RESEARCH ACTIVITY

at the Division of
Ear, Nose and Throat Diseases

2023

Karolinska Institutet

KAROLINSKA Universitetssjukhuset

CONTENT

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Antti Mäkitie, Affiliated Professor
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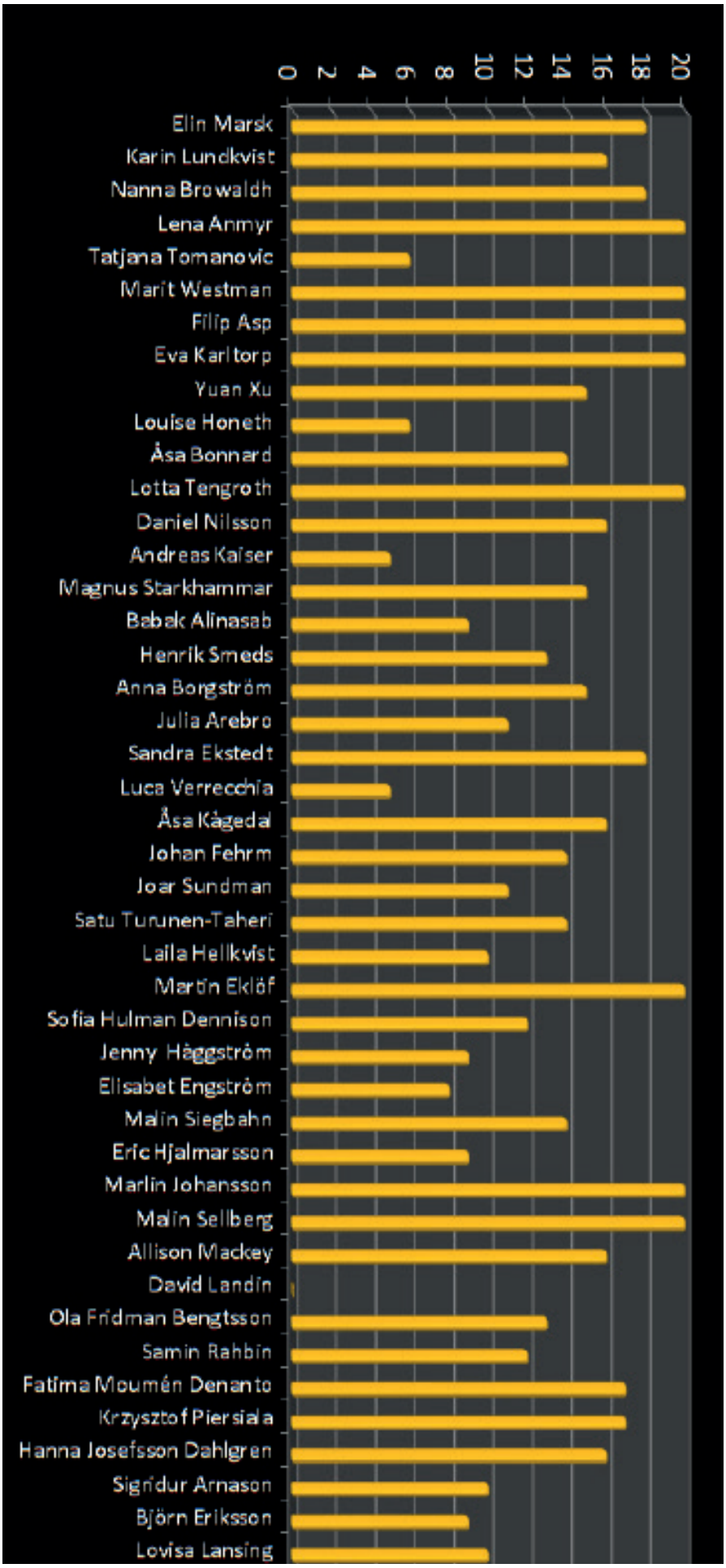
Linda Marklund
Riitta Möller
Inger Uhlén
Mathias von Beckerath

Dissertations / Half time seminars 2023

Date		Name	Title
2023-03-30	Half time	Lovisa Lansing	
2023-03-31	Dissertation	Marlin Johansson	Children with congenital unilateral sensorineural hearing loss: etiology, newborn diagnostics, and hearing aid amplification
2023-05-17	Half time	Evelina Gille	
2023-06-01	Half time	Clara Svenberg Lind	
2023-06-09	Dissertation	Magnus Starkhammar	Airway hyperresponsiveness and viral recognizing toll-like receptors
2023-08-25	Half time	Karin Åberg	
2023-09-29	Half time	Elnaz Sepehri	
2023-11-24	Dissertation	Malin Siegbahn	Growing up with one ear: central auditory structure and function in unilateral ear canal atresia
2023-12-06	Half time	Vilma Lagebro	
2023-12-08	Half time	Malin Dahlby Skoog	

Participation at halftime seminars during 2010-10 to 2023-12-31



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

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

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

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

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Samin Rahbin	

Ethical permit No.

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

Publications 2021, 2022, 2023

1. Functional and Esthetic Outcomes of Either Surgically or Conservatively Treated Anterior Frontal Sinus Wall Fractures: A Long-Term Follow-Up Oscar Solmell MD, Babak Alinasab, M.D., Ph. D. The Journal of Craniofacial Surgery. Accepted.
2. Differences Between Patient and Surgeon Perspectives: A Long-term Follow-up of 180 Patients with Zygomaticomaxillary Complex Fractures Following Either Conservative or Surgical Treatment Samin Rahbin, M.D, Ola Sunnergren, M.D., Ph. D., Ellen Lindgren, M.D., Hatef Darabi, Ph. D., Babak Alinasab, M.D., Ph. D. Craniomaxillofac Trauma Reconstruction reference id CMTR-2023-08-1728-OA
3. The Volume Difference Along the External Surface of the Zygomatic Bone: A Novel Method of Measuring Zygomatic Bone Asymmetry Samin Rahbin, MD, Tina Toufani, MD, Anna-Maria Al-Khabbaz, MD, Julius Lindblom, MD,y Ola Sunnergren, MD, PhD,z Hatef Darabi, PhD,§ Abdul Rashid Qureshi, MD, PhD,jj and Babak Alinasab, MD, PhD The Journal of Craniofacial Surgery Volume 00, Number 00, Month 2021
4. A superficial nasal dermoid cyst excised through a novel horizontal zig-zag incision in a 49-year old man. Jeremy Wales, Babak Alinasab, Ola Fridman-Bengtsson. Acta Oto-Laryngologica Case Reports. Accepted

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Local mapping of middle ear disease

The underlying causes of middle ear disease like chronic otitis including chronic perforations of the tympanic membrane and cholesteatoma/retraction of the tympanic membrane is highly unknown. We aim to search for underlying causes through a patient based pre-clinical and clinical mapping project.

The cause of and presentation of chronic mastoiditis, often caused by atypical mycobacteria, needs to be better evaluated why we review on nearly 20 paediatric patients over 20 years to improve patient outcome.

Oral squamous cell carcinoma (OSCC) remains an under-studied and significant global cancer killer; dismal survival rates have not changed in decades. A better understanding of the molecular basis of OSCC progression and metastasis is needed to provide new treatment/disease management options. We aim to find new strategies in diagnosing and treting this diseaes through stydying fibroblasts in the tumor microenvironment and signalling of miRNA in extracellular vesicles.

WHO have stated COPD to be the third most common cause of death worldwide. In Sweden, up to 700,000 people suffer from COPD generating a yearly coast of 15 billion SEK. Todays methods for diagnosing, treating and monotoring COPD and chronic bronchitis are insufficient. It is well known that smokers with COPD and/or chronic bronchitis suffer from repeated airway infections but the underlying mechanisms are unknown. We aim to investigate IL-26, IL-17 and other markers from Th17 helper cells in the upper airway in a attempt to see if COPD and chronic bronchitis can be monitored through markers in the upper airways.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Elnaz Sepehri

Ethical permit No.

H15-02913	2022-06851-01	2023-02989-01	2018/362-32	2022-06108-01

Publications 2021, 2022, 2023

1. Arebro J, Lee CM, Bennewith KL, Garnis C. Cancer-associated fibroblast heterogeneity in oral cancer. Re-submitted with major revision Jan 2024 IJMS.
2. Khan A et al. Identification and Characterization of Severe Health-related Quality of Life Impairment in Patients With Chronic Rhinosinusitis With Nasal Polyposis using Cluster Analysis. Submitted to Rhinology Nov 2023, under peer-review.
3. Flahat B, Bonnard Å, Arebro J. Bilateral intracochlear hemorrhage: a rare onset of chronic myelogenous leukemia. Submitted to Clinical Case Reports Nov 2023, under peer-review.
4. Arebro J, Towle R, Lee CM, Bennewith KL, Garnis C. Extracellular vesicles promote activation of pro-inflammatory cancer-associated fibroblasts in oral cancer. Front Cell Dev Biol. 2023 Sep 7;11:1240159.
5. Arebro J, Palmgren B. Post-surgical pyoderma gangrenosum and flap necrosis in a head and neck cancer patient following neck dissection. Clin Case Rep. 2020;00:1–5

Filip Asp
PhD

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Effects of impaired spatial hearing and auditory implants

The goals with my projects are to alleviate the negative impact of hearing impairment, to improve hearing through cochlear implants, and increase our understanding of how impaired spatial hearing affects humans, specifically during periods of development.

To this end, we study the effects of congenital and aquired hearing loss and interventions with for example auditory implants on sound localization from as early as 6 months of age, using a rapid and objective technique. Our innovative method measures latency and accuracy of eye-movements towards auditory events, as an index of sound localization ability.

We also study the long-term hearing outcomes of cochlear implantation in individuals who received cochlear implants as young children and now are young adults. We are interested in the interplay between age at implantation, hearing sensitity, technical settings of the cochlear implant system, and intracochlear electrode placement and the combined effect of these variables on functional hearing.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Fatima Moumèn Denanto	Hanna Josefsson

Ethical permit No.

2019-04696	2022-00863-02			

Publications 2021, 2022, 2023

1. Asp, F., Stokroos, R. J., & Agterberg, M. J. H. (2021). Toward Optimal Care for Children With Congenital Unilateral Aural Atresia. Front Neurol, 12, 687070. https://doi.org/10.3389/fneur.2021.687070
2. Siegbahn, M., Engmer Berglin, C., Hultcrantz, M., & Asp, F. (2021). Adults with unilateral congenital ear canal atresia - sound localization ability and recognition of speech in competing speech in unaided condition. Acta Otolaryngol, 141(7), 689-694. https://doi.org/10.1080/00016489.2021.1921843
3. Smeds, H., Wales, J., Karltorp, E., Anderlid, B. M., Henricson, C., Asp, F., Anmyr, L., Lagerstedt-Robinson, K., & Lofkvist, U. (2021). X-linked Malformation Deafness: Neurodevelopmental Symptoms Are Common in Children With IP3 Malformation and Mutation in POU3F4. Ear Hear. https://doi.org/10.1097/AUD.0000000000001073
4. Moumèn-Denanto, F., Tideholm, B., Hellström S., Asp, F., (2022). Differing bilateral benefits for spatial release from masking and sound localization accuracy using bone conduction devices. Ear Hear. 2022 May 19. doi: 10.1097/AUD.0000000000001234
5. Eklöf, M., Asp, F., Berninger, E., (2022). The development of sound localization latency in infants and young children with normal hearing. Trends in hearing. Accepted and in press.
6. Asp, F.; Karltorp, E.; Berninger, E. Development of Sound Localization in Infants and Young Children with Cochlear Implants. J. Clin. Med. 2022, 11(22), 6758; https://doi.org/10.3390/jcm11226758. https://www.mdpi.com/2077-0383/11/22/6758
7. Johansson, M., Karltorp, E., Asp, F., Berninger, E. A Prospective Study of Genetic Variants in Infants with Congenital Unilateral Sensorineural Hearing Loss. J. Clin. Med. 2023, 12, 495. https://doi.org/10.3390/jcm12020495.
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9. Niki Karpeta, Filip Asp, Kaijsa Edholm, Åsa Bonnard, Jeremy Wales, Eva Karltorp, Maoli Duan & Luca Verrecchia (2023) Vestibular function in children with vestibulocochlear nerve aplasia/hypoplasia, Acta Oto-Laryngologica, 143:10, 861-866, DOI: 10.1080/00016489.2023.2285453

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Chronic rhinosinusitis with nasal polyps: from cytokines to biologicals

Chronic rhinosinusitis with nasal polyps (CRSwNP) is predominantly a type 2 inflammatory disease associated with type 2 (T2) cell responses and epithelial barrier, mucociliary, and olfactory dysfunction. The inflammatory cytokines interleukin (IL)-4, IL-13, and IL-5 are key mediators driving and perpetuating type 2 inflammation. The inflammatory responses driven by these cytokines include the recruitment and activation of eosinophils, basophils, mast cells, goblet cells, M2 macrophages, and B cells. The activation of these immune cells results in a range of pathologic effects including immunoglobulin E production, an increase in the number of smooth muscle cells within the nasal mucosa and a reduction in their contractility, increased deposition of fibrinogen, mucus hyperproduction, and local edema. The cytokine-driven structural changes include nasal polyp formation and nasal epithelial tissue remodeling, which perpetuate barrier dysfunction. Type 2 inflammation may also alter the availability or function of olfactory sensory neurons contributing to loss of sense of smell. Targeting these key cytokine pathways has emerged as an effective approach for the treatment of type 2 inflammatory airway diseases, and a number of biologic agents are now available or in development for CRSwNP. In this review, we provide an overview of the inflammatory pathways involved in CRSwNP and describe how targeting key drivers of type 2 inflammation is an effective therapeutic option for patients.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2021, 2022, 2023

1. Jonstam K, Alsharif S, Bogaert S, Suchonos N, Holtappels G, Jae-Hyun Park J, Bachert C. Extent of inflammation in severe nasal polyposis and effect of sinus surgery on inflammation. Allergy 2021;76(3):933-936
2. Bachert C, Han JK, Wagenmann M, Hosemann W, Lee SE, Backer V, Mullol J, Gevaert P, Klimek L, Prokopakis E, Knill A, Cavaliere C, Hopkins C, Hellings P. EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: Definitions and management. J Allergy Clin Immunol. 2021 Jan;147(1):29-36.
3. Laidlaw TM, Bachert C, Amin N, Desrosiers M, Hellings PW, Mullol J, Maspero JF, Gevaert P, Zhang M, Mao X, Khan AH, Kamat S, Patel N, Graham NMH, Ruddy M, Staudinger H, Mannent LP. Dupilumab improves upper- and lower-airway disease control in chronic rhinosinusitis with nasal polyps and asthma. Ann Allergy Asthma Immunol. 2021 Jan 16:S1081-1206(21)00020-X.
4. Peters AT, Han JK, Hellings P, Heffler E, Gevaert P, Bachert C, Xu Y, Chuang CC, Neupane B, Msihid J, Mannent LP, Guyot P, Kamat S. Indirect Treatment Comparison of Biologics in Chronic Rhinosinusitis with Nasal Polyps. J Allergy Clin Immunol Pract. 2021 Feb 3:S2213-2198(21)00159-8
5. Han JK, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE, Smith SG, Martin N, Mayer B, Yancey SW, Sousa AR, Chan R, Hopkins C; SYNAPSE study investigators. Mepo-lizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021 Oct;9(10):1141-1153.
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11. Delemarre T, Bochner BS, Simon HU, Bachert C. Rethinking Neutrophils and Eosinophils in Chronic Rhinosinusitis. JACI 2021 Apr 21:S91-6749(21)00545-5
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15. Duan S, Zhao L, Zhang Y, Zhang N, Zheng M, Wang Q, Zhang X, Wang X, Ying S, Bachert C, Zhang L, Lan F. Tropomyosin in mugwort cross-reacts to house dust mite, eliciting non-Th2 response in allergic rhinitis patients sensitized to house dust mite. Clin Mol Allergy. 2021 Apr 2;19(1):2.
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33. Bousquet J, Agache I, Blain H, Jutel M, Ventura MT, Worm M, Del Giacco S, Benetos A, Bilo BM, Czarlewski W, Abdul Latiff AH, Al-Ahmad M, Angier E, Annesi-Maesano I, Atanaskovic-Markovic M, Bachert C, ... Akdis CA, Zuberbier T, Klimek L. Management of anaphylaxis due to COVID-19 vaccines in the elderly. Allergy. 2021 Oct;76(10):2952-2964.
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Head & Neck Cancer

Ongoing projects:

- Prospective study: Use of anchor in extirpation of non-palpable lymph nodes and cysts in the neck.
- Marginal vs. segmental resection of the mandible in gingival cancer patients- comparison study including patients from Karolinska and Örebro?
- The risk for regional metastasis in patients with gingival cancer in relation to tumor size, localization (maxilla/mandible), T-class and histopathology.
- Sentinel-node assisted neck dissection in N+ oral cancer patients. Prevalence of occult metastases.
- Salivary gland tumors- the use of sentinel node technique to predict lymphatic drainage (colaboration with Caroline Gahm)
- Prevalence of regional recurrence/disease free survival in oral cancer N+ patients after SN-assisted neck dissection: 2 years follow up.
- Distinguishing branchial cleft cysts from malignancy with fine-needle aspiration cytology and HPV-DNA analysis in aspirate
- Prevalence of pharyngocutaneous fistulas after total laryngectomy and associated risk factors.

Future projects:

- Clinical predicting biomarkers in oropharyngeal cancer patients whith goal to decrease the side effect profile.
- HPV-DNA and p16 in fine-needle aspiration cytology in patients with unknown primary tumor in head- and neck.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Evelina Jörtsö

Ethical permit No.

2020-00448	2021-00697	2021-01265		

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Digital twins for predictive, preventive and personalised treatment

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

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Martin Smelik	
Samuel Schäfer	
Yelin Zhao	

Ethical permit No.

Publications 2021, 2022, 2023

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

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

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

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

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

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2012/494-31/1; 2018/1500-31 (Approved addendum, 2020-06-10)	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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Cholesteatoma in Sweden and Results from the Swedish Quality Registry of Ear Surgery, SwedEar

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. Unfortunately, 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 is used to map cholesteatoma surgery in Sweden in regard to incidence and prevalence, risks with surgery, factors increasing risk for disease and recurrency of disease. In a study from 2023 we shoved an increased risk for Cholesteatoma in individuals with a first degree relative surgically treated for the disease. This sub study will be followed by a genetic study regarding families in Stockholm County with multiple family members with cholesteatoma. A longside with this, a regional follow-up study is ongoing in regard to hearing, balance and quality of life after cholestatoma surgery.

2. The Swedish Quality Registry of Ear Surgery, SwedEar, is a nationwide registry collecting pre- and postoperative data in regard to ear surgery for all types of chronic otitis including cholesteatoma. Several papers based on this registry has been published showing the outcome of Myringoplasty and the risk for complications regarding tinnitus and taste disturbances related to surgery. New studies regarding the hearing results, patient satisfaction and complications after Ossiculoplasty are ongoing.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Agnes Modée	Sara Olaison, Örebro Universitetssjukhus Kvalitetsregisterkopplat projekt om ossikuloplastik
Mikolaj Stachurski (under review)	

Ethical permit No.

2014/2203-31/4	2019-05190	2020-00245	2021-05727-02	2020-05935

Publications 2021, 2022, 2023

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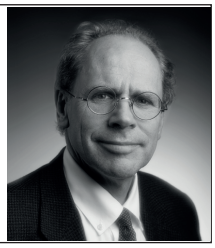

Immunological Insights into Neutrophils, T-cells, and B-cells: Understanding Their Impact on Allergic Airway Inflammation and Head and Neck Squamous Cell Carcinoma

Our research group is currently investigating the roles of neutrophils, T-cells, and B-cells in the development and progression of both allergic airway inflammation and head and neck squamous cell carcinoma. This exploration is grounded in the growing understanding within allergy immunotherapy and cancer immunology that the mechanisms of tolerance development, involving these immune cells, are pivotal in both disorders. Our work seeks to illuminate the dysregulation and dysfunction within these pathways, which contribute substantially to the disease burden in both allergies and cancer.

At the heart of our study is the concept that these diseases represent two extremes within a spectrum of immune tolerance. In allergic reactions, there is an overactive immune response leading to continuous, localized inflammation. In contrast, cancerous cells often evade and suppress the immune system, allowing for unchecked growth and spread. Our research aims to understand how inducing permanent local tolerance in allergies and disrupting this tolerance in cancer can be therapeutically beneficial. This approach predominantly involves modulating various T-cell functions.

While the role of B-cells is well-established in allergy contexts, their function in cancer remains less explored, which our research aims to address. Additionally, we are focusing on the under-researched potential role of neutrophils in allergy, juxtaposed against their recognized significance in cancer immunology, where their exact function is yet to be fully understood.

Our overarching goal is to provide comprehensive insights into the immunological events occurring in lymph nodes during the development and progression of allergic airway inflammation and head and neck squamous cell carcinoma, with a particular focus on the interplay of neutrophils, T-cells, and B-cells."

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Maryam Jafari, Aeneas Kolev, Vilma Lagebro	Martin Smelik
Eirini Paziou, Krzysztof Piersiala, Carl Skröder	Yelin Zhao

Ethical permit No.

2021-03633	2019-03518	2020-02579	2021-05597	2021-00325	

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Neutrophils in airway inflammation and head-and-neck cancers

Neutrophils are key effector cells in host defense against pathogenic bacteria, which they eliminate via phagocytosis, formation of extracellular traps (NETs), and release of antimicrobial proteins. Nevertheless, accumulation and hyperactivation of neutrophils at sites of inflammation can contribute to airway diseases such as asthma, chronic rhinosinusitis with nasal polyps, Covid-19, and chronic obstructive pulmonary disease. Moreover, an expanding body of literature suggests that neutrophils have immunesuppressive roles in the tumor microenvironment.

Combining clinical and pre-clinical studies, our group aims to define the contribution of neutrophils to different inflammatory conditions of the airways, as well as to head-and-neck cancers. By elucidating the roles of neutrophils in these conditions, we hope to provide new potential targets for therapy.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Maryam Jafari

Ethical permit No.

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Disorders affecting hearing and balance in children - the importance of early diagnosis and early intervention

Early diagnosis and intervention of HI and vestibularis dysfunction/disorders (VD) in infants and young children is a still hot topic in audiology and neurotology. There are needs for an increasing knowledge on how to optimize the care for as well as to improve development of the children. The majority of HI and VD infants still do not get a specific genetic diagnosis of their illness despite 50% being genetic. NGS methods will dramatically improve the possibilities to identify different genetic causes of HI and VD. Furthermore, despite quite high prevalence of VD in HI children this has not been paid too high attention. We will investigate the HI/VD children using physiological and genetic methods to study etiology, and further develop the means for the diagnosis for clinical routine in the near future. We will develop the screening program for HI/VD children.

