

Department of Clinical Physiology and Nuclear Medicine

Annual Report 2021





Rigshospitalet

King Frederik V founded Rigshospitalet in 1757. Today it has app. 1,250 beds and 12,000 employees. Research at Rigshospitalet is published in more than 2,000 peer review papers per year, including >200 higher academic theses (PhD and Doctor of Medical Science). Rigshospitalet is part of The Capital Region of Denmark and is a Copenhagen University Hospital.

University of Copenhagen

The University of Copenhagen was founded in 1479. The Faculty of Health and Medical Sciences has 10,000 students, including medicine and bioengineering in collaboration with The Technical University of Denmark, DTU. The University of Copenhagen is member of IARU, the International Alliance of Research Universities and LERU, League of the European Research Universities. www.ku.dk



Contents

Preface 2

Mission and objectives 4

Highlights 2021 6

Professor accession 8

Nuclear medicine technologists, radiographers, nurses, and laboratory technicians..... 10

KF section..... 16

Glostrup Section..... 18

PET Scanner section 20

Cardiac Investigations 22

Lung investigations 24

Pediatric Nuclear Medicine..... 28

RIS/PACS 30

The Physicist and Technology Group 32

Neuro PET 36

PET/MRI 40

MRI 42

QUADRA 44

Opening of our new Super-scanners 46

Merging of the Cyclotron and Radiochemistry sections..... 50

Radiochemistry 51

Cyclotrons 54

Medical Secretaries 56

Education 58

Equipment..... 60

Organisation and Staff..... 62

Studies 2021 66

Invitation to collaboration 68

Publications 2021 70

Academic and other activities 90

Research 94

Cluster for Molecular Imaging 102

Collaboration with The National Hospital of the Faroe Islands 106

Neurobiology Research Unit 108

Bioengineer in Medicine and Technology..... 110

Preface

2021 was the second year with Corona. We learned to cope, and patients, research, innovation, and education were successfully managed due to the tremendous and positive effort from staff and student, leadership, and professors.

We were serious in our approach to preventive measures for the sake of our patients and their safety – and the safety of the staff. We spent extra time cleaning all scanners, equipment, and rooms between every patient. We avoided major disease chains among the staff, but employees inevitably were infected by their family members with the SARS Covid-2 virus disease. The staff has been very diligent in wearing masks and taking all precautionary measures, and it has been a success story. All patients have, despite the challenges, been treated with state-of-the-art quality in a professional, dignified, and friendly atmosphere. For that we would like to express a warm thank you to all staff members.

Lung diffusion capacity measurements seem essential to monitor *long-Covid disease*, where reduced lung diffusion capacity is an important quantitative parameter for the longtime side effects. There were many more patients in 2021 referred to lung function tests, and a new additional room and equipment came end of the year. Thank you very much to DIA, Center Director Helle Konradsen, MD, DMSc, and Vice Director Lene Ørnstrup Christensen

We still spend extra time every day due to the old malfunctioning Agfa RIS/PACS ICT system with its lack of stability and performance. The Capital Region of Denmark has initialized the procurement of a new system to all the hospitals in the region, and Consultant Johan Löfgren and Professor and Head of Department Liselotte Højgaard have together with many other experts from the department and outside worked hard for a new solution with a modern, well-

functioning, state-of-the-art system. The contract will be signed Spring 2022.

The absolute highlight of the year was the opening of the two new “super-scanners” October 26 2021. Our CEO, Hospital Director Per Christiansen welcomed the guests of honor Birthe Meyer, Gitte Meyer Brandt and Søren Drost-Nissen from The John and Birthe Meyer Foundation. The new rooms in the Finsen Building were designed nicely for patients, staff and the new scanners: the PET/MRI mMR and the Siemens QUADRA total body PET/CT. Thank you very much to the John and Birthe Meyer Foundation for all the generosity and thank you very much to the Capital Region of Denmark, to our CEO Per Christiansen, and the Center Director Helle Konradsen for making it possible.

Research and innovation are key activities of our department, and we have a comprehensive research

program directed towards innovative solutions to solve unmet clinical needs. 2021 was the hitherto finest year with > 170 peer review publications. Our special focus is on implementation of personalized medicine in collaboration with other research groups at Rigshospitalet and internationally. AI, artificial intelligence, is another new important research area with the young research group CAAI, Clinically Applied Artificial Intelligence. To all our research groups: A sincere thank you for the dedicated and important work. During this second Corona-year we have tried to protect the research projects, but of course the situation has led to some unavoidable postponements.

Due to prohibition of larger meetings and travel, conferences were changed to e-learning and webinars, and the educational situation adapted to the new conditions. We have used a lot of e-learning but look much forward to conferences and meetings in Denmark and abroad next year.

Thank you very much to Center Director Helle Konradsen, MD, DMSc, and Vice Director Lene Ørnstrup Christensen for help, support, and collaboration throughout the year.

Thank you to the Department of Radiology, Head of Department Martin Lundsgaard Hansen, and Chief Radiographer Johnny Madelung, for an excellent collaboration throughout the year

We would like to praise the great achievements of our staff from the youngest newly arrived technologist to the most senior professor. We are “clinician scientist” working in an interdisciplinary team effort, where all are engaged and striving towards the best patient treatment, research, innovation, and education – in a positive and friendly working environment with equity, diversity and inclusion.

