RESEARCH ACTIVITY

at the Division of
Ear, Nose and Throat Diseases

2022

Karolinska Institutet

KAROLINSKA Universitetssjukhuset

CONTENT

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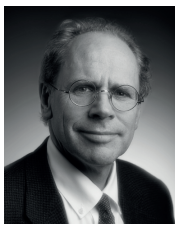

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Antti Mäkitie, Affiliated Professor
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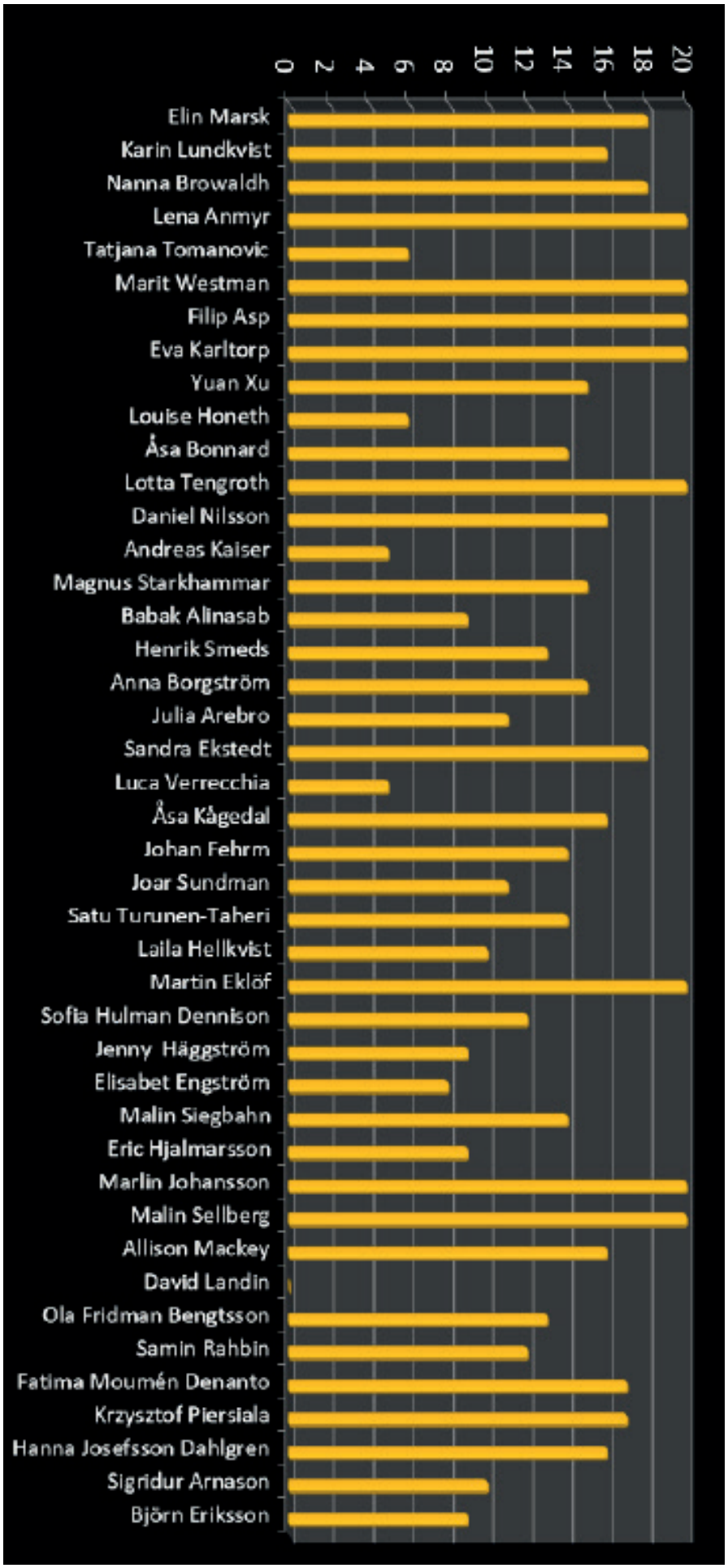
Riitta Möller
Inger Uhlén

Dissertations / Half time seminars 2022

Date		Name	Title
2022-06-02	Half time	Fatima Moumén Denanto	
2022-06-03	Dissertation	David Landin	Clinical use of prognostic markers in head- and neck cancer
2022-06-14	Dissertation	Malin Sellberg	Students' and supervisors' experiences of supervision and training in clinical learning environment
2022-06-16	Half time	Krzysztof Piersiala	
2022-09-02	Half time	Hanna Josefsson Dahlgren	
2022-10-07	Dissertation	Eric Hjalmarsson	Allergic rhinitis and intralymphatic vaccination: immune response and tolerance
2022-10-14	Dissertation	Allison Mackey	Perspectives on screening strategies for early detection of childhood hearing impairment
2022-12-02	Half time	Sigurdur Arnason	
2022-12-09	Half time	Björn Eriksson	

Participation at halftime seminars during 2010-10 to 2022-12-31



Affiliated not presented in this book:
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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 2020, 2021, 2022

1. The Volume Difference Along the External Surface of the Zygomatic Bone: A Novel Method of Measuring Zygomatic Bone Asymmetry. The Journal of Craniofacial Surgery Volume 00, Number 00, Month 2021
2. Loss of Malar Bags in Lower Eyelid In Orbital Blow Out Fracture Reconstruction Following Pre- or Retro-septal Transconjunctival Incision. Craniomaxillofacial Trauma Reconstruction. The Journal of Craniofacial Surgery Volume 31, Number 3, May/June 2020
3. New Algorithm for Management of Orbital Blow Out Fracture Based on Prospective Study. Babak Alinasab, Karl-Johan Borstedt, Rebecka Rudström, Michael Ryott, Abdul Rashid Qureshi, Mats O. Beckman, Pär Stjärne. Craniomaxillofac Trauma Reconstr. 2018 Dec;11(4):285-295. doi: 10.1055/s-0038-1641714. Epub 2018 May 1.
4. Prospective Randomized Controlled Pilot Study on Orbital Blow out Fracture. Babak Alinasab, Karl-Johan Borstedt, Rebecka Rudström, Michael Ryott, Abdul Rashid Qureshi, Pär Stjärne. Craniomaxillofac Trauma Reconstr. 2018 Sep;11(3):165-171.
5. Supra Blepharoplasty Approach for Correcting Fractures of Frontal Bone Fracture. Babak Alinasab, Ola Fridman Bengtsson, Pär Stjärne. J Craniofac Surg. 2018 Oct;29(7):1906-1909.
6. Prospective study on ocular motility limitation due to orbital muscle entrapment or impingement associated with orbital wall fracture. Alinasab B, Qureshi AR, Stjärne P. Injury. 2017 Jul;48(7):1408-1416.

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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 as well as otosclerosis is highly unknown. We aim to search for underlying causes (studying RNA, proteins an immunological aspect as well as microbiological factors) through a patient based pre-clinical mapping project on .

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*

Ethical permit No.

H15-02913	2022-06851-01			

Publications 2020,2021, 2022

1. Arebro J, Towle R, Li CM, Garnis C. CAFs activated through oral cancer derived EVs display unique pro-inflammatory properties. Manuscript
2. Khan A, et al. Identification and Characterization of a Severe Burden Subgroup of Chronic Rhinosinusitis With Nasal Polyposis Patients using Cluster Analysis. Manuscript
3. 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

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Bilateral benefits and long-term outcomes of auditory implants and hearing aids in children

Hearing with two ears (binaural hearing) improves spatial hearing, which facilitates recognition of speech in conditions with multiple talkers, and sound localization. Horizontal sound localization is an ideal ability for the study of deficits in binaural hearing, since high accuracy is dependent on precise temporal processing and interaural comparison of acoustic signals. Hearing loss has a negative impact on sound localization, also in mild cases, for example unilateral hearing loss. We study the effects of congenital and aquired hearing loss and various interventions (e.g. auditory implants and hearing aids) 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 localization ability.

We also study the long-term hearing outcomes of cochlear implantation in individuals who received cochlear implants by 2.5 years of age, 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.

The ultimate goal with these projects is to alleviate the negative impact of hearing impairment, and increase our understanding of how impaired spatial hearing affects humans, specifically during critial periods of development.

Supervision of PhD-students:

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	Malin Siegbahn
	Hanna Josefsson

Ethical permit No.

2016/414-16 (Gothenburg)	2019-04696	2022-00863-02		

Publications 2020, 2021, 2022

1. Asp, F., & Reinfeldt, S. (2020). Effects of Simulated and Profound Unilateral Sensorineural Hearing Loss on Recognition of Speech in Competing Speech. Ear Hear, 41(2), 411-419. https://doi.org/10.1097/AUD.0000000000000764
2. Johansson, M., Asp, F., & Berninger, E. (2020). Children With Congenital Unilateral Sensorineural Hearing Loss: Effects of Late Hearing Aid Amplification-A Pilot Study. Ear Hear, 41(1), 55-66. https://doi.org/10.1097/AUD.0000000000000730
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7. 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

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12. 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
13. 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.
14. Eklof, M., Asp, F., & Berninger, E. (2020). Sound localization latency in normal hearing and simulated unilateral hearing loss. Hear Res, 395, 108011. https://doi.org/10.1016/j.heares.2020.108011
15. 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
16. 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
17. 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

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Inflammation in the Upper Airways

Supervision of PhD-students:

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Ethical permit No.

