

FORSKNINGENS DAG



RESEARCH ACTIVITY

at the
Division of Ear, Nose and Throat
Diseases

2019



**Karolinska
Institutet**

KAROLINSKA
Universitetssjukhuset

Välkommen till Forskningens dag fredagen den 15 november 2019

Ny lokal: John, Våningsplan 2 i Widerströmska huset.

Tomtbodavägen 18 A, Solna

Tid: 08.00 – 14.00

08.00 Inledning (Lars Olaf)

08.10 Forskargrupperpresentation I – Cecilia Engmér Berglin

08.30 Nya forskningsprojekt

Tankar kring projekt på Hubben i Danderyd

- Do you need a turbinoplasty for a good result in septoplasty? (Sofia)

- Besvärsmfrihetsvalidering av tonsillkirurgi” samt
”Tonsillektomismärta hos vuxna (Pia)

- Is reboot surgery an anti-inflammatory procedure? (Sofia)

Nya doktorandprojekt

- Kolestatom i Sverige – en studie i stort och smått (Åsa).

- Immunologiska lymfkörtelstudier av luftvägsinflammation
med ultraljudsvägledd behandling och provtagning (Lars Olaf)

09.15 Hur blir man docent? (Lars Olaf)

09.40 Forskargrupperpresentation II – Lalle Hammarstedt Nordenvall

10.00 Grupparbete: Kombinera klinik, forskning, ST-projekt och
kvalitetsindikatorer (Alexander)

10.10 Kaffe följt av grupparbete

11.15 Återsamling och genomgång av grupparbete
(Alexander leder, Julia sekreterare)

12.00 Lunch

13.00 Vad kan våra forskningssköterskor hjälpa till med?

13.10 Hur och var söker man forskningsanslag? – ev utgå om många
tävlande

13.30 Tävling om bästa projekt/presentation, vinnaren belönas med en
forskarmånad, 2:an får två veckor (Julia)

13.50 Avslutning med prisutdelning (Lars Olaf)

Väl mött!

FOUU-rådet

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Management

Management at CLINTEC



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Professors and Docents

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

Docents

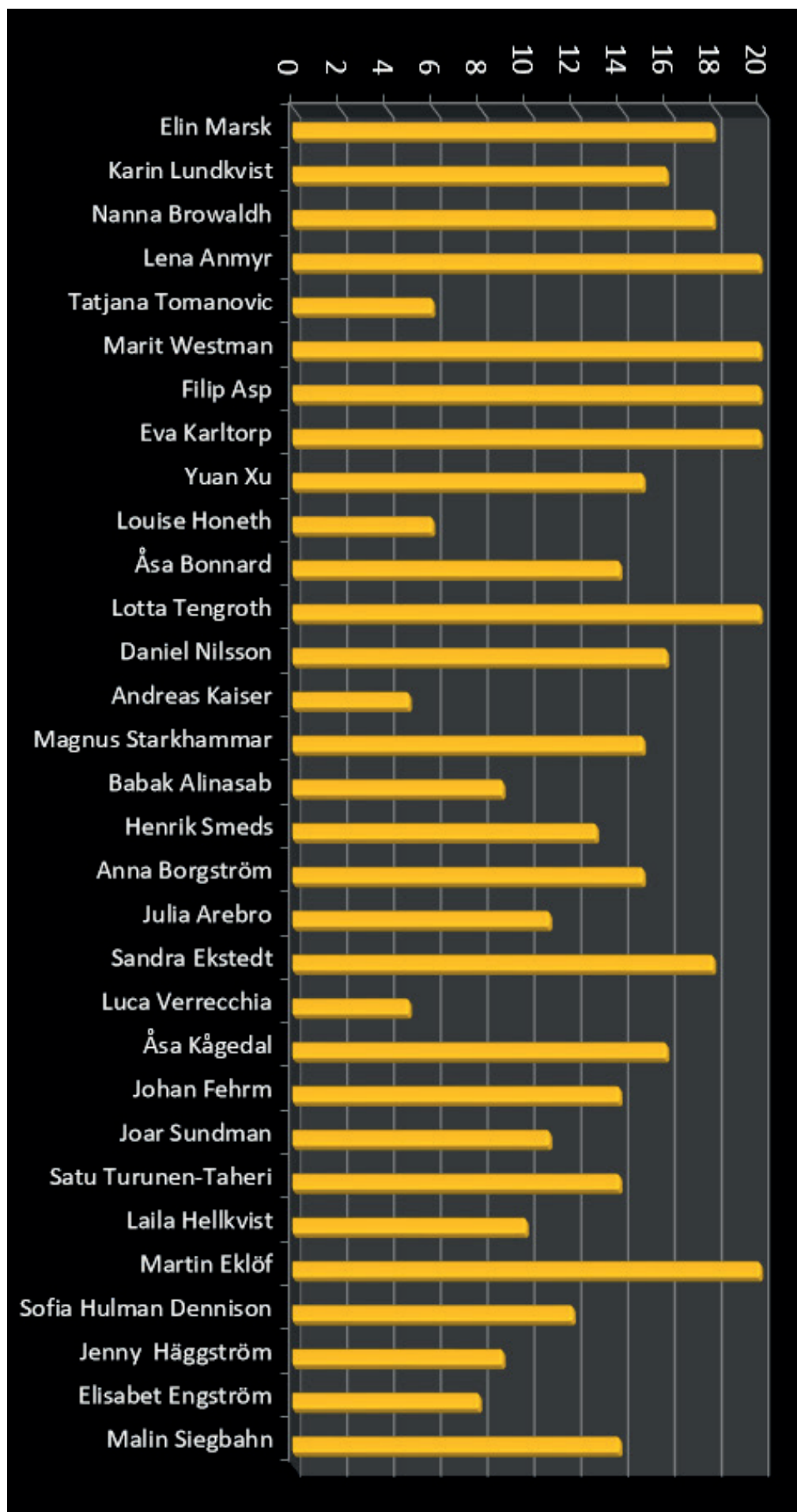
Erik Berninger
Maoli Duan
Riitta Möller
Inger Uhlén

Dissertations / Half time seminars 2018-2019



Date		Name	Title
2018			
2018-02-02	Half time seminar	Johan Fehrm	Surgical treatment for obstructive sleep apnea; randomized controlled studies in children and adults
2018-02-23	Half time seminar	Joar Sundman	Upper Airway Surgery in Adult Obstructive Sleep Apnea
2018-04-19	Half time seminar	Satu Turunen-Taheri	Adult patients with severe-to-profound hearing loss. A register-based and interview study.
2018-10-26	Dissertation	Luca Verrecchia	Development of vestibular evoked myogenic potentials and audiometry for the clinical diagnosis of superior canal dehiscence syndrome
2018-11-09	Dissertation	Åsa Kågedal	Immune response and tumour cell detection in lymph nodes of head and neck cancer
2019-11-23	Dissertation	Alexandra Elliot	Inverted Papilloma and Sinonasal Malignancies in Sweden
2018-11-28	Half time seminar	Martin Eklöf	Bilateral Hearing with Cochlear Implants
2018-12-07	Dissertation	Andreas Kaiser	Auditory Organotypic Cultures and Progenitor Cell Implantation
2018-12-14	Half time seminar	Sofia Hultman Dennison	Complications to rhinosinusitis in children before and after introduction on pneumococcal conjugate vaccine in Stockholm
2019			
2019-05-20	Half time seminar	Jenny Häggström	Central auditory function, cognition and aging
2019-06-05	Half time seminar	Elisabet Engström	Neurophysiological conditions for hearing in hearingimpaired and deaf children using hearing aids or cochlear implants – an intervention and follow-up study
2019-10-11	Half time seminar	Malin Siegbahn	Central Auditory Pathways in Congenital Conductive Hearing Impairment
2019-11-29	Dissertation	Sandra Ekstedt	Neutrophil subsets in airway inflammation and hyperreactivity

Participation at halftime seminars during 2010-10 to 2019-10-16



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.

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		
1.	Grönt ljus ansökan	<p>Blankett: Ansökan, Blankett: Appendix 1-3 samt synopsis avseende tilltänkt projekt på max 2 A4 sida (font Arial, 12 punkter, enkelt radavstånd). Synopsis skall omfatta:</p> <ul style="list-style-type: none"> • Projekttitel • Övergripande projektplan • Delstudier • Lärandemål <p>Lämnas in, i original och enkelsidig, enligt resp. inlämningsdag med deadline för inlämnandet av ansökan till enhetschef, se schema på hemsidan.</p> <p>Resp. enhetschef kallas som föredragande av ansökan till grönt ljusmöte. Rekommendera de sökande går igenom ansökan med sin enhetschef innan mötet.</p> <p>Eventuella kompletteringar alt. godkänd ansökan meddelas enhetschef för vidarebefordran till den sökande.</p>
2.	Inrättade av doktorandplats	<p>Efter godkänd grönt ljusansökan ansöker den blivande huvudhandledare om att få inrätta en doktorandplats genom att lämna in Blankett: Inrättande av doktorandplats.</p> <p>Ansökan med bilagor lämnas till LADOK-administratören</p>
3.	Bedömning av behörighet	<p>Efter att steg 1-2 är avklarade. Får den blivande doktoranden epost från LADOK-administratören med vidare instruktioner om hur dokument skall laddas upp i Varbi. Bedömningen bedöms utifrån uppladdade dokument.</p> <p>Föreligger behörighet skickas ett behörighetsutlåtande via epost till kandidat och handledare, vilket skriv ut och bifogas "Beslut om antagning"</p>

4.	Beslut om antagning	<p>Efter att steg 1-3 är klara lämnas nedanstående blanketter med bilagor in till LADOK-administratören inför beslut av studierektorn och prefekt.</p> <p>Blankett: Beslut om antagning till utbildning på forskarnivå Blankett: Finansieringplan</p>
5.	Individuell studieplan	<p>Efter beslut om antagning skall doktoranden inkomma med sin individuella studieplan inom 1 månad.</p> <p>Blankett: Individuell studieplan</p> <p>Framöver kommer alla nya studieplaner upprättas digitalt i ISP-systemet som inte tagits i bruk ännu.</p>
6.	Antagningsseminarium	<p>Doktoranden kommer att kallas till ett antagningsseminarium vid CLINTEC för att presentera sitt projekt under 5 minuter.</p> <p>Innan rutinerna för antagningsseminarium har satt sig kommer presentationen att ske vid antingen CLINTECs institutionsråd alt. grönt ljus möte, där max 2 doktorander inbjuds per tillfälle. Presentationen skall framföras på engelska.</p> <p>Presentationen (max 4 bilder (ppt)) skickas till LADOK-administratören senast två dagar innan seminariet.</p>

All information och blanketter återfinns på CLINTECs hemsida om forskarutbildningen, <https://ki.se/clintec/forskarutbildning-vid-clintec>.

Vid eventuella frågor, kontakta LADOK-administratören

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Immunologiska lymfkörtelstudier av luftvägsinflammation med ultraljudsvägledd behandling och provtagning

Bakgrund: Vår forskargrupp har under många år studerat luftvägsinflammation, på senare år främst från en immunologisk synvinkel. Trots att lymfkörtlarna utgör grunden för det immunologiska skeendet finns det förvånansvärt få humana studier av vad som sker i desamma. Troligen beror detta på att körtlarna är tekniskt svåra att komma åt. På senare tid har dock ultraljud utvecklats för att visualisera även små strukturer väl. Med hjälp av detta och i kombination med flödescytometri kan vi idag både ta prover från lymfkörtlar och ge behandling i lymfkörtlar i form av intralymfatisk allergivaccination.

Upplägg: Arbete sker i grupp och bygger på en nära relation mellan klinik och laboratorium.

Mål: Fem studier där vi belyser lymfkörtlarnas roll för utveckling och behandling av allergisk rinit, näs-lypos och astma.

Handledare: Lars Olaf Cardell, Laila Hellkvist, Susanna Kumlien Georén

Intresserad: Sänd ett mail till lars-olaf.cardell@ki.se eller laila.hellkvist@sll.se

Future projects at our coming's Danderyd unit

Kolesteatom i Sverige – en studie i stort och smått

Kolesteatomkirurgi är ett av våra vanligaste otokirurgiska ingrepp där både hörsel, balans och smak mm riskerar att påverkas i samband med kirurgin. Många fallstudier har gjorts av resultatet av kirurgi och dess risker vid olika kliniker samt i regioner. I detta projekt ska vi ta oss an kolesteatomsjukdomen ur ett nationellt perspektiv via Patientregistret och titta på incidens, prevalens, hur olika andra sjukdomar som ansiktsmissbildningar och slemhinnesjukdomar påverkar risken för insjuknande samt prognosen för ny sjukdom. Risken för ovanliga biverkningar av kirurgin som DVT/lungemboli, facialispares, meningit, sinustrombos mm kan här studeras eftersom kohorten är stor och insamlingen skett under lång tid.

Kolesteatom har aldrig sett som en ärftlig sjukdom men i den kliniska vardagen stöter man på familjer där fler familjemedlemmar har drabbats och opererats. Ett forskarteam i England har kartlagt 14 familjer från Norfolk där man sett ett nedärvningsmönster varför bilden är på väg att ändras. Genom att samköra Patientregistret med Flergenerationsregistret möjliggörs en kartläggning av familjär anhopning i Sverige. Detta ska kombineras med genetiska studier på familjer från Stockholmsregionen med familjär anhopning i ett samarbetsprojekt med Klinisk genetik. Förhoppningen är att detta kan leda till nya möjligheter att behandla och förebygga utvecklandet av sjukdomen i framtiden.

Forskningen kommer att ske tillsammans med öronkirurgiska kollegor från övriga Sverige och som lokala handledare och ansvariga står Åsa Bonnard och Cecilia Engmér Berglin.

”Besvärsfrihetsvalidering av tonsillkirurgi” samt ”Tonsillektomismärta hos vuxna”

Syfte:

1. Utvärdera olika smärtlindringspreparat
2. Validera smärtrådgörarna i Tonsillregistrets 30-dagar-postoperativa enkät
3. Validera fråga om besvärsfrihet på tonsilloperationsenkäten 6-månader efter operation
4. Utveckla en egen enkät för att utvärdera de symtom som oftast lett till tonsilloperation, och hur dessa förändrats efter operation. Arbetsnamn på enkäten: STOQ = Swedish Tonsill Operation Questionnaire.

Bakgrund:

När vi gjorde en kort översyn så verkar vuxensmärta vara närmast outforskat. Samtidigt verkar vi ju ha en smärtproblematik eftersom 20-35% av de vuxna kontakter sjukvården pga. smärta efter operation. Angeläget då vi har ägnat mkt tid åt barnsmärta men väldigt lite tid åt vuxensmärta de sista tio åren inom Tonsilloperationsregistrets styrgrupp.

Besvärsfrihet är naturligtvis indikationen för operation, men vi ser oroande en sjunkande trend i besvärsfrihet. Vi behöver därför analysera och förbättra utvärderingen av besvären, för att kunna tolka detta.

Metod:

- A Pröva två olika smärtlindringsregimer mot varandra utifrån smärtlindringseffekt:

Grupp A Paracetamol, Ibuprofen, Catapresan

Grupp B Paracetamol, Ibuprofen, Oxycontin

(Sömnapnoiker får inte vara med).

Alla får en smärtdagbok som Jönköping ÖNH redan gjort ett förslag till.

Detta skulle kunna göras på ett par enheter Danderyd, Jönköping etc.

- B Validera registrets smärta variabler för vuxna (tre frågor på 1-månadersenkäten: om sökt sjukvårdskontakt pga smärta, när man återgick till normal kost och hur många dagar man åt smärtstillande medicin), mot denna smärtdagbok.
- C Validera registrets besvärsfrihetsvariabel gentemot OSA-18 enkäten på de barn som tonsillopererats med obstruktionsindikation. Följ OSA-18 före och efter operation och jämföra med hur föräldrarna skattar besvärsfrihetsgraden postoperativt.
- D Utveckla en egen enkät för besvärsfrihetsskattning. Arbetsnamn på enkäten kan vara STOQ = Swedish Tonsill Operation Questionnaire.

Enkäten skulle fyllas i före och 6 månader efter operation. Enkäten ska identifiera det huvudbesvär som föranledde operation och gradera besvärsgraden av listade besvär. Förslagsvis finns en del besvär kopplade till obstruktion, recidiverande tonsilliter, kronisk tonsillit etc listade och patienten/anhörig skattar besvärsgraden av dessa på en VAS-skala. Vidare ska patienten välja det huvudbesvär som ska behandlas med halsmandeloperationen. Detta huvudbesvär kan också vårdplanerande läkare uppmanas ange, för att kunna göra en jämförelse om patient och läkare har samma indikation.

- E Validera registrets besvärsfrihetsvariabel mot PSG fynd. Utav de patienter som genomgått PSG före och efter operation, kan vi extrahera en objektiv grad av besvärsfrihet, som vi sedan kan jämföra med hur familjerna besvarat tonsilloperations besvärsfrihetsfråga. Vi tar fram studiematerial från patienter i det stora PSG-flödet.

Bonusvinster av projektet

En viktig patientgrupp på ÖNH-Hubben känner sig bemötta, och personalen får större förståelse för problematiken kring tonsilloperation.

Stöd/Medförfattarskap:

Tonsilloperationsregistret styrgrupp är intresserade att vara behjälpliga med stora delar av denna studie. Gruppen har stor erfarenhet av tonsilloperation, resultat, validering och metodutveckling. Ola Sunnergren (ordf) är docent och hans doktorand Filip i Jönköping är intresserade medförfattare. Troligen lämpligt med en multicenterstudie.

Försteförfattarskap kan tänkas på delar av projektet.

Pia Froissart-Nerfeldt kan verka som lokal handledare.

Do you need a turbinoplasty for a good result in septoplasty?

Background: The success rate for septoplasty in Sweden for septoplasty is approximately 50% at a one year follow up. The relatively poor results in Sweden is probably not unique. The reason for the poor result is not understood but one of the reasons is certainly patient selection. However, another issue might be the surgical difficulty of creating a straight septal cartilage, a tissue that is very flexible and which tries to retain its previous configuration – to the dismay of the surgeon.

Hypothesis: The addition of a turbinoplasty will compensate for the common lack of perfect reconfiguration of the septal cartilage.

Study design: This will be a prospective randomized controlled trial where patients with a unilateral nasal blockage are randomized to either septoplasty or septoplasty combined with a bilateral turbinoplasty. The patients will be pre- and post-operatively evaluated (after one year) clinically as well as with rinomanometry and PNIF. Furthermore, a disease specific and generic quality of life instrument will be used (NOSE/SF36).

Impact: No previous study has been performed that prospectively evaluated the impact of turbinoplasty, which may compensate for the innate propensity of the septal cartilage to retain its original configuration.

Is reboot surgery an anti-inflammatory procedure?

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a disease that affects approximately 2% of the Swedish population. Typically, it is driven by a Th 2 type of inflammation and is characterized by nasal congestion due to nasal polyps bilaterally, late onset asthma (60% of patients) and may also be complicated by aspirin intolerance. The treatment consists of nasal and oral steroids supplemented by endoscopic sinus surgery in non-responders. Recently, authors have proposed that extended surgical procedures with removal of not only polyps but also the mucosa of the affected sinuses in patients with severe disease may have an anti-inflammatory effect which reduces recurrence of polyp formation and the number of surgical procedures.

Hypothesis: A reboot operation i.e. surgical removal of not only polypoid tissue but also sinus mucosa has an anti-inflammatory effect and reduces the recurrence of polyp formation compared to traditional “full house” surgical procedures with simple polyp removal and the preservation of sinus mucosa.

Study design: Patients with CRSwNP that are failing on medical treatment with nasal and short courses of oral steroids and that are planned for “full house” FESS are asked to participate in the study. Preoperatively patients are evaluated with SNOT 22 as well as RAND 36.

Inclusion criteria:

1. Polyp score of at least 5/8 (Davos score) with not less than 2 on either side.
 2. At least two of the following symptoms: nasal congestion, rhinorrhea, facial fullness, hyposmia/anosmia.
- Patients are randomized to either reboot surgery or traditional “full house” FESS.
 - During the operation bacterial cultures, biopsies from polyp tissue and blood samples are secured.
 - Postoperatively all patients are treated with a 12 week course of doxycycline, Bactroban ointment, nasal steroids as well as saline lavage.
 - At 16 weeks and 1 year patients are followed with nasal cultures from the middle meatus, polyp biopsies, blood samples as well as SNOT22 and RAND 36.

Impact: The treatment of patients with severe CRSwNP is evolving and presently biologics (anti IL4, anti IL5 and anti IgE) are being introduced as an alternative or supplement to surgical treatment. These drugs represent a new but more expensive treatment modality and the understanding of the effect of reboot surgery and its effect as an anti-inflammatory treatment is imperative.

Senior Researchers

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Affiliated but not presented in this book:

Baumgartner, Wolf-Dieter; Ekborn, Andreas; Juto, Jan-Erik; Karltorp, Eva; Lindestad, Per-Åke; Lundkvist, Karin; Nordemar, Sushma; Toll, Karin, Vlastos, Andrea

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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.

Ethical permit No.

2009/331-31	2018/302-31			
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Publications 2016, 2017, 2018, 2019

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. Babak Alinasab, Karl-Johan Borstedt, Rebecka Rudström, Michael Ryott, Abdul Rashid Qureshi, Mats O. Beckman, Pär Stjärne. New Algorithm for Management of Orbital Blow Out Fracture Based on Prospective Study. Craniomaxillofac Trauma Reconstr. 2018 Dec;11(4):285-295. doi: 10.1055/s-0038-1641714. Epub 2018 May 1.
3. Babak Alinasab, Karl-Johan Borstedt, Rebecka Rudström, Michael Ryott, Abdul Rashid Qureshi, Pär Stjärne. Prospective Randomized Controlled Pilot Study on Orbital Blow out Fracture. Craniomaxillofac Trauma Reconstr. 2018 Sep;11(3):165-171.
4. Babak Alinasab, Ola Fridman Bengtsson, Pär Stjärne. Supra Blepharoplasty Approach for Correcting Fractures of Frontal Bone Fracture. J Craniofac Surg. 2018 Oct;29(7):1906-1909.
5. Alinasab B, Qureshi AR, Stjärne P. Prospective study on ocular motility limitation due to orbital muscle entrapment or impingement associated with orbital wall fracture. Injury. 2017 Jul;48(7):1408-1416.
6. Babak Alinasab, Michael Ryott, Pär Stjärne. Still No Reliable Consensus in Management of Blow-Out Fracture. Injury. 2014 Jan;45(1):197-202. doi: 10.1016/j.injury. 2012.09.009. Epub 2012 Nov 8
7. Alinasab B, Haraldsson PO. Rapid Resorbable Sutures Are a Favourable Alternative to Non-resorbable Sutures in Closing Transcolumellar Incision in Rhinoplasty. Aesthetic Plast Surg. 2016 Aug;40(4):449-52

Lena Anmyr

PhD, Affiliated Researcher

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I am involved in clinically related projects concerning children with cochlear implant:

1. Development of reading skill and the cognitive and linguistic abilities that affect reading development in deaf children who use cochlear implants (CI). Longitudinal study. Malin Wass is in charge of the studies.
2. "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 well-being. 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:

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

Ethical permit No.

2014/2068-31/2	2011/295-31	2015/992-31		
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Publications 2016, 2017, 2018, 2019

1. X-linked Malformation and Cochlear Implantation. Smeds Henrik; Wales Jeremy; Asp Filip; Löfkvist Ulrika; Fala-hat Babak; Anderlid Britt-Marie; Anmyr Lena; Karltorp Eva. *Otology & Neurotology*, 2017, Vol.38(1), pp.38-46
2. Correlates of Orthographic Learning in Swedish Children With Cochlear Implants. Malin Wass ; Ulrika Löfkvist ; Ulrika Löfkvist ; Lena Anmyr ; Lena Anmyr ; Eva Karltorp ; Eva Karltorp ; Elisabet Östlund ; Björn Lyxell ; Björn Lyxell. *Frontiers in Psychology*, 01 March 2019, Vol.10
3. Predictors of Reading Comprehension in Children With Cochlear Implants. Malin Wass ; Lena Anmyr; Björn Lyxell ; Elisabet Östlund; Eva Karltorp ; Ulrika Löfkvist. *Frontiers in Psychology*, 01 September 2019, Vol.10

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Immunology in airway inflammation and head and neck cancer

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, head and neck cancer and malignant melanoma in the head and neck area. Our findings enable new therapeutic possibilities for these diseases.

Supervision of PhD-students:

Main Supervisor	Co-supervisor

Ethical permit No.

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Publications 2016, 2017, 2018, 2019

1. 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. doi: 10.4193/Rhin19.158.
2. 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.
3. 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 rhinosinusitis 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.
4. 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.
5. 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.
6. Tomassen P, Vandeplas G, Van Zele T, Cardell LO, Arebro J, Olze H, Förster-Ruhrmann U, Kowalski ML, Olszewska-Ziaber A, Holtappels G, De Ruyck N, Wang X, Van Drunen C, Mullol J, Hellings P, Hox V, Toskala E, Scadding G, Lund V, Zhang L, Fokkens W, Bachert C. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol*. 2016 May;137(5):1449-1456.e4. doi: 10.1016/j.jaci.2015.12.1324. Epub 2016 Mar 4.
7. Arebro J, Tengroth L, Razavi R, Kumlien Georén S, Winqvist O, Cardell LO. Antigen-presenting epithelial cells can play a pivotal role in airway allergy. *J Allergy Clin Immunol*. 2016 Mar;137(3):957-60.e7. doi: 10.1016/j.jaci.2015.08.053. Epub 2015 Nov 10. No abstract available.