Our aim is to deliver the best patient treatment and the best research and education. Thank you to all staff members, collaborators and international colleagues for making this possible – also in this Corona year 2.

Liselotte Højgaard,
MD, DMSc
Professor,
Head of Department

Ida Kjær Robsøe,
MPG, Chief Nuclear
Medicine Technologist





Mission and objectives

We strive to provide the best for each and every patient:

- ▶ Clinical physiology and nuclear medicine patient investigations and treatment
- ▶ Research at the highest international level
- ▶ Undergraduate and postgraduate education
- ▶ Good patient experiences through state-of-the-art quality, high patient security and focus on the wellbeing of each patient
- ▶ The best possible everyday worklife for all staff members

Highlights 2021



Cyclotron and Radiochemistry Section

The Cyclotron and the Radiochemistry sections have been united to one strong unit with a team leadership: Jacob Madsen (Head of Cyclotron and Radiochemistry Section, Chief Radiochemist), Nic Gillings (Chief Radiochemist, QP), Holger Jensen (Cyclotron Chief) and Tina Wikke Hallund (Staff Technologist).



Children with neuroblastoma

As the first and only hospital in Northern Europe we initiated treatment of children with cerebral neuroblastoma with the new OmburtaMAB, targeted treatment developed at SKCCNY. Prior to this treatment the prognosis was poor, now most of the children can be treated.



Alexander Foss Gold Medal

Liselotte Højgaard, Professor and Head of Department, member of the ERC Scientific Council, received the Alexander Foss Gold Medal from DTU, The Technical University of Denmark.



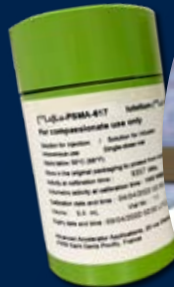
Hyper-PET

We obtained permission to human use of our hyperpolarized tracers for PET/MRI, and the preclinical program can now be extended into clinical use.



Malene Fischer, new professor

September 1, Malene Fischer, was appointed new professor in clinical physiology and nuclear medicine with special focus on hybrid imaging and PET oncology.



PSMA Treatment

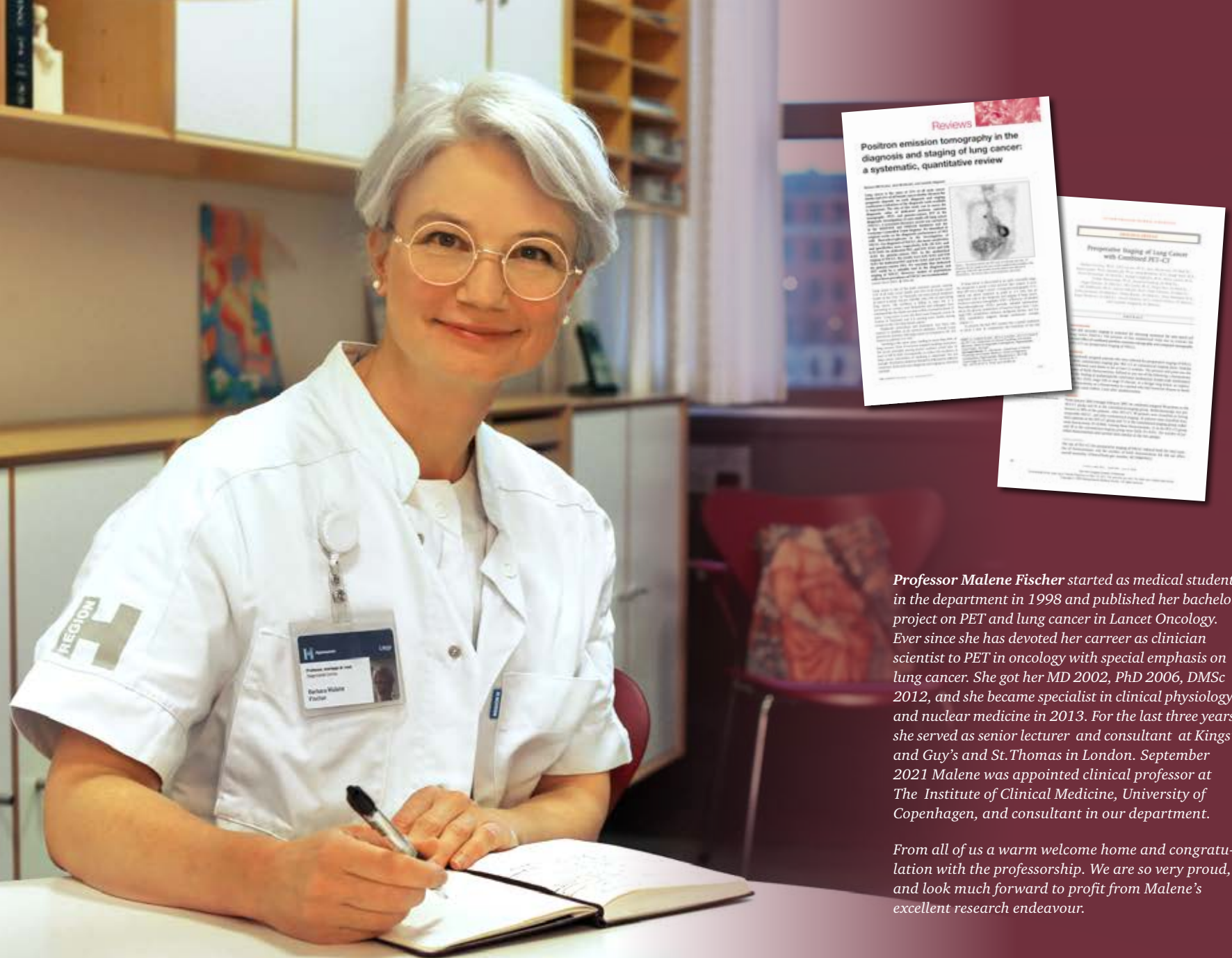
Patients with prostate cancer were treated with Lu-177 PSMA in an international protocol. The treatment seems of great benefit for patients.