Publications 2020, 2021, 2022

1. IF 12.339 Bachert C, Humbert M, Hanania NA, Zhang N, Holgate S, Buhl R, Bröker BM. Staphylococcus aureus and its IgE-inducing Enterotoxins in Asthma: Current Knowledge. Eur Respir J. 2020 Apr 3;55(4):1901592
2. IF 10.228 Bachert C, Zhang N, Cavaliere C, Weiping W, Gevaert E, Krysko O. Biologics for chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2020 Mar;145(3):725-739.
3. IF 6.780Xepapadaki P, Korovessi P, Bachert C, Finotto S, Jartti T, Lakoumentas J, Kowalski ML, Lewandowska-Polak A, Lukkarinen H, Zhang N, Zimmermann T, Papadopoulos NG. Evolution of Airway Inflammation in Preschoolers with Asthma-Results of a Two-Year Longitudinal Study. J Clin Med. 2020 Jan 9;9
4. IF 5.329 Ascari G, Peelman F, Farinelli P, Rosseel T, Lambrechts N, Wunderlich KA, Wagner M, Nikopoulos K, Martens P, Balikova I, Derycke L, Holtappels G, Krysko O, Van Laethem T, De Jaegere S, Guillemyn B, De Rycke R, De Bleecker J, Creytens D, Van Dorpe J, Gerris J, Bachert C, Neuhofer C, Walraedt S, Bischoff A, Pedersen LB, Klopstock T, Rivolta C, Leroy BP, De Baere E, Coppieters F. Functional characterization of the first missense variant in CEP78, a founder allele associated with cone-rod dystrophy, hearing loss and reduced male fertility. Hum Mutat. 2020 Jan 30.
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6. IF 10.228 Cardell LO, Stjärne P, Jonstam K, Bachert C. Endotypes of chronic rhinosinusitis: impact on management. J Allergy Clin Immunol. 2020 Jan 27 Rostrum
7. IF 10.228 Howarth P, Chupp G, Nelsen LM, Bradford ES, Bratton DJ, Smith SG, Albers FC, Brusselle G, Bachert C. Severe eosinophilic asthma with nasal polyposis: A phenotype for improved outcomes with mepolizumab therapy. J Allergy Clin Immunol. 2020 Feb 18 LtE
8. IF 3.35 European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, Toppila-Salmi S, Bernal-Sprekelsen M, Mullol J, Alobid I, Terezinha Anselmo-Lima W, Bachert C, Baroody F, von Buchwald C, Cervin A, Cohen N, Constantinidis J, De Gabory L, Desrosiers M, Diamant Z, Douglas RG, Gevaert PH, Hafner A, Harvey RJ, Joos GF, Kalogjera L, Knill A, Kocks JH, Landis BN, Limpens J, Lebeer S, Lourenco O, Matricardi PM, Meco C, O Mahony L, Philpott CM, Ryan D, Schlosser R, Senior B, Smith TL, Teeling T, Tomazic PV, Wang DY, Wang D, Zhang L, Agius AM, Ahlstrom-Emanuelsson C, Alabri R, Albu S, Alhabash S, Aleksic A, Aloulah M, Al-Qudah M, Alsaleh S, Baban MA, Baudoin T, Balvers T, Battaglia T, Bedoya JD, Beule A, Bofares KM, Braverman I, Brozek-Madry E, Richard B, Callejas C, Carrie S, Caulley L, Chussi D, de Corso E, Coste A, Devyani L, El Hadi U, Elfarouk A, Eloy PH, Farrokhi S, Felisati G, Ferrari MD, Fishchuk R, Grayson W, Goncalves PM, Grdinic B, Grgic V, Hamizan AW, Heinichen JV, Husain S, Ping TI, Ivaska J, Jakimovska F, Jovancevic L, Kakande E, Kamel R, Karpischenko S, Kariyawasam HH, Kjeldsen A, Klimek L, Kim SW, Letort JJ, Lopatin A, Mahdjoubi A, Netkovski J, Nyenbue Tshipukane D, Obando-Valverde A, Okano M, Onerci M, Ong YK, Orlandi R, Ouennoughy K, Ozkan M, Peric A, Plzak J, Prokopakis E, Prepageran N, Psaltis A, Pugin B, Raftopulos M, Rombaux P, Sahtout S, Sarafoleanu CC, Searyoh K, Rhee CS, Shi J, Shkoukani M, Shukuryan AK, Sicak M, Smyth D, Snidvongs K, Soklic Kosak T, Stjarne P. Rhinology. 2020 Feb 20;58(Suppl S29):1-464.
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10. IF 7.574 Naclerio R, Baroody F, Bachert C, Bleier B, Borish L, Brittain E, Chupp G, Fisher A, Fokkens W, Gevaert P, Kennedy D, Kim J, Laidlaw TM, Lee JJ, Piccirillo JF, Pinto JM, Roland LT, Schleimer RP, Schlosser RJ, Schwaninger JM, Smith TL, Tan BK, Tan M, Toskala E, Wenzel S, Togias A. Clinical Research Needs for the Management of Chronic Rhinosinusitis with Nasal Polyps in the New Era of Biologics. A National Institute of Allergy and Infectious Diseases Workshop. JACIiP 2020 Mar 3
11. IF 3.895 Abdurrahman G, Schmiedeke F, Bachert C, Bröker B, Holtfreter S. Allergy – a new role for T cell superantigens of Staphylococcus aureus? Toxins 2020 Mar 12;12(3).
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16. IF 8.71 Klimek L, Jutel M, Akdis C, Bousquet J, Akdis M, Bachert C, Agache I, Ansotegui I, Bedbrook A, Bosnic-Anticevich S, Canonica GW, Chivato T, Cruz AA, Czarlewski W, Giacco SD, Du H, Fonseca JA, Gao Y, Haahtela T, Hoffmann-Sommergruber K, Ivancevich JC, Khaltaev N, Knol EF, Kuna P, Larenas-Linnemann D, Melen E, Mullol J, Naclerio R, Ohta K, Okamoto Y, O'Mahony L, Onorato GL, Papadopoulos NG, Pawankar R, Pfaar O, Samolinski B, Schwarze J, Toppila-Salmi S, Shamji MH, Ventura MT, Valiulis A, Yorgancioglu A, Matricardi P, Zuberbier T; ARIA-MASK study group. Handling of allergen immunotherapy in the COVID-19 pandemic: An ARIA-EAACI statement. Allergy. 2020 Apr 24. doi: 10.1111/all.14336
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21. IF 10.228 Delemarre T, Holtappels G, De Ruyck N, Zhang N, Nauwynck H, Bachert C, Gevaert E. Type 2 Inflammation in Chronic Rhinosinusitis without Nasal Polyps: Another Relevant Endotype. JACI 2020;146:337-343
22. IF 10.228 Förster-Ruhrmann U, Szczepek AJ, Bachert C, Olze H. COVID-19 in a patient with severe chronic rhinosinusitis with nasal polyps during therapy with dupilumab. J Allergy Clin Immunol. 2020 Jul;146(1):218-220
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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
- Prevalence of regional recurrence/disease free survival in oral cancer N+ patients after SN-assisted neck dissection: 2 years follow up.
- Prospective study: Can HPV be used as a predictor in differentiating between cystic metastasis and lateral branchial cleft cyst?

Future projects:

- -Clinical predicting biomarkers in oropharyngeal cancer patients whith goal to decrease the side effect profile.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Evelina Jörtsö

Ethical permit No.

2020-00448	2021-00697	2021-01265		

Publications 2020, 2021, 2022

1. Vujasinovic M, Marsk E, Tsolakis AV, Hynning B, Nordberg M, Lindblad M, Lindqvist C, Hammarstedt- Nordenvall L, Bark R, Elbe P. Complications of gastrostomy tubes in patients with head and neck cancer. Laryngoscope. 2022 Sep;132(9):1778-1784.
2. Hammarstedt-Nordenvall L, Evelina J, 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.
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Digital Twins for personalised medicine

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 are now planning to show clinical feasibility by treating individual patients. The ultimate aim is that each healthy individual should have her/his digital twin for predictive, preventive, personalised and participatory medicine.

Supervision of PhD-students:

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

Ethical permit No.

Publications 2020, 2021, 2022

1. Lilja S, Li X, Lee EJ, Loscalzo J, Zhang H, Zhao Y, Gawel D, Wang H, Benson M. Multi-organ single cell analysis reveals an on/off switch system with potential for personalized treatment of immunological diseases. Cell Reports Medicine 2023
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5. Lee EJ, Lilja S, Li X, Schäfer S, Zhang H, Benson M. Bulk and single cell transcriptomic data indicate that a dichotomy between inflammatory pathways in peripheral blood and arthritic joints complicates biomarker discovery. Cytokine 2020;127:154960
6. Lee EJ, Lilja S, Li X, Schäfer S, Zhang H, Benson M. Analysis of expression profiling data suggests explanation for difficulties in finding biomarkers for nasal polyps. Rhinology 2020;58:360-67
7. Li X, Lilja S, Lee EJ, Schäfer S, Benson M. Meta-analysis of expression profiling data indicates need for combinatorial biomarkers in pediatric ulcerative colitis. J Infl Research 2020;127:154960

Review articles

1. Digital Twins for personalized medicine. ATVB 2023
2. Franks P….multiple authors from Genomic Medicine Sweden, including M Benson. Strategies for Implementing Genomic-Driven Precision Medicine for Complex Diseases in Sweden. J Int Med 2021
3. Gawel D, Jacobsson B, Jönsson JI, Melen E, Sysoev O, Ynnander A, Benson M. Clinical implementation of genomic and digital technologies for precision medicine. Swedish Med J 2021
4. Björnsson B, ..Benson M; Swedish Digital Twin Consortium. Digital twins to personalize medicine. Genome Med. 2020;12(1):4.

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

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

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

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

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

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Marlin Johansson	

Ethical permit No.

2012/494-31/1; 2018/1500-31 (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

Publications 2020, 2021, 2022

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2. Berninger E, Drott M, Romanitan M, Tranebjærg L, Hellström S. Congenital Nonprofound Bilateral Sensorineural Hearing Loss in Children: Comprehensive Characterization of Auditory Function and Hearing Aid Benefit. Audiology research. 2022;12(5):539-63.
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4. Eklöf M, Asp F, Berninger E. The Development of Sound Localization Latency in Infants and Young Children with Normal Hearing. Trends in hearing. 2022;26:23312165221088398.
5. Johansson M, Asp F, Berninger E. Children With Congenital Unilateral Sensorineural Hearing Loss: Effects of Late Hearing Aid Amplification-A Pilot Study. Ear Hear. 2020;41(1):55-66. doi: 10.1097/AUD.0000000000000730.
6. Johansson M, Karltorp E, Asp F, Berninger E. A Prospective Study of Genetic Variants in Infants with Congenital Unilateral Sensorineural Hearing Loss. Journal of clinical medicine. 2023;12.
7. Johansson M, Karltorp E, Edholm K, Drott M, Berninger E. A Prospective Study of Etiology and Auditory Profiles in Infants with Congenital Unilateral Sensorineural Hearing Loss. Journal of clinical medicine. 2022;11(14).
8. Johansson M, Olofsson Å, Berninger E. Twin study of neonatal transient-evoked otoacoustic emissions. Hear Res. 2020;398:108108.(doi):10.1016/j.heares.2020.108108. Epub 2020 Oct 28.
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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 at the ENT-department and the disease is known as a non-hereditary disease. But recently our researchgroup showed that there is an almost 4-times higher risk for having surgery for cholesteatoma in individuals with a first-degree relative surgically treated for the disease. The number of individuals with hereditary disease is quite low but this group will be of special interest for further studies regarding the genetic background of the disease.
Cholesteatoma 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 will be 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. A combination with the Swedish Patient Registry and The Swedish Multiple Generation Register will be used to identify different aspects of hereditary cholesteatoma. 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 will be performed 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

Ethical permit No.

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

Publications 2020, 2021, 2022

1. Bonnard Å, Bark R, Hederstierna C. Clinical update on sensorineural hearing loss in Turner syndrome and the X-chromosome. Am J Med Genet C Semin Med Genet. 2019 Mar;181(1):18-24. doi: 10.1002/ajmg.c.31673. Epub 2019 Jan 10. Review. PMI: 30632288
2. Prakash SK, San Roman AK, Crenshaw M, Flink B, Earle K, Los E, Bonnard Å, Lin AE. ”Donating our bodies to science”: A discussion about autopsy and organ donation in Turner syndrome. Am J Med Genet C Semin Med Genet. 2019 Mar;181(1):36-42. doi: 10.1002/ajmg.c.31671. Epub 2019 Jan 11. Review. PMID: 30633443
3. Berglund M, Olaison S, Bonnard Å, Fransson M, Hultcrantz M, Florentzson R, Dahlin C, Olof Eriksson P, Westman E1. Hearing outcome after myringoplasty in Sweden. A nationwide registry-based cohort study. Clin Otolaryngol. 2020 Jan 23. doi: 10.1111/coa.13506.
4. Bonnard Å., Engmér Berglin C., Wincent J., Eriksson PO., Westman E., Feychting M., Mogensen H., JAMA Otolaryngology - Head and Neck Surgery 2023 Accepted in press.
5. Bonnard Å; Karltorp E; Verrecchia L. Vestibular loss in children affected with LVAS and IP2 malformation and operated with cochlear implant. Audiology Research. 2023 Accepted, in press. DOI: 10.3390/audiolres13010013

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Evaluation and surgical treatment of children with tonsil hypertrophy and sleep disordered breathing

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

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Isabella Sjölander

Ethical permit No.

Publications 2019, 2020, 2021

1. Borgström A, Nerfeldt P, Friberg D; Postoperative pain and bleeding after adenotonsillectomy vs adenotonsillotomy in pediatric obstructive sleep apnea: an RCT; European Archives of Oto-Rhino-Laryngology, 2019 Aug (3), 1-8
2. Sjölander I, Borgström A, Larsson JO, Smedje H, Friberg D.Sjölander I, et al. Randomised trial showed no difference in behavioural symptoms between surgical methods treating paediatric obstructive sleep apnoea. Acta Paediatr. 2020 Oct;109(10):2099-2104. doi: 10.1111/apa.15210. Epub 2020 Mar 6

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

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

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

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

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

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

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2019-04851				

Publications 2020, 2021, 2022

1. Sundman J, Friberg D, Bring J, Lowden A, Nagai R, Browaldh N Sleep Quality After Modified Uvulopalatopharyngoplasty: Results From the SKUP3 Randomized Controlled Trial Sleep 2018 Sep 25
2. Fehrm J, Nerfeldt P, Browaldh N, Friberg D. Effectiveness of adenotonsillectomy vs watchful waiting in young children with mild to moderate obstructive sleep apnea: a randomized clinical trial. JAMA Otolaryngol - Head Neck Surg. May 28, 2020
3. Friberg D, Sundman J, Browaldh N. Long-term evaluation of satisfaction and side effects after modified uvulopalatopharyngoplasty. Laryngoscope. 2020;130(1):263–8
4. Sundman J, Browaldh N, Fehrm J, Friberg D. Eight-year Follow-up of Modified Uvulopalatopharyngoplasty in Patients with Obstructive Sleep Apnea. Laryngoscope. 2020, 24 July. doi:10.1002/lary.28960

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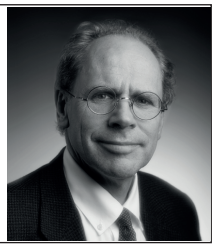

Neutrophils, T- and B-cells in the development and progression of allergic airway and head and neck squamous cell cancer inflammation

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

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

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
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Krzysztof Piersiala	
Aeneas Kolev	
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Vilma Lagebro	

Ethical permit No.

2021-03633	2021-00325	2021-01265	2020-02579	2019-03518	

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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 child. 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.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
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Andra Lazar	

Ethical permit No.