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Spatial Hearing - Effects of Auditory Implantable Devices and Hearing Loss

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 eye-movements towards auditory events, as an index of horizontal sound localization accuracy. Since high accuracy is dependent on binaural hearing, the technique is an ideal tool to assess access to binaural cues. The ultimate goal is to alleviate the negative impact of hearing impairment on spatial hearing, and increase our understanding of how impaired spatial hearing affects humans, specifically during critical periods of development.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
	Marlin Johansson
	Martin Eklöf

Ethical permit No.

2016/414-16 (Gothenburg)	2015/1878-31/2	2013/4:2	2013/2248-3	
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Publications 2016, 2017, 2018, 2019

1. Asp, F., A. Olofsson, and E. Berninger, Corneal-Reflection Eye-Tracking Technique for the Assessment of Horizontal Sound Localization Accuracy from 6 Months of Age. *Ear Hear*, 2016. 37(2): p. e104-18.
2. 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
3. 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.
4. 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.
5. 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*
6. Asp, F. and S. Reinfeldt, Effects of Simulated and Profound Unilateral Sensorineural Hearing Loss on Recognition of Speech in Competing Speech. *Ear Hear*, 2019.
7. 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 Paediatrica, Early Online*



The interaction of eosinophils and neutrophils in persistence of nasal polyps

In the center of the interest of our research work was the interaction of eosinophils and neutrophils, and their role in maintaining persistent inflammation in chronic rhinosinusitis with nasal polyps (CRSwNP). CRSwNP is characterized by a Th2-biased eosinophilic inflammation and associated with EETosis and Charcot Leyden Crystal (CLC) deposition.

Galectin 10 protein and number of tissue CLCs were increased in CRSwNP and correlated with tissue macrophages and neutrophils, in addition to eosinophils. Stimulation of polyp tissue and primary epithelial cells with CLCs resulted in pro-inflammatory cytokine release characterized by elevated levels of IL-1 α , IL-1 β , GM-CSF, TNF α , IL-6 and IL-8. In addition, CLCs were shown to decrease E-cadherin expression in epithelial cells. This epithelial response was sufficient to promote neutrophil migration, and stimulation of neutrophils with CLCs resulted in NETosis. Further data showed that CLCs cause epithelial cells to recruit neutrophils and to produce cytokines that prime neutrophil function. Subsequently, CLCs steer neutrophils to undergo NETosis which may serve as a hallmark of intense activation. In response to CLCs, epithelial cells from nasal polyp tissue as well as isolated nasal epithelial cells produced GM-CSF, a known priming stimulus for neutrophils. Other cytokines that prime neutrophils for crystal-induced NETosis like IL-1 β and TNF were also found to be produced by polyp tissue and epithelium under these conditions. The precise mechanisms by which CLCs trigger NETosis require further study. Potentially, the size of the crystals and inability of crystals to be phagocytized by neutrophils might be involved in turning on NETosis via the ROS-dependent translocation of neutrophil elastase to the nucleus, a mechanism proposed for sensing of large extracellular pathogens.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
	Karin Jonstam

Ethical permit No.

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Publications 2016, 2017, 2018, 2019

- Zhang N, van Crombruggen K, Gevaert E, Bachert C. Barrier function of the nasal mucosa in health and type-2 biased airway diseases. *Allergy* 2016 Mar;71(3):295-307
- Tomassen P, Vandeplas G, van Zele T, Cardell LO, Arebro J, Olze H, Förster-Ruhrmann U, Kowalski ML, Olszewska-Zięber A, Holtappels G, De Ruyck N, Wang XD, Van Druenen C, Mullol J, Hellings P, Hox V, Toskala E, Scadding G, Lund V, Zhang L, Fokkens W, Bachert C. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol* 2016 May;137(5):1449-1456. e4. doi: 10.1016/j.jaci.2015.12.1324
- Feng Lan, XD Wang, HJ Nauwynck, Gabriele Holtappels, L Zhang, SL Johnston, NG Papadopoulos, C Bachert, Nan Zhang. Th2 biased upper airway inflammation is associated with an impaired response to viral infection with Herpes simplex virus 1. *Rhinology* 2016 Jun;54(2):141-9
- Bachert C, Hamilos D. Are Antibiotics Useful for Chronic Rhinosinusitis? *J Allergy Clin Immunol Pract*. 2016 Jul-Aug;4(4):629-38. doi: 10.1016/j.jaip.2015.12.008
- Lou H, Meng Y, Piao Y, Zhang N, Bachert C, Wang C, Zhang L. Cellular phenotyping of chronic rhinosinusitis with nasal polyps. *Rhinology* 2016 Jun;54(2):150-9. doi: 10.4193/ Rhin15.271
- Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, Hellings P, Jiao L, Wang L, Evans RR, Pirozzi G, Graham NM, Swanson B, Hamilton JD, Radin A, Gandhi NA, Stahl N, Yancopoulos GD, Sutherland R. Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients with Chronic Sinusitis and Nasal Polyposis. A Randomized Clinical Trial. *JAMA* 2016;315(5):469-479
- Wang X, Zheng M, Lou H, Wang C, Zhang Y, Bo M, Ge S, Zhang N, Zhang L, Bachert C. An increased prevalence of self-reported allergic rhinitis in major Chinese cities from 2005 to 2011. *Allergy* 2016 Aug;71(8):1170-80. doi: 10.1111/all.12874

8. Stentzel S, Teufelberger A, Nordengrün M, Kolata J, Schmidt F, van Crombruggen K, Michalik S, Kumpfmüller J, Tischer S, Schweder T, Hecker M, Engelmann S, Völker U, Krysko O, Bachert C, Bröker BM. Spls: Staphylococcus serine protease-like proteins are pacemakers of allergic airway reactions. *J Allergy Clin Immunol*. 2017 Feb;139(2):492-500.
9. Wang XD, Zhang N, Bo M, Holtappels G, Zheng M, Lou H, Wang H, Zhang L, Bachert C.
10. Diversity of T-helper cytokine-profiles in chronic rhinosinusitis: A multicenter study in Europe, Asia and Oceania, *JACI* 2016 Nov;138(5):1344-1353.doi: 10.1016/j.jaci.2016.05.041
11. Bachert C, Akdis CA. Phenotypes and Emerging Endotypes of Chronic Rhinosinusitis. *J Allergy Clin Immunol in Pract*. 2016 Jul-Aug;4(4):621-628
12. Feng Lan, Nan Zhang, Elie Gevaert, L Zhang, C Bachert. Viruses and bacteria in Th2 biased allergic airway disease. *Allergy* 2016 Oct;71(10):1381-92.
13. Bachert C, Gevaert E. Advances in rhinitis and rhinosinusitis in 2015. *J Allergy Clin Immunol*. 2016 Nov;138(5):1277-1283
14. Henmyr V, Lind-Hallden C, Hallden, Sall T, Carlberg D, Bachert C, Cardell LO. Chronic rhinosinusitis patients show accumulation of genetic variants in PARS2. *PLoS One*. 2016 Jun 27;11(6):e0158202.
15. Schmidt F, Meyer T, Sundaramoorthy N, Michalik S, Surmann K, Depke M, Dhople V, Salazar MG, Holtappels G, Zhang N, Bröker BM, Bachert C, Völker U. Characterization of human and Staphylococcus aureus proteins in respiratory mucosa by in vivo- and immunoproteomics. *Proteomics*. 2017 Feb 23;155:31-39
16. Gevaert Elie, Zhang Nan, Krysko Olga, Lan Feng, 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
17. 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.
18. 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
19. 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
20. 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
21. De Schryver E, Derycke L, Calus L, Holtappels G, Hellings PW, Van Zele T, Bachert C, Gevaert P. The effect of systemic treatments on periostin expression reflects their interference with the eosinophilic inflammation in chronic rhinosinusitis with nasal polyps. *Rhinology* 2017 May 14. doi:
22. Zhang Y, Gevaert E, Lou H, Wang X, Zhang L, Bachert C, Zhang N. Chronic rhinosinusitis in Asia: Current perspectives. *J Allergy Clin Immunol*. 2017 Nov;140(5):1230-1239.
23. 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)
24. Song J, Wang H, Zhang YN, Cao PP, Liao B, Wang ZZ, Shi LL, Yao Y, Zhai GT, Wang ZC, Liu LM, Zeng M, Lu X, Wang H, Yang XP, Yu D, Bachert C, Liu Z. Ectopic Lymphoid Tissues Support Local Immunoglobulin Production in Chronic Rhinosinusitis with Nasal Polyps. *J Allergy Clin Immunol*. 2017 Nov 2. pii: S0091-6749(17)31671-8. doi: 10.1016/j.jaci.2017.10.014.
25. Vandenplas O, Vinnikov D, Blanc PD, Agache I, Bachert C, Bewick M, Cardell LO, Cullinan P, Demoly P, Descatha A, Fonseca J, Haahtela T, Hellings PW, Jamart J, Jantunen J, Kalayci Ö, Price D, Samolinski B, Sastre J, Tian L, Valero AL, Zhang X, Bousquet J. Impact of Rhinitis on Work Productivity: A Systematic Review. *J Allergy Clin Immunol Pract*. 2017 Oct 7. pii: S2213-2198(17)30725-0. doi: 10.1016/j.jaip.2017.09.002
26. 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. *J Proteomics*. 2018 May 30;180:53-60
27. 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
28. Van Zele T, Pauwels B, Dewaele F, Gevaert P, Bachert C. Prospective study on the outcome of the sphenoid drill out procedure. *Rhinology*. 2018 Feb 15.
29. Scheerens H, Smith A, Li O, Honigberg L, Harris JM, Holtappels G, Bachert C. Elevated IgE M1 prime transcripts in nasal tissues in patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2018 Oct 22. pii: S0091-6749(18)31478-7.
30. Altunbulakli C, Costa R, Lan F, Zhang N, Akdis M, Bachert C, Akdis CA. Staphylococcus aureus enhances the tight junction barrier integrity in healthy nasal tissue, but not in nasal polyps. *J Allergy Clin Immunol*. 2018 Mar 5. pii: S0091-6749(18)30312-9.
31. 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
32. 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
33. Wei B, Liu F, Zhang J, Liu Y, Du J, Liu S, Zhang N, Bachert C, Meng J. Multivariate analysis of inflammatory endotypes in recurrent nasal polyposis in a Chinese population. *Rhinology* 2018 May 22. doi: 10.4193/Rhin17.240.
34. Chalermwatanachai T, Vilchez-Vargas R, Holtappels G, Lacoere T, Jáuregui R, Kerckhof FM, Pieper DH, Van de Wiele T, Vaneechoutte M, Van Zele T, Bachert C. Chronic rhinosinusitis with nasal polyps is characterized by dysbacteriosis of the nasal microbiota. *Sci Rep*. 2018 May 21;8(1):7926.
35. Zhang Y, Derycke L, Holtappels G, Wang XD, Zhang L, Bachert C, Zhang N. Th2 cytokines orchestrate the secretion of MUC5AC and MUC5B in IL-5 positive chronic rhinosinusitis with nasal polyps. *Allergy* 2018 May 26. *Allergy* 2019;74:131-140
36. 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 Druenen 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 rhinosinusitis cohort: a large European cross-sectional study of chronic rhinosinusitis patients with and without nasal polyps. *Rhinology* 2018 Jun 17. doi: 10.4193

37. 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
38. 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.
39. 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
40. 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)
41. Lou H, Zhang N, Bachert C, Zhang L. Highlights of eosinophilic chronic rhinosinusitis with nasal polyps in definition, prognosis, and advancement. *Int Forum Allergy Rhinol*. 2018; 8(11):1218-1225
42. Khan A, Thi Minh Thao Huynh, G Vandeplas, VN Joish, Leda Mannent, P Tomassen, T van Zele, LO Cardell, J Arebro, H Olze, U Foerster-Ruhrmann, M Kowalski, A Olszewska-Zięber, W Fokkens, C van Drunen, J Mullol, I Alobid, PW
43. Hellings, V Hox, E Toskala, G Scadding, V Lund, C Bachert. The GALEN Rhinosinusitis Cohort: Chronic rhinosinusitis with nasal polyps affects health-related quality of life. *Rhinology*. 2019 Jul
44. Bachert C, Hellings P, Mullol J, Hamilos DL, Gevaert P, Naclerio RM, Joish VN, Chao J, Mannent L, Amin N, Abbe A, Taniou C, Fan C, Pirozzi G, Graham N, Mahajan P, Staudinger H, Khan A. Dupilumab improves health-related quality of life in patients with chronic rhinosinusitis with nasal polyposis. *Rhinology*. 2019 Jul 18.
45. 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 Jan 21. doi: 10.1002/lary.27815
46. Schreiber J, Bröker BM, Ehmann R, Bachert C. Non-atopic severe asthma might still be atopic: Sensitization towards Staphylococcus aureus enterotoxins. *J Allergy Clin Immunol*. 2019 Jan 29. pii: S0091-6749(19)30114-9. doi: 10.1016/j.jaci.2019.01.018.
47. Shamji M, Thomsen I, Layhadi J, Kappen J, Holtappels G, Sahiner U, Switzer A, Kouser L, Durham SR, Pabst O, Bachert C. Broad Immunoglobulin G Repertoire in Chronic Rhinosinusitis with Nasal Polyps regulates pro-inflammatory IgE responses. *J Allergy Clin Immunol*. 2019 Feb 11
48. Jonstam K, Swanson BN, Mannent L, Cardell LO, Tian N, Wang Y, Zhang D, Fan C, Holtappels G, Hamilton JD, Grabher A, Graham NMH, Pirozzi G, Bachert C. Dupilumab reduces local Type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis. *Allergy* 2019;00:1–10. <https://doi.org/10.1111/all.13685>
49. Humbert M, Bousquet J, Bachert C, Palomares O, Pfister P, Kottakis I, Jaumont X, Thomsen FS, Papadopoulos NG. IgE-mediated multimorbidities in allergic asthma and the potential for omalizumab therapy. *JACI iPract*. 2019 Mar 27 pii: S2213-2198(19)30245-4.
50. Krysko O, Teufelberger A, Van Nevel S, Krysko DV, Bachert C. Protease/ anti-protease network in allergy: the role of S. aureus protease like proteins. *Allergy* 2019 Mar 19
51. Bachert C, Hellings PW, Mullol J, Naclerio RM, Chao J, Amin N, Grabher A, Swanson BN, Hamilton JD, Guillonneau S, Taniou C, Zhang D, Pirozzi G, Graham NMH, Staudinger H, Mannent LP, Khan A. Dupilumab improves patient reported outcomes in patients with chronic rhinosinusitis with nasal polyps and comorbid asthma. *J Allergy Clin Immunol in Pract*. 2019 Mar 27. pii: S2213-2198(19)30304-6.
52. Persson EK, Kenneth Verstraete, Ines Heyndrickx, Elien Gevaert, Helena Aegerter, Jean-Michel Percier, Kim Deswarte, Koen Verschueren, Ann Dansercoer, Delphine Gras, Pascal Chanez, Claus Bachert, Amanda Gonçalves, Hanne Van Gorp, Hans De Haard, Christophe Blanchetot, Michael Saunders, Hamida Hammad, Savvas N. Savvides, Bart N. Lambrecht. Protein crystallization promotes type 2 immunity and is reversible by antibody treatment. *Science* 2019 May 24;364(6442).
53. Bachert C, Zhang N. Medical Algorithm: Diagnosis and Treatment of Chronic Rhinosinusitis. *Allergy*. 2019 Apr 16.
54. Arebro J, Draskog 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.
55. Teufelberger AR, Bröker BM, Krysko DV, Bachert C, Krysko O. Staphylococcus aureus Orchestrates Type 2 Airway Diseases. *Trends Mol Med*. 2019 Jun 5.
56. Qing H, Wang X, Zhang N, Zheng K, Du K, Zheng M, Li Y, Chang Y, Zhang L,
57. Bachert C. The Effect of PM2.5 on the Inflammatory Responses in Human Upper Airway Mucosa. *Am J Respir Crit Care Med*. 2019 Jul 16.
58. Wang M, Zhang N, Ming Z, Li Y, Meng L, Ruan Y, Han J, Zhao N, Wang X, Zhang L, Bachert C. Cross-talk between Th2 and Th17 pathways in chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol*. 2019 Jul 1.
59. Calus L, Van Bruaene N, Bosteels C, Dejonckheere S, Van Zele T, Holtappels G, Bachert C, Gevaert P. Twelve-year follow-up study after endoscopic sinus surgery in patients with chronic rhinosinusitis with nasal polyposis. *Clin Transl Allergy*. 2019 Jun 14;9:30.
60. Kim HJ, Ahn HS, Kang T, Bachert C, Song WJ. Nasal Polyps and Future Risk of Head and Neck Cancer: A Nationwide Population-based Cohort Study. *J Allergy Clin Immunol*. 2019 Jul 3. pii: S0091-6749(19)30886-3.
61. Sintobin I, Siroux V, Holtappels G, Pison C, Nadif R, Bousquet J, Bachert C. Sensitisation to staphylococcal enterotoxins and asthma severity: a longitudinal study in the EGEA cohort. *Eur Respir J* 2019 Jul 8
62. Bachert C, Hellings PW, Mullol J, Hamilos DL, Gevaert P, Naclerio RM, Joish VN, Chao J, Mannent L, Amin N, Abbe A, Taniou C, Fan C, Pirozzi G, Graham NMH, Mahajan P, Staudinger H, Khan A. Dupilumab improves health-related quality of life in patients with chronic rhinosinusitis with nasal polyposis. *Allergy*. 2019 Jul 15.
63. Gevaert E, Delemarre T, De VolderIJ, Zhang N, Holtappels G, De Ruyck N, Persson E, Heyndrickx I, Verstraete K, Aegerter H, Nauwynck H, Savvides SN, Lambrecht BN, Bachert C. Charcot-Leyden crystals promote neutrophilic inflammation in nasal polyposis. *J Allergy Clin Immunol*. 2019 Sept 4
64. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SF, Mullol J, Greos LS, Bosso JV, Laidlaw TM, Cervin A, Maspero JF, Hopkins C, Olze H, Canonica GW, Paggiaro P, Cho SH, Fokkens W, Fujieda S, Zhang M, Lu Y, Fan C, Draikiwicz S, Kamat SA, Khan A, Pirozzi GL, Patel N, Graham N, Ruddy M, Staudinger H, Weinreich CD, Stahl N, Yancopoulos GD, Mannent LP. Dupilumab Efficacy and Safety in Severe Chronic Rhinosinusitis with Nasal Polyps in the Multicentre, Randomised, Double-blind, Placebo-controlled, Parallel Group Phase 3 Trials LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52. *Lancet*. 2019 Sep 19. pii: S0140-6736(19)31881-1.



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ENT-cancer

On going projects:

- The risk for regional metastasis in patients with gingival cancer (n=215) in relation to tumor size, localization (maxilla/mandible), T-class and histopathology.
- Retrospective study on the prevalence of cystic metastasis in patients who had undergone surgery for lateral branchial cleft cyst at Karolinska between 2003-2018.

Future project:

- Prospective study: Can HPV be used as a predictor in differentiating between cystic metastasis and lateral branchial cleft cyst?
- Prospective study: Use of ancor in extirpation of non-palpable lymphnodes in the neck.

Sex hormones & Hearing

- Longitudinal prospective study of the hearing in women with breast cancer treated with anti-Estrogens.
- The effect of Estrogen substitution on hearing in Turner mice.

Supervision of PhD-students:

Main Supervisor	Co-supervisor

Ethical permit No.

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Publications 2016, 2017, 2018, 2019

1. Bonnard Å, Hederstierna C, Bark R, M Hultcrantz. The effect of estrogen treatment on hearing in young women with Turner syndrome: a cohort study. *Otology & Neurotology* 2019. In press.
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.
3. 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.
4. Bark R, Mercke C, Munck-Wikland E, Wisniewski NA, Hammarstedt-Nordenvall L. Cancer of the Gingiva. *Eur Arch Otorhinolaryngol*. 2016 Jun;273(6):1335-45.
5. Svedbrant J, Bark R, Hultcrantz M, Hederstierna C. Hearing decline in Menopausal Women – A Ten-Year Follow-up. *Acta Otolaryngol*. 2015 Aug;135(8):807-13.

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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 brain-stem 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	Martin Eklöf

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
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Publications 2016, 2017, 2018, 2019

- Alvan G, Berninger E, Gustafsson LL, Karlsson KK, Paintaud G, Wakelkamp M. Concentration-Response Relationship of Hearing Impairment Caused by Quinine and Salicylate: Pharmacological Similarities but Different Molecular Mechanisms. *Basic Clin Pharmacol Toxicol*. 2017;120(1):5-13. doi: 0.1111/bcpt.12640. Epub 2016 Sep 29.
- Asp F, Jakobsson AM, Berninger E. The effect of simulated unilateral hearing loss on horizontal sound localization accuracy and recognition of speech in spatially separate competing speech. *Hear Res*. 2018;357:54-63.(doi):10.1016/j.heares.2017.11.008. Epub Nov 22.
- Asp F, Olofsson A, Berninger E. Corneal-Reflection Eye-Tracking Technique for the Assessment of Horizontal Sound Localization Accuracy from 6 Months of Age. *Ear Hear*. 2016;37(2):e104-18. doi: 10.1097/AUD.0000000000000235.
- Johansson M, Asp F, Berninger E. Children With Congenital Unilateral Sensorineural Hearing Loss: Effects of Late Hearing Aid Amplification – a Pilot Study. *Ear Hear*. 2019;16(10):0000000000000730.
- Filip Asp, Erik Berninger. Differential maturation of auditory and auditory-visual horizontal sound localization accuracy in children, 2016 MidWinter Research Meeting, Association for Research in Otolaryngology, San Diego, California, USA, February 20-24, 2016.
- Marlin Johansson, Filip Asp, Erik Berninger. Children with Congenital Unilateral Sensorineural Hearing Loss: Effects of Late Hearing Aid Amplification, 2017 MidWinter Research Meeting, Association for Research in Otolaryngology, Baltimore, Maryland, USA, February 11-15, 2017.
- Martin Eklöf, Filip Asp, Erik Berninger. Reaction time of horizontal sound localization responses in normal hearing adults, 2017 MidWinter Research Meeting, Association for Research in Otolaryngology, Baltimore, Maryland, USA, February 11-15, 2017.
- Filip Asp, Anne-Marie Jakobsson, Erik Berninger. The effect of acute, reversible, unilateral hearing loss on horizontal sound localization and speech recognition in competing speech, 2017 MidWinter Research Meeting, Association for Research in Otolaryngology, Baltimore, Maryland, USA, February 11-15, 2017.
- Martin Eklöf, Filip Asp, Erik Berninger. Does a simulated unilateral hearing loss affect sound localization latency?, 2018 MidWinter Research Meeting, Association for Research in Otolaryngology, San Diego, California, USA, February 9-14, 2018.



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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 2016, 2017, 2018, 2019

1. Nacci A, Romeo SO, Cavaliere MD, Macerata A, Bastiani L, Paludetti G, Galli J, Marchese MR, Barillari MR, Barillari U, Berrettini S, Laschi C, Cianchetti M, Manti M, Ursino F, Fattori B. Comparison of electroglottographic variability index in euphonic and pathological voice. *Acta Otorhinolaryngol Ital.* 2019 Jan 31. doi: 10.14639/0392-100X-2127. [Epub ahead of print]
2. Forli F, Giuntini G, Ciabotti 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 Otorhinolaryngol.* 2018 Feb;105:56-62. doi: 10.1016/j.ijporl.2017.12.006. Epub 2017 Dec 8.
3. Forli F, Turchetti G, Giuntini G, Bellelli S, Fortunato S, Bruschini L, Barillari MR, Berrettini S. Cochlear implant in prelingually deafened oralist adults: speech perception outcomes, subjective benefits and quality of life improvement. *Acta Otorhinolaryngol Ital.* 2017 Oct;37(5):416-422. doi: 10.14639/0392-100X-1493.
4. Nacci A, Romeo SO, Berrettini S, Matteucci J, Cavaliere MD, Mancini V, Panicucci E, Ursino F, Fattori B. Stabilometric findings in patients affected by organic dysphonia before and after phonosurgery. *Acta Otorhinolaryngol Ital.* 2017 Aug;37(4):286-294. doi: 10.14639/0392-100X-1035.
5. Milazzo M, Danti S, Inglese F, Jansen van Vuuren G, Gramigna V, Bonsignori G, De Vito A, Bruschini L, Stefanini C, Berrettini S. Ossicular replacement prostheses from banked bone with ergonomic and functional geometry. *J Biomed Mater Res B Appl Biomater.* 2017 Nov;105(8):2495-2506. doi: 10.1002/jbm.b.33790. Epub 2016 Sep 23
6. Berrettini S, De Vito A, Bruschini L, Fortunato S, Forli F. Idiopathic sensorineural hearing loss in the only hearing ear. *Acta Otorhinolaryngol Ital.* 2016 Apr;36(2):119-26. doi: 10.14639/0392-100X-587. Epub 2016 Apr 29.
7. Giuntini G, Forli F, Nicastro R, Ciabotti A, Bruschini L, Berrettini S. Early care in children with permanent hearing impairment. *Acta Otorhinolaryngol Ital.* 2016 Feb;36(1):51-9. doi: 10.14639/0392-100X-1079. Epub 2016 Feb 29.
8. Forli F, Giuntini G, Bruschini L, Berrettini S. Aetiologic diagnosis of hearing loss in children identified through newborn hearing screening testing. *Acta Otorhinolaryngol Ital.* 2016 Feb;36(1):29-37. doi: 10.14639/0392-100X-1076. Epub 2016 Feb 29.
9. Bruschini L, Berrettini S, Forli F, Murri A, Cuda D. The Carina© middle ear implant: surgical and functional outcomes. *Eur Arch Otorhinolaryngol.* 2016 Nov;273(11):3631-3640. Epub 2016 Mar 23.

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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 familial 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:

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

Ethical permit No.