Opening of our two new Superscanners

The new PET/MRI and the new QUADRA total body PET/CT were opened with symposium and reception Monday, October 26, by Per Christiansen, CEO Rigshospitalet and our guests of honor from The John and Birthe Meyer Foundation. Birthe Meyer, Gitte Meyer Brandt and Søren Drost-Nissen together with guests and friends from abroad and Denmark.





Professor Malene Fischer started as medical student in the department in 1998 and published her bachelor project on PET and lung cancer in Lancet Oncology. Ever since she has devoted her career as clinician scientist to PET in oncology with special emphasis on lung cancer. She got her MD 2002, PhD 2006, DMSc 2012, and she became specialist in clinical physiology and nuclear medicine in 2013. For the last three years she served as senior lecturer and consultant at Kings' and Guy's and St. Thomas in London. September 2021 Malene was appointed clinical professor at The Institute of Clinical Medicine, University of Copenhagen, and consultant in our department.

From all of us a warm welcome home and congratulation with the professorship. We are so very proud, and look much forward to profit from Malene's excellent research endeavour.

Professor accession

The common thread of Malene Fischer's research is the exploration and implementation of functional imaging in diagnosing and treatment of patients with cancer. Her research is always multidisciplinary and the overall purpose being to improve diagnosis and treatment for patients, often involves modalities other than imaging. An example of this being the SUPE_R trial, a national randomized trial on surveillance after treatment for lung cancer, exploring the use of PET and ctDNA as well as quality of life and costs. The trial is led by Malene Fischer and finalized recruitment of the planned 750 patients in December 2021. Other examples of research projects initiated and completed by Malene Fischer during the last 5-years includes studies on the feasibility of PET/MR as a one-stop shop for radiotherapy planning in head-and-neck and cervical cancer, FLT-PET/CT for improved diagnosis of relapse after radiotherapy in patients with lung cancer and studies on response prediction and early response evaluation using FDG-PET/CT, immunological profiling and ctDNA.

Malene Fischer returns from a position as senior lecturer at the School of Biomedical Engineering and Imaging Sciences at Kings College London- Finally and honorary consultant at The PET Centre at Guy's & St Thomas Hospital in London. A position she has held since 2018. During her years at Kings College London she has been working with leading experts on clinical projects in infection, lymphoma and radiotherapy as well as on the use of AI in hybrid imaging with a special focus on information on healthy tissue metabolism and possible impact on side effects and patient outcome. Malene Fischer will continue her engagement with Kings College London in an adjunct position.

In her new role as professor Malene Fischer will be responsible for oncology PET research, implementation of the new Quadra PET/CT as well as leading her research group CRHIC (Clinical Research on Hybrid Imaging in Cancer). CRHIC works to improve treatment of patients with cancer through improved diagnosis and tissue characterization. The

group currently consists of 10 dedicated people with a background in medicine, engineering, physics, or computer science. However, the roots are firmly planted in clinical soil and with implementation as a key goal. All research projects are performed in collaboration with clinical and paraclinical colleagues at Rigshospitalet, as well as with national and international collaborators. Examples of on-going and planned projects are evaluation and implementation of improved follow-up of patients with lung, improved tumor characterization and staging of patients with gastrointestinal cancer by evaluating a new tracer (FAPI) and total body PET/CT and application of AI-based methods to a) explore the predictive value of healthy tissue metabolism on side-effects and outcome in cancer patients and b) extract imaging biomarkers to enable automated integration with other clinical data. Last, but not least clinical implementation and exploration of the perspectives rendered possible with the new total body PET/CT will be on the top of the agenda.



Nuclear medicine technologists, radiographers, nurses, and laboratory technicians

Chief Nuclear Medicine Technologist, MPG Ida Kjær Robsøe

There are high expectations for excellent quality, rapid examinations, and coherent procedures for all our patients. This requires a fully dedicated and well-trained staff to succeed - every day. We are most grateful to all our many technologists, radiographers, nurses, and laboratory technicians, who contribute to fulfill this so very nicely every day.

2021 has been characterized by an increased demand for our examinations and to accomplish this, we have focused on optimizing utilization of

our equipment, such as gamma-cameras, PET/CT scanners etc. The opening hours of the department was extended with consequent changes in the working schedule and organisation for the staff. We would like to thank everyone for the good cooperation implementing these changes. We have succeeded in ensuring both patient treatment and a good work-life balance for the staff.

Keeping our well-trained employees as well as recruitment of new employees is, as in the

surrounding society, an increasing challenge. We are most grateful for the many experienced members of the staff, who have stayed for many years, and we are committed to be as attractive a department as possible. First of all, education, courses and training have been prioritized. Next we try to involve and encourage everyone in professional teams, developmental work and innovation. We see this as both beneficial for the department and for the enthusiastic employees.