2013/1177-31	2015/1296-31/2	2019-02019		

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

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2020, ,2021, 2022

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Long time outcomes after early cochlear implant intervention

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.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2022-03381-01	2021-04345			

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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 2020, 2021, 2022

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6. Ekstedt S, Georen SK, Cardell LO. Effects of MP-AzeFlu enhanced by activation of bitter taste receptor TAS2R. ALLERGY ASTHMA AND CLINICAL IMMUNOLOGY 2020 16;1 45-

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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		

Publications 2020, 2021, 2022

1. Tumour-draining lymph nodes in head and neck cancer are characterized by accumulation of CTLA-4 and PD-1 expressing Treg cells Krzysztof Piersiala , Pedro Farrajota Neves da Silva , Vilma Lagebro , Aeneas Kolev , Magnus Starkhammar , Alexandra Elliot , Linda Marklund , Eva Munck-Wikland , Gregori Margolin , Susanna Kumlien Georén , Lars-Olaf Cardell . Transl Oncol. 2022 Jun 14;23:101469. doi: 10.1016/j.tranon.2022.101469. Online ahead of print.
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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:

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

Ethical permit No.

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

Publications 2020, 2021, 2022
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3. Cortés Fuentes IA, Pierre PV, Berglin CE. Improving Clinical Outcomes in Cochlear Implantation Using Glucocorticoid Therapy: A Review. Ear Hear. 2020 Jan/Feb;41(1):17-24. doi: 10.1097/AUD.0000000000000740.

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

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

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

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

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

Ethical permit No.

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

Publications 2020, 2021, 2022

1. Fehrm J, Nerfeldt P, Browaldh N, Friberg D. Effectiveness of Adenotonsillectomy vs Watchful Waiting in Young Children with Mild to Moderate Obstructive Sleep Apnea: A Randomized Clinical Trial. JAMA Otolaryngol - Head Neck Surg. 2020;146(7):647-654.
2. Fehrm J, Borgström A, Nerfeldt P, Friberg D. Postoperative morbidity after adenotonsillectomy versus adenopharyngoplasty in young children with obstructive sleep apnea: an RCT. Eur Arch Oto-Rhino-Laryngology. May 2020:1-
3. Sundman J, Browaldh N, Fehrm J, Friberg D. Eight-Year Follow-up of Modified Uvulopalatopharyngoplasty in Patients With Obstructive Sleep Apnea. Laryngoscope. 2021;131(1):E307-E313.
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6. Sundman J, Nerfeldt P, Fehrm J, Bring J, Browaldh N, Friberg D. Effectiveness of Tonsillectomy vs Modified Uvulopalatopharyngoplasty in Patients With Tonsillar Hypertrophy and Obstructive Sleep Apnea: The TEAMUP Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg. 2022 Dec 1;148(12):1173-1181. doi: 10.1001/jamaoto.2022.3432. PMID: 36326742; PMCID: PMC9634593.
7. Correlations between objective and subjective outcomes after adenotonsillar surgery in children with OSA. Laryngoscope Investig Otolaryngol. 2022 Nov 4;7(6):2161-2170. doi: 10.1002/lio2.967. PMID: 36544930; PMCID: PMC9764786.

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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 2020, 2021, 2022

1. Haggstrom J, Hederstierna C, Rosenhall U, Ostberg P, Idrizbegovic E. Prognostic Value of a Test of Central Auditory Function in Conversion from Mild Cognitive Impairment to Dementia. Audiology & neuro-otology. 2020:1-7.

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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 2020, 2021, 2022

1. Adenopharyngoplasty vs. adenotonsillectomy in children with severe obstructive sleep apnea: a randomized controlled trial Johan Fehrm, MD; Pia Nerfeldt, MD, PhD; Joar Sundman, MD; Danielle Friberg, MD, PhD JAMA ORL 2018;144(7):580-586
2. Postoperative pain and bleeding after adenotonsillectomy versus adenotonsillotomy in pediatric obstructive sleep apnea: an RCT Borgström Anna, MD; Nerfeldt Pia MD, PhD; Friberg Danielle, MD, PhD Eur Arch Otorhinolaryngol 2019 doi.org/10.1007/s00405-019-05571-ww
3. Obstructive sleep apnea in children with Down syndrome - Prevalence and evaluation of surgical treatment Nerfeldt Pia MD PhD, Sundelin Amalia MD Int J Pediatr Otorhinolaryngol. 2020 Feb 26;133:109968. doi:10.1016/j.ijporl.2020.109968.
4. Postoperative morbidity after adenotonsillectomy versus adenopharyngoplasty in young children with obstructive sleep apnea: an RCT Johan Fehrm, MD; Pia Nerfeldt, MD, PhD; Anna Borgström, MD, PhD; Danielle Friberg, MD, PhD Eur Arch Otorhinolaryngol 2020 Oct;277(10):2821-2827
5. Effectiveness of Adenotonsillectomy vs Watchful Waiting in Young Children With Mild to Moderate Obstructive Sleep Apnea: A Randomized Clinical Trial. Fehrm J, Nerfeldt P, Browaldh N, Friberg D. JAMA Otolaryngol Head Neck Surg. 2020 Jul 1;146(7):647-654

6. 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
7. 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.
8. 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 Accepted for publication in JAMA ORL September 2022.
9. 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 doi.org/10.1002/lio2.967

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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 2020, 2021, 2022

1. Supraglottoplasty for severe laryngomalacia was successful and safe also in children with high-risk comorbidites -experience from Karolinska University Hospital. Submitted January 2023.
2. 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. Gahm C, Näsman A, Papatziamos G. Int J Ped Otorhinolaryngol. 2021 Sept;148
3. Osteoradionecrosis, an increasing indication for microvascular head and neck reconstruction. Danielsson D, Gahm C, Haghdoost S, Munck-Wikland E, Halle M. Int J Oral Maxillofac Surg. 2019 Jul 8. S0901-5027 (19)31185-3
4. Eriksson B, Gahm, C, Halle M. Upregulation of Plasminogen Activator Inhibitor-1 in irradiated recipient arteries and veins from free tissue transfer reconstruction" Mediators of inflammation. Oct 4;2018:4058986.

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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 and analysis of these results is underway. Studies on the outcomes of treatment (quality of life, hearing outcomes) with cochlear implants related to age at surgery, cognitive abilities as performed in MoCA test and the impact of social environment are in the pipeline. The study is performed in cooperation with staff and researchers at Karolinska Ear and Hearing and the department for Physiotherapy.

Mastoditis in Stockholm 2003-2016

A study on mastoiditis in Region Stockholm before and after the introduction of conjugate pneumococcal vaccine for infants is recently beeing completed and covers alla cases of mastoiditis in children at Karolinska University Hospital 2003-2016. This study is a cooperation between the ENT-department, Astrid Lindgren Children Hospital and the Swedish Public Health Agency.

Deep neck infections at Karolinska University Hospital

A recently finished master thesis (Mia Hermansson, study programme in Medicine, 30p) on epiglottitis at the medical Karolinska and KI has been performed as a quality control. An ethical permit has been aquired, in cooperation with the Department for Oral and Maxillofacial Surgery and Jaw Orthopedics, to enable future studies on deep neck infections originating from the upper airways and from the teeth and oral cavity. This study is still on the drawing board.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

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

Publications 2020, 2020, 2022

1. 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
2. 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-
3. Submitted 2022 (under review): Sofia Hultman Dennisona, Anna Granatha,Mats Holmström, Pär Stjärne, Olof Hertting: Complications to acute bacterial rhinosinusitis in children - a prospective study; bacterial cultures, virus detection, allergy sensitization and immunoglobulins

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Studier på H&N Cancer

1. Studier i ACCROBAT-studien på prediktiva markörer vid HPV positiv orofarynxcancer, immunologiska samt radiologiska, i syfte att kunna de eskalera behandling
2. Sentinel node studier vid spottkörteltumörer
3. Multicenterstudie om livskvalitet efter tungresektion, med eller utan rekonstruktion.
4. Retrospektiva studier på tungcancer, sentinel node och prediktiva faktorer
5. Sinonasala SNUC och SmarqB1-deficient, genomgång av nationellt material.
6. Studier på patienter ur svenskt kvalitetsregister för huvud halscancer, i nuläget hypofarynx, spottkörtlar och larynx T1 samt T4.

Supervision of PhD-students:

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

Ethical permit No.

Publications 2020, 2021, 2022

1. Carpén T, Gille E, Hammarstedt-Nordenvall L, Hansen J, Heikkinen S, Lynge E, Selander J, Mehlum IS, Torfadottir JE, Mäkitie A, Pukkala E.BMC Occupational risk variation of nasopharyngeal cancer in the Nordic countries. Cancer. 2022 Nov 4;22(1):1130. doi: 10.1186/s12885-022-10209-y.PMID: 36333796
2. Landin D, Nasman A, Jonmarker Jaraj S, 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, 14(8), 1693; https://doi.org/10.3390/v14081693 - 30 Jul 2022
3. Vujasinovic M, Marsk E, Tsolakis AV, Hynning B, Nordberg M, Lindblad M, Lindqvist C, Nordenvall LH, Bark R, Elbe P Complications of Gastrostomy Tubes in Patients With Head and Neck Cancer. Laryngoscope. 2022 Jan 18. doi: 10.1002/lary.30017. Online ahead of print.PMID: 35041225
4. 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 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. Acta Oncol. 2022 Apr;61(4):433-440. doi: 10.1080/0284186X.2022.2027516. Epub 2022 Jan 26.PMID: 35081863
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6. Wu S, Hammarstedt-Nordenvall L, Jangard M, Cheng L, Radu SA, Angelidou P, Zha Y, Hamsten M, Engstrand L, Du J, Ternhag A Tonsillar Microbiota: a Cross-Sectional Study of Patients with Chronic Tonsillitis or Tonsillar Hypertrophy. .mSystems. 2021 Mar 9;6(2):e01302-20. doi: 10.1128/mSystems.01302-20.PMID: 33688019
7. Kamali A, Docherty Skogh AC, Edsander Nord Å, Lundgren K, Jergovic D, Hammarstedt Nordenvall L, Sommar P, Halle M.J Increased salvage rates with early reexploration: A retrospective analysis of 547 free flap cases. Plast Reconstr Aesthet Surg. 2021 Oct;74(10):2479-2485. doi: 10.1016/j.bjps.2021.03.001. Epub 2021 Mar 19.PMID: 33879412

8. 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
9. 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 Sep;278(9):3489-3496. doi: 10.1007/s00405-020-06545-z. Epub 2021 Jan 2.PMID: 33389006
10. Hammarstedt L, Holzhauser S, Zupancic M, Kapoulitsa F, Ursu RG, Ramqvist T, Haeggblom L, Näsman A, Dalianis T, Marklund L. The value of p16 and HPV DNA in non-tonsillar, non-base of tongue oropharyngeal cancer. Acta Otolaryngol. 2020 Sep 17:1-6. doi: 10.1080/00016489.2020.1813906. Online ahead of print.PMID: 32940116
11. Gebre-Medhin M, Brun E, Engström P, Haugen Cange H, Hammarstedt-Nordenvall L, Reizenstein J, Nyman J, Abel E, Friesland S, Sjödin H, Carlsson H, Söderkvist K, Thomasson M, Zackrisson B, Nilsson P.J ARTSCAN III: A Randomized Phase III Study Comparing Chemoradiotherapy With Cisplatin Versus Cetuximab in Patients With Locoregionally Advanced Head and Neck Squamous Cell Cancer. Clin Oncol. 2020 Oct 14:JCO2002072. doi: 10.1200/JCO.20.02072. Online ahead of print. PMID: 33052757
12. Marklund L, Holzhauser S, de Flon C, Zupancic M, Landin D, Kolev A, Haeggblom L, Munck-Wikland E, Hammarstedt-Nordenvall L, Dalianis T, Näsman A Survival of patients with oropharyngeal squamous cell carcinomas (OPSCC) in relation to TNM 8 - Risk of incorrect downstaging of HPV-mediated non-tonsillar, non-base of tongue carcinomas. Eur J Cancer. 2020 Nov;139:192-200. doi: 10.1016/j.ejca.2020.08.003. Epub 2020 Sep 17.PMID: 32951963

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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 18 study centers in Sweden during 2019-2023 and a total of 500 patients will be included. Prednisolone 1 mg/kg x 1 perorally in 10 days will be evaluated vs placebo. Clinical data, including clincial outcome (House-Brackmann, Sunnybrook, FaCE scale and FDI) will be documented up until the 12-months follow-up.

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

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

The study protocol is published at ClincialTrials.gov NCT03781700

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Sofia Karlsson	
Sigurdur Arnason	

Ethical permit No.