2014/2203-31/4	Ethic permit for the National Cholesteatoma study is pending
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Publications 2016, 2017, 2018, 2019

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. PMID: 30632288
3. Prakash SK, San Roman AK, Crenshaw M, Flink B, Earle K, Los E, Bonnard Å, Lin AE. "Donating our bodies to science": A discussion about autopsy and organ donation in Turner syndrome. Am J Med Genet C Semin Med Genet. 2019 Mar;181(1):36-42. doi: 10.1002/ajmg.c.31671. Epub 2019 Jan 11. Review. PMID: 30633443.

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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:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
	Isabella Sjölander

Ethical permit No.

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Publications 2016, 2017, 2018, 2019

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
2. Borgström A, Nerfeldt P, Friberg D; Adenotonsillotomy versus Adenotonsillectomy in Pediatric Obstructive Sleep Apnea: An RCT; *Pediatrics*, 2017 Apr; 139(4)
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.

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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 measurement (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 4-5 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 functions and structures.

Supervision of PhD-students:

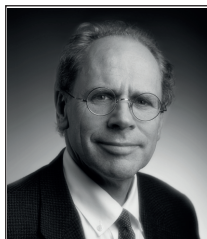
Main Supervisor	Co-supervisor
	Johan Fehrm
	Joar Sundman

Ethical permit No.

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Publications 2016, 2017, 2018, 2019

1. Browaldh N, Bring J, Friberg D. SKUP3 RCT; continuous study: Changes in sleepiness and quality of life after modified UPPP. Laryngoscope. 2016 Jun;126(6):1484-91. doi: 10.1002/lary.25642.
2. Browaldh N, Bautista T, Dutschmann M, Berkowitz R. The Kölliker-Fuse Nucleus: A Review of Animal Studies and the Implications for Cranial Nerve Function in Humans. Eur Arch Otorhinolaryngol. 2016 Nov;273(11):3505-3510. Review.
3. Fehrm J, Friberg D, Bring J, Browaldh N. Blood pressure after modified uvulopalatopharyngoplasty: results from the SKUP3 randomized controlled trial. Sleep Med. 2017 Jun;34:156-161
4. Browaldh N, Bring J, Friberg D. SKUP3: 6 and 24 months follow-up of changes in respiration and sleepiness after modified UPPP. Laryngoscope. 2017 Sept. doi:10.1002/lary.26835
5. Sundman J, Friberg D, Bring J, Lowden A, Nagai R, Browaldh N. Sleep Quality After Modified Uvulopalatopharyngoplasty: Results From the SKUP3 Randomized Controlled Trial. Sleep 2018 Sep 25

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The interaction of eosinophils and neutrophils in persistence of nasal polyps

Inflammation is a key feature of allergic rhinitis, nasal polyposis, asthma and epithelial derived cancer in the head and neck region. The mediators involved appear to be the same even though their profile varies depending on the diseases involved.

Previously, neutrophils have been treated as a relatively homogenous cell type. New information indicates that they can be divided into different subsets, each with diverse roles in inflammatory disease. Similarly, continuous neuro-peptide production was once believed to be central to the maintenance of ongoing airway inflammation. However, the relevance for this could not be shown clinically. Our goal is to introduce new concepts, where neutrophil subsets are pivotal for airway disease and neuropeptides are rapid initiators of innate immune inflammation, identifying them as novel key players in acute asthma, allergy and microbial induced airway disease exacerbations.

Intralymphatic immunotherapy (ILIT) is an emerging form of AIT that requires only 3 intralymphatic injections over a period of 12 weeks. For six years, we are working to develop an effective ILIT for clinical praxis. Our group also have an ambitious agenda focusing on the mechanisms behind chronic rhinosinusitis both with and without nasal polyposis

We have recently developed a flowcytometry based method for the detection of lymph node metastasis in oral and oropharyngeal squamous cell carcinoma. With this we hope to improve the diagnostic accuracy of detecting metastatic tumor cells in surgical samples of resected lymph nodes. We also expect to gain new knowledge on the interaction between the immune system and tumor. A distinct shift in the lymphocyte composition of tumor-adjacent and metastatic lymph nodes compared with unaffected lymph nodes has been detected. By assessing the lymphocyte reactivity towards cancer cells and cancer cell derived antigens, it may be possible to detect disease spread or recurrence before a macroscopic tumor has developed. I

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
Magnus Starkhammar	
Laila Hellkvist	
Sandra Ekstedt	
Eric Hjalmarsson	
Krzysztof Piersiala	

Ethical permit No.

2019_03518	2016_1344	2017_1791	2016_821	2016_823	
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Publications 2016, 2017, 2018, 2019

1. Arebro J, Draskog C, Winqvist O, Bachert C, Kumlien Georén S, Cardell LO. Subsetting reveals CD16^{high}CD62L^{dim} neutrophils in chronic rhinosinusitis with nasal polyps. *Allergy* (IF: 6.7) 2019 May 22. doi: 10.1111/all.13919. [Epub ahead of print]
2. Khan A, Huynh TMT, Vandeplas G, Joish VJ, Cardell LO, ..., Lund V, Bachert C. The GALEN Sinusitis Cohort: Impact on Health-Related Quality of Life in Patients With Chronic Rhinosinusitis With Nasal Polyps. *Rhinology* (IF: 3.7), accept 190506
3. 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 rhinosinusitis cohort: a large European cross-sectional study of chronic rhinosinusitis patients with and without nasal polyps. *Rhinology*. (IF: 3.7), 2019;1:57:32-42.
4. Ekstedt S, Stenberg H, Tufvesson E, Diamant Z, Bjermer L, Kumlien Georén S, Cardell LO. The potential role of CD16^{high}CD62L^{dim} neutrophils in the allergic asthma. *Allergy* (IF: 6.7) 2019 May 9. doi: 10.1111/all.13861. [Epub ahead of print]
5. 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. *Clin Exp Allergy* (IF: 4.7) 2019;49:285-291.

6. Jonstam K, Swanson BN, Mannent LP, Cardell LO, Tian N, Wang Y, Zhang D, Fan C, Holtappels G, Hamilton JD, Grabher A, Graham NMH, Pirozzi G, Bachert C. Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis. *Allergy* (IF: 6.7) 2019;74:743-752.
7. Senti G, Freiburghaus AU, Larenas-Linnemann D, Hoffmann HJ, Patterson AM, Klimek L, Di Bona D, Pfaar O, Ahlbeck L, Akdis M, Weinfeld D, Contreras-Verduzco FA, Pedroza-Melendez A, Skaarup SH, Lee SM, Cardell LO, Schmid JM, Westin U, Dollner R, Kündig TM. Intralymphatic Immunotherapy: Update and Unmet Needs. *Int Arch Allergy Immunol.* (IF: 2.9) 2019;178:141-149.
8. Kågedal Å, Millrud CR, 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.* (IF:2.5), 2018 Apr 21. doi: 10.1111/coa.13122.
9. Häyry V, Kågedal Å, Hjalmarsson E, Farrajota Neves da Silva P, Drakskog C, Margolin G, Georen S, Munck-Wikland E, Winqvist O, Cardell LO. Nodal staging of neck dissection specimens with flow-cytometry. *Br. J Cancer,* (IF:6.2) 2018;118:421
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. *J Allergy Clin Immunol.* 2018;142:1338-1341
11. Larsson O, Uddman R, Kumlien Georén S, Cardell LO. Reply. *J Allergy Clin Immunol.* (IF: 12.5), 2018;142:1677-1678.
12. 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. *J Allergy Clin Immunol.* (IF: 12.5), 2018;141:128
13. 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.
14. Vandenplas O, Vinnikov D, Blanc PD, Agache I, Bachert C, Bewick M, Cardell LO, Cullinan P, Demoly P, Descatha A, Fonseca J, Haahtela T, Hellings PW, Jamart J, Jantunen J, Kalayci Ö, Price D, Samolinski B, Sastre J, Tian L, Valero AL, Zhang X, Bousquet J. Impact of Rhinitis on Work Productivity: A Systematic Review. *J Allergy Clin Immunol Pract* (IF: 7.0), 2018;6:1274-1286.e9.
15. 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.* (IF: 5.2), 2017;7:43568.
16. Björstad Å, Cardell LO, Hahn-Pedersen J, Svärd M. A Cost-Minimisation Analysis Comparing Sublingual Immunotherapy to Subcutaneous Immunotherapy for the Treatment of House Dust Mite Allergy in a Swedish Setting. *Clin Drug Investig.* (IF:1.8) 2017;37:541-549.
17. Bao A, Che K, Bozinovski S, Ji J, Gregory JA, Kumlien Georén S, Adner A, Cardell LO, Lindén A. Recombinant Human IL-26 Facilitates the Innate Immune Response to Endotoxin in the Bronchoalveolar Space of Mice in Vivo *PLoSone* (IF:3.5) 2017 Dec 5;12(12):e0188909.
18. Calderón M, Bousquet J, Canonica W, Cardell LO, Hernandez Fernandez de Rojas D, Kleine-Tebbe J, Demoy P. Guideline recommendations on the use of allergen immunotherapy in house dust mite allergy: time for a change? *J Allergy Clin Immunol* (IF: 12.5), 2017; S0091-6749(17)30761-3.
19. Henmyr V, Carlberg D, Manderstedt E, Lind-Halldén C, Säll T, Cardell LO, Halldén C. Genetic variation of the Toll-like receptors in a Swedish allergic rhinitis case population. *BMC Med Genet.* (IF: 2.4), 2017;18:18.
20. Hoffmann HJ, Valovirta E, Pfaar O, Schmid JM, Moingeon P, Larche M, Simonsen K, Cardell LO, Helbo Skaarup S, Durham S, Sørensen P. Novel Approaches and Perspectives in Allergen Immunotherapy. *Allergy* (IF: 6.3), 2017;72:1022-1034.
21. 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. *Int J Cancer.* (IF: 5.3), 2017;140:2557-2567.
22. Xu Y, Cardell LO Long-term nicotine exposure dampens LPS-induced nerve mediated airway hyperreactivity in murine airways. *Am J Physiol Lung Cell Mol Physiol* (IF: 4.7), 2017;313:L516-L523.
23. Arebro J, Tengroth L, Razavi R, Kumlien Georén S, Winqvist O, Cardell LO. Antigen-presenting epithelial cells can play a pivotal role in airway allergy. *J Allergy Clin Immunol* (IF: 12.5), 2016;137:957-60.e7.
24. Cardell LO, Olsson P, Andersson M, Welin KO, Svensson J, Tennvall GR, Hellgren J. TOTALL: high cost of allergic rhinitis-a national Swedish population-based questionnaire study. *NPJ Prim Care Respir Med* (IF: 2.9), 2016;26:15082.
25. Gudnadottir G, Ehnage A, Bende M, Andersson M, Cervin A, Cardell LO, Hellgren J. Healthcare provider contact for children with symptoms of sleep-disordered breathing: a population survey. *J Laryngol Otol* (IF: 0.7), 2016;130:296-301.
26. Henmyr V, Lind-Halldén C, Halldén C, Säll T, Carlberg D, Bachert C, Cardell LO. Chronic Rhinosinusitis Patients Show Accumulation of Genetic Variants in PARS2. *PLoS One* (IF: 3.5), 2016;11:e0158202.
27. Henmyr V, Lind-Halldén C, Carlberg D, Halldén C, Melén E, Wickman M, Bergström A, Säll T, Cardell LO. Characterization of genetic variation in TLR8 in relation to allergic rhinitis. *Allergy.* (IF: 6.3), 2016;71:333-41.
28. Hoffmann HJ, Valovirta E, Pfaar O, Moingeon P, Schmid JM, Skaarup SH, Cardell LO, Simonsen K, Larché M, Durham SR, Sørensen P. Novel approaches and perspectives in allergen immunotherapy. *Allergy.* 2017;72:1022-1034.
29. Hylander T, Larsson O, Petersson-Westin U, Eriksson M, Kumlien Georén S, Winqvist O, Cardell LO. Intralymphatic immunotherapy of pollen-induced rhinoconjunctivitis: a double-blind placebo-controlled trial. *Respir Res* (IF: 3.1), 2016;17:10.
30. Larsson O, Hellkvist L, Peterson-Westin U, Cardell LO. Novel strategies for the treatment of grass pollen-induced allergic rhinitis. *Expert Opin Biol Ther.* 2016;16:1143-50.
31. Larsson OJ, Manson ML, Starkhammar M, Fuchs B, Adner M, Kumlien Georén S, Cardell LO. The TLR7 agonist imiquimod induces bronchodilation via a nonneuronal TLR7-independent mechanism: a possible role for quinoline in airway dilation. *Am J Physiol Lung Cell Mol Physiol* (IF: 4.7), 2016;310:L1121-9.
32. Larsson OJ, Manson ML, Starkhammar M, Fuchs B, Adner M, Kumlien Georén S, Cardell LO. The bronchodilatory capacity of imiquimod: the existence of two mechanisms. *Am J Physiol Lung Cell Mol Physiol.* 2016 Jul 1;311(1):L178-9.
33. Tomassen P, Vandeplas G, Van Zele T, Cardell LO, Arebro J, Olze H, Förster-Ruhrmann U, Kowalski ML, Olszewska-Zięba A, Holtappels G, De Ruyck N, Wang X, Van Drunen C, Mullol J, Hellings P, Hox V, Toskala E, Scadding G, Lund V, Zhang L, Fokkens W, Bachert C. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol* (IF: 12.5), 2016;137:1449-1456.e4.



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Dysregulation of the immunesystem in the middle ear disease cholesteatoma

The middle ear is a small and hard to reach compartment which limits the amount of tissue that can be extracted, restricting the possibilities for studying the molecular mechanisms behind diseases like otitis media and cholesteatoma. The tympanic cavity (TC) forms the major part of the middle ear and contains the tympanic membrane (the ear drum) which forms the border between the outer ear canal and the middle ear. Cholesteatoma is a disease involving the TC, where the keratinising squamous epithelium is believed to possess hyperproliferative characteristics. The pathogenesis of the acquired cholesteatoma is not fully understood, but it is believed that inflammation is often part of the pathology. There is a relationship between a good immunologic response and the protection against chronic middle ear disease. Toll Like Receptors (TLRs), as part of the mucosal innate immune system, play an important role as the first line of defense against an invasion of pathogenic infectious agents. There is a lack of knowledge about the expression of TLRs in middle ear mucosa in cholesteatomas in comparison to healthy mucosa specimen.

Two limiting factors for studies related to middle ear diseases is the amount of tissue that can be extracted without causing severe adverse side effects to the patient, as well as the restricted access to relevant healthy control tissue. QPCR is a useful method because multiple factors can be analysed using small amounts of tissue with high sensitivity, specificity and reproducibility.

The aims is determine which reference genes are best suited to use for normalisation in qPCR analysis of the mucosa in middle ear and develop a stable method were relevant healthy control tissue could be confirmed and the underlying mechanisms of different diseases can be studied. Finally the goal is to use these new methods to investigate if TLR and other inflammatory genes are dysregulated in cholesteatoma.

Supervision of PhD-students:

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

Ethical permit No.

2011/88-31				
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Publications 2016, 2017, 2018, 2019

1.

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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 contexts 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 aminoglycosides 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 importance 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 dynamic 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) will be a source for improvement projects.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
Niki Karpeta	Anna-Karin Strömberg

Ethical permit No.

2013/1177-31	2015/1296-31/2			
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Publications 2016, 2017, 2018, 2019

1. Strömberg AK, Olofsson Å, Westin M, Duan M, Stenfelt S. Changes in cochlear function related to acoustic stimulation of cervical vestibular evoked myogenic potential stimulation. *Hear Res.* 2016 Oct;340:43-49. doi: 10.1016/j.heares.2015.12.022. PMID: 26724755
2. Zhou Y, Qing J, Dong Y, Nie J, Li J, Wang C, Liu Y, Peng T, Duan M, Liu X, Xie D The role of transcription factors of neurosensory cells in non-syndromic sensorineural hearing loss with or without inner ear malformation. *Acta Otolaryngol.* 2016;136(3):277-82. doi: 10.3109/00016489.2015.1109706. PMID: 26634621
3. Li FJ, Wang DY, Wang HY, Wang L, Yang FB, Lan L, Guan J, Yin ZF, Rosenhall U, Yu L, Hellstrom S, Xue XJ, Duan ML, Wang QJ. Clinical Study on 136 Children with Sudden Sensorineural Hearing Loss. *Chin Med J (Engl).* 2016 Apr 20;129(8):946-52. doi: 10.4103/0366-6999.179791. PMID: 27064040
4. Verrecchia L, Westin M, Duan M, Brantberg K. Ocular vestibular evoked myogenic potentials to vertex low frequency vibration as a diagnostic test for superior canal dehiscence. *Clin Neurophysiol.* 2016 Apr;127(4):2134-9. doi: 10.1016/j.clinph.2016.01.001. PMID: 26818880
5. Zhao D, Wang Q, Tong B, Hellstrom S, Duan M. Systemic and intratympanic steroid therapy for sudden sensorineural hearing loss: a Meta-analysis. *Journal of Otology* 11 (2016) 18-23

6. Zhang L, Niu K, Zhu K, Xia C, Yan J, Zhao W, Wei J, Duan M, Zheng G. Long-Term Prognostic Analysis after Endoscopic Endonasal Surgery for Olfactory Neuroblastoma: A Retrospective Study of 13 Cases. *PLoS One*. 2016 Nov 2;11(11):e0166046. doi: 10.1371/journal.pone.0166046. PMID: 27806104
7. Zhou P, Ma W, Sheng Y, Duan M, Zhang X. Protective Effects of Acupuncture Against Gentamicin-Induced Ototoxicity in Rats: Possible Role of Neurotrophin-3. *Med Sci Monit*. 2017 Jan 25;23:446-451.
8. Lei Zhou, Miaolin Feng, Xinsheng Huang, Maoli Duan* Fatigue Analysis of Tympanic Membrane after Ossiculoplasty. 2017. See comment in PubMed Commons below *Acta Otolaryngol*. 2017 Jul;137(7):679-685. doi: 10.1080/00016489.
9. Marques P, Duan M, Perez-Fernandez N, Spratley J Gentamicin delivery to the inner ear: Does endolymphatic hydrops matter? *PLoS One*. 2018 Nov 15;13(11):e0207467. doi: 10.1371/journal.pone.0207467. eCollection 2018.
10. Yao W, Zhong J, Duan M. Three-dimensional finite-element analysis of the cochlear hypoplasia. *Acta Otolaryngol*. 2018 Nov;138(11):961-965. doi: 10.1080/00016489.2018.1497304. Epub 2019 Feb 13.
11. 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. doi: 10.1080/00016489.2018.1536297. Epub 2019 Jan 21.
12. Luca Verrecchia, Krister Brantberg, Zheer Tawfique, Duan Maoli. The diagnostic accuracy of oVEMP for superior canal dehiscence syndrome in a large cohort of dizzy patients. *Ear & Hearing* 2019 Mar/Apr;40(2):287-294. doi: 10.1097/AUD.0000000000000613.
13. Hu J, Wang H, Chen Z, Zhang Y, Wang W, Duan M, Xu M, Zhang Q Recovery of ocular and cervical vestibular evoked myogenic potentials after treatment of inner ear diseases. *Int J Neurosci*. 2019 May 9:1-9. doi: 10.1080/00207454.2019.1608201. [Epub ahead of print]
14. Zhou L, Shen N, Feng M, Liu H, Duan M, Huang X Study of age-related changes in Middle ear transfer function. *Comput Methods Biomech Biomed Engin*. 2019 Jul 3:1-10. doi: 10.1080/10255842.2019.1632297. [Epub ahead of print]

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HHT in Sweden: prevalence, morbidity and mortality

Supervision of PhD-students:

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

Ethical permit No.

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Publications 2016, 2017, 2018, 2019

1. Gudnadottir, G; Ehnhage, A; Bende, M; Andersson, M; Cervin, A; Cardell, L O; Hellgren, J. Healthcare provider contact for children with symptoms of sleep-disordered breathing: a population survey. The Journal of Laryngology & Otology, 2016, Vol.130(3), pp.296-301
2. Ehnhage, Anders; Johnsson, Pernilla Sahlstrand; Ahlström-Emanuelsson, Cecilia; Andersson, Morgan; Knutsson, Johan; Lien, Jacob; Norlander, Tomas; Olsson, Petter; Friis-Liby, Jan-Eric; Holmström, Mats. Treatment of idiopathic rhinitis with kinetic oscillations - a multi-centre randomized controlled study. Acta Oto-Laryngologica, 02 August 2016, Vol.136(8), pp.852-859
3. Sahlstrand-Johnson, P; Holmström, M; Ehnhage, A. Does the oral steroid treatment of patients with nasal polyposis cause osteopenia or osteoporosis? Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery, 17 September 2019

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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 of 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.

Supervision of PhD-students:

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

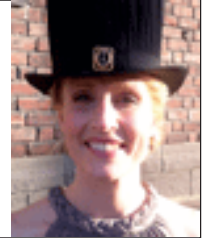
Ethical permit No.

2019-03518				
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Publications 2016, 2017, 2018, 2019

1. "Stathmin and epidermal growth factor receptor (EGFR) expression in sinonasal inverted papillomas (IP) and its correlation to human papillomavirus (HPV) status and clinical outcome", accepted for publication in Rhinology aug 2019
2. Elliot A, Näsman A, Westman M, Marklund L, Stjärne P, Hammarstedt-Nordenvall L. Human papillomavirus and infiltration of CD8- and Foxp3-positive immune cells in sinonasal inverted papillomas. Acta Otolaryngol. 2019 Nov;139(11):1019-1023. doi: 10.1080/00016489.2019.1654616. Epub 2019 Sep 5
3. Elliot A, Marklund L, Håkansson N, Song H, Ye W, Stjärne P, Hammarstedt-Nordenvall L. Incidence of IP and risk of malignant transformation in the Swedish population 1960-2010. Eur Arch Otorhinolaryngol. 2017 Mar;274(3):1445-1448. doi: 10.1007/s00405-016-4321-x. Epub 2016 Oct 18

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1) 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 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.

2) Development of central auditory pathways in patients with unilateral canal atresia 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. Both children and adults with or without hearing habilitation 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, diffusion MRI and resting state functional MRI.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
Elnaz Sepehri	Malin Siegbahn
	Hanna Josefsson

Ethical permit No.

2018/364	2017/2011-31	2012/1661-31/3	N191/14	N113/15
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Publications 2016, 2017, 2018, 2019

1. Cortés Fuentes IA, Pierre PV, Berglin CE. Improving Clinical Outcomes in Cochlear Implantation Using Glucocorticoid Therapy: A Review. Ear Hear. 2019 Apr 30. Epub ahead of print
2. Counter SA, Nikkhoun-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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Hearing in children with cleft lip and palate

Hearing and cognition

Hearing and estrogen

Hearing preservation in patients with vestibular schwannoma

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
Birgitta Tengroth	Jenny Häggström

Ethical permit No.

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Publications 2016, 2017, 2018, 2019

1. Hederstierna, C. and U. Rosenhall, Age-related hearing decline in individuals with and without occupational noise exposure. *Noise Health*, 2016. 18(80): p. 21-5.
2. Idrizbegovic, E., C. Hederstierna, and U. Rosenhall, Mismatch Negativity and Ear Laterality in Alzheimer's Disease and in Mild Cognitive Impairment. *J Alzheimers Dis*, 2016. 53(4): p. 1405-10.
3. 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.
4. Tengroth, B., et al., Hearing thresholds and ventilation tube treatment in children with unilateral cleft lip and palate. *International Journal of Pediatric Otorhinolaryngology*, 2017.
5. 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.
6. Bonnard, A., 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. 181(1): p. 18-24.

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Randomized controlled studies of adults and children with obstructive sleep apnea undergoing pharyngeal surgery, and flow-cytometry of tonsils

We are investigating adults and children with obstructive sleep apnea (OSA), if surgery is more effective than non-treatment, when investigating our primary outcome, changes in apnea-hypopnea index with polysomnography. We also investigate which surgical method is superior to treat OSA in adults and children. In adults we only operate those who fail non-surgical treatment. In children surgery is first-line treatment. We have five ongoing RCT, 2 in adults and 3 in children. 1) There are so far 4 publications from the first RCT in 65 adults, which showed that our modified Uvulopalatopharyngoplasty (UPPP, pharyngoplasty with tonsillectomy) significantly improved nocturnal respiration, daytime sleepiness and quality of life, compared to untreated controls after 6 months. Also, the blood pressure improved significantly. We have also submitted results from 2-years follow-up which showed persistent and stable results. 2) The other RCT in adults compares UPPP with only tonsillectomy (TE), to investigate which part of the interventions; TE with or without pharyngoplasty, contributes to the effect. We have so far recruited 75 patients of 100. 3) We have published the results from our first pediatric RCT; 80 children 2-6 years were randomized to adenotonsillectomy (ATE) or adenotonsillotomy (ATT). The results showed that ATT was non-inferior to ATE, but the risk of OSA-recurrence was 13% in the ATT group. This is of importance when deciding surgical treatment. 4) The other published RCT in 80 children with severe OSA compared ATE with ATE + resection of the palatal pillars with 2 sutures, which showed no significant group differences. 5) A third RCT in 60 children 2-5 years with mild to moderate OSA compares ATE with untreated controls for 6 months, submitted manuscript. We are also collecting tonsils from these patients to investigate their content of lymphoid cells with flow-cytometry.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
Johan Fehrm	
Joar Sundman	
Isabella Sjölander (Uppsala)	

Ethical permit No.