Nuclear medicine technologists, radiographers, nurses, and laboratory technicians

Despite 2021 having been a year with several cancelled meetings, we have participated in *The World Congress of the International Federation of Biomedical Laboratory Science (IFBLS)*. Clinical Teacher Mia Hjorth Albers together with three colleagues from Rigshospitalet, contributed with the presentation “Let somebody else teach – with Inquiry Based Science Education” and furthermore Mia Hjorth Albers together with a colleague from department of Pathology presented a poster: “Inquiry based Science Education (IBSE) – New eyes on biomedical Laboratory Scientists teaching in clinical departments”. At the European Congress EANM, Technologist Marianne Federspiel contributed with the presentation “Safety and radiation protection in a hybrid PET/MRI scanner”. Thank you to both of you, for representing us so well.

To ensure the best education for students and to support innovation and progress for the staff, we have chosen to upgrade the numbers of certified teachers, so we now are privileged to have both technologists and a radiographer dedicated this important task.

In 2021 two of our technologists, Kristin Varpe and Nynne Abrahamsen were accepted at UCSF, Scientist class for healthcare bachelors, University of Copenhagen. Thank you to Professor Jann Mortensen and Professor Malene Fischer for their great help in the process.



This year we are also pleased to congratulate Technologist Marianne Federspiel, mentioned above, on her 25-year anniversary as technologist in the department. Marianne is a notable member of our staff, the latest years with special association to PET/MR.

Marianne is also Vice Chair of ‘Lokalt MED-udvalg’ (the department’s cooperation committee).

Also, this year, we celebrated Staff Technologist Anne Sørensen at her 40-years anniversary in the department. Anne joined the staff in 1981 and is appreciated especially for her many years at the Radiochemistry Section.

Organisation

After more than 40 years at the department, and the last years as Staff Technologist Anne Sørensen retired October 2021. We are grateful for her dedicated and wise contributions to the Radiochemistry Section throughout the many years. We will all miss her, but she leaves behind a laboratory in good shape. From all of us, a warm thank you and the best wishes for a happy life further on.

Technologist Tina Wikke Hallund, who is a familiar face in the laboratory, took over as staff technologist at the Radiochemistry at 1. November 2021. We are looking forward to the cooperation.



Thank you to Anne Sørensen



Welcome to Tina Wikke Hallund





KF section

Head of Section, Consultant Lotte Hahn Enevoldsen and Nuclear Medicine Staff Technologist Mariam Hassan

The KF section offers a broad variety of nuclear medicine examinations. Among these are SPECT/CT and scintigraphy for various oncological, pulmonary, endocrine, and nephrourological diseases. Other frequent investigations are PET/CT for cardiac, neuroendocrine, and pediatric diseases. Furthermore, DXA-scan for bone mineral density, lung function test and DTPA-clearance for GFR measurement are performed in our section. In 2021 we introduced the use of diagnostic ultrasound in estimating LVEF in patients receiving potentially cardiotoxic chemotherapy. Furthermore, ultrasound is used as an adjunct in patients having thyroid diseases.

To provide these state-of-the-art nuclear medicine investigations we have a constant focus on study quality and patient-friendly procedures, and the implementation of new studies, new indication areas and acquisition of new equipment are all an integral part of the expanding field of nuclear medicine.

In addition to nuclear medicine diagnostics our section also comprises radionuclide therapy of patients with neuroendocrine tumors (^{177}Lu -DOTATATE), patients with castration resistant prostate cancer and symptomatic bone metastases (^{223}Ra), and patients with benign thyroid diseases (^{131}I -Iodine).

Furthermore, we participate in various weekly and monthly multidisciplinary team conferences discussing neuroendocrine tumors, thyroid diseases, adrenal diseases, cardiac diseases, and lung diseases with our clinical colleagues.

Glostrup Section

Head of Section, Consultant Lotte Hahn Enevoldsen and Nuclear Medicine Staff Technologist Helle Møllegård Dahl

Offering a variety of nuclear medicine and clinical physiological examinations Glostrup Section examines patients hospitalized at the Glostrup location of Rigshospitalet as well as patients from the Glostrup outpatient clinics and patients from general practice in the surrounding area.

In close collaboration with our colleagues in the PET Scanner Section we examine patients referred from both Glostrup and the PET Scanner Section with wholebody ¹⁸F-FDG PET/CT scans as well as dedicated brain scans for Parkinson’s disease.

Bone scintigraphy for rheumatologic diseases and evaluation of spine surgery with various prostheses are performed in patients referred from Center for Rheumatology and Spine Diseases, Rigshospitalet.

We diagnose renal artery stenoses in adults and children with Doppler ultrasound of renal arteries, receiving patients from the Capital Region of Denmark and the Region of Sealand, and participate in the multidisciplinary conferences on invasive treatment of renovascular disease in Eastern Denmark.

Diagnostic ultrasound is also used together with thyroid scintigraphy in patients with thyroid diseases.

We perform subacute examinations of the carotid arteries with Doppler ultrasound for plaques and stenoses in all patients entering the hospital with stroke or transitory ischemia as part of the National Stroke Prevention Program.