Supervision of PhD-students:

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

Ethical permit No.

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

The study is aimed to evaluate the life span, prevalence, occurrence of known sequelae, medical and surgical treatment, and possible regional differences of HHT patients in Sweden. Data is collected from Registerservice at The National Board of Health and Welfare.
In order to evaluate the life span of the group, data from the years 2001-2018 was obtained from Registerservice. Data was also obtained from Statistics Sweden in order to compare the life span of the group to that of the rest of the Swedish population.
This is the first study of HHT patients in Sweden. International studies have shown that the life span of the group usually is decreased, but that a uniform strategy might increase the life span of HHT patientsto the same level as the rest of the national population.
Data about the other questions are collected from the inpatient as well as the outpatient care throughout the years of 2007-2018.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2020-06950				

Publications 2021, ,2022, 2023

1.

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Sound localization latency in bilateral cochlear implant and other interventions

The first patients with early cochlear implant intervention have now become adolescent. We assess and analyze the outcomes in terms of hearing, language, and balance in a prospective study. Cochlear implant programming and mastoid morphology will be correlated to speech perception and interaural abilities. Furthermore, novel methods of the diagnostics of balance disorders is developed using inertial motion sensors and Artificial Intelligence.
We are also analysing the programming difficulties in X-linked cochlear implant patients

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2022-03381-01	2021-04345			

Publications 2021, ,2022, 2023

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Neutrophils in airway inflammation and head and neck cancer

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 these four subsets.

We have in the past characterised neutrophil subsets in blood before and after an inhaled allergen provocation. The fraction of CD16high/CD62Lhigh neutrophils decreased and the CD16high/CD62Ldim neutrophils increased as a result of the challenge. We have also seen functinal canges in the airways after co-cultures between segmets of airways and the subset CD16high/CD62Ldim. Theses neutrophil subsets seems to have different roles during inflammation and we are now foucusing on their role during head and necka cancer and there presents in lymph nodes.

These new findings may lead to a better understanding of the role of neutrophil subset in inflammation, and potentially to new treatments

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2021, 2022, 2023

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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 succesfull. The use of 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. Studies conducted in our group assess the benefits of the sentinel node techniques for different head and neck cancer subsites and different clinical cases and analyze the imunological features and of the sentinel nodes evaluating the predictiveness of different markers.

The overall aim of the studies is to assess tumour biology and interaction with the immune system, to asssess tumour spread-patterns for different tumour types and to individualize their treatment aiming to improve treatment effects and minimize their related complications .

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

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

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

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

We will identify stem cells and proliferative zones in normal human tympanic membranes as well as in tympanic membranes that has been mechanically and chemically injured. The goal is to better understand the healing mechanism of the tympanic membrane.

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

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

The main purpose of this project is to evaluate the effect on the brain in individuals with unilateral canal atresia, which is when a child is born without a developed hearing canal causing a severe conductive hearing loss. Children with hearing habilitation and untreated adults are 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, questionnaires, diffusion MRI and resting state functional MRI. The heraing outcome in children with unilateral canal atresia treated with active middle ear implants and active transcutanous bone conduction devices will be evaluated regarded to directional hearing and spech in competing speech as well as assesment of quality of life through questionnaires.

Supervision of PhD-students:

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Ethical permit No.

2021-02984	2018/364	2017/2011-31	2012/1661-31/3	N191/14	N113/15

Publications 2021, 2022, 2023

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5. Bonnard Å, Engmér Berglin C, Wincent J, Eriksson PO, Westman E, Feychting M, Mogensen H. The Risk of Cholesteatoma in Individuals With First-degree Relatives Surgically Treated for the Disease. JAMA Otolaryngol Head Neck Surg. 2023 May 1;149(5):390-396. doi: 10.1001/jamaoto.2023.0048. PMID: 36929420; PMCID: PMC10020932.
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Hearing in the elderly and cognition

Hearing in the elderly and cognition, noise and, diet. Epidemiological studies where the influence of various factors on hearing function is assessed in patients, and in population databases such as H70.

Hearing preservation in subjects with vestibular schwannoma

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

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Jenny Häggström	

Ethical permit No.

Publications 2021, 2022, 2023

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Obstructive Sleep Apnea in children and adults, a surgical therapeutic perspective. Subglottic stenosis in adults, measurements and treatment efficiency.

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

Further the Swedish National Tonsill Surgery Registra is another field of research were we evaluate incidence, morbitidy and symtom relief etc using the registra as source of epidemiology research and possibility to evaluate rare concequenses etc.

Within the field of subglottic stenosis we have a project evaluating intralesional steroid injections, as well as retrospecitve and prospective evaluations of other treatment forms, for the adult population with subglottic stenosis. We are investigating the diagnosic method of a handheld peak inspiratory flow meter (PIF-meter) gathering a healthy population besides our subglottic stenosis patients

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2021-02110	2015/755-31/2	2013/2274-32	2021-00716	2014/1000-31/1

Publications 2021, 2022, 2023

1. A validation study of data in the National Tonsil Surgery Register in Sweden: High agreement with medical records ensures that data can be used to monitor clinical practices and outcomes Filip Lundström, Erik Odhagen, Fredrik Alm, Claes Hemlin, Pia Nerfeldt, Ola Sunnergren. BMC Med Res Methodol. 2022 Jan 7;22(1):3. doi: 10.1186/s12874-021-01467-8
2. Adenotonsillotomy versus adenotonsillectomy in pediatric obstructive sleep apnea: a 5-year RCT Isabella Sjölander, Anna Borgström, Pia Nerfeldt, Danielle Friberg. Sleep Med X. 2022 Sep 8;4:100055. doi:0.1016/j.sleepx.2022.100055.
3. Tonsillectomy vs Modified Uvulopalatopharyngoplasty in Patients with Tonsillar Hypertrophy and Obstructive Sleep Apnea - The TEAMUP Randomized Controlled Trial. Joar Sundman, MD, PhD1; Pia Nerfeldt, MD, PhD1; Johan Fehrm, MD, PhD1; Johan Bring, PhD2 Nanna Browaldh, MD, PhD1; Danielle Friberg, MD, PhD3 JAMA ORL 2022 Dec 1;148(12):1173-1181. doi: 10.1001/jamaoto.2022.3432.
4. Correlations between objective and subjective outcomes after adenotonsillar surgery in children with OSA.Sjölander I, Borgström A, Nerfeldt P, Fehrm J, Friberg D. Laryngoscope Investigative Otolaryngology 2022 Nov 4;7(6):2161-2170. doi.org/10.1002/lio2.967
5. Long-term complications after tonsil surgery – an analysis of 54 462 patients from the Swedish Quality Register for Tonsil Surgery. Erik Odhagen, Fredrik Alm, Sara Axelsson, Claes Hemlin, Pia Nerfeldt, Joacim Stalfors, Ola Sunnergren. Front Surg 2023 Dec 12:10:1304471. doi: 10.3389/fsurg.2023.1304471.
6. Pain management after tonsil surgery in children and adults - a national survey related to pain outcome measures from the Swedish Quality Register for Tonsil Surgery Roskvist M, Alm F, Nerfeldt P, Ericsson E. Accepted for publication in PLOS ONE (PONE-D-23-35389R1)

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

I) 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

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

III) Studies on laryngotracheal airway diseases.
- Long-term outcome of reconstrutive airway surgery in pediatric and adult patients
- Studies on surgical outcome after supraglottoplasty for laryngomalacia

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Björn Eriksson	

Ethical permit No.

2019-05211	2008/114-31	2012/1663-32	2018/1972-31	2021-06074-02

Publications 2021, 2022, 2023

1. Medin G, Wendt M, Ekborn A, Andersson A, Gahm C. Supraglottoplasty for severe laryngomalacia can be effective and safe also in children with high-risk comorbidities – experience from a tertiary center. International Journal of Pediatric Otothinolaryngology 2023 171; 111632- PMID: 37352590
2. Hammarstedt-Nordenvall L, Bark R, Elliot A, Von Beckerath M, Gahm C. Distribution of sentinel nodes from parotid tumors-a feasibility study – Cancer Med 2023 Sept 30. PMID: 37776164
3. Holmqvist A, Wendt M, Papatziamos G, Svensson J, Wester T, Mesas-Burgos C, Gahm C. Endoscopic chemocauterization with trichloroacetic acid for congenital or recurrent tracheoesophageal fistula in children with esophageal atresia – experience from a tertiary center. J Pediatric Surgery, 2023 oct 28:S0022-3468(23)00659-0 PMID: 37978000
4. Gahm C, Näsman A, Papatziamos G. Segmental congenital deficiency of tracheal rings in cervical trachea managed by tracheal resection: A case report and literature review. Int J Pediatr Otorhinolaryngol. 2021 Sep;148:110844.
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Early prediction of cancers

Cancer is an aggressive disease that is usually diagnosed at a very late stage. Patients respond differently to disease management strategies, some have poor survival and some have better overall survival. Cancer management of patients is a heavy burden on the healthcare budget and a burden on society. Early detection of cancer can help save the patient's life, optimize healthcare resource allocation and reduce the burden on society. In this project, molecular data will be integrated with clinical data to determine biomarkers beneficial for early detection of cancer. Cancers included in this project are solid tumors, hematological tumors and other tumors.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Yelin Zhao
	Martin Smelik

Ethical permit No.

2018/1032-31	2011/44-31/1	2022-03398-01		

Publications 2021, 2022, 2023

1. Mansour Aly D, Dwivedi OP, Prasad RB, Käräjämäki A, Hjort R, Thangam M, Åkerlund M, Mahajan A, Udler MS, Florez JC, McCarthy MI; Regeneron Genetics Center; Brosnan J, Melander O, Carlsson S, Hansson O, Tuomi T, Groop L, Ahlqvist E. Genome-wide association analyses highlight etiological differences underlying newly defined subtypes of diabetes. Nat Genet. 2021 Nov;53(11):1534-1542. doi:10.1038/s41588-021-00948-2. Epub 2021 Nov 4. PMID: 34737425.
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5. Simonsen JR, Käräjämäki A, Antikainen AA, Toppila I, Ahlqvist E, Prasad R, Mansour-Aly D, Harjutsalo V, Järvinen A, Tuomi T, Groop L, Forsblom C, Groop PH, Sandholm N, Lehto M. Genetic factors affect the susceptibility to bacterial infections in diabetes. Sci Rep. 2021 May 4;11(1):9464. doi: 10.1038/s41598-021-88273-w. PMID: 33947878; PMCID: PMC8096814.
6. Slieker RC, Donnelly LA, Fitipaldi H, Bouland GA, Giordano GN, Åkerlund M, Gerl MJ, Ahlqvist E, Ali A, Dragan I, Elders P, Festa A, Hansen MK, van der Heijden AA, Mansour Aly D, Kim M, Kuznetsov D, Mehl F, Klose C, Simons K, Pavo I, Pullen TJ, Suvitaival T, Wretlind A, Rossing P, Lyssenko V, Legido Quigley C, Groop L, Thorens B, Franks PW, Ibberson M, Rutter GA, Beulens JWJ, 't Hart LM, Pearson ER. Distinct Molecular Signatures of Clinical Clusters in People With Type 2 Diabetes: An IMI-RHAPSODY Study. Diabetes. 2021 Nov;70(11):2683-2693. doi: 10.2337/db20-1281. Epub 2021 Aug 10. PMID: 34376475; PMCID: PMC8564413.
7. Slieker RC, Donnelly LA, Fitipaldi H, Bouland GA, Giordano GN, Åkerlund M, Gerl MJ, Ahlqvist E, Ali A, Dragan I, Festa A, Hansen MK, Mansour Aly D, Kim M, Kuznetsov D, Mehl F, Klose C, Simons K, Pavo I, Pullen TJ, Suvitaival T, Wretlind A, Rossing P, Lyssenko V, Legido-Quigley C, Groop L, Thorens B, Franks PW, Ibberson M, Rutter GA, Beulens JWJ, 't Hart LM, Pearson ER. Replication and cross-validation of type 2 diabetes subtypes based on clinical variables: an IMI-RHAPSODY study. Diabetologia. 2021 Sep;64(9):1982-1989. doi: 10.1007/s00125-021-05490-8. Epub 2021 Jun 10. PMID: 34110439; PMCID: PMC8382625.
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10. Strausz S, Ruotsalainen S, Ollila HM, Karjalainen J, Kiiskinen T, Reeve M, Kurki M, Mars N, Havulinna AS, Luonsi E, Mansour Aly D, Ahlqvist E, Teder-Laving M, Palta P, Groop L, Mägi R, Mäkitie A, Salomaa V, Bachour A, Tuomi T; FinnGen; Palotie A, Palotie T, Ripatti S. Genetic analysis of obstructive sleep apnoea discovers a strong association with cardiometabolic health. Eur Respir J. 2021 May 6;57(5):2003091. doi: 10.1183/13993003.03091-2020. PMID: 33243845.
11. Edstorp J, Ahlqvist E, Alfredsson L, Mansour Aly D, Grill V, Rasouli B, Sørgjerd EP, Tuomi T, Åsvold BO, Carlsson S. Incidence of LADA and Type 2 Diabetes in Relation to Tobacco Use and Genetic Susceptibility to Type 2 Diabetes and Related Traits: Findings From a Swedish Case-Control Study and the Norwegian HUNT Study. Diabetes Care. 2023 May 1;46(5):1028-1036. doi: 10.2337/dc22-2284. PMID: 36867461; PMCID: PMC10154663.
12. Bennet L, Nilsson C, Mansour-Aly D, Christensson A, Groop L, Ahlqvist E. Adult-onset diabetes in Middle Eastern immigrants to Sweden: Novel subgroups and diabetic complications-The All New Diabetes in Scania cohort diabetic complications and ethnicity. Diabetes Metab Res Rev. 2021 Sep;37(6):e3419. doi: 10.1002/dmrr.3419. Epub 2020 Nov 6. PMID: 33119194; PMCID: PMC8518927.

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Effects of ageing on treatment with cochlear implants.

Study on effects of cochlear implants in adults with special respect to vestibular functions, hearing outcomes and cognitive abilities in the elderly. Vestibular evaluation before and after cochlear implantation is completed. Analysis of the are currently beeing compiled to a paper ready for publication during late spring 2024. Studies on the outcomes of treatment (quality of life, hearing outcomes) with cochlear implants related to age at surgery, cognitive abilities according to standardized physiological and cognitive tests are on the planning stage, with possible start during autumn 2024. There are also plans for studies on the effect of auditory training in elderly CI-users, and also inventory of tinnitus in elderly patients with hard of hearing. The study is performed in cooperation with staff and researchers at Karolinska Ear and Hearing and the department for Physiotherapy.

Mastoditis in Stockholm 2003-2019

A retrospective study on acute mastoiditis in Region Stockholm before and after the introduction of conjugate pneumococcal vaccine for infants is recently beeing completed. The study covers all cases of mastoiditis in children at Karolinska University Hospital 2003-2019. The study is a cooperation between the ENT-department, Astrid Lindgren Children Hospital and the Swedish Public Health Agency.

Atypical mastoiditis in children

A study on atypicle, chronic, mastoditis in children at Karolinska. Supervisory function in collaboration with main researcher dr Julia Arebro and junior dr Lara Kakabas. The study is retrospective. Main focuses are clinical appearance, outcomes and microbiological findings.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2018/1032-31	2011/44-31/1	2023-02989-01		

Publications 2021, 2022, 2023

1. Alfven T, Bennet R, Granath A, Dennison SH, Eriksson M. The pneumococcal conjugate vaccine had a sustained effect on Swedish children 8 years after its introduction. ACTA PAEDIATRICA 2024 ;
2. Hultman Dennison S, Granath A, Holmstrom M, Stjarne P, Hertting O. Complications to acute bacterial rhinosinusitis in children - a prospective study; bacterial cultures, virus detection, allergy sensitization and immunoglobulins. Rhinology 2023 61;5 412-420
3. Westerberg J, Granath A, Drakskog C, Tideholm E, Kumlien Georén S, Weitzberg E, Cardell LO. Nitric Oxide Is Locally Produced in the Human Middle Ear and Is Reduced by Acquired Cholesteatoma. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology 2022 43;2 e198-e204
4. Hultman Dennison S, Hertting O, Bennet R, Eriksson M, Holmström M, Schollin Ask L, Lindstrand A, Dimitriou P, Stjärne P, Granath A. A Swedish population-based study of complications due to acute rhinosinusitis in children 5-18 years old. International journal of pediatric otorhinolaryngology 2021 150; 110866-

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Clinical studies in Head and Neck Cancer

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Evelina Gille	Björn Eriksson
	Rasmus Blomkvist
	Clara Svenberg Lind
	Caroline de Flon
	Anahita Mobarga

Ethical permit No.

Publications 2021, 2022, 2023

1. Endoscopic management of sinonasal tumours in the Nordic university hospitals: a survey. Korsström C, Lilja M, Hammarstedt-Nordenvall L, Mäkitie A, Haapaniemi A. Eur Arch Otorhinolaryngol 2024:281(2):785-794.
2. Distribution of sentinel nodes from parotid tumors - A feasibility study. Hammarstedt-Nordenvall L, Bark R, Elliot A, Von Beckerath M, Gahm C. 2023
3. Diagnosis of locally recurrent head and neck squamous cell carcinoma in the Nordic HNC centers and feasibility of the Odense-Birmingham definition. Rohde M, Eriksen JG, Pareek M, Bratland Å, Mäkitie A, Hammarstedt-Nordenvall L, Wessel I, Lybeck JS, Mäenpää H, Gebre-Medhin M, Godballe C. Acta Oncol 2023:62(9):1102-1105
4. Radiotherapy-Dose Escalated for Large Volume Primary Tumors-And Cetuximab with or without Induction Chemotherapy for HPV Associated Squamous Cell Carcinoma of the Head and Neck-A Randomized Phase II Trial. Mercke C, Wickart-Johansson G, Sjödin H, Farrajota Neves da Silva P, Alexandersson von Döbeln G, Margolin G, Jonmarker Jaraj S, Carstens H, Berglund A, Lax I, Hellström M, Hammarstedt-Nordenvall L, Friesland S. Cancers (Basel) 2023:15(9)
5. Treatment and outcome among patients with laryngeal squamous cell carcinoma in Stockholm-A population-based study. Blomkvist R, Marklund L, Hammarstedt-Nordenvall L, Gottlieb-Vedi E, Mäkitie A, Palmgren B. Laryngoscope Investig Otolaryngol 2023:8(2):441-449.
6. Occupational risk variation of nasopharyngeal cancer in the Nordic countries. Carpén T, Gille E, Hammarstedt-Nordenvall L, Hansen J, Heikkinen S, Lynge E, Selander J, Mehlum IS, Torfadottir JE, Mäkitie A, Pukkala E. BMC Cancer 2022:22(1):1130.
7. Post-treatment neck dissection of tonsillar and base of tongue squamous cell carcinoma in the era of PET-CT, HPV, and p16. Landin D, Näsman A, Jonmarker Jaraj S, Hammarstedt Nordenvall L, Munck-Wikland E, Dalianis T, Marklund L. Viruses 2022:14(8):1693.
8. Base of tongue squamous cell carcinomas, outcome depending on treatment strategy and p16 status. A population-based study from the Swedish Head and Neck Cancer Register. Högmo A, Holmberg E, Haugen Cange H, Reizenstein J, Wennerberg J, Beran M, Söderkvist K, Hammerlid E, Sjödin H, Farnebo L, Sandström K, Hammarstedt-Nordenvall L, Zborayova K, Brun E. Acta Oncol 2022:61(4):433-440.
9. Complications of Gastrostomy Tubes in Patients With Head and Neck Cancer. Vujasinovic V, Marsk E, Tsolakis A, Nordberg, Lindblad M, Lindqvist C, Hammarstedt Nordenvall L, Bark R, Elbe P, Elbe P. Laryngoscope 2022:132(9):1778-1784.
10. Prevalence of cystic metastases in a consecutive cohort of surgically removed branchial cleft cysts. Hammarstedt Nordenvall L, Jörtsö E, von Beckerath M, Tani E, Nordemar S, Bark R. Acta Otolaryngol 2022:142(1):100-105.

11. Results from a prospective, randomised study on (accelerated) preoperative versus (conventional) postoperative radiotherapy in treatment of patients with resectable squamous cell carcinoma of the oral cavity - The ARTSCAN 2 study. Wennerberg J, Gebre-Medhin M, Nilsson P, Brun E, Kjellén E, Carlwig K, Reizenstein J, Kristiansson S, Söderkvist K, Wahlgren M, Zackrisson B;
12. ARTSCAN study group. Radiother Oncol 2022:166:26-32.
13. Long-Term Survival and Recurrence in Oropharyngeal Squamous Cell Carcinoma in Relation to Subsites, HPV, and p16-Status. Friesland S, Zupancic M, Friesland S, Landin D, Munck-Wikland E, Dalianis T, Näsman A, Marklund L. Cancers (Basel) 2021:13(11)
14. Tonsillar Microbiota: a Cross-Sectional Study of Patients with Chronic Tonsillitis or Tonsillar Hypertrophy. Wu S, Hammarstedt-Nordenvall L, Jangard M, Cheng L, Radu S, Angelidou P, Zha Y, Hamsten M, Engstrand L, Du J, Ternhag A. mSystems 2021:6(2)
15. Enteral tube feeding of head and neck cancer patients undergoing definitive chemoradiotherapy in the Nordic Countries: Survey of the Scandinavian Society for Head and Neck Oncology. Illmarinen T, Bäck L, Hammarstedt-Nordenvall L, Mäkitie A. Eur Arch Otorhinolaryngol 2021:278(9):3489-3496.
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The FACE study - a randomized double-blinded placebo-controlled multicenter trial for evaluation of cortisone treatment in children with acute facial nerve palsy

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

The overall purpose is to assess the utility of cortisone treatment to children with acute facial nerve palsy in a well-designed RCT.

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

The primary outcome is defined as total recovery of the facial nerve palsy, measured with the House-Brackmann scale (grade 1) at 12-months follow-up.

Clincal relevance: If the total recovery rate is significantly improved in the prednisolone group as compared to the placebo group, prednisolone treatment will be introduced in clinical practice for children with acute facial nerve palsy in order to reduce the risk of persistent impairement and disability. Guidelines will be pubished for evidens-based treatment of children with acute facial nerve palsy.

The study protocol is published in 2020 and at ClincialTrials.gov NCT03781700
253 patients are included so far, at 16 swedish centers and the inclusion continues until 2025.
2 PhD students in the project have done half-time seminar at CLINTEC.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Sofia Karlsson	
Sigurdur Arnason	

Ethical permit No.

2017/554	2019-01546	2021-01926	2023-02323-02	

Publications 2021, 2022, 2023

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Allergy vaccination- novel strategies and biomarkers for outcome

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

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

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

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Maryam Jafari
	Eirini Paziou

Ethical permit No.