Ö21-2007	2011/333-31/4	2014/1000-31/1	2015/755-31/2	
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Publications 2014, 2015, 2016

- Enqvist M, Jacobs B, Junlén HR, Schaffer M, Melén CM, Friberg D, Wahlin BE, Malmberg KJ. Systemic and Intra-Nodal Activation of NK Cells After Rituximab Monotherapy for Follicular Lymphoma. *Front Immunol*. 2019 Sept 12;10:2085. Doi:10.3389/fimmu.2019.02085. eCollection 2019. JIF 4.716
- Borgström A, Nerfeldt P, Friberg D. Postoperative pain and bleeding after adenotonsillectomy vs adenotonsillotomy in pediatric obstructive sleep apnea: an RCT. *Eur Arch ORL*. 2019 Aug 3. doi: 10.1007/s00405-019-05571-w. JIF 1.546
- Mazzurana L, Forkel M, Rao A, Van Acker A, Kokkinou E, Ichiya T, Almer S, Höög C, Friberg D, Michaelsson J, Mjösberg J. Suppression of Aiolos and Ikaros expression by lenalidomide reduces human ILC3-ILC1/NK cell transdifferentiation. *Eur J Immunol*. May 2019 doi: 10.1002/eji.201848075. JIF 4.248
- Crump C, Friberg D, Li X, Sundquist J, Sundquist K. Preterm birth and risk of sleep-disordered breathing from childhood into mid-adulthood. SDB and obstructive sleep apnea. *Int J Epidemiol* 2019 Apr 21. pii: dyz075. doi: 10.1093/ije/dyz075. JIF 8.360
- Friberg D, Sundman J, Browaldh N. Longterm evaluation of satisfaction, taste disturbance and side-effects after modified uvulopalatopharyngoplasty. *Laryngoscope* 2019 Mar 12. doi: 10.1002/lary.27917. JIF 2.442.
- Vangeti S, Gertow J, Yu M, Kiu S, Baharom F, Scholz S, Friberg D, Starkhammar M, Ahlberg A, Smed-Sörensen A. Human blood and tonsil plasmacytoid dendritic cells display similar gene expression profiles but exhibit differential type I interferon responses to IAV infection. *J Immunol* 2019. 1;202(7):2069-2081. JIF 4.54
- Maric J, Ravindran A, Mazzurana L, van Acker A, Rao A, Kokkinou E, Ekoff M, Thomas D, Fauland A, Nilsson G, Wheelock CE, Dahlén SE, Ferreirós N, Geisslinger G, Friberg D, Heinemann A, Konya V, Mjösberg J. Cytokine-induced endogenous production of PGD2 is essential for human ILC2 activation. *J Allergy Clin Immunol* 2018 Dec 19. pii: S0091-6749(18)32774-X. doi: 10.1016/j.jaci.2018.10.069. JIF 13.258

8. Fehrm J, Nerfeldt P, Sundman J, Friberg D. Adenopharyngoplasty vs adenotonsillectomy in children with severe obstructive sleep apnea: an RCT. *JAMA Otolaryngol Head Neck Surg.* 2018;144(7):580-586. JIF 3.295
9. Sundman J, Fehrm J, Friberg D. Low inter-examiner agreement of the Friedman staging system indicating limited value in patient selection. *Eur Arch ORL.* 2018;275(6):1541-1545. JIF 1.546
10. Sundman J, Friberg D, Bring J, Nagai R, Lowden A, Browaldh N. Sleep quality after modified uvulopalatopharyngoplasty: Results from the SKUP3 randomized controlled trial. *Sleep* 2018;1;41(1). JIF 5.135
11. Browaldh N, Bring J, Friberg D. SKUP3: 6 and 24 months follow-up of changes in respiration and sleepiness after modified UPPP. *Laryngoscope* 2018;128(5):1238-1244. JIF 2.442.
12. Maric J, Ravindran A, Mazzurana L, Björklund ÅK, Van Acker A, Rao A, Friberg D, Dahlén SE, Heinemann A, Konya V, Mjösberg J. Prostaglandin E2 suppresses human group 2 innate lymphoid cell function. *J Allergy Clin Immunol.* 2018 141(5):1761-1773. JIF 13.08.
13. Konya V, Czarnewski P, Forkel M, Rao A, Kokkinou E, Villablanca EJ, Almer S, Lindforss U, Friberg D, Höög C, Bergman P, Mjösberg J. Vitamin D downregulates the IL-23 receptor pathway in human mucosal group 3 innate lymphoid cells. *J All Clin Imm.* 2018;141(1):279-292. JIF 13.258.
14. Forkel M, Berglin L, Kekäläinen E, Carlsson A, Svedin E, Michaëlsson J, Nagasawa M, Erjefält JS, Mori M, Flodström-Tullberg M, Bergquist A, Ljunggren HG, Westgren M, Lindforss U, Friberg D, Jorns C, Ellis E, Björkström NK, Mjösberg J. Composition and functionality of the intrahepatic innate lymphoid cell-compartment in human non-fibrotic and fibrotic livers . *Eur J Immunol.* 2017;47(8):1280-1294. JIF 4.248.
15. Pajedine E, Bileviciute-Ljungar I, Friberg D. Sleep patterns among patients with chronic fatigue: A polysomnography-based study. *Clin Resp Journal.* 2018;12(4):1389-1397. JIF 2.21 Citations 1
16. Borgström A, Nerfeldt P, Friberg D. Adenotonsillotomy Versus Adenotonsillectomy in Pediatric Obstructive Sleep Apnea: An RCT. *Pediatrics* 2017;139(4). JIF 5.515. Citations 8. Among top 5% cited publications: Yes
17. Fehrm J, Friberg D, Bring J, Browaldh N. Blood pressure after modified uvulopalatopharyngoplasty: results from the SKUP randomized controlled trial. *Sleep Med.* 2017;34:156-161. JIF 3.339
18. Sundman J, Bring J, Friberg D. Poor interexaminer agreement on Friedman tongue position. *Acta Otolaryngol.* 2017;137(5):554-556. JIF 1.13
19. Borgström A, Nerfeldt P, Friberg D, Sunnergren, O, Stalfors J. Trends and changes in paediatric tonsil surgery in Sweden 1987-2013: a population-based cohort study. *BMJ open.* 2017; 13;7(1):e013346. JIF 2.56
20. Nerfeldt P, Friberg D. Effectiveness of Oral Appliances in Obstructive Sleep Apnea with Respiratory Arousals. *J Clin Sleep Med.* 2016;12(8):1159-65. JIF 2.71
21. Browaldh N, Bring J, Friberg D. SKUP(3) RCT; continuous study: Changes in sleepiness and quality of life after modified UPPP. *Laryngoscope.* 2016;126(6):1484-91. JIF 2.27
22. Marquardt N, Ivarsson MA, Sundström E, Åkesson E, Martini E, Eidsmo L, Mjösberg J, Friberg D, Kublickas M, Ek S, Tegerstedt G, Seiger Å, Westgren M, Michaëlsson J. Fetal CD103+ IL-17-Producing Group 3 Innate Lymphoid Cells Represent the Dominant Lymphocyte Subset in Human Amniotic Fluid. *J Immunol.* 2016;15,197(8):3069-3075. JIF 4.98
23. Björklund ÅK, Forkel M, Picelli S, Konya V, Theorell J, Friberg D, Sandberg R, Mjösberg J. The heterogeneity of human CD127(+) innate lymphoid cells revealed by single-cell RNA sequencing. *Nat Immunol.* 2016;17(4):451-60. JIF 21.08. Among top 5% cited publications: Yes

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Studies on radiotherapy-induced tissue inflammation and patients with salivary gland cancer

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.

1. The impact of irradiation on acute and long-term changes in tissues (blood vessels, fat, bone and skin) following radiotherapy treatment.
 - Study underlying mechanisms in human tissue and using 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

Supervision of PhD-students:

Main Supervisor	Co-supervisor
Björn Eriksson	

Ethical permit No.

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Publications 2014, 2015, 2016

1. Osteoradionecrosis, an increasing indication for microvascular head and neck reconstruction. Danielsson D, Gahm C, Haghdoust S, Munck-Wikland E, Halle M. Int J Oral Maxillofac Surg. 2019 Jul 8.
2. Upregulation of plasminogen activator inhibitor-1 in irradiated recipient arteries and veins from free tissue transfer reconstruction. Eriksson BO, Gahm C, Halle M. Hindawi Mediators of infl. 2018
3. Haeggbloom L, Ursu RG, Mirzaie L, Attof T, Gahm C, Hammarstedt-Nordenvall L, Näsman A. No evidence for human papilloma virus having a casual role in salivary gland tumors. Diagn Pathol. 2018 Jul 18;13
4. Ramqvist T, Ursu RG, Haeggbloom 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, Halle M, Hammarstedt-Nordenvall L. Regional recurrence in early stage I-II oral tongue cancer: a single institutional study and review of the literature. Acta oto-laryngologica 2017 137;7 755-761



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Effect of ageing on treatment with cochlear implants

The project is designed to investigate the outcomes of treatment with cochlear implants in adults, with special respect to ageing. Many candidates for treatment with cochlear implants are 70 years old or more. There are special concerns for this group, such as if there are higher risks for major complications during surgery, higher risk for vestibular disturbances due to implantation and possible effect on outcome of cognitive difficulties and dementia. We aim to compare younger vs older cochlear implant recipients (< 60 y vs > 70 y). The majority of the adult CI-recipients are eligible for the study. Participants over 70 years old will undergo extended vestibular testing. This part includes testing at the vestibular laboratory and testing by a team of physiotherapists. Cognitive testing (MoCa test) will also be amended in a near future. All participants give permission to review their medical history and medical charts, and they all answer two questionnaires about vestibular problems (FES-1 and DHI). Medical records, hearing results, technical performance and specifics of implants will also be surveyed. There is also ethical permission for a retrospective study including review of medical charts, hearing performance and also amendment of FES-1 and DHI.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
	Sofia Hultman Dennison
	Johanna Westerberg (Linköping)

Ethical permit No.

2018/1032-31				
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Publications 2016, 2017, 2018, 2019

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
5. Preciado D, Granath A, Lin J, Val S, Kurabi A, Johnston N, Vijayasekaran S, Valdez T, Depireux D, Hermansson A. Panel 8: Report on Recent Advances in Molecular and Cellular Biochemistry. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2017 156;4_suppl S106-S113
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 biopsy and other predictive and prognostic 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 oropharyngeal cancer

Supervision of PhD-students:

Main Supervisor	Co-supervisor
	Björn Eriksson
	Clara Svenberg Lind

Ethical permit No.

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Publications 2016, 2017, 2018, 2019

1. Mäkitie Antti, Kamali Alexander, Mroueh Rayan, Lindford Andrew, Koivunen Petri, Autio Timo, Lassus Patrik, Halle Martin, Bäck Leif, Palmgren Björn, and Hammarstedt-Nordenvall Lalle. Differences in the treatment protocol for oral tongue cancer in Sweden and Finland. Submitted Acta Otolaryngol
2. Elliot A, Näsman A, Westman A, Hammarstedt-Nordenvall L, Stjärne P, Marklund L. Stathmin and EGFR expression and its correlation to HPV status and clinical outcome in sinonasal inverted papilloma. Accepted for publication Rhinology sept 2019
3. Elliot A, Näsman A, Westman M, Marklund L, Stjärne P, Hammarstedt-Nordenvall L. Human papillomavirus and infiltration of CD8- and Foxp3-positive immune cells in sinonasal inverted papillomas. Acta Otolaryngol. 2019 Sep 5:1-5. doi: 10.1080/00016489.2019.1654616. [Epub ahead of print] PMID:31486701 <http://www.ncbi.nlm.nih.gov/pubmed/31486701>
4. Haeggbloom L, Attoff T, Yu J, Holzhauser S, Vlastos A, Mirzae L, Ährlund-Richter A, Munck-Wikland E, Marklund L, Hammarstedt-Nordenvall L, Ye W, Ramqvist T, Näsman A, Dalianis T. Changes in incidence and prevalence of human papillomavirus in tonsillar and base of tongue cancer during 2000-2016 in the Stockholm region and Sweden. Head Neck. 2018 Dec 24. doi: 10.1002/hed.25585. [Epub ahead of print] PMID:30584688 <http://www.ncbi.nlm.nih.gov/pubmed/30584688>
5. Haeggbloom 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. doi: 10.1186/s13000-018-0721-0. PMID:30021645 <http://www.ncbi.nlm.nih.gov/pubmed/30021645>
6. Ramqvist T, Ursu RG, Haeggbloom 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. PMID:29715110 <http://www.ncbi.nlm.nih.gov/pubmed/29715110>
7. Haeggbloom L, Attoff T, Hammarstedt-Nordenvall L, Näsman A. Human papillomavirus and survival of patients per histological subsite of tonsillar squamous cell carcinoma. Cancer Med. 2018 May;7(5):1717-1722. doi: 10.1002/cam4.1400. Epub 2018 Mar 23. PMID: 29573210 <http://www.ncbi.nlm.nih.gov/pubmed/29573210>
8. Mäkitie A, Ruuskanen M, Bentzen J, Brun E, Gebre-Medhin M, Friesland S, Marsk E, Hammarstedt-Nordenvall L,

- Gille E, Reizenstein J, Adell G, Farnebo L, Rzepecki J, Haugen H, Söderström K, Zackrisson B, Bergström S, Löden B, Cederblad L, Laurell G, Smeland E, Folkvard Evensen J, Lund JÅ, Tøndel H, Karlsdottir Å, Jóhannsson J, Johansen J, Kristensen CA, Jensen K, Andersen LJ, Koivunen P, Korpela M, Voutilainen L, Wigren T, Minn H, Joensuu H, Overgaard J, Saarilahti K.
9. The management and survival outcomes of nasopharyngeal cancer in the Nordic countries. *Acta Oncol.* 2018 Apr;57(4):557-560. doi: 10.1080/0284186X.2017.1408961. Epub 2017 Dec 5. No abstract available. PMID:29202641 <http://www.ncbi.nlm.nih.gov/pubmed/29202641>
 10. 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>
 11. Kamali A, Gahm C, Palmgren B, Marklund L, Halle M, Hammarstedt-Nordenvall L. Regional recurrence in early stage I-II oral tongue cancer: a single institutional study and review of the literature. *Acta Otolaryngol.* 2017 Feb 22:1-7. doi: 10.1080/00016489.2017.1279751. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/28361597>
 12. 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>
 13. Elliot A, Marklund L, Håkansson N, Song H, Ye W, Stjärne P, Hammarstedt-Nordenvall L. Incidence of IP and risk of malignant transformation in the Swedish population 1960-2010 *EUR ARCH OTORHINOLARYNGOL.* 2016 Oct 18. [Epub ahead of print] PMID:27757542 DOI:10.1007/s00405-016-4321-x <http://www.ncbi.nlm.nih.gov/pubmed/27757542>

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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 occurs 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 excessive tear secretion, pronounciation, drooling on top of social/cosmetic problems due to asymmetry 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 double blinded placebo-controlled multicenter trial on children with acute facial nerve palsy. Patients are being recruited consecutively at 11 study centers in Sweden during 2019-2020 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 clinical 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.

Clinical 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 impairment and disability. National and international guidelines will be published for evidence-based treatment of children with acute facial nerve palsy.

The study protocol is published at [ClinicalTrials.gov NCT03781700](https://clinicaltrials.gov/ct2/show/study/NCT03781700)

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
Sofia Karlsson	
Sigurdur Arnason	

Ethical permit No.

2017/554				
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Publications 2016, 2017, 2018, 2019



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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 investigating 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 of studies on children. This field has an enormous potential to become a national and international frontline research area.
3. To study plasminogen, a proinflammatory 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 performed at Umeå Univ in collaboration with a Canadian drug company, PROMETIC Life Sci Inc.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
Satu Turunen-Taheri	Niki Karpeta

Ethical permit No.

2012/057	2014/2101-31			
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Publications 2016, 2017, 2018, 2019

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. (2018). Severe-to-profound hearing impairment: demographic data, gender differences and benefits of audiological rehabilitation. *Disability and Rehabilitation*, 12: 1-9.
3. Turunen-Taheri, S., Skagerstrand, Å., Hellström, S., & Carlsson, P-I. (2017). Patients with severe-to-profound hearing impairment and simultaneous severe vision impairment: a quality-of-life study. *Acta Oto-Laryngologica*, 137:3, 279-285.
4. Krakau M, Dagöö BR, Hellström S, Granath A. (2017). Long-term hearing outcomes after recurrent acute otitis media during early childhood. *Acta Otolaryngol.* 137:1238-1243.
5. Myburgh HC, van Zijl WH, Swanepoel D, Hellström S, Laurent C. (2016). Otitis Media Diagnosis for Developing Countries Using Tympanic Membrane Image-Analysis. *EBioMedicine*. 5:156-60.
6. Li FJ, Wang DY, Wang HY, Wang L, Yang FB, Lan L, Guan J, Yin ZF, Rosenhall U, Yu L, Hellstrom S, Xue XJ, Duan ML, Wang QJ. (2016). Clinical Study on 136 Children with Sudden Sensorineural Hearing Loss. *Chin Med J (Engl)*. 129:946-52.

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

Before and after both subglottal stenosis operation and airway stent operation breathing symptoms and capacity is evaluated with box spirometry and impulse 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:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
	Joar Sundman

Ethical permit No.

2014/100-31/2	2015/1543-32	2014/93-31/2		
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Publications 2016, 2017, 2018, 2019

1. Circulatory Collapse due to Hyperinflation in a Patient with Tracheobronchomalacia: A Case Report and Brief Review, Lundström, Niclas et al, 2019

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Reconstruction of vocal fold scarring with mesenchymal stem cells

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

From 2012 an ongoing study in cooperation with Professor Katarina LeBlanc at KI is including and treating patients with severe hoarseness and scarring of the vocal folds. The patients are recruited from Karolinska and other parts of Sweden. Vocal folds are dissected and scar tissue is reduced/removed followed by a local injection of autologous MSCs. At present 16 patients are treated. Preliminary results at 1 year follow up for the patients shown clearly improved vocal fold function without side effects. Application for a subsequent study is ongoing.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
Emma Malmström	Srinivasa Rou Nagubothu

Ethical permit No.

2010/1650	2014/51432			
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Publications 2016, 2017, 2018, 2019

1. Nygren U, Isberg B, Södersten M, Hertegård S, Nordenskjöld A. Magnetic Resonance Imaging of the Vocal Folds in Women With Congenital Adrenal Hyperplasia and Virilized Voices. *J Speech Lang Hear Res*. 2016 Aug 1;59(4):713-21. doi: 10.1044/2016_JSLHR-S-14-0191. PMID: 27537527
2. Fishman JM, Long J, Gugatschka M, De Coppi P, Hirano S, Hertegård S, Thibeault SL, Birchall MA. Regenerative medicine approaches for vocal fold reconstruction. *2016 Laryngoscope* 2016 Jan 17. doi: 10.1002/lary.25820. [Epub ahead of print]
3. Hertegård S. Tissue engineering of the Larynx and Airway. *Current Opinion in Otolaryngology and Head & Neck Surgery*. 2016 Dec;24(6):469-476.. [Epub ahead of print] PMID: 27585078
4. Herbst CT, Hertegård S, Zangger-Borch D, Lindestad P-Å. Freddie Mercury-acoustic analysis of speaking fundamental frequency, vibrato, and subharmonics. *Logopedics Phoniatics Vocology* 2017 Apr;42(1):29-38. Doi:10.3109/14015439.2016.1156737. Epub 2016 Apr 15. PMID: 27079680
5. Malmström E, Hertegård S. Background Factors and Subjective Voice Symptoms in Patients with Acquired Vocal Fold Scarring and Sulcus Vocalis. *Folia Phoniatica et logopaedica*. 2018 Jan 18;69(3):125-130. doi: 10.1159/000484169. [Epub ahead of print]
6. Kelly V, Hertegård S, Eriksson J, Nygren U, Södersten M. Effects of gender-confirming pitch-raising surgery in transgender women A long-term follow-up study of acoustic and patient-reported data. *Journal of Voice*. 2018 Aug 1. pii: S0892-1997(17)30548-9. doi: 10.1016/j.jvoice.2018.03.005. [Epub ahead of print] PMID: 30077418
7. Södersten M, Nygren U, Hertegård S, and Dhejne C. A Multidisciplinary Approach to Transgender Health. Chapter 1 p 1-21. In: Adler RK, Hirsch S, Pickering J. (Eds) . *Voice and Communication Therapy for the Transgender/ Transsexual Client. A Comprehensive Clinical Guide*. Third Edition. 2018. ISBN 978-1-9444883-0. Plural publishing. San Diego USA

8. Olafur Sveinsson*, Bjarne Udd*, Per Svenningsson, Christoph Gassner, Charlotte Engström, José Laffita-Mesa, Stellan Hertegård, Irina Savitcheva, Hans Jung, Markus Tolnay, Beat M. Frey and Martin Paucar. Novel Xp21.1 deletion associated with unusual features in a large McLeod syndrome kindred. *Parkinsonism Relat Disord*. 2018 Sep 26. pii: S1353-8020(18)30399-7. doi: 10.1016/j.parkreldis.2018.09.014. [Epub ahead of print]
9. 9. Nagubothu S.R., Davies L.C., Sugars R., Tudzarovski N., Törnqvist Andrén A., Bottai M, Hertegård S. and Le Blanc K. Mesenchymal stromal cells modulate tissue repair responses after local injection within scarred vocal folds. *Laryngoscope*. 2019 Mar 5. doi: 10.1002/lary.27885. [Epub ahead of print]
10. 10. Hertegård S, Nagubothu SR, Malmström E, Ström C, Tolf A , Davies L, LeBlanc K. Hyaluronan hydrogels for the local delivery of mesenchymal stromal cells to the injured vocal fold. *Stem Cells and Development*. 2019 Jun 27. doi: 10.1089/scd.2019.0102. [Epub ahead of print] PMID: 31244387
11. 11 . Sveinsson O, Udd B, Svenningsson P, Gassner C, Engström C, Laffita-Mesa J, Solders G, Hertegård S, Savitcheva I, Jung HH, Tolnay M, Frey BM, Paucar M. Involuntary movements, vocalizations and cognitive decline. *Parkinsonism Relat Disord*. 2019 May 29. pii: S1353-8020(19)30250-0. doi:10.1016/j.parkreldis. 2019.05.029. [Epub ahead of print] No abstract available. PMID: 31153763



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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.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
	Caroline Bengtsson
	Joar Sundman
	Sofia Hultman Dennison
	Karin Åberg

Ethical permit No.

2005:245	2012/1472-31	2014/448	2013/397	
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Publications 2016, 2017, 2018, 2019

1. Sahlstrand-Johnson P, Holmström M, Ehnhage A. Does the oral steroid treatment of patients with nasal polyposis cause osteopenia or osteoporosis? Clin Otolaryngol. 2019 Sep 17.
2. Bengtsson C, Jonsson L, Holmström M, Hellgren J, Franklin K, Gíslason T, Holm M, Johannessen A, Jögi R, Schlünssen V, Janson C, Lindberg E. Incident Chronic Rhinosinusitis Is Associated With Impaired Sleep Quality: Results of the RHINE Study. J Clin Sleep Med. 2019 Jun 15;15(6):899-905.
3. Bjermer L, Westman M, Holmström M, Wickman MC. The complex pathophysiology of allergic rhinitis: scientific rationale for the development of an alternative treatment option. Allergy Asthma Clin Immunol. 2019 Apr 16;15
4. Morén S, Lindestad PÅ, Holmström M, Mani M. Voice Quality in Adults Treated for Unilateral Cleft Lip and Palate: Long-Term Follow-Up After One- or Two-Stage Palate Repair. Cleft Palate Craniofac J. 2018 Sep;55(8):1103-1114
5. Bengtsson C, Lindberg E, Jonsson L, Holmström M, Sundbom F, Hedner J, Malinovschi A, Middelveld R, Forsberg B, Janson C. Chronic Rhinosinusitis Impairs Sleep Quality: Results of the GA2LEN Study. Sleep. 2017 Jan 1;40(1)
6. Peroz R, Holmström M, Mani M. Can objective measurements of the nasal form and function represent the clinical picture in unilateral cleft lip and palate? J Plast Reconstr Aesthet Surg. 2017 May;70(5):653-658.
7. Löfstedt H, Hagström K, Bryngelsson IL, Holmström M, Rask-Andersen A.
8. Respiratory symptoms and lung function in relation to wood dust and monoterpene exposure in the wood pellet industry. Ups J Med Sci. 2017 Jun;122(2):78-84.
9. Morén S, Mani M, Lilian S, Lindestad PÅ, Holmström M. Speech in Adults Treated for Unilateral Cleft Lip and Palate: Long-Term Follow-Up After One- or Two-Stage Palate Repair. Cleft Palate Craniofac J. 2017 Nov;54(6):639-649.
10. Ehnhage A, Johnsson PS, Ahlström-Emanuelsson C, Andersson M, Knutsson J, Lien J, Norlander T, Olsson P, Friis-Liby JE, Holmström M. Treatment of idiopathic rhinitis with kinetic oscillations - a multi-centre randomized controlled study. Acta Otolaryngol. 2016 Aug;136(8):852-9.

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Periferal and central hearing pathways.

Facial palsy

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, neurop-hysiologists, 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 hi-stochemically 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:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
Malin Siegbahn	Hanna Josefsson
	Sigurdur Arnason
	Sofia Karlsson
	Lovisa Lansing
	Rebecka Ohm
	Zane Upate (under registration)

Ethical permit No.

