Akershus University Hospital and Institute of Clinical Medicine, University of Oslo (Campus Ahus) – Impact case #1

Institution: **Name:** Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus and Campus Ahus
Administrative unit: **Name:** Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus_Campus Ahus
Title of case study: Cardiac biomarkers
Period when the underpinning research was undertaken:2012-present
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-present
Period when the impact occurred: 2012-present

1. Summary of the impact (indicative maximum 100 words)

This section should briefly state what specific impact is being described in the case study.

The Cardiovascular Research Group at Akershus University Hospital (Ahus, hospital) and Campus Ahus (University of Oslo) is a leading international group in studies on cardiac biomarkers. The group received a prestigious grant as a K. G. Jebsen Center for Cardiac Biomarkers in 2022: K.G. Jebsen Centre for Cardiac Biomarkers - Stiftelsen Kristian Gerhard Jebsen (stiftkgj.no). The work from 2012-2022 includes clinical studies with established cardiac biomarkers, which have had direct relevance on patient care, and integrated, translational research on novel cardiac biomarkers. The work was performed in close collaboration with industry partners and has led to significant advancements for clinical care, intellectual property rights (IPR), and the establishment and development of two Norwegian biotechnology companies.

2. Underpinning research (indicative maximum 500 words)

The Cardiovascular Research Group, led by Professor Omland, aims to improve diagnostics and care for patients with cardiovascular disease through studies on novel and established cardiac biomarkers. We combine excellent large-scale clinical cohorts and state-of-the-art laboratory research. The group utilizes a bed-to-bench strategy to advance our understanding of the complex pathophysiology of cardiovascular disease- see **Fig.1** for research strategy:

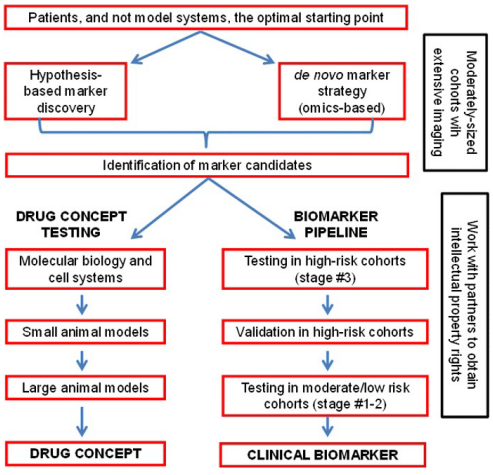


Fig.1. Bed-to-bench strategy to identify and test candidates as biomarkers and drug concepts

We will present two main research focuses of the period to exemplify the work: ***(1)*** use of high-sensitivity (hs) cardiac troponin I and T to identify subclinical and clinical myocardial injury, and ***(2)*** translational research to develop secretoneurin (SN) as a novel cardiac biomarker and potential therapeutic strategy. For hs-troponin work, we have collaborated closely with major international industrial partners such as Abbott Diagnostics and Roche Diagnostics, and with the local Norwegian partner SpinChip Diagnostics (https://spinchip.no).

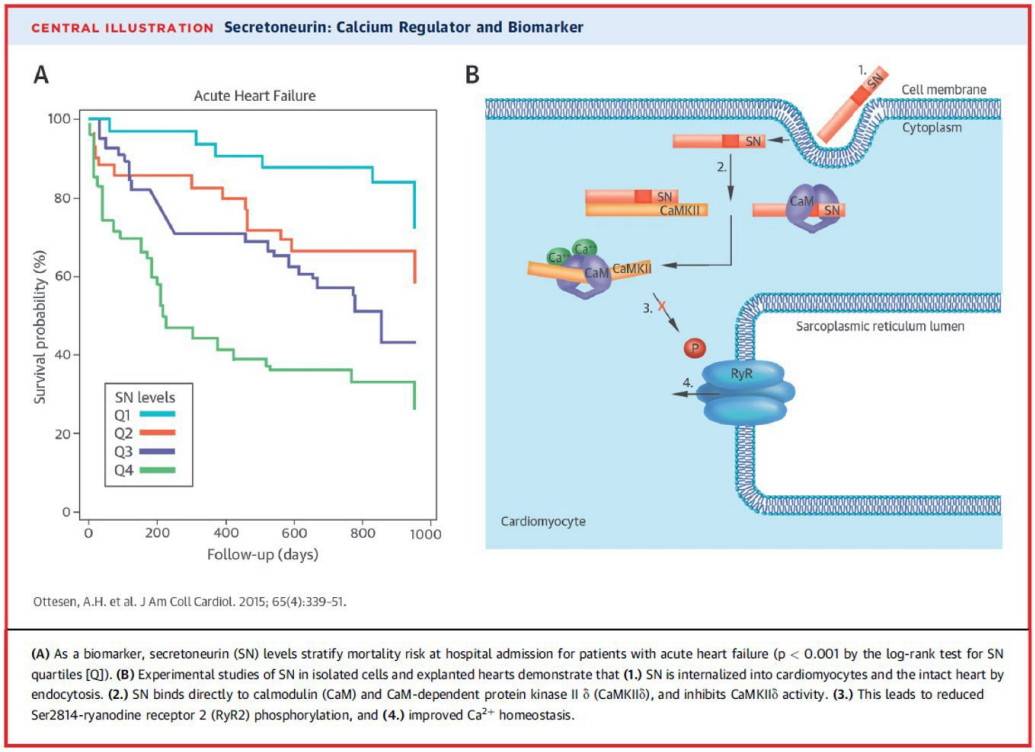
SN is currently being commercialized by the Norwegian company CardiNor AS (https://cardinor.com) and Professors Omland and Røsjø share IPR for SN as a cardiac biomarker.

In patients with chronic cardiovascular disease, we were among the first groups to demonstrate that hs-troponin concentrations represent early and accurate markers of pathological left ventricular

remodeling (*Ref. 1, Section 4*). We advanced this work by validating hs-troponin measurements as markers of heart failure risk in the general population, prior to the development of symptoms (i.e., subclinical disease) (*Ref. 6, Section 4*). For the work on subclinical disease, we designed and executed the Akershus Clinical Examination (ACE) 1950 Study between 2012-2015 with extensive clinical, biochemical, and imaging phenotyping of 3706 subjects from general population. Using data also from the large-scale Trøndelag Health (HUNT) Study, we found hs-troponin measurements to provide especially strong prognostic information in women (*Ref. 3, Section 4*). Contrary to the initial hypothesis, we also found lower hs-troponin concentrations in current smokers than in non-smokers (*Ref. 4, Section 4*). Our competence in clinical trials and established research infrastructure at Ahus enabled us to perform important studies on cardiac biomarkers during the covid-19 pandemic. In covid-19 patients from Akershus University Hospital, we identified growth-differentiation factor-15 as a strong marker for adverse outcome, while hs-troponin or natriuretic peptide concentrations did not significantly improve risk prediction (*Ref. 5, Section 4*).

We have since 2012 been the principal clinical partner for SpinChip Diagnostics, who develop a state-of-the-art hs-troponin point-of-care (POC) assay. We recently validated the SpinChip troponin I POC assay to have similar performance as the best laboratory-based hs-troponin assays (Abbott, Roche), and the SpinChip troponin I POC assay can be used for assessing chest pain patients according to the ESC 0/1 h triage pathway (*Ref. 4, Section 6*). Professor Røsjø is co-PI of a pan-European prospective multicentre study to validate the SpinChip troponin I POC assay in the ED setting.

During the period, we have performed studies of several biomarkers according to the strategy reported in **Fig.1**. The work on SN has been most advanced, and we have identified SN as a strong and independent prognostic cardiovascular biomarker, and as a direct inhibitor of Ca^{2+}/calmodulin (CaM)-dependent protein kinase II δ (CaMKIIδ) activity (**Fig.2**, from *Ref. 2, Section 4*):



(A) As a biomarker, secretoneurin (SN) levels stratify mortality risk at hospital admission for patients with acute heart failure ($p < 0.001$ by the log-rank test for SN quartiles [Q]). **(B)** Experimental studies of SN in isolated cells and explanted hearts demonstrate that **(1.)** SN is internalized into cardiomyocytes and the intact heart by endocytosis. **(2.)** SN binds directly to calmodulin (CaM) and CaM-dependent protein kinase II δ (CaMKIIδ), and inhibits CaMKIIδ activity. **(3.)** This leads to reduced Ser2814-ryanodine receptor 2 (RyR2) phosphorylation, and **(4.)** improved Ca^{2+} homeostasis.

Fig.2. SN is a strong and independent prognostic cardiovascular biomarker, and a direct inhibitor of CaMKIIδ activity

As the principal partner to CardiNor AS (Oslo, Norway), we have helped develop a CE-approved SN ELISA assay, which we currently are validating in clinical studies. In parallel molecular work, we are also pursuing SN as a drug concept for treatment of ventricular arrhythmias with on-going IPR work.

3. Names of the key researchers and what positions they held at the administrative unit at the time of the research

Professor Torbjørn Omland MD, PhD, MPH: Primary investigator, Head of research group and Head of the K. G. Jebsen Center for Cardiac Biomarkers. Responsible for work on hs-troponin and covid-19 studies, and Steering board member for the Norwegian biotech company CardiNor AS.
Torbjørn Omland - Institute of Clinical Medicine (uio.no)

Professor Helge Røsjø MD, PhD: Deputy Head of research group and Deputy Head of the K. G. Jebsen Center for Cardiac Biomarkers. Responsible for translational work and work on SN, and for the collaboration between Akershus University Hospital and SpinChip Diagnostics. Røsjø coordinates collaboration with Uppsala Clinical Research Center (UCR) and SWEDEHEART after his post-doctoral and clinical stay in Uppsala 2017-2019.
Helge Rørvik Røsjø - Institute of Clinical Medicine (uio.no)

Associate Professor Magnus N. Lyngbakken MD, PhD: Research fellow (2013-2016), post-doctoral fellow 50% (2017-2025), and Associate Professor from 2021. Local PI for the ACE 1950 Study and important for work on hs-troponin in the Trøndelag Health (HUNT) Study.
Magnus Nakrem Lyngbakken - Institute of Clinical Medicine (uio.no)

Associate Professor Peder L. Myhre MD, PhD: Research fellow (2013-2017), post-doctoral fellow 50% (2017-2022), and Associate Professor from 2022. Performed work on SN and has central role in the covid-19 projects. Leading important collaborative projects with researchers at Harvard Medical School, Brigham and Women's hospital (Boston, MA) after post-doctoral research visit (2017-2018).
Peder Langeland Myhre - Institute of Clinical Medicine (uio.no)

Senior researcher Anett H. Ottesen PhD: Research fellow (2012-2017), post-doctoral fellow (2017-2021), and special advisor for research from 2021. PI for basic science work on SN, circulating micro-RNAs, and for demonstrating the importance of glycosylation for NT-proBNP and chromogranin A measurements and processing.