2017/554				

Publications 2020, 2021, 2022

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2. Borgstrom M, Bergsten A, Tunebjer M, Skogman BH, Nevéus T. Fecal disimpaction in children with enuresis and constipation does not make them dry at night. J Pediatr Urol 2022 May 19; (doi: 10.1016/j.jpurol.2022.05.008, online ahead of print).
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4. Arnason S, Skogman BH. Effectiveness of antibiotic treatment in children with Lyme neuroborreliosis - a retrospective study. BMC Pediatr. 2022; 22:332 (doi: 10.1186/s12887-022-03335-w)
5. Nilsson T. Leijon A, Sillen U, Hellström AL, Skogman BH. Bowel and bladder function in infant toilet training (BABITT) – protocol for a randomized, two-armed intervention study. BMC Pediatr. 2022;22:294 (doi:10.1186/s12887-022-03355-6)

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9. Karlsson S, Arnason S, Hadziosmanovic N, Laestadius A , Hultcrantz M, Marsk E, Skogman BH. 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 (doi: 10.1186/s12887-021-02571-w)
10. Skogman BH, Wilhelmsson P, Atallah S, Petersson AC, Lindgren PE. Lyme neuroborreliosis in Swedish children—PCR as a complementary diagnostic method for detection of Borrelia burgdorferi sensu lato in cerebrospinal fluid. Eur J Clin Microbiol Infect Dis. 2021; 40:1003–12 (doi: 10.1007/s10096-020-04129-7)
11. Appelgren D, Enocsson H, Skogman BH, Nordberg M, Perander L, Nyman D, Nyberg C, Knopf J, Munoz LE, Sjowall C, Sjowall J. Neutrophil Extracellular Traps (NETs) in the Cerebrospinal Fluid Samples from Children and Adults with Central Nervous System Infections. Cells. 2020;9(43):1-14 (doi: 10.3390/cells9010043)
12. Skogman BH, Lager M, Brudin L, Jenmalm MC, Tjernberg I, Henningsson AJ. Cytokines and chemokines in cerebrospinal fluid in relation to diagnosis, clinical presentation and recovery in children being evaluated for Lyme neuroborreliosis. Ticks and tick-borne diseases. 2020; 11 (3):1-11 (doi: 10.1016/j.ttbdis.2020.101390)

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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

Ethical permit No.

2009/714	2021-03633			

Publications 2020, 2021, 2022

1. A preseason booster prolongs the increase of allergen specific IgG4 levels, after basic allergen intralymphatic immunotherapy, against grass pollen seasonal allergy. Weinfeld D, Westin U, Hellkvist L, Mellqvist U-H, Jacobsson I, Cardell L-O. Allergy Asthma Clin Immunol. 2020 Apr 28;16:31. doi: 10.1186/s13223-020-00427-z. eCollection 2020.
2. 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
3. A five-year open follow up of a randomized, double-blind placebo-controlled trial of intralymphatic immunotherapy for birch and grass reveals remaining beneficial effects. Hjalmarsson E, Hellkvist L, Karlsson A, Winquist O, Kumlien Georén S, Westin U, Olaf Cardell L. J Investig Allergol Clin Immunol. 2022 Jun 2:0. doi: 10.18176/jiaci.0832. Epub ahead of print. PMID: 35671100.

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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
	Marlin Johansson

Ethical permit No.

2012/057	2014/2101-31			

Publications 2020, 2021, 2022

4. Xie W, Dai Q, Liu J, Liu Y, Hellström S, Duan M. Analysis of Clinical and Laboratory Findings of Idiopathic Sudden Sensorineural Hearing Loss. Sci Rep. 2020 Apr 8;10(1):6057.
5. 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.
6. Tong B, Wang Q, Dai Q, Hellstrom S, Duan M. Efficacy of Various Corticosteroid Treatment Modalities for the Initial Treatment of Idiopathic Sudden Hearing Loss: A Prospective Randomized Controlled Trial. Audiol Neurootol. 2021;26(1):45-52.
7. Berninger E, Drott M, Romanitan M, Tranebjærg L, Hellström S. Congenital Nonprofound Bilateral Sensorineural Hearing Loss in Children: Comprehensive Characterization of Auditory Function and Hearing Aid Benefit. Audiol Res. 2022 Oct 7;12(5):539-563.
8. Duan M, Xie W, Persson L, Hellstrom S, Uhlén I. Postnatal hearing loss: a study of children who passed neonatal TEOAE hearing screening bilaterally. Acta Otolaryngol. 2022 Jan;142(1):61-66.

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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 2020, 2021, 2022

1.

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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 are recruiting up to 15 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 2020, 2021, 2022

1. Hertegård S., Nagubothu S.R., Malmström E., LeBlanc K. Treatment of Vocal Fold Scarring with Autologous Bone Marrow Derived Human Mesenchymal Stromal Cells- First Phase I/II Human Clinical Study. Stem Cell Research and Therapy. 2020 Mar 20;11(1):128. doi: 10.1186/s13287-020-01632-8. DOI:10.1186/s13287-020-01632-8. SCRT-D-20-00039R22020
2. Hertegård S., LeBlanc K. Treatment of vocal fold scarring with autologous bone marrow-derived human mesenchymal stromal cells—first phase I/II human clinical study: commentary to response. Stem Cell Res Ther. 2020 Jun 16;11(1):235. doi: 10.1186/s13287-020-01748-x. PMID: 32546218
3. 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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Dendritic cells in tumor-draining lymph nodes and their involvement in tumor escape in head and neck cancer

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	019-03518			

Publications 2021, 2022, 2022

1. Kågedal Å, Hjalmarsson E, Farrajota Neves da Silva P, Piersiala K, Georén SK, Margolin G, et al. Activation of T helper cells in sentinel node predicts poor prognosis in oral squamous cell carcinoma. Sci Rep. 2020;10(1):22352.
2. Piersiala K, Farrajota Neves da Silva P, Hjalmarsson E, Kolev A, Kågedal Å, Starkhammar M, et al. 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;112(3):1048-59.

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Different aspects on nasal physiology and disease

1. 1. Rhinomanometry - to create normal values on a national basis and to estimate the use as a tool to select patients for septoplasty

2. 2. Hereditary Hemorrhagic Telangiectasi (HHT) in Sweden - a register based study about mortality, morbidity,prevalence and treatment

3. 3. Chronic rhinosinusitis in adolescence: prevalence, clinical characteristics and inflammatory markers. Predictors of upper airway symptoms in the BAMSE birth cohort.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Karin Åberg

Ethical permit No.

2019-06015	2016/1380 - 31/2			

Publications 2020, 2021, 2022

1. Bengtsson C, Jonsson L, Theorell-Haglöw J, Holmström M, Jansson C, Lindberg E.Sinonasal outcome test-22 and peak nasal inspiratory flow –valuable tools in obstructive sleep apnoea. Rhinology 2020; 58(4); 341-8
2. S Hultman Dennison , Olof Hertting , Rutger Bennet , Margareta Eriksson , Mats Holmström , Lina Schollin Ask , Ann Lindstrand , Praxitelis Dimitriou , Pär Stjärne , Anna Granath . A Swedish population-based study of complications to acute rhinosinusitis in children 5 to 18 years old. J Pediatr Otorhinolaryngol 2021; Aug 5
3. Hultman-Dennison S, Granath A, Holmström M, Stjärne P, Hertting O Bacterial cultures, virus detection, allergy sensitization and immunoglobulins in children with complications to acute bacterial rhinosinusitis – a prospective study. Submitted
4. Morén S, Lindestad P-Å, Stålhammar L, Holmström M, Mani, M. Speech in Adults Treated for Unilateral Cleft Lip and Palate as Rated by Naïve Listeners, Speech-Language Pathologists and Patients. J Plast Reconstr Aesthet Surg Oct;75(10):3804-3812; 2022

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Complications to acute rhinosinusitis in chilren

PhD june 2021: Complication to acute rhinosinusitis in children.

Masoiditis

Currently working on article regarding mastoiditis.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Jenny Häggström

Ethical permit No.

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

Publications 2020, 2021, 2022

1. C“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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The goal of this project is to establish an assessment method by which central auditory function can be verified in patients with cognitive impairment, thereby allowing for prevention of accelerated cognitive decline and hearing rehabilitation adapted to cognitive level.

The hypothesis is that combined measures of central auditory function and cognitive function will accurately identify persons with both hearing impairment and cognitive deficits.

In our recent studies (Häggström et al., 2018 and 2020) it has been suggested that the Dichotic Digit Test (DDT) as a central auditory test, may reflect ongoing process resulting in dementia and may be suitable when evaluating cognitive decline.

The aim of the ongoing study is to determine the relationship between central auditory function, measured by DDT, and the cerebrospinal fluid (CSF) markers concentrations of total tau (T-tau), phosphorylated tau (P-tau) and beta amyloid 42 (ßA42) in individuals with subjective memory complaints (SMC), Mild Cognitive Impairment (MCI) and Alzheimer disease (AD).

The preliminary results have showed that subjects with pathological levels of the CSF markers T-tau, P-tau, and ßA42 perform significantly worse on DDT, independent of clinical diagnosis. This further strengthens the relationship between the central auditory processing dysfunction (CAPD) and cognitive function.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Jenny Häggström

Ethical permit No.

2005/914-3	2014/2087-31-2	2018/1291-32		

Publications 2020, 2021, 2022

1. Cederroth CR, PirouziFard M, Trpchevska N, Idrizbegovic E, Canlon B, Sundquist J, Sundquist K, Zöller B.Association of Genetic vs Environmental Factors in Swedish Adoptees With Clinically Significant Tinnitus.JAMA Otolaryngol Head Neck Surg. 2019 Mar 1;145(3):222-229. doi: 10.1001/jamaoto.2018.3852.
2. Häggström J, Hederstierna C, Rosenhall U, , Östberg P, Idrizbegovic E. Prognostic Value of a Test of Central Auditory Function in Conversion from Mild Cognitive Impairment to Dementia, Audiol Neurootol. 2020; 25 (5): 276-282. doi: 10.1159/000506621. Epub 2020 May.

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Studies in chronic rhinosinusitis and in pediatric patients with tracheostomy

1. I) Long term follow-up in Swedish patients with chronic rhinosinusitis with nasal polyps participating in the GA2LEN cohort.

2. II) Long term follow up in pediatric patients with tracheostomy - morbidity, mortality and long-term outcome.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2020, 2021, 2022

1. Cardell LO, Stjärne P, Jonstam K, Bachert C. Endotypes of chronic rhinosinusitis: Impact on management. J Allergy Clin Immunol 2020; 145:752-6.
2. Jonstam K, Alsharif S, Bogaert S, Suchonos N, Holtappels G, Jae-Hyun Park J,
3. et al. Extent of inflammation in severe nasal polyposis and effect of sinus surgery on inflammation. Allergy 2020.
4. Jonstam K, Delemarre T, Holtappels G, Cardell LO, Westamn M, Bachert C. Type 2 Inflammatory Shift in Chronic Rhinosinusitis During 2007-2018 in Belgium. Laryngoscope 2020.

Susanna Kumlien Georén
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Immune responses in airway inflammatory diseases and head- and neckcancer.

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 airways

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Magnus Starkhammar
	Krzysztof Piersiala
	Vilma Lagebro
	Maryam Jafari

Ethical permit No.