2009/714	2021-03633			

Publications 2021, 2022, 2023

1. High dose pollen intralymphatic immunotherapy: Two RDBPC trials question the benefit of dose increase. Hellkvist L, Hjalmarsson E, Weinfeld D, Dahl Å, Karlsson A, Lundkvist K, Westman M, Kumlien Georén S, Winqvist O, Westin U, Cardell LO. Allergy. 2021; 00:1-14
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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 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 further support the development of Scientific Center for Advanced Pediatric Audiology (SCAPA). The hearing and vestibular research in children at Karolinska has an enormous potential to become a national and international frontline research area.
3. To study plasminogen (plg), a preinflammatory protein, and its involvement in healing wounds like chronic tympanic membrane perforation. The focus is now on the production of recombinant plg for use in humans. Within one year a large clinical trial on healing of diabetic foot ulcers will be started. The project is directed from Umeå University.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Niki Karpeta
	Fatima Moumén Denanto
	Susanne Gripenberg

Ethical permit No.

2012/057	2014/2101-31			

Publications 2021, 2022, 2023

1. Tong B, Niu K, Ku W, Xie W, Dai Q, Hellström S, Duan M. Comparison of Therapeutic Results with/without Additional Hyperbaric Oxygen Therapy in Idiopathic Sudden Sensorineural Hearing Loss: A Randomized Prospective Study. Audiol Neurootol. 2021;26(1):11-16.
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Evaluation of the treatment of subglottic stenosis. Quality follow-up and evaluation of the result of treatment inclusive Establishment of normalmaterial for oral Peak Inspiratory Flow measurements used in the study.

Patients with subglottical stenosis and proximal tracheal stenosis undergoing surgery or local treatment with cortison between 1998 and today and onwards will be monitored regarding improvement in breathing, PIF, PEF, health inquiry, dyspnea index, voice handicap index and other clinical observations as years between surgery (if reoperated) and possible explanations to the upcome of their stenosis (as Wegener/GPA och earlier intubation). In a separate study we will obtain normal values for the oral Peak Inspiratory Flow apparatus we use in this clinic

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2021-02110				

Publications 2021, 2022, 2023

1. Management and outcomes in a consecutive series of patients with aero-digestive fistula at a tertiary gastro-esophageal surgery center, Fahad Murad 1, Fredrik Klevebro 1, Gert Henriksson 2, Ioannis Rouvelas 1, Mats Lindblad 1, Magnus Nilsson 1, Dis Esophagus. 2023 Dec 14:doad068. doi: 10.1093/dote/doad068.

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Reconstruction of vocal fold scarring with mesenchymal stem cells

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

From 2012 an ongoin study in cooperation with Professor Katarina LeBlanc at KI is including and treating patients with severe hoaseness 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. Sixteen patients were treated. Preliminary results at 1 year follow up for the patients shown clearly improved vocal fold function without side effedts.

At present a clinical trial approved by EPM and Swedish Product Agency (Läkemedelsverket) is ongoing, We have treated 8 patients with severe dysphonia and voca fold scarring which are treated with an autologous MSC product injected into the operated scarred vocal folds.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Emma Malmström	Erik Bergström Börlin

Ethical permit No.

2019-06160	2020-04565	2021-00933	2021-03904	

Publications 2021, 2022, 2023

1. Björck G., Hertegård S.,Ekelund J., Marsk E. Voice rest after vocal fold polyp surgery: a study of 588 patients in the Swedish National Register for Phonosurgery. Accepted for publication in Laryngoscope Investigative Otolaryngology. 2021

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Enhanced PD-L1 Expression on Conventional Dendritic Cells in Tumor-Draining Lymph Nodes Associates with Metastasis Risk and Poor Prognosis in Oral Squamous Cell Carcinomar

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common cancer globally. This cancer has a poor prognosis, especially in patients with nodal involvement, the most important factor adversely affects the treatment and outcome. The treatment for HNSCC has evolved considerably over the past decades, with new surgical techniques, radiation oncology, and chemotherapeutics. However, a new era was the introduction of immune checkpoint inhibitors (ICI). ICIs targeting programmed cell death protein 1 (PD1), and its ligand (PDL-1) has substantially impacted survival and quality of life. However, only 20% experience a positive treatment response despite these improvements.

Dysfunctional CD8+ T-cells are believed to be fundamental for cancer immune escape. In this process, PD-L1 is integral by changing the differentiation of CD8+ T cells into a dysfunctional state. PDL1 expression on tumor cells and tumor-infiltrating leukocytes has been shown to correlate with clinical response. Yet, some patients that are PDL-1 negative in the tumor still benefit from treatment, and vice versa, implying that the mechanism is more complex than blocking PD-1 activation on CD8+ T-cells in the tumor. Dendritic cells are central for initiating and maintaining a T-cell immune response in lymph nodes, yet their involvement in tumor immune escape and ICI treatment response is largely unknown. We hypothesize that DCs in tumor-draining lymph nodes promotes tumor immune escape by increased expression of PDL-1.

This research project aims to evaluate the presence and function of DC and CD8+ T-cells in tumor-draining lymph nodes. The goal is to understand the mechanisms that drive immune escape and restoration of cancer immunity by ICI in tumor-draining lymph nodes. We aim to detect prognostic markers and introduce an improved selection of patients who need more rigorous follow-up and those who would benefit from ICI.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2019-03518				

Publications 2021, 2022, 2023

1. Regulatory B cells producing IL-10 are increased in human tumor draining lymph nodes.Piersiala K, Hjalmarsson E, da Silva PFN, Lagebro V, Kolev A, Starkhammar M, Elliot A, Marklund L, Munck-Wikland E, Margolin G, Georén SK, Cardell LO. Int J Cancer. 2023

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Complications to acute rhinosinusitis in chilren.
Pneumococcal vaccine.
Mastoiditis

PhD june 2021: Complication to acute rhinosinusitis in children.
Currently worked on project regarding complications and PCV vaccine.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2021, 2022, 2023

1. ”The pneumococcal conjugate vaccine had a sustained effect on Swedish children 8 years after its introduction” Acta Paediatr. 2024 Jan 12. doi: 10.1111/apa.17108. Online ahead of print.PMID: 38217260
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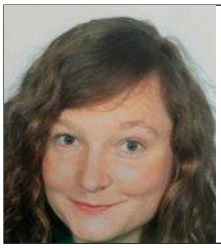
3. “A Swedish population-based study of complications due to acute rhinosinusitis in children 5-18 years old.” Int J Pediatr Otorhinolaryngol. 2021 Aug 5;150:110866. doi: 10.1016/j.ijporl.2021.110866. Online ahead of print. PMID: 34416439



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Hearing maturation, speech-language development and very early intervention of children with congenital unilateral sensorineural hearing loss

BACKGROUND: Congenital sensorineural hearing loss (SNHL, 2 in 1000 births) is one of the most common chronic impairments in children. In 25% of cases, only one ear is affected, i.e., unilateral sensorineural hearing loss (uSNHL). Children with uSNHL are at significant risk of hearing disability, despite hearing aids. The difficulties experienced vary greatly among children, and it is unclear how much of the variation that can be attributed to co-morbidity and the cause for the uSNHL.

OBJECTIVE: To study how early hearing and communication development are affected by uSNHL and hearing aid amplification, and to investigate the relationship between etiology and early hearing ability and communication.

DESIGN: During the years 2019-2020, we recruited all children with congenital uSNHL from the Stockholm Region newborn hearing screening program, a total of 20 children. Every six months from the age of 0.5 to 2.5 years, we studied the development of the hearing pathways by recording the auditory brainstem response (ABR, the ear's EEG), sound localization accuracy with an eye-tracking technique, as well as assessing hearing behavior and communication development with questionnaires (with and without hearing aids). We are done with all data collection, and the project will generate several manuscripts for publication in international journals (two first: Journal of Clinical Medicine 2022, 2023).

SIGNIFICANCE: There are no studies describing the outcomes of early hearing aid intervention (before the age of 3) for children with uSNHL, and none regarding early sound localization accuracy in children with uSNHL. Regarding hearing and communication development during the first years, there are only a few studies, with small heterogeneous study groups and mixed outcomes. Our results will thus generate essential clinical implications

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Jenny Häggström

Ethical permit No.

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

Publications 2021, 2022, 2023

1. Johansson, M., Karltorp, E., Edholm, K., Drott, M., & Berninger, E. (2022). A Prospective Study of Etiology and Auditory Profiles in Infants with Congenital Unilateral Sensorineural Hearing Loss. Journal of Clinical Medicine, 11(14), 3966.
2. Johansson, M., Karltorp, E., Asp, F., & Berninger, E. (2023). A Prospective Study of Genetic Variants in Infants with Congenital Unilateral Sensorineural Hearing Loss. Journal of Clinical Medicine, 12(2), 495

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Retrospective and prospective studies regarding complications, quality of life and swallowing difficulties in pediatric patients with tracheostomy

The Long-term Intensive Care Units (LIVA) primary task is to care for children with tracheostomies. Between 1998 and 2023, 180 children have undergone follow-up from tracheostomy to decannulation at LIVA. Currently, about 80 children with tracheostomies are being monitored at LIVA.
We are currently evaluating this surveillance program for children with tracheostomy, characterize types of complications and risk factors in order to improve and possibly individualize follow-up with the aim to avoid unnecessary endoscopies and anaesthesia.
In a prospective study we also investigate the anaesthesiologic risks associated with the current surveillance program for children with tracheostomy, identify risk factors and weight risk versus benefit with regards to surveillance endoscopies of asymptomatic patients.

Furthermore, we are conducting two prospective studies on quality of life in patients with tracheal cannula and their care givers and investigating the prevalence of feeding difficulties within this cohort in order to develop targeted interventions for early feeding training with the aim to improve nutrition and quality of life.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2018/1972-31	2021-06074-02	2023-07493-01		

Publications 2021, 2022, 2023

1.

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Immune responses in head- and neck cancer and airway inflammatory diseases

1. Cancer immunotherapies (CPI) have revolutionised the field of oncology and significantly improved survival in a wide range of malignancies. Tumour draining lymph nodes (TDLNs) have generally been overlooked in the initial phase of the research in immunotherapy in cancer. We will characterise the cellular architecture and immunological function of immunological cells such as T and B lymphocytes in TDLNs in head and neck carcinoma (HNSCC). Furthermore, we will describe how CPI changes the immunology of TDLNs using an in vitro model based on human TDLNs and in vivo by conducting a clinical trial using neoadjuvant treatment with anti-PD-1 in patients with locally advanced HNSCC and analysing their TDLNs
2. Intralymphatic AIT (ILIT) conjure a novel route of delivery with shorter duration and good compliance (3 injections over 8 weeks). Our previous studies have demonstrated that ILIT is safe with a sustained ability to reduce symptoms and medication during the pollen season. No studies have compared ILIT with traditional AIT. A recent study has shown that oral vitamin D (vitD) given in parallel to SLIT improves the symptom reduction. Our aim is to investigate if supplementation of vitD in parallel with ILIT can further improve the efficacy. We will also, for the first time, compare ILIT with SLIT
3. We aim to elucidate the role of neutrophils in inflammatory resolution and how this process differs between patients with allergic asthma and healthy controls. Special attention will be given to mechanisms related to these differences and the identification of key targets for future therapeutic development The goal is to highlight neutrophils as a heterogeneous cell population and to demonstrate that an imbalance between its various subgroups can be the basis of a defective resolution of inflammation within the lower airway.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Krzysztof Piersiala
	Vilma Lagebro

Ethical permit No.

2017_1791	2021_01265	2021_00325	2022_002039	

Publications 2021, 2022, 2023

1. Hjalmarsson E, Hellkvist L, Karlsson A, Winquist O, Kumlien Georén S, Westin U, Cardell LO. A 5-Year Open-Label Follow-up of a Randomized Double-Blind Placebo-Controlled Trial of Intralymphatic Immunotherapy for Birch and Grass Allergy Reveals Long-term Beneficial Effects. Journal of investigational allergology & clinical immunology 2023 33;5 362-372
2. Kakabas L, Piersiala K, Kolev A, Kumlien Georén S, Cardell LO. Allergic sensitization does not influence advancement or survival in oral cancer. Scientific reports 2023 13;1 21696-
3. Lagebro V, Piersiala K, Petro M, Lapins J, Gryback P, Margolin G, Georen SK, Cardell LO. A Novel Method Using Fine Needle Aspiration from Tumor-Draining Lymph Nodes Could Enable the Discovery of New Prognostic Markers in Patients with Cutaneous Squamous Cell Carcinoma. CANCERS 2023 15;13
4. van der Burg N, Stenberg H, Ekstedt S, Diamant Z, Bornesund D, Ankerst J, Kumlien Georén S, Cardell LO, Bjermer L, Erjefält J, Tufvesson E. Neutrophil phenotypes in bronchial airways differentiate single from dual responding allergic asthmatics. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 2023 53;1 65-77
5. Ekstedt S, Lagebro V, Kumlien Georén S, Cardell LO. Prolonged inflammatory resolution in allergic asthma relates to dysfunctional interactions between neutrophils and airway epithelium. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 2023 131;3 349-355.e3

6. Piersiala K, Hjalmarsson E, da Silva PFN, Lagebro V, Kolev A, Starkhammar M, Elliot A, Marklund L, Munck-Wikland E, Margolin G, Georén SK, Cardell LO. Regulatory B cells producing IL-10 are increased in human tumor draining lymph nodes. International journal of cancer 2023 153;4 854-866
7. Bark R, Kolev A, Elliot A, Piersiala K, Näsman A, Grybäck P, Georén SK, Wendt M, Cardell LO, Margolin G, Marklund L. Sentinel node-assisted neck dissection in advanced oral squamous cell carcinoma-A new protocol for staging and treatment. Cancer medicine 2023 12;11 12524-12534
8. Hjalmarsson E, Petro M, Georén SK, Winqvist O, Cardell LO. Upregulated expression of Notch1/4 - JAG-1/DLL-1 detected in allergic rhinitis. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology 2023 19;1 41-
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Sentinel Node detection in patients with Sinonasal Tumours

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

Immune response in COVID 19 patients.

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

Immune Respons and Tumour Cell Detection in Head and Neck Cancer

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

Ethical permit No.

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The use of HPV in post treatment surveillance 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. Out studies aim to use HPV in surveillance oft HPV-positive cancer, this together with radiology and clinical examination

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2009/1278-31/4				

Publications 2021, 2022, 2023

1. Landin D, Näsman A, Jaraj SJ, Hammarstedt-Nordenvall L, Munck-Wikland E, Dalianis T, Marklund L. Post-Treatment Neck Dissection of Tonsillar and Base of Tongue Squamous Cell Carcinoma in the Era of PET-CT, HPV, and p16. Viruses. 2022 Jul 30;14(8):1693. doi: 10.3390/v14081693. PMID: 36016315; PMCID: PMC9413897.
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Early prediction of cancers

1. Multi-Organ Single Cell Analysis Reveals an On/Off Switch System with Potential for Personalized Treatment of Immunological Diseases: In this project we organized those into a multi-organ multicellular disease model, which shows predicted molecular interactions within and between organs. That model supports that inflammation is switched on or off by altered balance between pro- and anti-inflammatory upstream regulators (URs) and downstream pathways. Meta-analyses of human IMIDs show a similar, but graded, on/off switch system. This system has the potential to prioritize, diagnose, and treat optimal combinations of URs on the levels of IMIDs, subgroups, and individual patients.

2. SLE has multiple manifestations including musculoskeletal, renal, haematological, serosal, and neuropsychiatric involvement. Treatment for SLE is centred on immunosuppression and anti-inflammatory therapy, depending on the degree of end organ involvement. In this project we will use the methods we have built in the previous project to develop these methods to find URs that can be targeted by combinatorial treatment, as well as biomarkers for such combinations. We will focus on systematic lupus erythematosus (SLE), which is one of the most serious ADs

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2021, 2022, 2023

1. CELL REPORTS MEDICINE. 2023;4(3):100956 Multi-organ single-cell analysis reveals an on/off switch system with potential for personalized treatment of immunological diseases. Lilja S; Li X; Smelik M; Lee EJ; Loscalzo J; Marthanda PB; Hu L; Magnusson M; Sysoev O; Zhang H; Zhao Y; Sjöwall C; Gawel D; Wang H; Benson M
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Long-term follow-up of adolescents and young adults who have undergone surgery with cochlear implants during early childhood

Long-term outcomes in deaf youth who have received cochlear implants (CIs) early in life is rare so far in the literature. For example outcome related to higher-levels of language competence like figurative understanding, psychosocial well-being, and listening skills in more complex listening conditions reflecting everyday life. In addition, it is yet unclear whether the chronic electrical stimulation in the inner ear and the CI procedure itself affects vestibular function. The ongoing multi-disciplinary research program aims to investigate possible effects of early age at 1st cochlear implantation (CI) in a larger cohort of adolescents and young adults who received their 1st CI before 30 months of age, and in relation to typical hearing controls.
The overall two PICO-questions motivating the multi-disciplinary research program (including five study projects):

1. How do adolescents with mono- or multilingual background implanted before 30 months with cochlear implant(s), perform long-term in linguistics, cognition, hearing, balance, self-efficacy and health-related quality of life (HRQoL), and in comparison to age-, socioeconomic and language-matched controls with typical hearing?
2. How do adolescents and young adults with CIs perceive their listening and communication experiences with CIs in different everyday life situations and activities (school, work, leisure), and in relation to controls with typical hearing?

The data collection has finished in the study group, while we are still collecting some control data. During spring 2023 we conducted 3 focus-group interviews and 15 individual interviews in youth with CI. This qualitative material is currently being analyzed, quantitiative survey data related to mental health and self-efficacy is also being analysed, and many manuscripts are currently ”in preparation”.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Malin Dahlby Skoog	Jonas Fogels
	Karolina Falkenius Schmidt

Ethical permit No.

2015/992-31	2022-01159-01				

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Multiomics data analysis to reveal the overlapping molecular mechanism in pancreatic ductal adeno carcinoma (PDAC) and malignant cysts for early prediction and prevention of Malignant transformation

Understanding the molecular mechanisms underlying the transition from pancreatic cysts to pancreatic ductal adenocarcinoma (PDAC) is crucial for early disease diagnosis and the development of targeted therapies. The identification of shared and distinct molecular mechanism between high-grade dysplasia (HGD) intraductal papillary mucinous neoplasms (IPMN) and PDAC offers a unique insight into the cellular processes that drive pancreatic tumorigenesis. The aim of this study is to determine biomarkers that can uniquely differentiate benign from malignant pancreatic cysts that could be implemented for early prediction of risk and prognosis of the pancreatic cyst. We have analyzed UKBB cohort of half a million people to find the genomic architecture of pancreatic cyst. Genome-wide association study (GWAS) was performed for the individuals with benign pancreatic cysts (cases) versus healthy controls as well as individuals diagnosed with pancreatic cancer (PC) (cases) versus individuals with pancreatic cysts (controls) to determine the differential genetic variants that are associated with the development of PC versus pancreatic cysts. Furthermore, we combined multiomics data such as scRNA-seq, bulk mRNA and proteomics data of PDAC and Cyst to find the mechanistic insight of overlapping mechanism between PDAC and cyst. These allowed us to identify key molecular links potentially critical for understanding the transition from precancerous cysts to pancreatic cancer in the tumor microenvironment's cellular landscape.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2019-03518	2021-01265			

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Sentinel Node Biopsy: The Integration of Gamma Detection and Quantitative Ultrasound for Superior Metastasis Detection

The goal of this project is to improve the metastasis detection in cancer by developing novel multimodal technologies that combine quantitative ultrasound and gamma detection.Vi integrate multidisciplinary expertise in oncology, medical imaging, nuclear medicine, and radiation physics . The project goal is to deliver validated techology and develop a device for reginal lymph node characterirization and biopsy.

Othe ongoing projcts:
Selection of lymf node target for head and neck irradiation based on tumor -draining lymf node node (TDLN).

Prospectiv study to analyze tumor control, toxity and aestetic outcome of patient with skin cancer treated with iridium-192 high-dose-rate contact brachytherapy.

Development of laryngoskop holder.The claimed invention relates to medicine and more particularly to the 4eld of laryngology, and can be used when carrying out direct suspension laryngoscopy for visualising the structure of the larynx and for carrying out manipulations by means of surgical intervention in said structures.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Aeneas Kolev
	Emma Malmström
	Ejnar Björgvinsson

Ethical permit No.

2019-03518	2021-01265			

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Studies on tumour markers and surgical techniques to individualize treatment and improve outcome for patients with head neck tumours

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

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Rasmus Blomkvist	Aeneas Kolev
Evelina Jörtsö	

Ethical permit No.

2017/1333-31/1	2023-05249-01	2023-05724-02	2023-03476-01	2023-00134-01

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- Bells palsy during pregnancy and puerperium
-Surgical intervention in patients with peripheral facial palsy
-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 or botox injections.

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

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Lovisa Lansing	Rebecka Ohm
	Sigurdur Arnason
	Sofia Karlsson

Ethical permit No.

Publications 2021, 2022, 2023

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Head and neck cancer

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

Daniel studies ”Osteoradionecrosis (ORN) - riskfactors and reconstructive outcome” including biomarkers for increased risk for ORN, proportion of ORN in reconstructive surgery, quality of life after reconstruction and the risk for ORN in patients with base of tongue cancer treated with brachytherapy.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Daniel Danielsson	Krzysztof Piersiala
	Vilma Lagebro

Ethical permit No.