4. References to the research (indicative maximum of six references)- *Ahus/ Campus Ahus-affiliated researchers are highlighted by blue color.*

1) Omland T, Pfeffer MA, Solomon SD, de Lemos JA, Røsjø H, Šaltytė Benth J, Maggioni A, Domanski MJ, Rouleau JL, Sabatine MS, Braunwald E. Prognostic Value of Cardiac Troponin I Measured With a Highly Sensitive Assay in Patients With Stable Coronary Artery Disease. *J Am Coll Cardiol* 2013;61:1240-9. **IF 27.21**, **Times cited: 345**
https://pubmed.ncbi.nlm.nih.gov/23414791/

2) Ottesen AH, Louch WE, Carlson CR, Landsverk OJB, Kurola J Johansen RF, Moe MK, Aronsen JM, Høiseth AD, Jarstadmarken H, Nygård S, Bjørås M, Sjaastad I, Pettilä V, Stridsberg M, Omland T, Christensen G, Røsjø H. Secretoneurin is a novel prognostic cardiovascular biomarker associated with cardiomyocyte calcium handling. *J Am Coll Cardiol* 2015;65:339-51. **IF 27.21**, **Times cited: 51**
https://pubmed.ncbi.nlm.nih.gov/25634832/

3) Omland T, de Lemos JA, Holmen OL, Dalen H, Šaltytė Benth J, Nygård S, Hveem K, Røsjø H. Impact of Sex on the Prognostic Value of High-Sensitivity Cardiac Troponin I in the General Population: The HUNT Study. *Clin Chem* 2015;61:646-56. **IF 12.11, Times cited: 116**
https://pubmed.ncbi.nlm.nih.gov/25695851/

4) Lyngbakken MN, Skranes JB, de Lemos JA, Nygård S, Dalen H, Hveem K, Røsjø H, Omland T. Impact of smoking on circulating cardiac troponin I concentrations and cardiovascular events in the general population: The HUNT Study. *Circulation* 2016;134:1962-72. **IF 39.92, Times cited: 45**
https://pubmed.ncbi.nlm.nih.gov/27815376/

5) Myhre PL, Prebensen C, Strand H, Røysland R, Jonassen CM, Rangberg A, Sørensen V, Søvik S, Røsjø H, Svensson M, Berdal JE, Omland T. Growth Differentiation Factor 15 Provides Prognostic Information Superior to Established Cardiovascular and Inflammatory Biomarkers in Unselected Patients Hospitalized With COVID-19. *Circulation* 2020; 142(22):2128-2137. **IF 39.92, Times cited: 83**

https://pubmed.ncbi.nlm.nih.gov/33058695/

6) Lyngbakken MN, Aagaard EN, Kvisvik B, Berge T, Pervez MO, Brynildsen J, Tveit A, Steine K, Røsjø H, Omland T. Cardiac Troponin I and T Are Associated with Left Ventricular Function and Structure: Data from the Akershus Cardiac Examination 1950 Study. *Clin Chem* 2020;66(4):567-578. **IF 12.11, Times cited: 23**
https://pubmed.ncbi.nlm.nih.gov/32227098/

5. Details of the impact (indicative maximum 750 words)

Cardiovascular disease and myocardial dysfunction are among the leading causes of death in the Western world. Accordingly, biomarkers that reflect disease progression and response to therapy will prove important information and improve treatment for large patient groups. Biomarkers may also reflect cardiovascular pathophysiology and thereby also help to identify new drug candidates.

Several conditions and exposures (triggers or risk factors) can result in myocardial injury, dysfunction, and cardiomyopathy (**Fig.3**). Regardless of the trigger, myocardial dysfunction normally develops through distinct disease stages and the common endpoint is end-stage heart disease (**Fig.3**). Sensitive molecular markers may identify patients at risk, prior to the development of symptoms (subclinical disease). Hence, we have focused on the identification of biomarkers that are associated with outcome in state-of-the-art clinical and population-based cohorts.

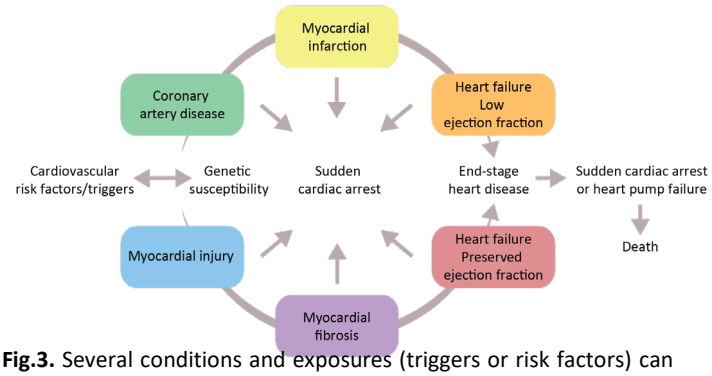


Fig.3. Several conditions and exposures (triggers or risk factors) can result in myocardial injury, dysfunction, and cardiomyopathy

Chronic, low-level elevations of hs-troponins reflect subclinical myocardial injury and cardiac remodeling and are strong predictors of heart failure, a paradigm first introduced by Prof Omland *et al.* in the *New England Journal of Medicine* in 2009. During the period from 2012-2022, our research group has validated this model and hs-troponins are currently considered the leading candidate biomarkers for early detection of cardiac remodeling and heart failure development. We are still leaders in this field internationally, and based on our work, hs-troponin I (Abbott Diagnostics, Abbott Park, IL) has received CE-approval in the EU as screening tools for cardiovascular disease in the general population. The use of hs-troponins as biomarkers of subclinical injury and myocardial dysfunction, and our contribution to this work, is recognized by international research colleagues (*Ref. 1, Section 6 as an example*). The innovative work related to cardiac biomarkers, and especially hs-troponins, was the basis for Professor Omland to be honored with the Prize for cardiac research from the Norwegian Health Organization in 2019, with the prize being presented to Professor Omland by His Majesty King Harald V of Norway (**Fig.4**, *Ref. 2*).

Fig.4. Professor Omland (front left) receiving the prestigious Prize for cardiac research from His Majesty King Harald V of Norway.

The Cardiovascular Research Group have been the principal clinical partner for the Norwegian biotechnology company SpinChip Diagnostics to develop hs-troponin I Point-of-Care (POC) assay since 2012 (*Ref. 3, Section 6*). [redacted] By moving high-sensitivity assays out to pre-hospital services and health care facilities in primary care, the collaborative work

between our research group and SpinChip Diagnostics will provide a fundamental change in early triage of patients with suspected acute coronary syndrome. We are committed to continue our close collaboration with SpinChip to make a full cardiovascular panel on the SPINCHIP POC platform. The Cardiovascular Research Group has also performed extensive testing of biomarkers from established IVD companies like Roche Diagnostics and Abbott Diagnostics, and this work has also been highlighted in the press (*Ref. 5 and 6, Section 6*).

Professors Røsjø and Omland are also inventors of secretoneurin (SN) as a cardiac biomarker. As outlined in **Fig. 2**, we have performed extensive experimental and clinical studies on SN and we find that SN directly can influence cardiomyocyte function by inhibiting the key intracellular kinase CaMKIIδ, which we currently are pursuing as therapeutic strategy for ventricular arrhythmias. Moreover, SN is also recognized as a promising novel cardiovascular biomarker, which seems to provide additional prognostic information to established risk indices by integrating information on cardiac status, systemic stress, and renal dysfunction. Our work on SN has received substantial interest from leading scientists across the world (**Fig.2** and *Ref. 7, Section 6*) and from the press (*Ref. 8, Section 6)*. The work on SN has led to the establishment of a Norwegian biotechnology company (CardiNor AS, Oslo, Norway) and the development of a CE-marked SN ELISA assay.

During the covid-19 pandemic, we also performed important clinical studies, both relating to cardiac biomarkers and clinical interventional trials. By utilizing data warehouse Ahus for patient identification and inclusion, we could include 75% of all eligible covid-19 patients at Ahus during the first wave for epidemiological/ biomarker studies and 42% of all eligible patients for the pharmacological randomized-controlled trial of testing hydroxychloroquine for treating covid-19. These studies received significant academic interest and impact with publications in the leading cardiology journals for the biomarker work (*Ref 5, Section 4* as an example) and two high-impact publications in Nature Communication for the randomized-controlled trial (*Refs. 9 + 10, Section 6).* The work on covid-19 received significant interest from the press (*Refs. 6 + 11, Section 6).* In addition to the academic value of our covid-19 work, we collaborated with international colleagues and demonstrated a significantly increase in morality in covid-19 patients treated with hydroxychloroquine (*Ref. 10, Section 6*). Hence, in addition to advancing research, we informed the public that hydroxychloroquine should be avoided for treatment of covid-19, which had a direct and important contribution to patient safety across the world (*Ref. 11, Section 6*).

6. Sources to corroborate the impact (indicative maximum of ten references)

1) Cardiac Troponins and the Future of Precision Medicine | Circulation: Cardiovascular Interventions (ahajournals.org)
2) Viktig forskning hedret av Kongen | Nasjonalforeningen for folkehelsen (ntb.no)
3) Hjem - SpinChip
4) Koechlin L, [….], Omland T, Lyngbakken MN, Røsjø H, Mueller C. Clinical and Analytical Performance of a Novel Point-of-Care High-Sensitivity Cardiac Troponin I. *Submitted.*
5) https://www.forskning.no/royking-hjertet/vanskelig-a-forutsi-hjerteproblemer-hos-roykere/380654)
6) Norske forskere tror blodprøve kan avdekke koronarisiko (aftenposten.no)
7) Will Secretoneurin Be the Next Big Thing?∗ (sciencedirectassets.com)
8) Ny prognostisk biomarkør ved hjertesvikt | Tidsskrift for Den norske legeforening (tidsskriftet.no)
9) A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics - PMC (nih.gov)
10) Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials - PubMed (nih.gov)
11) Studie: Lovprist covid-medisin øker risikoen for å dø (dagensmedisin.no)

Akershus University Hospital and Institute of Clinical Medicine, University of Oslo (Campus Ahus) – Impact case #2

Institution: **Name:** Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus and Campus Ahus
Administrative unit: **Name:** Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus_Campus Ahus
Title of case study: Cardio-oncology
Period when the underpinning research was undertaken:2012-present
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-present
Period when the impact occurred:2015-present

1. Summary of the impact (indicative maximum 100 words)

This section should briefly state what specific impact is being described in the case study.