2017_1791	2021_01265	2021_00325	2022_002039	

Publications 2020, 2021, 2022

1. 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
2. Hjalmarsson E, Hellkvist L, Karlsson A, Winquist O, Kumlien Georén S, Westin U, Olaf Cardell L. A five-year open follow up of a randomized, double-blind placebo-controlled trial of intralymphatic immunotherapy for birch and grass reveals remaining beneficial effects. Journal of investigational allergology & clinical immunology 2022 ;
3. Ekstedt S, Piersiala K, Petro M, Karlsson A, Kågedal Å, Kumlien Georén S, Cardell LO. A prolonged innate systemic immune response in COVID-19. Scientific reports 2022 12;1 9915-
4. Hellkvist L, Hjalmarsson E, Weinfeld D, Dahl Å, Karlsson A, Westman M, Lundkvist K, Winqvist O, Georén SK, Westin U, Cardell LO. High-dose pollen intralymphatic immunotherapy: Two RDBPC trials question the benefit of dose increase. Allergy 2022 77;3 883-896

5. Cardenas EI, Ekstedt S, Piersiala K, Petro M, Karlsson A, Kågedal Å, Kumlien Georén S, Cardell LO, Lindén A. Increased IL-26 associates with markers of hyperinflammation and tissue damage in patients with acute COVID-19. Frontiers in immunology 2022 13; 1016991-
6. 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
7. 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. Translational oncology 2022 23; 101469-
8. 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
9. 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
10. Ma JJ, Tibbitt CA, Georen SK, Christian M, Murrell B, Cardell LO, Bachert C, Coquet JM. Single-cell analysis pinpoints distinct populations of cytotoxic CD4(+) T cells and an IL-10(+)CD109(+) T(H)2 cell population in nasal polyps. SCIENCE IMMUNOLOGY 2021 6;62
11. Larsson O, Sunnergren O, Bachert C, Kumlien Georén S, Cardell LO. The SP-TLR axis, which locally primes the nasal mucosa, is impeded in patients with allergic rhinitis. Clinical and translational allergy 2021 11;1 e12009-
12. Kagedal A, Hjalmarsson E, da Silva PFN, Piersiala K, Georen SK, Margolin G, Munck-Wikland E, Winqvist O, Hayry V, Cardell LO. Activation of T helper cells in sentinel node predicts poor prognosis in oral squamous cell carcinoma. SCIENTIFIC REPORTS 2020 10;1 22352-
13. Ekstedt S, Tufvesson E, Bjermer L, Georen SK, Cardell LO. A new role for ”eat me” and ”don’t eat me” markers on neutrophils in asthmatic airway inflammation. ALLERGY 2020 75;6 1510-1512
14. Ekstedt S, Larsson O, Kumlien Georén S, Cardell LO. CD16high CD62Ldim neutrophils induce nerve-mediated airway hyperreactivity. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 2020 50;6 756-759
15. Ekstedt S, Georen SK, Cardell LO. Effects of MP-AzeFlu enhanced by activation of bitter taste receptor TAS2R. ALLERGY ASTHMA AND CLINICAL IMMUNOLOGY 2020 16;1 45-
16. Drakskog C, de Klerk N, Westerberg J, Mäki-Torkko E, Georén SK, Cardell LO. Extensive qPCR analysis reveals altered gene expression in middle ear mucosa from cholesteatoma patients. PloS one 2020 15;9 e0239161-
17. Larsson OJ, Georen SK, Cardell LO. Rapid activation of brainstem nuclei following TLR stimulation of the nasal mucosa. ACTA NEUROBIOLOGIAE EXPERIMENTALIS 2020 80;4 353-357

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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.

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

Publications 2020, 2021, 2022

1. Kågedal Å, Margolin G, Held C, Farrajota Neves da Silva P, Piersiala K, Munck-Wikland E, Jacobsson H, Häyry V, Cardell LO. A novel sentinel lymph node biopsy approach in oral squamous cell carcinoma. Curr Pharm Des. 2020;26(31):3834-3839
2. Kågedal Å, Hjalmarsson E, Farrajota Neves da Silva P, Piersiala K, Georén SK, Margolin G, Munck-Wikland E, Winqvist O, Häyry V, Cardell LO. Activation of T helper cells in sentinel node predicts poor prognosis in oral squamous cell carcinoma. Sci Rep. 2020 Dec 18;10(1):22352.
3. Piersiala, K; Farrajota Neves da Silva, P; Hjalmarsson, E; Kolev, A; Kågedal, Å; Starkhammar, M; Elliot, A; Marklund, L; Margolin, G; Munck af Rosenschold Wikland, E; Kumlien Georén, S; Cardell, L O T cells in sentinel nodes exhibit distinct pattern of PD-1, CD69 and HLA-DR expression compared to tumour tissue in OSCC. Cancer Sci. 2021 Mar;112(3):1048-1059.
4. A prolonged innate systemic immune response in COVID-19. Ekstedt S, Piersiala K, Petro M, Karlsson A, Kågedal Å, Kumlien Georén S, Cardell LO.Sci Rep. 2022 Jun 15;12(1):9915. doi: 10.1038/s41598-022-13986-5.PMID: 35705573
5. Increased IL-26 associates with markers of hyperinflammation and tissue damage in patients with acute COVID-19. Cardenas EI, Ekstedt S, Piersiala K, Petro M, Karlsson A, Kågedal Å, Kumlien Georén S, Cardell LO, Lindén A.Front Immunol. 2022 Nov 17;13:1016991. doi: 10.3389/fimmu.2022.1016991. eCollection 2022. PMID: 36466824

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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 2020, 2021, 2022

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.
2. 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; PMCID: PMC8196945.
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Pancreatic cancer

LncRNA as RNA molecules not only can participant in regulating apoptosis and autophagy cancer, also can promote and decrease the proliferation of tumor cells. Recent studies also showed that lncRNAs have critical role in the pathogenesis, prognosis and diagnosis of pancreatic cancer. As we know, single-cell omics technologies provide an unprecedented opportunity to decipher molecular mechanisms underlying various biological processes in a cell-heterogeneous manner. The emergence of such technique can promote the exploration of mRNA, meanwhile provide the opportunity to capture and/ decipher lncRNA in a specific cell type or a certain cellular state. So different layers of single-cell omics data for lncRNA of pancreatic cancer will be used in a combination way to construct gene regulatory networks using bioinformatic tools. Genomic, chromatinal, transcriptome data of pancreatic cancer will be combined to reveal patterns of lncRNAs in specific expression and regulation of pancreatic cancer and predict potential biomarker and drug targets.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

Publications 2020, 2021, 2022

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Long-term follow-up of adolescents and young adults who have undergone surgery with cochlear implants during early childhood

We have previously reported that cochlear implantation in infancy is safe and highly important for children who are congenitally hard-of-hearing/deaf to develop early spoken language abilities (Karltorp et al., 2019), which is in line with the current literature. However, long-term outcomes are relatively unknown, for example finer language competence, psychosocial well-being, and listening skills in more complex listening conditions reflecting everyday life. In addition, it is 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 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 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?

Data collection is ongoing: multidisciplinary follow-up visits and questionnaire studies in participants with CI and in age-matched typical hearing controls. During spring 2023 we will also conduct focus group interviews for adolescents with CI.

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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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	2012/49-31/2	2019/03518		

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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 2020, 2021, 2022

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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	

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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

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

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Undergraduate students' clinical learning environment and lifelong learning

Undergraduate students' clinical learning environment (CLE).
It is widely acknowledged that CLE impacts students' professional development and their ability to achieve the learning outcomes. This project aims to identify and provide an in-depth understanding of students' perception of the clinical learning environment and the relationship to self-reported health-related quality of life across four different undergraduate programs. The first study assessed the CLE by the Undergraduate Clinical Education Environment Measure (UCEEM) and showed signifigant differences between the programs with physiotherapy students rating highest and medical students lowest their CLE. Th eporjecst has been progressed with two new qualitative studies.

The other research path concerns undergraduate students scientific development and attitudes to lifelong learning. Ethical application is to be submitted in the begiining of the this year and two new studies are to be started in 2022.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
Malin Sellberg	

Ethical permit No.

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

Publications 2019, 2020, 2021

1. Möller R, Wallberg A, Shoshan M. Faculty perceptions of factors that indicate successful educational outcomes of medical students' research projects: a focus group study. BMC Med Educ. 2021 Oct 3;21(1):519. doi: 10.1186/s12909-021-02954-8. PMID: 34600506; PMCID: PMC8487494.
2. 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
3. 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.
4. Möller R. Reformeringen av läkarutbildningen i Sverige. Finska Läkaresällskapets Handlingar 2020; 180:2; 52-57.
5. Rosengren B, Möller R, Hellman J, Jood K, Ekstedt M, Särnbland S, Alm S, Gummesson C. EPA (Entrustable professional activities)- an international approach to define key tasks that a doctor should be able to perform. Läkartidningen. 2019 May 7;116.
6. Möller R. It's time to define the Swedish Doctor? Lessons learnt from the evaluation of the Finnish undergraduate medical education. Läkartidningen. 2019 May 7;116.
7. Hultin M, Möller R. En grundutbildning i förändring. Läkartidningen. 2019 May 7;116
8. Möller R, Shoshan M. Does reality meet expectations? An analysis of medical students' expectations and perceived learning during mandatory research projects. BMC Med Ed 2019 19;1 93-
9. Möller R, Hultin M. [Examination of future colleagues: We need an assessment culture]. Läkartidningen 2019 116;
10. Bexelius T, Lachmann H, Järnbert-Pettersson H, Kalén S, Möller R, Ponzer S. Stress among medical students during clinical courses: a longitudinal study using contextual activity sampling system. IJME 2019 10; 68-74
11. Möller R, Safa S, Östberg P. A prospective study for evaluation of structural and clinical validity of the Eating Assessment Tool. BMC Geriatr 20, 269 (2020). https://doi.org/10.1186/s12877-020-01654-0

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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 2020, 2021, 2022

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-
5. Mackay AJ, Kostikas K, Roche N, Frent SM, Olsson P, Pfister P, Gupta P, Patalano F, Banerji D, Wedzicha JA. Impact of baseline symptoms and health status on COPD exacerbations in the FLAME study. Respiratory research 2020 21;1 93-
6. Muro S, Yoshisue H, Kostikas K, Olsson P, Gupta P, Wedzicha JA. Indacaterol/glycopyrronium versus tiotropium or glycopyrronium in long-acting bronchodilator-naïve COPD patients: A pooled analysis. Respirology (Carlton, Vic.) 2020 25;4 393-400

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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 2020, 2021, 2022

1. 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
2. Postsurgical pyoderma gangrenosum and flap necrosis in a head and neck cancer patient following neck dissection. Arebro J, Palmgren B.Arebro J, et al. Clin Case Rep. 2020 Apr 8;8(7):1121-1125. doi: 10.1002/ccr3.2828. eCollection 2020 Jul.Clin Case Rep. 2020. PMID: 32695340
3. 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. doi:10.1002/lio2.1034

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Cochlear Implantation in Children with Cochlear Malformation

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

Supervision of PhD-students:

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

Ethical permit No.

2014/2068-31/2				

Publications 2020, 2021, 2022

1. X-linked Malformation Deafness: Neurodevelopmental Symptoms Are Common in Children With IP3 Malformation and Mutation in POU3F4. Smeds H, Wales J, Karltorp E, Anderlid BM, Henricson C, Asp F, Anmyr L, Lagerstedt-Robinson K, Löfkvist U. Ear Hear. 2021 Jun 15;43(1):53-69.
2. Wideband tympanometry in ears with superior canal dehiscence before and after surgical correction. Velikoselskii A, Papatziamos G, Smeds H, Verrecchia L. Int J Audiol. 2021 Aug 21:1-6.

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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 2020, 2021, 2022

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. 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
3. 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.

4. Lundström J, Stjärne P. Förlorat luktsinne – möjligt tidigt tecken på covid-19. Lakartidningen. 2020 Apr 8;117:F3P9
5. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, Toppila-Salmi S, Bernal-Sprekelsen M, Mullol J, Alobid I, Terezinha Anselmo-Lima W, Bachert C, Baroody F, von Buchwald C, Cervin A, Cohen N, Constantinidis J, De Gabory L, Desrosiers M, Diamant Z, Douglas RG, Gevaert PH, Hafner A, Harvey RJ, Joos GF, Kalogjera L, Knill A, Kocks JH, Landis BN, Limpens J, Lebeer S, Lourenco O, Matricardi PM, Meco C, O Mahony L, Philpott CM, Ryan D, Schlosser R, Senior B, Smith TL, Teeling T, Tomazic PV, Wang DY, Wang D, Zhang L, Agius AM, Ahlstrom-Emanuelsson C, Alabri R, Albu S, Alhabash S, Aleksic A, Aloulah M, Al-Qudah M, Alsaleh S, Baban MA, Baudoin T, Balvers T, Battaglia T, Bedoya JD, Beule A, Bofares KM, Braverman I, Brozek-Madry E, Richard B, Callejas C, Carrie S, Caulley L, Chussi D, de Corso E, Coste A, Lal D, El Hadi U, Elfarouk A, Eloy PH, Farrokhi S, Felisati G, Ferrari MD, Fishchuk R, Grayson W, Goncalves PM, Grdinic B, Grgic V, Hamizan AW, Heinichen JV, Husain S, Ping TI, Ivaska J, Jakimovska F, Jovancevic L, Kakande E, Kamel R, Karpischenko S, Kariyawasam HH, Kjeldsen A, Klimek L, Kim SW, Letort JJ, Lopatin A, Mahdjoubi A, Netkovski J, Nyenbue Tshipukane D, Obando-Valverde A, Okano M, Onerci M, Ong YK, Orlandi R, Ouennoughy K, Ozkan M, Peric A, Plzak J, Prokopakis E, Prepageran N, Psaltis A, Pugin B, Raftopulos M, Rombaux P, Sahtout S, Sarafoleanu CC, Searyoh K, Rhee CS, Shi J, Shkoukani M, Shukuryan AK, Sicak M, Smyth D, Snidvongs K, Soklic Kosak T, Stjarne P. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020 Feb 20;58(Suppl S29):1-464. doi: 10.4193/Rhin20.600. PubMed PMID: 32077450.
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Long-term follow-up of RCT Uvulopalatopharyngoplasty vs Tonsillectomy

The TEAMUP randomized clinical trial demonstrated that modified uvulopalatopharyngoplasty (UPPP) was not more effective than tonsillectomy (TE) alone in treating patients with tonsillar hypertrophy and moderate to severe obstructive sleep apnea (OSA). Because TE alone is less extensive, it could be considered as an alternative to mUPPP in this selected group of patients with OSA. The longterm effect is still unknown, but could be evaluated by performing an additional polysomnography 5-7 years after surgery. The present study aims to do this.

