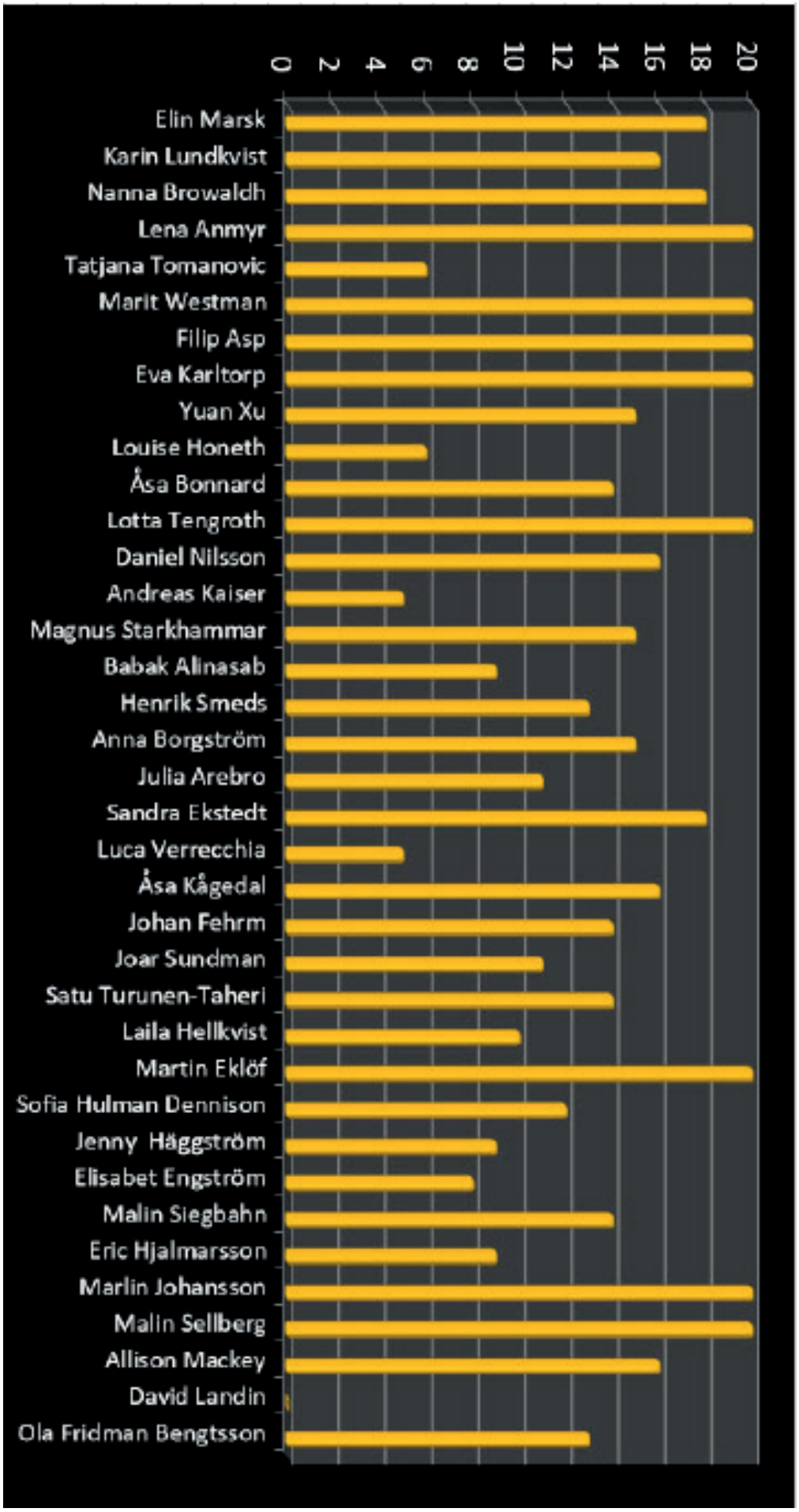
Docents

Erik Berninger
Maoli Duan
Lalle Hammarstedt Nordenvall
Linda Marklund
Riitta Möller
Inger Uhlén

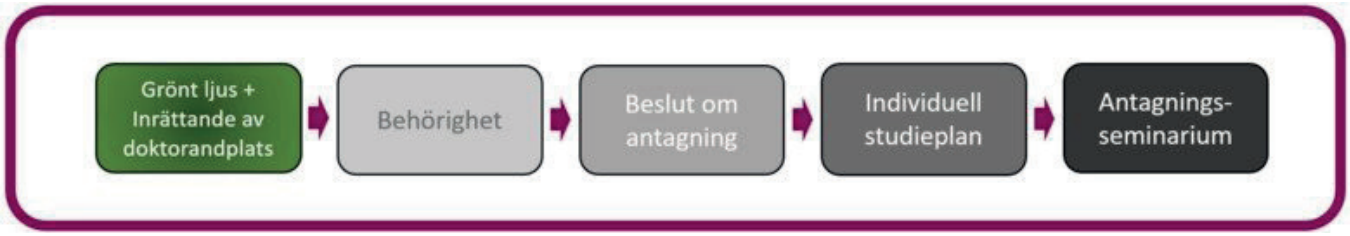
Dissertations / Half time seminars 2020

Date		Name	Title
2020-03-18	Licentiate	Birgitta Tengroth	Hearing in Children with cleft palate
2020-05-20	Dissertation	Karin Jonstam	A personalized approach to chronic rhinosinusitis with nasal polyps, based on biomarkers, phenotypes and new surgical thinking
2020-06-05	Dissertation	Laila Hellkvist	Intralymphatic immunotherapy in allergic rhinitis: Evaluating safety, efficacy and mechanisms
2020-09-11	Half time	Malin Johansson	Children with Congenital Unilateral Sensorineural Hearing Loss: The effect of Auditory Stimulation in the Impaired Ear During Development
2020-09-21	Half time	Allison Mackey	Perspectives on screening strategies for early detection of childhood hearing impairment
2020-10-02	Dissertation	Johan Fehrm	Surgical treatment of obstructive sleep apnea: randomized controlled studies in children and adults
2020-10-09	Half time	Malin Wendt	Optimizing treatment – tumor markers and sclerotherapy in head and neck lesions
2020-10-16	Half time	Malin Sellberg	Students' perceptions of their learning environment and health related quality of life – an interprofessional study
2020-10-16	Dissertation	Martin Eklöf	Effects of age and stimulation strategies on cochlear implantation and a clinically feasible method for sound localization latency
2020-11-13	Dissertation	Joar Sundman	Uvulopalatopharyngoplasty; Patient Selection, Long-Term Outcome and Side Effects
2020-12-11	Half time	David Landin	Clinical Use of Prognostic Markers in Head- and Neck Cancer

Participation at halftime seminars during 2010-10 to 2020-12-31



Admission process at CLINTEC (In Swedish)



Rekrytering:
Alla doktorandplatser vid KI ska utlysas genom annonsering, förutom i de fall då undantag från kravet på utlysning medges https://ki.se/medarbetare/antagning-till-forskarutbildning
Vid inlämnandet av grönt ljus ansökan skall även Appendix 1-3 bifogas och Inrättande av doktorandplats.

Doktorandplatser ska:
- annonseras via KIs rekryteringssystem Varbi med den annonsmall som finns i systemet.
- annonseras under lämplig tidpunkt och ansökningstiden rekommenderas att vara tre veckor eller längre.
- annons ska finnas på svenska och/eller engelska.

Flödesschema där undantag för annonsering föreligger

Steg 1	Beredningsmöte inför antagning	Blankett: Inrättande av doktorandplats Blankett: Finansieringsplan Blankett: Grönt ljus ansökan, Blankett: Appendix 1-3 Lämnas in enligt resp. inlämningsdag med deadline för inlämnandet av ansökan till enhetschef, se schema. Alla dokument lämnas in enkelsidiga! Resp. enhetschef inbjuds som föredragande av ansökan till ett beredningsmöte. Rekommenderar att de sökande går igenom ansökan med sin enhetschef innan mötet. Godkänd/avslagen ansökan meddelas enhetschef för vidarebefordran till den sökande.
Steg 2	Bedömning av behörighet	Efter att steg 1 är avklarad. Får den sökande epost från LADOK-administratören med vidare instruktioner och länk till Varbi, där den blivande doktoranden skall ansökan om behörighet till forskarutbildningen vid KI. Föreligger behörighet skickas ett behörighetsutlåtande via epost till kandidat och handledare, vilket skrivs ut och bifogas ”Beslut om antagning”

Steg 3	Beslut om antagning	Efter att steg 1-2 är klara lämnas nedanstående blanketter med bilagor in till LADOK-administratören inför beslut av studierektorn och prefekt. Blankett: Beslut om antagning till utbildning på forskarnivå
Steg 4	Individuell studieplan	Fr o m 1 februari 2021 lanserades digital individuell studieplan (ISP). Samtliga institutioner ska börja använda digital ISP för doktorander antagna från 1 februari 2021. Huvudhandledare tilldelas behörighet till den digitala ISP via epost från LADOK-administratören. Huvudhandledare skapar här en ny ISP till sin doktorand. Mer information om hur du skapar en ny ISP inkl. manualer finns på KIs hemsida ”Create, write and submit ISP”
Steg 5	Antagningsseminarium	Doktoranden kommer att bjudas till ett antagnings-seminarium vid CLINTEC, tillsammans med sin huvudhandledare, för att presentera sitt projekt under 5 minuter. Presentationen (max 4 bilder utan animeringar (ppt)) skickas till LADOK-administratören senast två dagar innan seminariet. Presentationen skall framföras på engelska. Kommer presentationen att ske via länk (ZOOM) delar doktoranden sin presentation via länken

Vid eventuella frågor, kontakta LADOK-administratören

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Affiliated not presented in this book:
Baumgartner, Wolf-Dieter; Karltorp, Eva; Toll, Karin

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I. Mapping of Sinonasal cancer in Sweden.
Treatment for sinonasal malignancies, like other malignancies includes surgery, radiotherapy and chemotherapy of which surgery is the most central. What combination treatment that is most effective, however, is disputed.
Recent publications of treatment combinations has found that multimodal treatment was superior, as measured by survival. Herein there is a knowledge gap that this project will attempt to address.
The aim of this ongoing project is to both map the incidence, prevalence and relative survival of patients with sinonasal cancer. Different treatment modalities will be compared and evaluated in relation to long term survival and recurrence.

II. Isolated Orbital Floor Fractures – To operate or not to operate.
A significant BOF needs surgical treatment otherwise it may lead to double vision and aesthetic deformities such as sunken eye. It is highly important to differentiate which patients need to be operated on or which do not.
In the on going projects below, we aim to identify which patients with BOF need an operation and which do not require an operation to prevent functional and aesthetic disorders.
1. Controlled randomized studies on patients with BOF with inferior BOF with a herniation > 1mL.
2. Prospective cohort study on isolated medial BOF.

III. Zygomaticomaxillary Complex Fractures: aspects of diagnostic methods, treatment and sequelae
In zygomaticomaxillary Complex fractures, the surgeons' individual training, experience and preference influences the treatment and not systematic evidence, even though earlier studies on surgical treatment have shown that the choice of treatment have an impact on surgical outcome. As the degree and success of the reconstruction of a fractured zygoma is assessed by evaluating the contralateral, non-fractured side, the unfractured zygoma is used as a reference when planning for surgery.

In this ongoing project we aim to:
-Evaluate the long-term results of patients with ZMC fractures.
-Detect correlations between complications and to evaluate the overall management of ZMC fractures.
-To introduce a reliable treatment algorithm based on evidence based medicine.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Samin Rahbin	

Ethical permit No.

2009/331-31	2018/302-31	2019-04287-1		

Publications 2017, 2018, 2019, 2020

1. Loss of Malar Bags in Lower Eyelid In Orbital Blow Out Fracture Reconstruction Following Pre- or Retro-septal Transconjunctival Incision. Craniomaxillofacial Trauma Reconstruction. J Craniofac Surg. 2019. Accepted.
2. New Algorithm for Management of Orbital Blow Out Fracture Based on Prospective Study. Babak Alinasab, Karl-Johan Borstedt, Rebecka Rudström, Michael Ryott, Abdul Rashid Qureshi, Mats O. Beckman, Pär Stjärne. Craniomaxillofac Trauma Reconstr. 2018 Dec;11(4):285-295. doi: 10.1055/s-0038-1641714. Epub 2018 May 1.
3. Prospective Randomized Controlled Pilot Study on Orbital Blow out Fracture. Babak Alinasab, Karl-Johan Borstedt, Rebecka Rudström, Michael Ryott, Abdul Rashid Qureshi, Pär Stjärne. Craniomaxillofac Trauma Reconstr. 2018 Sep;11(3):165-171.
4. Supra Blepharoplasty Approach for Correcting Fractures of Frontal Bone Fracture. Babak Alinasab, Ola Fridman Bengtsson, Pär Stjärne. J Craniofac Surg. 2018 Oct;29(7):1906-1909.
5. Prospective study on ocular motility limitation due to orbital muscle entrapment or impingement associated with orbital wall fracture. Alinasab B, Qureshi AR, Stjärne P. Injury. 2017 Jul;48(7):1408-1416.

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Word makes difference

I am involved in clinically related projects concerning children with cochlear implant:
”Words make a difference” is a population-based Swedish research program, with international partners. The aim of the program is to explore how different environmental factors like early listening- and spoken language stimulation is associated to early language development and psychosocial wellbeing. This is examined in different sociocultural and linguistic contexts, in young children with hearing impairment (HI) and compared to age-matched controls with normal hearing (NH). Ulrika Löfkvist is in charge of the studies.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2015/992-31				

Publications 2017, 2018, 2019, 2020

1. Smeds H, Wales J, Asp F, Löfkvist U, Falahat B, Anderlid B-M, Anmyr L, Karltorp E. X-linked Malformation and Cochlear Implantation Otology & neurotology (2017), Vol.38 (1), p.38-46
2. Löfkvist U, Anmyr L, Henricson C, Karltorp Eva. Executive Funnctions, Pragmatic Skills, and Mental Health in Children With Congenital Cytomegalovirus (CMV) Infection With Cochlear Implants: A Pilot Study Frontiers in psychology (2019) Vol.10, p.2808-2808
3. Wass M, Anmyr L, Lyxell B, Östlund E, Karltorp E, Löfkvist U. Predictors of Reading Comprehension in Children With Cochlear Implants Frontiers in psychology (2019) Vol.10, p.2155-2155
4. Wass M, Löfkvist U, Anmyr L, Karltorp E, Östlund E, Lyxell B. Correlates of Orthographic Learning in Swedish Children With Cochlear Implants Frontiers in psychology, 2019, Vol.10, p.143-143

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Immunology in airway inflammation and head and neck cancer and biomarkers in OSCC

It is well accepted that immunological imbalance is one of the most important aspects behind CRSwNP, allergic rhinitis, COPD and asthma. In addition, this imbalance drives these diseases. Today, it is also broadly accepted that immunological imbalance is a key factor in head and neck tumors as well as other forms of cancer disease. We aim to detect how neutrophils and epithelial cells through a different receptor pattern can participate in the origin and development of airway inflammation and head and neck cancer. Our findings enable new therapeutic possibilities for these diseases.
Oral squamous cell carcinoma (OSCC) remains an under-studied and significant global cancer killer; dismal survival rates (~50% over 5 years) have not changed in decades. Lymph node metastasis makes the prognosis even poorer but is not always detected at clinical examination or through radiology. We aim to detect biomarkers for lymph node metastasis in this disease to improve the treatment for the single patient.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

H15-02913 (UBC REB)				

Publications 2017, 2018, 2019, 2020

1. Arebro J, Palmgren B. Postsurgical pyoderma gangrenosum and flap necrosis in a head and neck cancer patient following neck dissection. Clin Case Rep. 2020 Apr 8;8(7):1121-1125.
2. Khan A, Huynh TMT, Vandeplas G, Joish VN, Mannent LP, Tomassen P, van Zele T, Cardell LO, Arebro J, Olze H, Forster-Ruhrmann U, Kowalski ML, Olszewska-Ziaber A, Fokkens W, van Drunen C, Mullol J, Alobid I, Hellings PW, Hox V, Toskala E, Scadding G, Lund V, Bachert C. The GALEN rhinosinusitis cohort: chronic rhinosinusitis with nasal polyps affects health-related quality of life. Rhinology. 2019 Oct 1;57(5):343-351.
3. Arebro J, Drakskog C, Winqvist O, Bachert C, Kumlien Georén S, Cardell LO. Subsetting reveals CD16high CD62Ldim neutrophils in chronic rhinosinusitis with nasal polyps. Allergy. 2019 May 22. doi: 10.1111/all.13919. [Epub ahead of print] No abstract available.
4. Khan A, Vandeplas G, Huynh TMT, Joish VN, Mannent L, Tomassen P, Van Zele T, Cardell LO, Arebro J, Olze H, Foerster-Ruhrmann U, Kowalski ML, Olszewska-Ziaber A, Holtappels G, De Ruyck N, van Drunen C, Mullol J, Hellings PW, Hox V, Toskala E, Scadding G, Lund VJ, Fokkens WJ, Bachert C. The Global Allergy and Asthma European Network (GALEN rhino-sinusitis cohort: a large European cross-sectional study of chronic rhinosinusitis patients with and without nasal polyps. Rhinology. 2019 Feb 1;57(1):32-42. doi: 10.4193/Rhin17.255.
5. Tengroth L, Arebro J, Larsson O, Bachert C, Georén SK, Cardell LO. Activation of Activin receptor-like kinases curbs mucosal inflammation and proliferation in chronic rhinosinusitis with nasal polyps. Sci Rep. 2018 Jan 24;8(1):1561. doi: 10.1038/s41598-018-19955-1.
6. Arebro J, Ekstedt S, Hjalmarsson E, Winqvist O, Kumlien Georén S, Cardell LO. A possible role for neutrophils in allergic rhinitis revealed after cellular subclassification. Sci Rep. 2017 Mar 8;7:43568. doi: 10.1038/srep43568.

Filip Asp
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Spatial Hearing - Effects of Hearing Loss and intervention

The ability to hear out a voice in a background of spatially separate competing voices, and localize sounds--e.g. spatial hearing--is fundamental to human communication. It relies to a large extent on hearing with both ears (binaural hearing). Hearing loss may have a negative effect on spatial hearing abilities, also in mild cases, for example unilateral hearing loss. We study the effects of hearing loss and various interventions (e.g. auditory implants) on spatial hearing from as early as 6 months of age, using rapid and objective techniques. One such technique measures latency and accuracy of eye-movements towards auditory events, as an index of horizontal sound localization accuracy. Horizontal sound localization is an ideal ability for the study of deficits in binaural hearing, since high accuracy is dependent on precise temporal processing of acoustic signals. The ultimate goal is to alleviate the negative impact of hearing impairment, and increase our understanding of how impaired spatial hearing affects humans, specifically during critial periods of development.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Fatima Moumèn Denanto	Marlin Johansson
	Malin Siegbahn

Ethical permit No.

2016/414-16 (Gothenburg)	2015/1878-31/2	2013/4:2	2013/2248-3	2019-04696

Publications 2017, 2018, 2019, 2020

1. Smeds H, Wales J, Asp F, Lofkvist U, Falahat B, Anderlid B. M, Anmyr L, Karltorp E. 2017. X-linked Malformation and Cochlear Implantation. Otol Neurotol 38: 38-46
2. Asp, F., Jakobsson, A.M., Berninger, E. 2018. The effect of simulated unilateral hearing loss on horizontal sound localization accuracy and recognition of speech in spatially separate competing speech. Hearing research 357, 54-63.
3. Asp, F. and S. Reinfeldt, Horizontal sound localisation accuracy in individuals with conductive hearing loss: effect of the bone conduction implant. Int J Audiol, 2018: p. 1-8.
4. Johansson, M., Asp, F., Berninger, E. 2019. Children With Congenital Unilateral Sensorineural Hearing Loss: Effects of Late Hearing Aid Amplification—A Pilot Study, Ear Hear, Early Online
5. Asp, F. and S. Reinfeldt, Effects of Simulated and Profound Unilateral Sensorineural Hearing Loss on Recognition of Speech in Competing Speech. Ear Hear, 2019.
6. Karltorp, E., Eklöf, M., Östlund, E., Asp, F., Tideholm, B., Löfkvist, U. 2019. Cochlear implants before 9 months of age led to more natural spoken language development without increased surgical risks. Acta Pediatrica.
7. Videhult Pierre, P., Eklöf, M., Smeds, H., Asp., F. 2019. Cochlear Implantation with the CI512 and CI532 Precurved Electrode Arrays: One-Year Speech Recognition and Intraoperative Thresholds of Electrically Evoked Compound Action Potentials. Audiol Neurootol. 24(6):299-308
8. Rigato, C., Reinfeldt, S., Asp, F. 2020. The effect of an active transcutaneous bone conduction device on spatial release from masking. Int J Audiol. 59(5):348-359.
9. Eklöf, M., Asp, F., Berninger, E. 2020. Sound localization latency in normal hearing and simulated unilateral hearing loss. Hear Res, 15;395:108011

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A personalized treatment approach to CRSwNP

Chronic rhinosinusitis (CRS) is a prevalent disease causing a substantial burden for the patient and the society. CRS is divided into CRS with (CRSwNP) and without nasal polyps (CRSsNP). Based on current knowledge on inflammatory markers, CRS can be further divided into endotypes, with CRSsNP mainly being characterized by a neutrophilic type 1 inflammatory response and CRSwNP being characterized by an eosinophilic type 2 inflammation. With the increase of type 2 inflammation in CRSwNP patients, asthma comorbidity and relapse of disease becomes more frequent. In recent years, monoclonal antibodies (mAbs) directed towards the type 2 inflammatory response have been demonstrated to be efficacious in CRSwNP.