The cardio-oncology research at Akershus University Hospital has the been in the international research forefront in this developing field. The pioneering, randomized, placebo-controlled PRADA trial assessed the cardioprotective effect of beta adrenoceptor and angiotensin receptor blockade during adjuvant breast cancer therapy using state-of-the-art imaging and biomarker methods. The results have been published in leading academic journals and have been frequently cited. This work contributed significantly to enhanced co-operation between oncologists and cardiologists, benefitting this vulnerable patient group, and led to the establishment of Norway's first cardio-oncology outpatient clinic. Furthermore, external funding has been secured for two new cardio-protective interventional trials.

2. Underpinning research (indicative maximum 500 words)

During the past 15 years, professor Omland and collaborators have conducted high impact research on the prognostic value of asymptomatic, subclinical myocardial injury. Using a novel, prototype high sensitivity assay that for the first time permitted high precision measurement of cardiac troponin T, a biomarker of myocardial injury, these studies demonstrated a very strong and independent association between low level elevation of cardiac troponins and the risk of subsequent heart failure development and death in patients with chronic coronary syndrome and in the general population (Omland et al, N Engl J Med 2009;26:2538-47, de Lemos et al. JAMA 2010.

Advances in cancer therapy has improved cancer outcomes and contributes to an increasing number of long-term survivors, but also raised concern over potentially serious side effects. In adjuvant breast cancer therapy, potentially cardiotoxic agents like anthracyclines, monoclonal antibodies and radiotherapy have been associated with chronic myocardial injury with troponin elevation and cancer therapy–related cardiac dysfunction (CTRCD). Prior small-scale studies indicated promising effects of early or preventive neurohormonal blockade on the cardiotoxic effects of anthracyclines but were limited by methological weaknesses. The 2x2 factorial, placebo-controlled, double-blind "PRevention of cArdiac Dysfunction during Adjuvant breast cancer therapy" (PRADA) trial was conducted at Akershus University Hospital between 2011 and 2015. 130 patients with early breast cancer were randomized to the angiotensin receptor blocker candesartan vs placebo and the beta beta-blocker metoprolol vs placebo, and examined serially with state-of-the-art cardiovascular magnetic resonance (CMR), circulating biomarker measurements and echocardiography. In the primary results, preventive angiotensin blockade significantly attenuated a small reduction in left ventricular systolic function at the end of adjuvant

therapy, while no effect of beta blockade on ventricular function was observed. However, during anthracycline therapy concomitant beta-blockade was associated with attenuated myocardial injury, expressed as circulating cardiac troponin I and T concentrations. The PRADA trial was at the time the largest randomized, placebo-controlled preventive study in the field of cardio-oncology. The 2-year follow-up results were published in 2021 in the leading journal Circulation, (2022 IF 37.8). At follow-up there was a persistent small decline in systolic function, but significant myocardial dysfunction was uncommon and there was no persistent effect of either intervention. The study results demonstrated that adjuvant breast cancer therapy is safe in patients without pre-existing cardiovascular disease, and highlighted the need to identify patient groups at high risk who will benefit from cardioprotective therapy. The PRADA trial also provided unique longitudinal assessment of myocardial function and structure during cancer therapy using state of the art CMR and circulating biomarker analyses. By implementing novel CMR sequences, data from the trial demonstrated that higher anthracycline doses were associated with expansion of the myocardial extracellular space as an expression of myocardial edema or fibrosis. The study also confirmed that low-level myocardial injury assessed by cardiac troponins is very common at the end of anthracycline therapy, and troponin elevation has been implemented in the definition of CTRCD in the first European Guidelines of CardioOncology that were published in 2021.

Names of the key researchers and what positions they held at the administrative unit at the time of the research

Professor Torbjørn Omland Primary investigator and head of research group

Geeta Gulati (in charge of patient inclusion and echocardiography)

2010- 2018 PhD candidate In PRADA

2018-to date postdoctoral researcher (20%) in the PRADAII trial

Siri Lagethon Heck (in charge of CMR)

2011- 2018 PhD candidate In PRADA

2018-2023 postdoctoral researcher (50%) in the PRADAII trial

2023-to date Associate Professor II

Albulena Mecinaj PhD candidate 2020-to date in the PRADAII trial (patient inclusion and echocardiography)

Victoria Vinje PhD candidate 2022-to date in the PRADAII and NARNIA trials (patient inclusion and study coordinator)

3. References to the research (indicative maximum of six references)

Gulati G, Heck SL, Ree AH et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J 2016;37:1671-80. **Times cited: 388 (Web of science)**

1. Heck SL, Mecinaj A, Ree AH et al. Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA): Extended Follow-Up of a 2x2 Factorial, Randomized, Placebo-Controlled, Double-Blind Clinical Trial of Candesartan and Metoprolol. Circulation 2021;143:2431-2440. **Times cited: 51**
2. Omland T, Heck SL, Gulati G. The Role of Cardioprotection in Cancer Therapy Cardiotoxicity: JACC: CardioOncology State-of-the-Art Review. JACC CardioOncol 2022;4:19-37. **Times cited: 35. Most read/downloaded**
3. Gulati G, Heck SL, Rosjo H et al. Neurohormonal Blockade and Circulating Cardiovascular Biomarkers During Anthracycline Therapy in Breast Cancer Patients: Results From the PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) Study. J Am Heart Assoc 2017;6. **Times cited: 25**

4. Heck SL, Gulati G, Hoffmann P et al. Effect of candesartan and metoprolol on myocardial tissue composition during anthracycline treatment: the PRADA trial. Eur Heart J Cardiovasc Imaging 2018;19:544-552. **Times cited: 17**
5. Heck SL, Gulati G, Ree AH et al. Rationale and design of the prevention of cardiac dysfunction during an Adjuvant Breast Cancer Therapy (PRADA) Trial. Cardiology 2012;123:240-7. **Times cited: 39**
6. Mecinaj A, Gulati G, Heck SL et al. Rationale and design of the PRevention of cArdiac Dysfunction during Adjuvant breast cancer therapy (PRADA II) trial: a randomized, placebo-controlled, multicenter trial. Cardiooncology 2021;7:33. **Times cited: 10**

4. Details of the impact (indicative maximum 750 words)

Although cardiovascular side effects of cancer therapy have been known since the late seventies, the medical field of cardio-oncology gained momentum around 2015 coinciding with the publication of the primary results of the PRADA trial. The publication in European Heart Journal gained both scientific acclaim and to date 388 citations including eight citations in central European and US cardiology guidelines and position statements. In addition, there was considerable media attention with several interviews and > 2 million unique hits on the internet of the initial presentation at the American Heart Association's 2015 Scientific Sessions. (Figure 1)

Figure 1 Examples of the impact of the cardio-oncology research at Akershus University Hospital

The experiences and collaborations established during the trial contributed to the establishment of Norway's first cardio-oncology outpatient clinic at Akershus University Hospital. In 2018 the PRADA trial was selected as the main study presented to the Minister of Health, Bent Høie at the annual research meeting of the Regional Health Authorities in Norway. Following the presentation, the Minister of Health was given a tour of the Cardio-Oncology outpatient clinic (Figure 2), praising this initiative in national media.

Kreftbehandling:

Ny studie: Slik kan hjertemedisin forebygge seinskader av brystkreft

- Viktig å behandle tidlig i forløpet.

GODE RESULTATER: Etter behandling her ved den nye Kardio-onkologiske poliklinikken på Ahus, er pumpekraft til Anne-Grethe Delets (53) hjerte nå oppe i 56 prosent - godt innenfor normalen. Helseminister Bent Høie blir vist rundt på poliklinikken, her sammen med Tone Nerdrum, overlege i kariologi.
Foto: Thomas Rasmus Skaug

Figure 2: Dagbladet, tirsdag 12. juni 2018 Health minister Bent Høie visits the Cardio-oncology outpatient clinic

Drs Geeta Gulati and Siri Lagethon Heck, research fellows in the project, obtained their PhDs from the PRADA trial, and both are pursuing a combined clinical and academic career. Dr Gulati, now a cardiologist, has founded and is chair of the Nordic Cardio-Oncology Society as well as a member of the Cardio-Oncology nucleus of the European Society of Cardiology. She is now in charge of the cardioloncology outpatient clinic at Oslo University Hospital Ullevål. The key researchers have been invited to write editorials and a state-of-the-art review on the role of cardioprotection in cancer therapy cardiotoxicity in leading journals like Circulation and JACC Cardio-Oncology and a chapter in a leading cardiology textbook (European Society of Cardiology Textbook of Cardiology), as well as to participate in international conference debates. The review paper was the most read article in the hjgh-ranking scientific journal JACC CardioOncology in 2022.

In the future, a main focus will be to identify patients at risk for CTRCD and those who will benefit from cardioprotective treatment. In 2017, professor Omland received two grants from the National Program for Clinical Treatment Research in the Specialist Health Service (KLINBEFORSK) and the Norwegian Cancer Society (Open Call) totaling 25 million NOK to conduct PRADA II, a Norwegian multicenter study of the cardioprotective effect of the Angiotensin Receptor-Neprilysin Inhibitor (ARNI) during adjuvant breast cancer therapy. By including more patients and patients with more risk factors, the study aims to identify subgroups who will benefit most from cardioprotective therapy. Recently, the team initiated another randomized, placebo-controlled interventional study in collaboration with the award-winning Akershus University Hospital researcher Evandro Fei Fang. The aim of the study is to assess whether prevention of CTRCD is achievable by Nicotinamide Riboside (NAD+) supplementation in patients with metastatic breast cancer. In 2022, the research group of professor Omland was awarded a grant of 55 million NOK from Kristian Gerhard Jebsen Foundation, the University of Oslo and Akershus University Hospital to establish the K.G. Jebsen Centre for Cardiac Biomarkers. One of the main focuses of the new center is cardiooncological research. In addition to the ongoing randomized controlled preventive

trials, the center will conduct studies on changes in plasma proteomics during cancer therapy and studies on the complex interaction between heart failure and cancer using data from large population based studies like the HUNT (Helse-undersøkelsen I Trøndelag) study.