N113/15	2012/1874-32	2012/1661-31/3	014/1619-32	2018/1154-32
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Publications 2016, 2017, 2018, 2019

1. Moverare T, Hultcrantz M, Lohmander A, Sjögren L. Peripheral facial palsy: Speech, communication and oral motor function. European Annals of Otorhinolaryngology, Head and Neck diseases 2017;134(1):27-31. PMID: 27836742
2. Berglund M, Florentzson R, Fransson M, Hultcrantz M, Eriksson PO, Englund E, Westman E. Myringoplasty outcomes from the Swedish National Quality Register. Laryngoscope 2017 Apr 20, 87; 4-13. PMID 28420278.
3. Bylund N, Jansson D, Enghag S, Berg T, Marsk E, Hultcrantz M, Hadziosmanovic N, Rodriguez-Lorenz A, Jonsson L. Synkinesis in Bell's palsy in a randomised controlled trial. Clin Otolaryngol. Clin Otolaryngol. 2017;42 (3):673-680. PMID: 27882653

4. Bonnard Å, Bark R, Hederstierna C, Hultcrantz M. Audiometric features in young adults with Turner syndrome. 2017 Int J Audiology, Apr 19:1-7. PMID 28420278
5. Hultcrantz M. Case Report after Introducing a New Abutment Surface for Bone Anchored Hearing Implants: Hydroxiapatite Abutment Surfaces and Skin Reaction. JMIS 2017, Vol 2.
6. Trobos M, Johansson M, Jonhede S, Peters H, Hoffman M, Omar O, Thomsen P, Hultcrantz M. The clinical outcome and microbiological profile of bone-anchored hearing systems (BAHS) with different abutment topographies: a prospective pilot study. Eur Arch Otorhinolaryngol 2018: 275; 1395-408. PMID 29623410
7. Berglund M, Suneson P, Florentzson R, Fransson M, Hultcrantz M, Westman E, Eriksson PO. Tinnitus and taste disturbances reported after myringoplasty: Data from a national quality registry. Laryngoscope. 2019 Jan;129(1):209-215. 27325.
8. Bonnard Å, Hederstierna C, Bark R, Hultcrantz M. The effect of hormonal treatment on hearing in young women with Turner syndrome: A cohort study. Accepted 2019.
9. Arnason S, Hultcrantz M, Nilsson A, Laestadius Å. Peripheral facial palsy in children in a Borrelia high endemic area: epidemiology and evaluation of clinical recovery. A retrospective one-year follow up. Accepted Acta Ped 2019.
10. Håkansson B, Reinfeldt S, Persson A.C, Freden Jansson C-J, Rigato C, Hultcrantz M, Eeg-Olofsson, M. The bone conduction implant – a review and one year follow up. Accepted I J Audiology 2019.
11. Siegbahn M, Jörgens D, Zantop K, Engmér Berglin C, Hultcrantz M, Moreno R. Unilateral Ear Canal Atresia: Does it change cortical morphology or functional connectivity? Submitted Ear and Hearing 2019.
12. Malin Siegbahn, Filip Asp, Malou Hultcrantz, Cecilia Engmér-Berglin. Adults with unilateral congenital ear canal atresia – sound localization ability and recognition of speech in competing speech in unaided condition. In manuscript.
13. Nina Bylund, MD; Malou Hultcrantz, MD, PhD; Lars Jonsson, MD, PhD; Elin Marsk, MD, PhD Quality of Life in Bell's Palsy: Evaluation of FaCE-scale and FDI and Correlation with Sunnybrook and House-Brackmann Grading over Time . In manuscript
14. Bookchapter: M Hultcrantz. Turner Syndrome: Translational Research Concerning Ear and Hearing. A Summary from recent Years. In: Cholesteatoma and ear surgery: An update. Ed: M Young. Kugler Publications 2017.

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Aging, cognition and central auditory function

This project is about relationships between aging, cognitive decline, and central auditory function. Many elderly retain adequate sensitivity to sound but are poor at recognizing relevant sounds such as speech in background noise, indicating central auditory dysfunction (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.

Auditory function was assessed with pure tone audiometry, speech perception in quiet and in background noise, and dichotic digit tests (DDT) with two digits in a consecutive group of men and women (136) diagnosed at baseline with Alzheimer's disease (AD), mild cognitive impairment (MCI), or with subjective memory complaint (SMC). Subjects were retested after 1, 5 years and again after 6 years.

In the first longitudinal study (Häggström et al., 2018) it has been demonstrated that central auditory function, as measured with the DDT, differed between the groups, while pure tone audiometry and speech in noise test did not. The results suggested that DDT may reflect on ongoing process resulting in dementia. In the second, a retrospective study the aim was to assess whether or not the DDT can be used as a predictor of conversion from MCI to AD and other types of dementia. It has been shown that a low score on the DDT implies a higher risk for conversion to dementia from MCI.

In the coming study it will be investigated if CAD is related to morphological changes in the brain, in order to further evaluate the diagnostic validity of the DDT. The DDT results of the participants in the three diagnostic groups will be correlated to morphological changes in the corpus callosum on existing MRI images.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
Jenny Häggström	

Ethical permit No.

2005/914-31	2014/2087-31-2	2018/1291-32		
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Publications 2016, 2017, 2018, 2019

1. Idrizbegovic E, Hederstierna C, Rosenhall U. Mismatch Negativity and Ear Laterality in Alzheimer's Disease and in Mild Cognitive Impairment. *J Alzheimers Dis.* 2016 Jul 1;53(4):1405-10. doi: 10.3233/JAD-160323.
2. Müller K, Edvall NK, Idrizbegovic E, Huhn R, Cima R, Persson V, Leineweber C, Westerlund H, Langguth B, Schlee W, Canlon B, Cederroth CR. Validation of Online Versions of Tinnitus Questionnaires Translated into Swedish. *Front Aging Neurosci.* 2016 Nov 22;8:272. eCollection 2016.
3. Häggström J, Rosenhall U, Hederstierna C, Östberg P, Idrizbegovic E. A Longitudinal Study of Peripheral and Central Auditory Function in Alzheimer's Disease and in Mild Cognitive Impairment. *Dement Geriatr Cogn Dis Extra.* 2018 Oct 22;8(3):393-401. doi: 10.1159/000493340. eCollection 2018 Sep-Dec.
4. Cederroth CR, PirouziFard M, Trpchevska N, Idrizbegovic E, Canlon B, Sundquist J, Sundquist K, Zöller B. Association of Genetic vs Environmental Factors in Swedish Adoptees With Clinically Significant Tinnitus. *JAMA Otolaryngol Head Neck Surg.* 2019 Mar 1;145(3):222-229. doi: 10.1001/jamaoto.2018.3852.



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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:

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

Ethical permit No.

C100115/15				
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Publications 2016, 2017, 2018, 2019

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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Innate and adaptive immune response in airway inflammatory diseases.

The overall goal of the research is to characterise the involvement of both the innate and adaptive immune system and the peripheral nervous system (PNS) in inflammatory and functional changes in upper and lower airway diseases. The projects focuses on airway allergy, chronic rhinosinusitis, asthma and Head and Neck Squamous Cell Carcinoma (HNSCC).

*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 investigate how activation of innate immune receptors impact upper and lower airway inflammation, as well as inflammation following respiratory infection, while simultaneously determining 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
	Sandra Ekstedt
	Eric Hjalmarsson
	Magnus Starkhammar
	Krzysztof Piersiala

Ethical permit No.

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Publications 2016, 2017, 2018, 2019

1. Arebro J, Tengroth L, Razavi R, Georen SK, Winqvist O, Cardell LO. Antigen-presenting epithelial cells can play 1.Subsetting reveals CD16high CD62Ldim neutrophils in chronic rhinosinusitis with nasal polyps. Arebro J, Drakskog C, Winqvist O, Bachert C, Kumlien Georén S, Cardell LO. Allergy. 2019 May 22. doi: 10.1111/all.13919.
2. The potential role of CD16high CD62Ldim neutrophils in the allergic asthma. Ekstedt S, Stenberg H, Tufvesson E, Diamant Z, Bjermer L, Kumlien Georén S, Cardell LO. Allergy. 2019 May 9. doi: 10.1111/all.13861.
3. Ekstedt S, Säfholm J, Kumlien Georén S, Cardell LO. Dividing neutrophils in subsets reveals a significant role for activated neutrophils in the development of airway hyperreactivity. Clin Exp Allergy 2018 Nov 11. doi: 10.1111/cea.13311.
4. 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.

5. Activation of Activin receptor-like kinases curbs mucosal inflammation and proliferation in chronic rhinosinusitis with nasal polyps. Tengroth L, Arebro J, Larsson O, Bachert C, Georén SK, Cardell LO. *Sci Rep* . 2018 Jan 24;8(1):1561. doi: 10.1038/s41598-018-19955-1.
6. Oropharyngeal squamous cell carcinoma induces an innate systemic inflammation, affected by the size of the tumour and the lymph node spread. Kågedal Å, Rydberg Millrud C, Häyry V, Kumlien Georén S, Lidegran M, Munck-Wikland E, Cardell LO. *Clin Otolaryngol*. 2018 Apr 21.
7. Recombinant human IL-26 facilitates the innate immune response to endotoxin in the bronchoalveolar space of mice in vivo. Bao A, Che KF, Bozinovski S, Ji J, Gregory JA, Kumlien Georén S, Adner M, Cardell LO, Lindén A. *PLoS One* . 2017 Dec 5;12(12):e0188909. doi: 10.1371/journal.pone.0188909. eCollection 2017
8. Rapid nodal staging of head and neck cancer surgical specimens with flow cytometric analysis. Häyry V, Kågedal Å, Hjalmarsson E, Neves da Silva PF, Drakskog C, Margolin G, Georén SK, Munck-Wikland E, Winqvist O, Cardell LO *Br J Cancer* (IF: 6.2). 2017 Nov 21. doi: 10.1038/bjc.2017.408
9. A possible role for neutrophils in allergic rhinitis revealed after cellular subclassification. Arebro J, Ekstedt S, Hjalmarsson E, Winqvist O, Kumlien Georén S, Cardell LO. *Sci Rep*. 2017 Mar 8;7:43568.
10. NET-producing CD16high CD62Ldim neutrophils migrate to tumor sites and predict improved survival in patients with HNSCC. Millrud CR, Kågedal Å, Kumlien Georén S, Winqvist O, Uddman R, Razavi R, Munck-Wikland E, Cardell LO. *Int J Cancer*. 2017 Jun 1;140(11):2557-2567.
11. Substance P represents a novel first-line defense mechanism in the nose. Larsson O, Tengroth L, Xu Y, Uddman R, Kumlien Georén S, Cardell LO. *J Allergy Clin Immunol*. 2018 Jan;141(1):128-136.e3.
12. The bronchodilatory capacity of imiquimod: the existence of two mechanisms. Larsson OJ, Manson ML, Starkhammar M, Fuchs B, Adner M, Kumlien Georén S, Cardell LO. *Am J Physiol Lung Cell Mol Physiol*. 2016 Jul 1;311(1):L178-9.
13. The TLR7 agonist imiquimod induces bronchodilation via a nonneuronal TLR7-independent mechanism: a possible role for quinoline in airway dilation. Larsson OJ, Manson ML, Starkhammar M, Fuchs B, Adner M, Kumlien Georén S, Cardell LO. *Am J Physiol Lung Cell Mol Physiol*. 2016 Jun 1;310(11):L1121-9.
14. Intralymphatic immunotherapy of pollen-induced rhinoconjunctivitis: a double-blind placebo-controlled trial. Hylander T, Larsson O, Petersson-Westin U, Eriksson M, Kumlien Georén S, Winqvist O, Cardell LO. *Respir Res*. 2016 Jan 27;17:10.

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Immune Respons and Tumour Cell Detection in Head and Neck Cancer

Many patients with head and neck squamous cell carcinoma present with regional spread to the cervical lymph nodes. Lymph nodes metastases are today the most important factor influencing both the treatment and outcome for this type of cancer. The developments of new cancer treatments and especially immune oncology with the use of new antibodies have changed the field of cancer medicine. In order to fully benefit from this development we have to improve the select patients for the various treatments that can be offered. The overall goal of my research is to study the immune responses in tumour tissue, lymph nodes and blood in patients with head and neck cancer with focus on leukocytes, flow cytometry detection of tumour cells and T cell activity.

Ethical permit No.

2011/717-31-1	2008/317 Lund	2008/866-31-4	2013/1943-3-4	2015/1650-31-2	2018/811-32
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Publications 2016, 2017, 2018, 2019

1. Å Kågedal, G Margolin, V Häyry, P Farrajota Neves da Silva, E Munck-Wikland and LO Cardell A novel sentinel lymph node biopsy approach in oral squamous cell carcinoma Submitted 2019
2. Å Kågedal , E Hjalmarsson, P Farrajota Neves da Silva, K Piersiala, S Kumlien Georén, G Margolin, E Munck-Wikland, O Winqvist, V Häyry, L O Cardell, CD4+CD69+ T-cells in dissected neck lymph nodes associate with survival in oral squamous cell carcinoma Submitted 2019
3. V Häyry, Å Kågedal, E Hjalmarsson, , C Drakskog, G Margolin, E Munck-Wikland, O Winqvist, LO Cardell Nodal staging of neck dissection specimens with flow-cytometry British Journal of Cancer (2018) 118,421-427
4. Å Kågedal, C Rydberg-Millrud, V Häyry, S Kumlien-Georén, M Lidegran, Eva Munck-Wikland and LO Cardell 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.
5. C Rydberg Millrud, Å Kågedal, S Kumlien Georén, R Uddman, R Razavi, E Munck-Wikland and LO Cardell, 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.
6. Millrud CR, Hylander T, Kumlien Georen S, Kågedal Å, Winqvist O, Cardell LO. Inverse immunological responses induced by allergic rhinitis and head and neck squamous cell carcinoma. PLoS One. 2014 Jan 22;9(1):e86796. doi: 10.1371/journal.pone.0086796. eCollection 2014. PMID:24466243.



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How to read when speech sounds different? A longitudinal study of the development of reading strategies in children with cochlear implants

The aim is to study reading development in a sample of deaf children with cochlear implants (CI), aged 6-11 years. The project has a multidisciplinary approach but mainly focuses on the longitudinal development of reading and related cognitive and linguistic skills, in relation to the participants hearing background characteristics, psychosocial wellbeing and socioeconomic status level in the family, in a group of Swedish-speaking children with CI (N=45) who are patients at the Hearing implant Clinic, Karolinska University Hospital. The data collection has been finalized and the material is currently being analysed and presented in several manuscripts. Two publications from the project indicate that the children with CI learn to read in similar ways as normal hearing children, despite their initial period with auditory deprivation before the first cochlear implantation. Predictor of reading comprehension was receptive vocabulary together with phonological decoding ability in the sample. Orthographic learning in children with CI is strongly dependent on similar cognitive and linguistic skills as in hearing peers. Efforts should be made to support phonological decoding skills, vocabulary, and phonological skills in this population. The project is financed by Riksbankens Jubileumsfond.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
	Karolina Falkenius Schmidt

Ethical permit No.

2011/295-31	2015/992-31			
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Publications 2016, 2017, 2018, 2019

1. Logopedics Phoniatrics Vocology, (in press)
2. Wass, M., Anmyr, L., Lyxell, B., Östlund, E., Karltorp, K., Löfkvist, U. (2019). Predictors of Reading Comprehension in Children with Cochlear Implants, *Frontiers in Psychology*, 10:2155. doi:10.3389/fpsyg.2019.02155
3. Karltorp, E., Eklöf, M., Östlund, E., Asp, F., Tideholm, B., Löfkvist, U. (2019). Cochlear implants before nine months of age led to more natural spoken language development without increased surgical risks, *Acta Paediatrica*, DOI:10.1111/apa.14954. [Epub ahead of print]
4. Wass, M., Löfkvist, U., Anmyr, L., Karltorp, E., Östlund, E., Lyxell, B. (2019). Correlates of Orthographic Learning in Swedish Children With Cochlear Implants, *Frontiers in Psychology*, 10:143. doi:10.3389/fpsyg.2019.00143
5. Huttunen, K., Erixon, E., Löfkvist, U., Mäki-Torkko, E. (2019). The impact of early-onset unilateral hearing impairment in children – A systematic review. *Int J Pediatr Otorhinolaryngol.* 120:173-183. doi: 10.1016/j.ijporl.2019.02.029.
6. Sundström, S., Löfkvist, U., Lyxell, B., Samuelsson, C. (2018). Phonological and grammatical production in children with developmental language disorder and children with hearing impairment. *Child Language Teaching and Therapy.* 34(3) 289-302. doi.org/10.1177/0265659018805202.
7. Sundström, S., Löfkvist, U., Lyxell, B., Samuelsson, C. (2018). Prosodic and segmental aspects of nonword repetition in 4- to 6-year-old children who are deaf and hard of hearing compared to controls with normal hearing. *Clin Linguist Phon.* 32(10):950-971. doi: 10.1080/02699206.2018.1469671.
8. Forli F, Giuntini G, Ciabotti A, Bruschini L, Löfkvist U, Berrettini S. (2018). 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 Otorhinolaryngol.* 105:56-62. doi: 10.1016/j.ijporl.2017.12.006.
9. Smeds, H., Wales, J., Asp, F., Löfkvist, U., Falahat, B., Anderlid, B.-M., Anmyr, L., Karltorp, E. (2016). X-linked Malformation and Cochlear Implantation. *Otology & Neurology*, Jan;38(1):38-46.

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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 treatment is loss of nerve function, pain, stiffness, swallowing problems, dryness of mouth which have major impact of the 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 aim of all studies is to optimize and individualize the treatment 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

Ethical permit No.

2017/1333-31/1	2012/49-31/2	2019/03518		
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Publications 2016, 2017, 2018, 2019

1. Sivars L, Landin D, Haeggbloom L, Tertipis N, Grün N, Bersani C, Marklund L, Ghaderi M, Näsman A, Ramqvist T, Nordfors, Munck-Wikland E, Tani E, Dalianis T. Human papillomavirus DNA detection in fine-needle aspirates as indicator of human papillomavirus-positive oropharyngeal squamous cell carcinoma: A prospective study. *Head Neck*. 2016 Nov 29. doi: 10.1002/hed.24641. PMID: 27898186
2. Kamali A, Gahm C, Palmgren B, Marklund L, Halle M, Hammarstedt Nordenvall L. Regional Recurrence in early stage tongue cancer - a single institutional study and a review of the literature. *Acta Otolaryngol*. 2017 Feb 22;1-7. doi: 10.1080/00016489.2017.1279751
3. 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
4. Sivars L, Landin D, Rizzo M, Haeggbloom L, Bersani C, Munck-Wikland E, Näsman A, Dalianis T, Marklund L. Human papillomavirus (HPV) is absent in branchial cleft cysts of the neck distinguishing them from HPV positive cystic metastasis. *Acta Otolaryngol*. 2018 Sep;138(9):855-858. doi: 10.1080/00016489.2018.1464207. Epub 2018 May 15
5. Grønhoj C, Jensen DH, Dehlendorff C, Marklund L, Wagner S, Mehanna H, Munck-Wikland E, Ramqvist T, Näsman A, Wittekindt C, Würdemann N, Sharma SJ, Gattenlöhner S, Kiss K, Andersen E, Spruce R, Batis N, Robinson M, Harrington K, Winter S, Jones TM, Klussmann JP, Dalianis T, Friberg J, von Buchwald C. Development and external validation of nomograms in oropharyngeal cancer patients with known HPV-DNA status: a European Multicentre Study (OroGrams). *Br J Cancer*. 2018 Jun;118(12):1672-1681. doi: 10.1038/s41416-018-0107-9. Epub 2018 May 24.
6. Bersani C, Haeggbloom L, Ursu RG, Giusca SE, Marklund L, Ramqvist T, Näsman A, Dalianis T. Overexpression of FGFR3 in HPV-positive Tonsillar and Base of Tongue Cancer Is Correlated to Outcome. *Anticancer Res*. 2018 Aug;38(8):4683-4690. doi: 10.21873/anticancer.12774.
7. Haeggbloom L, Attoff T, Yu J, Holzhauser S, Vlastos A, Mirzae L, Åhrlund-Richter A, Munck-Wikland E, Marklund L, Hammarstedt-Nordenvall L, Ye W, Ramqvist T, Näsman A, Dalianis T. Changes in incidence and prevalence of human papillomavirus in tonsillar and base of tongue cancer during 2000-2016 in the Stockholm region and Sweden. *Head Neck*. 2018 Dec 24. doi: 10.1002/hed.25585.
8. Elliot A, Näsman A, Westman A, Hammarstedt-Nordenvall L, Stjärne P, Marklund L. Stathmin and EGFR expression and its correlation to HPV status and clinical outcome in sinonasal inverted papilloma. Accepted for publication *Rhinology* sept 2019
9. Elliot A, Näsman A3, Westman M, Marklund L, Stjärne P, Hammarstedt-Nordenvall L. Human papillomavirus and infiltration of CD8- and Foxp3-positive immune cells in sinonasal inverted papillomas. *Acta Otolaryngol*. 2019 Sep 5:1-5. doi: 10.1080/00016489.2019.1654616.



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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 palsy is studied and different neurophysiological 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:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
Lovisa Lansing	Rebecka Ohm
	Sigurdur Arnason
	Zane Upate (under registration)

Ethical permit No.

2009/15631/2	2011/598-32	2012/1874-32		
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Publications 2016, 2017, 2018, 2019

1. Bylund N, Jensson D, Enghag S, Berg T, Marsk E, Hultcrantz M, Hadziosmanovic N, Rodriguez-Lorenzo A, Jonsson. Synkinesis in Bell's palsy in a randomised controlled trial. L. Clin Otolaryngol. 2017 Jun

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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 but if we could select patients with poor response to oncological treatment 2015 these patients would fare better with primary surgical treatment.

Malin also studies OK 432 therapy for patients with ranula and branchial cleft cysts.

David also studies HPV in benign and malignant neck lesions.

Daniel studies osteoradionecrosis after radiotherapy, 8-oxo-dG levels, brachytherapy as risk factors and quality of life before and after reconstruction.

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

Tingting Huang does epidemiological studies in head and neck cancer.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
Malin Wendt	Lina Nygren
Daniel Danielsson	Tingting Huang
David Landin	

Ethical permit No.

2015/0157-32	2016/506-31	2016/277-32	2013/553-31	2010/1705-32
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Publications 2016, 2017, 2018, 2019

1. Osteoradionecrosis, an increasing indication for microvascular head and neck reconstruction. Danielsson D, Gahm C, Haghdoust S, Munck-Wikland E, Halle M. Int J Oral Maxillofac Surg. 2019 Jul 8. pii: S0901-5027(19)31185-3.
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.
3. Changes in incidence and prevalence of human papillomavirus in tonsillar and base of tongue cancer during 2000-2016 in the Stockholm region and Sweden. Haegglblom L, Attoff T, Yu J, Holzhauser S, Vlastos A, Mirzae L, Ährlund-Richter A, Munck-Wikland E, Marklund L, Hammarstedt-Nordenvall L, Ye W, Ramqvist T, Näsman A, Dalianis T. Head Neck. 2019 Jun;41(6):1583-1590. doi: 10.1002/hed.25585.
4. Development and external validation of nomograms in oropharyngeal cancer patients with known HPV-DNA status: a European Multicentre Study (OroGrams). Grønhoj C, Jensen DH, Dehlendorff C, Marklund L, Wagner S, Mehanna H, Munck-Wikland E, Ramqvist T, Näsman A, Wittekindt C, Würdemann N, Sharma SJ, Gattenlöhner S, Kiss K, Andersen E, Spruce R, Batis N, Robinson M, Harrington K, Winter S, Jones TM, Klusmann JP, Dalianis T, Friborg J, von Buchwald C. Br J Cancer. 2018 Jun;118(12):1672-1681.
5. Human papillomavirus (HPV) is absent in branchial cleft cysts of the neck distinguishing them from HPV positive cystic metastasis. Sivars L, Landin D, Rizzo M, Haegglblom L, Bersani C, Munck-Wikland E, Näsman A, Dalianis T, Marklund L. Acta Otolaryngol. 2018 Sep;138(9):855-858.
6. Oropharyngeal squamous cell carcinoma induces an innate systemic inflammation, affected by the size of the tumour and the lymph node spread. Kågedal Å, Rydberg Millrud C, Häyry V, Kumlien Georén S, Lidegran M, Munck-Wikland E, Cardell LO. Clin Otolaryngol. 2018 Apr 21. doi: 10.1111/coa.13122. [Epub ahead of print]
7. Protein Expression in Tonsillar and Base of Tongue Cancer and in Relation to Human Papillomavirus (HPV) and Clinical Outcome. Ramqvist T, Näsman A, Franzén B, Bersani C, Alexeyenko A, Becker S, Haegglblom L, Kolev A, Dalianis T, Munck-Wikland E. Int J Mol Sci. 2018 Mar 25;19(4). pii: E978.