We first focus on biomarkers and clinical characteristics to identify type 2 CRSwNP. Serum periostin can, together with serum IgE and Staphylococcus aureus enterotoxin (SE)-IgE, identify formation of IL-5 and SE-IgE in nasal polyp tissue with a reasonable sensitivity and specificity. Eosinophilic blood count correlates poorly with inflammatory markers in nasal polyp tissue, but can, together with clinical history of asthma, allergy and/or aspirin exacerbated respiratory disease, help identify most type 2 CRSwNP patients in a clinical setting. Furthermore, we show that a shift towards an increase in type 2 inflammation is seen in CRS over recent years in Central Europe, measurable both as an increase in inflammatory markers and as a shift of endotype.

We then focus on novel treatment strategies. Treatment with dupilumab, a mAb directed to the IL-4 Receptor a, reduces local type 2 inflammatory parameters in nasal secretions and nasal polyp tissue. Also Reboot surgery, removing the mucosal lining from the sinuses, yielded a better result vs. conventional surgery and reduces type 2 inflammatory markers in nasal secretions, 12 months after surgery, in the same magnitude as dupilumab.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2017, 2018, 2019, 2020

1. Gevaert E, Zhang N, Krysko O, Lan F, Holtappels G, De Ruyck N, Nauwynck H, Yousefi S, Simon HU, Bachert C. Extracellular eosinophilic traps in association with Staphylococcus aureus at the site of epithelial barrier defects in severe airway inflammation. J Allergy Clin Immunol. 2017 Jun;139(6):1849-1860
2. Bachert C, Sousa AR, Lund VJ, Scadding GK, Gevaert P, Nasser S, Durham SR, Cornet ME, Kariyawasam HH, Gilbert H, Austin D, Maxwell AC, Marshall RP, Fokkens WJ. Reduced need for surgery in severe nasal polyposis with mepolizumab: a randomised trial. J Allergy Clin Immunol. 2017 Oct;140(4):1024-1031.e14. doi: 10.1016/j.jaci.2017.05.044.
3. Sørensen M, Klingenberg C, Wickman M, Sollid J, Furberg AS, Bachert C, Bousquet C. Staphylococcus aureus enterotoxin-sensitization is associated with allergic poly-sensitization and allergic multimorbidity in adolescents. Allergy 2017 Apr 5. doi: 10.1111/all.13175
4. Bachert C, Gevaert P, Hellings P. Biotherapeutics in chronic rhinosinusitis with and without nasal polyps. J Allergy Clin Immunol in Pract. 2017 May 16. pii: S2213-2198(17)30321-5
5. Teufelberger AR, M. Nordengrün, H. Braun, T. Maes, K. de Grove, G. Holtappels, C. O'Brien, S. Provoost, H. Hammad, A. Gonçalves, R. Beyaert, W. Declercq, P. Vandenabeele, D.V. Krysko, B.M. Bröker, C. Bachert and O. Krysko. The IL-33/ST2 axis is crucial in type 2 airway responses induced by the S. aureus protease SplD. J Allergy Clin Immunol. 2018 Feb;141(2):549-559

6. Jonstam K, Westman M, Holtappels G, Holweg CTJ, Bachert C. Serum periostin, IgE and SE-IgE can be used as biomarkers to identify moderate to severe chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2017 Sep 1. pii: S0091-6749(17)31352-0. doi: 10.1016/j.jaci.2017.07.031 (Letter)
7. Bachert C, Holtappels G, Merabishvili M, Meyer T Murr A, Zhang N, Van Crombruggen K, Gevaert E, Völker U, Bröker BM, Vaneechoutte M Schmidt F. Staphylococcus aureus controls interleukin-5 release in upper airway inflammation possibly via secreted proteins.
8. J Proteomics. 2018 May 30;180:53-60
9. Calus L, Derycke L, Dullaers M, Van Zele T, De Ruyck N, Pérez-Novo C, Holtappels G, De Vos G, Lambrecht BN, Bachert C, Gevaert P. IL-21 Is Increased in Nasal Polyposis and after Stimulation with Staphylococcus aureus Enterotoxin B. Int Arch Allergy Immunol. 2017 Nov 9. doi: 10.1159/000481435
10. Tengroth L, Arebro J, Larsson O, Bachert C, Georén SK, Cardell LO. Activation of Activin receptor-like kinases curbs mucosal inflammation and proliferation in chronic rhinosinusitis with nasal polyps. Sci Rep. 2018 Jan 24;8(1):1561
11. Bachert C, Zhang N, Hellings PW, Bousquet J. Endotype-driven care pathways in patients with chronic rhinosinusitis. J Allergy Clin Immunol. 2018; 141(5):1543-1551
12. Lan F, Zhang N, Holtappels G, Ruyck N, Krysko O, Crombruggen KV, Braun H, Johnston SL, Papadopoulos NG, Zhang L, Bachert C. Staphylococcus aureus Induces Mucosal Type 2 Immune Response via Epithelial Cell Derived Cytokines. Am J Respir Crit Care Med. 2018; 198(4):452-463
13. Potaczek DP, Unger SD, Zhang N, Taka S, Michel S, Akdağ N, Lan F, Helfer M, Hudemann C, Eickmann M, Skevaki C, Megremis S, Sadewasser A, Alashkar Alhamwe B, Alhamdan F, Akdis M, Edwards MR, Johnston SL, Akdis CA, Becker S, Bachert C, Papadopoulos NG, Garn H, Renz H. Development and characterization of DNAzyme candidates demonstrating significant efficiency against human rhinoviruses. J Allergy Clin Immunol. 2018 Aug 13. pii: S0091-6749(18)31139-4. doi: 10.1016/j.jaci.2018.07.026
14. Kim YC, Won HK, Lee JW, Sohn KH, Kim MH, Kim TB, Chang YS, Lee BJ, Cho SH, Bachert C, Song WJ. Staphylococcus aureus nasal colonization and asthma in adults: systematic review and meta-analysis. J Allergy Clin Immunol Pract. 2018 Sep 4. pii: S2213-2198(18)30556-7. doi: 10.1016/j.jaip.2018.08.020.
15. Lan F, H Zhong, N Zhang, SL. Johnston, W Wen, N Papadopoulos, L Zhang, C Bachert. Interferon-lambda1 enhances Staphylococcus aureus clearance in healthy nasal mucosa, not in nasal polyps. J Allergy Clin Immunol. 2018 Nov 30. pii: S0091-6749(18)31719-6
16. Van Crombruggen K, Taveirne S, Holtappels G, Leclercq G, Bachert C. Innate lymphoid cells in the upper airways; importance of CD117 and IL-1RI expression. Eur Respir J 2018 Dec 6;52(6)
17. Alsharif S, Jonstam K, van Zele T, Gevaert P, Holtappels G, Bachert C. Endoscopic Sinus Surgery for Type-2 CRSwNP: an Endotype-Based Retrospective Study. Laryngoscope 2019; 129:1286–1292
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ENT-cancer

On going projects:

- Retrospective study on the prevalence of cystic metastasis in patients who had undegone surgery for lateral branchial cleft cyst at Karolinska between 2003-2019.
- Prospective study: Use of ancor in extirpation of non-palpable lymphnodes and cysts in the neck.
- The risk for regional metastasis in patients with gingival cancer (n=215) in realation to tumor size, localization (maxilla/mandible), T-class and histopathology.
- PILGRIM-Microbiota study of head- and neck cancer patients with prophylactic intravenous antibiotics during/after surgery.

Future project:

- Prospective study: Can HPV be used as a predictor in differentiating between cystic metastasis and lateral branchial cleft cyst?

Sex hormones & hearing

- Longitudinal prospective study of the hearing in women with breast cancer treated with anti-Estrogens.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2017, 2018, 2019, 2020

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Digital Twins for personalised medicine

One greatest health care problems today is that many patients do not respond to drug treatment. This reflects the complexity of the human body, which consists of trillions of cells, each of which may express thousands of genes, in different combinations, at different time points, before and during disease. There is a wide gap between this complexity and modern health care. The Swedish Digital Twin Consortium (sdtc.se) proposes that this gap can be bridged by digital twins of individual patients. Each twin will be computationally treated (computreated) with thousands of drugs, in order to find the best treatment for the patient The twins are constructed and treated by applying network tools and artificial intelligence (AI) to single cell RNA-seq (scRNA-seq) and clinical data from each patient. We have shown clinical feasibility by treating a mouse model of arthritis, and diagnostic studies of multiple diseases (all references are found in sdtc.se). In January this year Nature Medicine published a case report of scRNA-guided treatment of a patient that did not respond to conventional treatment. However, that treatment was based on empirical analyses of the data. By contrast, our digital twin strategy is based on systematic prioritization of drugs and computreatment of the twins with those drugs, before actually treating individual patients. We are now planning to show clinical feasibility by treating individual patients. The ultimate aim is that each healthy individual should have her/his digital twin for predictive, preventive, personalised and participatory medicine.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2017, 2018, 2019, 2020

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12. Shalek AK, Benson M. Single-cell RNA-sequencing to tailor treatments. Science Transl Med 2017 ep 20;9(408)

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Hearing impairment in newborns. New objective technologies and intervention strategies during a sensitive period of development to improve subsequent communication

Our research project aims at very early diagnosis and intervention to reduce or reverse disability and thus improve the communication capacity of the hearing-impaired child. The long-term goal is to find the causes and mechanisms behind various nonsyndromic congenital sensorineural hearing losses (SNHL) and to develop future treatment options. The main research directions are:

A. Causes and mechanisms behind nonsyndromic congenital SNHL
B. Impact of early intervention during a critical period of development
C. Sound localization as a clinical tool
D. Rapid and objective ABR technique for newborns and infants

Overall aims of the research directions are: A.) To identify and precisely diagnose various forms of congenital SNHL, as determined at the level of specific anatomical structures down to the molecular level. To identify and develop future treatment options on the basis of highly specific diagnoses, as determined at birth. B.) To study the impact of relevant auditory stimulation during a sensitive period of development, and to identify the extent of that period. C.) To study the relationship between behavioural development and maturation of the central auditory pathways and the physiology of binaural interaction at the brainstem level. Development of a new rapid noninvasive and objective test for e.g. central auditory processing dysfunction from 6 months of age. Evaluation of various intervention/care strategies. D.) To develop a rapid, valid, and reliable electrophysiological technique applicable in newborns and infants for diagnostics and as a basis for fine-tuning of e.g. nonlinear hearing aids.

Part of the studies will be supervised by PhD Filip Asp and Senior Professor Sten Hellström. All the studies will be performed at the recently established Scientific Center for Advanced Pediatric Audiology (SCAPA), Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Marlin Johansson	

Ethical permit No.

2012/494-31/1; 2018/1500-31	2014/1162-31/1; 2015/1878-21/2	2012/189-31/3; 2013/2248-3	2013/104-31/4; 2017/293-31/4	2008/1961-31; 2019-03826

Publications 2017, 2018, 2019, 2020

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Ear research in collaboration with Karolinska

A research collaboration is established between Karolinska Institutet and University of Pisa in the area of audiology and otology, focusing on deafness in adults and children and on the cochlear implant procedure. Regarding cochlear implant procedure the joint research regards various aspects, such as cochlear implantation in malformed cochleas and cochlear implant outcome in bilingual children. One conducted research project focus on Language Environmental Analysis (LENA), an advanced technique to record a child´s listening and language environment, with the aim to correlate it to language development both in normal hearing and deaf children.

Publications 2017, 2018, 2019, 2020

1. I. Nacci A, Macerata A, Bastiani L, Paludetti G, Galli J, Marchese MR, Barillari MR, Barillari U, Laschi C, Cianchetti M, Manti M, Berrettini S, Faltori B, Ursino F. Evaluation of the electroglottographic signal variability in organic and functional dysphonia. J Voice, 2020, on line ahead of publication.
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3. Forli F, Lazzerini F, Paletta G, Bruschini L, Berrettini S. Enlaged vestibular aqueduct and Mondini malformation: Audiologocal, clinical, radiologic and genetic features. Eur Arch Otorhinolaryngol, 2020, on line ahead of print
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5. Nacci A, Romeo SO, Cavaliere MD, Macerata A, Bastiani L, Palude G, Galli J, Marchese MR, Barillari MR, Barillari U, Berrettini S, Laschi C, Cianche M, Manti M, Ursino F, Fattori B. Comparison of electroglottographic variability index in euphonic and pathological voice. Acta Otorhinolaryngol Ital. 2019; 31.
6. Forli F, Giuntini G, Ciabo A, Bruschini L, Löfkvist U, Berrettini S. How does a bilingual environment affect the results in children with cochlear implants compared to monolingual-matched children? An Italian follow-up study. Int J Pediatr Oto- r- hinolaryngol. 2018 ;105:56-62.
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Cholesteatoma in Sweden and Results from the Swedish Quality Registry of Myringoplasty and Ossiculoplasty

1. Surgery for Cholesteatoma is a quite common ear procedure. The disease is accompanied with risks for severe side effects as meningitis, intracranial abscess, sinus thrombosis, hearing loss, facial palsy and dizziness if not treated but the surgical procedure also have side effects due to the need for extensive surgery to eradicate the disease.
In this nationwide study, the Swedish Patient Registry will be used to map cholesteatoma surgery in Sweden in regard to incidence and prevalence, risks with surgery, factors increasing risk for disease and multiple surgery. A combination with the Swedish Patient Registry and The Swedish Multiple Generation Register will be used to identify the frequency of familiar cholesteatoma. This sub study will be followed by a genetic study regarding families in Stockholm County with multiple family members with cholesteatoma. A long with this, a regional follow-up study will be performed in regard to hearing, balance and quality of life after cholestatoma surgery.

2. The Swedish Quality Registry of Myringoplasty and Ossiculoplasty is a nationwide registry collecting pre- and postoperative data in regard to ear surgery with the aim to heal a perforated ear drum or restore the conductive chain in the ear. Several papers based on this registry has been published showing the outcome of Myringoplasty and the risk for complications regarding tinnitus and taste disturbances related to surgery. New studies regarding the hearing results, patient satisfaction and complications after Ossiculoplasty are ongoing.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Sara Olaison, Örebro Universitetssjukhus Kvalitetsregisterkopplat projekt om ossikuloplastik

Ethical permit No.

2019-05190	2020-05935, pending	2014/2203-31/4		

Publications 2017, 2018, 2019, 2020

1. Bonnard Å, Hederstierna C, Bark R, Hultcrantz M. Audiometric features in young adults with Turner syndrome. Int J Audiol. 2017 Sep;56(9):650-656. doi: 10.1080/14992027.2017.1314559. Epub 2017 Apr 19.
2. Bonnard Å, Bark R, Hederstierna C. Clinical update on sensorineural hearing loss in Turner syndrome and the X-chromosome. Am J Med Genet C Semin Med Genet. 2019 Mar;181(1):18-24. doi: 10.1002/ajmg.c.31673. Epub 2019 Jan 10. Review. PMI: 30632288
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Evaluation and surgical treatment of children with tonsil hypertrophy and sleep disordered breathing

Research in the field of pediatric obstructive sleep apnea,with evaluation of diagnostic tools and of surgical treatment. The focus has been on tonsil surgery and a randomized clinical trial comparing tonsillectomy and tonsillotomy in children with OSA. Data for long-term follow-up from this trial are now being collected.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Isabella Sjölander

Ethical permit No.

Publications 2017, 2018, 2019, 2020

1. Borgström A, Nerfeldt P, Friberg D, Sunnergren O, Stalfors J; Trends and changes in pediatric tonsil surgery in Sweden 1987-2013: a population-based cohort study; BMJ Open, 2017 doi: 10.1136/bmjopen-2016-013346
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3. Borgström A, Nerfeldt P, Friberg D; Postoperative pain and bleeding after adenotonsillectomy vs adenotonsillotomy in pediatric obstructive sleep apnea: an RCT; European Archives of Oto-Rhino-Laryngology, 2019 Aug (3), 1-8
4. Sjölander I, Borgström A, Larsson JO, Smedje H, Friberg D.Sjölander I, et al. Randomised trial showed no difference in behavioural symptoms between surgical methods treating paediatric obstructive sleep apnoea. Acta Paediatr. 2020 Oct;109(10):2099-2104. doi: 10.1111/apa.15210. Epub 2020 Mar 6

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Effects on Cardiovascular Parameters in Children with Severe Obstructive Sleep Apnea before and after Adenotonsillectomy

Obstructive sleep apnea (OSA) is a common disorder and recognized as a significant cause of morbidity in children. The intermittent episodes of airway obstruction and desaturations may result in changes within the autonomic nervous system, which results in significant changes in the cardiovascular system.

In this study we will investigate cardiovascular sequelae of severe OSA in children (for example changes in heart rate, blood pressure, and cardiac morphology by echocardiography) and changes before and after treatment with adenotonsillectomy (removal of the tonsils and adenoid).

The children in the study will be 2-5 years of age with apneahypopnea index >19.9 and tonsil size 2-4.

1. Substudy 1 is a descriptive study with 25 patients with polysomnography before and after adenotonsillectomy. In connection to the polysomnography the patients will also undergo echocardiography and blood pressure measurment (24-h ambulatory blood pressure monitoring, or in some cases office (in house) blood pressure monitoring for 3-4 hours).
2. Substudy 2 is a randomised controlled study with 60-80 patients. The patients will be randomised to either adenotonsillectomy within 1-2 weeks or delayed surgery/expectancy for 4 weeks. As in substudy 1, the children will undergo echocardiography and blood pressure measurement in connection to the polysomnography pre- and postoperatively.

Primary outcome in both studies: change in blood pressure.
Secondary outcomes in both studies: changes in cardiac funtions and structures.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2017, 2018, 2019, 2020

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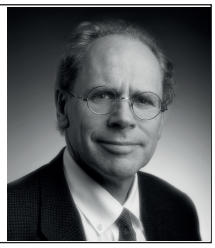

Neutrophils, T- and B-cells in the development and progression of allergic airway and head and neck squamous cell cancer inflammation

Research in allergy immunotherapy and cancer immunology have shown that the tolerance development that takes place in both diseases, involves the same type of immune cells. It is also evident that it is dysregulation and dysfunction in these pathways that causes a significant part of the disease burden in both allergy and cancer. To simplify, these diseases represent two opposite poles in a tolerance spectrum. In allergy, the immune system over-reacts causing a continues on-going local inflammation, whereas in cancer the natural defence mechanisms are circumvented and turned down in order to let malignantly transformed cells roam free and unhindered. Hence, the modern concept of treatment in both allergy and cancer aims at eradicating these illnesses by inducing permanent local tolerance in the former and by breaking the local tolerance in the latter. Notably, this can be achieved in both situations by affecting various types of T-cells. The role of B-cells is well established in similar way in allergy, whereas their role in cancer is far less researched. Furthermore, there is a long-standing notion that neutrophils play a notable role in cancer immunology (even though exactly how remains to be elucidated), whereas the potential role of these cells in allergy has been hidden behind a towering interest for the eosinophils.

The overall goal is to investigate the role of neutrophils, T-cells and B-cells in the development and progress of allergic airway inflammation and head and neck squamous cell cancer with special reference to immunological events taking place in lymph nodes.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Magnus Starkhammar	
Eric Hjalmarsson	
Krzysztof Piersiala	
Aeneas Kolev	
Carl Skröder	

Ethical permit No.

2019_03518	2017/1863-31/2	2018/697-31	2017/1791-31/2	2016/822-31/2	

Publications 2017, 2018, 2019, 2020

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Hearing loss and vestibular disorders

Hearing loss and vestibular disorders are two of the common diseases in the society which affect both children and adults. We have two sub-projects in the field:

1. Vestibular disorders projects include PhD students, Niki Karpeta and Med dr Luca Verrecchia focusing on:
   a. Testing the diagnostic ability of VEMP in different clinical contests such as vestibularis neuronitis and middle ear disorders
   b. Exploring the differential diagnostic accuracy of VEMP for SSCD when compared with other clinical conditions.
   c. early diagnosis of young children with vestibular disorder
   d. Exploring the diagnostic accuracy of VEMP for SSCD modifying the parameters of stimulation, the conduction of the test or the recording of the responses.
   e. Permeability of the round window membrane to aminoglicosides and corticosteroids differ between normal and hydropic ears (animal study-Med dr Pedro Marques-University of Porto Medical School, Porto, Portugal)?
2. Hearing impairment (HI) in newborns – The importantce of early diagnosis and early intervention. This project will focus on:
   a. To develop new objective diagnostic methods for determination of hearing thresholds, to characterize the dyna- mic range in young infants, and to assess whether the origin of the hearing loss is cochlear, neural or conductive.
   b. To establish evidence for the advantage of very early intervention with hearing aids before the age of 2-3 months and cochlear implants (before the age of 9 months) with regard to development of the central auditory pathways, and speech and language evaluated by objective electrophysiological, psychoacoustic and behavioral scientific methods.
   c. To identify and study predictors for early onset and progressive hearing impairments. Through continuous studies and analyses of the regional (Stockholm County Council) quality data bases Audioscreen and Audiohab the efficacy, sensitivity and specificity of the universal newborn hearing screening (UNHS

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Niki Karpeta	Anna-Karin Strömberg

Ethical permit No.