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*

Ethical permit No.

2015/755-31/2				

Publications 2020, 2021, 2022

1. 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 22;6(64)
2. Long-term evaluation of satisfaction and side effects after modified uvulopalatopharyngoplasty. Friberg D, Sundman J, Browaldh N. Laryngoscope. 2020 Jan
3. Eight-Year Follow-up of Modified Uvulopalatopharyngoplasty in Patients With Obstructive Sleep Apnea. Sundman J, Browaldh N, Fehrm J, Friberg D. Laryngoscope. 2021 Jan
4. Effectiveness of Tonsillectomy vs Modified Uvulopalatopharyngoplasty in Patients With Tonsillar Hypertrophy and Obstructive Sleep Apnea The TEAMUP Randomized Clinical Trial Sundman, J, MD, PhD; Pia Nerfeldt, MD, PhD; Johan Fehrm, MD, PhD; Johan Bring, PhD; Nanna Browaldh, MD, PhD; Danielle Friberg, MD, PhD JAMA Otolaryngol Head Neck Surg. 2022 (2022 Nov, online)

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Hearing and speech with bilateral implants

The research focus on language development in children who have undergone surgery with hearing implants, on the development of both language and other development in these subjects. There is new material, non-analyzed subgroups and other aspects to use to deepen the research field and knowledge. The research will elucidate the language development in subjects operated with cochlear implants and bone anchored hearing aids. Language understanding and development, localization of sound is focus

Supervision of PhD-students:

Main Supervisor	*Co-supervisor*
	Fatima Moumén Denanto

Ethical permit No.

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

Publications 2020, 2021, 2022

1. Denanto FM, Wales J, Tideholm B, Asp F. Differing Bilateral Benefits for Spatial Release From Masking and Sound Localization Accuracy Using Bone Conduction Devices. Ear Hear. 2022 Nov-Dec 01;43(6):1708-1720.
2. Karltorp E, Eklöf M, Östlund E, Asp F, Tideholm B, Löfkvist U. Cochlear implants before 9 months of age led to more natural spoken language development without increased surgical risks. Acta Paediatr. 2020 Feb;109(2):332-341.

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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 2020, 2021, 2022

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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

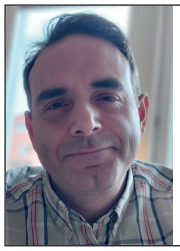
Ethical permit No.

2020-07203				

Publications 2020, 2021, 2021

1. 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 ; 1-7View in Medline
2. Edvall NK, Mehraei G, Claeson M, Lazar A, Bulla J, Leineweber C, Uhlén I, Canlon B, Cederroth CR. Alterations in auditory brain stem response distinguish occasional and constant tinnitus. The Journal of clinical investigation 2022 132;5 View in Medline View in Web of Science
3. 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 2022 ; 9691413221126677- View in Medline View in Web of Science
4. Flynn T, Uhlén I, Miniscalco C. Hearing aid use in 11-year-old children with mild bilateral hearing loss: Associations between parent and child ratings and datalogging. International journal of pediatric otorhinolaryngology 2022 156; 111120- View in Medline View in Web of Science
5. Duan ML, Xie W, Persson L, Hellstrom S, Uhlen I. Postnatal hearing loss: a study of children who passed neonatal TEOAE hearing screening bilaterally. ACTA OTO-LARYNGOLOGICA 2022 142;1 61-66 View in Medline View in Web of Science
6. Mackey AR, Bussé AML, Del Vecchio V, Mäki-Torkko E, Uhlén IM. Protocol and programme factors associated with referral and loss to follow-up from newborn hearing screening: a systematic review. BMC pediatrics 2022 22;1 473- View in Medline View in Web of Science
7. Mackey AR, Bussé AML, Hoeve HLJ, Goedegebure A, Carr G, Simonsz HJ, Uhlén IM, EUS€REEN Foundation. Assessment of hearing screening programmes across 47 countries or regions II: coverage, referral, follow-up and detection rates from newborn hearing screening. International journal of audiology 2021 60;11 831-840 View in Medline View in Web of Science
8. Bussé AML, Mackey AR, Carr G, Hoeve HLJ, Uhlén IM, Goedegebure A, Simonsz HJ, EUS€REEN Foundation. Assessment of hearing screening programmes across 47 countries or regions III: provision of childhood hearing screening after the newborn period. International journal of audiology 2021 60;11 841-848 View in Medline View in Web of Science

9. Bussé AML, Mackey AR, Hoeve HLJ, Goedegebure A, Carr G, Uhlén IM, Simonsz HJ, EUS€REEN Foundation. Assessment of hearing screening programmes across 47 countries or regions I: provision of newborn hearing screening. International journal of audiology 2021 60;11 821-830 View in Medline View in Web of Science
10. Engström E, Kallioinen P, Nakeva von Mentzer C, Lindgren M, Sahlén B, Lyxell B, Ors M, Uhlén I. Auditory event-related potentials and mismatch negativity in children with hearing loss using hearing aids or cochlear implants - A three-year follow-up study. International journal of pediatric otorhinolaryngology 2021 140; 110519- View in Medline View in Web of Science
11. Verkleij ML, Heijnsdijk EAM, Bussé AML, Carr G, Goedegebure A, Mackey AR, Qirjazi B, Uhlén IM, Sloot F, Hoeve HLJ, de Koning HJ, Country-Committees Joint-Partnership of EUSCREEN Study Consortium. Cost-Effectiveness of Neonatal Hearing Screening Programs: A Micro-Simulation Modeling Analysis. Ear and hearing 2021 42;4 909-916 View in Medline View in Web of Science
12. Cederroth CR, Lugo A, Edvall NK, Lazar A, Lopez-Escamez JA, Bulla J, Uhlen I, Hoare DJ, Baguley DM, Canlon B, Gallus S. Association between Hyperacusis and Tinnitus. JOURNAL OF CLINICAL MEDICINE 2020 9;8 View in Medline View in Web of Science
13. Engström E, Kallioinen P, Lindgren M, Nakeva von Mentzer C, Sahlén B, Lyxell B, Uhlén I. Computer-assisted reading intervention for children with hearing impairment using cochlear implants: Effects on auditory event-related potentials and mismatch negativity. International journal of pediatric otorhinolaryngology 2020 137; 110229- View in Medline View in Web of Science
14. Uhlén I, Kovacsovics B, Möller C. [Possibilities to diagnose hearing impairment in children]. Lakartidningen 2020 117; View in Medline
15. Uhlen I, Mackey A, Rosenhall U. Prevalence of childhood hearing impairment in the County of Stockholm - a 40-year perspective from Sweden and other high-income countries. INTERNATIONAL JOURNAL OF AUDIOLOGY 2020 59;11 866-873 View in Medline View in Web of Science
16. Lugo A, Edvall NK, Lazar A, Mehraei G, Lopez-Escamez JA, Bulla J, Uhlen I, Canlon B, Gallus S, Cederroth CR. Relationship between headaches and tinnitus in a Swedish study. SCIENTIFIC REPORTS 2020 10;1 8494- View in Medline View in Web of Science
17. Niu K, Brandström A, Skenbäck S, Duan M, Uhlén I. Risk factors and etiology of childhood hearing loss: a cohort review of 296 subjects. Acta oto-laryngologica 2020 140;8 668-674. View in Medline View in Web of Science
18. Trpchevska N, Bulla J, Prada Hellberg M, Edvall NK, Lazar A, Mehraei G, Uhlen I, Schlee W, Canlon B, Gallus S, Lopez-Escamez JA, Cederroth CR. Sex-Dependent Aggregation of Tinnitus in Swedish Families. Journal of clinical medicine 2020 9;12 View in Medline View in Web of Science



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Objective balance testing in children

This project, linked to the doctoral eduction of MD Niki Karpeta, of PT Susanne Gripenberg and post doctoral studies of M.Sc.EE., PhD Martin Eklöf aims to validate a modern pediatric objective balance testing in clinical practice. An ongoing validation study is about the balance screening of newborns with vestibular evoked miogenic potentials (VEMP), along with the universal hearing screening program. An observational study deals with the testining of vestibular function and motor proficiency in CI recipients grown up to teenage with the help also of inertial sensors for an automatized analysis by machine learing. A third study is a retrospective analysis of the vestibular function in a cohort of deaf children with eight nerve aplasia/hypoplasia. This project is supported by SCAPA (https://ki.se/clintec/om-scapa), a research organisation at CLINTEC for advanced clinical research in pediatric audiology and neurotology, which I lead togheter with assoc. professor Erik Berninger and M. Sc. CS, PhD Filip Asp.

New methods for a better diagnosis of dizziness by bone conducted stimulation

The project represents my post-doctoral studies, as guest researcher at the Department of Electrical Engineering, Chalmers University of Technology. Supervised by full professor Bo Håkansson and assoc professor Sabine Reinfeldt, I´m testing the clinical use of a new bone transducer prototype, the Ortofon B250. In a recently published study we presented a new hearing test based on bone conducted stimulation at malleolus by B250 as a screening test for superior canal dehiscence syndrome (SCDS). We are also investigating the role of B250 in easing and promoting the clinical balance testing by VEMP. Finally we will introduce this device in VEMP testing for children and in testing the so called vibration induced nystagmus.

Supervision of PhD-students:

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

Ethical permit No.

2013/1177-31	2019-05214	2019-02019	2022-00863-02	

Publications 2020, 2021, 2022

1. Verrecchia L, Fredén Jansson KJ, Westin M, Velikoselskii A, Reinfeldt S, Håkansson B. Ankle Audiometry: A Clinical Test for the Enhanced HearingSensitivity for Body Sounds in Superior Canal Dehiscence Syndrome. Audiol Neurootol. 2023 Jan 12:1-11. PMID:36634643.
2. Verrecchia L, Edholm K, Pekkari M. Asymptomatic superior semicircular canal dehiscence. J Laryngol Otol. 2022 Jan;136(1):87-90. PMID: 34702381.
3. Velikoselskii A, Papatziamos G, Smeds H, Verrecchia L. Wideband tympanometry in ears with superior canal dehiscence before and after surgical correction. Int J Audiol. 2022 Aug;61(8):692-697. PMID: 34420430.
4. Lazar A, Löfkvist U, Verrecchia L, Karltorp E. Identical twins affected bycongenital cytomegalovirus infections showed different audio-vestibularprofiles. Acta Paediatr. 2021 Jan;110(1):30-35. PMID: 32956548.
5. Verrecchia L, Galle Barrett K, Karltorp E. The feasibility, validity and reliability of a child friendly vestibular assessment in infants and children candidates to cochlear implant. Int J Pediatr Otorhinolaryngol. 2020 Aug;135:110093. PMID: 32422368.
6. Wibble T, Engström J, Verrecchia L, Pansell T. The effects of meclizine on motion sickness revisited. Br J Clin Pharmacol. 2020 Aug;86(8):1510-1518. PMID: 32077140.

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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*
	Eleftherios Ntouniadakis
	Olof Nilsson
	Anna Oldaeus Almeren
	Clara Svenberg Lind

Ethical permit No.

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

Publications 2020, 2021, 2022

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 Jul;25(3):e433-e42. PubMed PMID: 34377181. Pubmed Central PMCID: PMC8321641. Epub 2021/08/12. eng.
2. Ntouniadakis E, Brus O, von Beckerath M. Dyspnea Index: An upper airway obstruction instrument; translation and validation in Swedish. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery. 2021 Mar;46(2):380-7. PubMed PMID: 33277799. Pubmed Central PMCID: PMC7986702. Epub 2020/12/06.
3. von Beckerath M, Svensson J, Landstrom F. Feasibility of an inexperienced examiner using trans-cervical ultrasound in the diagnosis of peritonsillar abscesses. Acta Otolaryngol. 2021 Sep;141(9):847-50. PubMed PMID: 34392793. Epub 2021/08/17.
4. Hammarstedt Nordenvall L, Jortso 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):100-5. PubMed PMID: 34962438. Epub 2021/12/29.