8. Rapid nodal staging of head and neck cancer surgical specimens with flow cytometric analysis. Häyry V, Kågedal Å, Hjalmarsson E, Neves da Silva PF, Draskog C, Margolin G, Georén SK, Munck-Wikland E, Winqvist O, Cardell LO. *Br J Cancer*. 2018 Feb 6;118(3):421-427.
9. WRAP53β, survivin and p16INK4a expression as potential predictors of radiotherapy/chemoradiotherapy response in T2N0-T3N0 glottic laryngeal cancer. Tiefenböck-Hansson K, Haapaniemi A, Farnebo L, Palmgren B, Tarkkanen J, Farnebo M, Munck-Wikland E, Mäkitie A, Garvin S, Roberg K. *Oncol Rep*. 2017 Oct;38(4):2062-2068. doi: 10.3892/or.2017.5898.
10. Targeted sequencing of tonsillar and base of tongue cancer and human papillomavirus positive unknown primary of the head and neck reveals prognostic effects of mutated FGFR3. Bersani C, Sivars L, Haeggbloom L, DiLorenzo S, Mints M, Ährlund-Richter A, Tertipis N, Munck-Wikland E, Näsman A, Ramqvist T, Dalianis T. *Oncotarget*. 2017 May 23;8(21):35339-35350.
11. A model using concomitant markers for predicting outcome in human papillomavirus positive oropharyngeal cancer. Bersani C, Mints M, Tertipis N, Haeggbloom L, Sivars L, Ährlund-Richter A, Vlastos A, Smedberg C, Grün N, Munck-Wikland E, Näsman A, Ramqvist T, Dalianis T. *Oral Oncol*. 2017 May;68:53-59. doi: 10.1016/j.oraloncology.2017.03.007.
12. NET-producing CD16high CD62Ldim neutrophils migrate to tumor sites and predict improved survival in patients with HNSCC. Millrud CR, Kågedal Å, Kumlien Georén S, Winqvist O, Uddman R, Razavi R, Munck-Wikland E, Cardell LO. *Int J Cancer*. 2017 Jun 1;140(11):2557-2567.
13. 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. Sivars L, Landin D, Grün N, Vlastos A, Marklund L, Nordemar S, Ramqvist T, Munck-Wikland E, Näsman A, Dalianis T. *Anticancer Res*. 2017 Feb;37(2):665-673.
14. Human papillomavirus is a favourable prognostic factor in cancer of unknown primary in the head and neck region and in hypopharyngeal cancer. Sivars L, Bersani C, Grün N, Ramqvist T, Munck-Wikland E, Von Buchwald C, Dalianis T. *Mol Clin Oncol*. 2016 Dec;5(6):671-674. doi: 10.3892/mco.2016.1050.
15. Human papillomavirus DNA detection in fine-needle aspirates as indicator of human papillomavirus-positive oropharyngeal squamous cell carcinoma: A prospective study. Sivars L, Landin D, Haeggbloom L, Tertipis N, Grün N, Bersani C, Marklund L, Ghaderi M, Näsman A, Ramqvist T, Nordfors C, Munck-Wikland E, Tani E, Dalianis T. *Head Neck*. 2017 Mar;39(3):419-426. doi: 10.1002/hed.24641.
16. Tonsillectomy and Incidence of Oropharyngeal Cancers. Chaturvedi AK, Song H, Rosenberg PS, Ramqvist T, Anderson WF, Munck-Wikland E, Ye W, Dalianis T. *Cancer Epidemiol Biomarkers Prev*. 2016 Jun;25(6):944-50. doi: 10.1158/1055-9965.EPI-15-0907.
17. Human Papillomavirus as a Diagnostic and Prognostic Tool in Cancer of Unknown Primary in the Head and Neck Region. Sivars L, Tani E, Näsman A, Ramqvist T, Munck-Wikland E, Dalianis T. *Anticancer Res*. 2016 Feb;36(2):487-93. Review.
18. Phylogenetic analysis of multiple FISH markers in oral tongue squamous cell carcinoma suggests that a diverse distribution of copy number changes is associated with poor prognosis. Wangsa D, Chowdhury SA, Ryott M, Gertz EM, Elmberger G, Auer G, Åvall Lundqvist E, Küffer S, Ströbel P, Schäffer AA, Schwartz R, Munck-Wikland E, Ried T, Heselmeyer-Haddad K. *Int J Cancer*. 2016 Jan 1;138(1):98-109. doi: 10.1002/ijc.29691.

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Treatment Outcome, Prognostic Markers, and New Reconstruction 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.

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Publications 2016, 2017, 2018, 2019

Selected KI-publications for 2016-2019

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

1. Al-Samadi A, Tuomainen K, Kivimäki A, Salem A, Al-Kubati S, Hyytiäinen A, Parikka M, Mesimäki K, Wilkman T, Mäkitie A, Grenman R, Salo T. PCR-based zebrafish model for personalised medicine in head and neck cancer. *J Transl Med.* 2019 Jul 22;17(1):235.
2. Al-Samadi A, Poor B, Tuomainen K, Liu V, Hyytiäinen A, Suleymanova I, Mesimäki K, Wilkman T, Mäkitie A, Saavalainen P, Salo T. In vitro humanized 3D microfluidic chip for testing personalized immunotherapeutics for head and neck cancer patients. *Exp Cell Res.* 2019 Jul 26 [Epub ahead of print]
3. Alabi RO, Elmusrati M, Sawazaki-Calone I, Kowalski LP, Haglund C, Coletta RD, Mäkitie AA, Salo T, Leivo I, Almangush A. Machine learning application for prediction of locoregional recurrences in early oral tongue cancer: a Web-based prognostic tool. *Virchows Arch.* 2019 Aug 17. [Epub ahead of print]
4. Dickinson A, Saraswat M, Mäkitie A, Silén R, Hagström J, Haglund C, Joenväärä S, Silén S Label-free tissue proteomics can classify oral squamous cell carcinoma from healthy tissue in a stage-specific manner. *Oral Oncol.* 2018 Nov;86:206-15.
5. Saraswat M, Mäkitie A, Tohmola T, Dickinson A, Saraswat S, Joenväärä S, Renkonen S. Tongue Cancer Patients Can be Distinguished from Healthy Controls by Specific N-Glycopeptides Found in Serum Proteomics Clin Appl. 2018 Nov;12(6):e1800061.
6. Mäkitie AA, Ruuskanen M, Bentzen J, Brun E, Gebre-Medhin M, Friesland S, Marsk E, Hammarstedt-Nordenvall L, Gille E, Reizenstein J, Ardell G, Farnebo L, Rzepecki J, Haugen H, Söderström K, Zackrisson B, Bergström S, Löden B, Cederblad L, Laurell G, Smeland E, Folkvard Evensen J, Lund JÅ, Tøndel H, Karlsdottir Å, Jóhannsson J, Johansen J, Kristensen CA, Jensen K, Andersen LJ, Koivunen P, Korpela M, Voutilainen L, Wigren T, Minn H, Joensuu H, Overgaard J, Saarilahti K. The Management and Survival Outcomes of Nasopharyngeal Cancer in the Nordic Countries. *Acta Oncol* 2018;57:557-60.
7. Tiefenböck-Hansson K, Haapaniemi A, Farnebo L, Palmgren B, Tarkkanen J, Farnebo M, Munck-Wikland E, Mäkitie A, Garvin S, Roberg K. WRAP53β, survivin and p16INK4a expression as potential predictors of radiotherapy/chemoradiotherapy response in T2N0-T3N0 glottic laryngeal cancer. *Oncol Rep.* 2017 Oct;38(4):2062-8.
8. Farnebo L, Laurell G, Mäkitie A. A Nordic survey on the management of head and neck CUP. *Acta Otolaryngol.* 2016;136:1159-63.

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Swallowing in health elderly persons/ Undergraduate students' clinical learning environment

The prevalence of dysphagia increases with advancing age and specifically in persons with neurological disorders. In an acute phase after stroke up to 80% of patients have difficulties to swallow. In many cases, the ability to swallow improves afterwards, but about 15% may have remaining dysphagia that may cause nutritional problems. Dysphagia also impacts the quality of life as patients cannot eat and drink as they wish. A common procedure to examine oropharyngeal swallowing is fiberendoscopic 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. Are results questions are: How do elderly healthy persons swallow in terms of timing (initiation) and effectiveness of pharyngeal swallowing, reaction to retention in pharynx and larynx as well as aspiration? The analysis of the results is partly completed.

The other research path explores undergraduate students' clinical learning environment. It is widely acknowledged that learning environment impacts students' professional development and their ability to achieve learning outcomes. Evaluation of the learning environment also allows the identification of weaknesses in a course or a curriculum and provides a scaffold for further development of courses and programs. 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.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
Malin Sellberg	

Ethical permit No.

636/03	2010/1606-31/5	2010/1100-31/1.	2010/1100-31/1	2011/493-32	2013/2212-31/4	2017/38-31/4.
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Publications 2016, 2017, 2018, 2019

1. Rosengren B, Möller R, Hellman J, Jood K, Ekstedt M, Särnblom S, Alm S, Gummesson C. EPA (Entrustable professional activities)- an international approach to define key tasks that a doctor should be able to perform. *Läkartidningen*. 2019 May 7;116.
2. Möller R. It's time to define the Swedish Doctor? Lessons learnt from the evaluation of the Finnish undergraduate medical education. *Läkartidningen*. 2019 May 7;116. En grundutbildning i förändring.
3. Hultin M, Möller R. En grundutbildning i förändring. *Läkartidningen*. 2019 May 7;116
4. Möller R, Shoshan M. Does reality meet expectations? An analysis of medical students' expectations and perceived learning during mandatory research projects. *BMC medical education* 2019 19;1 93-
5. Möller R, Hultin M. [Examination of future colleagues: We need an assessment culture]. *Läkartidningen* 2019 116;
6. Bexelius T, Lachmann H, Järnbert-Pettersson H, Kalén S, Möller R, Ponzer S. Stress among medical students during clinical courses: a longitudinal study using contextual activity sampling system. *International journal of medical education* 2019 10; 68-74
7. Kalén S, Lachmann H, Varttinen M, Möller R, Bexelius TS, Ponzer S. Medical students' experiences of their own professional development during three clinical terms: a prospective follow-up study. *BMC medical education* 2017 17;1 47-
8. Möller R, Ponzer S, Shoshan M. Medical students' perceptions of their learning environment during a mandatory research project. *International journal of medical education* 2017 8; 375-381
9. Möller R, Shoshan M. Medical students' research productivity and career preferences; a 2-year prospective follow-up study. *BMC medical education* 2017 17;1 51-
10. Geneid A, Lindestad PA, Granqvist S, Möller R, Sodersten M. Long-Term Follow-Up of Patients with Spasmodic Dysphonia and Improved Voice despite Discontinuation of Treatment. *Folia Phoniatrica et logopaedica* 2016 68;3 144-151
11. Möller R, Safa S, Östberg P. Validation of the Swedish translation of eating assessment tool (S-EAT-10). *Acta oto-laryngologica* 2016 136;7 749-53

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OSA in children and adults, a mainly surgical therapeutic perspective

The group has research in surgical treatment of sleep apnea, and have 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 tonsil 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 Tonsil Surgery Registra is another field of research where we evaluate incidence, morbidity and symptom relief etc

Supervision of PhD-students:

Main Supervisor	Co-supervisor
	Johan Fehrm

Ethical permit No.

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Publications 2016, 2017, 2018, 2019

1. Effectiveness of Oral Appliances in OSA with Respiratory Arousals. Nerfeldt P, Friberg D. J Clin Sleep Med. 2016;12:1159-65
2. Trends and changes in paediatric tonsil surgery in Sweden 1987- 2013: a population-based cohort study. Borgström A, Nerfeldt P, Friberg D, Sunnergren O, Stalfors J. BMJ Open. 2017 doi: 10.1136/bmjopen-2016-013346
3. Adenotonsillotomy vs Adenotonsillectomy in pediatric obstructive sleep apnea – a randomized clinical trial reporting polysomnographic data. Borgström A, Nerfeldt P, Friberg D. Pediatrics 2017;139(4):e20163314
4. Tonsil surgery in Sweden 2013-2015. Indications, surgical methods and patient-reported outcome from the National Tonsil Surgery Register. Hallenstål N, Sunnergren O, Ericsson E, Hemlin C, Hessén Söderman A-C., Nerfeldt P, Odhagen E, Ryding M, Stalfors J. Acta Otolaryngol 2017;137(10) 1096–1103
5. Patient reported pain-related outcome measures after tonsil surgery: an analysis of 32,225 children from the National Tonsil Surgery Register in Sweden 2009-2016. Alm Fredrik RNA, Msc. Stalfors Joacim M.D., Ph.D. Nerfeldt Pia M.D., Ph.D. Ericsson Elisabeth RNA, Ph.D. Eur Arch Otorhinolaryngol 2017;274(10):3711-3722
6. Adenopharyngoplasty vs. adenotonsillectomy in children with severe obstructive sleep apnea: a randomized controlled trial. Johan Fehrm, MD; Pia Nerfeldt, MD, PhD; Joar Sundman, MD; Danielle Friberg, MD, PhD. JAMA Otol 2018;144(7):580-586
7. Postoperative pain and bleeding after adenotonsillectomy versus adenotonsillotomy in pediatric obstructive sleep apnea: an RCT. Borgström Anna, MD; Nerfeldt Pia MD, Ph D; Friberg Danielle, MD, PhD. Eur Arch Otorhinolaryngol 2019 doi. org/10.1007/s00405-019-05571-ww



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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				
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Publications 2016, 2017, 2018, 2019

1. Larsson K, Janson C, Stallberg B, Lisspers K, Olsson P, Kostikas K, Gruenberger JB, Gutzwiller FS, Uhde M, Jorgensen L, Johansson G. Impact of COPD diagnosis timing on clinical and economic outcomes: the ARCTIC observational cohort study. *International Journal of Chronic Obstructive Pulmonary Disease* 2019 14; 995-1008
2. Muro S, Yoshisue H, Kostikas K, Olsson P, Gupta P, Wedzicha JA. Indacaterol/glycopyrronium versus tiotropium or glycopyrronium in long-acting bronchodilator-naïve COPD patients: A pooled analysis. *Respirology (Carlton, Vic.)* 2019 ;
3. FLASH Investigators, Frith PA, Ashmawi S, Krishnamurthy S, Gurgun A, Hristoskova S, Pilipovic V, Hamann AM, Backer A, Olsson P, Kostikas K, Diaz DV. Efficacy and safety of the direct switch to indacaterol/glycopyrronium from salmeterol/fluticasone in non-frequently exacerbating COPD patients: The FLASH randomized controlled trial. *Respirology (Carlton, Vic.)* 2018 23;12 1152-1159
4. Vogelmeier CF, Chapman KR, Miravitlles M, Roche N, Vestbo J, Thach C, Banerji D, Fogel R, Patalano F, Olsson P, Kostikas K, Wedzicha JA. Exacerbation heterogeneity in COPD: subgroup analyses from the FLAME study. *International Journal of Chronic Obstructive Pulmonary Disease* 2018 13; 1125-1134
5. Janson C, Johansson G, Ställberg B, Lisspers K, Olsson P, Keininger DL, Uhde M, Gutzwiller FS, Jörgensen L, Larsson K. Identifying the associated risks of pneumonia in COPD patients: ARCTIC an observational study. *Respiratory research* 2018 19;1 172-
6. Roche N, Chapman KR, Vogelmeier CF, Herth FJF, Thach C, Fogel R, Olsson P, Patalano F, Banerji D, Wedzicha JA. Blood Eosinophils and Response to Maintenance Chronic Obstructive Pulmonary Disease Treatment. Data from the FLAME Trial. *American journal of respiratory and critical care medicine* 2017 195;9 1189-1197
7. Bjermer L, van Boven JFM, Costa-Scharplatz M, Keininger DL, Gutzwiller FS, Lisspers K, Mahon R, Olsson P, Roche N. Indacaterol/glycopyrronium is cost-effective compared to salmeterol/fluticasone in COPD: FLAME-based modelling in a Swedish population. *Respiratory Research* 2017 18; 206-

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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 evaluate follow-up regimens for laryngeal cancer patients at the Karolinska University Hospital.
3. To specifically evaluate treatment and outcome for large cancers of the larynx, i.e. T3 and T4 tumours.

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.

Submitted okt-19				
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Publications 2016, 2017, 2018, 2019

1. WRAP53 β , survivin and p16INK4a expression as potential predictors of radiotherapy/chemoradiotherapy response in T2N0-T3N0 glottic laryngeal cancer. Katharina Tiefenböck-hansson, Aaro Haapaniemi, Lovisa Farnebo, Björn Palmgren, Jussi Tarkkane, Marianne Farnebo, Eva Munck-Wikland, Antti Mäkitie, Stina Garvin, Karin Roberg. 2017-08-11, ONCOLOGY REPORTS 3 2062 8: 2062-2068
2. Regional recurrence in early stage I-II oral tongue cancer: a single institutional study and review of the literature. Kamali, Gahm, Palmgren, Marklund, Halle, Hammarstedt-Nordenvall. Acta Otolaryngol. 2017 Jul;137(7):755-761. doi: 10.1080/00016489.2017.1279751. Epub 2017 Feb 22.



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Clinical studies on upper airway inflammation, skullbase and sinonasal tumor and treatment of facial 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. • Epidemiologic studies on 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	Karin Jonstam
Ola Fridman Bengtsson	
Sofia Hultman Dennison	

Ethical permit No.

2012/4931	2012/89131	2012/4:8		
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Publications 2016, 2017, 2018, 2019

1. Elliot A, Näsman A, Westman M, Marklund L, Stjärne P, Hammarstedt-Nordenvall L. Human papillomavirus and infiltration of CD8- and Foxp3-positive immune cells in sinonasal inverted papillomas. *Acta Otolaryngol.* 2019 Nov;139(11):1019-1023.
2. Fridman-Bengtsson O, Höybye C, Porthén L, Stjärne P, Hulting AL, Sunnergren O. Evaluation of different hydrocortisone treatment strategies in transsphenoidal pituitary surgery. *Acta Neurochir (Wien).* 2019 Aug;161(8):1715-1721
3. Stjärne P, Strand V, Theman K, Ehnhage A. Control of allergic rhinitis with MP-AzeFlu: a noninterventional study of a Swedish cohort. *Rhinology.* 2019 Aug 1;57(4):279-286.
4. 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. *Int J Pediatr Otorhinolaryngol.* 2019 Jun;121:50-54
5. Alinasab B, Borstedt KJ, Rudström R, Ryott M, Qureshi AR, Beckman MO, Stjärne P. New Algorithm for the Management of Orbital Blowout Fracture Based on Prospective Study. *Craniomaxillofac Trauma Reconstr.* 2018 Dec;11(4):285-295

6. Alinasab B, Fridman-Bengtsson O, Sunnergren O, Stjärne P. The Supratarsal Approach for Correction of Anterior Frontal Bone Fractures. *J Craniofac Surg*. 2018 Oct;29(7):1906-1909
7. Hummel T, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM, Damm M, Frasnelli J, Gudziol H, Gupta N, Haehne A, Holbrook E, Hong SC, Hornung D, Hüttenbrink KB, Kamel R, Kobayashi M, Konstantinidis I, Landis BN, Leopold DA, Macchi A, Miwa T, Moesges R, Mullol J, Mueller CA, Ottaviano G, Passali GC, Philpott C, Pinto JM, Ramakrishnan VJ, Rombaux P, Roth Y, Schlosser RA, Shu B, Soler G, Stjärne P, Stuck BA, Vodicka J, Welge-Luessen A. Position paper on olfactory dysfunction. *Rhinol Suppl*. 2017 Mar;54(26):1-30
8. Hellings PW, Borrelli D, Pietikainen S, Agache I, Akdis C, Bachert C, Bewick M, Botjes E, Constantinidis J, Fokkens W, Haahtela T, Hopkins C, Illario M, Joos G, Lund V, Muraro A, Pugin B, Seys S, Somekh D, Stjärne P, Valiulis A, Valovirta E, Bousquet J. European Summit on the Prevention and Self-Management of Chronic Respiratory Diseases: report of the European Union Parliament Summit (29 March 2017). *Clin Transl Allergy*. 2017 Dec 27;7:49.
9. Förander P, Bartek J Jr, Fagerlund M, Benmaklouf H, Dodoo E, Shamikh A, Stjärne P, Mathiesen T. Multidisciplinary management of clival chordomas; long-term clinical outcome in a single-institution consecutive series. *Acta Neurochir (Wien)*. 2017 Oct;159(10):1857-1868. doi: 10.1007/s00701-017-3266-1.
10. Hummel T, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM, Damm M, Frasnelli J, Gudziol H, Gupta N, Haehner A, Holbrook E, Hong SC, Hornung D, Hüttenbrink KB, Kamel R, Kobayashi M, Konstantinidis I, Landis BN, Leopold DA, Macchi A, Miwa T, Moesges R, Mullol J, Mueller CA, Ottaviano G, Passali GC, Philpott C, Pinto JM, Ramakrishnan VJ, Rombaux P, Roth Y, Schlosser RA, Shu B, Soler G, Stjärne P, Stuck BA, Vodicka J, Welge-Luessen A. Position paper on olfactory dysfunction. *Rhinology*. 2016 Jan 31;56(1):1-30.
11. 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 Paediatr*. 2017 Feb;106(2):268-273.
12. Elliot A, Marklund L, Håkansson N, Song H, Ye W, Stjärne P, Hammarstedt-Nordenvall L. Incidence of IP and risk of malignant transformation in the Swedish population 1960-2010. *Eur Arch Otorhinolaryngol*. 2017 Mar;274(3):1445-1448.
13. Klimek L, Bachert C, Stjärne P, Dollner R, Larsen P, Haahr P, Agache I, Scadding G, Price D. MP-AzeFlu provides rapid and effective allergic rhinitis control in real life: A pan-European study. *Allergy Asthma Proc*. 2016 Sep;37(5):376-86.
14. Alinasab B, Qureshi AR, Stjärne P. Prospective study on ocular motility limitation due to orbital muscle entrapment or impingement associated with orbital wall fracture. *Injury*. 2017 Jul;48(7):1408-1416.
15. Alinasab B, Borstedt KJ, Rudström R, Ryott M, Qureshi AR, Stjärne P. Prospective Randomized Controlled Pilot Study on Orbital Blowout Fracture. *Craniomaxillofac Trauma Reconstr*. 2018 Sep;11(3):165-171.

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Inner Ear Malformations**Outcome of Active Bone Anchored Hearing Solutions**

The aim of Dr Edholms project is to study the anatomy of inner ear malformations, as seen on CT and MRI, with emphasis on the Large Vestibular Aqueduct Syndrome (LVAS) which is the most common inner ear malformation. This malformation shows a variable degree of anatomic alterations of the inner ear structures with widened vestibular aqueduct, often combined with a cochlear malformation (Incomplete Partition type 2, IP-2) and there is also a variable degree of clinical symptoms. The most common clinical presentation is a progressive hearing loss and vestibular symptoms but some patients also feature goitre. Some patients have a genetic predisposition for the syndrome with mutation of the SLC26A4 gene.

The aim of Dr Koros project is to look at outcomes of active bone conducting implants. Patients with chronic otitis often have conductive or mixed hearing loss. A bone conducting implant is a treatment option for individuals with conductive or mixed hearing loss.

Supervision of PhD-students:

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

Ethical permit No.

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Publications 2016, 2017, 2018, 2019

1. Occurrence of primary brain tumors in cochlear implant patients in Sweden between 1989 and 2014. Smeds H, Wales J, Mathiesen T, Talbäck M, Feychting M. Clin Epidemiol. 2018 Oct 5;10:1401-1405.
2. X-linked Malformation and Cochlear Implantation. Smeds H, Wales J, Asp F, Löfkvist U, Falahat B, Anderlid B-M, Anmyr L, Karltorp E. Otol Neurotol. 2017 Jan;38(1):38-46.
3. Cochlear implants in the etiopathogenesis of glioblastoma-an interesting observation or independent finding? Kalakoti P, Murray RD, Pettersson-Segerlind J, Smeds H, Nanda A. Acta Neurochir (Wien). 2016 May;158(5):907-12.

Book chapters

1. Implantable Hearing Devices and Chronic Otitis Media. Briggs RJ, Mlynski, R, Smeds H. Chapter 43, The Chronic Ear, 1st Edition. Thieme 2016, ISBN: 9781604068641.

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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
Martin Eklöf	

Ethical permit No.

2013/104-31/	2013/1127-31/2	2013/104-31/4		
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Publications 2016, 2017, 2018, 2019

1. The choice of stimulation strategy affects the ability to detect pure tone inter-aural time differences in children with early bilateral cochlear implantation. Eklöf M, Tideholm B. Acta Otolaryngol. 2018 Jun;138(6):554-561.
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.



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Effekten av antisekretorisk protein-haltig Salovurn® på symptomen vid Menieres sjukdom

Antisecretory factor (AF) is an endogenous protein, first detected due to its ability to inhibit experimental diarrhoea. AF seems to have a modulating effect on the proliferation of memory/effector T-cells and is expressed by cells in the immune system. Antibodies to AF have in experimental animal studies been shown to result in upregulation of the inflammatory cytokines IL8 and IL6, and down regulating of the anti-inflammatory cytokine IL10. Endogenous AF activity shows an increase after exposition to bacterial toxins, and an increased AF activity in combination with an immunity reaction could be a part of the normal defence against the secretory and inflammatory component of diarrhoeal disease.

AF also seems to have an effect on the dizziness symptoms in Meniere's disease, a disease which is presumed to be a consequence of an endolymphatic hydrops in the inner ear. There are some studies showing therapeutic effects of SPC Flakes (a food for special medical purposes increasing endogenous AF production) on the symptoms dizziness and hearing problems in patients with Meniere's disease. Salovum is a product based on the egg powder B221 as a source of AF. Salovum is classified as a "food for special medical purposes" by the EU.

To evaluate the effect of Salovum compared to Placebo on the symptoms from endolymphatic hydrops in the inner ear in patients with Meniere's disease

Supervision of PhD-students:

Main Supervisor	Co-supervisor

Ethical permit No.

2018/2628/31				
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Publications 2016, 2017, 2018, 2019

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. Frykholm C1, Klar J1,2, Tomanovic T3, Ameer A2, Dahl N4,5. Stereocilin gene variants associated with episodic vertigo: expansion of the DFNB16 phenotype. Eur J Hum Genet. 2018 Dec;26(12):1871-1874. doi: 10.1038/s41431-018-0256-6. Epub 2018 Sep 24.

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Neurophysiological conditions for hearing in hearing-impaired and deaf children using hearing aids or cochlear implants – an intervention and follow-up study.

This multi-center study is focusing on central auditory processes and language development in children with hearing aids and/or cochlear implants (CI). A specific purpose is to examine how an individually designed phonological intervention programme can affect neurophysiological development and cognitive and reading skills. Central auditory processing is assessed with event-related potentials (ERP) and mismatch negativity (MMN). Mismatch negativity (MMN) provides a measure for detecting minor differences in sound, which are important for the ability to understand speech.