2013/1177-31	2015/1296-31/2			

Publications 2017, 2018, 2019, 2020

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Hereditary hemorrhagic telangiectasia, HHT, in Sweden- a registerbased study about mortality, morbidity, prevalence and treatment

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

The application currently processed by the local ethics comitte				

Publications 2017, 2018, 2019, 2020

1. Control of allergic rhinitis with MP-AzeFlu: a noninterventional study of a Swedish cohort. Stjarne P, Strand V, Theman K, Ehnhage A. Rhinology. 2019 Apr 2. [Epub ahead of print] PMID: 30938376.

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Optimizing use of sentinel node technique in head and neck cancer.

Head and neck cancer treatment is associated with difficult side-effects. The treatment and prevention of regional metastasis and recurrences is not always successful. The use sentinel node technique for head and neck cancers is increasing both as an investigation tool to find micro-metastasis and single tumour cells but also as a treatment to avoid more extensive surgery.

In our projects we intend to analyse the use of sentinel node technique to optimize and individualize the treatment of head and neck cancers, also for cases where sentinel node is not yet standard treatment.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2019-03518				

Publications 2017, 2018, 2019, 2020

1. "Stathmin and epidermal growth factor receptor (EGFR) expression in sinonasal inverted papillomas (IP) and it's correla on to human papillomavirus (HPV) status and clinical outcome" , https://www.researchgate.net/journal/0300-0729_Rhinology
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Assessment and activation of tympanic membrane progenitor/stem cells - clinical and laboratory studies

With this project we aim to increase knowledge about the normal healing process and to improve the treatment of tympanic membrane perforations with the ultimate goal to design a simple, out-patient procedure without the need for advanced surgery.
In laboratory studies we will identify stem cells and proliferative zones in normal human tympanic membranes as well as in tympanic membranes that has been mechanically and chemically injured. The goal is to better understand the healing mechanism of the tympanic membrane.
Plasminogen is an endogenous protein and has a role in cell migration and wound healing and has been identified as a possible drug for medical treatment of chronical tympanic membrane perforation. In a clinical trial different doses of plasminogen are injected close to the tympanic membrane in the ear canal in patients with chronic perforations and the effect on healing of the ear drum is evaluated.

Development of central auditory pathways in patients with unilateral conductive hearing loss and effects of early intervention

The main purpose of this project is to evaluate the effect on the brain in individuals with unilateral canal atresia, which is when a child is born without a developed hearing canal causing a severe conductive hearing loss. Children with hearing habilitation and untreated adults will be included in the study. An animal model will also be used for longitudinal studies to achieve information about when to expect changes in the auditory pathways of the brain. Methods used in the project are different types of audiometric testing including corneal reflection eye-tracking (a new method for evaluation of sound localization), questionnaires, diffusion MRI and resting state functional MRI.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Elnaz Sepehri	Hanna Josefsson
Malin Siegbahn	

Ethical permit No.

2018/364	2017/2011-31	2012/1661-31/3	N191/14	N113/15

Publications 2017, 2018, 2019, 2020

1. Cortés Fuentes IA, Pierre PV, Berglin CE. Improving Clinical Outcomes in Cochlear Implantation Using Glucocorticoid Therapy: A Review. Ear Hear. Jan/Feb 2020;41(1):17-24.
2. Counter SA, Nikkhou-Aski S, Damberg P, Berglin CE, Laurell G. Ultra-high-field (9.4 T) MRI Analysis of Contrast Agent Transport Across the Blood-Perilymph Barrier and Intrastrial Fluid-Blood Barrier in the Mouse Inner Ear. Otol Neurotol. 2017 Aug;38(7):1052-1059

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Surgical Treatment of Obstructive Sleep Apnea - Randomized Controlled Studies in Children and Adults

Obstructive sleep apnea (OSA) is a common disorder in both children and adults. Surgery is the primary treatment for children and an alternative for adults in selected cases.

This project consists of three RCTs and aims to evaluate:
- If surgery (uvulopalatopharyngoplasty) decreases blood pressure in adult patients with OSA.
- If adenotonsillectomy (ATE, the primary surgical treatment for pediatric OSA) is more effective than no treatment for young children with mild to moderate OSA.
- If a modified ATE is more effective for treating children with severe OSA.

Results from the project shows that:
- Surgery decreases blood pressure in adult patients with OSA.
- ATE is more effective in improving quality of life but not objective respiratory parameters in children with mild to moderate OSA
- Modified ATE is not more effective to treat children with severe OSA.

Future studies include:
- Long-term follow-ups
- Analyses of tonsillar tissue to better understand the etiology of tonsillar growth
- The effect on other cardiovascular endpoints (eg. blood lipids and systemic inflammatory markers) after surgery in adults

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2007/449-31/3	Ö21-2007	2014/1000-31/1		

Publications 2017, 2018, 2019, 2020

1. Fehrm J, Friberg D, Bring J, Browaldh N. Blood pressure after modified uvulopalatopharyngoplasty: results from the SKUP 3 randomized controlled trial. Sleep Med. 2017;34:156-161.
2. Fehrm J, Nerfeldt P, Sundman J, Friberg D. Adenopharyngoplasty vs adenotonsillectomy in children with severe obstructive sleep apnea a randomized clinical trial. JAMA Otolaryngol - Head Neck Surg. 2018;144(7):580-586.
3. Sundman J, Fehrm J, Friberg D. Low inter-examiner agreement of the Friedman staging system indicating limited value in patient selection. Eur Arch Oto-Rhino-Laryngology. 2018;275(6):1541-1545.
4. Fehrm J, Nerfeldt P, Browaldh N, Friberg D. Effectiveness of Adenotonsillectomy vs Watchful Waiting in Young Children with Mild to Moderate Obstructive Sleep Apnea: A Randomized Clinical Trial. JAMA Otolaryngol - Head Neck Surg. 2020;146(7):647-654.
5. Fehrm J, Borgström A, Nerfeldt P, Friberg D. Postoperative morbidity after adenotonsillectomy versus adenopharyngoplasty in young children with obstructive sleep apnea: an RCT. Eur Arch Oto-Rhino-Laryngology. May 2020:1-
6. Sundman J, Browaldh N, Fehrm J, Friberg D. Eight-Year Follow-up of Modified Uvulopalatopharyngoplasty in Patients With Obstructive Sleep Apnea. Laryngoscope. 2021;131(1):E307-E313.

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Hearing and Cognition, Hearing Preservation in Vestibular Schwannoma

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.

Hearing in vestibular schwannoma - Gamma knife surgery vs initial conservative treatment for vestibular schwannoma patients with preserved hearing, a prospective randomized study. Collaborator Ass Prof Förander and others, Department of Neurosurgery.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Jenny Häggström

Ethical permit No.

Publications 2017, 2018, 2019, 2020

1. Haggstrom, J., et al., Prognostic Value of a Test of Central Auditory Function in Conversion from Mild Cognitive Impairment to Dementia. Audiol Neurootol, 2020: p. 1-7.
2. Tengroth, B., A. Lohmander, and C. Hederstierna, Hearing Thresholds in Young Children With Otitis Media With Effusion With and Without Cleft Palate. Cleft Palate Craniofac J, 2019: p. 1055665619889744.
3. Bonnard, A., R. Bark, and C. Hederstierna, Clinical update on sensorineural hearing loss in Turner syndrome and the X-chromosome. Am J Med Genet C Semin Med Genet, 2019. 181(1): p. 18-24.
4. Haggstrom, J., et al., A Longitudinal Study of Peripheral and Central Auditory Function in Alzheimer's Disease and in Mild Cognitive Impairment. Dement Geriatr Cogn Dis Extra, 2018. 8(3): p. 393-401.
5. Tengroth, B., et al., Hearing thresholds and ventilation tube treatment in children with unilateral cleft lip and palate. International Journal of Pediatric Otorhinolaryngology, 2017.
6. Bonnard, A., Hederstierna, C, Bark, R, Hultcrantz, M Audiometric features in young adults with Turner syndrome. Int J Audiol, 2017. 56(9): p. 650-656.

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Radiotherapy induced tissue inflammation, treatment of salivary gland cancer and reconstructive laryngotracheal airway surgery

1. Studies on radiotherapy-induced tissue inflammation. The project is a multidisciplinary collaboration between surgeons, dermatologists, pathologists and oncologists. The main area of interest is clinical outcome in patients treated for head and neck malignancies.
   - The impact of irradiation on acute and long-term changes i tissues (blood vessels, fat, bone and skin) following radiotherapy treatment.
   - Underlying mechanisms in human tissue and in an experimental mouse model

2. Studies on patients treated for salivary gland cancer
   - To validate the sentinel node technique in salivary gland cancer
   - To validate a histopathological risk model for patients with salivary gland cancer

3. Studies on laryngotracheal airway diseases.
   - Long-term outcome of reconstrutive airway surgery in pediatric and adult patients
   - Psychosomatic development and life quality in children with tracheostomy

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Björn Eriksson	

Ethical permit No.

2019-05211	2008/114-31	2006/834-31	2012/1663-32	2018/1972-31

Publications 2017, 2018, 2019, 2020

1. Segmental congenital deficiency of tracheal rings in cervical trachea managed by tracheal resection: A case report and literature review. Gahm C, Näsman A, Papatziamos G. Int J Pediatric Otorhinolaryngol. In press.
2. Osteoradionecrosis, an increasing indication for microvascular head and neck reconstruction. Danielsson D, Gahm C, Haghdoost S, Munck-Wikland E, Halle M. Int J Oral Maxillofac Surg. 2019 Jul 8. S0901-5027 (19)31185-3
3. Eriksson B, Gahm, C, Halle M. Upregulation of Plasminogen Activator Inhibitor-1 in irradiated recipient arteries and veins from free tissue transfer reconstruction" Mediators of inflammation. Oct 4;2018:4058986. 3. Haeggblom L, Ursu RG, Mirzaie L, Attoff T, Gahm C, Nordenvall LH, Näsman A. No evidence for human papillomavirus having a causal role in salivary gland tumors. Diagn Pathol. 2018 Jul 18;13(1):44.
4. Ramqvist T, Ursu RG, Haeggblom L, Mirzaie L, Gahm C, Hammarstedt-Nordenvall L, Dalianis T, Näsman A. Human Polyomaviruses Are Not Frequently Present in Cancer of the Salivary Glands. Anticancer Res. 2018 May;38(5):2871-2874.
5. Halle M, Eriksson BO, Docherty Skogh AC, Sommar P, Hammarstedt L, Gahm C. Improved Head and Neck Free Flap Outcome-Effects of a Treatment Protocol Adjustment from Pre- to Postoperative Radiotherapy. Plastic and reconstructive surgery. Global open 2017 5;3 e1253-
6. Kamali A, Gahm C, Palmgren B, Marklund L, Hammarstedt,-Nordenvall L. Regional recurrence in early stage I-II oral tongue cancer- a single institutional study and review of the litterature. Acta Oto-laryngologica 2017 137;7 755-761

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Effects of cochlear implants in elderly individuals

Ongoing project Co-supervision for Dr Sofia Hultman-Dennison, PhD project on acute rhinosinusitis in children.
Ongoing and planned: Study on effects of cochlear implants in adults with special respect to vestibular functions, hearing outcomes and cognitive abilities in the elderly. Vestibular testing before and after cochlear implantation is ongoing. Studies on the outcomes of treatment (quality of life, hearing outcomes) with cochlear implants related to age, cognition and social environment are planned. The intention is to start a PhD project (S. Mikelöv) during 2021.The main aim of the project is to establish if there are certain specific risks for impairment of vestibular function after cochlear implantation i younger and older (+70y) adults respectively. We also want to investigate the impact of social environment and cognitive functions in individuals older than 70y. Vestibular testing, questionnaires, hearing tests, technical data from implants and cognitive tests will be used for the surevey.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Sara Mikelöv (Planned project)	Sofia Hultman Dennison

Ethical permit No.

2018/1032-31				

Publications 2017, 2018, 2019, 2020

1. Dennison SH, Ask LS, Eriksson M, Granath A, Hertting O, Bennet R, Lindstrand A, Masaba P, Dimitriou P, Stjärne P. Serious complications due to acute rhinosinusitis in children up to five years old in Stockholm, Sweden - Still a challenge in the pneumococcal conjugate vaccine era. International journal of pediatric otorhinolaryngology 2019 121; 50-54
2. Cars T, Eriksson I, Granath A, Wettermark B, Hellman J, Norman C, Ternhag A. Antibiotic use and bacterial complications following upper respiratory tract infections: a population-based study. BMJ open 2017 7;11 e016221-
3. Krakau M, Dagöö BR, Hellström S, Granath A. Long-term hearing outcomes after recurrent acute otitis media during early childhood. Acta oto-laryngologica 2017 137;12 1238-1243
4. Schollin Ask L, Hultman Dennison S, Stjärne P, Granath A, Srivastava S, Eriksson M, Lindstrand A, Ryd Rinder M. Most preschool children hospitalised for acute rhinosinusitis had orbital complications, more common in the youngest and among boys. Acta paediatrica (Oslo, Norway : 1992) 2017 106;2 268-273
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6. Granath A. Recurrent Acute Otitis Media: What Are the Options for Treatment and Prevention?. Current otorhinolaryngology reports 2017 5;2 93-100

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Studies on Head and Neck Cancer

Inflammatory changes of skin after radiotherapy-implications for treatment of head and neck cancer
Injury to the shoulder innervation after head and neck surgery-anatomical basis for new treatment strategies
Nasopharyngeal cancer in Sweden-characterization of a rare disease
Early tongue cancer- sentinel node biopsi and other predictive and progostic markers
Salivary gland tumors- the use of sentinel node to predict drainage and immunohistochemical markers to better predict aggressiveness
Oropharyngeal cancer- the value of HPV in non-tonsillar and non-base of tongue orofaryngeal cancer

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Evelina Gille	Björn Eriksson
	Rasmus Blomkvist

Ethical permit No.

Publications 2017, 2018, 2019, 2020

1. Gebre-Medhin M, Brun E, Engström P, Haugen Cange H, Hammarstedt-Nordenvall L, Reizenstein J, Nyman J, Abel E, Friesland S, Sjödin H, Carlsson H, Söderkvist K, Thomasson M, Zackrisson B, Nilsson P.Gebre-Medhin M, et al ARTSCAN III: A Randomized Phase III Study Comparing Chemoradiotherapy With Cisplatin Versus Cetuximab in Patients With Locoregionally Advanced Head and Neck Squamous Cell Cancer. J Clin Oncol. 2020 Oct 14:JCO2002072. doi: 10.1200/JCO.20.02072. Online ahead of print.J Clin Oncol. 2020. PMID: 33052757
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3. Hammarstedt L, Holzhauser S, Zupancic M, Kapoulitsa F, Ursu RG, Ramqvist T, Haeggblom L, Näsman A, Dalianis T, Marklund L.Hammarstedt L, et al. The value of p16 and HPV DNA in non-tonsillar, non-base of tongue oropharyngeal cancer. Acta Otolaryngol. 2020 Sep 17:1-6. doi: 10.1080/00016489.2020.1813906. Online ahead of print.Acta Otolaryngol. 2020. PMID: 32940116
4. Mäkitie A, Kamali A, Mroueh R, Lindford A, Koivunen P, Autio T, Lassus P, Halle M, Bäck L, Palmgren B, Hammarstedt-Nordenvall L. A descriptive study highlighting the differences in the treatment protocol for oral tongue cancer in Sweden and Finland. Acta Otolaryngol. 2019 Dec 18:1-7. doi: 10.1080/00016489.2019.1699663. [Epub ahead of print] PMID:31852347 http://www.ncbi.nlm.nih.gov/pubmed/31852347
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11. Halle, Martin; Eriksson, Bjorn O.; Docherty Skogh, Ann-Charlott; Sommar, Pehr; Hammarstedt, Lalle; Gahm, Caroline. Improved Head and Neck Free Flap Outcome—Effects of a Treatment Protocol Adjustment from Pre- to Postoperative Radiotherapy. Plastic and Reconstructive Surgery - Global Open Issue: Volume 5(3), March 2017, p e1253. DOI: 10.1097/GOX.0000000000001253 http://www.ncbi.nlm.nih.gov/pubmed/28458967
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13. Grün N, Mbuya W, Ternhag A, Ramqvist T, Ahlberg A, Jangard M, Dalianis T, Hammarstedt-Nordenvall L. Human papillomavirus prevalence in mouthwashes of patients undergoing tonsillectomy shows dominance of HPV69, without the corresponding finding in the tonsils. Infect Dis (Lond). 2017 Mar 15:1-6. doi: 10.1080/23744235.2017.1300319. http://www.ncbi.nlm.nih.gov/pubmed/28293975

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The FACE study - a randomized double-blinded placebo-controlled multicenter trial for evaluation of cortisone treatment in children with acute facial nerve palsy

Background
Acute facial nerve palsy occur in 15-20/100 000 children/year in Sweden. The facial nerve palsy may be associated to Borrelia infection or idiopathic. About 20 % of these children get a persistent impairment of the facial nerve with problems with excesive tear secretion, pronounication, drooling on top of social/cosmetic problems due to assymmetry in the face. Studies on cortisone treatment to adult patients with acute facial nerve palsy have shown beneficial effects, but no studies with strong quality have been performed in children. The overall purpose is to assess the utility of cortisone treatment to children with acute facial nerve palsy in a well-designed RCT.

Material/methods
We now perform a double-blind randomized doulbe blinded placebo-controlled multicenter trial on children with acute facial nerve palsy. Patients are being recruited consecutively at 12 study centers in Sweden during 2019-2022 and a total of 500 patients will be included. Prednisolone 1 mg/kg x 1 perorally in 10 days will be evaluated vs placebo. Clinical data, including clincial outcome (House-Brackmann, Sunnybrook, FaCE scale and FDI) will be documented up until the 12-months follow-up.
The primary outcome is defined as total recovery of the facial nerve palsy, measured with the House-Brackmann scale (grade 1) at 12-months follow-up.

Clincal relevance
If the total recovery rate is significantly improved in the prednisolone group as compared to the placebo group, prednisolone treatment will be introduced in clinical practice for children with acute facial nerve palsy in order to reduce the risk of persistent impairement and disability. National and international guidelines will be pubished for evidens-based treatmant of children with acute facial nerve palsy.
The study protocol is published at ClincialTrials.gov NCT03781700

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Sofia Karlsson	
Sigurdur Arnason	

Ethical permit No.

2017/554				

Publications 2017, 2018, 2019, 2020

1. Skogman BH, Lager M, Brudin L, Jenmalm MC, Tjernberg I, Henningsson AJ. Cytokines and chemokines in cerebrospinal fluid in relation to diagnosis, clinical presentation and recovery in children being evaluated for Lyme neuroborreliosis. Ticks and tick-borne diseases. 2020:101390 (DOI: 10.1016/j.ttbdis.2020.101390)
2. Appelgren D, Enocsson H, Skogman BH, Nordberg M, Perander L, Nyman D, Nyberg C, Knopf J, Munoz LE, Sjowall C, Sjowall J. Neutrophil Extracellular Traps (NETs) in the Cerebrospinal Fluid Samples from Children and Adults with Central Nervous System Infections. Cells. 2019;9(1).
3. Henningsson AJ, Lager M, Brannstrom R, Tjernberg I, Skogman BH. The chemokine CXCL13 in cerebrospinal fluid in children with Lyme neuroborreliosis. Eur J Clin Microbiol Infect Dis. 2018;37(10):1982-1991.
4. Backman K, Skogman, BH. Occurrence of erythema migrans in children with Lyme neuroborreliosis and the association with clinical characteristics and outcome - a prospective cohort study. BMC Pediatrics. 2018; 18:189 1-7.
5. Skogman BH, Lager M, Henningsson AJ, Tjernberg I. The recomBead Borrelia antibody index, CXCL13 and total IgM index for laboratory diagnosis of Lyme neuroborreliosis in children. Eur J Clin Microbiol Infect Dis. 2017;36(11):2221-9

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Allergy vaccination- novel strategies and biomarkers for outcome

Allergic rhinitis deprives quality of life, work capacity and social activities and costs the Swedish society about 1.3 billion SEK annually. Allergen-specific immunotherapy (AIT) gives a significant symptom reduction and also improves the course of the disease. Conventional AIT involves more than 50 subcutaneous injections at hospital or daily sublingual tablets, during 3-4 years. The long treatment duration, problems with side-effects and lack of allergology specialists limits the use; only a minority of the patients eligible for AIT gets the treatment.