5. Nilsson O, Knutsson J, Landstrom FJ, Magnuson A, von Beckerath M. Ultrasound accurately assesses depth of invasion in T1-T2 oral tongue cancer. Laryngoscope Investig Otolaryngol. 2022 Oct;7(5):1448-55. PubMed PMID: 36258857. Pubmed Central PMCID: PMC9575113. Epub 2022/10/20.
6. Nilsson O, Knutsson J, Landstrom FJ, Magnuson A, von Beckerath M. Ultrasound-assisted resection of oral tongue cancer. Acta Otolaryngol. 2022 Sep-Dec;142(9-12):743-8. PubMed PMID: 36537851. Epub 2022/12/21.
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 Sep;167(3):517-23. PubMed PMID: 34813409. Pubmed Central PMCID: PMC9442627. Epub 2021/11/24.

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

4. Tracheostomy in the era of Covid-19.
The 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.

Supervision of PhD-students:

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

Ethical permit No.

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

Publicatiions 2020, 2021, 2022

1. 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
2. Wales, J., Smeds, H., Karltorp, E., Anderlid, B.M., Henricson, C., Asp, F., Anmyr, L., Lagerstedt-Robinson, K., Löfkvist, U. X-linked Malformation Deafness: Neurodevelopmental Symptoms Are Common in Children With IP3 Malformation and Mutation in POU3F4. Ear and hearing 2021;():-
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 2021;():-
5. 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
6. Globalsurg Collaborative, Covidsurg Collaborative. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. Anaesthesia 2021;76(6):748-758
7. Wales, J., Alinasab, B., Fridman Bengtsson, O. A superficial nasal dermoid cyst excised through a novel horizontal zig-zag incision in a 49-year old man. Acta Otolaryngologica Case reports. 2020; 5:28-32.
8. Wales, J., Gladine, K., Silvola, J., Muyshondt, P., Topsakal, V., Van De Heyning, P., Dirckx, J., von Unge, M. Evaluation of artificial fixation of the incus and malleus with minimally invasive intraoperative laser vibrometry (MIVIB) in a temporal bone model. Otol. Neurotol. 2020; 41:45-51.

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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.

Publicatiions 2020, 2021, 2022

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

PhD-students

Sigurdur Arnason sigurdur.arnason@ki.se
Main supervisor Barbro Hedin Skogman
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 2020, 2021, 2022

1. Arnason S, Hultcrantz M, Nilsson A, Laestadius Å. Peripheral facial nerve palsy in children in a Borrelia high-endemic area, a retrospective follow-up study. Acta paediatrica. 2020;109(6):1229-35.
2. 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.
3. Arnason S, Skogman BH. Effectiveness of antibiotic treatment in children with Lyme neuroborreliosis - a retrospective study. BMC Pediatr. 2022 Jun 9;22(1):332.
4. 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.

Rasmus Blomkvist rasmus.blomkvist@ki.se
Main supervisor Linda Marklund
Co-supervisor Björn Palmgren, Lalle Hammarstedt-Nordenvall, Antti Mäkitie

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			

Publications/manuscripts 2020, 2021, 2022

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.

Malin Dahlby Skoos malin.dahlby.skoog@ki.se
Main supervisor Ulrika Löfkvist
Co-supervisor Eva Karltorp, Björn Lyxell, Tamara Kalandadze
Registered 2021-09-06
Halftime seminar
Planned dissertation

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

Early age at cochlear implantation has positive effects on early spoken language for congenitally deaf children, but there is need for more research on the long-term effects of early implantation to explain the large variability in outcomes seen in this group. The research regarding long term effects of cochlear implantation on higher linguistic skills, such as metaphor comprehension, is scarce. Executive functions are higher cognitive functions including working memory, attention shifting and inhibitory control. Executive functions develop in close relationship with linguistic skills.

The aim of this project, as part of a multidisciplinary follow up program, is to investigate long term effects of early cochlear implantation on the development of executive functions and metaphor comprehension. We are also interested in the possible relationship between executive functions and the higher linguistic skill of metaphor comprehension. The cohort is estimated to be around 100 individuals between 13 and 18 years old, fitted with CI before 30 months of age at the Hearing Implantation Center at Karolinska university hospital. There will also be a normal hearing control group matched for age, sex and socioeconomic status. Children from multilingual as well as monolingual homes will be included.

Metaphor comprehension will be measured using a multiple-choice task. Linguistic skills (vocabulary and reading) will be assessed with standardized tests. Executive functions will be assessed by task performance and the BRIEF questionnaire.

Data collection is planned to start in january 2022

Ethical permit No.

2021-04345				

Publications/manuscripts 2020, 2021, 2022

1. Löfkvist, U., Bäckström, K., Dahly-Skoog, M., Gunnarsson, S., Persson, M., Lohmander, A. (2019). Babbling and consonant production in children with hearing impairment who use hearing aids or cochlear implants – a pilot study. Logopedics Phoniatrics Vocology, Nov 29:1-9. doi: 10.1080/14015439.2019.1695929

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

Osteoradionecrosis - Riskfactors and reconstructive outcome

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

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

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

Aim of our studies:

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

Ethical permit No.

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

Publications/manuscripts 2020, 2021, 2022

5.

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Main supervisor Caroline Gahm
Co-supervisor Martin Halle, Liv Eidsmo, Lalle Hammarsted Nordenvall

Registered 2018-01-29
Halftime seminar 2022-12-09
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 2020, 2021, 2022

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)

Ola Fridman Bengtsson ola.bengtsson@ki.se
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Registered 2011-12-22
Halftime seminar 2021-01-22
Planed dissertation

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

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

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

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

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 11 organ donors as a base for our receptor studies.

Our aim is that these 2 studies are to be completed during 2022. 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, such as TGF Beta and Interleukin 6 among others in pituitary adenomas, compared to normal pitiuitary tissue

Ethical permit No.

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

Publications/manuscripts 2020, 2021, 2022

1. Remission, complications, and overall survival in transsphenoidal pituitary surgery-a Swedish single-center experience of 578 patients, Acta Neurochirurgica (2023) Jan 20. doi: 10.1007/s00701-022-05456-8. Online ahead of print

Evelina Gille
Main supevisor
Co-supervisor
Registered
Halftime seminar
Planned dissertation

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Lalle Hammarstedt Nordenvall
Antti Mäkitie, Elin Marsk
2020-05-25
2023-05-17

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 2020, 2021, 2022

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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Main supevisor Luca Verrecchia
Co-supervisor Cecilia Lidbeck, Sten Hellström
Registered 2022-08-24
Halftime seminar
Planned dissertation

Vestibular function and motor activities in children with hearing loss, balance disorders and motor delays

The vestibular function i.e the balance function in the inner ear, is crucial for typical motor development in children and it is known that vestibular impairment can cause delays in motor development, unprotected falls and affect orientation. Up to 70% children affected by severe hearing loss show vestibular dysfunction.

My project aims to explore how a vestibular loss affects motor functioning in children and it also aims to explore the effect of an early intervention in children with difficulties with motor functioning related to vestibular dysfunction.

In a first study we explore how motor functioning relate to vestibular function in a group children and young adults with hearing loss who received CI in early childhood. The participants are assessed for vestibular function by a medical doctor 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 a second study we collect data from children in study I, with inertial sensors applied on different body parts. We analyze with the help of machine learning. The principal question of this study 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. These two studies are part of a long-time follow-up and the collection of data is ongoing.

In a third study we are planning to assess if clinical motor assessments can detect vestibular impairment in infants with hearing loss or motor delay. The infants will be tested in a similar way as the young adults with motor tests. This study is planned to start this fall.

The last study will be a pilot study, where we will evaluate a vestibular rehab intervention designed for infants and 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 2020, 2021, 2022

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Main supevisor Christina Hederstierna Forshell
Co-supervisor Esma Idrizbegovic, Per Östberg, Nenad Bogdanovic

Registered 2016-11-14
Halftime seminar 2019-05-20
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 2020, 2021, 2022

1. Häggström J, Hederstierna C, Rosenhall U, Östberg P, Idrizbegovic E. Prognostic Value of a Test of Central Auditory Function in Conversion from Mild Cognitive Impairment to Dementia. Audiology & Neurotology 2020

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Halftime seminar
Planned dissertation

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Lars Olaf Cardell
Susanna Kumlien Georén, Laila Hellkvist
2022-09-30

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 2020, 2021, 2022

1.

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Registered	2016-11-03
Halftime seminar	2020-09-11
Planned dissertation	2023-03-31

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

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

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

In the second publication we studied heredity of transient evoked otoacoustic emissions (TEOAEs), that are recorded as part of the universal neonatal hearing-screening program. We found that the TEOAEs at birth are largely inherited, perhaps more than for young adult twins. Additionally, we found that sex and ear differences existed at birth, and that the twin testosterone transfer hypothesis, that female twins with male co-twins would have masculinized TEOAEs, was not supported for neonatal twins.

We have invited 20 neonates with congenital uSNHL born in Region Stockholm to study etiology, early hearing, speech-language and communication development, and the outcomes of very early hearing aid intervention longitudinally. The manuscript with focus on etiology has being finalized and sent for review.

Ethical permit No.

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

Publications/manuscripts 2020, 2021, 2022

1. Johansson, M., Asp, F., & Berninger, E. (2020a). Children With Congenital Unilateral Sensorineural Hearing Loss: Effects of Late Hearing Aid Amplification-A Pilot Study. Ear and Hearing, 41(1), 55-66.
2. Johansson, M., Olofsson, Å., & Berninger, E. (2020b). Twin study of neonatal transient-evoked otoacoustic emissions. Hearing Research, 398, 108108.
3. 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.
4. 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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Halftime sesminar 2022-09-02
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 2020, 2021, 2022

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Halftime sesminar
Planned dissertation

Predictive markers for head- and neck tumors

Branchial cleft cysts
* Investigate the prevalence of cystic metastases in patients whom had a supposed branchial cleft cyst surgically removed. 13 pat out of 436 had cystic metastases (4 papillary thyroid, 3 base of tongue, 1 tonsilar, 5 CUP). HPV posititvity was found in 3 out of the 9 oropharyngeal cancers and CUP.
(Paper 1, published in Acta Otolaryngologica Jan 2022)
* Investigate if the non-presence of HPV in the cytology report from the branchial cleft cysts can be used as a predictive marker for a cystic mass on the neck to truly be a branchial cleft cyst? Is it possible to rule out tonsillectomy and biopsies in the work-up diagnostics for these patients >40 y?
(Paper 2, collecting data)

Tonsilar and base of tongue cancer
* Investigate if EBV, alone or in combination with HPV, p16, CD8, HLA-class is a useful prognostic marker for HPV-neg and HPV-pos tonsilar and base of tongue cancer, and see if it is possible to optimize and individualize the treatment
* 300 patients with HPV/p16-positive tonsilar- and base of tongue cancer and 150 patients with HPV/p16-negative tonsilar and base of tongue cancer (collected 2006-2016). EBV-RNA will be detected with EBER stain.
* Overall and disease free survival in relation to EBV presence and presence of HPV, p16, CD8, HLA-class alone or in combination will be analyzed with Kaplan-Meier analysis and COX-regression.
(Paper 3, data is collected but EBV needs to be analyzed)

Anchored exstirpation of lymph node
or other cystic mass on the neck
* Prospective randomized study, until now:
16 included patients
9 with anchor-technique
* Evaluation of a surgical method/aiding tool when
performing exstirpation on difficult to palpate/non-palpable
masses
(Paper 4, collecting data)

Ethical permit No.

2015/0157-32	2009/1278-31/4	2005/431-31/4	2020-00448	2021-00697

Publications/manuscripts 2020, 2021, 2022

1. 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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Registered 208-10-08
Halftime sesminar
Planned dissertation

Corticosteroid treatment in children with acute facial nerve palsy

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

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

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

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

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

Ethical permit No.

2017/554	2019-01546			

Publications/manuscripts 2019, 2020, 2021

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Halftime seminar
Planned dissertation

Developing of objective balance tests in newborns and young children

Balance and vestibular disorders in adults are well studied, but in children are not well determined. Although motor and balance function is still under development throughout childhood, the vestibular function is present at birth and becomes fully integrated in puberty. A vestibular assessment in infants and children is increasingly required in clinical practice especially in those undergoing cochlear implantation as well as in children with neurological diagnoses with delayed motor skills. This knowledge will play a significant role in early rehabilitation and motor development of these children.
Video Impulse test (vHIT) and Vestibular Evoked Myogenic Potentials (VEMP)have been identified as two potential methods methods of high feasibility in children . The methods are harmless , quick and easy to perform.A test protocol of both has been adopted in the Audiological Department of Karolinska University Hospital in order to access the vestibular function in these underrepresented patient groups.