Three groups of children are included in the study: Deaf children with CI, hearing-impaired children with hearing-aids and normal hearing children. The study has a longitudinal design, where the children are followed over a period of three years, starting at five to seven years of age. The phonological intervention will be administrated via internet, supported by a speech pathologist. The effects of training will be evaluated with objective and behavioral methods.

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

EUSCREEN is an EU-projekt (Horizon 2020) with the aim to support vision and hearing screening programmes (VAHSP) for children in low- and middle income countries (LMIC). In this study, data relevant for screening, on demography, circumstances for screening, existing health systems, uptake, screening tests, diagnostics, treatment, health benefits, societal costs and adverse effects, will be gathered in all EU-countries and used by a decision-analytic, cost-effectiveness modelling framework of repeated screening to develop country-specific, cost-optimised, evidence-based VAHSPs that will be implemented in two LMICs. After the implementation studies, the costeffectiveness modelling framework and a strategy for implementation will be packed into a transferable TOOLKIT that will assist healthcare providers, policy makers and professionals in their decisions to introduce or modify childhood vision and hearing screening programs.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
Elisabet Engström	
Allison Mackey	

Ethical permit No.

2009/905-31/2	2010/1456 32			
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Publications 2016, 2017, 2018, 2019

- 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 117 (2019) 17–25 <https://doi.org/10.1016/j.ijporl.2018.11.005>
- 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 Oct;58(5):409-421. PMID: 28901574 <https://www.ncbi.nlm.nih.gov.proxy.kib.ki.se/pubmed/28901574>
- Kallioinen, P; Olofsson, J; Nakeva von Mentzer, C; Lindgren, M; Ors, M; Sahlén, BS; Lyxell, B; Engström, E; Uhlén, I. Semantic Processing in Deaf and Hard-of-Hearing Children: Large N400 Mismatch Effects in Brain Responses, Despite Poor Semantic Ability. Frontiers in psychology 2016 Aug 10;7:1146. PMID: 27559320 <https://www.ncbi.nlm.nih.gov.proxy.kib.ki.se/pubmed/27559320>
- Nakeva Von Mentzer, C; Lyxell, B; Sahlén, B; Dahlström, Ö; Lindgren, M; Ors, M; Kallioinen, P; Engström, E; Uhlén, I. Segmental and suprasegmental properties in nonword repetition--an explorative study of the associations with nonword decoding in children with normal hearing and children with bilateral cochlear implants. Clinical linguistics & phonetics 2015 Mar;29(3):216-35. PMID: 25489675 <https://www.ncbi.nlm.nih.gov.proxy.kib.ki.se/pubmed/25489675>. Written at Linköping University. Indicators c 4 JIF(2015) 1.364 cf 1.0



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Development of balance tests in newborns and children

The motor development in infants and children is dependent upon the function of the balance (vestibular) organ in the ears. A vestibular failure in developmental age, especially when bilateral, causes motor delays and a suboptimal motor proficiency. In 2015 we introduced a child friendly vestibular test battery and we are completing two studies about the validation of this method in two children cohorts: in children candidates to cochlear implantation and in children not passing the hearing screening control at birth. We plan to enlarge the study of vestibular function in children with motor delays, in newborns affected by brain injuries and in children complaining vertigo and balance disorders. These studies, included in the PhD project of MD Niki Karpeta, will ascertain the role of the vestibular function on the motor development of children with hearing impairment but also with motor and balance disorders.

New diagnostic and treatment options in superior canal dehiscence syndrome

The superior canal dehiscence syndrome (SCDS) is a rare but well defined inner ear disorder characterized by an abnormal inner ear sensitivity to sounds, especially the ones produced by own body, pressure changes and vibrations. The cause is a dehiscence at the roof of the temporal bone that alters the inner ear function. Sound and pressure evoked vertigo, dizziness, hyperacusis for body sounds and hearing impairment are often invalidating in SCDS patients. With previous studies, we have validated the role of the vestibular evoked myogenic potentials as a diagnostic tool for SCDS. Our SCDS research is nowadays focused on the definition of a clinical test for body sound hypersensitivity, the major reason for surgical indication in SCDS patients. Moreover, we are studying the acoustic properties of the ears affected by SCDS with the newly introduced wide band tympanometry testing. Finally, we are attempting a conservative approach for the correction of SCDS sound hypersensitivity and hearing impairment, by the use of bone anchored hearing aids (BAHA).

Supervision of PhD-students:

Main Supervisor	Co-supervisor
	Niki Karpeta

Ethical permit No.

2012/224-31/3	2015/1296-31/2	2019-02019		
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Publications 2016, 2017, 2018, 2019

- Skott H, Muntean-Firanesu C, Samuelsson K, Verrecchia L, Svenningsson P, Malmgren H, Cananau C, Espay AJ, Press R, Solders G, Paucar M. The cerebellar phenotype of Charcot-Marie-Tooth neuropathy type 4C. *Cerebellum Ataxias*. 2019 Jul 15;6:9.
- 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.
- 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.
- Brantberg K, Verrecchia L, Westin M. Enhanced Auditory Sensitivity to Body Vibrations in Superior Canal Dehiscence Syndrome. *Audiol Neurotol*. 2016;21(6):365-371.
- Verrecchia L, Westin M, Duan M, Brantberg K. Ocular vestibular evoked myogenic potentials to vertex low frequency vibration as a diagnostic test for superior canal dehiscence. *Clin Neurophysiol*. 2016 Apr;127(4):2134-9.

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New methods in Head and Neck surgery

I am involved in the following projects as a supervisor:

- * DI- a new swedish questionnaire to determine high airway stenosis. The project evaluates the questionnaire and validates it. With E Ntouniadakis
- * Kort-SGS an evaluation of the technique to treat tracheal stenosis with corticosteroid injections in the stenosis after surgery. With E Ntouniadakis
- * Ultrasound guided resections of tongue cancers and evaluation of ultrasound as method of determining tumour thickness in oral cancers compared with MR/CT and palpation. NBI-guided tongue resections to determine dysplasia/cancer in situ around tumors excised. With O Nilsson
- * A post treatment study of how HPV status affected the outcome of radiation therapy of oropharyngeal cancer. With Anna Oldaeus
- * A prospective study of the relationship between relapse and circulating HPV-virus after treatment of oropharyngeal HPV-positive cancer. With Anna Oldaeus
- * The use of ultrasound as an alternative to biopsy in diagnosis of Sjögrens syndrome. With Themistoklis Hadjicharaloumbus
- * The use of external ultrasound in the diagnosis of peritonsillar abscess. With Joacim Svensson

Supervision of PhD-students:

Main Supervisor	Co-supervisor
	Eleftherios Ntouniadakis
	Olof Nilsson
	Anna Oldaeus

Ethical permit No.

2019-03203	2018-104	2015-548	2016-275	2016-193
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Publications 2016, 2017, 2018, 2019

1. Transoral Robotic Surgery in the Nordic Countries: Current Status and Perspectives. Makitie AA, Keski-Santti H, Markkanen-Leppanen M, Back L, Koivunen P, Ekberg T, Sandstrom K, Laurell G, von Beckerath, M. et al. Front Oncol. 2018;8:289.
2. Long-term follow-up in patients treated with electrochemotherapy for non-melanoma skin cancer in the head and neck area. Kristiansson S, Reizenstein J, von Beckerath M, Landstrom F. Acta Otolaryngol. 2019;139(2):195-200.



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Cochlea malformation.

Children with cochlea malformations often present with a significant progressive hearing loss. Cochlea implantation is often the best solution to improve speech understanding and for the patient to develop their own ability to speak. We have focused our work on two types of malformation, Incomplete partition type 2 (IP2) and IP3. We are assessing new methods in radiological diagnosis, implantation technique, hearing result and related neurological factors.

Intraoperative assessment of the ossicular chain.

Ossicular fixation in the middle ear is one cause of conductive hearing loss. When a surgeon performs a tympanotomy, they will palpate the ossicular chain to assess where the fixation lies. We are developing an objective 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 improved ability to localise sound and hear when background noise is present if they are provided with bilateral BAHs.

Effect of ageing on treatment with cochlear implants

The project is designed to investigate the outcomes of treatment with cochlear implants in adults over the age of 70. There are special concerns for this group, such as a higher risk of major complications during surgery, higher risk for vestibular disturbances due to implantation and possible effect on the outcome of cognitive difficulties and dementia. We aim to compare younger (<60) vs older (>70) cochlear implant recipients. We will examine balance function (vestibular lab), cognitive tests (MoCA), and review medical notes for complications.

Supervision of PhD-students:

<i>Main Supervisor</i>	<i>Co-supervisor</i>
	Kaijsa Edholm
	Fatima Moumen Denanto

Ethical permit No.

2018/1032-31	2014/2068-31/2			
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Publications 2016, 2017, 2018, 2019

1. Wales, J., Gladine, K., Silvola, J., Muyschondt, P., Topsakal, V., Van De Heyning, P., Dirckx, J., von Unge, M. (2019) Evaluation of artificial fixation of the incus and malleus with minimally invasive intraoperative laser vibrometry (MIVIB) in a temporal bone model. Otol. Neurotol. Accepted.
2. Smeds, H., Wales, J., Mathiesen, T., Talbäck, M., Feychting, M. (2018) Occurrence of primary brain tumours in cochlear implant patients in Sweden between 1989 and 2014. Clin. Epidemiol. 10:1401-5
3. Wales, J., Gladine, K., Van de Heyning, P., Topsakal, V., von Unge, M., Dirckx, J. (2018) 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. 357, 46-53.
4. Smeds, H., Wales, J., Asp, F., Löfkvist, U., Falahat, B., Anderlid, B., Anmyr, L., Karltorp, E. (2017) X-linked malformation and cochlear implantation. Otol Neurotol. 38:38-46.
5. Grammatopoulos G, Wales J, Kothari A, Gill HS, Wainwright A, Theologis T. (2016) What Is the Early/Mid-term Survivorship and Functional Outcome After Bernese Periacetabular Osteotomy in a Pediatric Surgeon Practice? Clin Orthop Relat Res. 2016 May;474(5):1216-23.

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Prognostic factors and biomarkers for upper airway inflammation

Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) are among the most common chronic diseases in the population, sometimes starting early in life, and are often associated with asthma. Longitudinal analyses of these diseases enable us to study possible biomarkers for disease development and severity, in the aspect of prognosis and individually tailored treatment.

We use a large (N=4089), population-based birth cohort, BAMSE, started in 1994-1996. The children were included at birth and have been followed-up regularly by questionnaires and at three time points by clinical follow-ups, 4, 8 and 16 years, including blood samples for specific IgE and lung function tests. The fourth follow-up, at 24 years, was recently finalized, with a response rate of 75 % from baseline. At 16 and 24 years of age, subgroup studies among all children with symptoms of CRS (1.5 % at 16 yrs and 4 % at 24 yrs) have been performed at the Dept. of ENT-diseases, including nasal endoscopy, sampling for inflammatory markers, microbiome and epithelial cells. The subgroup-data is then merged with the all-cohort-data. This enables us, in addition to study the pathophysiology of different endotypes of CRS, to study the temporal association of symptoms – CRS, AR, asthma - as well as early symptoms and biomarkers as potential predictors of CRS and severe asthma. Some of the studies on both AR and CRS from the BAMSE-project are included in Karin Åberg's PhD-project. I am also co-supervising Karin Jonstam in her studies of CRSwNP.

Supervision of PhD-students:

Main Supervisor	Co-supervisor
Karin Åberg	Karin Jonstam

Ethical permit No.

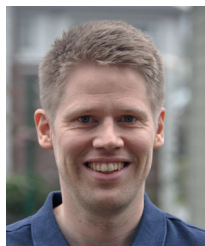
2016/1380-13/2	2018-209/32			
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Publications 2016, 2017, 2018, 2019

1. Elliot A, Nasman A, Westman M, Marklund L, Stjerne P, Hammarstedt-Nordenvall L. Human papillomavirus and infiltration of CD8- and Foxp3-positive immune cells in sinonasal inverted papillomas. *Acta oto-laryngologica*. 2019;139(11):1019-23.
2. Bjermer L, Westman M, Holmstrom M, Wickman MC. The complex pathophysiology of allergic rhinitis: scientific rationale for the development of an alternative treatment option. *Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology*. 2019;15:24.
3. Bousquet J, Arnavielhe S, Bedbrook A, Bewick M, Laune D, Mathieu-Dupas E, et al. MASK 2017: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma multimorbidity using real-world-evidence. *Clinical and translational allergy*. 2018;8:45.
4. Hallberg J, Ballardini N, Almqvist C, Westman M, van Hage M, Lilja G, et al. Impact of IgE sensitization and rhinitis on inflammatory biomarkers and lung function in adolescents with and without asthma. *Pediatr Allergy Immunol*. 2019;30(1):74-80.
5. Bousquet J, Devillier P, Anto JM, Bewick M, Haahtela T, Arnavielhe S, et al. Daily allergic multimorbidity in rhinitis using mobile technology: A novel concept of the MASK study. *Allergy*. 2018;73(8):1622-31.
6. Wise SK, Lin SY, Toskala E, Orlandi RR, Akdis CA, Alt JA, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *International forum of allergy & rhinology*. 2018;8(2):108-352.
7. Bousquet J, Agache I, Aliberti MR, Angles R, Annesi-Maesano I, Anto JM, et al. Transfer of innovation on allergic rhinitis and asthma multimorbidity in the elderly (MACVIA-ARIA) - EIP on AHA Twinning Reference Site (GARD research demonstration project). *Allergy*. 2018;73(1):77-92.
8. Westman M, Asarnoj A, Hamsten C, Wickman M, van Hage M. Windows of opportunity for tolerance induction for allergy by studying the evolution of allergic sensitization in birth cohorts. *Seminars in immunology*. 2017;30:61-6.
9. 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.
10. Anto JM, Bousquet J, Akdis M, Auffray C, Keil T, Momas I, et al. Mechanisms of the Development of Allergy (MeDALL): Introducing novel concepts in allergy phenotypes. *J Allergy Clin Immunol*. 2017;139(2):388-99.
11. Bousquet J, Anto JM, Akdis M, Auffray C, Keil T, Momas I, et al. Paving the way of systems biology and precision medicine in allergic diseases: the MeDALL success story: Mechanisms of the Development of ALLergy; EU FP7-CP-IP; Project No: 261357; 2010-2015. *Allergy*. 2016;71(11):1513-25.

PhD-Student

Arnason, Sigurdur	84.
Danielsson, Daniel	85.
Eklöf, Martin	86.
Ekstedt, Sandra	87.
Engström, Elisabet	88.
Eriksson, Björn	89.
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Tengroth, Birgitta	111.
Turunen-Taheri, Satu	112.
Wendt, Malin	113.
Åberg, Karin	114.

**Sigurdur Arnason**

Main supervisor
Co-supervisor
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Halftime seminar
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Barbro Hedin Skogman
Malou Hultcrantz, Åsa Laestadius, Elin Marsk
2019-09-27

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)
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Publications/manuscripts 2016, 2017, 2018, 2019

1. Peripheral facial nerve palsy in children in a Borrelia high-endemic area, a retrospective follow-up study. Manuscript, submitted, under revision. 2019.

**Daniel Danielsson**

Main supervisor

Co-supervisor

Registered

Halftime seminar

Planned dissertation

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Eva Munck-Wikland

Siamak Haghdooost

2008-10-08

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

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

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

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

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

ORN is for the individual patient a severe condition affecting daily life. Symptoms include trismus, pain, impaired nutritional capacity and infection not seldom associated with oro-cutaneous fistula. ORN is seldom reversible and will progress over time leading to pathological fractures and need for extensive reconstructive surgical intervention including free tissue transfer. This treatment is costly to both patient and society. Radiation therapy is dose dependant but individual differences exists. The incidence of ORN in the head and neck area is reported to 3-8%.

Aim of our studies:

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

Ethical permit No.

2006/1413-32	2016/277-32	2012/1663-32		
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Publications/manuscripts 2016, 2017, 2018, 2019

1. Osteoradionecrosis, an increasing indication for microvascular head and neck reconstruction. Danielsson D, Gahm C, Haghdooost S, Munck-Wikland E, Halle M. Int J Oral Maxillofac Surg. 2019 Jul 8. Pii: S0901-5027(19)31185-3.
2. Quality of life after microvascular mandibular reconstruction for osteoradionecrosis – A prospective study. Danielsson, Muck-Wikland, Hagel, Halle. Head Neck. 2019 Feb 5. DOI: 10.1002/hed.25681
3. Influence of genetic background and stress response on risk of mandibular osteoradionecrosis after radiotherapy of head and neck cancer. Danielsson, Brehwens, Halle, Marczyk, Sollazzo, Polanska, Muck-Wikland, Wojcik, Haghdooost. Head Neck. 2014 Oct 28. DOI: 10.1002/hed.23903

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ErikBerninger, Eva Karltorp, Filip Asp

2012-05-23

Methods and results from bilateral hearing with cochlear implants

Cochlear implantation before 9 month of age showed benefits in terms of speech production and language understanding. No increase in surgical risk were found. We have further found differences in fundamental binaural abilities with different cochlear implants sound processing algorithms. Children that received sound processors programmed with fine structure information were able to perceive interaural time difference limens, which is needed for localization of low frequency sounds. We have further found a method for assessing the sound localization latency. This latency increases with 7 ms for each dB of simulated unilateral hearing loss at 1000 Hz.

Ethical permit No.

2013/235-1/4	2013/1127-31/2	2013/104-31/4		
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Publications/manuscripts 2016, 2017, 2018, 2019

1. Eklöf, M., & Tideholm, B. (2018). The choice of stimulation strategy affects the ability to detect pure tone inter-aural time differences in children with early bilateral cochlear implantation. *Acta Oto-Laryngologica*, 0(0), 1–8. <https://doi.org/10.1080/00016489.2018.1424999>
2. 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 Paediatrica* (Oslo, Norway: 1992). <https://doi.org/10.1111/apa.14954>
3. Eklöf, M., Asp, F., & Berninger, E. Evaluation of Sound Localization Latency in Normal Hearing and Simulated Unilateral Hearing Loss – Towards a Clinically Feasible Method. Submitted

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2013-09-26

2016-10-18

2019-11-29

The role of neutrophils in airway smooth muscle contraction

Neutrophils are part of the first lines of defence against invading microbes. They play an essential role in antimicrobial host defence by recognizing microorganisms through the various receptor that can be expressed on its surface. Novel subsets with different functions of already classified cells are continuously discovered. In line with this, four different neutrophil subsets have been identified based on their expression of CD16 and CD62L. The subsets reflect different stages of cell maturity and activity. My research focuses on two of the four subsets. One of them, the high/high neutrophil, is considered mature and the other, the high/dim neutrophil, is activated.

We have characterised neutrophil subsets in blood before and after an inhaled allergen provocation. The fraction high/high neutrophils decreased and the high/dim neutrophils increased as a result of the challenge. To evaluate the effects of high/high and high/dim neutrophils on airways, human bronchi and mice trachea were co-cultured with the different subsets. The functional changes caused by the co-cultures were then evaluated in a myograph. The high/dim neutrophils increased the contractile response towards bradykinin. They also enhanced contractions induced by nerve-mediated stimulation. The increase in bradykinin response was related to a release of TNF α that subsequently upregulated the bradykinin receptor 2. The nerve-mediated airway hyperresponsiveness in conjunction with high/dim neutrophils was due to production of IL-1 β that caused an increase of substance P in the nerves via COX-2.

These new findings may lead to a better understanding of the role of neutrophils in severe asthma, and potentially to new treatments.

Ethical permit No.

NåN258/13	2014/260	2010/181-31/2	2014/299-13	N254/15
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Publications/manuscripts 2016, 2017, 2018, 2019

1. Ekstedt S, Stenberg H, Tufvesson E, Diamant Z, Bjermer L, Kumlien Georen S, et al. The potential role of CD16(high) CD62L(dim) neutrophils in the allergic asthma. *Allergy* 2019.
2. Ekstedt S, Safholm J, Georen 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.
3. 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.
4. Sandra Ekstedt, Ellen Tufvesson, Susanna Kumlien Georén and Lars Olaf Cardell. "Don't eat me" markers indicates that neutrophils from asthmatic patients resist phagocytosis, explaining the occurrence of prevailing airway infections. - Manuscript
5. Sandra Ekstedt, Olivia Larsson, Susanna Kumlien Georén and Lars Olaf Cardell. CD16highCD62Ldim neutrophils induce nerve mediated airway hyperreactivity - Manuscript

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2019-06-05

Prel. 2016

Neurophysiological conditions for hearing in hearing-impaired and deaf children using hearing aids or cochlear implants – an intervention and follow-up study

The aim of this study is to examine the neurophysiological conditions for auditory function in hearing impaired and deaf children using hearing aids or cochlear implants. It has been shown that these children perform more poorly in school as compared with normal hearing children, despite equal learning aptitude. The children who participate in the study are between five and seven years of age. It is a longitudinal study and we have followed them up after three years.

We also investigate whether a phonological computer-assisted training program can affect the event-related potentials (ERP) and mismatch negativity (MMN) in hearing impaired children with hearing aids or cochlear implants. Analyses of ERP and MMN can also give us further description of the central auditory processing in hearing impaired children using bilateral HA.

MMN is an automatic brain response to any discriminable change in auditory stimulation, irrespective of attention. Mismatch negativity (MMN) provides a measure for detecting minor differences in sound, which are important for the ability to understand speech. It is regarded as a subconscious process not requiring active listening.

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

Ethical permit No.

2009/905-31/2	2010/1456 32			
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Publications/manuscripts 2016, 2017, 2018, 2019

1. Semantic Processing in Deaf and Hard-of-Hearing Children: Large N400 Mismatch Effects in Brain Responses, Despite Poor Semantic Ability. Kallioinen P, Olofsson J, Nakeva von Mentzer C, Lindgren M, Ors M, Sahlén BS, Lyxell B, Engström E, Uhlén I. Front Psychol. 2016 Aug 10;7:1146
2. 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
3. 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

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2018-01-29

Inflammatory changes of skin after radiotherapy

Patients that have been successfully treated with radiotherapy for oncological purposes develop significant morbidity and mortality during long-term follow up. The molecular response to ionizing radiation in normal tissue is a developing research field, but much is still unknown regarding cellular and histological reactions to radiation and how this contributes to long-term consequences for patients.

In our first study, a cohort of patients that received preoperative radiotherapy followed by free tissue transfer, there was an increased incidence of fistulas and infection when compared to patients who received radiotherapy postoperatively. This indicates a disturbance in the microcirculation of the tissue following exposure to ionizing radiation.

In our second study, analysis of arteries and veins from irradiated areas (the neck) and unirradiated areas (the free tissue transfer) of the same patient showed an increase in the gene expression of plasminogen activator inhibitor-1 (PAI-1). Further immunohistochemical and immunofluorescence studies showed co-expression of PAI-1 and CD68, CD45 and alpha-SMA suggesting that PAI-1 was produced by macrophages (CD68), leukocytes (CD45) and myofibroblasts (alpha-SMA) in the adventitia of irradiated blood vessels.

So far, our results are consistent with the hypothesis that irradiation causes a long-term inflammatory response leading to activation of myofibroblasts and endothelial to mesenchymal transition.

We are currently gathering skin biopsies from irradiated and unirradiated skin of patients undergoing free tissue transfer, to further elucidate the effect of radiation on gene expression and immunohistological appearances in skin and how this contributes to the development of posttherapeutic skin fibrosis. We are also looking into pharmaceutical and surgical treatments to attenuate the fibrotic response in the skin of irradiated patients.

Ethical permit No.

2016/1578-32	2012/1663-32			
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Publications/manuscripts 2016, 2017, 2018, 2019

1. Improved Head and Neck Free Flap Outcome—Effects of a Treatment Protocol Adjustment from Pre- to Postoperative Radiotherapy, PRS Global Open, 2017;5:e1253, DOI: 10.1097/GOX.0000000000001253
2. Upregulation of Plasminogen Activator Inhibitor-1 in Irradiated Recipient Arteries and Veins from Free Tissue Transfer Reconstruction in Cancer Patients, Mediators of Inflammation, 2018, <https://doi.org/10.1155/2018/4058986>

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2018-02-02

Autumn 2020

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

Obstructive sleep apnea (OSA) is a common disorder for both children and adults. It is characterized by partial or complete upper airway obstruction during sleep, that disrupts ventilation and fragments normal sleep patterns. It is associated with numerous morbidities and complications, such as hypertension and behavioral disturbances, if left untreated.

This project 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 in young children with mild to moderate OSA.
- If a modified ATE is more effective in treating children with severe OSA.

So far we have published work that shows:

- That surgery decreases blood pressure in adult patients with OSA.
- That ATE is more effective in improving quality of life but not objective respiratory parameters in children with mild to moderate OSA
- That a modified ATE is not more effective to treat children with severe OSA.

Ethical permit No.

Ö21-2007	2014/1000-31/1			
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Publications/manuscripts 2016, 2017, 2018, 2019

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. doi:10.1016/j.sleep.2017.02.030.
2. Fehrm J, Nerfeldt P, Sundman J, Friberg D. Adenopharyngoplasty vs Adenotonsillectomy in Children With Severe Obstructive Sleep Apnea. *JAMA Otolaryngol Neck Surg.* May 2018. doi:10.1001/jamaoto.2018.0487
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. doi:10.1007/s00405-018-4970-z
4. Fehrm J, Nerfeldt P, Browaldh N, Friberg D. Adenotonsillectomy versus Watchful Waiting in Young Children with Mild to Moderate Obstructive Sleep Apnea: KATE—A Randomized Clinical Trial. Manuscript submitted September 2019.

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Pituitary adenomas, clinical aspects of treatment and prevalence of Galanin- and Pattern Recognition receptors.

Pituitary adenomas are classified into hormone secreting or clinically inactive. Symptoms arise either due to hormonal 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 unaccessible 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 du for submission within 2019 hopefully.