Intralymphatic immunotherapy (ILIT) is an emerging form of AIT, which requires only 3 ultrasound guided lymph node injections during a period of 12 weeks. The overall aims for this project are to optimize the ILIT treatment protocol and explore the immunological mechanisms behind tolerance induction in ILIT as well as in conventional AIT. We will investigate if using a lower dose of allergen than previously tested, will be equally or more efficient. In addition, we will investigate if concomitant medication can enhance the treatment effect. In the search for biomarkers for treatment outcome, immune cells sampled from the blood, lymph nodes and nasal mucosa will be characterized, mainly using flow cytometry.

If the treatment protocol in ILIT can be optimized, more patients with allergic rhinitis could benefit from the treatment, to a lower cost for the health care system.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Karin Jeppesen, Aarhus University

Ethical permit No.

2009/714				

Publications 2017, 2018, 2019, 2020

1. Intralymphatic immunotherapy in pollen-allergic young adults with rhinoconjunctivitis and mild asthma: A randomized trial. Konradsen JR, Grundström J, Hellkvist L, Tran TAT, Andersson N, Gafvelin G, Kiewiet MBG, Hamsten C, Tang J, Parkin RV, Shamji MH, Hedlin G, Cardell LO, van Hage M. J Allergy Clin Immunol. 2020 Mar;145(3):1005-1007.e7. doi: 10.1016/j.jaci.2019.11.017. Epub 2019 Nov 24.
2. Intralymphatic immunotherapy with 2 concomitant allergens, birch and grass: A randomized, double-blind, placebo-controlled trial. Hellkvist L, Hjalmarsson E, Kumlien Georén S, Karlsson A, Lundkvist K, Winqvist O, Westin U, Cardell LO. J Allergy Clin Immunol. 2018 Oct;142(4):1338-1341.e9. doi: 10.1016/j.jaci.2018.05.030. Epub 2018 Jun 13.
3. A preseason booster prolongs the increase of allergen specific IgG4 levels, after basic allergen intralymphatic immunotherapy, against grass pollen seasonal allergy. Weinfeld D, Westin U, Hellkvist L, Mellqvist U-H, Jacobsson I, Cardell L-O. Allergy Asthma Clin Immunol. 2020 Apr 28;16:31. doi: 10.1186/s13223-020-00427-z. eCollection 2020.

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Ear and hearing

The ear and hearing research focuses on three avenues.

1. To study quality and benefit of audiological rehabilitation for patients with severe-to-profound hearing loss with or without vision impairment. The study also aims at invesgating the type of audiological rehabilitation received by patients and whether it is necessary to improve rehabilitation efforts, for example, in terms of a gender perspective. Other questions regard e.g. do all patients which qualify for CI-implantation get a CI. An important basis for the studies is the national Quality Register for severe-to-profound hearing loss.
2. To supervise the development and establishment of a "Scientific Center for Advanced Pediatric Audiology". The hearing research at Karolinska dominates by studies on children. This field has an enormous potential to become a national and international frontline research area.
3. To study plasminogen, a preinflammatory protein, and its involvement in healing of wounds. One project concerns healing of tympanic membrane perforations but also chronic wounds, like diabetic foot ulcers. The study is performered at Umeå Univ in collaboration with international drug companies.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Satu Turunen-Taheri	Niki Karpeta
	Fatima Moumén Denanto

Ethical permit No.

2012/057	2014/2101-31			

Publications 2017, 2018, 2019, 2020

1. Xie W, Dai Q, Liu J, Liu , Hellström S, Duan M. Analysis of clinical and laboratory findings of idiopathic sudden sensorineural hearing loss. Sci Rep, 2020;10:6057-.
2. Tong B, Niu K, Ku W, Xie W, Dai Q, Hellström S, Duan M. Comparison of Therapeutic Results with/without Additional Hyperbaric Oxygen Therapy in Idiopathic Sudden Sensorineural Hearing Loss: A Randomized Prospective Study. Audiol Neurootol. 2020;12:1-6.
3. Tong B, Wang Q, Dai Q, Hellstrom S, Duan M. Efficacy of Various Corticosteroid Treatment Modalities for the Initial Treatment of Idiopathic Sudden Hearing Loss: A Prospective Randomized Controlled Trial. Audiol Neurootol. 2020;15:1-8.
4. Turunen-Taheri S, Edén M, Hellström S, & Carlsson P-I. Rehabilitation of adult patients with severe-to-pro- found hearing impairment – why not cochlear implants? Acta Oto-Laryngologica, 2019;139 (7): 604-611.
5. Turunen-Taheri S, Carlsson P-I, Johnson A-C, & Hellström S. Severe-to-profound hearing impairment: demographic data, gender differences and benefits of audiological rehabilitation. Disability and Rehabilitation, 2018;12: 1-9.
6. Turunen-Taheri S, Skagerstrand Å, Hellström S, & Carlsson P-I. Patients with severe-to-profound hearing impairment and simultaneous severe vision impairment: a quality-of-life study. Acta Oto-Laryngologica, 2017;137:3, 279-285.

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Submucosal endoscopic treatment of subglottal stenosis and tracheobronkiall stents of malignant stenosis of the airways

Before and after both subglottical stenosis operaation and airway stent operation breathing syptoms and capacity is evaluated with box spirometry and ímpuls oscillometry. Symptoms are evaluated with a validated inquiry (CAT). The stent patients are further evaluated after a week while the stenosis patients are tested after 3 months.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2014/100-31/2	2015/1543-32	2014/93-31/2		

Publications 2017, 2018, 2019, 2020

1. Lundström N, Henriksson G, Börjesson O, Jonsson Fagerlund M, Petersson J.Lundström N, et al. Among authors: henriksson g. Circulatory Collapse due to Hyperinflation in a Patient with Tracheobronchomalacia: A Case Report and Brief Review. Case Rep Crit Care. 2019 Jan 29;2019:2921819. doi: 10.1155/2019/2921819. eCollection 2019.Case Rep Crit Care. 2019. PMID: 30838137

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An open Phase I/II study in patients with dysphonia and vocal fold scarring to evaluate safety, tolerability and vocal function after surgery with local administration of autologous mesenchymal stromal 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. In a pilot study we have treated 16 patient with follow-up at least 3 years with significat improved voice function without side effects. After receiving permissions from the Swedish Medical Agency (Läkemedelsverket) and EPM(etikprövningsmyndigheten) we are 2020 starting a clinicial trial in 15 patients with vocal fold scarring and severe horseness which are treated with a MSC product

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Emma Malmström	

Ethical permit No.

2019–06160	2020-04565			

Publications 2017, 2018, 2019, 2020

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

Cleft lip and palate has functional and aesthetical impact on the face and upper airways. Patients were examined 20-40 years after primary surgery. A control group was examined in the same way. Objective evaluation of nasal form and function was performed as well as studies of QoL and voice function with blinded evaluation. The impact of chronic rhino sinusitis on sleep and obstructive sleep apnea are analyzed as well as vice versa. Variables for a poor outcome in CPAP treatment are also analyzed.
Hereditary Hemorrhagic Telangiectasia in Sweden, prevalence, morbidity and mortality.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Sofia Hultman Dennison
	Karin Åberg

Ethical permit No.

2005:245	2012/1472-31	2014/448	2013/397	

Publications 2017, 2018, 2019, 2020

1. Bengtsson C, Jonsson L, Theorell-Haglöw J, Holmström M, Jansson C, Lindberg E. Sinonasal outcome test-22 and peak nasal inspiratory flow –valuable tools in obstructive sleep apnoea. Rhinology 2020; 58(4); 341-8
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Facial Palsy and Quality Register

Bells palsy
A risk analysis can be performed 1 month after suffering from Bells palsy. A prospectiv study is ongoing with randomisation to either plastic surgery (cross facial (baby sitter) surgery) or conventional treatment. National research concerning Quality of life has been set up as well as studies on facial palsy in children in Sweden. Research and surgery has been established in a network between ENT, pediatricians, neurophysiologists, plastic surgeons, neurologists, physiotherapists with many ongoing projects.

Bone anchored hearing implants
Implantable hearing aids are evaluated after new surgical techniques and skinreactions are tested histochemically and bacterilologically to try to reduce side effects. A new implant is under development together with Sahlgrenska Akademin and Chalmers Technical University.
Functional MRI studies and connectivity have been performed in humans and in a longitudinal rat model with sutured ear canal at birth, in order to investigate central hearing pathways in patients and rats suffering from single sided hearing loss (atresia). In humans udiometric results are collected as well as testing hearing in noise. Eye reflex test, a new is implemented in to test binaural hearing. The rat model is tested with fMRI and DTI at 1 month, 3,6 and 12 months after birth. Histological samplas are investigated to localize pathology.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Sigurdur Arnason
	Sofia Karlsson
	Malin Berglund, ÖNH Trollhättan

Ethical permit No.

2014/2203-31/4	2016/1937-31/4			

Publications 2017, 2018, 2019, 2020

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Aging, cognition and central auditory function

This project is about relationships between aging, cognitive decline, and central auditory function (CAD). Our hypothesis is that combined measures of CAD and cognitive function will accurately identify persons with both hearing impairment and cognitive deficits.
The 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.

In the first longitudinal study (Häggström et al., 2018), it has been demonstrated that central auditory function, as measured with the Dichotic Digit Test (DDT), suggested that DDT may reflect on ongoing process resulting in dementia.

In the second study (Häggström et al., 2020), our objective was to evaluate the predictive capacity of the DDT in conversion from mild cognitive impairment (MCI) to dementia. It has been suggested that DDT as a central auditory test may be suitable when evaluating cognitive decline.

The correlation betwen the DDT and morphological changes in the corpus callosum on existing MRI images will be investigated in the coming study, in order to further evaluate the diagnostic validity of the DDT.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Jenny Häggström	

Ethical permit No.

2005/914-31	2014/2087-31-2	2018/1291-32		

Publications 2017, 2018, 2019, 2020

1. Häggström J, Rosenhall U, Hederstierna C, Östberg P, Idrizbegovic E.
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4. Häggström J, Hederstierna C, Rosenhall U, , Östberg P, Idrizbegovic E. Prognostic Value of a Test of Central Auditory Function in Conversion from Mild Cognitive Impairment to Dementia, Audiol Neurootol. 2020; 25 (5): 276-282. doi: 10.1159/000506621. Epub 2020 May.

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A personalized approach to chronic rhinosinusitis with nasal polyps, based on biomarkers, phenotypes and new surgical thinking.

I completed my PhD in May 2020 and are in the process of initiating coming research

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2017, 2018, 2019, 2020

1. Jonstam K, Westman M, Holtappels G, Holweg CTJ, Bachert C. Serum periostin, IgE, and SE-IgE can be used as biomarkers to identify moderate to severe chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2017;140(6):1705-8.e3.
2. Jonstam K, Swanson BN, Mannent L, Cardell LO, Tian N, Wang Y, et al. Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis. Allergy. 2018.
3. Alsharif S, Jonstam K, van Zele T, Gevaert P, Holtappels G, Bachert C. Endoscopic Sinus Surgery for Type-2 CRS wNP: An Endotype-Based Retrospective Study. Laryngoscope 2019.
4. Cardell LO, Stjärne P, Jonstam K, Bachert C. Endotypes of chronic rhinosinusitis: Impact on management. J Allergy Clin Immunol 2020; 145:752-6.
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6. Jonstam K, Delemarre T, Holtappels G, Cardell LO, Westamn M, Bachert C. Type 2 Inflammatory Shift in Chronic Rhinosinusitis During 2007-2018 in Belgium. Laryngoscope 2020.

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Auditory Organotypic Cultures and Progenitor Cell Implantation

Concluded PhD project during 2018. Presently finishing up planned publications within this project but is also looking to take part in clinical projects in neurotology

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

C100115/15				

Publications 2017, 2018, 2019, 2020

1. Kaiser A, Kale A, Novozhilova E, Olivius P. 2019.The Effects of Matrigel on the Survival and Differentiation of a Human Neural Progenitor Dissociated Sphere Culture. The Anatomical Record. DOI: 10.1002/ar.24131

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Immune responses in airway inflammatory diseases and head- and neckcancer.

Chronic rhinosinusitis s/w polyps and asthma exacerbations have lately been thought to have underlying infectious basis, and the innate immunity is thought to have a great importance. We aim to outline the interplay between the innate and adaptive immune response and different subgroups of neutrophils role for the development of the diseases.
The PNS is known to play a role in airway inflammation. Changes in neuropeptide production and neuronal signalling are known to be associated with allergic rhinitis and asthma. However, the role of the PNS in respiratory infections and exacerbations is unknown. We aim to investigae how activation of innate immune receptors impact upper and lower airway inflammation, as well as inflammation following respiratory infection, while simultaneorly determening how neuronally-derived mediators shape this process.
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 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:

Main Supervisor	*Co-supervisor*
	Eric Hjalmarsson
	Magnus Starkhammar
	Krzysztof Piersiala
	Vilma Lagebro

Ethical permit No.

Publications 2017, 2018, 2019, 2020

1. Ekstedt S, Tufvesson E, Bjermer L, Georen SK, Cardell LO. A new role for ”eat me” and ”don’t eat me” markers on neutrophils in asthmatic airway inflammation. ALLERGY 2020 75;6 1510-1512
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3. Ekstedt S, Georen SK, Cardell LO. Effects of MP-AzeFlu enhanced by activation of bitter taste receptor TAS2R. ALLERGY ASTHMA AND CLINICAL IMMUNOLOGY 2020 16;1 45-
4. Drakskog C, de Klerk N, Westerberg J, Mäki-Torkko E, Georén SK, Cardell LO. Extensive qPCR analysis reveals altered gene expression in middle ear mucosa from cholesteatoma patients. PloS one 2020 15;9 e0239161-
5. Westerberg J, Tideholm E, Piersiala K, Drakskog C, Kumlien Georén S, Mäki-Torkko E, Cardell LO. JAK/STAT Dysregulation With SOCS1 Overexpression in Acquired Cholesteatoma-Adjacent Mucosa. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology 2020 ;
6. Ekstedt S, Säfholm J, Georén SK, Cardell LO. Dividing neutrophils in subsets reveals a significant role for activated neutrophils in the development of airway hyperreactivity. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 2019 49;3 285-291

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10. Hellkvist L, Hjalmarsson E, Kumlien Georén S, Karlsson A, Lundkvist K, Winqvist O, Westin U, Cardell LO. Intralymphatic immunotherapy with 2 concomitant allergens, birch and grass: A randomized, double-blind, placebo-controlled trial. The Journal of allergy and clinical immunology 2018 142;4 1338-1341.e9
11. Kågedal Å, Rydberg Millrud C, Häyry V, Kumlien Georén S, Lidegran M, Munck-Wikland E, Cardell LO. Oropharyngeal squamous cell carcinoma induces an innate systemic inflammation, affected by the size of the tumour and the lymph node spread. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2018 ;
12. Häyry V, Kågedal Å, Hjalmarsson E, Neves da Silva PF, Drakskog C, Margolin G, Georén SK, Munck-Wikland E, Winqvist O, Cardell LO. Rapid nodal staging of head and neck cancer surgical specimens with flow cytometric analysis. British journal of cancer 2018 118;3 421-427
13. Larsson O, Uddman R, Kumlien Georén S, Cardell LO. Reply. The Journal of allergy and clinical immunology 2018 142;5 1677-1678
14. Larsson O, Tengroth L, Xu Y, Uddman R, Kumlien Georén S, Cardell LO. Substance P represents a novel first-line defense mechanism in the nose. The Journal of allergy and clinical immunology 2018 141;1 128-136.e3
15. Arebro J, Ekstedt S, Hjalmarsson E, Winqvist O, Georen SK, Cardell LO. A possible role for neutrophils in allergic rhinitis revealed after cellular subclassification. SCIENTIFIC REPORTS 2017 7; 43568-
16. Millrud CR, Kågedal Å, Kumlien Georén S, Winqvist O, Uddman R, Razavi R, Munck-Wikland E, Cardell LO. NET-producing CD16high CD62Ldim neutrophils migrate to tumor sites and predict improved survival in patients with HNSCC. International journal of cancer 2017 140;11 2557-2567
17. Bao A, Che KF, Bozinovski S, Ji J, Gregory JA, Kumlien Georén S, Adner M, Cardell LO, Lindén A. Recombinant human IL-26 facilitates the innate immune response to endotoxin in the bronchoalveolar space of mice in vivo. PloS one 2017 12;12 e0188909-

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Immune Respons and Tumour Cell Detection in Head and Neck Cancer.

Metastases in lymph nodes are an important factor for outcome in oral cancer patients. The development of the new immune therapies has changed the field of cancer medicine and it is important to define the selection of patients for these new treatments. The overall goal of this research is to study the immune response in tumour tissue, lymph nodes and blood in patients with oral cancer. We use sentinel node technique to find the draining lymph node where we detect tumour cells with flow cytometry and identify immunological biomarkers.

Sentinel Node detection in patients with Sinonasal Tumours

Sinonasal malignancies are rare but have a high mortality and the post treatment morbidity is severe with mutilating surgery and radiotherapy. The lymphatic drainage from the nasal cavity and the paranasal sinuses are not well studied. With sentinel node procedure and flow cytometry technique for early detection of metastases and new immunological biomarkers we hope to gain knowledge for better treatment both in terms of limiting the field of radiotherapy and improve the possibilities for immune therapy.

Immune response in COVID 19 patients.

COVID 19 patients presents with a high hah immune response. In our study we examine the immune response in blood with flow cytometry and main focus on neutrophils, with an aim to predict the severity of the disease.

Ethical permit No.

2011/717-31-1	2013/1943-3-4	2015/1650-31-2	2018/811-32		

Publications 2017, 2018, 2019, 2020

1. Rydberg Millrud, Å Kågedal C, Kumlien Georén S, Uddman R, Razavi R, Munck-Wikland E, Cardell LO. NET-producing CD16high CD62Ldim neutrophils migrate to tumour sites and predict improved survival in patients with HNSCC. Int J Cancer. 2017 Jun 1; 140(11):2557-2567.
2. Kågedal Å, Rydberg-Millrud C, Häyry V,Kumlien-Georén S, Lidegran M, Munck-Wikland E, Cardell LO. Oropharyngeal squamous cell carcinoma induces an innate systemic inflammation, affected by the size of the tumor and the lymph node spread. Clin Otolaryngol. (2018) Apr 21. doi: 10.1111/coa.13122.
3. Häyry V, Kågedal Å, Hjalmarsson E, Farrajota Neves da Silva P, DrakskogC, Margolin G, Munck-Wikland E, Winqvist O, Cardell LO. Nodal staging of neck dissection specimens with flow-cytometry. British Journal of Cancer (2018) 118,421-427
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5. Kågedal Å, Hjalmarsson E, Farrajota Neves da Silva P, Piersiala K, Georén SK, Margolin G, Munck-Wikland E, Winqvist O, Häyry V, Cardell LO. Activation of T helper cells in sentinel node predicts poor prognosis in oral squamous cell carcinoma. Sci Rep. 2020 Dec 18;10(1):22352.
6. Piersiala, K; Farrajota Neves da Silva, P; Hjalmarsson, E; Kolev, A; Kågedal, Å; Starkhammar, M; Elliot, A; Marklund, L; Margolin, G; Munck af Rosenschold Wikland, E; Kumlien Georén, S; Cardell, L O T cells in sentinel nodes exhibit distinct pattern of PD-1, CD69 and HLA-DR expression compared to tumour tissue in OSCC, Accepted Cancer Science (Jan 2021)

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Words make a difference

”Words make a difference” is a population-based Swedish research program, with international partners. The aim is to explore how environmental factors like listening environment, caregiver gender differences, and interaction patterns between caregivers and young children (0-4 years) are associated with children’s language development and social wellbeing. The quantity and quality of children’s language environment is examined longitudinally with the Language ENvironment Analysis (LENA) technology in childrens’ home environment, in children who are hard of hearing using hearing aids and/or hearing implants, and in age-matched controls with typical hearing. LENA is also validated in Swedish within the study program. The preliminary results show that LENA is accurate to use within a Swedish context. We have found significant caregiver gender differences with more exposure of female than male words around young children(Melsom-Kristensen et al., 2020; Löfkvist et al. (under review). Children who are hard of hearing were exposed to fewer conversational turns than controls with typical hearing, which may affect their language development negatively (Löfkvist et al., under review). Another part of the study program is to develop a new family-centered intervention program; Prevention Education Program for Parents (PEPP) for caregivers with infants who recently have been diagnosed with a hearing loss. The aims are to empower parents, promote fulltime use of hearing technology, natural communication, support psychosocial wellbeing and increase amount of conversational turns over time.The content of PEPP is based on current evidence-based strategies, includes regular evaluation with LENA and video recordings for more specific and individualized guidance of caregivers, and is conducted immediately after the identification of the child’s hearing loss. Pilot-data shows promising results. Next step is to conduct a RCT study with PEPP.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Karolina Falkenius Schmidt
	Jonas Fogels

Ethical permit No.