5. Sources to corroborate the impact (indicative maximum of ten references)

1. McDonagh TA, Metra M, Adamo M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-3726.
2. Heidenreich PA, Bozkurt B, Aguilar D et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e895-e1032.
3. Visseren FLJ, Mach F, Smulders YM et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). Eur Heart J 2021.
4. Lyon AR, Lopez-Fernandez T, Couch LS et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J 2022.
5. Omland T. Cardio-Protective Therapy in Cardio-Oncology: Quo Vadis? Circulation 2021;144:667-669.
6. Broberg AM, Tuohinen S, Skytta T et al. The Establishment of the Nordic Cardio-Oncology Society. JACC: CardioOncology 2020;2:333-335.
7. Omland T. Trastuzumab-related cardiotoxicity: epidemiology, surveillance, prophylaxis, management, and prognosis. ESC Textbook of Cardiology (Oxford University Press 2018)
8. Omland T, Heck SL, Gulati G. The role of cardio-protectionin cancer therapy cardiotoxicity. JACC CardioOncol 2022; 4:19-37. doi: 10.1016/j.jaccao.2022.01.101.
9. van der Meer P, Gietema JA, Suter TM, van Veldhuisen DJ. Cardiotoxicity of breast cancer treatment: no easy solution for an important long-term problem. Eur Heart J. 2016:ehw133.
10. Ghosh A. PRADA–the dawn of high-end Cardio-Oncology research? British Cardiovascular Society 16/08/2016.
11. https://www.dagbladet.no/tema/ny-studie-slik-kan-hjertemedisin-forebygge-seinskader-av-brystkreft/69893830

Akershus University Hospital and Institute of Clinical Medicine, University of Oslo (Campus Ahus) – Impact case #3

Institution:
Name: Akershus University Hospital and Institute of Clinical Medicine, University of Oslo
Short name: Ahus and Campus Ahus

Administrative unit:
Name: Akershus University Hospital and Institute of Clinical Medicine, University of Oslo
Short name: Ahus_Campus Ahus

Title of case study: Investigator-initiated prospective randomized controlled trials in orthopedic trauma surgery

Period when the underpinning research was undertaken: 2012-2022

Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022

Period when the impact occurred: 2017-2022

1. Summary of the impact

During the last five years, the Orthopedic Research Group has conducted five RCTs on hip, wrist, clavicular fractures and the world´s largest RCT on Achilles tendon ruptures (ATRs) influencing treatment for common orthopedic injuries. Two RCTs defined indications for internal fixation, hemiarthroplasty and total hip replacement for femoral neck fractures. Two RCTs investigating surgical treatment for displaced wrist fractures have defined the optimal implant choice and post-operative rehabilitation demonstrating that volar plate fixation is safe, cost-effective and returns the patients' independence quicker than traditional cast treatment. The multicenter RCT on ATRs demonstrated no difference in result between operative and non-operative treatment.

2. Underpinning research

High-quality, well-powered, randomized controlled trials (RCT) with minimal loss-to-follow-up are rare in surgical fields. The present impact case describes a series of such RCTs, influencing the routine management of common injuries like hip fractures, distal radius fractures and Achilles tendon injuries.

Hip fractures cause significant morbidity and are associated with increased mortality. It has previously been shown that displaced hip fractures in the elderly are better treated with hemiarthroplasty than internal (screw) fixation. However, it was unclear if elderly patients with undisplaced fractures would benefit equally from arthroplasty. We therefore randomized 219 patients >70 years to either screw fixation or hemiarthroplasty in a multicenter trial. We found that hemiarthroplasty improved mobility and led to fewer major reoperations. Following this study, we sought to explore whether younger hip fracture patients would benefit from total hip arthroplasty (THA) compared to fixation of the fracture. Thus, 102 patients aged 55-70 with a low-energy

displaced hip fracture were randomized to screw fixation or THA. The patients receiving a THA experienced better outcomes and less pain.

Volar locking plates were introduced in the early 2000s to treat distal radius fractures (DRFs). At the time, surgical fixation with external fixation (EF) was common. Thus, we randomized 266 patients to EF or volar locking plate fixation (VLP). Although there were no statistically or clinically relevant differences between the groups at two years, patients receiving VLP recovered quicker, reported less pain in the first six months, and returned to work earlier. VLP was also cost-effective compared to EF, which led to more minor complications and longer work absenteeism. In another RCT, post-operative care after VLP was randomized to either immobilization in a cast for two weeks or early mobilization. Early mobilization lead to earlier return to activity with no risk of increased complications.

Whether surgical repair of an acute Achilles tendon rupture is associated with better outcomes than nonsurgical treatment is not clear. We initiated a multicenter RCT that compared non-operative treatment, open repair, and minimally invasive surgery in adults with acute Achilles tendon rupture who presented to four trial centers. A total of 554 patients underwent randomization, and 526 patients were included in the final analysis. Pairwise comparisons provided no evidence of differences in patient-reported outcomes between the groups. The changes from baseline in physical performance and patient-reported physical function were similar in the three groups. The number of tendon re-ruptures was higher in the non-operative group (6.2%) than in the open-repair or minimally invasive surgery group (0.6% in each). There were nine nerve injuries in the minimally invasive surgery group (in 5.2% of the patients) as compared with five in the open-repair group (in 2.8%) and one in the non-operative group (in 0.6%). We conclude that in patients with Achilles' tendon rupture, surgery (open repair or minimally invasive surgery) was not associated with better outcomes than non-operative treatment at 12 months.

3. References to the research

Dolatowski FC, Frihagen F, **Bartels S**, Opland V, Šaltytė Benth J, Talsnes O, Hoelsbrekken SE, **Utvåg SE**. Screw Fixation Versus Hemiarthroplasty for Nondisplaced Femoral Neck Fractures in Elderly Patients: A Multicenter Randomized Controlled Trial. J Bone Joint Surg Am. 2019. doi: 10.2106/JBJS.18.00316.

Bartels S, Kristensen TB, Gjertsen JE, Frihagen F, Rogmark C, Dolatowski FC, Figved W, Benth JŠ, **Utvåg SE**. Total Hip Arthroplasty Leads to Better Results After Low-Energy Displaced Femoral Neck Fracture in Patients Aged 55 to 70 Years: A Randomized Controlled Multicenter Trial Comparing Internal Fixation and Total Hip Arthroplasty. J Bone Joint Surg Am. 2022. doi: 10.2106/JBJS.21.01411.

Hammer OL, **Clementsen S**, Hast J, Šaltytė Benth J, Madsen JE, **Randsborg PH**. Volar Locking Plates Versus Augmented External Fixation of Intra-Articular Distal Radial Fractures: Functional Results from a Randomized Controlled Trial. J Bone Joint Surg Am. 2019. doi: 10.2106/JBJS.18.00014.

Clementsen SØ, **Hammer OL**, Šaltytė Benth J, **Jakobsen RB**, **Randsborg PH**. Early Mobilization and Physiotherapy Vs. Late Mobilization and Home Exercises After ORIF of Distal Radial Fractures: A Randomized Controlled Trial. JB JS Open Access. 2019. doi: 10.2106/JBJS.OA.19.00012.

Myhrvold SB, Brouwer EF, **Andresen TKM**, Rydevik K, Amundsen M, Grün W, Butt F, Valberg M, **Ulstein S**, Hoelsbrekken SE. Nonoperative or Surgical Treatment of Acute Achilles' Tendon Rupture. N Engl J Med. 2022. doi: 10.1056/NEJMoa2108447.

4. Details of the impact

Our research on hip fracture treatment has directly influenced treatment choice for this common and severe injury. The Norwegian Hip Fracture Register reports an increased use of arthroplasty (both hemi and total) and a decline in the use of screw fixation following the dissemination of our results on national scientific conferences and in publications. The paper by Dolatowski et al. on screw fixation vs. hemiarthroplasty in elderly patients (2019) has over 100 citations, including an updated Cochrane review [1] and several updated systematic reviews (some referenced below) [2-12]. The study was cited in the Evidence-Based Clinical Practice Guideline for the Management of Hip Fractures in Older Adults (2021) issued by the American Academy of Orthopedic Surgeons (AAOS): https://www.aaos.org/globalassets/quality-and-practice-resources/hip-fractures-in-the-elderly/hipfxcpg.pdf

The RCT by Hammer comparing plate fixation and external fixation of wrist fractures has directly changed the guidelines for distal radius fractures issued by the American Academy of Orthopedic Surgeons (AAOS) [13]. The Guidelines mention Hammer´s paper and only two other high-quality RCTs as the basis for the recommendation. In addition, the project has led to changes in postoperative rehabilitation and follow-up algorithm following surgically treated distal radius fractures in our institution, and nationally. The cost-effective analysis has had an impact on healthcare services internationally and is included in the Swedish national guidelines for the treatment of distal radius fractures: https://figshare.com/articles/journal_contribution/Summary_of_the_Swedish_national_guidelines_/19155305

The study by Myhrvold et al. is the world's largest RCT comparing conservative treatment with surgery for Achilles tendon rupture. The results will change management and reduce Low-Value Care internationally, and its results have already had an impact on treatment algorithm for this common but potentially serious injury. The research provides high-level quality evidence to guide healthcare workers and patients in reaching a treatment strategy based on a shared decision-making progress, which ultimately reduces the number of unnecessary surgeries, benefiting the institutions, patients, and society as a whole. The study immediately attracted attention globally, with several media houses, news outlets, and academic journals publishing editorials, debate articles, and commentaries on the results and their consequences for treatment options. The study was highlighted by the Associated Press and picked up by newspapers such as the Chicago Sun-Times in the USA and the Independent in the UK. The New England Journal of Medicine published an editorial regarding the impact of the study (see links below). Within the first 18 months after publication in April 2022, the paper was cited 50 times. The paper has won several awards, including Best Paper for Akershus University Hospital 2022.

Newspapers, journals and media outlets discussing the Achilles tendon study:

Barfod KW, Hölmich P., Hölmich D. Acute Achilles' Tendon Rupture - Surgery or No Surgery. N Engl J Med. 2022. doi: 10.1056/NEJMe2202696

Maria C. For weekend warriors, most Achilles tendon ruptures heal as well without surgery, study finds. Chicago Sun Times. April 14. 2022. https://chicago.suntimes.com/2022/4/14/23025012/achilles-tendon-rupture-surgery-options-new-england-journal-medicine-stale-myhrvold-medical-research

Associated Press Health. Heal Thyself: Most who tear Achilles tendon can skip surgery. The Seattle Times Apr 13, 2022. The Independent. April 13, 2022.
https://www.seattletimes.com/seattle-news/health/heal-thyself-most-who-tear-achilles-tendon-can-skip-surgery/
Heal Thyself: Most who tear Achilles tendon can skip surgery | The Independent

Tassone P, Morris L. Acute Achilles tendon rupture: Skip the surgery? J Fam Pract. 2023 June. doi: 10.12788/jfp.0604

Phend C. Achilles' Tendon Rupture Surgery Not So Necessary? — Randomized trial suggests one advantage despite similar outcomes to nonoperative treatment. MedPage Today April 13, 2022.
https://www.medpagetoday.com/surgery/orthopedics/98197

Norton A. What Works Best for Ruptured Achilles Tendons? Health Day, April 14, 2022.
https://www.healthday.com/health-news/general-health/4-14-what-works-best-for-ruptured-achille-s-tendons-2657123373.html