2009/129-32	2012/1663-32	2016/27-32	2016/506	

Publications 2021, 2022, 2023

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2. Sjöström M, Danielsson D, Munck-Wikland E, Nyberg J, Sandström K, Thor A, Johansson H, Ceghafi P, Dybeck Udd S, Emanuelsson J, Forsberg Pettersson L, Halle M, Laurell G. Mandibular resection in patients with head and neck cancer: acute and long-term complications after reconstruction. Acta Otolaryngol. 2022 Jan;142(1):78-83. doi: 10.1080/00016489.2021.2021283. Epub 2022 Jan 13. PMID: 35023428
3. Landin D, Näsman A, Jara SJ, Hammarstedt-Nordenvall L, Munck-Wikland E, Dalianis T, Marklund L. Post-Treatment Neck Dissection of Tonsillar and Base of Tongue Squamous Cell Carcinoma in the Era of PET-CT, HPV, and p16.Viruses. 2022 Jul 30;14(8):1693. doi: 10.3390/v14081693. PMID: 36016315 Free PMC article.
4. Piersiala K, da Silva PFN, Lagebro V, Kolev A, Starkhammar M, Elliot A, Marklund L, Munck-Wikland E, Margolin G, Georén SK, Cardell LO. Tumour-draining lymph nodes in head and neck cancer are characterized by accumulation of CTLA-4 and PD-1 expressing Treg cells.Transl Oncol. 2022 Jun 14;23:101469. doi: 10.1016/j.tranon.2022.101469. Online ahead of print. PMID: 35714487
5. Wendt M, Hammarstedt-Nordenvall L, Zupancic M, Friesland S, Landin D, Munck-Wikland E, Dalianis T, Näsman A, Marklund L. Long-Term Survival and Recurrence in Oropharyngeal Squamous Cell Carcinoma in Relation to Subsites, HPV, and p16-Status. Cancers (Basel). 2021 May 23;13(11):2553. doi: 10.3390/cancers13112553. PMID: 34070952 Free PMC article.
6. Mints M, Landin D, Näsman A, Mirzaie L, Ursu RG, Zupancic M, Marklund L, Dalianis T, Munck-Wikland E, Ramqvist T. Tumour inflammation signature and expression of S100A12 and HLA class I improve survival in HPV-negative hypopharyngeal cancer. Sci Rep. 2021 Jan 19;11(1):1782. doi: 10.1038/s41598-020-80226-z. PMID: 33469045 Free PMC article.
7. Piersiala K, Farrajota Neves da Silva P, Hjalmarsson E, Kolev A, Kågedal Å, Starkhammar M, Elliot A, Marklund L, Margolin G, Munck-Wikland E, Kumlien Georén S, Cardell LO. CD4+ and CD8+ T cells in sentinel nodes exhibit distinct pattern of PD-1, CD69, and HLA-DR expression compared to tumor tissue in oral squamous cell carcinoma. Cancer Sci. 2021 Mar;112(3):1048-1059.
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Diagnostic and Prognostic Markers for Head and Neck Cancer management

1. Identification of early diagnostic and prognostic markers (both clinical and 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. 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. We also apply machine learning applications to better overcome challenges encountered in the management of HNSCC.

2. The Nordic Head and Neck Cancer (HNC) Study: management and outcome of various subsites of HNC 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.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Evelina Gille
	Rasmus Blomkvist

Publications 2021, 2022, 2023

1. Alabi RO, Elmusrati M, Leivo I, Almangush A, Mäkitie AA. Machine learning explainability in nasopharyngeal cancer survival using LIME and SHAP. Sci Rep. 2023 Jun 2;13(1):8984.
2. Tikkanen J, Nieminen T, Lassus P, Tenhunen M, Lehtonen L, Mäkitie A. Costs of oropharyngeal squamous cell cancer treatment in Finland. Eur Arch Otorhinolaryngol. 2023 Dec;280(12):5499-5506.
3. Nikkilä R, Hirvonen E, Haapaniemi A, Tapiovaara L, Pitkäniemi J, Malila N, Mäkitie A. Significant risk of second primary cancer among laryngeal squamous cell carcinoma patients even after 20 years. Acta Oncol. 2023 Oct;62:1322-30.
4. Orell H, Pohju A, Tuokkola J, Junttila K, Heikkilä A, Österlund P, Schwab U, Mäkitie A. Time to act! - A cross-sectional study on how nutritional risk increases during hospitalization and associates with worse outcome. Clin Nutr ESPEN. 2023 Oct;57:364-374.
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7. Alabi RO, Almangush A, Elmusrati M, Leivo I, Mäkitie A. Measuring the Usability and Quality of Explanations of a Machine Learning Web-Based Tool for Oral Tongue Cancer Prognostication. Int J Environ Res Public Health. 2022 Jul 8;19(14):8366.
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9. Almangush A, Alabi RO, Mäkitie AA, Leivo I. Machine learning in head and neck cancer: Importance of a web-based prognostic tool for improved decision making. Oral Oncol. 2021 Jul 12:105452.
10. Tuomainen K, Hyytiäinen A, Al-Samadi A, Ianevski P, Ianevski A, Potdar S, Turunen L, Saarela J, Kuznetsov S, Wahbi W, Risteli M, Mäkitie A, Monni O, Salo T. High-throughput compound screening identifies navitoclax combined with irradiation as a candidate therapy for HPV-negative head and neck squamous cell carcinoma. Sci Rep. 2021 Jul 20;11(1):14755.
11. Filippou A, Pehkonen H, Karhemo PR, Väänänen J, Nieminen AI, Klefström J, Grénman R, Mäkitie AA, Joensuu H, Monni O. ANO1 Expression Orchestrates p27Kip1/MCL1-Mediated Signaling in Head and Neck Squamous Cell Carcinoma. Cancers (Basel). 2021 Mar 9;13(5):1170. doi: 10.3390/cancers13051170.
12. Ilmarinen T, Hammarstedt-Nordenvall L, Bäck L, Mäkitie A. Enteral tube feeding of head and neck cancer patients undergoing definitive chemoradiotherapy in the Nordic Countries: Survey of the Scandinavian Society for Head and Neck Oncology. Eur Arch Otorhinolaryngol. 2021 Jan 2.
13. Koivuholma A, Aro K, Mäkitie A, Salmi M, Mirtti T, Hagström J, Atula T. Three-Dimensional Presentation of Tumor Histopathology: A Model Using Tongue Squamous Cell Carcinoma. Diagnostics (Basel). 2021 Jan 12;11(1):109

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A 10-year evaluation of the students' reserach project course

Scientific research plays a fundamental role in current medical practice and it is of great importance that medical students relate to it already from the beginning of their professional careers. Consequently, medical schools across the world are increasingly implementing research methods and research project courses in their education. Typical characteristics of students' research projects are that the students spend considerable but delimited time on research activities and do so under the supervision of an experienced scientist. In addition, students are usually required to produce a research report of an acceptable standard.Finally, each student remains engaged within one learning environment for a longer period of time than during any other course during their education. These elements combined make the research project course a challenging learning opportunity motivating a more detailed investigation of its outcomes.
Research-based knowledge should guide education and pedagogy. We therefore plan to carry out a 10-year follow-up of the degree project course in medicine aiming to evaluate the scientific output of these projects, i.e., to which extent our students contribute to KI's scientific output and the creation of new knowledge, and to which extent the students show persistent interest in scientific research. More specifically, we will study: 1) which research areas students have chosen; 2) whether the students' success (passed/failed exam, publications, PhD studies) varies across the research areas; 3) whether the failure projects have any common characteristics; 4) whether there is any correlation between failed research project course and subsequent progress in the medical program; 5) which research methodologies have been used, 5) the departments' commitment to taking on students' projects.

Ethical permit No.

2022-00611-01						

Publications 2021, 2022, 2023

1. Gummesson C, Alm S, Cederborg A, Ekstedt M, Hellman J, Hjelmqvist H, Hultin M, Jood K, Leanderson C, Lindahl B, Möller R, Rosengren B, Själander A, Svensson PJ, Särnblad S, Tejera A. Entrustable professional activities (EPAs) for undergraduate medical education - development and exploration of social validity. BMC Med Educ. 2023 Sep 4;23(1):635. doi: 10.1186/s12909-023-04621-6. PMID: 37667366.
2. Boursicot K, Kemp S, Norcini J, Nadarajah VD, Humphrey-Murto S, Archer E, Williams J, Pyörälä E, Möller R. Synthesis and perspectives from the Ottawa 2022 conference on the assessment of competence. Med Teach. 2023 Sep;45(9):978-983. doi: 10.1080/0142159X.2023.2174420.
3. Sellberg M, Palmgren PJ, Möller R. Balancing between act and adapt - Medical students experiences of early clinical placements: a qualitative study. BMC Med Ed 2022, 22, 659 https://doi.org/10.1186/s12909-022-03714-y
4. Sanmark E, Rantanen N, Oksanen LM, Tuhkuri Matvejeff A, Möller R, Geneid A. Comparison of aerosol generation between electrocautery and cold dissection tonsillectomy. J Laryngol Otol. 2023 Jul;137(7):732-740. doi: 10.1017/S0022215123000324. Epub 2023 Mar 27. PMID: 36971276.
5. Sellberg M, Halvasson A, Nygren-Bonnier M, Palmgren PJ, Möller R. Relationships matter: a qualitative study of physiotherapy students' experiences of their first clinical placement. Physical Therapy Reviews 2022; https://doi.org/10.1080/10833196.2022.2106671
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7. Sellberg M, Palmgren PJ, Möller R. A cross-sectional study of clinical learning environments across four undergraduate programs using the undergraduate clinical education environment measure. BMC Medical Education (2021) 21:258 https://doi.org/10.1186/s12909-021-02687-8
8. Möller R, Ringsted C, Danielsen N. Portföljen synliggör lärandet och kompetensutvecklingen [Portfolio - a tool for making learning and competence development visible]. Lakartidningen. 2021 Sep 20;118:21099. Swedish. PMID: 34542895

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Hearing in cholesteatoma surgery and evaluation of preceding myringoplasty in cholesteatoma patients.

Post doctoral studies as part of the project SweChole regarding cholesteatoma in Sweden.

I) Prospective study regarding hearing in patients undergoing cholesteatoma surgery. Hearing is tested before surgery as well as six months, one year and five years post surgery. The hearing test methods are pure tone audiometry (PTA), horizontal sound localization and speech in competing speech. PTA is used in clinical practice to measure the hearing of the cholestetoma patients. We want to evaluate if the other two methods are better to represent the useful hearing in the patients, compare the data to normal hearing subjects and describe eventual auditory plasticity in spatial hearing over time.

II) Retrospective study of cholesteatoma patients in Sweden using the Swedish Patient Registry and the Swedish Quality Registry for Ear Surgery. We will combine these registries to evaluate the risk of developing cholesteatoma after myringoplasty. We will analyze parameters such as time from myringoplasty to cholesteatoma surgery and also parameters regarding surgical procedure of the myringoplasty and complications during the healing period.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2022-04517-02	2020-05935			

Publications 2020, 2021, 2022

1.

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Upper airway disease; treatments and health economy

Research interests include the epidemiology of rhinitis and nasal polyposis, the medical and surgical management of nasal polyposis and more recently, immunotherapy and biologic treatments of upper airway disease, inluding health economy

Ethical permit No.

2016/2158-31/2				

Publications 2021, 2022, 2023

1. Luong AU, Chua A, Alim BM, Olsson P, Javer A. Allergic Fungal Rhinosinusitis: The Role and Expectations of Biologics. The journal of allergy and clinical immunology. In practice 2022 10;12 3156-3162
2. Taniguchi M, Heffler E, Olze H, White A, Côrte-Real J, Olsson P, Lazarewicz S. The Role of Omalizumab in NSAID-Exacerbated Respiratory Disease: A Narrative Review. The journal of allergy and clinical immunology. In practice 2022 10;10 2570-2578
3. Tsabouri S, Ntritsos G, Koskeridis F, Evangelou E, Olsson P, Kostikas K. Omalizumab for the treatment of allergic rhinitis: a systematic review and meta-analysis. Rhinology 2021 Oct 29. doi: 10.4193/Rhin21.159
4. Olsson P, Skroder C, Ahlbeck L, Hjalte F, Welin KO, Westin U, Andersson M, Ahlstrom-Emanuelsson C, Cardell LO. HealthSWEDE: costs with sublingual immunotherapy-a Swedish questionnaire study. Allergy Asthma and Clinical Immunology 2021 17;1 55

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Laryngeal cancer at the Karolinska University Hospital 2000-2020

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

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

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

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

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Rasmus Blomkvist

Ethical permit No.

2019-04829				

Publications 2021, 2022, 2023

1. Treatment and outcome among patients with laryngeal squamous cell carcinoma in Stockholm—A population-based study Rasmus Blomkvist, Linda Marklund, Lalle Hammarstedt-Nordenvall, Eivind Gottlieb-Vedi, Antti Mäkitie, Björn Palmgren Laryngoscope Investig Otolaryngol. 2023 Mar 6;8(2):441-449. doi: 10.1002/lio2.1034. eCollection 2023 Apr.
2. A descriptive study highlighting the differences in the treatment protocol for oral tongue cancer in Sweden and Finland. Mäkitie A, Kamali A, Mroueh R, Lindford A, Koivunen P, Autio T, Lassus P, Halle M, Bäck L, Palmgren B, Hammarstedt-Nordenvall L.Mäkitie A, et al. Acta Otolaryngol. 2020 Feb;140(2):188-194. doi: 10.1080/00016489.2019.1699663. Epub 2019 Dec 18.Acta Otolaryngol. 2020. PMID: 31852347

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The focus of my research is to investigate the variation in outcomes related to communication in young children who are deaf and hard of hearing and to develop and validate methods to evalute these outcomes in clinical practice. Another area of research interest is to examine the long-term effects of early intervention on health-related outcomes.

Validation of LittlEARS Early Expressive Speech Questionnaire
Feasable and validated measures and assessments of early auditory, speech and language development in Swedish are lacking. This project aims to translate, evaluate and validate a questionnaire on early expressive speech 0-18 months. We do this with a cross-sectional design, collecting data from around 200 parents of children aged 0-18 months with typical hearing.

Health-related quality of life and mental health in adolescents and young adults who received cochlear implants before 2.5 years of age
It has been well documented that early cochlear implantation has led to benefits in terms of speech and language outcomes but long-term outcomes on quality of life and academic outcomes in this target group are lacking. Methods used are questionnaires, focus groups and individual interviews which aim to provide unique data in terms of personal everyday life experiences of a group of early implanted individuals in the ages between 12-22 years of age.

Bimodal pediatric
The goal of this project is to investigate how clinicians can better determine when a second implant is needed, e.g., that an individual child will have significant improvement in outcomes from a sequential CI compared to their bimodal hearing. Participants include children with bimodal fitting 4-15 years of age with a follow-up of those who receive a second CI within in the time frame of the current study.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Andra Lazar

Ethical permit No.

2022-02763-01	2022-01159-01	2023-01945-02		

Publications 2021, 2022, 2023

1. Persson A, Marklund U, Lohmander A, Flynn T. Expressive vocabulary development in children with moderate hearing loss - the impact of auditory variables and early consonant production. Clin Linguist Phon. 2022 Jun 3;36(6):547-564. doi: 10.1080/02699206.2021.1944321. Epub 2021 Jul 7. PMID: 34231440.
2. Persson A, Flynn T, Miniscalco C, Lohmander A. Impact of auditory variables on consonant production in babbling and early speech in children with moderate hearing loss - a longitudinal study. Clin Linguist Phon. 2022 Oct 3;36(10):833-848. doi: 10.1080/02699206.2021.1958260. Epub 2021 Jul 29. PMID: 34324384

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Growing up with one ear: central auditory structure and function in unilateral ear canal atresia

I defended my thesis entitled ”Growing up with one ear: central auditory structure and function in unilateral ear canal atresia” in november, 2023. The thesis included studies on human participants with unilateral ear atresia, and a rat model with unilateral surgically created atresia. We studied the effects of unilateral severe conductive hearing loss on central auditory perception, as well as imaging of central auditory structures of the brain. Human participants had worse speech perception in a cocktail party setting and sound localization. We also observed a shift in asymmetry pattern of the grey matter thickness of the Heschl’s gyrus, the primary auditory cortex of the brain in atresia. Rats with atresia had differences in the auditory white matter tracts of the brain.

I am also involved in a project on localization in unilateral deafness together with Filip Asp and Martin Eklöf, CLINTEC, that is ongoing.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

113/15	191/4	2012/3:9	2017/4:3	

Publications 2021, 2022, 2023

1. Siegbahn M, Engmér Berglin C, Hultcrantz M, Asp F. Adults with unilateral congenital ear canal atresia -sound localization and recognition of speech in competing speechin unaided condition. Acta Otolaryngol. 2021 Juli;141(7):689-694. doi:10.1080/00016489.2021.1921843.
2. Siegbahn M, Engmér Berglin C, Moreno R. Automated segmentation of the core of the acoustic radiation in humans. Front Neurolog. 2022 sept 23. doi: 10.3389/fneur.2022.934650
3. Siegbahn M, Jörgens D, Asp F, Hultcrantz M, Engmér Berglin C, Moreno R. Asymmetry in cortical thickness of the Heschl’s gyrus in unilateral ear canal atresia. Otol. Neurotology. 2024 feb. 16. doi: 10.1097/MAO.0000000000004137
4. Siegbahn M, Lundin K, Olsson GB, Stillesjö F, Kinnefors A, Rask-Andersen H, Nyberg G. Auditory brainstem implants (ABIs) -20 years of clinical experience in Uppsala, Sweden. Acta Otolaryngol. 2014 Oct;134(10):1052-61. doi: 10.3109/00016489.2014.909051

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Clinical studies on upper airway inflammation, skullbase and sinonasal tumors 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: 1. Studies of mechanisms in pregnancy rhinitis and its effect on the pregnant woman's quality of life.

2. Epidiologic studies om acute rhinosinusitis in children. The overall objective is to understand the basic epidemiology and mechanisms and but also to improve the treatment of these patient groups.

Studies on olfactory basic mechanisms and effects on quality of life in olfactory dysfunction.

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*
Ola Fridman Bengtsson	Samin Rahbin
	Sofie Henecke

Ethical permit No.

2012/4931	2018/302-31	2019/04287-1		

Publications 2021, 2022, 2023

1. Bengtsson OF, Sunnergren O, Segerhammar I, Förander P, Olsson M, Hulting AL, Stjärne P. Remission, complications, and overall survival in transsphenoidal pituitary surgery-a Swedish single-center experience of 578 patients. Acta Neurochir (Wien). 2023 Mar;165(3):685-692. doi: 10.1007/s00701-022-05456-8. Epub 2023 Jan 20.PMID: 36662287
2. Whitcroft KL, Altundag A, Balungwe P, Boscolo-Rizzo P, Douglas R, Enecilla MLB, Fjaeldstad AW, Fornazieri MA, Frasnelli J, Gane S, Gudziol H, Gupta N, Haehner A, Hernandez AK, Holbrook EH, Hopkins C, Hsieh JW, Huart C, Husain S, Kamel R, Kim JK, Kobayashi M, Konstantinidis I, Landis BN, Lechner M, Macchi A, Mazal PP, Miri I, Miwa T, Mori E, Mullol J, Mueller CA, Ottaviano G, Patel ZM, Philpott C, Pinto JM, Ramakrishnan VR, Roth Y, Schlosser RJ, Stjärne P, Van Gerven L, Vodicka J, Welge-Luessen A, Wormald PJ, Hummel T. Position paper on olfactory dysfunction: 2023. Rhinology. 2023 Jul 16. doi: 10.4193/Rhin22.483. Online ahead of print.PMID: 37454287

3. Hultman Dennison S, Granath A, Holmstrom M, Stjarne P, Hertting O. Complications to acute bacterial rhinosinusitis in children - a prospective study; bacterial cultures, virus detection, allergy sensitization and immunoglobulins.Rhinology. 2023 Oct 1;61(5):412-420. doi: 10.4193/Rhin22.168.PMID: 37338824
4. Sunnergren O, Pakpour AH, Bergquist H, Sahlstrand-Johnson P, Stjärne P, Broström A. Validation and psychometric evaluation of the Swedish version of the Nasal Obstruction Symptom Evaluation scale.Laryngoscope Investig Otolaryngol. 2023 Mar 6;8(2):357-366. doi: 10.1002/lio2.1036. eCollection 2023 Apr.PMID: 37090889
5. Bengtsson OF, Sunnergren O, Segerhammar I, Förander P, Olsson M, Hulting AL, Stjärne P. Remission, complications, and overall survival in transsphenoidal pituitary surgery-a Swedish single-center experience of 578 patients.Acta Neurochir (Wien). 2023 Mar;165(3):685-692. doi: 10.1007/s00701-022-05456-8. Epub 2023 Jan 20.PMID: 36662287
6. Stjärne P, Nguyen DT, Kuhl HC. Real-Life Effectiveness of MP-AzeFlu (Dymista®) in Swedish Patients with Persistent Allergic Rhinitis, Assessed by the Visual Analogue Scale. Pragmat Obs Res. 2023 Jan 4;14:1-11. doi: 10.2147/POR.S375403. eCollection 2023.PMID: 36628265
7. Hultman Dennison S, Hertting O, Bennet R, Eriksson M, Holmström M, Schollin Ask L, Lindstrand A, Dimitriou P, Stjärne P, Granath A. A Swedish population-based study of complications due to acute rhinosinusitis in children 5-18 years old. Int J Pediatr Otorhinolaryngol. 2021 Nov;150:110866. doi: 10.1016/j.ijporl.2021.110866. Epub 2021 Aug 5

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Longterm Effectiveness of Tonsillectomy vs Modified Uvulopalatopharyngoplasty in Patients With Tonsillar Hypertrophy and Obstructive Sleep Apnea: Follow-up Study in The TEAMUP Randomized Clinical Trial

Background: Modified uvulopalatopharyngoplasty (mUPPP) is a surgical treatment for selected adults with obstructive sleep apnea (OSA). Tonsillectomy (TE) alone is a less extensive alternative treatment. A previous randomized clinical trial demonstrated that mUPPP was not more effective than TE alone in treating patients with tonsillar hypertrophy and moderate to severe OSA. However, there was a small difference in favor of TE. The long term effectiveness is not clear. The patients in the RCT are currently undergoing a 5 year follow-up to evaluate if there is a long-term difference between the methods.

Objective: To investigate whether mUPPP is more effective in the long-term than TE alone in treating adult patients with tonsillar hypertrophy and moderate to severe OSA.

Method: RCT

Main outcomes and measures: Between-group differences on the apnea-hypopnea index (AHI) and Epworth sleepiness scale (ESS).

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2015/755-31/2				

Publications 2021, 2022, 2023

1. Eight-Year Follow-up of Modified Uvulopalatopharyngoplasty in Patients With Obstructive Sleep Apnea. Sundman J, Browaldh N, Fehrm J, Friberg D. Laryngoscope. 2021 Jan
2. Long-term evaluation of satisfaction and side effects after modified uvulopalatopharyngoplasty. Friberg D, Sundman J, Browaldh N. Laryngoscope. 2020 Jan
3. Effectiveness of Tonsillectomy vs Modified Uvulopalatopharyngyplasty in Patients With Tonsillar Hypertrophy and Obstructive Sleep Apnea - The TEAMUP Randomized Clinical Trial. Sundman, Nerfeldt, Fehrm, Bring, Browaldh, Friberg. JAMA ORL Oct 2022
4. Identification of resident memory CD8+ T cells with functional specificity for SARS-CoV-2 in unexposed oropharyngeal lymphoid tissue. Niessl J, Sekine T, Lange J, Konya V, Forkel M, Maric J, Rao A, Mazzurana L, Kokkinou E, Weigel W, Llewellyn-Lacey S, Hodcroft EB, Karlsson AC, Fehrm J, Sundman J, Price DA, Mjösberg J, Friberg D, Buggert M. Sci Immunol 2021 Oct

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Treatment with monoclonal antibodies in patients with chronic rhinosinusitis with nasal polyps

A randomized, double-blind, head to head comparison of dupilumab versus omalizumab in severe chronic rhinosinusitis with nasal polyps (CRSwNP) and comorbid asthma patients.
This is a multicenter study and the aim of the study is to evaluate the efficacy profile of dupilumab is superior compared to omalizumab in treating patients with severe CRSwNP and comorbid asthma.