2015/992-31				

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Optimizing treatment for head and neck tumors

Treatment of head and neck tumors consists surgery, radiotherapy and chemotherapy, used as single treatment or combined in advanced tumors. Today treatment is standardized and mainly based on TNM-status although the tumors vary in aggressiveness and sensitivity to treatment. Complications to treatmet is loss of nerve function, pain, stifness, swallowing problems, dryeness of mouth wich have major impact of th quality of life. A number of molecular markers have been evaluated for predictive value at head and neck tumors. However, few studies have been performed specifically for each subgroup of tumors although these differ considerably in terms of treatment response and prognosis. Therefore, the overall iam of all studies is to optimize and individualize the tratment for patients with head and neck tumors. We evaluate the predictive value of a number of markers in order to be able to select patients for surgery or oncologic treatment, and also be able to better select type and intensity of oncologic treatment and also the extent of surgery, both on the tumor site and the neck.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Malin Wendt
	David Landin
	Aeneas Kolev

Ethical permit No.

2017/1333-31/1	2012/49-31/2	2019/03518		

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- **Bells palsy during pregnancy and puerperium**
- **Surgical intervention in patients with peripheral facial palsy**
- **Neurophysiological approaches and role in facial nerve damage in subacute and late stages**
- **Facial nerve palsy in children; treatment and clinical outcome**

Bell's palsy is an acute peripheral facial nerve palsy with unknown etiology that can affect both adults and children. There is a higher incidence among pregnant women and in the puerperium. 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. Many patients need surgical interventions. Neurophysiological tests can help predicting the outcome of the palsy when performed at different time points.

In our work, we study different aspects of Bell's palsy in both adults (especially among pregnant women) and children. Surgical interventions with nerve transfers and neurotomy on adults with severe facial plays is studied and different neurofysiologiscal tests are described. A multi-center randomised, clinical trial is performed on children with acute facial palsy to study the effect of prednisolone on the facial outcome

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Lovisa Lansing	Rebecka Ohm
	Sigurdur Arnason
	Evelina Gille
	Zane Upate (under registration)

Ethical permit No.

Publications 2017, 2018, 2019, 2020

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2. Quality of Life in Bell's Palsy: Correlation with Sunnybrook and House-Brackmann Over Time. Bylund N, Hultcrantz M, Jonsson L, Marsk E. Laryngoscope. 2020 May 28. doi: 10.1002/lary.28751. Online ahead of print.
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Head and neck cancer

We study predictive and prognostic markers in head and neck cancer aiming at individualize and optimize treatment for our patients.

Hypopharyngeal cancer patients show dismal survival rates and if we could select patients with poor response to oncological treatment these patients would fare better with primary surgical treatment. (Malin and David)

Malin also studies OK 432 therapy for patients with ranula and branchial cleft cysts. Half time control 201009.

David also studies HPV in benign and malignant neck lesions.

Daniel studies osteoradionecrosis (ORN) after radiotherapy, 8-oxo-dG levels, brachytherapy as a risk factor for ORN and quality of life before and after reconstructive surgery for ORN. Half time control 200617.

Krzysztof studies different immune cells in sentinel nodes, their interactions and impact on response to therapy and survival.

Tingting Huang does epidemiological studies, diet habits and microbiome, in nasopharyngeal carcinoma. Thesis planned dec 2020.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Malin Wendt	Krzysztof Piersiala
Daniel Danielsson	Tingting Huang
David Landin	

Ethical permit No.

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

1. Identification of biomarkers that predict HNSCC treatment outcome. This collaborative project aims to identify markers that predict treatment response and can be analyzed in a tissue biopsy from a suspected tumor and/or in the patient's blood sample or saliva or possibly in exhaled breath. 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 Head and Neck Cancer (HNC) Study: management and outcome of various subsites of head and cancer in the Nordic countries. Our aim is to evaluate current treatment outcome of HNC in the Nordic countries and to form a recommendation for a unified treatment protocol for this entity to be used in this area. The secondary aim is to find prognostic markers for clinical use by using multi-institutional series of HNC patients and available samples.

Ethical permit No.

Publications 2017, 2018, 2019, 2020

For complete list please, see: https://pubmed.ncbi.nlm.nih.gov/?term=Makitie+a

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Undergraduate students' clinical learning environment

The prevalence of dysphagia increases with advancing age and specifically in persons with neurological disorders. In a acute phase after stroke up to 80% of patients have difficulties to swallow. A common procedure to examine oropharyngeal swallowing is fiberendocopic examination of swallowing (FEES) but a few studies have used FEES to evaluate normal swallowing. Thus, we examined the oropharyngeal swallowing by FEES in healthy elderly (65-85 years) who also completed the Swedish version of the Eating Assessment Tool (S-EAT 10). The health-related quality of life was assessed by Short Form 36 (SF-36) Health Survey. The latest study has investigated the structural validity of the EAT.

The other research path explores undergraduate students' clinical learning environment (CLE). It is widely acknowledged that CLE impacts students' professional development and their ability to achieve the learning outcomes. This project aims to identify and provide an in-depth understanding of students' perception of the clinical learning environment and the relationship to self-reported health-related quality of life across four different undergraduate programs. The first study assessed the CLE by the Undergraduate Clinical Education Environment Measure (UCEEM).

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Malin Sellberg	

Ethical permit No.

2017/38-31/4	2013/2212-31/4.	2010/1100-31/1	2010/1606-31/5	2010/1100-31/1	2011/493-32	636/03

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10. Möller R, Shoshan M. Medical students' research productivity and career preferences; a 2-year prospective follow-up study. BMC Med Ed 2017 17;1 51-

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Obstructive Sleep Apnea in children and adults, a surgical therapeutic perspective

Within surgical treatment for obstructive sleep apnea, the group has performed five randomized controlled trials. The main focus for adult sleep apnea is on uvulopalatopharyngoplasty including tonsillectomy, which we have compared to expectancy and to plain tonsillectomy. In children, the main focus is on different techniques and additions to tonsill surgery. We compare expectancy, tonsillotomy, tonsillectomy and tonsillectomy with additional suturing of the pillars. Patients are evaluated with both objective and subjective parameters such as polysomnography findings (the gold standard sleep registration), vigilans, daytime sleepiness, quality of life, blood pressure, inflammatory markers etc.
Further the Swedish National Tonsill Surgery Registra is another field of research were we evaluate incidence, morbitidy and symtom relief etc.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2017, 2018, 2019, 2020

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HealthSWEDE (Health economy and sublingual immunotherapy in Sweden) : Costs with sublingual immunotherapy

Primary objective:
To assess direct and indirect costs in the treatment of grass allergy with sublingual immunotherapy in Sweden vs standard of care, without subcutaneous immunotherapy.

The main question that was answered in this study was the economic impact of work absence (absenteeism) or reduced working capacity (presentism) and direct costs of medications and health care consumption in relation to adults with sublingual immunotherapy for grass pollen allergy in Sweden vs a control population with standard of care, waiting for subcutaneous immunotherapy

STUDY DESIGN
A cross-sectional study: A questionnaire was to a randomized, stratified, representative selection of the adult population groups of patients; 1 group with patients with treatment with sublingual immunotherapy (SLIT) for grass pollen allergy, and 1 group waiting for allergen specific subcutaneous immunotherapy (SCIT) for pollen allergy just after the end of grass allergy season in Sweden.
295 subjects, 18 years or older, answered (53.8% response rate)

Ethical permit No.

2016/2158-31/2				

Publications 2017, 2018, 2019, 2020

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Laryngeal cancer at the Karolinska University Hospital 2000-2020

In this project, we want to investigate laryngeal cancer treatment strategies and outcome in patients treated at the Karolinska University Hospital 2000-2020. Furthermore, we want to see if we can find good predictors to better select those patients whose tumors should receive radiotherapy (read radiation sensitive) and those where surgery becomes the primary choice. We also want to see if we can streamline care and follow-up without affecting the quality of care.

The research project preliminarily consists of several sub-projects, all with the aim of highlighting the characteristics and treatment outcomes of laryngeal cancer:

1. A descriptive retrospective study with the purpose to acquire data on the management and outcome of laryngeal squamous cell cancer for patients treated at the Karolinska University Hospital 2000-2020.
2. To specifically evaluate treatment and outcome for large cancers of the larynx, i.e. T3 and T4 tumours. We will specifically analyse x-rays and control the tumors for size, extension of growt and destruction of cartillage.
3. To evaluate the treatment of T3, T4 laryngeal cancer with the Bayesian network model based on observation data. We will analyse 18 variables on aproximately 300 Swedish and Finnish patients.

In the research group we also have collaboration with Prof. Mäkitie from Helsinki, Finland. Thus, we aim to compare data on the management and outcome for laryngeal cancer patient in Sweden and Finland.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Rasmus Blomkvist (intended)

Ethical permit No.

Okt-19				

Publications 2016, 2017, 2018, 2019, 2020

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

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.
• Epidiologic studies om acute rhinosinusitis in children.
The overall objective is to understand the basic epidemiology and mechanisms and but also to improve the treatment of these patient groups. Zygomatic and orbital blow out 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*
Ann Abrahamsson	
Ola Fridman Bengtsson	
Sofia Hultman Dennison	

Ethical permit No.

2012/4931	2012/89131	2012/4:8		

Publications 2017, 2018, 2019, 2020

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Cochlear Implantation in Children with Cochlear Malformation

Cochlear implantation makes hearing restoration possible in patients with severe to profound hearing loss. Our research today focus on clinical studies of cochlear implantation in children with cochlear malformations. During the last years we have examined the effects of cochlear implant surgery on children with x-linked (DFNX2) inner ear malformation. We describe surgical techniques necessary for safe cochlear implantation, and further show that implantation permits hearing restoration and the development of spoken language in these children. Further analysis of hearing and language outcomes, cognition and mental health revealed poorer outcome in hearing, language and mental health and lower executive functional level, as compared to a control group. Genetic analysis confirmed mutations in the POU3F4 gene on the X-chromosome. X-linked malformation deafness is usually considered non-syndromic. However, yet unpublished data shows that these children exhibit signs of neuro-developmental problems consistent with attention deficit and hyperactivity, which is likely related to the POU3F4 mutation. Hence, x-linked cochlear malformation should possibly be re-classified as a syndromic form of hearing loss. Additionally, during the last years the group has focused on refinement of the classification of inner ear malformations on CT and MRI, including the vestibular system.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Kaijsa Edholm	Eleonor Koro (Umeå)
	Jonas Frodlund

Ethical permit No.

2014/2068-31/2				

Publications 2017, 2018, 2019, 2020

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Uvulopalatopharyngoplasty: Patient Selection, Long-Term Outcomes, and Side Effects

Uvulopalatopharyngoplasty is the predominant surgical treatment for adult patients with Obstructive Sleep Apnea. The short-term efficacy is well established and rather recently demonstrated in several randomized controlled trials. Less is known, however, about the long-term efficacy as well as the effect on subjective parameters. There has been a long-running discussion about the best way to select patients and whether the predominant method is safe. Finally, there has been controversies about the procedure's possible side-effects.

My projects aim to evaluate the long-term subjective and objective efficacy, appropriate patient selection, and possible side-effects. This far we have published work that conclude that the effect on subjective parameters are good and that the side-effects are few in both the short and long-term perspective. The results also indicated that surgery had a significant positive effect as a long-term treatment for OSA, although the effect significantly decreased over time. Daytime sleepiness, on the other hand, appeared to remain improved even in the long term. The method for patient selection that we evaluated was poor and unreliable and patient selection remaines a challenge.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2007/44931/3	Ö21-2007	2016/331-32	2015/75531/2	2018/214-32

Publications 2017, 2018, 2019, 2020

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Aspects of hearing in children with cleft palate

The aim of study I was to examine the prevalence of hearing loss, tympanic membrane perforation and acquired cholesteatoma among children with unilateral cleft lip and palate without any associated anomalies.The second aim was to examine if the risk for permanent hearing loss and acquired cholesteatoma increases due to the treatment with ventilation tubes (VT).

The aim of study II was to investigate longitudinal data on hearing thresholds between 0 – 3 years of age in children born with cleft palate and in children with otitis media with effusion but no cleft palate

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

97-372	2012/46-31/2	Tillägg 2013-03-06		

Publications 2017, 2018, 2019, 2020

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3. Lohmander, A. Westberg, L. R. Olsson, S. Tengroth, B. Flynn, T. (2020). Canonical Babbling and Early Consonant Development Related to Hearing in Children With Otitis Media With Effusion With or Without Cleft Palate. Cleft Palate Craniofac J, 2020 Oct 21, doi:10.1177/1055665620966198

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Bilateral hearing with cochlear implants

A Cochlear Implant (CI) is an electronic auditory prosthesis capable of restoring hearing in the profoundly deaf and severely hearing impaired. The transfer of information between the array of intra-cochlear electrodes and the hearing nerve is the most limiting factor for the outcome of the treatment. The spread of the electrical field is messing up the temporal information since other electrodes are interfering the temporal pattern. Development is needed to enhance this bottleneck in the cochlear implant hearing chain. The project study sound coding strategy and improvements. The benefit of bilateral implantation can differ due to age at implantation and the choice of implant technology and sound coding programming. The benefit from early implantation is studied.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Fatima Moumén Denanto

Ethical permit No.

2013/104-31/	2013/1127-31/2	2013/104-31/4		

Publications 2017, 2018, 2019, 2020

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2. Cochlear implants before 9 months of age led to more natural spoken language development without increased surgical risks. Karltorp E, Eklöf M, Östlund E, Asp F, Tideholm B, Löfkvist U. Acta Paediatr. 2019 Jul 27.
3. Psychometric properties of the Swedish version of the Glasgow Benefit Inventory in otosclerosis subjects. Redfors YD, Jönsson R, Tideholm B, Finizia C.Laryngoscope Investig Otolaryngol. 2019 Nov 27;4(6):673-677. doi: 10.1002/lio2.320. eCollection 2019 Dec.

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Menieres disease and inner ear hydrops

Hydropic inner ear disease, initially described by Prosper Menière, is one of the most frequent vertigo disorders. Meniere disease is the syndrome of endolymphatic hydrops which until 2007 could be diagnostically confirmed only by post-mortem histology. With the milestone achievement of endolymphatic hydrops imaging, today the pathology can be ascertained. ‘‘HYDROPS’’ (Hybrid of the reverse image of the positive endolymph signal and native image of the positive perilymph signal) image is developed by Shinji Naganawa, Tsutomu Nakashima, 2013. This method was introduced in Karolinska University Hospital in November 2019 and in collaboration with Neuroradiology department we have started with clinical use of visualization the endolymphatic hydrops to ascertain the Meniere diagnosis in living patients. After one year of use we have noticed many possibilities of this method. The relationship between the image of the endolymphatic space and functional tests, must be examined soon. MD symptoms demonstrated an immense degree of diversity. Recent MRI confirmed the presence of cochlear and vestibular MD. The relationship between the clinical symptoms and EH is still unclear. Our project will be collaboration between Hearing/Balance and Neuroradiology Department to understand MD symptoms and with this bring a new insight in etiology.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2015/741-31/4				

Publications 2017, 2018, 2019, 2020

1. Tatjana Tomanovic & Béla Büki The diagnostic framework of peripheral positional vertigo and dizziness (PPVD): a new concept based on the observation of alcohol-induced posterior canal light cupula. 2016 Sep: acta case
2. Carina Frykholm, Joakim Klar, Tatjana Tomanovic, Adam Ameur & Niklas Dahl Stereocilin gene variants associated with episodic vertigo: expansion of the DFNB16 phenotype European Journal of Human Geneticsvolume 26, pages1871–1874 (2018)

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Central auditory processes, cognitive development and reading in hearing-impaired and deaf children with cochlear implants or hearing aids - developmental and training effects.

This is a multicenter project with Linköping and Lund Universities. Children using hearing aids or cochlear implants have been assessed with a language development test protocol and auditory evoked potentials (mismatch negativity) before and and after a computer-assisted reading intervention. Results have been published and will be presented as a thesis in 2021. Further studies of the impact of hearing impairment in children are being conducted together with Örebro University.

EUscreen- H2020-SC1-2016-RTD. Implementation of cost-optimized childhood vision and hearing screening programs in middle-income countries in Europe.

PI for KI and Karolinska University Hospital as one of eight university partners. The purpose is to analyse the current provision of hearing screening across the EU and the clinical outcomes of this by comparing to the WHO principles for screening (Wilson and Junger, 1968). Focus will be placed on the circumstances (geographical, social, economic, policy) in which screening protocols have been designed, implemented and developed, aiming to understand the factors which lead to successful and sustainable programmes. The clinical outcome and cost effectiveness of these programmes will be assessed and packed into a transferable TOOLKIT that will assist healthcare providers and professionals in their decisions to introduce or modify childhood vision and hearing screening programs.

Planned project: Early Detection of Hearing Impairment in Children: Are we doing enough?
The purpose of this research project is to improve the detection pathways for children with hearing impairment (HI) that are not currently detected through newborn hearing screening (NHS). Answers to these questions will help guide policy on how to improve pathways and protocol for detecting children with HI as early as possible.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Elisabet Engström	
Allison Mackey	

Ethical permit No.

FAS 2008-1209	2014/1735-32			

Publications 2017, 2018, 2019, 2020

1. Cederroth CR, Lugo A, Edvall NK, Lazar A, Lopez-Escamez JA, Bulla J, Uhlen I, Hoare DJ, Baguley DM, Canlon B, Gallus S. Association between Hyperacusis and Tinnitus JOURNAL OF CLINICAL MEDICINE 2020 9:8 View in Medline
2. Engström E, Kallioinen P, Nakeva von Mentzer C, Lindgren M, Sahlén B, Lyxell B, Ors M, Uhlén I. Auditory event-related potentials and mismatch negativity in children with hearing loss using hearing aids or cochlear implants - A three-year follow-up study International journal of pediatric otorhinolaryngology 2020 : 110519- View in Medline
3. Engström E, Kallioinen P, Lindgren M, Nakeva von Mentzer C, Sahlén B, Lyxell B, Uhlén I. Computerassisted reading intervention for children with hearing impairment using cochlear implants: Effects on auditory event-related potentials and mismatch negativity International journal of pediatric otorhinolaryngology 2020 137: 110229-View in Medline

4. Uhlen I, Mackey A, Rosenhall U. Prevalence of childhood hearing impairment in the County of Stockholm - a 40-year perspective from Sweden and other high-income countries INTERNATIONAL JOURNAL OF AUDIOLOGY 2020 59:11 866-873 View in Medline
5. Lugo A, Edvall NK, Lazar A, Mehraei G, Lopez-Escamez JA, Bulla J, Uhlen I, Canlon B, Gallus S, Cederroth CR. Relationship between headaches and tinnitus in a Swedish study SCIENTIFIC REPORTS 2020 10:1 8494-View in Medline
6. Niu K, Brandström A, Skenbäck S, Duan M, Uhlén I. Risk factors and etiology of childhood hearing loss: a cohort review of 296 subjects Acta oto-laryngologica 2020 140:8 668-674 View in Medline
7. Trpchevska N, Bulla J, Prada Hellberg M, Edvall NK, Lazar A, Mehraei G, Uhlen I, Schlee W, Canlon B, Gallus S, Lopez-Escamez JA, Cederroth CR. Sex-Dependent Aggregation of Tinnitus in Swedish Families Journal of clinical medicine 2020 9:12 View in Medline
8. Engström E, Kallioinen P, Nakeva von Mentzer C, Lindgren M, Ors M, Sahlén B, Lyxell B, Uhlén I. Computer-assisted reading intervention for children with sensorineural hearing loss using hearing aids: Effects on auditory event-related potentials and mismatch negativity International journal of pediatric otorhinolaryngology 2019 117: 17-25 View in Medline
9. Simonsz H, Carlton J, Griffith H, Horwood A, Uhlen I, Fronius M, Qirjazi B, Rajka D, Vladutiu C, Hoeve H, Heijns-dijk E, de Koning H, EUSCREEN Fdn. Cost-effectiveness comparison of childhood vision and hearing screening programmes throughout Europe (EUSCREEN Study) ACTA OPHTHALMOLOGICA 2018 96: 12-12
10. Uhlén I, Engström E, Kallioinen P, Nakeva von Mentzer C, Lyxell B, Sahlén B, Lindgren M, Ors M. Using a multi-feature paradigm to measure mismatch responses to minimal sound contrasts in children with cochlear implants and hearing aids Scandinavian journal of psychology 2017 58:5 409-421 View in Medline

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Objective balance testing in children and infants

The first research project started in 2015 with the aim to retrieve valid and feasible methods fpr the study the vestibular function in infants and children. We could develop and validate a child friendly vestibular testing, suitable for clinical use. The project continues with the application of these methods for the study of vestibular function in infants at hearing screeninng program, in children affected by neurodevelopmental disorders and in those developing dizziness or vertigo. These studies are included in the doctoral educational program at KI of MD Niki Karpeta. This research program is supported by SCAPA (scientific center for advanced pediatric audiology) at KI.