Medical Dialogues Editorial Team. Should surgery be opted for Achilles Tendon rupture? Study says no benefit. Medical Dialogues, May 18, 2022.
https://medicaldialogues.in/surgery/news/should-surgery-be-opted-for-achilles-tendon-rupture-study-says-no-benefit-92762

Ebell MH. Surgery Is No Better Than Nonoperative Treatment for Achilles Tendon Rupture in Adults Am Fam Physician. 2022. (editorial)
https://www.aafp.org/pubs/afp/issues/2022/0900/poems-achilles-tendon-rupture.html

5. Sources to corroborate the impact

1. Lewis SR, Macey R, Stokes J, Cook JA, Eardley WG, Griffin XL. Surgical interventions for treating intracapsular hip fractures in older adults: a network meta-analysis. Cochrane Database Syst Rev. 2022 Feb 14;2(2):CD013404.
2. Kumar J, Symonds T, Quinn J, Walsh T, Platt S. What is the best method of fixation for minimally displaced subcapital neck of femur fractures? A systematic review. J Orthop. 2023 Nov;45:54-60.
3. Ramadanov N, Jozwiak K, Hauptmann M, Lazaru P, Marinova-Kichikova P, Dimitrov D, et al. Cannulated screws versus dynamic hip screw versus hemiarthroplasty versus total hip arthroplasty in patients with displaced and non-displaced femoral neck fractures: a systematic review and frequentist network meta-analysis of 5703 patients. J Orthop Surg Res. 2023 Aug 26;18(1):625.
4. Jiang J, Chen J, Xing F, Liu H, Xiang Z. Comparison of femoral neck system versus cannulated screws for treatment of femoral neck fractures: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2023 Apr 13;24(1):285.
5. Wang W, Huang Z, Peng J, Fan J, Long X. Preoperative posterior tilt can be a risk factor of fixation failure in nondisplaced femoral neck fracture: a systematic review and meta-analysis. Eur J Orthop Surg Traumatol. 2023 Oct;33(7):3197-205.
6. Cui L, Zhao S, Tian H, Guo W, Dong X. Curative efficacy of surgical procedures for older patients with femoral neck fracture: a network meta-analysis and systematic review. J Orthop Surg Res. 2022 Mar 2;17(1):127.
7. Zelle BA, Salazar LM, Howard SL, Parikh K, Pape HC. Surgical treatment options for femoral neck fractures in the elderly. Int Orthop. 2022 May;46(5):1111-22.

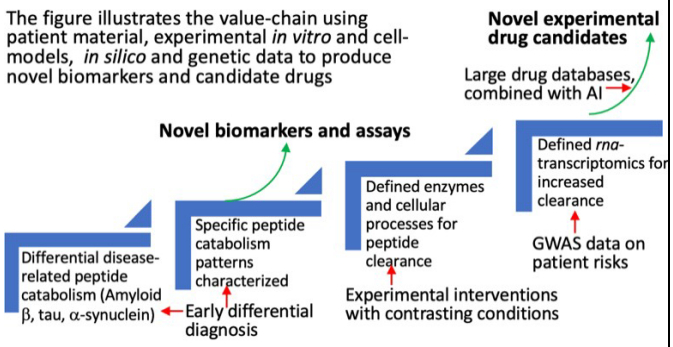
8. Xu WN, Xue QY. Long-Term Efficacy of Screw Fixation vs Hemiarthroplasty for Undisplaced Femoral Neck Fracture in Patients over 65 Years of Age: A Systematic Review and Meta-Analysis. Orthop Surg. 2021 Feb;13(1):3-13.
9. Cui S, Wang D, Wang X, Li Z, Guo W. The choice of screw internal fixation and hemiarthroplasty in the treatment of femoral neck fractures in the elderly: a meta-analysis. J Orthop Surg Res. 2020 Sep 21;15(1):433.
10. Kim SJ, Park HS, Lee DW. Complications after internal screw fixation of nondisplaced femoral neck fractures in elderly patients: A systematic review. Acta Orthop Traumatol Turc. 2020 May;54(3):337-43.
11. Lutnick E, Kang J, Freccero DM. Surgical Treatment of Femoral Neck Fractures: A Brief Review. Geriatrics (Basel). 2020 Apr 1;5(2).
12. Ma HH, Chou TA, Tsai SW, Chen CF, Wu PK, Chen WM. Outcomes of internal fixation versus hemiarthroplasty for elderly patients with an undisplaced femoral neck fracture: a systematic review and meta-analysis. J Orthop Surg Res. 2019 Oct 11;14(1):320.
13. AAOS. Management of Distal Radius Fractures Evidence-Based Clinical Practice Guideline. 2020 5.12.2020. Report No.: www.aaos.org/drfcpg.

Akershus University Hospital and Institute of Clinical Medicine, University of Oslo (Campus Ahus) – Impact case #4

Institution: **Name**: Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus and Campus Ahus
Administrative unit: **Name:** Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus_Campus Ahus
Title of case study: Dementia Disease Initiation: Predictors for dementia, biomarkers and novel drug candidates
Period when the underpinning research was undertaken: 2008-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2008-2022
Period when the impact occurred: 2012-2022 (ongoing)

1. Summary of the impact

Our research on biomarkers with data and samples from longitudinal pre-dementia cohorts impacts early differential diagnosis of major dementia-giving diseases, gives improved prediction of prognosis and future precision interventions. Early Alzheimer's and Lewy Body diseases (AD, LBD), Late-Life Depression and small vessel disease develop insidiously with overlapping clinical presentations making diagnosis contingent on biomarkers (fluid/proteomic, imaging, genetic) and improved neuropsychological tests. Brain pathologies are currently irreversible, and early personalized intervention is needed. We introduced fluid biomarkers for neurodegenerative diseases in Norway, following this Ahus still is the center for this type of analyses. We have also developed and implemented advanced MRI imaging techniques tested and validated in large in-house cohorts staged with fluid biomarkers and neuropsychology. Multi-modal data reciprocally underpins results from applied technologies, with increasing impact from a planned value-chain (biomarkers -> early differential diagnosis -> novel treatment alternatives, see **figure**) leading to innovation and commercialization via licensing to biotech firms and foundations combined with R&D contracts (21.3 mill to CNG 2018-2022) and further new academic research contracts (e.g. JPND DEBBIE).



2. Underpinning research (indicative maximum 500 words)

Development of novel markers for preclinical or prodromal diseases leading to dementia is contingent on advances in proteomics, imaging, genetics and neuropsychology. To find biomarkers, evaluate performance and predictive power (i. e., prediction of clinical progression to dementia) we established a large national and European longitudinal cohort. Corresponding customized data- and biobanks serve to study and improve marker performance and develop and evaluate novel treatments.

Cohorts and biobanks. NFR NASATS ("Nasjonale Satsninger") for DDI (Dementia Disease Initiation) funding in 2012, and ensuing funding from EU/JPND (BIOMARKAPD, APGeM (Pre -clinical genotype -phenotype predictors of Alzheimer's disease and other dementias, PMI-AD (Precision Medicine in Alzheimer's Disease), DEBBIE (Developing BBB-ASL as a non-Invasive Early biomarker) has been used to establish a unique national and European longitudinal cohort with biennial follow-ups of control, at-risk, preclinical and prodromal (mild cognitive impairment) cases over up to 10 years (as of 2022) with dementia as the final outcome variable. Deep phenotyping (neuropsychology, imaging, blood, CSF at every visit) and GWAS at baseline of > 1000 included cases (2022) allow study of biomarkers, mechanisms for disease initiation and clinical progression through the pre-dementia disease processes.

Clinical trials. The cohorts are "*trial ready*", i. e. patients are investigated (every two years) to such an extent that we already know with a fairly high degree of certainty whether they confirm to or fall outside of inclusion/exclusion criteria for any given trial. This means that costly screening failures can be avoided, and recruiting and entering of patients in trials is effective. Thus, we have been running a continuous set of trials (phase I-III) on pre-dementia AD and Lewy-body patients during the period (2012-2022), see citation (Andreasen et al. section 3).

Fluid biomarkers and proteomics. Our early research (pre-2012) employed fairly simple neuropsychological testing, but more advanced MRI imaging and proteomics incl. mass spectrometry on in-house pre-dementia AD and LBD cohorts. This enabled us to introduce fluid biomarker testing as diagnostic tool for Alzheimer's Disease in Norway, as our practice was adopted at the Ahus' clinical chemistry lab (increasingly used, 2400 samples/patients tested in 2020), and it gave spin-offs also for Creutzfeld Jacob testing. Testing on cerebrospinal fluid (CSF) and plasma from smaller longitudinal cohorts allowed us to file early patents on blood and CSF biomarkers, finally granted in 2014-2017 [a,b section 3]. As of 2013 these and later patents are licensed by a biotech start-up, Pre Diagnostics. Lisbeth Johnsen, Hanne Mali Møllergård and Kaj Blennow (Gothenburg University)were main collaborators at the early stage.

Unique AD-related degradation patterns of Aβ, the main peptide forming brain amyloid plaques implied dysfunctional endolysomal enzymatic activity, in accordance with ultrastructural observations in AD brain with evidence for similar dysfunction in other neurodegenerative diseases with CNS peptide deposition (e. g. Lewy Body diseases) and tauopathies. For this, we employed Mass Spectrometry using biobanked patient material combined with *in vitro* experiments with endolysosomal enzymes and customised peptides. Marianne Wettergreen and Magnus Røgeberg (post doc) as well as Berglind Gisladottir were the main responsible on these series of experiments. Emerging evidence from our cooperation with large GWAS consortia pointed to a major involvement of myelogenic cells in AD pathogenesis, spurring use of a hybridoma monocyte cell model and patient-derived stem cells to further study peptide degradation patterns and how this could be modified leading to novel candidate therapeutic drug combinations[c, d, section 3]. Testing these drugs in combination with stressors, mechanistic analysis based on RNA*seq* on model cells combined with AI led to later DOFIs on novel drug targets and drugs (not yet patented 2022). Kulbushan Sharma (post doc at the lab, now head of the Ahus stem cell facility), Marianne Wettergreen, Berglind Gisladottir, Per Selnes (bioinformatics) and Bjørn-Eivind Kirsebom (statistics) were main responsible during this phase with Panpan You (molecular biology) and Peter Arnesen (bioinformatics, AI) joining in 2022.

Imaging MRI is essential in early diagnosis, non-invasive and relatively accessible. Increasingly advanced protocols and post-processing including AI-based techniques has made this a preferred tool for supporting studies for us, also thanks to a tight collaboration with CRAI at OUS/Rh (prof. Atle Bjørnerud, Per Selnes/CNG key collaborator). At an early stage we adopted morphometric and diffusion-weigthed techniques. Combined with our clinical cohort, molecular/pathological staging with CSF fluid biomarkers and PET imaging, this has given new insights into disease-specific mechanisms for neurodegeneration.