In cooperation with the Geriatric Falls Clinics we perform tilt table tests, 24-hour blood pressure measurements and DXA-scans for bone density, body composition and screening for sarcopenia.

We also perform tilt table tests to investigate autonomous neural dysfunction and unexplained syncope.

Other physiological examinations offered are testing of lung function, blood pressure measurements on the extremities in patients with claudication or ulcers, as well as 24-hour measurement of systemic blood pressure for diagnosis and evaluation of hypertension in adults and children.



PET Scanner Section

Head of Section, Consultant Annika Loft Jakobsen and Nuclear Medicine Staff Technologist Maria Pejtersen

In the complex world of personalized medicine PET/CT has a natural place for patients suffering from oncological or inflammatory diseases not only in helping to diagnose, stage and depict the right patients for the right treatment, but also to monitor their treatment. We work in close collaboration with clinical colleagues as well as researchers from different fields.

We have implemented new digital PET/CT scanners and the total body Quadra PET/CT with increased sensitivity and improved image quality at high scan speed. This enables us to increase through-put to meet the increasing demand from the clinical departments. This implementation has caused a larger refurbishment of the department.

In our daily clinical life, ¹⁸F-FDG PET/CT is the work horse investigation for a vast amount of indications but use of ⁶⁸Ga- and ¹⁸F-PSMA for prostate cancer patients is increasing. FDG PET/CT is included in clinical radiotherapy planning in collaboration with the department of Radiotherapy. We also participate in research protocols to optimize the methods including PET/MRI and to increase the use of other tracers. FDG PET/CT also plays an increasing role in the management of patients with inflammatory and infectious diseases in diagnosing as well as treatment monitoring, an exciting area to exploit in the clinical every-day work as well as in research.

Our dedicated team of nuclear medicine physicians, radiologists, technologists, and radio-

graphers are involved in research protocols and clinical trials testing new treatments as well as new PET tracers. This is an important and inspirational part of the daily work with patients which improves our knowledge to their diseases. As a result of this work, we have implemented new indications and scanning procedures.

The total body QUADRA PET/CT scanner and artificial intelligence improves image quality in combination with radiation dose reduction and shorter scan time which is highly appreciated by our patients. The possibility of reducing the radiation doses to the staff is also an important issue that always has the highest concern.





Cardiac Investigations

Consultant Philip Hasbak

Rigshospitalet was the first hospital in Scandinavia and one of the first in Europe to introduce Rubidium-PET. A cardiac rubidium-PET test can provide information about blood flow to the heart muscle at rest and during stress, assess damage to the heart muscle from a prior heart attack, and provide information about the pumping function of the heart.

At Rigshospitalet there is a special need to provide cardiac PET every day, since a large proportion of our patients with ischemic heart disease need an acute or sub-acute work-up that requires quick decision making as to coronary revascularisation strategy. Patients with unstable angina or non-STEMI should be revascularized with percutaneous coronary intervention (PCI) within 3 days after admission or with coronary artery bypass graft surgery (CABG) within 5-7 days according to The Danish National Board of Health. Non-invasive assessment of myocardial function is an important

domain of cardiac rubidium-PET. Traditionally, cardiac PET images have been visually interpreted, using uptake as a measure of function. This approach, however, takes only a fraction of the full PET information into account. The application of tracer kinetic modelling to dynamically measured data is able to extract objective measures of perfusion and/or metabolism, depending on the tracer. While such true cardiac quantification has been troublesome and time-consuming in the past our new cardiac tools now makes this state-of-the-art technology readily available.

Further, we offer CT coronary angiography (CTCA) which is useful for planning many invasive cardiac procedures, particularly complex PCI procedures including chronic total occlusions (CTOs) and bifurcation stenting.

Fluorodeoxyglucose (FDG) positron emission tomography (PET) cardiology viability imaging

is used in patients with known heart disease or those who have had a heart attack. The test assesses the level of heart muscle damage by injecting glucose (sugar) and then determining which areas of the heart are using the glucose. Damaged heart muscle will not use glucose, while healthy (or recovering) heart muscle will.

Cardiac sarcoid FDG PET imaging is used in individuals with known or suspected sarcoidosis, an autoimmune disease that can cause inflammation and arrhythmias. This test helps to detect areas of sarcoid.

Further we use pyrophosphate imaging to assess the presence of transthyretin amyloidose in the heart.

Research-wise we have a close and good cooperation with various clinical departments.