A randomized, double-blind, parallel group Phase III study to acsess the efficacy and safety of 100mg Depemokimab in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) compared to placebo.
This is a multicenter study. The aim of the study is to evaluate the efficacy and safety of depemokimab which is a new monoclonal antibody administered every 6 months in a period of 52 weeks in patients with CRSwNP.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2021, 2022, 2023

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Effekt av olika behandlingar på symptom hos Menieres sjukdom-retrospektiv studie

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

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2021-06481-02				

Publications 2021, 2022, 2023

1. Surano S, Grip H, Öhberg F, Karlsson M, Faergemann E, Bjurman M, Davidsson H, Ledin T, Lindell E, Mathé J, Tjernström F, Tomanovic T, Granåsen G, Salzer J. Internet-based vestibular rehabilitation versus standard care after acute onset vertigo: a study protocol for a randomized controlled trial. Trials. 2022 Jun 16;23(1):496. doi: 10.1186/s13063-022-06460-0. PMID: 35710448; PMCID: PMC9205069.
2. Tomanovic T. Intratympanic dexamethasone in Manières disease and symptom control. Acta Otolaryngol. 2023 Aug;143(8):681-686. doi: 10.1080/00016489.2023.2244003. Epub 2023 Sep 8. PMID: 37682583.

Satu Turunen-Taheri
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Mental fatigue, tinnitus, with or without hearing loss.

A study is planned on mental fatigue, hearing loss and tinnitus as continued research on the previous study IV that was included in the thesis. A prospective study comparing the Tinnitus Handicap Inventory (THI) questionnaire and the Tinnitus Functional Index (TFI) instrument is also planned.

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II. Turunen-Taheri S, Carlsson PI, Johnson AC & Hellstrom S. (2019). Severe-to-profound hearing impairment: demographic data, gender differences and benefits of audiological rehabilitation. Disability and rehabilitation, 41 (23): 2766-74.
III. Turunen-Taheri SK, Eden M, Hellstrom S & Carlsson PI. (2019). Rehabilitation of adult patients with severe-to-profound hearing impairment - why not cochlear implants? Acta Oto-Laryngologica, 139 (7): 604-11.
IV. Turunen-Taheri S, Carlsson PI, Ternevall E & Hellström S. Mental fatigue in patients with hearing loss and/or tinnitus undergoing extended audiological rehabilitation – a pilot study. J. Clin. Med. 2023, 12, 6756. https://doi.org/10.3390/jcm12216756
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Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Andra Lazar

Ethical permit No.

2012/057	2014/2101-31			

Publications 2021, 2022, 2023

1. Turunen-Taheri, S.; Carlsson, P.-I.; Ternevall, E.; Hellström, S. Mental Fatigue in Patients with Hearing Loss and/or Tinnitus Undergoing Audiological Rehabilitation—A Pilot Study. J. Clin. Med. 2023, 12, 6756. https://doi.org/10.3390/jcm12216756
2. Turunen-Taheri, S., Hagerman Sirelius, A., Hellström, S., Skjönsberg, Å., & Backenroth, G. (2023). Combined severe-to-profound hearing and vision impairment – experiences of daily life and need of support, an interview study. Plos One, Jun 15;18(6): e0280709, 2023. https://doi.org/10.1371/journal.pone.0280709
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4. Al-Wathinani, A., Al-Sudairi, N., Alhallaf, M., Albaqami, N., Alghamdi, A., Turunen-Taheri, S., . . . Goniewicz, K. (2022). Raising Awareness of Hearing and Communication Disorders Among Emergency Medical Services Students: Are Knowledge Translation Workshops Useful? Disaster Medicine and Public Health Preparedness, 1-5. https://doi.org/10.1017/dmp.2022.120
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Pre-/retrospective, genetic studies and habilitation of hearing loss in children.

The goal is to better understand the etiopathology and evolution of sensorineural hearing loss (SHL) in children. It will help build up better interventional methods and habilitation models for children with SHL In Sweden children undergo a newborn hearing screening as well as childhood hearing tests to detect SHL for early intervention important for the development of normal speech and language. All children diagnosed are enrolled in our Hearing and habilitation centre for children and youth, registered in a database called Audiohab, where they are followed until adulthood by a multiprofessional team covering their medical, behavioral, psychological and social needs. All children in Stockholm are gathered in a single medical unit which gives us a unique opportunity to assess and follow-up hearing loss in childhood

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Andra Lazar

Ethical permit No.

2020-07203				

Publications 2021, 2022, 2023

1. Kik J, Heijnsdijk EAM, Mackey AR, Carr G, Horwood AM, Fronius M, Carlton J, Griffiths HJ, Uhlen IM, Simonsz HJ, Consortium CCJPOTES. Availability of data for cost-effectiveness comparison of child vision and hearing screening programmes. JOURNAL OF MEDICAL SCREENING 2023 30;2 62-68
2. Hoeve HLJ, Goedegebure A, Carr G, Davis A, Mackey AR, Bussé AML, Uhlén IM, Qirjazi B, Kik J, Simonsz HJ, Heijnsdijk EAM. Modelling the cost-effectiveness of a newborn hearing screening programme; usability and pitfalls. International journal of audiology 2023 ; 1-7
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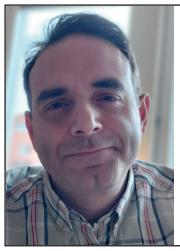

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1. **TAYACY : Long follow up of Teen agers and Young adults with CI- motor proficiency and vestibular function.**
2. **VESTPED: Objective balance testing in children.**
3. **MOVEST: Pediatric physioteraphy for children with vestibular disorders.**
4. **Post-doc studies: New methods for a better diagnosis of dizziness by bone conducted stimulation.**
5. **VIBAN: Bone conducted stimulation in audiology and neurotology, new perspectives**

I´m research leader at the SCAPA (Scientific Center for Advanced Pediatric Audiology -https://ki.se/clintec/om-scapa) and I supervise the doctoral studies of MD Niki Karpeta(NK), PT Susanne Gripenberg(SG), MD Andra Lazar(AL) and MD Zheer Tawfique(ZT). Their studies are included in different research projects. The TAYACI is an interprofessional project aiming to ascertain the functional level of TeenAgers and Young Adults, CI recipients since infancy. NK´s and SG´s studies focus on the reached functional level relating to the motor proficiency and vestibular function.
The VESTPED project is about the application of an own developed balance assessment for infants and preschoolers. NK and ZT conduct studies about the application of the vestibular myogenic potentials (VEMP) as a balance screening test in infants. The project includes also observational studies about the vestibular assessment of pediatric cohorts at risk for vestibular failure.
SG´s doctoral studies continue in the MOVEST project, in which it is investigated the role of the pediatric physioteraphy in children with vestibular loss.
AUDIOHAB project is the AL´s doctoral program, an analysis of the hearing habilitation registry of Stockholm region, instituted 15 years ago. A registry study and three more cross-sectional studies explore the results obtained by the hearing habilitation program in Stockholm on hearing impaired children reaching now the teenage.
I´m concluding my post-doc studies at the Biomedical Signals and Systems (BSS) research group, Chalmers University of Technology, headed by assoc professor Sabine Reinfeldt. The research is about the clinical application of a new bone transducer prototype, the Ortofon B250. B250 is tested in a new hearing test, the ankle audiometry, but also in VEMP and in the vibration induced nystagmus test. The collaboration with BSS is continued with ZT´s doctoral project (VIBAN), about innovative applications of vibratory stimulation in audiology and neurotology.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Susanne Gripenberg	Niki Karpeta
	Andra Lazar
Zheer Tawfique	

Ethical permit No.

2023-04525-02	2023-01762-02	2022-03381-01	2022-00863-02	

Publications 2021, 2022, 2023

1. Karpeta N, Asp F, Edholm K, Bonnard Å, Wales J, Karltorp E, Duan M, Verrecchia L. Vestibular function in children with vestibulocochlear nerve aplasia/hypoplasia. Acta Otolaryngol. 2023 Oct;143(10):861-866.
2. Verrecchia L, Jansson KF, Reinfeldt S, Håkansson B. The Validation of a Simultaneous Ocular and Cervical VEMP Recording Protocol to Unilateral AC Stimuli. Otol Neurotol. 2023 Dec 1;44(10):e739-e746.

3. Bonnard Å, Karltorp E, Verrecchia L. Vestibular Loss in Children Affected by LVAS and IP2 Malformation and Operated with Cochlear Implant. Audiol Res. 2023 Feb 9;13(1):130-142.
4. Verrecchia L, Fredén Jansson KJ, Westin M, Velikoselskii A, Reinfeldt S, Håkansson B. Ankle Audiometry: A Clinical Test for the Enhanced Hearing Sensitivity for Body Sounds in Superior Canal Dehiscence Syndrome. Audiol Neurootol. 2023;28(3):219-229.
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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 questionaire to determine high airway stenosis. The project evaluates the questionaire 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 tounge cancers and evaluation of ultrasound as method of determening tumour thickness in oral cancers compared with MR/CT and palpation. NBI-guided tounge resections to determine dysplasia/cancer in situ around tumors excised. Outcome of different resections in mandibular cancers. 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 realtionship between relapse and circulating HPV-virus after treatment of orofaryngeal HPV-positive cancer. With Anna Oldaeus
- Outcome after tracheostomies during the Covid-19 pandemic. With Clara Svenberg Lind. Apart from this i am focusing on the Sentinel Node technique in oral and salivary gland cancers and also in cutaneus malignancies.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Olof Nilsson
	Anna Oldaeus Almeren
	Clara Svenberg Lind

Ethical permit No.

2019-0323	2018-104	2015-548	2016-275	2016-193

Publications 2021, 2022, 2023

1. Axelsson L, Holmberg E, Nyman J, Hogmo A, Sjodin H, Gebre-Medhin M, et al. Swedish National Multicenter Study on Head and Neck Cancer of Unknown Primary: Prognostic Factors and Impact of Treatment on Survival. Int Arch Otorhinolaryngol. 2021;25(3):e433-e42.
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7. Ntouniadakis E, Sundh J, von Beckerath M. Monitoring Adult Subglottic Stenosis With Spirometry and Dyspnea Index: A Novel Approach. Otolaryngol Head Neck Surg. 2022;167(3):517-23.
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10. Ntouniadakis E, Sundh J, Soderqvist J, von Beckerath M. How can we identify subglottic stenosis in patients with suspected obstructive disease? Eur Arch Otorhinolaryngol. 2023.

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

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

3. Bilateral bone conductive devices (BCD).
Bone-anchored hearing solutions are often implanted unilaterally. We are assessing whether patients have an imporved ability to localise sound and understand speech when background noise is present if they are provided with bilateral BCD.

4. Late upper airway complications after trachesotomy during the COVID-19 pandemic.
We have seen an increased incidence of late tracheal stenosis in patients that received a trachesotomy during the COVID-19 pandemic. We are assessing incidence, causative factors, screening and diagnostic methods for tracheal stenosis.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Clara Svenberg Lind	Fatima Moumen Denanto

Ethical permit No.

2020-02779	2022-05241-01	2022-05241-01		

Publications 2021, 2022, 2023

1. Karpeta , N., Asp, F., Edholm, K., Bonnard, Å., Wales, J., Karltorp, E., Duam, M., Verrecchia, L. Vestibular function in children with vestibulocochlear nerve aplasia/hypoplasia. ACTA Otolaryngolgica 2024
2. Denanto, F.M., Wales, J., Tideholm, B., Asp, F. Differing bilateral benefits for spatial release from masking and sound localization accuracy using bone conduction devices. Ear and Hearing 2022
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4. Globalsurg Collaborative, Covidsurg Collaborative. Effects of pre-operative isolation on postoperative pulmonary complications after elective surgery: an international prospective cohort study. Anaesthesia 2021;76(11):1454-1464.
5. Globalsurg Collaborative, Covidsurg Collaborative. SARS-CoV-2 infection and venous thromboembolism after surgery: an international prospective cohort study. Anaesthesia 2022;77(1):28-39
6. Covidsurg Collaborative Globalsurg Collaborative. SARS-CoV-2 vaccination modelling for safe surgery to save lives: data from an international prospective cohort study. The British journal of surgery 2021;108(9):1056-1063
7. Globalsurg Collaborative, Covidsurg Collaborative. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. Anaesthesia 2021;76(6):748-758

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Lymphocytes differentiation and autoimmune diseases

My research aims to to understand the molecular mechanisms of lymphocytes development and differentiation and their contribution to the pathogenesis of autoimmune diseases. We have mainly focused on T lymphocytes (Cell Mol Immunol 2021; Cell Rep 2021; J Clin Invest 2022) and B lymphocytes (Theronostics 2021; Front Immunol 2022; Cell Rep Med 2023). We have for the first time developed a Cre transgenic mouse model for tracing and targeting B1 lymphocyte (Front Immunol 2022). We are currently studying two mitotic kinases in regulating T and B cell differentiation and autoimmunity. We aims to repurpose the usage of the drugs inhibiting the mitotic kinases for treating autoimmune diseases by focusing on systemic lupus erythematosus

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Hui Li	
Weixing Yan	

Ethical permit No.

202211S011	201909A019			

Publications 2021, 2022, 2023

1. Xu M, Ren J, Jia W, Wang S, Liu Y, Chen X, Shi J, and Wang H (2023) Regulation of B-1 cell numbers and B cell-mediated antibody production by Inpp4b. Scand J Immunol: e13309.
2. Lilja S, Li X, Smelik M, Lee EJ, Loscalzo J, Marthanda PB, Hu L, Magnusson M, Sysoev O, Zhang H, Zhao Y, Sjowall C, Gawel D, Wang H, and Benson M (2023) Multi-organ single-cell analysis reveals an on/off switch system with potential for personalized treatment of immunological diseases. Cell Rep Med 4: 100956.
3. Gao S, Shi Y, Bai R, Li H, Ren J, Chen X, Hu L, Shi Z, Zhao S, and Wang H (2023) Sputum basophils from allergic asthmatic patients do not express IL-7Rα that is essential for TSLP signalling. Scand J Immunol 97: e13236.
4. Li X, Lee EJ, Lilja S, Loscalzo J, Schafer S, Smelik M, Strobl MR, Sysoev O, Wang H, Zhang H, Zhao Y, Gawel DR, Bohle B, and Benson M (2022) A dynamic single cell-based framework for digital twins to prioritize disease genes and drug targets. Genome Med 14: 48.
5. Li H, Tang Y, Ren J, Bai R, Hu L, Jia W, Cao Y, Hong L, Xu M, Gao S, Shi Y, Pan S, Wang L, Zheng K, Zhao S, and Wang H (2022) Identification of novel B-1 transitional progenitors by B-1 lymphocyte fate-mapping transgenic mouse model Bhlhe41dTomato-Cre. Front Immunol 13:946202.
6. He C, Gao S, Zhao X, Shi Y, Tang Y, Cao Y, Bai R, Ren J, Zhao S, Shi Z, and Wang H (2022) An efficient and cost-effective method for the purification of human basophils. Cytometry Part A 101: 150-158.
7. Chen X, Hu J, Wang Y, Lee Y, Zhao X, Lu H, Zhu G, Wang H, Jiang Y, Liu F, Chen Y, Kim BS, Zhou Q, Liu X, Wang X, Chang SH, and Dong C (2022) The FoxO4/DKK3 axis represses IFN-gamma expression by Th1 cells and limits antimicrobial immunity. J Clin Invest 132.
8. Xie X, Zhu L, Jie Z, Li Y, Gu M, Zhou X, Wang H, Chang JH, Ko CJ, Cheng X, and Sun SC (2021) TRAF2 regulates T cell immunity by maintaining a Tpl2-ERK survival signaling axis in effector and memory CD8 T cells. Cell Mol Immunol 18: 2262-2274.
9. Sun L, Zhao X, Liu X, Zhong B, Tang H, Jin W, Clevers H, Wang H, Wang X, and Dong C (2021) Transcription factor Ascl2 promotes germinal center B cell responses by directly regulating AID transcription. Cell Rep 35: 109188.
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11. Jie Z, Ko CJ, Wang H, Xie X, Li Y, Gu M, Zhu L, Yang JY, Gao T, Ru W, Tang SJ, Cheng X, and Sun SC (2021) Microglia promote autoimmune inflammation via the noncanonical NF-kappaB pathway. Sci Adv 7: eabh0609.
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Studies on laryngotracheal airway diseases

Long-term outcome of reconstructive airway surgery in pediatric and adult patients
- Pediatric tracheostomy - mortality, morbidity and long-term outcome
- Psychosomatic development and quality of life in pediatric patients with tracheostomy
- Supraglottoplasty for laryngomalacia in pediatric patients with comorbidities

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2021, 2022, 2023

1. Wendt M, Hammarstedt L, Dalianis T, Landin D, Munck-Wikland E, Näsman A, Marklund L. Long-term survival and recurrence in oropharyngeal squamous cell carcinoma, in relation to HPV and p16-status. Cancers 2021 May 23;13(11):2553.
2. Wendt M, Papatziamos G, Munck-Wikland E and Marklund L. Sclerotherapy with OK 432 on ranula – a prospective, randomised, double-blinded placebo-controlled study. ACTA Otolaryngol. 2021; 27:1-6
3. Medin G, Wendt M, Ekborn A, Andersson A, Gahm C. Supraglottoplasty for severe laryngomalacia can be effective and safe also in children with high-risk comorbidities - Experience from a tertiary center. Int J Ped Otorhinolaryngol. 2023 Aug:117:111632

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Co-supervisor Åsa Laestadius, Elin Marsk, Malou Hultcrantz,
Registered 2019-09-27
Halftime seminar 2022-12-02
Planed dissertation

Facial nerve palsy in children; treatment and clinical outcome.

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

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

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

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

Ethical permit No.

2016/1937-31/4	2017/554	2010/106	2021-01926	2022-03295-02

Publications/manuscripts 2021, 2022, 2023

1. Karlsson S, Arnason S, Hadziosmanovic N, Laestadius Å, Hultcrantz M, Marsk E, et al. The facial nerve palsy and cortisone evaluation (FACE) study in children: protocol for a randomized, placebo-controlled, multicenter trial, in a Borrelia burgdorferi endemic area. BMC pediatrics. 2021;21(1):220.
2. Arnason S, Skogman BH. Effectiveness of antibiotic treatment in children with Lyme neuroborreliosis - a retrospective study. BMC Pediatr. 2022 Jun 9;22(1):332.
3. Arnason S, Molewijk K, Henningsson AJ, Tjernbeg I, Skogman BH. Brain damage markers neuron-specific enolase (NSE) and S100B in serum in children with Lyme neuroborreliosis – detection and evaluation as prognostic biomarkers for clinical outcome. Eur J Clin Microbiol Infect Dis. 2022 Jul;41(7):1051-1057

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Registered 2021-02-16
Halftime seminar
Planed dissertation

Predictive markers for laryngeal cancer

Cancer of the vocal cords, laryngeal cancer, is one of the most common tumor types in the head and neck region with approximately 180 new cases each year in Sweden. Whereas the survival rate for small tumors (T1) is relatively good, more advanced disease (T2-T4) is associated with poor outcome and has not improved significantly in recent decades. In Sweden and in Stockholm according to national guidelines, patients with T2 and T3 laryngeal cancer are treated with radiotherapy (RT) or chemoradiotherapy (CRT) to preserve the patient's larynx, while patients with T4-tumors are treated surgically with laryngectomy, i.e. resection of the entire larynx and upper trachea often in combination with adjuvant RT/CRT. Our own data and other studies show that there is poorer survival for patients with T3 compared with T4 laryngeal cancer. It is clear that many patients with tumors classified as T3 are undertreated. The question is how to identify which laryngeal tumors that are in need of extended treatment to avoid recurrence and death from laryngeal cancer.

All our sub-studies in this research project aim to identify clinically useful markers and methods that can help us to optimize the choice of treatment strategy for patients with advanced laryngeal cancer.

Ethical permit No.

2019-04829	2021-06907-02		

Publications/manuscripts 2021, 2022, 2023

1. Blomkvist, R, Marklund, L, Hammarstedt-Nordenvall, L, Gottlieb-Vedi, E, Mäkitie, A, Palmgren, B. Treatment and outcome among patients with laryngeal squamous cell carcinoma in Stockholm—A population-based study. Laryngoscope Investigative Otolaryngology. 2023; 1- 9.

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Planned dissertation

Long term effects of early age at cochlear implantation on metaphor comprehension and executive functions in Swedish teenagers

This study is part of the TAYACI (Teenagers and young adults with cochlear implants) project. Early age at cochlear implantation (CI) in congenitally deaf children has positive effects on early spoken language by reducing the period of auditory deprivation. However, the research regarding long term effects of cochlear implantation on higher linguistic and cognitive skills is scarce.

The aim of this project is to investigate long term effects of early cochlear implantation on the development of executive functions and metaphor comprehension. The cohort consists of 44 individuals between 12 and 22 years old, fitted with CI before 30 months of age at the Hearing Implantation Center at Karolinska university hospital. There is a control group with 27 typicallyhearing indviduals matched on age.

Metaphor comprehension was measured using a multiple-choice task. Linguistic skills (vocabulary and reading) is assessed with standardized tests. Executive functions were assessed by task performance (reading span, non word repetition and trail making test) and the BRIEF questionnaire.

preliminary resultsNo difference was found regarding metaphor comprehension between the group with CI and controls. Further analysis indicates a moderate negative correlation ($r = -0.40$, $p<0.05$) between metaphor comprehension and age at implantation.

Conclusions: Our results indicate that earlier age at 1st CI is associated with better metaphor comprehension in adolescents and young adults growing up with CI.

The next step is to analyze the executive function skills of the cohort, followed by a qualitative analysis of verbal responses in the metaphor task as well as further investigating the role of executive function and vocabulary organization in metaphor comprehension.

Ethical permit No.

2021-04345				

Publications/manuscripts 2021, 2022, 2023

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Planned dissertation

Osteoradionecrosis - Riskfactors and reconstructive outcome

Irradiation, surgery and chemotherapy are the three main treatment modalities for head and neck cancer patients. Irradiation, especially in combination with chemotherapy, is associated with considerable side effects. Osteoradionecrosis, ORN, is a late and often severe side effect to irradiation. It is defined as necrotic bone exposed through a mucosal and/or skin defect without tumor recurrence and with a duration of more than three months. There is no exact definition of the pathophysiology of ORN but the current thesis include:

1. Direct damage to local micro vessels causing vascular necrosis in the irradiated area.
2. Production of ROS(reactive oxygen species) that gives an irreversible damage to osteoblasts, -cytes, -clasts.
3. Cytokine mediated dysregulation of fibroblasts and collagen metabolism leading to fibrotic tissue. ORN is for the individual patient a severe condition affecting daily life. Symptoms include trismus, pain, im- paired nutritional capacity and infection not seldom associated with oro-cutanous fistula. ORN is seldom reversible and will progress over time leading to pathological fractures and need for extensive reconstruc- tive surgical intervention including free tissue transfer. This treatment is costly to both patient and society.