Neuropsychological testing is essential for the study of disease-initiation and progression as well as underpinning of fluid and imaging biomarkers, but inadequate norms have hampered early

detection of clinically relevant symptoms. To alleviate this problem, we have employed our large national database, combined with other Scandinavian databases and developed and published updated regression-based norms for cognitive tests. This is an ongoing project, but fairly well cited and uptake across Norway is good also outside of our group.

Collaboration with industry. The DDI cohort, and innovations described above (citations section 3) has also formed the basis for extensive collaborations with Pre Diagnostics (the licensing partner for our patents) in several projects, e. g. the EU Horizon 2020 project "Verdad" (https://pre-diagnostics.com/eu-horizon-2020/), with a EUR 3.36 mill. total cost.

3. References to the research

a) EP2245463/ US9625474: Diagnostic method. Granted EU 2014/US 2017.
Inventors: Tormod Fladby, Lisbeth Johnsen, Kaj Blennow.

b) EP2646462/13/989959: Methods and compositions for monitoring phagocytic activity. Granted EU 2017/Undergoing examination US. Inventors: Tormod Fladby. .

c) PCT/EP2020/061018: Combination therapy comprising an ffar4 agonist and an alpha-7 nAcChr agonist or positive modulator. EU, US, India, Mexico appl. ongoing. Inventors: Tormod Fladby. .

d) PCT/EP2022/055950: Clearance assay. EU, US, India, Mexico, China patent application ongoing. Inventors: Tormod Fladby, .

Academic reports on this research include:

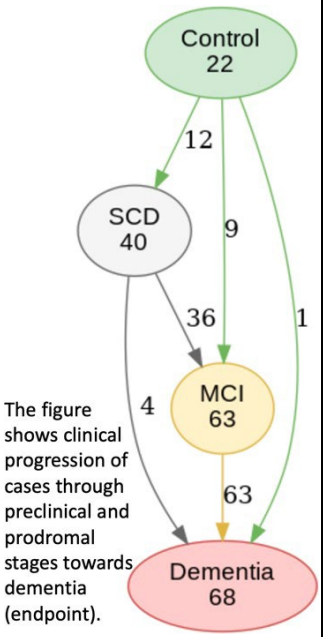
Andreasen N . . Fladby T . . First administration of the Fc-attenuated anti-β amyloid antibody GSK933776 to patients with mild Alzheimer's disease: a randomized, placebo-controlled study PLos One 2015 Mar 19;10(3) doi: 10.1371/PMID: 25789616

Rogeberg M . . Fladby T. **Isobaric Quantification of Cerebrospinal Fluid Amyloid-β Peptides in Alzheimer's Disease: C-Terminal Truncation Relates to Early Measures of Neurodegeneration.** J Proteome Res. 2015 Nov 6;14(11):4834-43. doi: 10.1021/PMID: 26452689.

Nordengen K,. . Fladby T. **Phenotype-informed polygenic risk scores are associated with worse outcome in individuals at risk of Alzheimer's disease**. Alzheimers Dement (Amst). 2022 Aug 15;14(1):e12350. doi: 10.1002/ PMID: 35991219

4. Details of the impact

With the DDI-NASATS project in 2012, we set up 4 linked goals: 1) To explore the underlying mechanisms involved in the initial development of the major neurodegenerative dementia diseases in the elderly: AD and PD / DLB at early stages of development that are accessible for preventive strategies; 2) To identify early diagnostic markers for AD and DLB at pre-dementia stages; 3) To identify prognostic markers towards dementia (AD, PD dementia, and DLB),in pre-clinical and pre-dementia cognitive impairment; 4) To improve and harmonize pre-dementia diagnostic procedures at the national level, including large clinical and control cohorts, standardizing assembly of clinical- and biomaterial in biobanks and imaging databanks, and making this available at the different research centers nationwide and internationally.

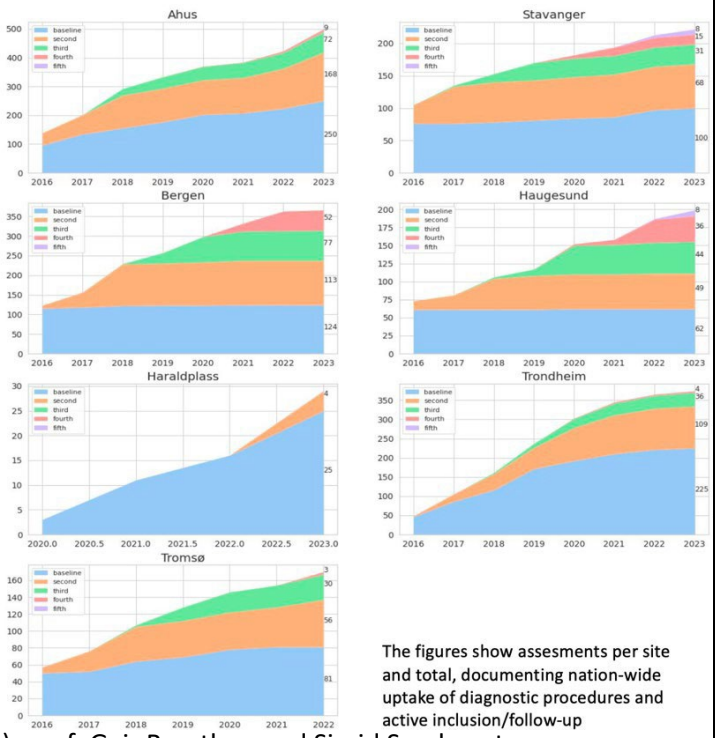


The figure shows clinical progression of cases through preclinical and prodromal stages towards dementia (endpoint).

Establishing a national network was crucial for all the goals. We invited leading colleagues within neurology, geriatrics, old-age psychiatry and neuropsychology from all university hospitals, and Helse Fonna (Haugesund) and established standardized protocols / CRFs for clinical examinations and testing, scanning, blood, CSF based on international standards as developed in our BIOMARKAPD/ JPND project. To explore risk factors for dementia, we focused on at-risk (i. e. first-degree relatives with dementia), preclinical and early stages (subjective cognitive decline (SCD) and mild cognitive impairment (MCI)) as well as age-matched controls (largely spouses and patients admitted for orthopedic surgery), with dementia as the endpoint (see figure). Sub-cohorts with Parkinson's disease and age-related neuropsychiatric disorders (including LLD) have also been included using

the same protocols. All examinations, including repeat CSF are performed at baseline and at 2-year intervals for all clinical subgroups and controls. Close to 1000 baseline cases were included as of 311223 (see figure). Centralized GWAS has been performed at inclusion, also contributing to the material of large international consortia with large impacts on the genetic understanding of AD. This has been provided and organized by prof. Ole Andreassen/Norment (a partner in JPND/APGeM).

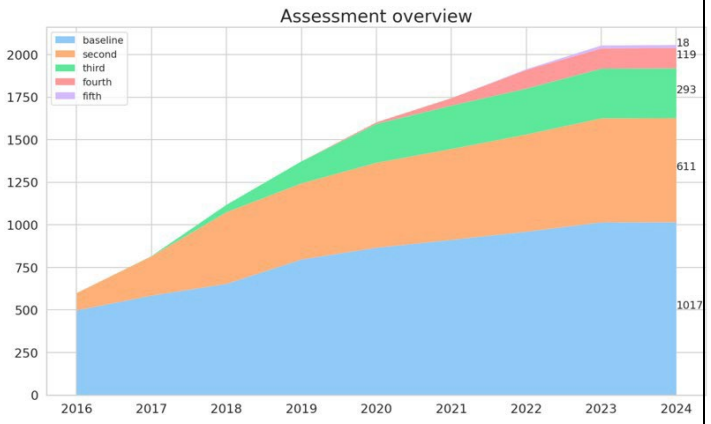
Inclusions and follow-ups have been diligent from all sites, ultimately depending on local resources but with biobank- and databank-service supplied from CNG/Ahus. In return, access to material from an increasingly valuable bio- and databank has been provided. We have also developed a customized searchable database containing all raw and derived measures including MRIs using the XNAT platform, contained on TSD/UiO (a secure server, accessible for co-workers). External data access is also provided upon request and approval form data protection officers etc.



The figures show assesments per site and total, documenting nation-wide uptake of diagnostic procedures and active inclusion/follow-up

The main collaborators at UiT/UNN (Tromsø) are prof. Knut Waterloo, Stein Harald Johnsen and Bjørn-Eivind Kirsebom, at NTNU/St. Olav (Trondheim), prof. Geir Braathen and Sigrid Sando , at Haraldsplass/Bergen Ragnhild Eide Skogseth, at SUS (Stavanger) prof, Dag Aarsland and at Haugesund Arvid Rongve. (Validation cohorts have been contributed by several European partners as parts of APGeM and PMI-AD, but are not described here.)

As the focus has been on early and incipient stages (Dementia Disease Initiation), fairly long follow-ups have been necessary but as the bio- and database is being completed with 8- and 10-year follow-ups the value increases rapidly. Development and validation of non-invasive and accessible biomarkers (MRI and plasma), including those based on in-house IP (see above) will be essential going forward. Applications using AI on MRI and multimodal data is being explored.



As for existing impacts, a large number of publications have been submitted, largely on baseline and cross-sectional data but lately also on longitudinal data outlining use of fluid, MRI, neuropsychology and genetic data in diagnosis and risk-factor assessments. We believe the data- and biobank is unique and surpasses e. g. the ADNI database (US) in breadth of phenotypes, early-stage cases and depth of phenotyping.

5. Sources to corroborate the impact

Description of cohort:

Fladby T, . . Aarsland D. **Detecting At-Risk Alzheimer's Disease Cases.** J Alzheimers Dis. 2017;60(1):97-105. doi: 10.3233/JAD-170231.PMID: 28826181.

Kirsebom BE, . . Blennow K, Fladby T. **Stable cerebrospinal fluid neurogranin and β-site amyloid precursor protein cleaving enzyme 1 levels differentiate predementia Alzheimer's disease patients.** Brain Commun. 2022 Sep 24;4(5):fcac244. doi: 10.1093/braincomms/fcac244. eCollection 2022. PMID: 36262371.

Identification of amyloid beta mid-domain fragments in human cerebrospinal fluid. Rogeberg M, Wettergreen M, Nilsson LN, Fladby T. Biochimie. 2015 Jun;113:86-92. doi: 10.1016/j.biochi.2015.03.022. Epub 2015 Apr 10.

Siafarikas N, . . . Fladby T. **Cerebrospinal fluid markers for synaptic function and Alzheimer type changes in late life depression**. Sci Rep. 2021 Oct 13;11(1):20375.