Lung investigations

Professor Jann Mortensen and Associate Professor Ronan Berg

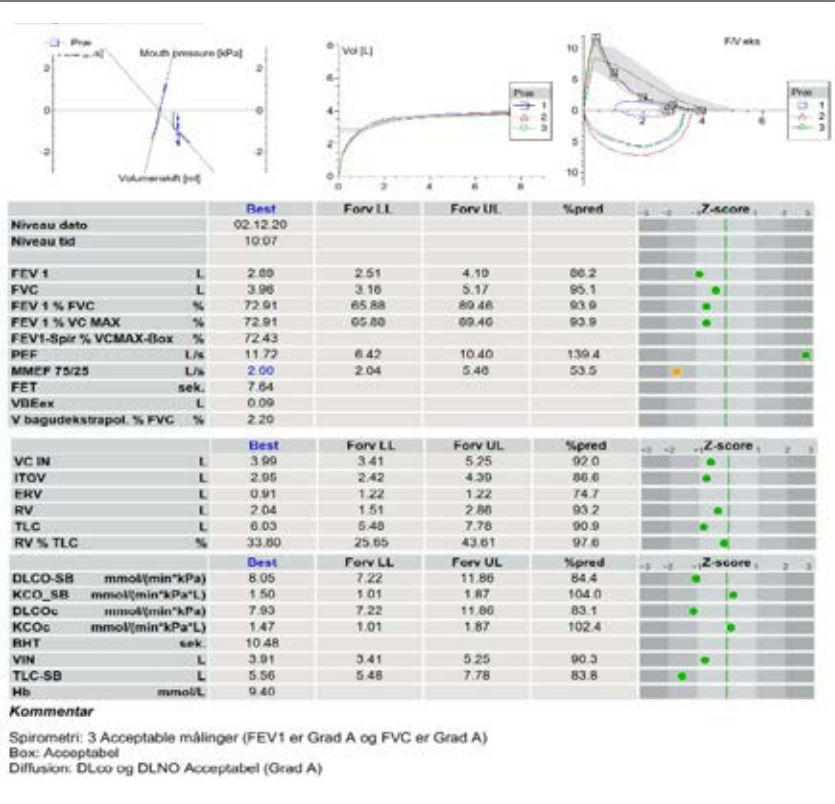
Lung function tests such as spirometry, body plethysmography and diffusion capacity are routinely performed for diagnosis and monitoring in patients with COPD and emphysema, many types of cancer and hematologic diseases, before thoracic surgery and radiation treatment, and pulmonary hypertension. If needed, we have now added measurements of respiratory muscle strength, mannitol provocation test, small airways disease with impulse oscillometry (IOS) and the forced oscillation technique (FOT), or multiple breath nitrogen washout (MBN2W), and dual tracer diffusion capacity (using both carbon

monoxide [CO] and nitric oxide [NO] as tracers) to our standard panel of lung function tests.

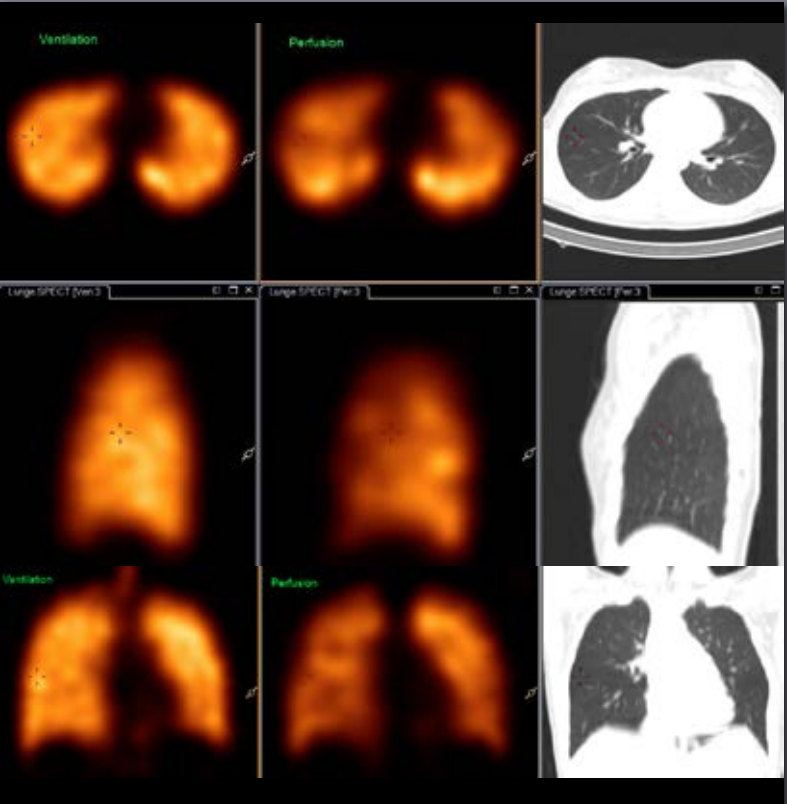
In terms of imaging, we were the first to implement simultaneous ventilation-perfusion (V/P) scintigraphy as SPECT/CT for the diagnosis of pulmonary embolism. The high diagnostic performance of V/P SPECT/CT combined with a relatively low radiation dose is a benefit to the many patients that we study before and after lung volume reduction, lung transplantation, lung cancer, and for the work-up of pulmonary embolism and pulmonary hypertension. Radioaerosol

inhalation and subsequent bronchoscintigraphy was developed by us to assess mucociliary clearance in patients with lung diseases e.g. recurrent lung infections. We use it for diagnosing primary ciliary dyskinesia and to assess if mucus transport can be increased by intervention e.g. physiotherapy or salt inhalation.

The above mentioned diagnostic methods are used in the daily clinical routine as well as in clinical research studies. Two examples are given below.



Example 1 is a clinical routine lung function report that includes spirometry, body plethysmography and measurement of the diffusion capacity of carbon monoxide. The lung function was normal in this patient.



Example 2. V/P SPECT/CT was performed in a patient suspected of having pulmonary embolism. The scan shows multiple small mismatched perfusion defects. Hence bilateral pulmonary embolism was diagnosed.



Pediatric Nuclear Medicine

Consultant Lise Borgwardt

In 2021 we performed more than 3,000 pediatric nuclear medicine investigations. It is a special focus area for our clinic to perform children’s investigations at the highest level of excellence, and at the same time make it a positive experience for both the child and parents.