New diagnostic methods in audiology and otoneurology based on bone vibration

A parallel research program is conducted as post doctoral studies in collaboration with Chalmers University, Biomedical signals and systems research group. The main focus is to develop clinical tests based on bone vibration in the field of audiology and neurotology.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Niki Karpeta

Ethical permit No.

2013/1177-31	2019_02019	2020-04214		

Publications 2017, 2018, 2019, 2020

1. Lazar A, Löfkvist U, Verrecchia L, Karltorp E. Identical twins affected by congenital cytomegalovirus infections showed different audio-vestibular profiles. Acta Paediatr. 2020 Sep 21.
2. Verrecchia L, Galle Barrett K, Karltorp E. The feasibility, validity and reliability of a child friendly vestibular assessment in infants and children candidates to cochlear implant. Int J Pediatr Otorhinolaryngol. 2020 Aug;135:110093.
3. Wibble T, Engström J, Verrecchia L, Pansell T. The effects of meclizine on motion sickness revisited. Br J Clin Pharmacol. 2020 Aug;86(8):1510-1518.
4. Verrecchia L, Karpeta N, Westin M, Johansson A, Aldenklint S, Brantberg K, Duan M. Methodological aspects of testing vestibular evoked myogenic potentials in infants at universal hearing screening program. Sci Rep. 2019 Nov 21;9(1):17225.
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6. Verrecchia L, Glad K, Frisk R, Duan M. Vestibular myogenic potentials evoked by air-conducted stimuli at safe acoustic intensity levels retain optimal diagnostic properties for superior canal dehiscence syndrome. Acta Otolaryngol. 2019 Jan;139(1):11-17.
7. Verrecchia L, Brantberg K, Tawfique Z, Maoli D. Diagnostic Accuracy of Ocular Vestibular Evoked Myogenic Potentials for Superior Canal Dehiscence Syndrome in a Large Cohort of Dizzy Patients. Ear Hear. 2019 Mar/Apr;40(2):287-294.

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Head and Neck diagnosis and treatment

Several projects:

- Tracheal Stenosis - Validation of DI (Dyspné Index) in swedish. Can outpatient corticosteroid injections in the stenosis extend the procedure free interval for patients with recurrent tracheal stenosis. Which spirometric values are best suited to diagnose and evaluate tracheal stenosis.
- Oral Cancer - Which diagnostic does best predict the depth of invasion in tounge cancer, CT, MRI, Ultrasound or palpation. How does perioperative ultrasound affect the tumor free zone in tounge cancer surgery. Will Narrow Band Imaging (NBI) better predict a zone of dysplasia around tounge cancers. Does a full thickness resection of the mandible give a better outcome in gingival cancer surgery than none-full thickness resection.
- Circulation HPV-DNA as a follow up marker of recurrence of oropharyngeal cancer.
- Can ultrasound be used in the diagnosis of Sjögrens Syndrome and replace salivary gland biopsies.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Eleftherios Ntouniadakis
	Olof Nilsson
	Anna Oldaeus

Ethical permit No.

2016/193	2016/275	2020-05509	2016/2463	2019-03-27

Publications 2017, 2018, 2019, 2020

1. Ntouniadakis E, Brus O, von Beckerath M. Dyspnea Index: An upper airway obstruction instrument; translation and validation in Swedish. Clin Otolaryngol. 2020 Dec 5. doi: 10.1111/coa.13682. Epub ahead of print. PMID: 33277799.
2. Kristiansson S, Reizenstein J, von Beckerath M, Landström F. Long-term follow-up in patients treated with electrochemotherapy for non-melanoma skin cancer in the head and neck area. Acta Otolaryngol. 2019 Feb;139(2):195-200. doi: 10.1080/00016489.2018.1543950. Epub 2019 Feb 8. PMID: 30734631.
3. Mäkitie AA, Keski-Säntti H, Markkanen-Leppänen M, Bäck L, Koivunen P, Ekberg T, Sandström K, Laurell G, von Beckerath M, Nilsson JS, Wahlberg P, Greiff L, Norberg Spaak L, Kjærgaard T, Godballe C, Rikardsen O, Channir HI, Rubek N, von Buchwald C. Transoral Robotic Surgery in the Nordic Countries: Current Status and Perspectives. Front Oncol. 2018 Jul 27;8:289. doi: 10.3389/fonc.2018.00289. PMID: 30101130; PMCID: PMC6072842.

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Temporal bone malformation.
Children with temporal bone malformations often present with a significant progressive hearing loss. Cochlea implantation is often needed to improve speech understanding and for the patient to develop the ability to communicate. We are investigating large vestibular aqueduct, and incomplete partition types 2 and 3 malformations. We are assessing new methods in radiological diagnosis, implantation technique, hearing and related neurological factors.

Intraoperative assessment of the ossicular chain.
Ossicular fixation in the middle ear is one cause of conductive hearing loss where there is no reliable objective system to assess this. We are developing a system (MIVIB) utilising laser vibrometry to assess the movement of the ossicular chain to determine which operation and which prosthesis will give the best hearing result.

Bilateral bone anchored hearing solutions.
Bone-anchored hearing solutions are often implanted unilaterally. We are assessing whether patients have an imporved ability to localise sound and hear when background noise is present if they are provided with bilateral BAHS.

Tracheostomy in the era of Covid-19.
During the first wave of the COVID-19 pandemic, 275 patients received a tracheostomy during their admission to intensive care (29%). 68 of these were performed percutaneously. This patient group will allow us to directly assess the complication rate of tracheostomy related to ARDS/COVID and compare the safety of the two techniques.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Clara Svenberg Lind (intended)	Kaijsa Edholm
	Fatima Moumen Denanto

Ethical permit No.

2020-02779	2018/1032-31	2014/2068-31/2		

Publications 2017, 2018, 2019, 2020

1. Wales, J., Alinasab, B., Fridman Bengtsson, O. A superficial nasal dermoid cyst excised through a novel horizontal zig-zag incision in a 49-year old man. Acta Otolaryngologica Case reports. 2020; 5:28-32.
2. Wales, J., Gladine, K., Silvola, J., Muyshondt, P., Topsakal, V., Van De Heyning, P., Dirckx, J., von Unge, M. Evaluation of artificial fixation of the incus and malleus with minimally invasive intraoperative laser vibrometry (MIVIB) in a temporal bone model. Otol. Neurotol. 2020; 41:45-51.
3. Smeds, H., Wales, J., Mathiesen, T., Talbäck, M., Feychting, M. Occurrence of primary brain tumours in cochlear implant patients in Sweden between 1989 and 2014. Clin. Epidemiol. 2018; 10:1401-5
4. Wales, J., Galdine, K., Van de Heyning, P., Topsakal, V., von Unge, M., Dirckx, J. Minimally invasive laser vibrometry (MIVIB) with a floating mass transducer – a new method for objective evaluation of the middle ear demonstrated on stapes fixation. Hear Res. 2018; 357:46-53.
5. Smeds, H., Wales, J., Asp, F., Löfkvist, U., Falahat, B., Anderlid, B., Anmyr, L., Karltorp, E. X-linked malformation and cochlear implantation. Otol Neurotol. 2017; 38:38-46.

PHD-students not presented in this book:
Edholm, Kajsa

Sigurdur Arnason sigurdur.arnason@ki.se
Main supervisor Barbro Hedin Skogman
Co-supervisor Malou Hultcrantz, Åsa Laestadius, Elin Marsk
Registered 2019-09-27
Halftime seminar
Planed dissertation

Facial nerve palsy in children; treatment and clinical outcome.

I. Peripheral facial nerve palsy in children in a Borrelia high endemic area: epidemiology and evaluation of clinical recovery. A retrospective follow-up.
To identify the incidence, etiology and prognosis of acute peripheral facial nerve palsy (FNP) in children in the Stockholm area. A retrospective study identifying children from 0-17 years of age visiting a pediatric emergency department for acute FNP during a one-year period from 2014-2015 (77 patients).

II. Efficacy of cortisone vs. placebo in children with idiopathic facial nerve palsy and Lyme neuroborreliosis facial nerve palsy.
Participation in the FACE study (Facial nerve palsy And Cortisone Evaluation in children), a multicenter randomized placebo-controlled study on the efficacy of cortisone treatment in children with acute facial nerve palsy. For inclusion the cause of FNP will be either Lyme neuroborreliosis (LNB) or idiopathic facial palsy. Children with LNB will be treated with antibiotics according to present guidelines in combination with the treatment provided in the study (cortisone vs. placebo).
Follow-up will take place via telephone and with follow-up visits at 1 and 12 months. Subjects will be graded according to the House-Brackmann and the Sunnybrook facial grading scales and specific standardized facial palsy questionnaires.

III. Long term outcome and neurophysiologic findings in idiopathic facial nerve palsy in a pediatric population. This study will aim to highlight the long-term prognosis of 50 children affected by idiopathic facial nerve palsy. The aim is to follow-up the children with idiopathic facial palsy and record subjective, objective and neurophysiological findings.

IV. Detection of brain damage markers S-100B and NSE in serum in children with Lyme neuroborreliosis for evaluation as prognostic marker for clinical outcome. The brain damage markers S-100 B and NSE (Neuron-specific enolase) will be analyzed in serum in children with LNB and in a non-neuroinflammatory group.

Ethical permit No.

2016/1937-31/4 (Stockholm)	2017/554 (Uppsala)	2010/106 (Uppsala)	

Publications/manuscripts 2017, 2018, 2019, 2020

1. Arnason, S, Hultcrantz, M, Nilsson, A, Laestadius, Å. Peripheral facial nerve palsy in children in a Borrelia high-endemic area, a retrospective follow-up study. Acta Paediatr. 2020; 109: 1229– 1235. https://doi.org/10.1111/apa.15063.

Daniel Danielsson daniel.danielsson@ki.se
Main supervisor Eva Munck-Wikland
Co-supervisor Siamak Haghdoost
Registered 2008-10-08
Halftime seminar 2020-06-17
Planned dissertation

Osteoradionecrosis - Riskfactors and reconstructive outcome

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, im- paired nutritional capacity and infection not seldom associated with oro-cutanous fistula. ORN is seldom reversible and will progress over time leading to pathological fractures and need for extensive reconstruc- tive surgical intervention including free tissue transfer. This treatment is costly to both patient and society.

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

Aim of our studies:

1. Possible markers for individual radiosensitivity; oxidative stress response, genetic and protein level
2. Osteoradionecrosis impact on indications for exstensive maxillomandibular reconstruction
3. Quality of life comparative study for ORN patients before and after extensive reconstrucitve surgery with free tissue transfer.
4. Impact of Brachy therapy in onset of ORN in patients treated for cancer of the tounge

Ethical permit No.

2006/1413-32	2016/1578-32	2016/277-32	2016/506-31	

Publications/manuscripts 2017, 2018, 2019, 2020

1. Osteoradionecrosis, an increasing indication for microvascular head and neck reconstruction. Danielsson D, Gahm C, Haghdoost S, Munck-Wikland E, Halle M. Int J Oral Maxillofac Surg. 2020 Jan;49(1):1-6. doi: 10.1016/j.ijom.2019.06.009. Epub 2019 Jul 8. PMID: 31296436
2. Quality of life after microvascular mandibular reconstruction for osteoradionecrosis-A prospective study. Danielsson D, Munck-Wikland E, Hagel E, Halle M. Head Neck. 2019 Jul;41(7):2225-2230. doi: 10.1002/hed.25681. Epub 2019 Feb 5. PMID: 30721560

Elisabet Engström elisabet.engstrom@ki.se
Main supervisor Inger Uhlén
Co-supervisor Björn Lyxell

Registered 2007-02-12
Halftime seminar 2019-06-05
Planned dissertation 2021-03-26

Neurophysiological Conditions for Hearing in Children Using Hearing Aids or Cochlear Implants – An Intervention and Follow-Up Study

The studies involved children with hearing loss using hearing aids and cochlear implants and focused on the central auditory pathways by recording event-related potentials (ERP) and mismatch negativity (MMN). The design of the project was partly experimental, and it also included an intervention part, and finally, a follow-up-study after three years.

In study I, the method was tested and we worked out a model for how to interpret and analyse the results.

Study II demonstrated that differences in both obligatory responses in ERP and MMN between the children with hearing aids vs children with normal hearing disappeared after computer-assisted reading intervention, GraphoGame, suggesting a training effect among the children with hearing aids. Similar change could not be shown among the children with cochlear implants (study III).

After three years (study IV), there was a significant change in ERP regarding the children with hearing aids, indicating a possible catch-up. The children with cochlear implant did not show similar development. On the contrary, their mean ERP was significantly lower compared to the children with hearing aids and normal hearing after three years, indicating a poorer development of the central auditory system.

Ethical permit No.

2009/905-31/2	2010/1456 32			

Publications/manuscripts 2017, 2018, 2019, 2020

1. Using a multi-feature paradigm to measure mismatch responses to minimal sound contrasts in children with cochlear implants and hearing aids. Uhlén I, Engström E, Kallioinen P, Nakeva von Mentzer C, Lyxell B, Sahlén B, Lindgren M, Ors M. Scand J Psychol. 2017
2. Computer-assisted reading intervention for children with sensorineural hearing loss using hearing aids: Effects on auditory event-related potentials and mismatch negativity. Elisabet Engstrom, Petter Kallioinen, Cecilia Nakeva von Mentzer, Magnus Lindgren, Marianne Ors, Birgitta Sahlén, Bjorn Lyxell, Inger Uhlen. Int Journal of Pediatric Otorhinolaryngology, 2019
3. Computer-assisted reading intervention for children with hearing impairment using cochlear implants: Effects on auditory event-related potentials and mismatch negativity. Engström E, Kallioinen P, Lindgren M, Nakeva von Mentzer C, Sahlén B, Lyxell B, Uhlén I. Int J Pediatr Otorhinolaryngol. 2020 Oct; 137:110229
4. Auditory event-related potentials and mismatch negativity in children with hearing loss using hearing aids or cochlear implants – a three-year follow-up study. Engström E, Kallioinen P, Nakeva von Mentzer C, Magnus Lindgren†, Sahlén B, Lyxell B, Ors M, Uhlén I. Int J Pediatr Otorhinolaryngol. 2020; 2020 Nov 24, Online ahead of print.
5. Reading Ability and Working Memory in School-Age Children Who Are Deaf and Hard of Hearing Using Cochlear Implants and/or Hearing Aids: A 3-Year Follow-Up on Computer-Based Phonics Training . Cecilia Nakeva von Mentzer, Sonia Wallfelt, Elisabet Engström, Malin Wass, Birgitta Sahlén, Karin Pfändtner, Björn Lyxell, Petter Kallioinen, Magnus Lindgren, Marianne Ors, Inger Uhlén. Perspectives of the ASHA Special Interest Groups; Language Learning and Education, https://pubs.asha.org 185.113.96.207 on 12/07/2020

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Main supervisor Caroline Gahm
Co-supervisor Martin Halle, Liv Eidsmo, Lalle Hammarsted Nordenvall
Registered 2018-01-29
Halftime seminar
Planned dissertation

Inflammatory changes of skin after radiotherapy

An increasing number of long-term cancer survivors have a reduced quality of life due to sequelae from previous radiotherapy. Fibrosis of soft tissue leads to cosmetic as well as functional difficulties, e.g. stiffness, dysphagia and hoarseness. Exposure to ionizing radiation in the head and neck area and thorax also predispose to stroke or heart disease.

Our hypothesis is that radiotherapy leads to dysregulation of the innate and adaptive immune system, resulting in chronic inflammation, and deposition of extracellular matrix. A decrease in the size and number of blood vessels leads to a perpetual and worsening hypoxia of the tissue, which further exacerbates the problem.

We collect skin samples from previously irradiated patients undergoing surgery in the ENT unit and will compare these samples to a murine radiation model using immunohistochemistry, immunofluorescence and gene expression analysis. Through a better understanding of the biology causing these changes, we hope to ameliorate the morbidity of future cancer survivors.

Ethical permit No.

2015/696-32	2008/814-31	2012/1663-32	2008/484-31/2	2006/834-31/1

Publications/manuscripts 2017, 2018, 2019, 2020

1. Martin Halle, Bjorn O Eriksson, Ann-Charlott Docherty Skogh, Pehr Sommar, Lalle Hammarstedt, Caroline Gahm. Improved Head and Neck Free Flap Outcome-Effects of a Treatment Protocol Adjustment from Pre- to Postoperative Radiotherapy. IPlast Reconstr Surg Glob Open. 2017 Mar 30;5(3):e1253. eCollection 2017 Mar. PMID: 28458967, PMCID: PMC5404438. DOI: 10.1097/GOX.0000000000001253
2. Bjorn O Eriksson, Caroline Gahm, Martin Halle. Upregulation of Plasminogen Activator Inhibitor-1 in Irradiated Recipient Arteries and Veins from Free Tissue Transfer Reconstruction in Cancer Patients. Mediators Inflamm. 2018 Oct 4;2018:4058986. eCollection 2018. PMID: 30402041. PMCID: PMC6193344. DOI: 10.1155/2018/4058986

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Main supervisor Pär Stjärne
Co-supervisor Anna-Lena Hulting, Charlotte Höybye, Ola Sunnergren
Registered 2011-12-22
Halftime seminar 2021-01-22
Planed dissertation

Pituitary tumors; clinical aspects of treatment and expression of Galanin,- and pattern recognition receptors

Pituitary adenomas are classified into hormone secreting or clinically inactive. Symptoms arise either due to hormononal effects or local compression, usually the optic chiasm.
Treatment for these adenomas are either medical och surgical dependent on characteristics of the tumor. Sometimes radiation can be used for surgically unacessible locations.
My thesis aims to evaluate treatment in Karolinska University Hospital during the time period 2005-17, focusing on cure rates in ACTH and GH producing adenomas and complications within the group as a whole. This manuscript is due for submission.
We have also evaluated different treatment strategies in periopoperative cortison substitution and published on this topic 2019.
Since 2012 we have collected tissue from pituitary adenomas and pituitaries from 10 organ donors as a base for our receptor studies.
Our aim is that these 2-3 studies are to be completed during 2020. One study will evaluate prevalence of Galaninreceptors, especially type 3, which in previous materials have been indicated as a marker for pituitary adenomas as opposed to normal pituitary tissue.
The fourth study will investigate a new inflammatory marker, called TSLP (Thymic Stromal Lymphopoetin) and which has been described in inflammatory airway disease, but not yet been studied in pituitary adenomas. We will also look at neuropeptide Y, pattern recognition receptors and TGFbeta.
My aim is to publish study 2 during early 2021, write manuscripts for study 3 and 4 in autumn

Ethical permit No.

2012/1689-31/4 (2019-01941)	2012/891-31/2			

Publications/manuscripts 2017, 2018, 2019, 2020

1. Evaluations of different treatment strategies in transsphenoidal pituitary surgery,Acta Neurochirurgica (2019) 161:1715–1721. https://doi.org/10.1007/s00701-019-03885-6
2. Acta Neurochirurgica (2019) 161:1715–1721 ”Cure rate, complications and overall survival in transsphenoidal pituitary surgery at Karolinska University Hospital, manuscript.

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Halftime seminar
Planned dissertation

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Lalle Hammarstedt Nordenvall
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2020-05-25

Studies on Nasopharyngeal Cancer – a characterization of a rare disease

I: To describe the pattern of recurrence in patients treated for nasopharyngeal cancer in Stockholm.
Hypothesis: Local recurrences occur outside target volume.
Retrospective single institution study. Data from medical records and target volume, will be correlated to recurrence and place of recurrence, ie outside or inside target volume. Pattern of failure will teach us more on how to design treatment models in this disease. If recurrences occur outside treatment volume that might be an indication to improve treatment planning.

II: A register-based cohort study of Nasopharyngeal Carcinoma in Sweden, using SweHNCR: outcome, failure rate and site of failure
Hyphothesis: Local regional failure is more common than distant failure
Data from Swedish Head and Neck Cancer Registry (SweHNCR). All patients in Sweden diagnosed with Nasopharyngeal carcinoma, histology codes for Squamous cell carcinoma, Lymfoepithelioma or undifferentiated carcinoma will be included.
This study will describe the pattern of failure in Sweden and thus indirectly characterize the disease as resembling either the endemic type or the non-endemic type.

III: To describe the distribution of the different histopathological subgroups and to assess the viral correlation.
Hypothesis: The overall viral correlation is higher than in Finland
The Stockholm cohort will be used to assess viral association. Data on how the distribution of viral correlation is in Sweden will be of importance when addressing treatment options.

IV:To describe the risk profile for second primary in patients with NPC.
Hypothesis: Patients treated for NPC carries a higher risk for second primary than the general population.
A register-based study will be performed to characterize the population at risk for the disease. Linkage to multi-generation registry will be used in this regard, will be used to assess risk of second primary.

Ethical permit No.