New insights into the genetic etiology of Alzheimer's disease and related dementias. Bellenguez C et al. Nat Genet. 2022 Apr;54(4):412-436. PMID: 35379992

Brain amyloid and vascular risk are related to distinct white matter hyperintensity patterns Lene Pålhaugen, . . , Tormod Fladby J Cereb Blood Flow Met 2021 May;41(5):1162-1174

Amyloid Plaques and Symptoms of Depression Links to Medical Help-Seeking due to Subjective Cognitive Decline. Espenes R, Kirsebom BE, Eriksson C, Waterloo K, Hessen E, Johnsen SH, Selnes P, **Fladby T.** J Alzheimers Dis. 2020;75(3):879-890. doi: 10.3233/JAD-190712.PMID: 32333584

Akershus University Hospital and Institute of Clinical Medicine, University of Oslo (Campus Ahus) – Impact case #5

Institution: **Name:** Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus and Campus Ahus
Administrative unit: **Name:** Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus_Campus Ahus
Title of case study: The NAD^+-mitophagy pathway in human ageing and its broad clinical applications
Period when the underpinning research was undertaken: Sep. 2017-present
Period when staff involved in the underpinning research were employed by the submitting institution: Sep. 2017
Period when the impact occurred: Jan. 2019 and onwards

1. Summary of the impact (indicative maximum 100 words)

This 6-year research (and also continuing) generates big impacts

- **Science:** Provides novel mechanisms of human ageing and the causes of dementia with tier-one level publications;
- **Education:** trained over 40 students from more than 10 countries; initiated the first-ever PhD course on ageing 'Biology of Ageing' (MF9246) open to all the EU countries;
- **Clinic:** propelled 5 clinical trials, with one finished with success;
- **Collaboration with Industry:** issued one 'discovery' to a company for business development and is involved in a big business company in making the research-evidenced Norwegian Krill oil as a diet supplement (one of the best sellers in the world);
- **Social impact:** improved general population's awareness of the risks and protective factors of ageing and dementia, enabling them to improve their quality of life through publicly easy accessible approaches; and
- **Diversity:** As a scholar from China with 3-year trainings in Hong Kong, 6-year in the USA, and 6-year in Norway, the PI Evandro Fang is now leading a big international team of around 15 students from around 10 countries. The Fang Lab is an LGBTQ-friendly society. The diversity of the Fang Lab also has a positive impact to Epi-Gen and Ahus, bringing more scientific and social exposures of Epi-Gen/Ahus to the world.

2. Underpinning research (indicative maximum 500 words)

2.1 Roles for DNA damage-induced NAD^+ depletion in accelerated ageing (period 2017-2019, led Fang)

Mitochondrial dysfunction is a hallmark of neurodegeneration and aging, but the underlying mechanisms are largely unclear. DNA damage accumulates during life and is thought to contribute to aging and genomic instability. Thus, defining those proteins and pathways that maintain genome stability and mitochondrial health may be critical in preventing aging and age-related degeneration. Following the discoveries of the NAD^+/SIRT1-PGC1α (NSP) signaling in healthy ageing **[1, 2]** during his postdoc period at NIA/NIH, USA, the Evandro Fang lab at Ahus/UiO continued further mechanist studies from Sep. 217. The novel discoveries show impaired mitophagy is an accelerator of ageing, providing scientific evidence of turning up mitophagy as a maneuverable target to improve healthspan **[3]**. This study was started between 2017-2019 with funding supports from HELSE SØR-ØST (#2017056) and the Research Council of Norway (RCN) Young Talent grant (#262175) to Fang.

2.2 Compromised NAD^+-mitophagy axis contributes to cognitive impairment in Alzheimer's disease (Period 2017-2022, onwards, led by Evandro Fang)

Alzheimer's disease (AD) constitutes 70% of dementia cases and affects over 50 million individuals worldwide. Continued failure in drug development for AD suggests the importance in exploring alternative molecular mechanisms and drug targets for AD. Neurons affected in AD experience mitochondrial dysfunction and a bioenergetic deficit that occurs early and promotes the disease-defining amyloid beta peptide (Aβ) and Tau pathologies. We have proposed that defective mitophagy contributes to AD **[4]**. We have demonstrated that mitophagy is impaired in postmortem human brain tissue and iPSC-derived neurons from AD as well as in Aβ, Tau, and ApoE4 animal models of AD **[5]**; genetic and pharmacological upregulation of mitophagy inhibit AD pathologies and retain memory in AD animal models. Based on the studies from us and others, we propose that age-dependent reduction of mitophagy is a shared contributor to common neurodegenerative diseases **[6] (Fig. 1)**.

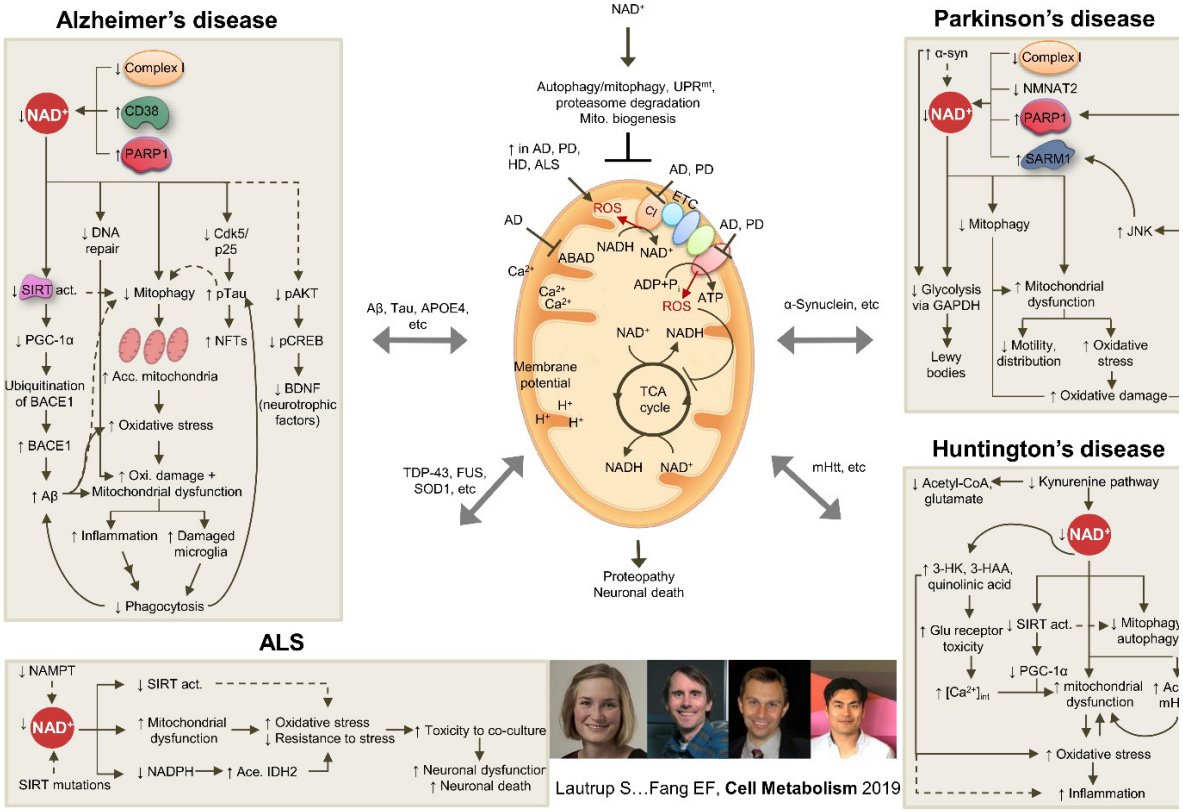


Fig. 1. A summary on the importance of the NAD⁺-mitophagy axis in inhibiting common neurodegenerative diseases.

3. References to the research (six maximum; #First author, *corresponding author)

1. **Fang EF#,** Scheibye-Knudsen M#, Brace L, Kassahun H, et al., Croteau DL, Bohr VA*. Defective Mitophagy in XPA via PARP1 hyperactivation and NAD⁺/SIRT1 reduction, ***Cell***, 2014, 157(4): 882-896. https://pubmed.ncbi.nlm.nih.gov/24813611/ (citations: 625 by 12 Jan. 2014, source Google Scholar, same below; the landmark paper linking reduced NAD+-mitophagy way as a common cause of many premature ageing diseases; with Prof. Hilde Nilsen/Ahus as coauthor).

2. **Fang EF#**, Kassahun H, Croteau DL, Scheibye-Knudsen M, Marosi K, Lu H, Shamanna RA, Kalyanasundaram S… Wollman BN, Morevati M, Li J, Kerr JS, Lu Q, Waltz TB, Tian J, Sinclair DA, Mattson MP, Nilsen H, Bohr VA*. NAD⁺ replenishment improves lifespan and healthspan in Ataxia telangiectasia models via mitophagy and DNA repair, ***Cell Metab***, 2016, 24(4):566-581. https://pubmed.ncbi.nlm.nih.gov/27732836/ (citations: 467; a landmark paper showing NAD+ supplementation improved lifespan and healthspan in a premature ageing Ataxia telangiectasia, the base of the 2-year clinical trial Nilsen/Fang just finished; with Prof. Hilde Nilsen/Ahus as coauthor).

3. **Fang EF#,*,** Hou Y#, Lautrup S#, Jensen MB, Yang B, SenGupta T, Caponio D, Khezri R, Demarest TG, Aman Y, Figueroa D, …, Jasper H, Nilsen H, Bohr VA*. NAD + augmentation restores mitophagy and limits accelerated aging in Werner syndrome. ***Nat Commun***, 2019. https://pubmed.ncbi.nlm.nih.gov/31754102/ (citations: 175; a landmark paper showing NAD+ supplementation improved lifespan and healthspan in a premature ageing Werner syndrome, base of the following clinical trial in Chiba Japan).

4. Kerr JS[#], Adriaanse BA, Greig NH, Mattson MP, Cader MZ, Bohr VA*****, **Fang EF***. Mitophagy and Alzheimer's disease: Cellular and molecular mechanisms, ***Trends Neurosci***. 2017, 40(3):151-166. https://pubmed.ncbi.nlm.nih.gov/28190529/ (Citations: 607; my hypothesis of compromised mitophagy as a driver of Alzheimer).

5. **Fang EF**[#,]*, Hou Y[#], Palikaras K[#], Adriaanse BA, Kerr JS, Yang B, Lautrup S, Hasan-Olive M, Caponio D, Dan X, Croteau DL, …, Cader MZ, Mattson MP, Tavernarakis N, Bohr VA*. Mitophagy inhibits Aβ and p-Tau pathologies and cognitive deficits in experimental models of Alzheimer's disease. ***Nature Neurosci***, 2019. https://pubmed.ncbi.nlm.nih.gov/30742114/ (**Citations: 1051**; the landmark paper evidenced compromised mitophagy contributes to AD and is a druggable target; one of the high cited papers in the field).