We have also evaluated different treatment strategies in perioperative 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) which has been described in inflammatory airway disease, but not yet been studied in pituitary adenomas. My aim is to do half time control in early 2020, and defend my thesis within approximately a year from then.

Ethical permit No.

2012/1689-31/4 (2019-01941)	2012/891-31/2			
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Publications/manuscripts 2016, 2017, 2018, 2019

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. Surgical success, survival and complications in pituitary surgery - a swedish perspective - Manuscript.

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Lars Olaf Cardell
Karin Lundkvist, Ulla Peterson Westin
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2018-06-08

Intralymphatic allergen specific immunotherapy (ILIT) in allergic rhinitis

Allergic rhinitis is increasing in the westernized world and has substantial impact on work, school, sleep and quality of life. Allergy vaccination, or allergen specific immunotherapy (AIT), is the only treatment that not only gives good symptom relief but also acts disease-modifying. However, AIT is underused, mainly due to the time-consuming process with up to 50 doctor appointments with subcutaneous injections over 3-5 years. An alternative to conventional AIT is sublingual immunotherapy in which the patient takes a tablet under the tongue every day for three years without the need of medical supervision. However, there is a problem with long-term patient adherence. It is natural to look for a better way to administer AIT. Previous studies have indicated that intralymphatic immunotherapy (ILIT) with ultrasound guided injections of allergen into a lymph node stimulates the immune system faster. In a series of randomized double blind placebo controlled trials we have investigated the clinical and immunological effects of ILIT. A combination of grass and birch allergen ILIT increased the allergen specific IgG4 levels, increased T-memory cells in the lymph node and blood, and reduced the pollen-triggered rhinitis symptoms at allergen challenge. In a 5-year follow up the long term results are being evaluated. ILIT after conventional AIT boosted the IgG4-levels and improved seasonal symptoms. ILIT was feasible in adolescents and safe with concomitant well-controlled asthma. In an up-dosing schedule of grass pollen ILIT, with close monitoring of side effects, patients suffered allergic side effects; increased doses doesn't seem to be the way to optimize ILIT. Still, if better understood, this new modality can be a valuable patient friendly option for the treatment of allergic rhinitis in the future. The long term goal is to develop ILIT as a fast and safe AIT regimen that can be offered to more patients than today.

Ethical permit No.

2012/1018-31/2	2013/561	2013/1422-31/1	2015/2257-31/1	2018/697-31
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Publications/manuscripts 2016, 2017, 2018, 2019

1. 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, L.O. The Journal of Allergy and Clinical Immunology, October 2018, Vol.142(4), pp.1338-1341.e9.
2. Intralymphatic immunotherapy in pollen allergic young adults with rhinoconjunctivitis and mild asthma: a randomized trial. Konradsen, J; Grundström, J; Hellkvist, L; Tran, T. A; Andersson, N; Gafvelin, G; Kiewiet, G; Hamsten, C; Shamji, M.H; Hedlin, G; van Hage, M; Cardell, L.O. In manuscript.
3. ILIT after SCIT- a randomized double blind placebo controlled trial of intralymphatic immunotherapy in an up-dosing schedule. Hellkvist, L; Weinfeld, D; Hjalmarsson, E; Dahl, Å; Kumlien Georén, S; Karlsson, A; Lundkvist, K; Westin, U; Cardell, L.O. In manuscript

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2017-06-20

The allergic immune response and mechanisms behind allergen tolerance

Intra lymphatic immunotherapy has been proposed as a faster and safer alternative to conventional allergy therapy. In my projects we have confirmed the safety of ILIT. We have also showed that concomitant ILIT with birch and grass allergen reduce allergen induced symptoms. Immunological finding in this study show that memory T-cells increase in the allergen injected lymph node. In blood an increase of effector memory CD4 Treg-cells were detected. This study show that ILIT can activate T-cells locally in the lymph node and that these cells spread systemically.

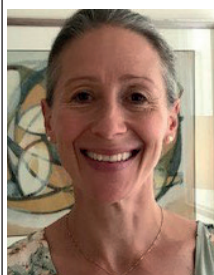
To further improve ILIT we intend to analyze if increased allergen dose induce even more symptom relief, compared to normal ILIT. We will also analyze if reduction in symptoms and immunological changes seen after ILIT still remain 5-years after therapy completion. Ongoing projects are also analyzing if functional changes in basophils and neutrophils can be used as biomarkers for detection of responders to allergen specific immunotherapy. Identification of improved biomarkers is much needed to further propagate allergen specific immunotherapy as an alternative to treat allergen induced symptoms.

Ethical permit No.

2016-823-31-2	2018-2645-32	2017-2257	2012-1018		
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Publications/manuscripts 2016, 2017, 2018, 2019

1. ILIT after SCIT- a randomized double blind placebo controlled trial of intralymphatic immunotherapy in an up-dosing schedule (manuscript)
2. Hellkvist L, Hjalmarsson E, Kumlien Georen S, Karlsson A, Lundkvist K, Winqvist O, et al. Intralymphatic immunotherapy with 2 concomitant allergens, birch and grass: A randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol*. 2018;142(4):1338-41 e9.
3. Hayry V, Kagedal A, Hjalmarsson E, Neves da Silva PF, Drakskog C, Margolin G, et al. Rapid nodal staging of head and neck cancer surgical specimens with flow cytometric analysis. *Br J Cancer*. 2018;118(3):421-7.
4. 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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2018-12-14

October 2020

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.

The first and second projects are completed and published. The first project clarified the incidence of complications in children up to five years old in Stockholm County before the introduction of the pneumococcal vaccine. A majority of the children admitted due to complicated rhinosinusitis had an orbital complication but postseptal complications were rare and only one child out of 213 admissions during the four year period needed surgery. Most of the admitted children were younger than two years old and a majority were boys. Streptococcus Pneumoniae were the most common pathogen.

Project two showed that complications continues to be very rare after the introduction of pneumococcal vaccine. Hospitalization decreased for children under five years old after PCV introduction, but the incidence of postseptal complications and surgery in the same population increased slightly. Predominantly bacteria other than Streptococcus pneumoniae was found.

Project number three concerns children from five up to 18 years old admitted during a nine year period. Data is collected and being analyzed.

Project number four is a prospective study of children up to 18 years old with rhinosinusitis admitted in Stockholm. Data is being collected.

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
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Publications/manuscripts 2016, 2017, 2018, 2019

1. 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. 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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Christina Hederstierna, Per Östberg, Nenad Bogdanovic
2016-11-14
2019-05-20

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		
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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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2016-11-03

Fall/Winter 2021/2022

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

Although audiological treatment is generally most effective early in life, this Ph.D. project is one of the first studying the outcomes of very early treatment of congenital unilateral sensorineural hearing loss (cUSNHL), and its causes and mechanism.

In the first publication we demonstrate a distinct relationship between neural transmission to the upper brainstem (impaired ear) and sound localization with a hearing aid ($r = 0.98$, $p = 0.02$, $n = 4$), not revealed previously. The relationship reflects a close link between neural maturation and a hearing ability that is generally impaired in children with uSNHL. The children had used hearing aids for more than 1.5 years and were fitted late (after >5 years of cUSNHL).

We also demonstrate the benefit of hearing aids in one-to-one communication, based on child and parent questionnaires. Contrary, sound localization was significantly worse in the aided compared to unaided condition. No significant hearing aid benefit or disbenefit existed in background noise or reverberation. Based on the close relationship between neural maturation and aided sound localization, a hearing aid probably needs to be fitted shortly after diagnosis, before the brain adapts to asymmetrical hearing, to obtain overall hearing aid benefit.

We are currently inviting all children with cUSNHL born in the Stockholm County Council for assessment to evaluate early hearing aid intervention longitudinally and we study the etiology as a factor in children with cUSNHL's hearing development. The project will run over a few more years.

Moreover, we study the physiological basic mechanisms of the inner ear and heredity, by using a twin model of neonatal otoacoustic emissions. In connection to the research project, a thorough understanding of typical inner ear function is useful in the study of the possible mechanisms affecting one of the inner ears in children with cUSNHL. A manuscript is currently under preparation.

Ethical permit No.

2015/1878-31/2	2018/1500-31	2019-03826		
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Publications/manuscripts 2016, 2017, 2018, 2019

1. Johansson, M., Asp, F., & Berninger, E. (2019). Children With Congenital Unilateral Sensorineural Hearing Loss: Effects of Late Hearing Aid Amplification-A Pilot Study. *Ear and Hearing*. doi:10.1097/aud.0000000000000730.

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2015-03-24
2017-11-21
2020-05-20

A personalized approach to Chronic Rhinosinusitis based on biomarkers, phenotypes and new surgical thinking.

Severe chronic rhinosinusitis with nasal polyps (CRSwNP) is in the western world mainly an eosinophilic disease with elevated type 2-markers, such as IgE, Interleukin-5 and Eosinophilic cationic protein in nasal polyp tissue, nasal secretions and serum. Treatment includes local and systemic corticosteroids and surgery and relapse is common.

This project focus on identifying severe CRSwNP with biomarkers, new treatment options with monoclonal antibodies and a new surgical approach (Reboot surgery) that reduces relapse of the disease.

Ethical permit No.

2017/686-32	2016/1748-31/4	2017/1461-31	EC UZG 2011/570	EC UZG 2017/0883
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Publications/manuscripts 2016, 2017, 2018, 2019

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.

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Cecilia Engmér Berglin
2017-04-07

**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	
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Publications/manuscripts 2016, 2017, 2018, 2019

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2019-09-10

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 (VHIT) 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.

2019-02019				
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Publications/manuscripts 2016, 2017, 2018, 2019

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Linda Marklund, Anders Näsman

2015-11-24

2021

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. The third study was regarding HPV as a prognostic marker for Cancer of Unknown Primary in the Head and Neck region. In the third study we tested branchial cleft cysts for HPV, all cysts turned out to be HPV-negative. The last studies investigate the use of other markers than HPV in hypopharyngeal cancer

Ethical permit No.

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Publications/manuscripts 2016, 2017, 2018, 2019

1. Sivars L, Landin D, Haeggbloom L, Tertipis N, Grün N, Bersani C, Marklund L, Ghaderi M, Näsman A, Ramqvist T, Nordfors C, Munck-Wikland E, Tani E, Dalianis T. Human papillomavirus DNA detection in fine-needle aspirates as indicator of human papillomavirus-positive oropharyngeal squamous cell carcinoma: A prospective study. *Head Neck*. 2017 Mar;39(3):419-426. doi: 10.1002/hed.24641. Epub 2016 Nov 29
2. 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.
3. Lars Sivars, David Landin, Marzia Rizzo, Linnea Haeggbloom, 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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2017-06-01

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				
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Publications/manuscripts 2016, 2017, 2018, 2019

1.

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2017-10-27

Paediatric hearing screening programs across EU countries - a utility and cost effectiveness study

Universal newborn hearing screening programmes have been widely implemented across the Europe, yet there is large variability in the protocols and procedures chosen by health care policy makers when implementing and sustaining such programmes.

As part of the EUSCREEN project, we are investigating the choices made when implementing a screening programme and protocol across countries in Europe. Early findings show large variability for certain protocol parameters (e.g., screening sequence, test choice) and low variability for other parameters (e.g., test location). These differences in chosen parameters will also be compared to the health care situation across participating countries. The aim of this study is to understand the variability of screening parameters within the context of the country and region studied.

Second, it is understood that outcomes of universal newborn hearing screening (e.g., pass/refer rate, loss to follow-up) are related to screening protocols; however, these relationships are not well understood. Many programmes still face challenges with high false positive rates and loss to follow-up from screening. To understand the relationship between screening outcomes and protocol/programme parameters, we have aggregated screening outcomes across multiple countries and regions across Europe that use a variety of protocols. One early finding from these data is that many screening programmes lack a valid and sustainable system for monitoring outcome measures and performing quality assurance assessments.

Furthermore, we are conducting a systematic review to quantify screening outcomes and determine the influence of protocol parameters to the outcome, in addition to understanding the relationship of different groups of infants (e.g., NICU) on these outcome measures.

Ethical permit No.

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Publications/manuscripts 2016, 2017, 2018, 2019

1.

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2012-05-24

Study of transfeminine patients satisfaction and subjective image assessment before and after chondroplasty.

Gender incongruence means that an individual cannot identify with the gender assigned at birth. A prominent adam's apple is a strong male marker, which can be psychologically stressful for transfeminine patients (patients who were given the gender "male" at birth but identify themselves as women).

To reduce this burden, the prominence (adam's apple) is reduced for those with a prominent larynx, so-called chondroplasty. About 20-30 patients per year undergo chondroplasty at the ENT clinic Karolinska and the number is increasing. The procedure is done under anesthesia, the thyroid cartilage is revealed after incision in the skin and the prominence (Adam's apple) is reduced by drill or scalpel.

We now want to study the degree of distress the patients are undergoing, regarding the appearance of the thyroid cartilage and how the thyroid cartilage is felt by palpation on the neck before and after surgery, by filling in a visual analog scale (VAS) form. The patients are also photographed before and after surgery. After a year, the patient is examined again, and the same questions, as pre surgery, are answered as well as further questions regarding satisfaction of the operation. Photos in the same positions as pre surgery are registered.

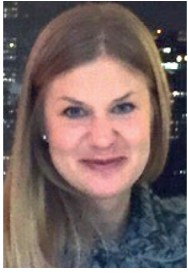
The change in the pre and post surgery photos are being evaluated on a scale of 0-3 (0=no change and 3=maximum change, where the prominence is not noted) and the questions forms are being analyzed.

At present, material is being collected at the ENT Clinic Karolinska

Ethical permit No.

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Publications/manuscripts 2016, 2017, 2018, 2019

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2017-11-30
Winter 2020

Surgical intervention in patients with peripheral facial palsy; assessment of regained function and quality of life

Persistent peripheral facial palsy (PFP) can be a devastating handicap. Two main complications are permanent paralysis and synkinesis, apart from psychological suffering.

Significant attention has been paid to acute management of Bell's palsy, but literature addressing long-term sequelae is sparse. We are conducting a large epidemiologic investigation covering all patients treated for non-traumatic PFP at Karolinska between 2008-2013 to study the prevalence of persistent PFP.

The goal of surgical treatment for PFP is to reestablish facial symmetry and movement. Reanimation through cross-facial nerve graft will offer a chance of mimic response to emotional stimuli in contrast to voluntary movement. In order to prevent denervation during axonal growth through the long cross-facial nerve graft, a supplementary short nerve graft is coapted to the ipsilateral hypoglossal nerve and the procedure is performed within 6 months from onset of disease. Variants of this 'babysitter procedure' is performed since the 90's, but has never been structurally evaluated for patients with non-traumatic PFP as is our aim.

The other main complication following PFP is synkinesis, which can be a dominant handicap. It is often successfully treated with repeated Botox injections, but an alternative when this fails is lacking. Promising case studies have described highly selective neurectomy of the periocular region as an option, but no systematic evaluation has yet been undertaken. The surgery is performed in two steps. Distal branches of the facial nerve are identified under the operating microscope and brought up above skin surface in the first phase. After awakening from the surgery, the patient collaborates during the second step when the nerve branches are stepwise divided under concomitant evaluation of relief of synkinesis and absence of paralysis. We are performing a prospective study to evaluate this surgery as an alternative treatment for patients with severe synkinesis.

Ethical permit No.

2009/156-31/2	2011/598-32	2018/1154-32	2018/2697-31	2019-00421
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Publications/manuscripts 2016, 2017, 2018, 2019

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2019-08-29

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 additional 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				
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Publications/manuscripts 2016, 2017, 2018, 2019

1. Piersiala K, Akst LM, Hillel AT, Best SR. Clinical practice patterns in laryngeal cancer and introduction of CT lung screening. *Am J Otolaryngol.* 2019;40(4):520-524.
2. Klimza H, Jackowska J, Tokarski M, Piersiala K, Wierzbicka M. Narrow-band imaging (NBI) for improving the assessment of vocal fold leukoplakia and overcoming the umbrella effect. *PLoS One* 2017;12:e0180590.
3. Klimza H, Jackowska J, Tokarski M, Piersiala K, Wierzbicka M, Komínek P. Narrow-band imaging (NBI) for improving the assessment of vocal fold leukoplakia and overcoming the umbrella effect. Maitland KC, ed. *PLoS One.* 2017;12(6):e0180590.
4. Jackowska J, Sjogren E V, Bartochowska A, Czerniejewska-Wolska H, Piersiala K, Wierzbicka M. Outcomes of CO2 laser-assisted posterior cordectomy in bilateral vocal cord paralysis in 132 cases. *Lasers Med Sci.* 2018;33(5):1115-1121.
5. Piersiala K, Klimza H, Jackowska J, Wierzbicka M. Parotid gland cholesteatoma in a 23-year-old male: Case report. *SAGE Open Med Case Reports.* 2017;5:2050313X1774908.
6. H.Klimza, W.Pietruszewska, J. Jackowska, K. Piersiala, M.Wierzbicka. Evaluation of narrow band imaging in the assessment of laryngeal granuloma (Manuscript accepted for publication in Scientific Reports, Sep 2019)

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2018-06-05

Prel. plan 2020

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 and the connection to quality of life. Further, clinical supervisors' perception of giving feedback during clinical rotations has been studied.

Students from four different undergraduate programs (medical, physiotherapy, speech-language pathology and nursing) at Ki has been invited to participate (studies 2 and 3). In the first study, the participants were clinical supervisors from the physiotherapy program.

The data collection for study 2 and 3 was done with following questionnaires:

The Undergraduate Clinical Education Environment Measure (UCEEM)

The Short Form 12 (SF12)

Brunnsviken Brief Quality of Life Scale (BBQ)

Medical Education in Nordic Countries (wellbeing subscale) (MEDNORD)

Interdisciplinary Education Perception Scale (IEPS)

Central scientific questions of the project are:

- How are the clinical learning environments perceived by the students?
- What are the students' perceptions of their well being and the quality of life during clinical integrated learning?
- How do the students assess the stress levels during clinical integrated learning?
- What are the students perceptions of the interprofessional learning during clinical integrated learning?
- What are the physiotherapy supervisors perceptions of feedback to students during clinical rotations?

Preliminary results from study 1; giving feedback to students was part of continuous development for the clinical supervisors who aimed at being professional while handling emotions in social interactions between supervisors and students. The analysis of collected for study 2 and 3 is ongoing.

Ethical permit No.

2016/1425-31	2017/38-31/4			
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Publications/manuscripts 2016, 2017, 2018, 2019

1. Clinical supervisors' experience of giving feedback to students during clinical integrated learning (Sellberg, Skavberg Roaldsen, Malin Nygren Bonnier, Halvarsson (submitted 2019)

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2019-03-18

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			
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Publications/manuscripts 2016, 2017, 2018, 2019

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2014-10-27

2019-10-11

Central Auditory Pathways in Unilateral Congenital Conductive Hearing Impairment

Ear canal atresia causes profound conductive hearing loss of the affected ear. Unilateral hearing loss is 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 shows that level of hearing loss of the atretic side affects ability to localize sound source.

Ethical permit No.

2012/1661-31/3	N113/15	N191/14		
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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 Atresia -Sound Localization Ability and Recognition of Speech in Competing Speech in Unaided Condition" Siegbahn M, Asp F, Hultcrantz M, Engmér-Berglin C -Manuscript

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2008-02-18

2014-05-19

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 which can identify viruses in the airway and by that evoke an inflammatory response. 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
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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.
2. Starkhammar M, Larsson O, Kumlien Georén S, Leino M, Dahlén S-E, Adner M, Cardell L-O. Toll-Like Receptor Ligands LPS and Poly (I:C) Exacerbate Airway Hyperresponsiveness in a Model of Airway Allergy in Mice, Independently of Inflammation. PLoS ONE. August 2014.
3. Starkhammar M, Kumlien Georén S, Dahlén S-E, Cardell L-O, Adner M. TNF α -blockade stabilizes local airway hyperresponsiveness during TLR-induced exacerbations in murine model of asthma. Respiratory Research. October 2015.
4. Adner M, Starkhammar M, Kumlien Georén S, Dahlén S-E, Cardell L-O. Toll-like receptor (TLR) 7 decreases and TLR9 increases the airway responses in mice with established allergic inflammation. European Journal of Pharmacology. October 2013.
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 quinine in airway dilation. Lung Cellular and Molecular Physiology. April 2016.
6. Larsson OJ, Manson ML, Starkhammar M, Fuchs B, Adner M, Kumlien Georén S, Cardell LO. The bronchodilatory capacity of imiquimod: the existence of two mechanisms. American Journal of Physiology, Lung Cellular and Molecular Physiology. July 2016

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2015-11-05
2018-02-23
Autumn 2020

Obstructive Sleep Apnea, patient selection, subjective outcomes, long-term efficacy 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 randomized controlled trials. Less is known, however, about the long-term efficacy as well as the effect on subjective parameters. In addition 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. However, the method for patient-selection that we evaluated was poor and unreliable.

Ethical permit No.

2018/214-32	2016/331-32	2009/1076-32		
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Publications/manuscripts 2016, 2017, 2018, 2019

1. J. Sundman, J. Bring, D. Friberg. Poor interexaminer agreement on Friedman tongue position Acta oto-laryngologica, 2016. E. Sandell, M. Berg, G. Sandblom, J. Sundman, U. Fränneby, L. Boström, Å.
2. Andrén-Sandberg. Surgical decision-making in acute appendicitis. BMC Surgery 2015 15:69.

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Anette Lohmander

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Aspects of hearing in children with cleft palate

Study I: The documented high prevalence of OME in children with CP±L leads to an increased risk for chronic otitis media. Moreover, chronic otitis media can lead to complications including permanent hearing impairment, perforation of the tympanic membrane and the increased risk to develop cholesteatoma. These complications were evident in the current study. Due to these complications, it is evident that children with CP±L should have regular follow-ups by an ENT doctor and audiologist even after the tubes have been rejected.

As part of the routine follow-up care, hearing assessments should be performed before and after VT-treatments.

Study II: In this prospective, longitudinal and group comparison study, we found that the hearing loss in children with CP±L was not more severe than among children with OME but without cleft palate. The air conduction thresholds improved with age in both groups of children. At 12 months of age the thresholds were significantly better in the CP±L-group than in the group without cleft, conceivably due to earlier ventilation tube treatment, which may have a favorable influence on early language development. However, the benefits associated with tube treatment should be weighed against the risks such as otorrhea and perforation of the tympanic membrane and the subsequent risk for hearing impairment.

Ethical permit No.

97-372	2012/2213-31	2013/1989-32		
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Publications/manuscripts 2016, 2017, 2018, 2019

1. Hearing thresholds and ventilation tube treatment in children with unilateral cleft lip and palate (Tengroth et al., 2017)
2. Hearing thresholds in young children with otitis media with effusion with and without cleft palate (manuscript accepted for publication 191010) (Tengroth et al.)



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2015-03-24

2019-04-19

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 and 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 study and the fifth is a clinical study 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: Effects on daily life quality and consequences of disability in deaf-blind persons – an interview study

Paper V: Effects of mental fatigue in patients with SPHI

Ethical permit No.

2012/057	2014/2101-31			
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Publications/manuscripts 2016, 2017, 2018, 2019

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. (2018). Severe-to-profound hearing impairment: demographic data, gender differences and benefits of audiological rehabilitation. *Disability and Rehabilitation*, online 12 June 2018.
3. Turunen-Taheri, S., Skagerstrand, Å., Hellström, S., & Carlsson, P-I. (2017). Patients with severe-to-profound hearing impairment and simultaneous severe vision impairment: a quality-of-life study. *Acta Oto-Laryngologica*, 137:3, 279-285.

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2010-03-11

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

The aim of the project is to find ways to optimize and individualise the treatment of hypopharyngeal cancer and ranula.

In patients with hypofaryngeal cancer we study presence of HPV and expression of p16, in relation to clinical outcome. We also evaluate expression of p 53 and P3K/Akt - PTEN.

In patients with ranula we have performed a randomized, double-blinded, placebo-controlled study to evaluate the effect of sclerotherapy with OK 432.

This study is terminated and to be published 2020.

Ethical permit No.

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Publications/manuscripts 2016, 2017, 2018, 2019

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Predictors of upper airway symptoms in the BAMSE birth cohort"

Background: Rhinitis and rhinosinusitis are inflammatory diseases in the upper airways, often associated with asthma.

Allergic rhinitis (AR) is an IgE-mediated disease. It is one of the most costly diseases to the society. Sensitization is a strong risk factor for later development of AR and, in some cases, asthma. During the last decade, there has been a rapid increase in knowledge about specific allergen proteins (allergen components). This has primarily been used within food allergy to be able to separate life threatening allergies from cross reactions (component resolved diagnostics).

Chronic rhinosinusitis (CRS) is a multifactorial inflammatory disease in the upper airways, with several different endotypes. The prevalence is somewhat uncertain since the diagnosis is difficult to ensure via questionnaires.

To be able to estimate prognosis and decide on treatment for these diseases, there is a need for prognostic biomarkers.

Aim: 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.

Methods: We will use data from the population based birth cohort BAMSE (Barn Allergi Miljö Stockholm Epidemiologi) consisting of 4089 children. The children were included at the age of 2 months and have been followed repeatedly by questionnaires. At 4, 8 and 16 years of age clinical examinations were performed, including blood samples for specific IgE. The follow-up at 24 years of age is finished this year. We have also started a subgroup study of the 24-year-olds with CRS symptoms (study 3 and 4).

Study: 1 "Longitudinal assessment of sensitization to grass pollen allergen molecules in a birth cohort – the importance of Phl p 4 for diagnosis and prediction of grass pollen allergy." (manuscript recently submitted)

Ethical permit No.

93:189	98:175	2007/1634-31	2010/1474-31/3	2016/1380-31/2
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Publications/manuscripts 2016, 2017, 2018, 2019

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