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

Aim of our studies:

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

Ethical permit No.

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

Publications/manuscripts 2020, 2021, 2022

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Planned dissertation

Inflammatory changes of soft tissue after radiotherapy

Reconstruction with free tissue transfer is a well established treatment modality for patients with advanced head and neck cancer. A majority of these patients also receive pre- or postoperative radiotherapy. Radiation-induced injury to surrounding healthy tissue is an important limitation of radiotherapy. Epidemiologic studies have shown an increased risk for cardiovascular events, e.g. stroke and myocardial infarction, in patients that have been irradiated. Biopsies from arteries and veins in this patient group have demonstrated acute and chronic inflammatory changes, believed to contribute to post-treatment complications and a decreased quality of life. Preoperative radiotherapy affects tissue healing properties and increased the risk of postoperative infections and fistulas in our material. Through investigations with immunohistochemistry and gene expression analysis of skin biopsies from patients as well as from a murine model we aim to contribute to the understanding of post-therapeutic inflammation and tissue fibrosis in skin after radiotherapy.

Ethical permit No.

2006/834-31	2012/1663-32	2016/1578-32	2008-484-31/2	2008/114-31

Publications/manuscripts 2021, 2022, 2023

1. Eriksson, B.O, Gahm C., Halle, M; Gene expression analysis and long-term presence of macrophages in irradiated skin in head and neck cancer patients compared to irradiated mice (manuscript, 2023)

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Planed dissertation

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

Pituitary adenomas are classified into hormone secreting or clinically inactive. Symptoms arise either due to hormononal effects or local compression, usually the optic chiasm.

Treatment for these adenomas are either medical och surgical dependent on characteristics of the tumor. Sometimes radiation can be used for surgically unacessible locations.

My thesis aims to evaluate treatment in Karolinska University Hospital during the time period 2005-17, focusing on cure rates in ACTH and GH producing adenomas and complications within the group as a whole. This manuscript is due for submission.

We have also evaluated different treatment strategies in periopoperative cortison substitution and published on this topic 2019.

Since 2012 we have collected tissue from pituitary adenomas and pituitaries from 10 organ donors as a base for our receptor studies.

Our aim is that these 2-3 studies are to be completed during 2020. One study will evaluate prevalence of Galaninreceptors, especially type 3, which in previous materials have been indicated as a marker for pituitary adenomas as opposed to normal pituitary tissue.

The fourth study will investigate inflammatory markers, not yet studied in pituitary adenomas. We will also look at neuropeptide Y, pattern recognition receptors and TGFbeta.

My aim is to conclude manuscript 3 2024, manuscript 4 and dissertation in 2025

Ethical permit No.

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

Publications/manuscripts 2021, 2022, 2023

1. Bengtsson, O.F., Sunnergren, O., Segerhammar, I. et al. Remission, complications, and overall survival in transsphenoidal pituitary surgery—a Swedish single-center experience of 578 patients. Acta Neurochir 165, 685–692 (2023). https://doi.org/10.1007/s00701-022-05456-8

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Studies on Nasopharyngeal Cancer – a characterization of a rare disease

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

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

III: To explore the risk of NPC among migrants and their children in Sweden. The possible improvement in outcome over time is to be compared with outcome of non-migrants. Hypothesis: Several studies indicates that there is a strong familial risk of NPC.

IV: To dentify occupations and work-related exposure agents linked to NPC in the Nordic countries. The study is based on a large cohort of almost 15 million persons from the Nordic countries diagnosed with NPC in 1961-2005. The study suggests that NPC may be associated with exposure agents that are work-related such as smoking, kitchen air pollution and solvents.

Ethical permit No.

2019-01933					

Publications/manuscripts 2021, 2022, 2023

1. Carpén T, Gille E, Hammarstedt-Nordenvall L, Hansen J, Heikkinen S, Lynge E, et al. Occupational risk variation of nasopharyngeal cancer in the Nordic countries. BMC cancer. 2022;22(1):1130.

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Halftime seminar
Planned dissertation

Doctoral project: Vestibular function and motor activities in children with hearing loss, balance disorders and motor delays, included in research projects: TAYACI and MOVEST.

I am a PhD student in a research group at SCAPA (Scientific Center for Advanced Pediatric Audiology). My project aims to explore how vestibular loss affects motor functioning in children and teenagers and it also aims to explore the effect of early intervention in children with difficulties with motor functioning related to vestibular dysfunction.

TAYACI is an interprofessional project aiming to ascertain the functional level of TeenAgers and Young Adults, CI recipients since infancy. In the first TAYACI study, we explore how motor functioning relates to vestibular function in a group of teenagers and young adults who received CI in early childhood. The participants are assessed for vestibular function by a MD and a parallel blinded assessment of motor function using motor tests, is conducted by a physiotherapist. Self-reported physical activity and experience of balance are measured with questionnaires. In the second study, we collect data from children in the first study, with inertial sensors applied on different body parts. We analyze with the help of machine learning. The principal question is whether a computerized system based on inertial sensors may implement the clinical evaluation of motor patterns in children with or without vestibular impairment in comparison with age-matched peers. Data analysis is ongoing.

MOVEST is a project aiming to investigate the role of pediatric physiotherapy in children with vestibular loss. In the first MOVEST study, we assess if clinical motor assessments can detect vestibular impairment in infants with hearing loss or motor delay. The infants are tested with age-appropriate test batteries and scores of motor function will be analyzed concerning vestibular function. Data collection is ongoing. The second study will be a pilot study, where we will design and evaluate a vestibular rehab intervention aimed to enhance motor functioning in children with vestibular impairment and motor delay. This study is under planning

Ethical permit No.

2021-04345	2021-00165	2021-04345	2022-00863-02		

Publications/manuscripts 2021, 2022, 2023

1. A manageable and challenging fall prevention intervention with impact on society" -Older womens perspectives on participation in the Stay Balanced training programme. C Halén*, S Gripenberg*, K Skavberg-Roaldsen, A Ståhle, A Halvarsson. doi.org/10.1080/09593985.2021.1972498

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Planned dissertation

Hearing, cognition and aging

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

Ethical permit No.

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

Publications/manuscripts 2021, 2022, 2023

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Studying the effects of allergen specific immunotherapy and tolerance development in allergic rhinitis

Allergic rhinitis (AR) is a chronic condition with a 30% prevalence in Sweden. Despite widespread availability and frequent use of standard of care medication including antihistamine and nasal steroids, the majority of patients are unsatisfied and report a marked impairment in their quality of life . The high prevalence of AR and lack of satisfactory treatment leads to a loss in productivity (presenteeism) resulting in high costs for the society. Allergen-specific immunotherapy (AIT) is currently the only treatment of AR resulting in long-lasting relief of symptoms. Unfortunately, only 5% of AR patients receive this therapy, due to the extended duration of treatment required for effect (3-5 years) and the risk of severe side effects. Hence, a shorter treatment duration and an improved safety profile are stated as important unmet needs in AIT.

Pharmacotherapy is offered for patients with mild to severe nasal allergy symptoms, while allergen-specific immunotherapy (ASIT) is the main treatment for inducing long-term immunological and clinical tolerance in patient with IgE-mediated allergic disease, and is the only curative treatment . Subcutaneous immunotherapy (SCIT) is a form of ASIT. Though efficacious, SCIT prevents the progression of AR to asthma, but is time-consuming and involves numerous injections. A new form of ASIT is intra lymphatic immunotherapy (ILIT). The treatment duration for ILIT is much shorter and has comparably mild side effects.

At present little is known about how a given injected allergen during SCIT and ILIT affects immune cells in lymph nodes and how it induces immunological tolerance. The overall aim of this doctoral project is to study the immunological changes that induce tolerance to allergen in patients undergoing SCIT and ILIT in combination with vitamin D. We will focus the different projects on memory type allergen-specific T and B cell responses.

Ethical permit No.

2021-03633	2021-00325	2021-06514-02		

Publications/manuscripts 2021, 2022, 2023

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Planned dissertation	

Bone Conduction Devices and Active Middle Ear Implants in Children with Unilateral Aural Atresia- Functional and Qualitative Assessments

Individuals with unilateral hearing loss are known to have difficulties in situations requiring binaural processing of sounds, such as listening in noisy environments and localizing 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 conduction devices (BCD) on audiological outcomes such as sound localisation ability (SLA) and speech recognition (SCS), surgical outcomes and the degree of patient satisfaction.

Study 1: Horizontal Sound Localization Ability and Speech Perception in Competing Speech in Children with Unilateral Aural Atresia Using Percutaneous BCD.
Children age 5-10 years with BCD is recruited for testing of PTA, SCS and SLA using corneal eye tracking.

Study 2: Evaluation of Bone Anchored Hearing Systems, Audiology and Fixture Mechanics.
Children with congenital conductive hearing loss suited for implantation with percutaneous BCD using a titanium fixture are included in this study that evaluates a new type of titanium screw, BHX. In collaboration with Oticon Medical.

Study 3: A Retrospective Chart Study of BCD Usage in Children with Aural Atresia at Karolinska University Hospital.
A retrospective chart review of children with aural atresia treated with percutaneous BCD at Karolinska University Hospital.

Study 4: Patient Satisfaction and Long-Term Usage of Percutaneous BCD
Subjects aged 0-18 operated with percutaneous BCD at Karolinska University Hospital 2010-2020 are asked to fill out a questionnaire regarding usage of their implant, and reasons for possible non-usage.

Study 5: BHAMBI, Binaural Hearing in children with unilateral Atresia using active Middle ear or Bone conduction Implants
Subjects aged 5-18 eligible for implantation with an aMEI or an active transcutaneous BCD. Per- and postoperative surgical complications are registered. Subjects will participate in standard clinical audiometry, SLA and SCS.

Ethical permit No.

2012/1661-313	2018/864-31	2021-02984		

Publications/manuscripts 2021, 2022, 2023

1. Josefsson Dahlgren H, Engmér Berglin C, Hultcrantz M and Asp F (2023) A pilot study on spatial hearing in children with congenital unilateral aural atresia. Front. Pediatr. 11:1194966. doi: 10.3389/fped.2023.1194966

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Predictive markers for head- and neck tumors

Head and neck cancer is rising, oropharyngeal cancer being the second most common. HPV is a known prognostic marker for oropharyngeal squamous cell carcinoma (OPSCC), especially for tonsillar and base of tounge squamous cell carcinoma (TSCC and BOTSCC). An important differential diagnosis for branchial cleft cysts (BrCCs) is OPSCC and Cancer of unknown origin (CUP). Study 1 is already published where all patients with surgical code for removal of branchial cleft cysts were included (n=436) and cystic metastases were demonstrated histologically after surgical excision in 13 patients (3%): 3 papillary thyroid cancer (PTC), 3 BOTSCC, 1 TSCC and 5 CUP. No HPV was found in the patients with BrCC, and all BOTSCCs were HPV positive while the other OPSCCs did not have enough cells to perform the HPV analyse, and in PTC it is not applicable. We will further investigate, in study 2, whether fine needle aspiration cytology (FNAC) with HPV DNA analysis on the aspirate is enough for diagnosing BrCCs. We will also include the CUP patients in this study to see if FNAC with HPV analysis is a predictive marker in that group as well. In study 3 we will investigate wheter EBV could be used as a predictive marker for OPSCC together with HPV or alone. In study 4 we are evaluating a surgical method for non-palpable lymph nodes that need to be exstirpated, often due to a hematological malignancy such as lymphoma. This study is on-going and we are including patients and they are randomized to either ultrasound-guidance or ultrasound- and anchor-guidance. The anchor is a small anchor that is connected to a guiding wire, that is introduced to the lymph node while with the help ultrasound to mark the right lymph node. Right now we have included 30 patients.

Ethical permit No.

2005/431-31/4	2009/1278-31/4	2015/0157-32	2017/1035-31/2	2021-00679

Publications/manuscripts 2021, 2022, 2023

1. Hammarstedt Nordenvall L, Jörtsö E, von Beckerath M, Tani E, Nordemar S, Bark R. Prevalence of cystic metastases in a consecutive cohort of surgically removed branchial cleft cysts. Acta Otolaryngol. 2022 Jan;142(1):100-105. doi: 10.1080/00016489.2021.2016951. Epub 2021 Dec 28. PMID: 34962438.

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Halftime sesminar 2024-01-15
Planned dissertation

Corticosteroid treatment in children with acute facial nerve palsy

Children with acute peripheral facial nerve palsy cannot yet be recommended corticosteroid treatment based on evidence. Adults with idiopathic facial nerve palsy are treated with corticosteroids, according to guidelines resulting from a meta-analysis comprising two major randomized placebo-controlled trials. Corresponding trials in children are lacking. Furthermore, acute facial nerve palsy in childhood is frequently associated with Lyme neuroborreliosis, caused by the spirochete Borrelia burgdorferi. The efficacy and safety of corticosteroid treatment of acute facial nerve palsy associated with Lyme neuroborreliosis, has not yet been determined in prospective trials in children. The FACE study is a placebo-controlled double-blinded randomized trial that aims to determine the efficacy of prednisolone treatment in children with acute facial nerve palsy of either idiopathic etiology or associated to neuroborreliosis and forms the basis of the doctoral project. Within the framework of the project a patient reported outcome meusure (PROM) will be evaluated using Rasch analysis, a method derived from modern test theory.

Ethical permit No.

2017/554	2019-01546	2021-01926	2009/156-31/2	2022-00501-02

Publications/manuscripts 2021, 2022, 2023

1. The facial nerve palsy and cortisone evaluation (FACE) study in children: protocol for a randomized, placebo-controlled, multicenter trial, in a Borrelia burgdorferi endemic area, Karlsson s, Arnason s, Hadziosmanovic N, Laestadius Å, Hultcrantz M, Marsk E, Skogman BH, BMC Pediatrics 2021
2. A modern test theory approach to evaluating the FaCE scale – a patient reported outcome measure (PROM) for patients with facial nerve palsy, Karlsson S, , Janeslätt G, Hultcrantz M, Marsk E, Skogman BH, In manuscript

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Halftime seminar		2023-06-28
Planned dissertation		Mars 2025

Developing of objective balance tests in newborns and young children

The vestibular function plays a key role in the child's motor development especially during the first two years of life. It is the only active sensory system at birth and is fully integrated at teenage. Normally a baby can achieve head control at 4 months and go a few steps at 12 months old.Kimura and Kaga with coworkers showed delayed motor skills in children with reduced vestibular reflexes in studies in 2018 and 2019, respectively. Moreover, vestibular problems are associated with falls without deflect movements navigation problems and reading difficulties.It has been reported that preoperatively 40% of CI candidates, have an accompanied vestibular dysfunction. The surgical operation itself is an independent risk factor for vestibular injury.We propose a systematic methodology for testing newborns and young chilfren with two child friendly and scientifically approved methods (VEMP, vHIT). The identification of the optimal testing approach for vestibular screening in clinical praxis is also of great importance as the identification of a possible vestibular dysfunction will lead to a correct assessment of balance and thus an early intervention with physiotherapy. This will improve the child's motor development in the long term and will also affect unnecessary health care contacts

Ethical permit No.

2015/1296-31/2	2014/2068-31/2	2022-02135-02	2021-00165	

Publications/manuscripts 2021, 2022, 2023

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2. Comorbidities and laboratory changes of sudden sensorineural hearing loss: a review.Xie W, Karpeta N, Tong B, Liu Y, Zhang Z, Duan M.Front Neurol. 2023 Apr 18;14:1142459. doi: 10.3389/fneur.2023.1142459. eCollection 2023.PMID: 37144001
3. Etiological analysis of patients with sudden sensorineural hearing loss: a prospective case-control study. Xie W, Karpeta N, Tong B, Liu J, Peng H, Li C, Hellstrom S, Liu Y, Duan M.Sci Rep. 2023 Mar 30;13(1):5221. doi: 10.1038/s41598-023-32085-7.PMID: 36997587
4. Diagnosis, differential diagnosis, and treatment for sudden sensorineural hearing loss: Current otolaryngology practices in China. Chen N, Karpeta N, Ma X, Ning X, Liu X, Song J, Jiang Z, Ma X, Liu X, Zhong S, Sun Q, Liu J, Chen G, Duan M, Yu L.Front Neurol. 2023 Feb 23;14:1121324. doi: 10.3389/fneur.2023.1121324. eCollection 2023. PMID: 36908605
5. Efficacy of intratympanic or postauricular subperiosteal corticosteroid injection combined with systemic corticosteroid in the treatment of sudden sensorineural hearing loss: A prospective randomized study.
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7. The relationship between clinical characteristics and magnetic resonance imaging results of Ménière disease: a prospective study.
8. Xie W, Shu T, Liu J, Peng H, Karpeta N, Marques P, Liu Y, Duan M.Sci Rep. 2021 Mar 30;11(1):7212. doi: 10.1038/s41598-021-86589-1.PMID: 33785791

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Halftime seminar
Planned dissertation

Sentinel node in oral and orofaryngeal cancer

Sentinel node biopsy is a technique used to investigate if a cancer that spread through the lymphatic system has metastasized. By injecting a radioactive and fluorescent tracer near the tumor, the sentinel nodes, which are the first lymph nodes to receive drainage from the tumor site, can be identified and removed. The sentinel nodes are the first locations where metastases typically occur. This research project focuses on the application of the sentinel node technique in oral and oropharyngeal cancer and its potential for further development.

One area of interest is the topography of the sentinel node, which can sometimes deviate from established lymphatic drainage pathways. In the first sub-study, the topographic placement of sentinel nodes and occult metastases in 40 patients with N0 tongue cancer is being investigated, along with the sensitivity of the technology as used at the clinic.

In the second sub-study, the use of the sentinel node technique in already metastatic (N+) oral cancer is being explored. The technique can be used as a guide to a more radical neck dissection.

In the third study, the application of the sentinel node technique in radiation planning for oral cancer treatment is being investigated. Although traditionally used as a diagnostic technique by surgeons, the sentinel node could also be used to individualize radiation plans by reflecting the true lymphatic pathways.

The fourth study will explore the applicability of the sentinel node technique in tonsil cancer. Specifically, we will investigate the best injection technique and the topography of sentinel nodes. As tonsil cancer is primarily treated with radiation therapy to the primary tumor and neck lymph nodes, the sentinel node technique could eventually be of interest to oncologists in radiation planning.

Ethical permit No.

2013/1943-31/4	2019-03518	2021-01265		

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1. Bark R, Kolev A, Elliot A, Piersiala K, Näsman A, Grybäck P, Georén SK, Wendt M, Cardell LO, Margolin G, Marklund L. Sentinel node-assisted neck dissection in advanced oral squamous cell carcinoma-A new protocol for staging and treatment.Cancer Med. 2023 Jun;12(11):12524-12534. doi: 10.1002/cam4.5966. Epub 2023 Apr 21.PMID: 37084007

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Halftime seminar 2023-12-06
Planned dissertation

Immunologic characterization of tumor draining lymph nodes in head and neck squamous cell carcinoma

Many patients with head and neck squamous cell cancer (HNSCC) present regional spread to the cervical lymph nodes (LN), while distant metastases are rare. Nodal involvement is the most important factor adversely affecting both the treatment and outcome. The treatment involves surgical removal of primary tumour, and removal of LN from one or more anatomical regions of the neck. However, extensive neck dissection is not without risks for severe complications. We want to provide an improved perioperative staging, so that only patients diagnosed with metastasis or unfavorable immunological features in sentinel node will receive a full neck dissection. Our preliminary results, clearly indicate that patients with low T-cells activation in LN have significantly higher risk of recurrence and death. Moreover, the development of new cancer treatments, especially immune checkpoint inhibitors (CPI), have changed the field of oncology. However, less than 20% of patients with HNSCC treated with CPI responds to this treatment. This is why, in order to fully benefit from this paradigm shift we have to improve the way we select patients for various treatment alternatives.

The overall goal is to provide a better outcome prognostic marker as well as introduce an improved selection of patients who need more rigorous follow-up and those who would benefit from CPI. The overall aims are firstly to provide a detailed characterization of different B cellular components of a lymph node. Secondly, to comprehensively investigate the humoral immune response against various tumour-associated antigens (TAAs) and lastly, to explore the mechanism of B cell cellular interactions and B cell mediated immune suppression in patients with oral cancer.

Ethical permit No.

2019-03518	2021-01265			

Publications/manuscripts 2021, 2022, 2023

1. Piersiala K, da Silva PFN, Lagebro V, Kolev A, Starkhammar M, Elliot A, Marklund L, Munck-Wikland E, Margolin G, Georén SK, Cardell LO. Tumour-draining lymph nodes in head and neck cancer are characterized by accumulation of CTLA-4 and PD-1 expressing Treg cells. Transl Oncol. 2022 Jun 14;23:101469. doi: 10.1016/j.tranon.2022.101469. Epub ahead of print. PMID: 35714487; PMCID: PMC9207719.
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Halftime seminar 2023-03-30
Planned dissertation

Bell's palsy in pregnancy and puerperium

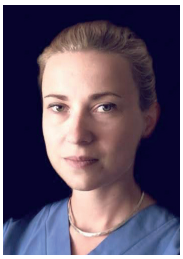
To examine the incidence of Bell's palsy among pregnant women in Stockholm during a 10-years period, to find risk factors for developing Bell's palsy during pregnancy and the puerperium (first 6 weeks post partum), to see how these women heal compared to non pregnant women with Bells palsy and how the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

Ethical permit No.

2015/2349-31/1				

Publications/manuscripts 2021, 2022, 2023

1. Lansing, L., Wendel, S.B., Hultcrantz, M. and Marsk, E. (2023), Bell's Palsy in Pregnancy and Postpartum: A Retrospective Case-Control Study of 182 Patients. Otolaryngol Head Neck Surg. https://doi.org/10.1002/ohn.188.



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Halftime seminar
Planned dissertation

Pre/retrospective, genetics study and habilitation of hearing loss in children

The purpose of this research project is to map the clinical picture of older children with bilateral moderate-severe sensorineural hearing loss registered in the hearing habilitation centre in Stockholm. A registry study and three more cross-sectional studies explore the natural evolution and investigations that have led to etiological diagnosis to give us a better understanding of the etiopathology and evolution of SHL in children in the Stockholm region.

Ethical permit No.