This year we implemented and started treating children and adolescents for relapsed or refractory cancers with intrathecal radio-immunotherapy in a close collaboration between the teams of pediatric oncology and pediatric nuclear medicine. The effort included a clinical trial with intrathecal iodine-131-omburtamab for intradural neuroblastoma (NCT03275402) and a first-in-human phase 1 trial of intrathecal lutetium-177-DTPA-omburtamab for relapsed or refractory medulloblastoma (NCT04167618). As some of the treatments necessitate hospitalization for up to 4 days, we also established a unit for radionuclide treatments in children at the Department for Clinical Physiology and Nuclear Medicine.

Late this year we started scanning children at our new Total Body PET-scanner. Early experience has

demonstrated very high sensitivity and improved image quality enabling ultra-fast or low dose scanning and the increased sensitivity can enable avoidance of general and sedation by fast and flexible PET acquisition. It will be very interesting to develop the concept in pediatric PET, as we get more experience the coming months and years.

We have been continuing the cooperation of the organisational work on preparing our new Children’s Hospital Copenhagen. The project is very visionary and contains a large Diagnostic Unit where Pediatric Nuclear Medicine, among other diagnostic specialties, will be located. We plan to develop an integration of the diagnostic specialties in a 24/7 MDT where the individual child is being discussed in a synergistic continuous diagnostic process with the purpose of accelerated personalized diagnostics and treatment. The Children’s Hospital Copenhagen will be finished 2025 and this year we started building it.

We already have a children’s section integrated in our department with a children-friendly atmosphere with a new vision PET/CT, SPECT/CT,

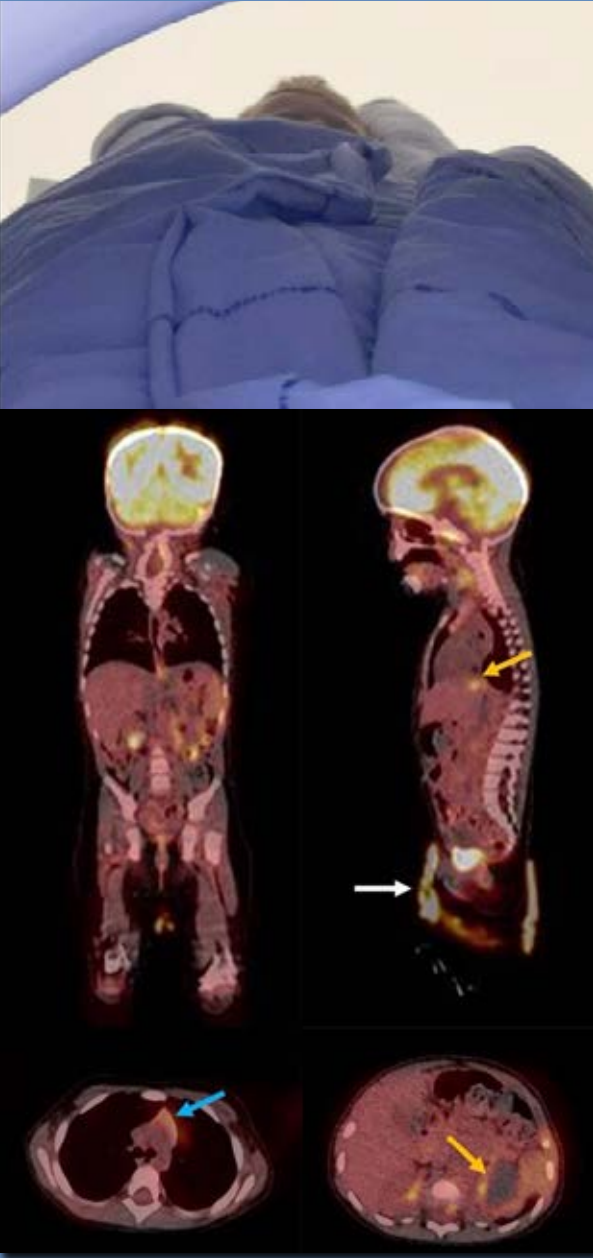
EDTA Clearance room and a renography room. PET/MR-scans are performed in the PET-section. In each scanner-room in the children’s section, high quality projectors are showing films at the ceiling to secure and entertain the child during the scan. In the waiting area the children have the opportunity to watch the animated decorations, use apps or watch films at the tablets giving when entering the section or play in the toy corner.

Our multidisciplinary pediatric hematology and oncology conferences are presented as a web-based nuclear medical platform combined with videoconference including districts outside the capital, so we now have patients for national multidisciplinary conference once a week. Our pediatric collaborators are very pleased with the possibilities and the advantages in the diagnostic evaluation of the children.

Research in Pediatric Nuclear Medicine and PET is necessary, as we have an increasing number of medical doctors, PhD-students and technicians involved in the field. The department undertakes many pediatric investigations including partici-

pation in an array of prospective studies. These research protocols, using of PET and SPECT, are carried out in cooperation with clinical departments, particularly within oncology and infections with FDG PET, kidney parenchyma studies and studies of the function of the hepato-biliary system. In this area we conduct research protocols in children with acute- and chronic liver diseases incl. translational piglet studies and the 2. PhD in the field was started this year. Furthermore, we have conducted protocols in pediatric non-oncological PET/MRI and our data from the pediatric PET/MRI protocol for children with CNS tumors are being analyzed. We started up AI- projects in pediatric oncological diseases.