2019-01933					

Publications/manuscripts 2017, 2018, 2019, 2020

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2017-06-20
2019-12-17

Increased expression of jagged-1, NOTCH-1 and NOTCH-4 in nasal mucosa of patients with allergic rhinitis

Intra lymphatic immunotherapy is proposed as a faster and safer alternative to conventional allergy therapy. In previous projects we have confirmed the safety of ILIT, we have also shown that concomitant ILIT with birch and grass allergen reduces allergen-induced symptoms during the pollen season.

It is well established that the subtypes of allergen-specific T-cells is altered in allergic patients compared to non-allergic control patients. The most evident difference is the increased level of Th2 T-cells expressing IL-4 in allergic patients and the increased level of Th1 T-cells expressing type I IFN in healthy individuals. The immunological findings in our previous study show that memory T-cells increase in the lymph node and blood in patients treated with ILIT. We also show that especially memory T-cells expressing CCR5 (Th1 T-cells) increase in ILIT treated patients. If the memory CCR5+ T-cells express type I IFNs would be interesting to follow up in future studies because a possible mechanism for ILIT would be that the balance between TH2 T-cells and TH1 expressing IFN type I is restored.

Ongoing projects are aimed at developing new protocols for the detection of allergen-specific changes;

- Analyzing changes in basophil sensitivity and circulating allergen-specific IgA, E, IgG.
- Analyzing the level allergen-specific Th2 T-cells, specific subtypes of Th1 T-cells, and T-regs in allergic and non-allergic individuals.
- Analyzing class switching on allergen-specific B-cells in lymph nodes and blood in allergic and non-allergic individuals.

Ethical permit No.

2016-823-31-2	2018-2645-32	2017-2257	2012-1018		

Publications/manuscripts 2017, 2018, 2019, 2020

1. ILIT after SCIT- a - a randomized double blind placebo controlled trial of intralymphatic immunotherapy in an up-dosing schedule. (manuscript)
2. A five-year open follow up of a randomized double-blind placebo-controlled trial of intralymphatic immunotherapy for birch and grass, reveals remaining beneficial effects. (Manuscript)
3. Increased expression of jagged-1, NOTCH-1 and NOTCH-4 in nasal mucosa of patients with allergic rhinitis. (Manuscript)
4. Activation of T helper cells in Sentinel Node predicts poor prognosis in oral squamous cell carcinoma. Sci Rep 2020
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7. Arebro J, Ekstedt S, Hjalmarsson E, Winqvist O, Kumlien Georen S, Cardell LO. A possible role for neutrophils in allergic rhinitis revealed after cellular subclassification. Sci Rep. 2017;7:43568.

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Planned dissertation	May 2021

Complications of acute bacterial rhinosinusitis in children and the implication of pneumococcal conjugate vaccine

AIM
To study all children up to 18 years old with complications due to acute rhinosinusitis in Stockholm County to get a better understanding of which children are at risk of developing such complications. Furthermore, to study the impact on these complications after the introduction of pneumococcal vaccine in Stockholm County.
The studies aim to enlighten the population-based incidence of complications in different age groups, the range of complications - degrees of orbital complications and intracranial complications, the need of surgical intervention, risk factors for developing complications and the causing bacteria of the infections and if it is linked to clinical prognosis. Furthermore, the last study will analyze the bacteria in different types of cultures (NPH and middle meatus, surgery and blood), and the results of virus swab, phadiatop, and immunoglobins in the cohort.

The first and second studies are completed and published. They clarified the incidence of admission and complications, and the results of bacterial cultures, before and after the introduction of the pneumococcal vaccine in children 0-5 years old. Study three is submitted. It analyzed the number och types of complications, and the bacterial culture results, in children 5-18 years old 2003-2016. Study four is a prospective study of children up to 18 years old with rhinosinusitis admitted in Stockholm, the manuscript is being completed.

Ethical permit No.

2011/44-31/1	2011/1407-32	2012/144-2/1	2013/1428-32	2015/779-32	2017/296-31	2016/1475-32

Publications/manuscripts 2017, 2018, 2019, 2020

1. L Schollin Ask*, S Hultman Dennison*, P Stjärne, A Granath, S Srivastava, M Eriksson, A Lindstrand, M Ryd Rinder (*Shared first authorship). Most preschool children hospitalised for acute rhinosinusitis had orbital complications, more common in the youngest and among boys. Acta Paediatr. 2017 Feb;106(2):268-273. doi: 10.1111/apa.13650. Epub 2016 Nov 24.
2. S. Hultman Dennisona, L. Schollin Ask, M. Eriksson, A. Granath, O. Hertting, R. Bennet, A. Lindstrand, P. Masaba, P. Dimitriou, P. Stjärne. Serious complications due to acute rhinosinusitis in children up to five years old in Stockholm, Sweden - Still a challenge in the pneumococcal conjugate vaccine era. Int J Pediatr Otorhinolaryngol. 2019 Jun;121:50-54. doi: 10.1016/j.ijporl.2019.02.034. Epub 2019 Feb 25

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Hearing, cognition and aging

Huvudsyfte är att belysa central hörselfunktion, hur vi kan mäta den, och dess relation till kognitiv svikt. Mer specifikt att öka förståelsen hur hjärnförändringar vid demens och kognitiv svikt påverkar central hörselfunktion. Antalet äldre ökar stadigt i befolkningen tack vare att vi lever allt längre. Med stigande ålder ökar också risken av att drabbas av kognitiv svikt, demens och hörselnedsättning. En form av hörselnedsättning hos främst äldre är s.k. central auditory processing dysfunction, (CAPD). Dessa personer har svårigheter att uppfatta vad som sägs i störande ljudmiljöer med bakgrundsbuller eller när flera personer talar samtidigt, och de har inte optimal nytta av hörapparatanvändning. Den centrala hörselstörningen beror på försämrad funktion i de delar av centrala nervsystemet som ansvarar för bearbetningen av ljudstimuli. CAPD har påvisats hos patienter med lindrig kognitiv störning och Alzheimers sjukdom genom dikotiska lyssningstest. I delarbete 1 följdes tre grupper av individer med varierande kognitiv funktion med perifera och centrala hörseltestunder efter fem år. I delarbete 2 tittade vi på kognitiv utveckling hos en grupp individer med mild kognitiv störning (MCI) och jämförde kognitivt utfall under 5 år med resultat på dikotiska tester med siffror (DDT) vid baseline. I delarbete 3 korreleras resultat på DDT till deltagarnas biomarkörer i cerebrospinalvätska. I delarbete 4 kommer vi att undersöka hur förändringar i corpus callosum, som förbinder de båda hjärnhalvorna, korrelerar till resultat på DDT hos personer med Alzheimers sjukdom (AD), MCI och subjektiv minnesstörning (SMC). DDT förutsätter en intakt förbindelse mellan hjärnhalvorna via corpus callosum.

Ethical permit No.

2005/914-31	2014/2087-31/2	2018/1291-32		

Publications/manuscripts 2016, 2017, 2018, 2019

1. A Longitudinal Study of Peripheral and Central Auditory Function in Alzheimer's Disease and in Mild Cognitive Impairment, 2018.
2. Prognostic value of a test of central auditory function, the dichotic digits test, in conversion from mild cognitive impairment to dementia, submitted 2019

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Planned dissertation	Planned for 2022

Children with Congenital Unilateral Sensorineural Hearing Loss: The effect of Auditory Stimulation in the Impaired Ear During Development

The overall aim is to study the causes and mechanisms underlying congenital unilateral sensorineural hearing loss (uSNHL) and the effects of intervention.

In the first publication we studied hearing aid outcomes in school-aged children with congenital uNSHL and demonstrate both hearing aid benefit and dis-benefit (n = 6). The statistically significant benefit was found in one-to-one communication, based on child and parent questionnaires. Hearing aid dis-benefit was found for sound localization measured with eye-tracking in sound field. Neither significant hearing aid benefit nor dis-benefit existed for speech understanding in background noise/speech (sound field and questionnaires) or reverberation (questionnaires). A close relationship between neural maturation and aided sound localization was also found, indicating that hearing aids may be more efficient if fitted earlier in development, before the brain adapts to asymmetrical hearing.

In the second publication we studied heredity of transient evoked otoacoustic emissions (TEOAEs), that are recorded as part of the universal neonatal hearing-screening program. Before the study, one publication had estimated TEOAE heritability based on young adult twins' TEOAEs. In a large consecutive sample of neonatal twins (n = 454), we found that the TEOAEs at birth are largely inherited, perhaps more than for young adult twins. Additionally, we found that sex and ear differences existed at birth, and that the twin testosterone transfer hypothesis, that female twins with male co-twins would have masculinized TEOAEs, was not supported for neonatal twins.

We are currently inviting all children with congenital uSNHL born in Region Stockholm to evaluate early hearing abilities, hearing loss progression, and the outcomes of very early hearing aid intervention longitudinally. Furthermore, we study the etiology as a factor in children with congenital uSNHL's hearing development. The project will run over a few more years.

Ethical permit No.

2015/1878-31/2	2018/1500-31	2019–03826		

Publications/manuscripts 2017, 2018, 2019, 2020

1. Johansson, M., Asp, F., Berninger, E. 2020. Children With Congenital Unilateral Sensorineural Hearing Loss: Effects of Late Hearing Aid Amplification-A Pilot Study. Ear and Hearing 41, 55-66. doi:10.1097/aud.0000000000000730.
2. Johansson, M., Olofsson, Å., & Berninger, E. (2020). Twin study of neonatal transient-evoked otoacoustic emissions. Hearing Research. doi:10.1016/j.heares.2020.108108.

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Development of central auditory systems in children with monaural canal atresia -Effects of early intervention

Individuals with unilateral hearing loss are known to have difficulties in situations requiring binaural processing of sounds, such as listening in noisy environments and localising sound. This project focuses on children born with unilateral aural atresia causing a conductive hearing loss on the affected side. We aim to study the effect of habilitation with bone anchored hearing aids on audiological outcomes and sound localisation ability as well as surgical outcomes and the degree of patient satisfaction.

Ethical permit No.

2018/ 1606-32	2012/1661-31/3	N 191/14	N113/15	2019-03090

Publications/manuscripts 2017, 2018, 2019, 2020

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Planned dissertation

Corticosteroid treatment in children with acute facial nerve palsy

My project is based on the Facial nerve palsy And Cortisone Evaluation (FACE) study in children. It is a randomized, placebo-controlled, double-blind, multicentre trial aiming to determine the efficacy of prednisolone treatment in children with acute facial nerve palsy.

Twenty percent of children acquiring an acute facial nerve palsy will not regain full facial function. Symptoms that these children report are, for example, pronunciation problems, drooling and tearing eye in addition to social and psychological consequences of having facial asymmetry. The aim of our study is to determine if prednisolone treatment will improve the outcome for children with acute facial nerve palsy as previously have been shown in adults.

The FACE study includes children with idiopathic facial nerve palsy as well as children with facial nerve palsy associated with Lyme neuroborreliosis. Enrolment takes place at 12 paediatric departments in Sweden and a total of 500 children will be randomized to either prednisolone 1mg/kg/day (maximum 50 mg/day) or placebo per orally for 10 days. The treatment procedure is double-blinded.

Our primary outcome is complete recovery (defined as House-Barackmann grade 1) at 12-months follow-up. In addition to determining the efficacy of prednisolone in children's acute facial nerve palsy, we will also evaluate the agreement between physician-assessed facial grading and self-/proxy-reported disability and quality of life. Furthermore, we will investigate factors of importance for predicting complete recovery in an early phase of the disease.

Inclusion in the FACE study is ongoing since May 2019 and is expected to continue throughout 2022.

Ethical permit No.

2017/554	2019-01546			

Publications/manuscripts 2017, 2018, 2019, 2020

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Development of objective balance tests in newborns and young children

Over the last few years there has been an increased interest in assessing the vestibular system in the paediatric population. Growing evidence for vestibular and balance problems in children with or without hearing loss and in children with delayed motor milestones point out the need in developing diagnostic skills for the assessment of the vestibular function.

We propose the introduction of Vestibular Evoked Myogenic Potentials (VEMP) and Video Impulse Test (V HIT) as diagnostic tools in early assessment of the vestibular function . We will also investigate the possibility of using VEMP as a screening test of the balance system in newborns and if it can be used as a predictive marker in the development of their motor skills.

Ethical permit No.

2015/1296-31/2				

Publications/manuscripts 2017, 2018, 2019, 2020

1. Luca Verrecchia , Niki Karpeta Magnus Westin. Methodologiacal aspects of testing vestibular evoked myogenic potentials in infants at a universal hearing screening programme. Scientific Reports ,Vol 9 Art n 1 7225 (2019)

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Halftime seminar
Planned dissertation

Immunological response in sentinel node and flow cytometric detection of satellitosis and micro metastasis

For a few years sentinel node technology has been used in our clinic in the diagnostics of oral cancer. A first sub-study aims to describe and follow up the patients where the technique has been used. The topographic location of the sentinel node is interesting because it sometimes does not match the established views of how transmission routes look like in oral cancer.

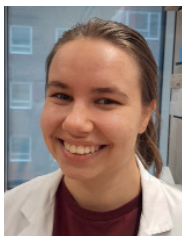
Our research group has also developed a method to detect squamous cell carcinoma in lymph nodes using flow cytometry. Markers for epithelial cells are detected and have been shown to respond well to the presence of metastases. In a previous project, lymph nodes from neck dissections performed on patients with oral cancer were analyzed with flow cytometry based on the presence of micro metastases. In my second sub-study, I do a follow up on these patients to see if there is a correlation between the incidence of micro metastases and recurrence.

In third sub-study investigates whether it is possible to detect cancer cells in muscle tissue with the same technology. During surgical resection of the tumor in patients with tongue cancer, biopsies are taken from the wound surface. The biopsies are analyzed by flow cytometry to see if it is possible to detect small foci of cancer cells. Patients are followed up to see if these findings orrelate with histology and recurence.
Patients with oral cancer have been shown to differ in sentinel node immunological activity. In a fourth sub-study, we investigate what the immunological response looks like in the sentinel node in tonsil cancer. At the clinic, a prototype has been developed that connects the gamma probe with an ultrasound probe. Then, one can locate the sentinel node with ultrasound and perform fine-needle aspiration. The sample is analyzed with standard cytology and immunological analyzes. Patients are then monitored to see if the immunological response can be correlated with cytological presence of cancer cells, treatment response and recurrence.

Ethical permit No.

2019-03518				

Publications/manuscripts 2017, 2018, 2019, 2020



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2021-01-25

Sentinel node B-cells and their interaction with host's immune system in head and neck cancer

Many patients with head and neck squamous cell cancer (HNSCC) present regional spread to the cervical lymph nodes (LN), while distant metastases are rare. Nodal involvement is the most important factor adversely affecting both the treatment and outcome. The treatment involves surgical removal of primary tumour, and removal of LN from one or more anatomical regions of the neck. However, extensive neck dissection is not without risks for severe complications. We want to provide an improved perioperative staging, so that only patients diagnosed with metastasis or unfavorable immunological features in sentinel node will receive a full neck dissection. Our preliminary results, clearly indicate that patients with low T-cells activation in LN have significantly higher risk of recurrence and death. Moreover, the development of new cancer treatments, especially immune checkpoint inhibitors (CPI), have changed the field of oncology. However, less than 20% of patients with HNSCC treated with CPI responds to this treatment. This is why, in order to fully benefit from this paradigm shift we have to improve the way we select patients for various treatment alternatives. The overall goal is to provide a better outcome prognostic marker as well as introduce an improved selection of patients who need more rigorous follow-up and those who would benefit from CPI. The overall aims are firstly to provide a detailed characterization of different B cellular components of a lymph node. Secondly, to comprehensively investigate the humoral immune response against various tumour-associated
antigens (TAAs) and lastly, to explore the mechanism of B cell cellular interactions and B cell mediated immune suppression in
patients with oral cancer.

Ethical permit No.

2019-03518				

Publications/manuscripts 2017, 2018, 2019, 2020

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Planned dissertation

Clinical use of prognostic markers in Head- and Neck Cancer

Numerous reports in recent decades have shown that, in addition to smoking and alcohol, human papilloma virus (HPV) is also associated with the development of oropharyngeal squamous cell carcinoma , predominantly in the tonsils and base of the tongue. In addition, patients with HPV-positive oropharyngeal SCC have a better clinical response to therapy than patients with HPV-negative oropharyngeal cancer. In hypopharyngeal cancer, which have a bad prognosis overall, HPV is less present, but still HPV-positive tumors have better clinical response to oncologic treatment.

Aim of the first study is to clarify the presence of HPV in all types of lumps of the neck, we didn't find HPV 16 or HPV 18 in any benign neck masses, published in 2016. In the second study we tested brancial cleft cysts for HPV, all cysts turned out to be HPV-negative. The third study investigate the use of other markers than HPV in hypopharyngeal cancer.

In the fourth study we looked immune related proteins and tumor infiltrating CD8+ lymphocytes in hypopharyngeal cancer in relation to human papillomavirus (HPV) and clinical outcome

Ethical permit No.

Publications/manuscripts 2017, 2018, 2019, 2020

1. Sivars L, Landin D, Grün N, Vlastos A, Marklund L, Nordemar S, Ramqvist T, Munck-Wikland E, Näsman A, Dalianis T.Validation of Human Papillomavirus as a Favourable Prognostic Marker and Analysis of CD8+ Tumour-infiltrating Lymphocytes and Other Biomarkers in Cancer of Unknown Primary in the Head and Neck Region. Anticancer Res. 2017 Feb;37(2):665-673.
2. Lars Sivars, David Landin, Marzia Rizzo, Linnea Haeggblom, Cinzia Bersani, Eva Munck-Wikland, Anders Näsman, Tina Dalianis & Linda Marklund. Human papillomavirus (HPV) is absent in branchial cleft cysts of the neck distinguishing them from HPV positive cystic metastasis. Pages 855-858 | Received 20 Feb 2018, Accepted 08 Apr 2018, Published online: 15 May 2018
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Planned dissertation

Bell's palsy in pregnancy and puerperium

To examine the incidence of Bell's palsy among pregnant women in Stockholm during a 10-years period, to find risk factors for developing Bell's palsy during pregnancy and the puerperium (first 6 weeks post partum), to see how these women heal compared to non pregnant women with Bells palsy and how the disease affects the patient's quality of life.

Ethical permit No.

2015/2349-31/1				

Publications/manuscripts 2017, 2018, 2019, 2020

1.

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Planned dissertation	

Perspectives on screening strategies for early detection of childhood hearing impairment

The benefits of early detection of hearing impairment are well understood. Yet, the diversity in screening strategies across countries makes it challenging for policy makers to choose a protocol that is optimal for their country or region. Via a comprehensive questionnaire on childhood hearing sceening, we gathered information on hearing screening programmes across 47 countries or regions, primarily in Europe. The aims of the project were to explain the diversity in childhood hearing screening strategies and investigate the performance of the various strategies. The data on quality indicators would then feed into a cost-effectiveness model of childhood hearing screening.

The following are some conclusions from the questionnaire. First, countries with newborn hearing screening that use only OAE screening on all infants (including NICU infants) had lower health care expenditure compared to countries that use more complex protocols, i.e., having a separate protocol for NICU infants, and using automated-ABR screening. Most countries have nurses perform screening, and screening is typically performed in the maternity hospital at least 24 hours after birth. Second, there was a widespread lack of data available on the performance of screening across the participating countries, suggesting that many programmes do not monitor or evaluate the of quality of their screening programme. Among programmes with data, coverage rates were generally high. Loss to follow-up between screening steps and from screening to diagnostic assessment was a common barrier to effective screening. Finally, a small proportion of participating countries provide hearing screening from 3 to 7 years of age. Pure-tone audiometry is used by all participating countries that offer universal screening. The lack of certainty to the cost-effectiveness of hearing screening at preschool age is perpetuated by the fact that the fact that data are mostly not available on the outcomes of screening.

Ethical permit No.

Publications/manuscripts 2017, 2018, 2019, 2020

1. Verkleij, M.L., Heijnsdijk, E.A.M., Bussé, A.M.L., Carr, G., Goedegeburge, A., Mackey, A.R., Qirjazi, B., Uhlén, I.M., Sloot, F., Hoeve, H.L.J., de Koning, H.J., EUSCREEN Study Consortium (In press). Cost-effectiveness of neonatal hearing screening programs: a micro-simulation modeling analysis. Ear and Hearing.
2. Uhlén, I., Mackey, A., Rosenhall, U. (2020). Prevalence of childhood hearing impairment in the County of Stockholm - a 40-year perspective from Sweden and other high-income countries. International Journal of Audiology, 59(11), 866-873.
3. Bussé, A.M.L., Hoeve, H.L.J., Nasserinejad, K., Mackey, A.R., Simonsz, H.J., Goedegeburge, A. (2020). Prevalence of permanent neonatal hearing impairment: systematic review and Bayesian meta-analysis. International Journal of Audiology, 59(6), 475-485.
4. Mackey, A.R., Hodgetts, W.E., Small, S.A. Materation of bone-conduction transcranial and forehead attenuation using a measure of sound pressure in the ear canal. (2018). International Journal of Audiology, 57(4), 283-290.