2020-07203	2023-01762-02			

Publications/manuscripts 2021, 2022, 2023

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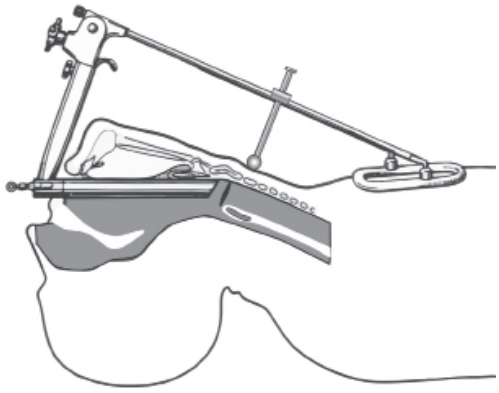
Halftime seminar
Planned dissertation

A new aid for better visibility during laryngoscopy: The cricoid depressor
A new improved laryngoscope stand



Transoral surgery of the larynx with a microscope under anesthesia (microlaryngoscopy) often requires external pressure over the larynx for good visualization of the vocal folds, especially when the pathology is located anteriorly. This requires the surgon to use one hand to apply pressure at the larynx or have an assistant doing that during all or part of the surgury. Aids such as using tape from one side of the operating table to the other side over the patient's larynx can be used, but rarely generate the pressure needed in more challenging patients.

The new aid "cricoid depressor", can be used in microlaryngoscopic surgery to improve visibility. The cricoid depressor is a metal arm that is attached to the support arm of the laryngoscope stand (see picture) and generates a stable pressure over the larynx during surgery. The pressure of the depressor can be varied as needed by adjusting it laterally and vertically.The cricoid depressor has been tested at Karolinska University Hospital for about two years (2020-2022) and has been shown to improve visibility and facilitate surgery in both microlaryngoscopy and major endoscopic tumor surgery. We therefore initially wish to examine how often external pressure is necessary during microlaryngoscopies (MLS). This is to evaluate whether there is a need for a cricoid depressor in vocal fold surgery. If so, we wish to investigate the cricoid depressor's pros and cons further.

Ethical permit No.

Publications/manuscripts 2021, 2022, 2023

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Planned dissertation

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2021-11-02

Adverse events in cholesteatoma surgery - risk, contributing factors and quality of life

Cholesteatoma, the growth of squamous cell epithelium into the middle ear may cause complications such as hearing loss, infections, bon destruction and facial palsy. The treatment is surgical, and surgery is performed in an area defined by the facial nerve, the sigmoid dura, the middle fossa dura plate, the labyrinth, the temporomandibular joint and the posterior wall of the ear canal. Sensitive structures that may be affected during surgery.

The aim of the thesis is analyzing different aspects of adverse events and effects on quality of life after cholesteatoma surgery as well as risk factors for the disease. This will be studied both nationally in a registry based study and locally in retrospective as well as prospective studies

Ethical permit No.

2020-05935	2019-05190	2020-00245		

Publications/manuscripts 2021, 2022, 2023

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Registered 2020-04-20
Halftime seminar 2022-06-02
Planned dissertation

Bilateral bone anchored hearing devices

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

Ethical permit No.

2019-04696				

Publications/manuscripts 2021, 2022, 2023

1. Differing Bilateral Benefits for Spatial Release From Masking and Sound Localization Accuracy Using Bone Conduction Devices, Ear and Hearing 43(6):p 1708-1720, November/December 2022. |DOI:10.1097/AUD.0000000000001234

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Registered 2017-11-30
Halftime seminar Planned May 2024
Planned dissertation

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

Persistent sequelae of peripheral facial palsy imposes a great reduction in quality of life. This thesis aims to evaluate sequelae from different perspectives; - Investigate incidence of long term sequelae and treatment needs after peripheral facial palsy

- Identify patients at risk for eye complications in a prospective study in collaboration with S:t Eriks Eye Hospital
- Evaluation of two surgical methods to target severe sequele following peripheral facial palsy; early cross facial nerve transplatations, the Babsitter procedure, in Bell's palsy and highly selective neurectomies to treat synkinesis, i.e. mass muscle movements.

Ethical permit No.

2011/598-32	2019-00421	2021-00246	2023-00761-01	

Publications/manuscripts 2021, 2022, 2023

1. Sequelae treatment needs following peripheral facial palsy: retrospective analysis of 525 patients - Accepted for publication, Otology & Neurotolog

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Halftime seminar
Planned dissertation

Intralymphatic immunotherapy (ILIT) empowered by vitamin D, a double-blind, randomized, placebo-controlled study and comparison with SLIT

Allergic rhinitis (AR) is a chronic condition with a 30% prevalence in Sweden. Despite widespread availability and frequent use of standard of care medication most patients are unsatisfied and report a marked impairment in their quality of life.
AIT is currently the only treatment that incudes long-lasting relief of symptoms. It can be administered either traditionary as subcutaneous injections (SCIT) every 6–8 weeks or as a sublingual alternative (SLIT). Both routes involve treatment during at least three years.
Ten years ago, intralymphatic injections (ILIT) were proposed as a new route for AIT. ILIT delivers allergen directly to the lymph nodes (in the groin) and as tolerance induction primarily is centred to the lymph nodes this method provides the maximal chance for tolerance induction.
Three injections with the same allergen-based vaccine as in SCIT but 100 times lower concentration injected with an interval of four weeks results in a comparable clinical effect as three years of traditional AIT (reduction of symptoms, skin prick sensitivity and serum Ig E levels) with fewer side effects and better compliance.
VitD is a hormone that after intake gets activated by UV-radiation. There is convincing evidence for a positive influence of vitD in treatment of allergic inflammation.The time of initiation of AIT (off pollen season) overlaps the time of the year when the level of naturally produced vitamin D (vitD) might be at its lowest. The hypothesis is that the addition of vitD during the ILIT markedly improves the outcome, potentially making all patients good responders, and ultimately resulting also in a curative effect. And further more a 'head to head' comparison
with SLIT will take place.
A successful outcome will promote the establishment of ILIT as an accesible alternative to the more difficult implement traditional forms of AIT.

Ethical permit No.

2022-02039-01				

Publications/manuscripts 2021, 2022, 2023

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Planned dissertation	2024-06-14

Tumor-Draining Lymph Nodes in Head nd neck cancer: Exploring immunological signatures, clinical implications, and therapeutic insights

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.

Current research is mainly focused on finding biomarkers for treatment response in the blood and in the tumour itself. The results are so far disappointing. Recently, tumour-draining lymph nodes (TDLN) and their interaction with the primary tumour have received increasing attention. TDLN are now believed to play a decisive role in regulating immunotherapy response and modulating anti-cancer immunity.

The aim of our pjects is to characterise immunological environment in TDLNs of patients suffering from oral squemous cell carcinoma and try to identify a new type of TDLNs-derived biomarkers that can predict the treatment outcome before initiation of CPI. These markers might also be used to monitor the progression of the disease in both responder and non-responders.

Ethical permit No.

2019-03518				

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15. Lechien JR, Hans S, Simon F, Horoi M, Calvo-Henriquez C, Chiesa-Estomba CM, Mayo-Yáñez M, Bartel R, Piersiala K, Nguyen Y, Saussez S. Association Between Laryngopharyngeal Reflux and Media Otitis: A Systematic Review. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology 2021 42;7 e801-e814
16. Piersiala K, Farrajota Neves da Silva P, Hjalmarsson E, Kolev A, Kågedal Å, Starkhammar M, Elliot A, Marklund L, Margolin G, Munck-Wikland E, Kumlien Georén S, Cardell LO. CD4+ and CD8+ T cells in sentinel nodes exhibit distinct pattern of PD-1, CD69, and HLA-DR expression compared to tumor tissue in oral squamous cell carcinoma. Cancer science 2021 112;3 1048-1059
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18. Weinreb SF, Piersiala K, Hillel AT, Akst LM, Best SR. Dysphonia and dysphagia as early manifestations of autoimmune inflammatory myopathy. American journal of otolaryngology 2021 42;1 102747-
19. Westerberg J, Tideholm E, Piersiala K, Drakskog C, Kumlien Georén S, Mäki-Torkko E, Cardell LO. JAK/STAT Dysregulation With SOCS1 Overexpression in Acquired Cholesteatoma-Adjacent Mucosa. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology 2021 42;1 e94-e100
20. Piersiala K, Akst LM, Hillel AT, Best SR. Laryngeal Pathologies and Their Associations With Mental Health Disorders. LARYNGOSCOPE 2021 131;1 E231-E239
21. Sidell DR, (…), Piersiala K, Prager JD, Pransky SM, Preciado D, Raynor T, Rinkel RNPM, Rodriguez H, Rodríguez VP, Russell J, Scatolini ML, Scheffler P, Smith DF, Smith LP, Smith ME, Smith RJH, Sorom A, Steinberg A, Stith JA, Thompson D, Thompson JW, Varela P, White DR, Wineland AM, Yang CJ, Zdanski CJ, Derkay CS. Systemic Bevacizumab for Treatment of Respiratory Papillomatosis: International Consensus Statement. The Laryngoscope 2021 131;6 E1941-E1949

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Registered 2020-08-18
Halftime seminar 2021-10-22
Planned dissertation

Zygomaticomaxillary Complex Fractures: Aspects of Diagnostic Methods, Treatments and Complications

Zygomaticomaxillary Complex (ZMC) fractures are one of the most common types of facial fractures and frequently managed at Karolinska University Hospital (KUH). Functional complixations (e.g. trismus, double vision or impaired sensation) and cosmetic complications (e.g. ocular dystopia or a sunken/broadened cheek) are common and managed either by conservative or surgical treatment. Although the body of literature offers a wide range of suggestions and algorithms for managing ZMC fractures, it is still largely the surgeons' individual training, experience and preference that influence the choice of treatment instead of systematic evidence.

Overall aim of the project:

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

Ethical permit No.

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

Publications/manuscripts 2021, 2022, 2023

1. A Shaikh, R Hammoud, E Al Duhirat, F Emam, A Aljariri, H Al Saey, M Al Sulaiti, S Ashkanani, M Alhail, S Rahbin, R Zahid, J Al Jufairi, S Ganesan: Retrospective analysis of nasal factors leading to intractable epistaxis post COVID-19 swab: A tertiary care experience (manuscript)
2. S Rahbin, O Sunnergren, E Lindgren, H Darabi, B Alinasab: Differences Between Patient and Surgeon Perspectives: A Long-Term Follow-Up of 180 Patients With Zygomaticomaxillary Complex Fractures Following Either Conservative or Surgical Treatment Craniomaxillofacial Trauma & Reconstruction (article under press) DOI: 10.1177/19433875231208463
3. Rahbin S, Toufani T, Al-Khabbaz AM, Lindblom J, Sunnergren O, Darabi H, Qureshi A R, Alinasab B: The Volume Difference Along the External Surface of the Zygomatic Bone: A Novel Method of Measuring Zygomatic Bone Asymmetry J Craniofac Surg. 2022 Mar/Apr 01;33(2):463-468. DOI: 10.1097/SCS.0000000000008186 (2022).
4. S Rahbin, M Kjellberg, M Söderlind & A Ekborn: Well-planned rather than rushed extraction of airway foreign body in 532 g preterm neonate Acta Oto-Laryngologica Case Reports. 6:1, 85-87. DOI: 10.1080/23772484.2021.2002153 (2021).
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Registered 2019-03-18
Halftime seminar 2023-09-29
Planned dissertation

Regenerative closure of tympanic membrane perforations- clinical and experimental 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	2018/362-32	2022-06108-01	

Publications/manuscripts 2021, 2023, 2023

Carl Skröder carl.skroder@ki.se
Main supervisor Lars Olaf Cardell
Co-supervisor Ulla Westin
Registered 2020-05-14
Halftime seminar
Planned dissertation

Treatment of allergic rhinitis with systemic steroids and health economic aspects

Allergic rhinitis (AR) is a chronic condition with a 30% prevalence in Sweden. Despite widespread availability and frequent use of standard of care medication the majority of patients are unsatisfied and report a marked impairment in their quality of life. When standard of care treatment fails, like in the middle of a severe pollen season, short-term systemic corticosteroids are often prescribed, especially in private practice. However, injected corticosteroids is not recommended in modern guidelines, due to risk for side effects and lack of documented efficacy. Despite this, the longstanding praxis of giving a pre-seasonal intramuscular injection methylprednisolone remains at several places around the world.

Primary hypothesis: 80 mg (2 ml) intramuscular injected methylprednisolone reduce symptomes more effeciently compared to placebo (2 ml intramuscular injected NaCl).
20 mg Prednisolone results in a significant symptome reduction compared to 20 mg Kestine.
Secondary hypothesis: A short-term systemic corticosteroids treatment improve quality-of-life (SNOT-22 and Juniper RQLQ) during the study period. Levels of bone turn over marker (CTX) will not change significantly.

In the methylprednisolone study there was a significant difference in daily symptom score (dSS), daily medical score (dMS) and daily combined symptome- and medical score (dCSMS) between the groups throughout the birch pollen season 2019. The slightly improved dCSMS in the patients treated with a single intramuscular injection of 80 mg methylprednisolone conjure no strong evidence for the beneficial effects of using systemic steroids in addition to standard of care for treatment of seasonal allergic rhinitis during the peak of the pollen season.
In the prednisolone study, no significant differnce was seen in dSS, dMS, dCSMS or QoL (SNOT-22 and Juniper RQLQ) between the groups, throghout the the birch pollen season 2018.

Ethical permit No.

2016/2158	2017/947	2018/11		

Publications/manuscripts 2021, 2022, 2023

1. HealthSWEDE: Costs with sublingual immunotherapy - a questionnaire study Petter Olsson, Carl Skröder, Lars Ahlbeck, Frida Hjalte, Karl-Olof Welin, Ulla Westin, Morgan Andersson, Cecilia Ahlström-Emanuelsson & Lars-Olaf Cardell. Allergy, Asthma & Clinical Immunology volume 17, Article number: 55 (2021) Manuscript:
2. It is advisable to be hesitant in the use of prednisolone tablets as treatment of pollen induced allergic rhinitis - Databearbetning Carl Skröder, Laila Hellkvist, Ulla Westin, Pernilla Sahlstrand-Johnsson, Åslög Dahl, Leif Bjermer, Lars Olaf Cardell
3. Limited beneficial effects of systemic steroids when added to standard of care treatment of seasonal allergic rhinitis Carl Skröder, Laila Hellkvist, Åslög Dahl, Ulla Westin, Leif Bjermer, Agneta Karlsson, Lars Olaf Cardell Sci Rep. 2023. PMID: 37950032

Martin Smelik martin.smelik@ki.se
Main supervisor Mikael Benson
Co-supervisor Oleg Sysoev, Cladio Cantu, Lars Olaf Cardell
Registered 2022-11-09
Halftime seminar 2024-01-12
Planned dissertation

Combining machine learning and multiomics to identify biomarkers for early prediction of complex and malignant diseases

1. Multi-Organ Single Cell Analysis Reveals an On/Off Switch System with Potential for Personalized Treatment of Immunological Diseases: In this project we use a large cohort of Lupus patients to identify patient subgroups having similar disease severity indicators and influential variables that define these subgroups. We constructed a machine learning model that jointly analyze the protein levels as well as the clinical data like age, gender, smoking history, recently prescribed drugs and many others. This model was tested for several subgroups of patients to compare the effects of influential variables on the disease severity indicators.

2. An interactive atlas of genomic, proteomic, and metabolomic biomarkers indicates that combinations of small numbers of proteins suffice to predict and diagnose complex diseases: Here, we make a systematic comparison of 90 million genetic variants, 1,453 proteins, and 325 metabolites from 500,000 individuals with complex diseases from the UK Biobank. A machine learning pipeline consisting of data cleaning, data imputation, feature selection, and model training using cross-validation and comparison of the results on holdout test sets showed that proteins were most predictive, followed by metabolites, and genetic variants. Only five proteins per disease resulted in median (min-max) areas under the curves for incidence of 0.79 (0.65-0.86) and 0.84 (0.70-0.91) for prevalence.

3. Multiomics biomarkers were not superior to clinical variables for pan-cancer screening
Objective: To evaluate whether cancer screening can be improved by identifying biomarkers via multiomics analyses of peripheral blood
Conclusions and Relevance: Our findings did not support significant improvement of pan-cancer screening based on biomarkers from multiomics analyses of peripheral blood. However, biomarkers for individual cancers may prove useful. We constructed a user-friendly Shiny app to identify such biomarkers.

Ethical permit No.

6798/18	202012A162	M75-08/2008		

Publications/manuscripts 2021, 2022, 2023

1. Sandra Lilja, Xinxiu Li, Martin Smelik, Eun Jung Lee, Joseph Loscalzo, Pratheek Bellur Marthanda, Lang Hu, Mattias Magnusson, Oleg Sysoev, Huan Zhang, Yelin Zhao, Christopher Sjöwall, Danuta Gawel, Hui Wang & Mikael Benson. Multi-Organ Single Cell Analysis Reveals an On/Off Switch System with Potential for Personalized Treatment of Immunological Diseases; Cell Reports Medicine (Will be published 28.2.2023

Clara Svenberg Lind clara.svenberg-lind@ki.se
Main supervisor Jeremy Wales
Co-supervisor Mathias von Beckerath, Jessica Kåhlin, Lalle Hammarstedt Nordenvall

Registered 2023-01-01
Halftime seminar 2023-06-01
Planned dissertation

Tracheostomy in the era of Covid-19

The Covid-19 pandemic led to an unprecedented amount of patients requiring tracheostomy. We analyse the immediate, short- and long-term complications of this technique when performed by otolaryngologists or intensivists.

Ethical permit No.

2020-2779	2022-05241-01			

Publications/manuscripts 2021, 2022, 2023

1. Globalsurg Collaborative, Covidsurg Collaborative. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. Anaesthesia 2021;76(6):748-75
2. Covidsurg Collaborative Globalsurg Collaborative. SARS-CoV-2 vaccination modelling for safe surgery to save lives: data from an international prospective cohort study. The British journal of surgery 2021;108(9):1056-1063
3. Globalsurg Collaborative, Covidsurg Collaborative. Effects of pre-operative isolation on postoperative pulmonary complications after elective surgery: an international prospective cohort study. Anaesthesia 2021;76(11):1454-1464.
4. Globalsurg Collaborative, Covidsurg Collaborative. SARS-CoV-2 infection and venous thromboembolism after surgery: an international prospective cohort study. Anaesthesia 2022 Jan;77(1):28-39.
5. To be submitted: Visible laryngotracheal pathologies one year after ICU-care and their relation to patient-care factors in a COVID-19 cohort.

Zheer Tawfique zheer.tawfique@ki.se
Main supervisor Luca Verrecchia
Co-supervisor Bo Håkansson, Sabine Reinfeldt, Karl Johan Freden Jansson

Registered 2023-11-02
Halftime seminar
Planned dissertation

Bone conducted stimulation in audiology and neurotology: new perspectives

Through our research project we aim to further expand upon the use of bone conduction stimulation (BC) in diagnostics and treatment within neurotology. By this, we hope to improve the current management of specific fields within clinical neurotology.
The research project comprises of four studies.

Two are diagnostic studies:
1. The diagnostic accuracy of ankle audiometry for superior canal dehiscence syndrome in patients affected by pulsatile tinnitus and/or autophony.
2. The role of a balance screening by VEMP in infants alongside the newborn hearing screening program.

Two are intervention studies:
1. BC stimulation in the treatment of benign paroxysmal positional vertigo.
2. BC stimulation in the teatment of bilateral vestibulopathy.

All studies are still in their planning phases.

Ethical permit No.

2020-04214	2023-04525-02			

Publications/manuscripts 2021, 2022, 2023

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Planned dissertation

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Oleg Sysoev, Claudio Cantu, Lars-Olaf Cardell
2022-11-23
2023-09-23

A single cell-based strategy to identify mechanisms and biomarkers for cancer diagnosis and prognosis

1: Identifying Shared Cell Types and Mechanisms in Common Cancers associated with cancer survival. In the this study, I developed a shared multi-cellular model that across five distinct cancer types. This model derived signature genes that showed significant association with survival in many cancers in two large cohorts (TCGA and UK biobank).

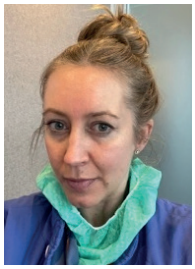
2: Using single-cell RNA analysis to fine-tune polygenic risk scores (PRS) for pancreatic cancer survival. We sucssesfully created PRS by mapping genetic variance that associated with pancreatic cancer in to programs that created by scRNA. The resulted PRS that associated with pancreatic cancer patients in the UK biobank. In contrast, the published PRS has non such association.

Ethical permit No.

6798/18	202012A162	M75-08/2008		

Publications/manuscripts 2021, 2022, 2023

1. Multi-Organ Single Cell Analysis Reveals an On/Off Switch System with Potential for Personalized Treatment of Immunological Diseases; Sandra Lilja, Xinxiu Li, Martin Smelik, Eun Jung Lee, Joseph Loscalzo, Pratheek Bellur Marthanda, Lang Hu, Mattias Magnusson, Oleg Sysoev, Huan Zhang, Yelin Zhao, Christopher Sjöwall, Danuta Gawel, Hui Wang & Mikael Benson; Cell Reports Medicine, 2023
2. Xinxiu Li, Eun Jung Lee, Sandra Lilja, Joseph Loscalzo, Samuel Schäfer, Martin Smelik, Maria Regina Strobl, Oleg Sysoev, Hui Wang, Huan Zhang, Yelin Zhao, Danuta R. Gawel, Barbara Bohle & Mikael Benson. A dynamic single cell-based framework for digital twins to prioritize disease genes and drug targets . (Published) Genome Medicine. 2022



Karin Åberg karin.aberg.1@ki.se
Main supervisor Marit Westman
Co-supervisor Marianne van Hage, Mats Holmström, Anna Asarnoj

Registered 2017-12-21
Halftime seminar 2023-11-14
Planned dissertation

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 use data from the population based birth cohort BAMSE (Barn Allergi Miljö Stockholm Epidemiologi) consisting of 4089 children. The children have been followed repeatedly by questionnaires. At 4, 8, 16 and 24 years of age clinical examinations were performed, including blood samples for specific IgE. We have also performed a subgroup study of the 24-year-olds with CRS symptoms. The data from this study has been analysed and the article is soon to be submitted.

Ethical permit No.

93:189	98:175	2007/1634-31	2010/1474-31/3	2016/1380-31/2

Publications/manuscripts 2021, 2022, 2023

1. Westman M, Åberg K, Apostolovic D, Lupinek C, Gattinger P, Mitterman I, Andersson N, Melèn E, Bergström A, Antò J M, Bousquet J, Valenta R, Wickman M, van Hage M. 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. JACI April 2020

Appendix 1

KAROLINSKA UNIVERSITY HOSPITAL

Checklista för ansvarig forskare/prövare: Uppstart av klinisk studie

Datum: 2021-11-04

Denna checklista är ett internt dokument som kan användas som stöd inför uppstart av forskningsprojekt på patienter och forskningspersoner som bedrivs vid Karolinska Universitetssjukhuset.

Det är en övergripande checklista med syfte att underlätta planeringen av olika typer av studier, såväl kliniska läkemedelsprövningar som mindre omfattande analyser av patientmaterial.