6. Lautrup S, Sinclair DA, Mattson MP, **Fang EF***. *NAD^+ in brain ageing and neurodegenerative disorders. **Cell Metab**, 2019, 30 (4): 630-655.* https://pubmed.ncbi.nlm.nih.gov/31577933/ (Citations: 434; proposed a hypothesis on why ageing is the primary driver of common neurodegenerative diseases).

4. Details of the impact (indicative maximum 750 words)

4.1. **Science: Provides novel mechanisms of human ageing and the causes of dementia**

As detailed in sections 2 and 3, these studies in-depth our understandings of the molecular mechanisms of human ageing and the age-predisposed Alzheimer's disease. These discoveries have fostered intensive scientific studies in this field (as evidenced by over 15000 citations and so on) and provided evidence for clinical trials (detailed in 4.3.).

4.2. **Education: opened a new course and trained many students**

Within the past 5 years, the Fang Lab has mentored (and is mentoring) more than 40 young scientists who are interested in ageing research. Among them, 32 students have graduated/worked in the Fang lab. All the 4 former postdocs have secured good positions: Dr. Domenica Caponio (postdoc 2019-2022), a teacher; Dr. Yahyah Aman (postdoc 2018.02-2021.01), an editor in Nature Ageing (London Office); Dr. Chenglong Xie (postdoc 2019.09-2020.11), an associate Professor in Wenzhou Medical Universtiy in China; and Dr. Noemí Villaseca González (postdoc 2022), an Assistant Professor in University of Castilla-La Macha in Spain. Further, the Fang lab has opened the 1st course on Biology of Ageing in Norway (with Hilde Nilsen) which is turning to be a popular course. E.g., in 2023 nearly 40 students attended the course from many universities in Norway, Denmark, Sweden, Germany, and the USA (with 88.3% satisfaction).

4.3. **Clinic: propelled 5 clinical trials, with one finished with success**

Guided by their original discoveries that reduced NAD+ is a cause/high risk factor of premature ageing and neurodegenerative diseases, Dr. Fang is actively involved many translational studies, such as:

- NAD+-based clinical trial on Ataxia Telangiectasia (A-T) (led by Prof. Hilde Nilsen; ClinicalTrials.gov Identifier: NCT04870866): with very positive clinical results just published (PMID: 37899683). We show that long-term use of NR appears to be safe and well tolerated, and it improves motor coordination and eye movements in patients with A-T of all ages.

- NAD+-based clinical trial on Amyotrophic Lateral Sclerosis (ALS) (led by Prof. Ole-Bjørn Tysnes with ClinicalTrials.gov Identifier: NCT04562831)
- NAD+-based clinical trial on reducing cardiovascular side effects after chemotherapy (led by Prof. Torbjorn Omland and Dr. Evandro F. Fang, with ClinicalTrials.gov Identifier: NCT03760588)

An important milestone for our 'bench-top' to 'bedside' study was just finished recently. Led by Prof. Hilde Nilsen, we just published a phase 2 clinical trial data entitled 'Long-Term Nicotinamide Riboside Use Improves Coordination and Eye Movements in Ataxia Telangiectasia' in the leading journal Movement disorders. Ataxia telangiectasia (A-T) is a DNA repair deficient disease with premature ageing features and there is no cure. In 2016, a pre-clinical study from Prof. Vilhelm Bohr, Prof. Hilde Nilsen, and Dr. Evandro F. Fang showed that supplementation with a NAD+ precursor nicotinamide riboside (NR) reduced A-T pathologies and extended lifespan in animal models (Fang EF et al., Cell Metabolism, 2016. Download). To check whether this 'bench-top' discovery could be applicable in 'bedside', Nilsen led a 2-year NR clinical trial to treat A-T kids in Norway. The data show that NAD+ concentrations increased rapidly in peripheral blood and stabilized at a higher level than baseline. NR supplementation was well tolerated for most participants. The total scores in the neuromotor test panels, as evaluated at the 18-month time point, improved for all but one participant, primarily driven by improvements in coordination subscores and eye movements. A comparison with historical data revealed that the progression of certain neuromotor symptoms was slower than anticipated. The study concludes that Long-term use of NR appears to be safe and well tolerated, and it improves motor coordination and eye movements in patients with A-T of all ages.

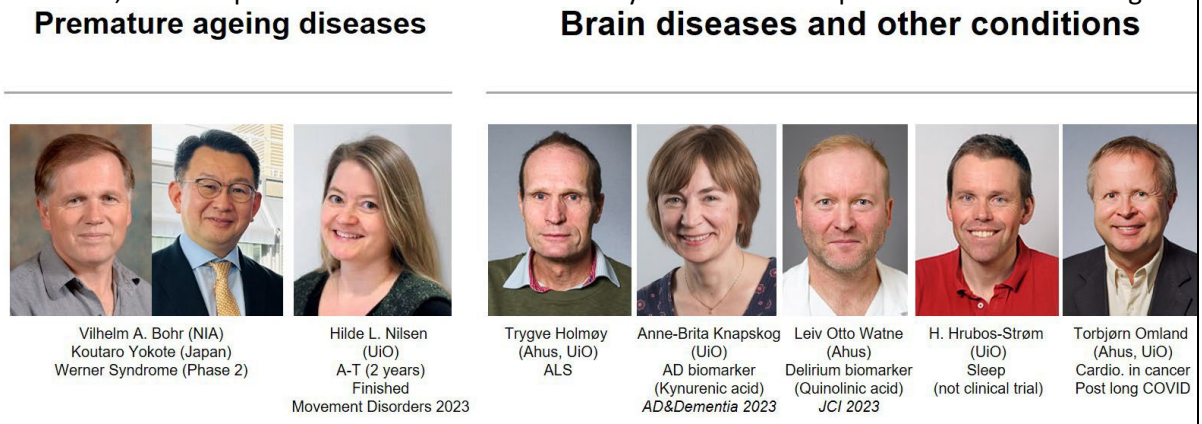


Fig. 2. A summary of the NAD+-related clinical studies, including clinical trials and clinical biomarker development Fang involved in.

4.4. Collaboration with Industry

In line with the Ahus theme to collaborate with industry, the Fang lab has been actively and successfully implemented their wet lab discoveries to industry with two examples presented.

i) Based on the Fang lab ground-breaking discovery of turning up mitophagy as a therapeutic strategy in Alzheimer's disease (Fang EF et al., Nature Neuroscience 2019; commentary in Nature Reviews Drug Discovery; highlighted in Nature 2022), the Fang lab has a License agreement with the anti-ageing company Molecule AG/VITADAO for further development and commercialization of 'Inducers of mitophagy'. Prosjektnummer: 282942 (Kostnadssted 900050; direct funding NOK 2,397,750 NOK).

ii) In collaboration with one of the Norwegian biggest companies AKER (here AKER BioMarine), the Nilsen and Fang labs showed anti-ageing potential of the Norway-made Antarctic Krill oil (PMID: 36367773; also news in the Norwegian National medium NRK). This led Fang to be invited as a paid Chief Scientific and Medical Officer of NYO3 (a Norway-registered Norwegian/Chinese company): now this company is developed into one of the world's largest companies in this field.

4.5.Social impact: improved general population's understanding of ageing and dementia
This case has shown its immediate and big social impact as different areas.

- Enabled the establishment of the Norwegian Centre on Healthy Ageing Network (NO-Age, www.noage100.com): Dr Fang built the network together with Profs. Hilde Loge Nilsen, Jon Storm-Mathisen, and Linda Hildegard Bergersen. NO-Age has strong scientific impact: it is composed of 7 advisors (including the late Prof. George Martin), 43 national members, 31 international members. Among them, three are Nobel Laureates. NO-Age has organized 4 national/international meetings and more than 50 seminars over the past 4 years.

- Enabled the establishment of the Norwegian National anti-Alzheimer's disease network (NO-AD, www.noad100.com): Fang built the network together with Prof. Menno P. Witter (NTNU, Norway). The NO-AD national network has significant scientific impact: it is composed of 8 advisors, 30 national members, and 32 international members. Together with NO-Age, NO-AD has organized more than 50 seminars over the past 4 years. As most of the talks were recorded, NO-Age/AD seminars have become a popular training resource for researchers on ageing and AD.

- Disseminated the science to the broad scientific community. The discoveries were being spoken in 123 invited public talks on ageing worldwide from 2 Oct 2017: 3 (2017), 25 (2018), 40 (2019), 10 (2020), 10 (2021), 35 (2022), with 8 already scheduled in 2023.

- Organized the 1st Norway-UK meeting on ageing and dementia on18-19 Sep. 2023 (co-hosted by Prof. Lynne Cox/Oxford and Richard Siow/KCL). More than 200 students, researchers, and clinicians attended this event.

- Based on the discoveries, Fang was invited by the Norwegian national TV channel NRK to be involved in its award-winning documentary TV programme 'The Dementia Choir' (season 1 with 6 episodes): this TV programme is of a big success, as it broadly educated the general population on care, awareness, and ways to slow down the disease. Fang was involved in episode 5, bringing his laboratory discoveries on how to slow down (if we cannot stop at the moment) the progression of dementia: such as to do exercise, fasting, having healthy diet and fruits (e.g., passion fruit based on the scientific paper from the Fang lab). This programme got many awards, including the Audience Award during the Gold Route (the Norwegian 'Grammy' Award), and the human right Award by the University of Oslo.

5. Sources to corroborate the impact (indicative maximum of ten references)

- Publication of the 2-year clinical trial showing the benefit of NAD+ in treating a premature ageing disease https://pubmed.ncbi.nlm.nih.gov/37899683/
- A list of all the meetings organized by NO-Age/AD https://noad100.com/meetings-events/
- Over 50 videos were recorded as educational source https://noage100.com/videos/
- Details of the 1st Noway-UK meeting on ageing and dementia https://noage100.com/2023/08/17/the-nyo3-5th-no-age-ad-meeting-andthe-1st-norway-uk-joint-meeting-on-ageing-and-dementia/
- Web of the Fang Lab https://evandrofanglab.com/
- The Norwegian national TV channel NRK-made The Dementia Choir TV series (season 1 with 6 episodes): from 25 min in episode 5 https://tv.nrk.no/serie/demenskoret
- Interviewed by the Norwegian leading newspaper VG on anti-AD drug development progress https://mynoad100.files.wordpress.com/2022/01/vg2022_alzheimers-e28093-vg.pdf
- The 2023 Human Right Award by UiO to the Dementia Choir Season 1 https://www.uio.no/english/about/facts/awards/human-rights/