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Halftime seminar
Planned dissertation

Effects on breast-feeding and development of hard palate in children with ankyglossia (tongue tie). Comparative measurements with alginate imprints of the hard palate, oral scanner, neonatal tongue screening test and TABBY (tongue assessment tool for tongue-tie in breastfed babies)

Hypothesis: A restriction of the mobility of the tongue affects the hard palate and gives a high palate.
Aim: The main purpose is to be able to determine with greater certainty which children who have a restricted tongue due to a tongue-tie, would benefit the most from a frenotomy .
Normally when nose-breathing, the muscle Buccinator and the periorbital muscles give an external pressure to the maxilla which the tongue counteracts hence giving a normal development of the hard palate. But when mouth-breathing occur, ie. nasal congestion or low muscle tone, the middle face becomes elongated with a narrowing of the maxilla and often a narrowing upwards of the hard palate. This event has also been suggested to happen, when tongue mobility is restricted and do not reach the hard palate. To clarify if there is any correlation between a tongue-tie and a high palate, we want to examine 25 newborn, full-term children who have undergone a normal pregnancy and birth at BB Danderyds Hospital. The hard palate is assessed in correlation with the appearance and function of the tongue, but also if there are any problems like breastfeeding, reflux, lip blisters, weight gain, ability to take a pacifier and baby bottle.

Study plan
Visit 1: at 3 days of age, casting of the hard palate with alginate imprint and the use of an intraoral scanner. Visual and palpable inspection of the tongue using Neonatal tongue screening test and TABBY tongue assessment (tool for tongue-tie in breastfed babies). Interview with the breastfeeding parent regarding breastfeeding.
Visit 2: at 6 weeks of age with telephone interview about breastfeeding, reflux, weight gain, whether the parents have received / need breastfeeding support and whether the child has had the tongue band fixed with a frenotomy. 3:
Visit 3: follow-up at 6 months of age with new alginate casting and intraoral scanning, examination of tongue as at visit 1, and answer the study's standard questionnaire.

Ethical permit No.

Publications/manuscripts 2017, 2018, 2019, 2020

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Registered	2020-04-20
Halftime seminar	
Planned dissertation	2025

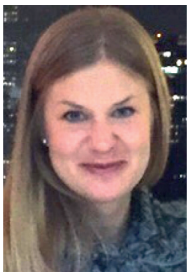
Bilateral bone anchored hearing devices

Binaural hearing is important for everyday listening tasks. The ability to localize sound and understanding speech in a noisy environment is dependent on the difference in time and level at which the sound reaches the two ears. In bone conducted sound this ability is affected due to the properties of the skull and surrounding tissue. In my doctoral project we study wether a bilateral fitting of bone conduction hearing devices (BAHS) gives a better hearing compared to one device in terms of sound localization accuracy and speech understanding in spatially separated competing speech. In addition, self-perceived benefit and quality of life will be assessed. Normal hearing subjects as well as patients with bilateral conductive/mixed hearing loss that are using one BAHS will be assessed and tested with bilateral fitting compared to unilateral BAHS.

Ethical permit No.

2019-04696				

Publications/manuscripts 2017, 2018, 2019, 2020



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Surgical treatment of peripheral facial palsy; assessment of regained function and quality of life

Persistent sequele of peripheral facial palsy imposes a great reduction in quality of life. The acute phase of the disease is well known, but the prevalence of long term sequele is unknown. We will map the prevalence in a large Stockholm based cohort.

A common sequele is synkinesis, ie mass muscle movement as a result of defect nerve healing. The gold standard treatment is physiotherapy and repeated Botox injections. If this treatment failes no evidence based treatment is currently available. We will evaluate highly selective neurectomy as a treatment option.

Ethical permit No.

2019-00421				

Publications/manuscripts 2017, 2018, 2019, 2020

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Halftime seminar
Planned dissertation

Sentinel node B-cells and their role in tumour specific immune suppression in head and neck cancer

For decades, cancer research was focused on finding external pharmaceutical agents bearing the ability to recognize and destroy cancer cells in cases of metastatic disease. A very recent clinical discovery of immune checkpoint inhibitors (CPI) proved that the human immune system in appropriate conditions has the capability to eradicate on its own even metastatic cancer disease. However, still only a small fraction of patients shows a positive durable response to CPI treatment.
The contribution of different immune cell subsets, especially T cells, in CPI mediated regained anti-tumour immune response is well established. In contrast to T cells, the anti-tumour contribution of B cells has been scarcely investigated. B-cells are often overlooked even though they are important players in a fully-integrated immune response and constitute a substantial fraction of lymphocytes draining tumour tissue. We hypothesise that by better understanding of B-cell mediated anti-tumour response, we can identify new biomarkers predicting survival, response to standard anti-cancer treatment, CPI therapy or even develop new immune therapy targets. At the same time, giving the foundation to personalized immunotherapy approach in advanced HNSCC, we intend to test drugs sensitivity, including CPI agents, on primary tumour cells culture in the presence of lymphocytes derived from neck lymphatic system of affected patients.

Ethical permit No.

2019-03518				

Publications/manuscripts 2017, 2018, 2019, 2020

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2. Piersiala K, Akst LM, Hillel AT, Best SR. Laryngeal Pathologies and Their Associations With Mental Health Disorders. LARYNGOSCOPE 2020 ;
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Planned dissertation

Zygomaticomaxillary Complex Fractures: aspects of diagnostic methods, treatment and sequelae

Zygomaticomaxillary Complex (ZMC) fractures are one of the most common types of facial fractures and frequently managed at Karolinska University Hospital (KUH). Functional complixations (such as trismus, double vision and impaired sensation) and cosmetic complications (such as ocular dystopia and a sunken/broadened cheek) are common and are managed either by conservative or surgical treatment. Even though recent publications have sought to outline different algorithms for treating ZMC fractures, it is still the surgeons' individual training, experience and preference that influence the choice of treatment and not systematic evidence.

Overall aim of the project:

- To describe a new complication following orbital floor reconstructions.
- To evaluate long-term results of patients with ZMC fractures managed at KUH and to gain an overview of the most common functional and cosmetic complications.
- To introduce the volume difference along the external surface (VDAES) as a novel method of assessing zygomatic bone asymmetry.
- To examine the feasibility of using a computer-aided method in assessing candidates for ZMC reconstructions.

Ethical permit No.

2017/960-31/1	2018-302/31			

Publications/manuscripts 2017, 2018, 2019, 2020

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Halftime seminar 2020-10-16
Planned dissertation Prel. plan 2022

Explore students' perceptions of the clinical learning environment and the relationship to quality of life

This project aims to get a deeper understanding of students' perception of the clinical learning environment (CLE) and the connection to quality of life (QoL). Further, clinical supervisors' percption of giving feeback during clinical rotations has been studied. In the first study the participants were clinical supervisors for physiotherapy students at Karolinska University Hospital. In the second study the participants were students from different undergraduate programs (medical, physiotherapy, speech-language pathology and nursing) at Ki. The data collection was done with The Undergraduate Clinical Education Environment Measure (UCEEM).

Central scientic questions of the project are:
- How are the CLEs perceived by the students?
- What are the students' perceptions of their QoL during clinical rotations?
- What are the supervisors perceptions of feedback to students during cinical rotations?

The first study resulted in identifying an overarching theme "Continuous development and support within the social network at the workplace facilitates the work of clinical supervisors". Results from study 2; overall, students' perceptions of their CLE were positive, the medical students rated their CLE lower than other students. The item with the lowest ratings concern supervisors familiarty with the learning objectives which medical students rated lower than other students.

Ethical permit No.

2016/1425-31	2017/38-31/4			

Publications/manuscripts 2017, 2018, 2019, 2020

1. Clinical supervisors' experience of giving feedback to students during clinical integrated learning (Sellberg, Skavberg Roaldsen, Nygren Bonnier, Halvarsson), published in Physiotherapy and Practice.
2. A cross-sectional study of clinical learning environments across four undergraduate programs using Undergraduate Clinical Education Environment Measure (Sellberg, Palmgren, Möller), under review in BMC Medical Education

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Halftime seminar
Planned dissertation

Assessment and activation of tympanic membrane progenitor/stem cells- clinical and laboratory studies

This PhD-project aims to map the occurrence and activation of regenerative zones in the human ear drum.

In laboratory studies we try to identify stem cells and proliferative zones in normal human tympanic membranes as well as in tympanic membranes that has been mechanically and chemically injured. The goal is to better understand the healing mechanism.

Plasminogen is an endogenous protein and has a role in cell migration and wound healing and has been identified as a possible drug for medical treatment of chronic tympanic membrane perforation. In a clinical trial different doses of plasminogen are injected close to the tympanic membrane in the ear canal in patients with chronic perforations and the effect on healing of the ear drum is evaluated.

With this project we aim to increase knowledge about the normal healing process and to improve the treatment of tympanic membrane perforations with the ultimate goal to design a simple, out-patient procedure without the need for advanced surgery.

Ethical permit No.

2018/364	2017/2011-31			

Publications/manuscripts 2017, 2018, 2019, 2020

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Halftime seminar 2019-10-11
Planned dissertation

Central Auditory Pathways in Unilateral Congenital Conductive Hearing Impairment

Ear canal atresia causes profound conductive hearing loss of the affected ear. Unilateral hearing loss in known to cause major problems in understanding of speech in a noisy environment as well as difficulties in localization of sound source. In deafness, stimuli via other senses can activate the auditory cortex, a phenomenon known as cross modal plasticity. The connectivity of large networks of the brain can be visualized with resting state functional magnetic resonance imaging, rs-f-MRI and the white matter tracts connecting brain regions can be examined with diffusion weighted imaging. Morphological changes to the cortex can be measured in T1 or T2 anatomical MRI. The present thesis aims to investigate changes to functional connectivity and morphological changes to the brain, as a result of unilaterally deprived hearing in childhood. Human subjects with ear canal atresia are studied as well as an animal model with unilateral conductive hearing impairment. Initial results of rat studies suggest changes within the auditory pathways in adolescence but not in adults. Adults (human) show no changes within the auditory cortices in cortical thickness, or in resting state activity, but non-significant trend ($p<0.02$) of increased activity of visuospatial active region precuneus cortex coupled to right side auditory cortex planum polare. Auditory testing show that level of hearing loss of the atretic side affect ability to localize sound source.

Ethical permit No.

2012/1661-31/3	N113/15	N191/14		

Publications/manuscripts 2016, 2017, 2018, 2019

1. “Assessment of Functional Connectivity in Rat Brains Following Single-sided Conductive Hearing Loss” Siegbahn M, Savva M, Remppis M, Jörgens D, Engmér-Berglin C, Damberg P, Hultcrantz M, Moreno R -Manuscript
2. “Unilateral Ear Canal Atresia: Does it change cortical morphology or functional connectivity?” Siegbahn M, Jörgens D, Zantop K, Engmér-Berglin C, Ingvar M, Hultcrantz M, Moreno R -Submitted manuscript
3. “Adults with Unilateral Congenital Ear Canal Atreia -Sound Localization Ability and Recongition of Speech in Competing Speech in Unaided Condition” Siegbahn M, Asp F, Hultcrantz M, Engmér-Berglin C -Manuscript

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Halftime seminar
Planned dissertation

Evaluating the effect of systemic cortisone as treatment of pollen induced AR

1. The aim of this cross-sectional survey was to compare the health-economic consequences for patients treated with SLIT, in terms of direct and indirect costs with patients receiving standard of care pharmacological therapy. The optimal control group for the SLIT cohort would have been patients waiting for SLIT, but since SLIT in Sweden usually starts more or less upon referral, there is practically no waiting list for this therapy. Thus, patients waiting for SCIT were used as comparision.
Sublingual immunotherapy was more cost beneficial compared to standard of care pharmacological treatment of grass pollen seasonal allergic rhinitis, mainly due to reduced indirect costs (absenteeism and presenteeism).

2. 35 individuals with moderate/severe birch pollen induced allergic symptoms were randomized into treatment with either prednisolone tablets (20 mg) or antihistamine tablets (20 mg) once a day for 7 days. Trial start was planned just before the pollen peak of the season. The participants registered daily symptom- and medication scores (calculated as the use of nasal steroids, antihistamine tablets, eye drops) in an electronic diary. Quality of life questionnaires (SNOT-22, RQLQ and ACQ) were registered at trial start, after 1- and 3 weeks respectively.

3. 45 individuals with moderate to severe birch pollen induced allergic symptoms were randomized into treatment with methylprednisolone (80 mg) or placebo (NaCl 0,9 % B. Braun) given just before the peak of the pollen season. The participants registered daily symptom- and medication scores (calculated as the use of nasal steroids, antihistamine tablets and eye drops) in an electronic diary. Quality of life questionnaires (SNOT-22, RQLQ and ACQ) were registered at trial start, 1- and 3 weeks respectively.

There was a difference between the groups in reported symptom score (TNSS) and combined symptom and medication score (CSMS). No difference was seen between the groups when comparing quality of life questionnaires.

Ethical permit No.

2016/2158-31/2	2018/11			

Publications/manuscripts 2017, 2018, 2019, 2020

1. Manuscript, submitted (2020) - HealthSWEDE: Costs with sublingual immunotherapy - a Swedish questionnaire study. Olsson P, Carl Skröder C, AhlbeckL, Hjalte F, Welin KO, Westin U, Andersson M, Ahlström Emanuelsson C, Cardell LO
2. Manuscript (2020) - Treating birh pollen induced AR with prednisolone tablets Skröder C, Hellkvist L, Sahlstrand-Johnsson P, Dahl Å, Aronsson D, Bjermer L, Westin U, Cardell LO
3. Manuscript (2020) - Treating birch pollen induced AR with methylprednisolone injections. Skröder C, Hellkvist L, Dahl Å, Karlsson A, Bjermer L, Westin U, Cardell LO

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Halftime seminar	2014-05-19
Planned dissertation	

Airway hyperresponsiveness in conjunction with stimulation of viral recognizing Toll-like receptors.

Viral respiratory tract infections are a common cause for acute exacerbations of asthma and rhinitis. During an airway infection, individuals with asthma suffer from longer lasting illness and more severe respiratory symptoms, such as airway hyperresponsiveness, compared to healthy persons. The mechanisms behind these phenomena are not fully understood and new ways of treatment are required.
Toll-like receptors (TLRs) are pattern recognition receptors wich can identify viruses in the airway and by that evoke an inflammatory reponse. TLRs are found located in different cell types implicated in the pathogenesis of asthma, as in airway epithelial cells, in smooth muscle cells or in leukocytes. TLRs may be an important link between viral infections and asthma exacerbations.

The aim of this project is to study the effects on airway reactivity and inflammatory patterns in connection with stimulation of viral recognizing TLRs.

Ethical permit No.

N152/06	N152/11	N348/11	N44/12	N41/14	N143/14

Publications/manuscripts 2016, 2017, 2018, 2019

1. Starkhammar M, Kumlien Georén S, Swedin L, Dahlén S-E, Ander M, Cardell L-O. Intranasal Administration of poly (I:C) and LPS in BALB/c Mice Induces Airway Hyperresponsiveness and Inflammation via Different Pathways. PLoS ONE. February 2012.
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3. Starkhammar M, Kumlien Georén S, Dahlén S-E, Cardell L-O, Adner M. TNFα-blockade stabilizes local airway hyperresponsiveness during TLR-induced exacerbations in murine model of asthma. Respiratory Research. October 2015.
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5. Larsson O, Manson M, Starkhammar M, Fuchs B, Adner M, Kumlien Georén S, Cardell L-O. The TLR/ agonist imiquimod induces bronchodilation via a non-neuronal TLR7-independent mechanism: a possible role for quinoline in airway dilation. Lung Cellular and Molecular Physiology. April 2016.
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Halftime seminar	2019-04-19
Planned dissertation	Prel. 2021

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

The Quality Register for severe-to-profound hearing loss has estimated the prevalence of severe-to-profound hearing impairment (≥70 dB) to affect 0.2 % of the population in Sweden. Approximately 2000 adults have cochlear implants iand there are approximately 1200 deaf-blind people. Patients with hearing loss experience fatigue due to mental strain in various hearing situations, in particular with surrounding noise. Extended audiological rehabilitation requires input from multiple professionals. Patients defined as having received extended audiological rehabilitation have participated in group rehabilitation or have been subjected to at least three individual efforts of various hearing care professionals. This includes audiologists, technicians, welfare officers, hearing pedagogues, psychologists and doctors.
The overall aim of this study is to present the quality and the benefit of audiological rehabilitation for patients with severe-to-profound hearing loss with or without vision impairment. One of the aims is also to investigate the type of audiological rehabilitation received by patients and whether it is necessary to improve rehabilitation efforts, for example, in terms of a gender perspective.
Methods: The three first papers are register-based studies, the fourth is an interview studie and the fifth is a clinical studie from self-reported questionnaires. The latter instrument is named Mental Fatigue Scale (MFS)but with additional analysis from medical records.
Paper I: Patients with severe-to-profound hearing impairment (SPHI) and simultaneous severe vision impairment: a quality-of-life study
Paper II: SPHI : Demographic data, gender differences and benefits of audiological rehabilitation
Paper III: Rehabilitation of adult patients with SPHI – why not cochlear implants?
Paper IV: Combined SPHI and vision impairment – experiences of daily life and need of support, an interview study
Paper V: Mental fatigue in patients with hearing loss and tinnitus

Ethical permit No.

2012/057	2014/2101-31			

Publications/manuscripts 2017, 2018, 2019, 2020

1. Turunen-Taheri, S., Edén M., Hellström, S., & Carlsson, P-I. (2019). Rehabilitation of adult patients with severe-to-profound hearing impairment – why not cochlear implants? Acta Oto-Laryngologica, 139 (7): 604-611.
2. Turunen-Taheri, S., Carlsson, P-I., Johnson, A-C., & Hellström, S. (2019). Severe-to-profound hearing impairment: demographic data, gender differences and benefits of audiological rehabilitation. Disability and Rehabilitation, 41:23, 2766-2774 (online 12 June 2018).
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4. Turunen-Taheri, S., Hagerman-Sirelius, A., Hellström, S., Skjönsberg, Å., & Backenroth G. (manuscript) Combined severe-to-profound hearing and vision impairment – experiences of daily life and need of support, an interview study. Ongoing manuscript.
5. Turunen-Taheri, S., Carlsson, P-I., Ternevall, E., & Hellström, S. (manuscript). Mental fatigue in patients with hearing loss and tinnitus in ongoing audiological rehabilitation – a pilot study. Ongoing manuscript.

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Halftime seminar 2020-10-08
Planned dissertation

Optimizing treatment- tumor markers and sclerotherapy in head and neck lesions

The project includes studies of two conditions within the head and neck area, hypopharyngeal cancer and ranula.
In hypopharyngeal cancer we study the prevalence and predictive value of HPV and overexpression of p16, and other tumor markers such as p 53, PTEN and EGFR.
In ranula we have assessed the safety and efficacy of OK 432-sclerotherapy on patients with ranula in a randomized, double-blinded, placebo-controlled trial.

Ethical permit No.

2009/1278-31/4	2010/1117 32	2013/553 31-1	2017-1007-32-1	

Publications/manuscripts 2017, 2018, 2019, 2020

1. Wendt M, Papatziamos G, Munck-Wikland E and Marklund L. Sclerotheraphy with OK 432 on ranula – a prospective, randomised, double-blinded placebo-controlled study. Manuscript

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Registered 2017-12-21
Halftime seminar
Planned dissertation

Predictors of upper airway symptoms in the BAMSE birth cohort"

Rhinitis and rhinosinusitis are inflammatory diseases in the upper airways, often associated with fatigue, reduced quality of life and asthma.To be able to estimate prognosis and decide on treatment for these diseases, there is a need for prognostic biomarkers. The overall aim of this project is to identify early prognostic factors for upper airway disease and to increase the understanding of the relationship between symptoms from the upper and lower airways.

We will use data from the population based birth cohort BAMSE (Barn Allergi Miljö Stockholm Epidemiologi) consisting of 4089 children born in Stockholm between 1994-1996. The children were included at the age of 2 months and have been followed repeatedly by questionnaires.
At 4, 8, 16 and 24 years of age clinical examinations were performed, including blood samples for specific IgE. Among those with blood samples from all three time points, 795 were randomly sampled for analysis of allergen components with a micro array chip. The follow-up with questionnaires and clinical examination at 24 years of age is completed in 2019/2020.
In the first work, published in 2020, sensitization to grass pollen allergy was analysed.

We have also performed a clinical subgroup study of those with reported symptoms of CRS, including nasal endoscopy to verify the diagnosis, nasal lavage for inflammatory markers, olfactory threshold test and a disease specific quality of life questionnaire. Data from this study will be used in further work.

Ethical permit No.

93:189				

Publications/manuscripts 2017, 2018, 2019, 2020

1. Westman M, Åberg K, Apostolovic D, Lupinek C, Gattinger P, Mitterman I, Andersson N, Melèn E, Bergström A, Antò J M, Bousquet J, Valenta R, Wickman M, van Hage M. Sensitization to grass pollen allergen molecules in a birth cohort – Phl p 4 as an early indicator of grass pollen allergy. JACI April 2020