Ethical permit No.

2015/1296-31/2				

Publications/manuscripts 2020, 2021, 2022

1. Methodological aspects of testing vestibular evoked myogenic potentials in infants at universal hearing screening program. Verrecchia L, Karpeta N, Westin M, Johansson A, Aldenklint S, Brantberg K, Duan M.Sci Rep. 2019 Nov 21;9(1):17225. doi: 10.1038/s41598-019-53143-z.PMID: 31754248
2. The relationship between clinical characteristics and magnetic resonance imaging results of Ménière disease: a prospective study. 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
3. Effects of lesions of the organ of corti on hearing. Yao W, Gao L, Su J, Karpeta N, Xie W, Duan M.Acta Otolaryngol. 2022 Feb;142(2):118-126. doi: 10.1080/00016489.2022.2027517. Epub 2022 Jan 29.PMID: 35098870

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Halftime seminar
Planned dissertation

Sentinel node in oral- and orofaryngealcancer

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.

2019-03518	2021-01265			

Publications/manuscripts 2020, 2021, 2022

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Registered 2021-01-25
Halftime seminar
Planned dissertation

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

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 2020, 2021, 2022

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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Registered 2017-06-01
Halftime seminar 2023-03-30
Planned dissertation

Bell's palsy in pregnancy and puerperium

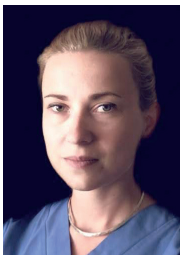
T
o examine the incidence of Bell's palsy among pregnant women in Stockholm during a 10-years period, to find risk factors for developing Bell's palsy during pregnancy and the puerperium (first 6 weeks post partum), to see how these women heal compared to non pregnant women with Bells palsy and how the disease affects the patient's quality of life.

Ethical permit No.

2015/2349-31/1				

Publications/manuscripts 2020, 2021, 2022

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

In this study, we focus on a group of older children with hearing loss requiring hearing aids who are enrolled in the Hearing Rehabilitation for Children and Youngsters. Among other things, we look at the cause and the natural course of their hearing loss as well as various factors that may have affected their habilitation.

Ethical permit No.

Publications/manuscripts 2020, 2021, 2022

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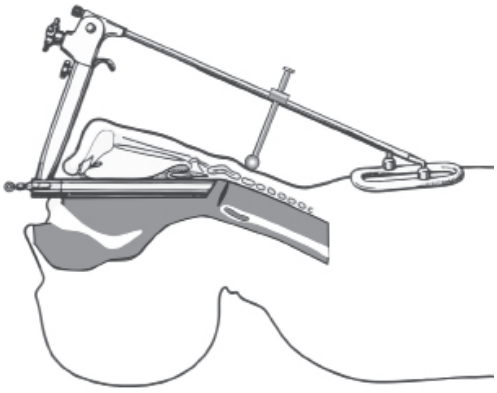
Halftime seminar
Planned dissertation

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 2020, 2021, 2022

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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 2020, 2021, 2022

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Co-supervisor Jeremy Wales, Bo Tideholm, Sten Hellström
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 2020, 2021, 2022

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 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 2020, 2021, 2022

1. Incidence and management of sequelae from peripheral facial palsy: retrospective analysis of 525 patients - submitted for publication

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Co-supervisor Laila Hellkvist
Registered
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 2020, 2021, 2022

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Registered 2019-08-29
Halftime seminar 2022-06-16
Planned dissertation

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

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

Ethical permit No.

2019-03518				

Publications/manuscripts 2020, 2021, 2022

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Co-supervisor Ola Sunnergren, Hatef Darabi, Pär Stjärne
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 2020, 2021, 2022

1. 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).
2. 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).
3. Rahbin, S; Liakos, A; Alinasab, B: Loss of Malar Bags in Lower Eyelid in Orbital Blow Out Fracture Reconstruction Following Pre- or Retro-Septal Transconjunctival Incision. J Craniofac Surg. May/Jun 2020;31(3):769-771. DOI: 10.1097/SCS.0000000000006103 (2020).

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Halftime seminar
Planned dissertation

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

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

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

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

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

Ethical permit No.

2018/364	2017/2011-31			

Publications/manuscripts 2020, 2021, 2022

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Co-supervisor	Filip Asp, Rodrigo Moreno
Registered	2014-10-27
Halftime seminar	2019-10-11
Planned dissertation	2023-11-24

Central auditory structure and function in unilateral hearing loss

Central auditory system of participants with unilateral hearing loss in congenital atresia is examined with functional hearing tests and MRI scans. An animal model, Sprague Dawley rats with unilateral induced conductive hearing loss through removal of the left ear canal was also created and examined with MRI. Further, a study was added with participants with unilateral sensorineural deafness and a localization test. So far, two studeis are published. One show findings of deteriorated localization capacity in unilateral atresia, dependent on level of hearing loss of the atretic ear. The other is a method description of defining the white matter pathway between the medial geniculate body and the auditory cortex in clinical MRI scans, but also show no evident differences of this pathway in atresia. Further studies will be presented during the year.

Ethical permit No.

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

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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 2020, 2021, 2022

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. Is the effect of methylprednisolone treating pollen induced allergic rhinitis mainly due to a placebo effect? - manus klart för inskick . Carl Skröder, Laila Hellkvist, Åslög Dahl, Leif Bjermer, Ulla Westin, Lars Olaf Cardell

Martin Smelik
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Halftime seminar
Planned dissertation

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Mikael Benson
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2022-11-09

Learning Disease Models for personalised medicine

In ”Multi-Organ Single Cell Analysis Reveals an On/Off Switch System with Potential for Personalized Treatment of Immunological Diseases” 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.

This project was a part of larger, multidisciplinary effort to identify systems with potential for personalized treatment in Immunological diseases. We constructed a machine learning model that jointly analysed 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.

Ethical permit No.

Publications/manuscripts 2020, 2021, 2022

1. A dynamic single cell-based framework for digital twins to prioritize disease genes and drug targets, Multi-Organ Single Cell Analysis Reveals an On/Off Switch System with Potential for Personalized Treatment of Immunological Diseases

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Registered	2008-02-18
Halftime seminar	2014-05-19
Planned dissertation	2024-06-09

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

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

Ethical permit No.

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

Publications/manuscripts 2020, 2021, 2022

1.

Clara Svenberg Lind clara.svenberg-lind@ki.se
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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 2020, 2021, 2022

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. Submittad artikel (nov 2022): Breathing, voice and swallowing difficulties one-year after tracheostomy in COVID-19-patients.

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Halftime seminar
Planned dissertation

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2022-11-23

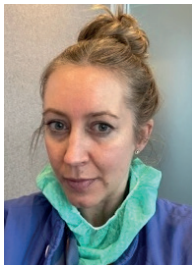
A single cell-based strategy to identify mechanisms and biomarkers for early diagnosis, prevention and treatment of common diseases

This project contains several sub-project. In one sub-project, I studied single-cell RNA sequencing of five different solid tumors, and constructed a shared multi-cellular model that could be used to prioritize possible pan-cancer diagnostic marker. By testing these candidate markers in both RNA and protein data of 20 differernt cancers samples, I found a combination of some of these biomarkers can be used as pan-cancer diagnostic marker. This manuscript is currently under review by Genome Medicine.

Ethical permit No.

Publications/manuscripts 2020, 2021, 2022

1. Yelin Zhao, Xinxiu Li, Berghtor Björnsson, Joseph Loscalzo, Martin Smelik, Oleg Sysoev, Dina Mansour Aly, Mikael Benson. A Scalable, Single Cell-Based Strategy for Prioritization of Multi-omics Pan-cancer Biomarkers. (Under review)
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.
3.



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Co-supervisor Marianne van Hage, Mats Holmström, Anna Asarnoj
Registered 2017-12-21
Halftime seminar
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 2020, 2021, 2022

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

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

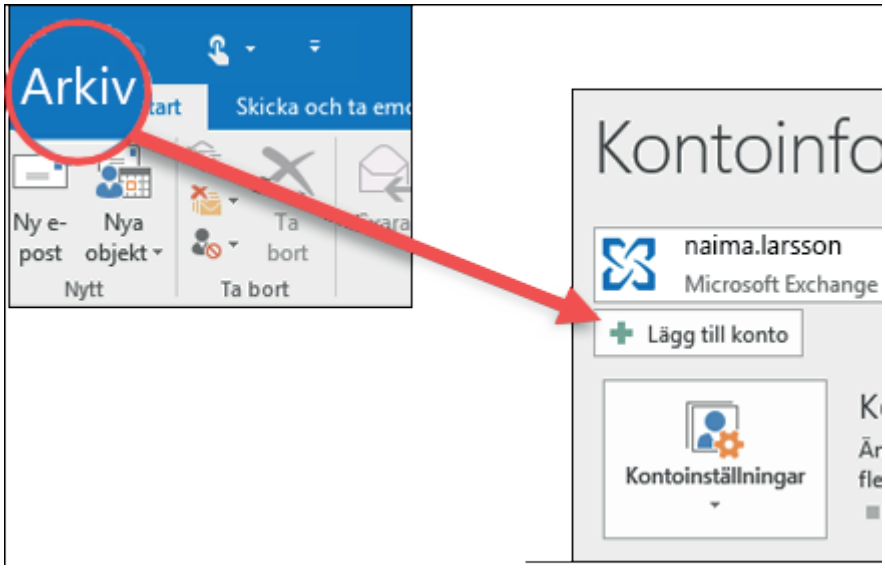
Det finns många olika typer av e-postkonton som du kan lägga till i Outlook, bland annat Microsoft 365, Gmail-, Yahoo-, iCloud- och Exchange-konton.

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**.



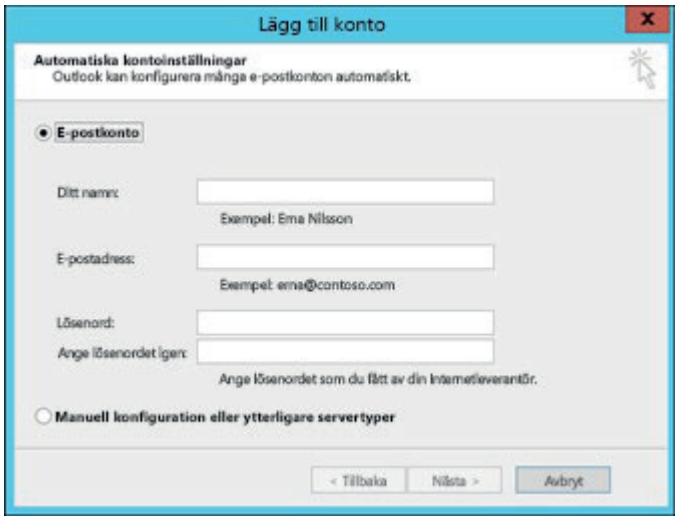
2. Vad som visas därnäst beror på vilken version av Outlook du har.

   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.

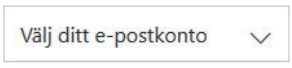
Outlook accepterar inte mitt lösenord

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.

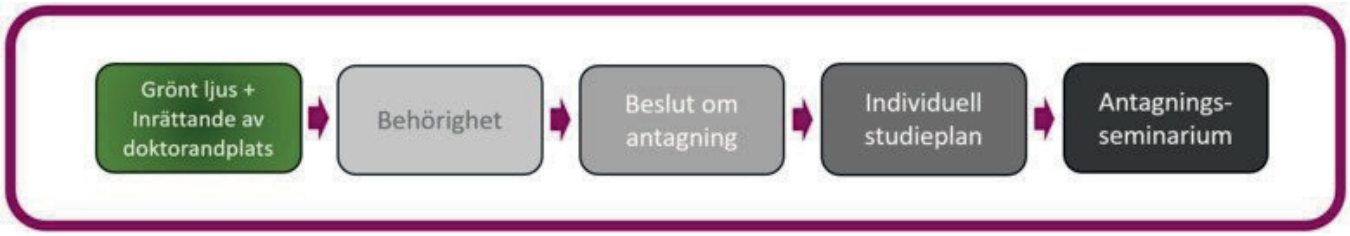
Se även

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

POP- och IMAP-e-postinställningar för Outlook

Appendix 3

Admission process at CLINTEC (In Swedish)



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

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

Flödesschema där undantag för annonsering föreligger

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

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

Vid eventuella frågor, kontakta LADOK-administratören

Agneta Wittlock
forskarutbildning@clintec.ki.se
08-585 87353