Dokumentet är tänkt att användas som en mall och kan anpassas utifrån specifika studier och verksamhetens interna rutiner. Alla delar av checklistan är därmed inte applicerbar på alla studier Checklistan upprättas för varje studie och förvaras hos ansvarig forskare. En kopia lämnas till verksamhetschefen där studiens huvudsakligen bedrivs i samband med att studien påbörjas.

Titel på forskningsprojektet/studien	Karolinska diarie nr
Tema/Funktion/Medicinsk enhet	Ansvarig verksamhetschef
Ansvarig forskare/prövare	Ansvarig Forskningssjuksköterska/forskningskoordinator
Sponsor för studien	

Id.	Karolinska Universitetssjukhusets databas för kliniska studier	Kommentar	Utfört
1.1	Alla studier som bedrivs inom Karolinska Universitetssjukhusets verksamhetsområde och där Karolinska Universitetssjukhuset står med på etikprövningsansökan ska registreras i databasen. Databas för kliniska studier (karolinska.se)		
Id.	**Ansökningar och godkännanden**	**Kommentar**	**Utfört**
2.1	DIARIENUMMER K Diarienummer:_____ Ansök om diarienummer för studien via Registrator.karolinska@regionstockholm.se Karolinska Universitetssjukhuset är en myndighet och omfattas därför av de regler och lagar som rör offentlighetsprincipen. Detta innebär bland annat att vi ska diarieföra eller registrera de flesta av våra handlingar. Alla avtal som Karolinska Universitetssjukhuset ingår med extern part ska enligt lag diarieföras.		
2.2	ANSVARSINTYG Ansvarsintygen utgör sjukhusinterna dokument och ska aldrig hanteras av extern part. Tillämpligt ansvarsintyg ska alltid vara upprättat innan uppstart av studien. **Ansvarsintyg K/KI** är avsett att användas för studier som kräver ett etikgodkännande och ska genomföras i samverkan mellan Karolinska Universitetssjukhuset och Karolinska Institutet. Samverkan avses när ansvarig forskare är knuten till både Karolinska Universitetssjukhuset och Karolinska Institutet Intyg om ansvarsfördelning K/KI (2018-06-25) **Ansvarsintyg K** är avsett att användas för studier som kräver ett etikgodkännande och som ska genomföras på fler än en Medicinsk enhet (ME) på Karolinska Universitetssjukhuset. Ansvarsintyg inom Karolinska Universitetssjukhuset (21-02-12)		

2.3	ETIKPRÖVNINGMYNDIGHETEN (EPM) inkl. strålskydd, ansökan och godkännande Diarienummer:_____ Ansökt datum:_____ Godkänt datum:_____ Ändringsansökan datum:_____ Viktig information och instruktion om hur och vad som ska inkluderas i etikprövningsansökan finns på https://etikprovningsmyndigheten.se/ Om studien godkänts med villkor måste dessa uppfyllas innan studien startar. För kliniska läkemedelsprövningar: Väsentliga ändringar till EPM (ändringsansökan) behöver även skickas till Läkemedelsverket. Undantag: Byte av ansvarig forskare (PI) vid ett center eller tillägg av center skall skickas till EPM, men behöver inte skickas in till LV om amendment inte omfattar något utöver detta. Informationen om byte av PI skickas då till LV vid nästa väsentliga amendment. Notera: Om studien inkluderar humana prover kan ett rådgivande möte bokas med Stockholms medicinska biobank (SMB) för diskussion innan inskick till EPM (se nedan under sektion 1.5 BIOBANK). Om **kompensation till forskningspersonerna** förekommer ska detta vara godkänt av Etikprövningsmyndigheten Notera: För medicintekniska kliniska prövningar används ett samlat förfarande där alla ansökningshandlingar skickas till LV som fördelar delar av dokumentationen till EPM. Specifika blanketter skall dock laddas ner från EPM på följande länk: https://etikprovningsmyndigheten.se/medicintekniska-produkter/		
2.4	LÄKEMEDELSVERKET, anmälan/ansökan och godkännande Diarienummer:_____ EudraCTnummer:_____ För medicinteknisk produkt Eudamed nummer:_____ Ansökt datum:_____ Godkänt datum:_____ Amendment: _____ Viktig information och instruktion om hur och vad som ska inkluderas i ansökan för klinisk läkemedelsprövning finns på: https://www.lakemedelsverket.se/sv/tillstand-godkannande-och-kontroll/klinisk-provning/lakemedel-for-manniskor/ansoka-om-klinisk-provning		

	Viktig information och instruktion om hur och vad som ska inkluderas i anmälan/ansökan om medicinteknisk klinisk prövning finns på: https://www.lakemedelsverket.se/sv/tillstand-godkannande-och-kontroll/klinisk-provning/medicinteknik/ansokan-eller-anmalan		
2.5	BIOBANK, ansökan och godkännande Diarienummer:_____ Ansökt datum:_____ Godkänt datum:_____ MTA Godkänt datum:_____ Biobanksavtal upprättas där extra forskningsprover tas inom studien. I Biobankslagen finns undantagsregel för prover som analyseras **inom 6 månader** efter provtagningsdatum **och destrueras** i direkt anslutning till analys. OBS! Båda villkoren måste vara uppfyllda. Är det aktuellt med undantagsregeln så skall detta beskrivas i ansökan till EPM under punkten 14.1.5. Multicenterbiobanksavtal (N1) upprättas vanligen för alla nya prover om det är fler center som medverkar i Sverige och kompletteras samtidigt med lokal biobank för varje site (L1 och L1a) om uttag från befintligt prov behövs. Kontakta SMB biobankstockholm.se vid frågor om hur biobanksansökan ska skrivas. Ett MTA (Material Transfer Agreement) behöver upprättas då biobanksprov med tillhörande provkod överförs från en huvudman till en annan. MTA information (biobanksverige.se) Ansökningsblanketter finns på www.biobanksverige.se/forskning och skickas elektroniskt till biobankstockholm.karolinska@regionstockholm.se samt i pappersform. Se Biobankens hemsida för information om hur många exemplar dokumenten skall upprättas i.		

2.6	GDPR **Anmälan av personuppgiftsbehandling vid Karolinska Universitetssjukhuset** Karolinska Universitetssjukhuset är skyldig att föra ett register över de personuppgiftsbehandlingar som utförs under sjukhusets ansvar. Varje personuppgiftsbehandling (t.ex. forskningsstudier, kvalitetsregister mm.) måste anmälas till detta register. Från och med 2021-10-01 ska samtliga personuppgiftsbehandlingar anmälas i Privacy Records (Draftit). Information om hur man registrerar i Privacy Records finns på inuti: Personuppgiftsbehandling (GDPR) – För dig som är forskare (karolinska.se) Inför vissa personuppgiftsbehandlingar behöver det upprättas en konsekvensbedömning/DPIA gällande personuppgiftsbehandlingen. Så är fallet när det rör sig om behandling av känsliga personuppgifter, när man behandlar personuppgifter i stor omfattning, när man använder ny teknik eller nya organisatoriska lösningar. Mall för DPIA finns här: Sjukhusgemensamma dokument (sll.se) **PUB-avtal (Personuppgiftsbiträdesavtal)** Enligt dataskyddsförordningen ska personuppgiftsansvariga och personuppgiftsbiträden reglera sina relationer genom ett skriftligt avtal. När sjukhuset låter en extern part hantera personuppgifter för sjukhusets räkning skall därför ett PUB-avtal upprättas. Information finns på https://www.datainspektionen.se/lagar--regler/dataskyddsforordningen/personuppgiftsansvariga-och-personuppgiftsbitraden/personuppgiftsbitradesavtal/ Mall för PUB-avtal finns på: https://inuti.karolinska.se/verksamheter/sjukhusovergripande/rattskansli/sjukhus--och-myndighetsjuridik/personuppgiftsbehandling-gdpr/personuppgiftsbehandling-gdpr--for-dig-som-ar-forskare/ Utlämnande av patientdata för forskningsändamål: Om data utlämnas till en annan part för egna forskningsändamål skall en Begäran om utlämnande av patientdata upprättas. På inuti finns en beskrivning och kontaktuppgifter		

	Utlämnande av patientdata för forskningsändamål (karolinska.se) Om sponsor finns i ett land utanför EU kan man på Integritetsmyndighetens hemsida hitta information om landet är godkänt för utlämning av uppgifter. Om landet inte finns med så behöver FoU-juristerna kontaktas innan studieavtal signeras		
2.7	REGISTRERING I OFFENTLIG DATABAS. Varje forskningsstudie som omfattar människor ska enligt Helsingforsdeklarationen registreras i en offentligt tillgänglig databas innan den första forskningspersonen rekryteras. *(Ref: Helsingforsdeklarationen, 35).* Registrering kan göras i t.ex. ClinicalTrials.gov. Kontakta Katarina Risbecker Sektionschef sektion forskningsstöd (katarina.risbeckeregionstockholm.se) för att få inlogg i clinicaltrials.gov På WHO:s hemsida finns exempel på andra offentliga databaser. https://www.who.int/clinical-trials-registry-platform/network/primary-registries OBS! Finansiärer och/eller tidskrifter kan ha särskilda krav på var registreringen ska ske.		
Id	Avtal och Ekonomi	Kommentar	Utfört
3.1	AVTAL Alla avtal som skrivs med extern part behöver inför avtalssignering granskas av jurist på Karolinska Universitetssjukhuset. Kontakta FoU jurist via email: forskningsavtal.karolinska@regionstockholm.se Kliniska studieavtal signeras enligt gällande arbets-och delegationsordning (Sjukhusgemensamma dokument (sll.se) med nedan förtydligande: **PI & Verksamhetschef (VC):** Det är viktigt att PI och VC är införstådda i vad avtalet omfattar. PI och VC signerar som indikator på ”läst och förstått” / ”read and understood”, vilket bekräftar att de ansvarar för genomförande av projektet / studien i enlighet med avtalet.		

	Temachef (TC/Funktionschef (FC)) signerar forskningsavtal upp till 5 MSEK under förutsättning att avtalet är granskat juridiskt, säkerställt att det är ekonomiskt kostnadstäckande och att PI/ VC läst och förstått, dvs vetenskapligt granskat avtalet. Även CDA/NDA avtal innefattas i denna punkt. **Sjukhusdirektören signerar forskningsavtal värda 5 MSEK och över** under förutsättning att avtalet är signerat av TC/FC, vilket då innebär att avtalet är: Juridiskt granskat av avtalsjurist eller i vissa fall av erfaren personal på kliniska studieverksamheten på temat/funktionen. Ekonomiskt granskat av PI och VC och/eller personal på kliniska studieverksamheten. Stöd för detta finns också centralt på sektion forskningsstöd (Se rubrik Ekonomiskt avtal). Vetenskapligt granskat av PI som ska efterleva avtalet och av VC som stöttar projektet. Sjukhusdirektören signerar alla EU-finansierade projekt eftersom dessa bedöms vara av särskild risk.		
3.2	EKONOMISKT AVTAL Studiens kostnader och tidsåtgång beräknas av enhet/sektionsschef eller av VC utsedd person. Därefter upprättas **ett** ekonomiskt avtal mellan Karolinska Universitetssjukhuset och sponsor. Detta avtal ska vara underskrivet och **klart innan** start av studie. Karolinska Universitetssjukhusets original skickas till registrator på Karolinska Universitetssjukhuset. Kopior på alla ekonomiska avtal för studien förvaras i prövarpärmen eller på annan avsedd plats (se punkt prövarpärm). För hjälp med underlagsmall för avtal och stöd för kostnadsberäkning och avtalsprocess kontakta sektionschef för sektion forskningsstöd: katarina.risbecker@regionstockholm.se Forskningsprislista gällande timpriser samt slutenvårdpriser finns att ladda ner från inuti http://inuti.karolinska.se/Inuti/Verksamheter/Centrala-staber/FoU/Kliniska-studier/		
3.3	INTERNA AVTAL Interna avtal mellan Karolinska Universitetssjukhusets verksamheter signeras av VC alternativt chef för klinisk studieenhet om budgetansvar för verksamheten åligger denne. Interna avtal / överenskommelser är inte juridiskt bindande i samma bemärkelse som externa avtal. Det kan vara av stort värde för ansvariga inom verksamheten och forskningsprojektet att ha en process på plats där ansvariga chefer i verksamheten är informerade om och tar ansvar för genomförande av kliniska studier.		

3.4	APOTEKET Ett avtal ska upprättas med apoteket när prövningsläkemedel ska användas. Avtal upprättas i de flesta fall direkt mellan sponsor och apoteket. Kopia av apoteksavtalet tillhandahålls av sponsor och förvaras i prövarpärmen. I de all Karolinska Universitetssjukhuset är sponsor/tecknar avtal med apoteksfunktion skall ApoEx anlitas. Email adress: klinprov.stockholm@apoex.se		
3.5	BILD OCH FUNKTION (BoF) Ett internavtal kan behöva upprättas med BoF för studiespecifika undersökningar tex CT/MR/PET, ultraljud mfl. Kontakta till BoF Enheten för kliniska studier (EKS) rtg.klinprov.karolinska@regionstockholm.se För barnstudier kontaktas FOBarnradiologikliniskastudier.karolinska@regionstockholm.se Röntgen återkommer med ett internavtal som signeras enligt gällande arbets-och delegationsordning.		
3.6	PATOLOGEN I vissa studier behöver ett avtal upprättas med patologen t.ex. när arkiverat tumörmaterial ska skickas för analys . Det kan då också behövas en ansvarig patolog för studien. Det finns två sorters avtal, biobanksavtal (skickas till puc.samordning.karolinska@regionstockholm.se) och kostnadsavtal (skickas till studiecenter på MDK) efter det att Patologen har tagit fram en offert på projektet. Projekt som omfattar humanvävnad insamlad inom Sverige ska ha ett biobanksavtal upprättat innan kostnadsavtal upprättas. I prövarpärmen ska det finnas instruktion för hur man beställer, hanterar och vart (lokalt/centralt lab) patologmaterial skickas.		

3.7	PROVTAGNING/STUDIECENTER lab Beroende på studiens upplägg kan avtal behövas, såsom vid provtagning utöver klinisk rutin, prover som ej finns i sortimentet m.m. Kontaktuppgifter: studiecenterlab.karolinska@regionstockholm.se Studiecenter återkommer med internavtal för signering enligt gällande arbets-och delegationsordning.		
3.8	ÖGON Om ögonundersökning ska utföras kan Stockholms ögonklinik användas. Skicka e-post med en kort sammanfattning om studien, vilka undersökningar som är aktuella och när undersökningarna ska utföras. Bifoga information från forskningsplanen/protokollet som beskriver vad som ska undersökas (flödesschema) till; kundcenter@stockholmsogonklinik.se för upprättande av internavtal		
3.9	FYSLAB Ett avtal ska upprättas om studiespecifika EKG ska utföras. För barnstudier kontaktas barnkardiologen.		

Appendix 2

Lägga till ett nytt e-postkonto i Outlook

Outlook för Microsoft 365 Outlook för Microsoft 365 för Mac Outlook 2021 Fler...

Håll kontakten och schemat

Du kan vara organiserad och hålla tidsplaneringen med Outlook – din livsorganisatör.

Prova 1 månad utan kostnad

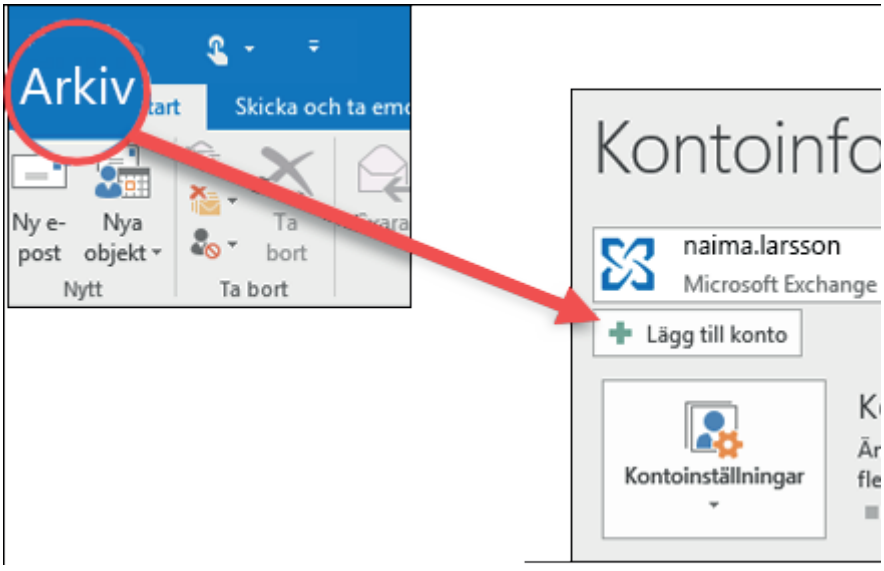
Det finns många olika typer av e-postkonton som du kan lägga till i Outlook, bland annat Microsoft 365, Gmail-, Yahoo-, iCloud- och Exchange-konton.

Vissa tredjepartsleverantörer av e-post, till exempel Gmail, Yahoo och iCloud, kräver att du ändrar vissa inställningar på respektive webbplats innan du kan lägga till dessa konton i Outlook.

Outlook för PCOutlook för MacMobil e-post

De här stegen är desamma oavsett om du lägger till ditt första e-postkonto eller andra e-postkonton i Outlook.

1. Välj **Arkiv** > **Lägg till konto**.



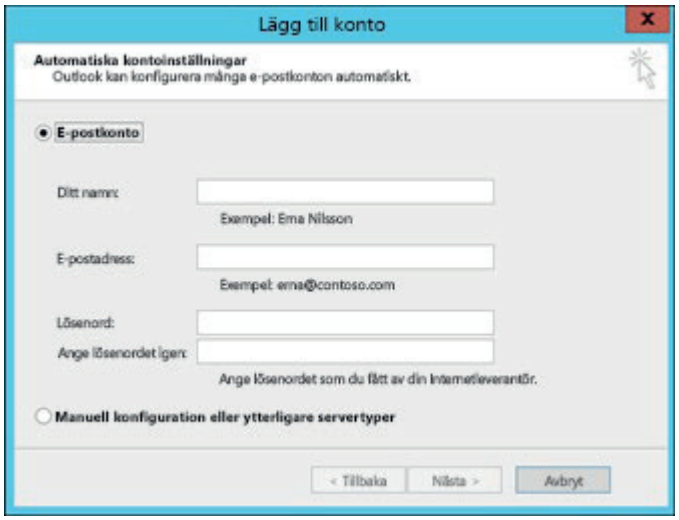
2. Vad som visas därnäst beror på vilken version av Outlook du har.

   För Outlook för Microsoft 365 och Outlook 2016

   För Outlook 2013 och Outlook 2010

Källa: https://support.microsoft.com/sv-se/office/l%C3%A4gga-till-ett-nytt-e-postkonto-i-outlook-6e27792a-9267-4aa4-8bb6-c84ef146101b

Ange din e-postadress och klicka på **Anslut**.



Ange namn, e-postadress och lösenord och klicka på **Nästa**.

3. Ange lösenordet igen om du uppmanas till det och välj sedan **OK** > **Slutför** för att börja använda ditt e-postkonto i Outlook.

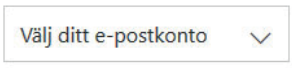
Outlook accepterar inte mitt lösenord

Om Outlook inte accepterar ditt lösenord och du vet att du använder rätt lösenord för e-postkontot, kanske du har ett e-postkonto som kräver ytterligare säkerhetsfunktioner.

Gmail-, Yahoo-, iCloud-, Outlook.com- och AOL-konton använder alla tvåfaktorautentisering för att verifiera att du är den person som försöker komma åt ditt e-postkonto.

För att lägga till ditt e-postkonto i Outlook behöver du ett applösenord, även kallat ett programlösenord. Det är ett annat lösenord än ditt vanliga lösenord för e-postkontot. Du vet att du behöver ett applösenord om du ser följande meddelande: *Tvåfaktorautentisering har ställts in för ditt konto. Logga in med ditt lösenord för programmet.*

Stegen för att hämta ett applösenord är olika för varje e-postleverantör. Välj din leverantör i listrutan för att få anvisningar.



Har du problem med att lägga till ditt e-postkonto? Använd avancerade inställningar.

Du kan behöva lägga till ditt e-postkonto manuellt. Välj någon av de avancerade metoderna nedan:

Använda avancerade inställningar för att lägga till ett POP- eller IMAP-konto i Outlook för Windows

Du kan använda Outlooks avancerade inställningar om du behöver ange specifika värden för namn på inkommande och utgående server, portnummer eller SSL-inställningar. Du kan använda de här anvisningarna för att lägga till ett POP- eller IMAP-konto i Outlook.

1. Öppna Outlook och välj **Arkiv** > **Lägg till konto**.
2. På nästa sida anger du din e-postadress och väljer **Avancerade alternativ**. Markera sedan kryssrutan för **Jag vill konfigurera mitt konto manuellt** och välj **Anslut**.
3. Välj din kontotyp. Oftast när du måste använda det här alternativet väljer du **IMAP**.
4. Sidan **Kontoinställningar** bör vara förifylld med de flesta av de kontoinställningar som du behöver. Men om du måste leta reda på inställningarna läser du avsnittet Inställningar för POP- och IMAP-konto. Ange inställningar för inkommande och utgående server och välj **Nästa**.
5. Ange ditt lösenord och välj sedan **Anslut**.

Använda avancerade inställningar för att lägga till ett IMAP-konto från tredje part i Outlook för Windows

Om du använder en MAPI-tredjepartsleverantör laddar du ned och konfigurerar leverantörens MAPI-e-postprogram som föreslås av leverantörsföretaget.

1. Öppna Outlook och välj **Arkiv** > **Lägg till konto**.
2. På nästa sida anger du din e-postadress och väljer **Avancerade alternativ**. Markera sedan kryssrutan för **Jag vill konfigurera mitt konto manuellt** och välj **Anslut**.
3. På sidan **Avancerad konfiguration** väljer du **Annan**.
4. Välj vilken typ av server som du vill ansluta till i listan på skärmen **Annan**.
   Obs! Alternativet **Annan** och din kontotyp som visas under det visas bara om du har installerat och konfigurerat MAPI-leverantören korrekt.
5. Klicka på **Anslut**.
6. Det MAPI-leverantörsprogram för tredje part som är installerat på datorn bör startas.
7. Slutför kontokonfigurationen genom att följa MAPI-leverantörens instruktioner.

Vill du uppdatera inställningar för ett befintligt e-postkonto i Outlook?

Om du redan har skapat ett e-postkonto och vill uppdatera befintliga inställningar på grund av ett aktuellt problem går du till Ändra eller uppdatera inställningar för e-postkonto i Outlook för Windows.

Se även

Ändra eller uppdatera inställningar för e-postkonto i Outlook för Windows

POP- och IMAP-e-postinställningar för Outlook

Appendix 3