In 2021 we continued participating in randomized clinical trials for experimental immunotherapy for children with cancer as a part of the Nordic Center for these treatments. We are part of the EpSSG in the Radiology Committee, participating in conducting the new European protocol and the SIOPE. Also targeted radionuclide therapy for cancer in children is currently an area of intense interest.



No sedation used at PET-scanning a 17 months-old girl

Total-Body PET (TBP) and long axial field-of-view (LAFOV) PET are game-changing innovations at the threshold of clinical implementation. Early experience has demonstrated very high sensitivity and improved image quality enabling ultra-fast or low-dose scanning. This scan illustrates how the increased sensitivity can enable avoidance of general anesthesia and sedation by fast and flexible PET acquisition in a 17 months-old girl admitted after 12 days of intermitting high fever and episodes of vomiting, earlier known with left heminephrectomy due to duplex kidney and repeated symptomatic urinary tract infections. Biochemical findings of B-leucocytes 22 E9/L, P-CRP 165 mg/L. No other abnormal findings. Referred to PET/CT to rule out underlying malignancy or focal infection. Atypical Kawasaki syndrome was suspected. The patient was treated with two series of IVIG and high dose ASA, after which the temperature normalized.

Figure 1: PET/CT in coronal (A), sagittal (B) and axial (C) reconstructions. Physiological FDG accumulation seen in the thymus (blue arrow), luminally in the anal part of the oesophagus and the stomach wall (yellow arrow). No pathological FDG accumulation was seen in the remaining left-sided duplex kidney. Accumulated urinary radiotracer activity in the diaper (despite being changed just before scanning) (white arrow).

RIS/PACS

Consultant Johan Löfgren

The Region has, since the first installation, had huge problems with our current RIS/PACS system. Problems including slow performance, lack of stability, client crashes, trouble with speech recognition and a few but alarming reports of patient mix-up. The extra expenditure for our budget and the negative influence on our daily workflow has been major.

Thanks to our Head of Department, Professor Liselotte Højgaard, and Sundhedsfaglig råd (the Speciality Counsel) for both radiology and clinical physiology and nuclear medicine in Region H, there was in 2020 taken a political decision to

start the process to buy a new RIS/PACS system. All imaging departments in the region understand that it means a lot of hard work but it's the only way to a future proof RIS/PACS system and patient safe operation.

In January 2021 the regional IT department in close collaboration with the hospitals imaging departments started an accelerated process to generate a requirement specification for a new RIS/PACS system. In June the tender was published and after a prequalification process qualifying 3 vendors, the autumn was spent on negotiations and clarifications with these 3 vendors.

Many experts from the Imaging Departments have spent a lot of time and effort on this, and I have had the privilege of chairing the "Clinical Working Group" leading the process together with the chief physician from Radiology, Dr. Thomas Axelsen.

In May 2022 we hope to sign a contract with one vendor, who will fulfil our hope for a brighter future, where IT is a true tool that support us in our everyday work and help us take clinical physiology and nuclear medicine to the next level with research, artificial intelligence, big data, advanced visualization and personalized medicine.



The Physicist and Technology Group

Chief Physicist Thomas Levin Klausen

The Physicist and Technology Group (physicists, engineers and computer scientists) is involved in many aspects of the work in the clinic. Our primary responsibility is to enhance, daily and on location, radiation safety and patient dosimetry. We are also responsible for optimization and maintenance of all our scanners (see Equipment), handling and storing of patient data and conducting and facilitating clinical research in the department.

This year’s most spectacular addition to our equipment portfolio was the procurement of the Siemens Vision Quadra that arrived on a rainy 17th of August. It is a total-body PET/CT system with an axial field of view of 108 cm and consequently a highly increased sensitivity. It allows scans with hitherto unseen low activity,

short imaging time, or a combination of the two. It also makes it feasible to perform dynamic scans of brain and trunk simultaneously with full time coverage without moving the patient.

The system is basically composed of 4, only slightly modified, Siemens Vision systems – therefore the name “Quadra” – providing a total of 320 detector elements (rings) in the axial direction and giving rise to an increase in sensitivity with a factor of 8 for a single bed position covering 78 cm (se Figure 1). In the first software release only coincidences up to a maximum ring difference of 85 are available, and only one bed position can be performed. Once the full ring difference can be exploited and continuous bed motion applied, the advantages of sensitivity will be even more impressive.

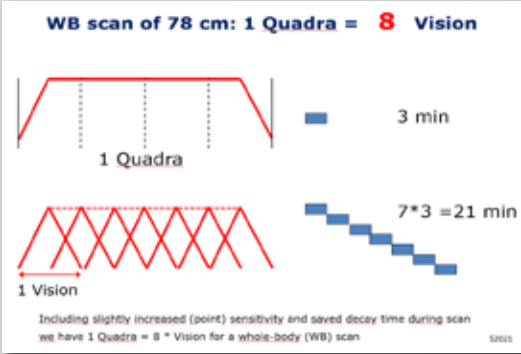


Figure 1

Several research and clinical studies have been launched to take advantage of this exciting new instrument.

The Physicist and Technology Group



Photos from Quadra installation

Artificial Intelligence

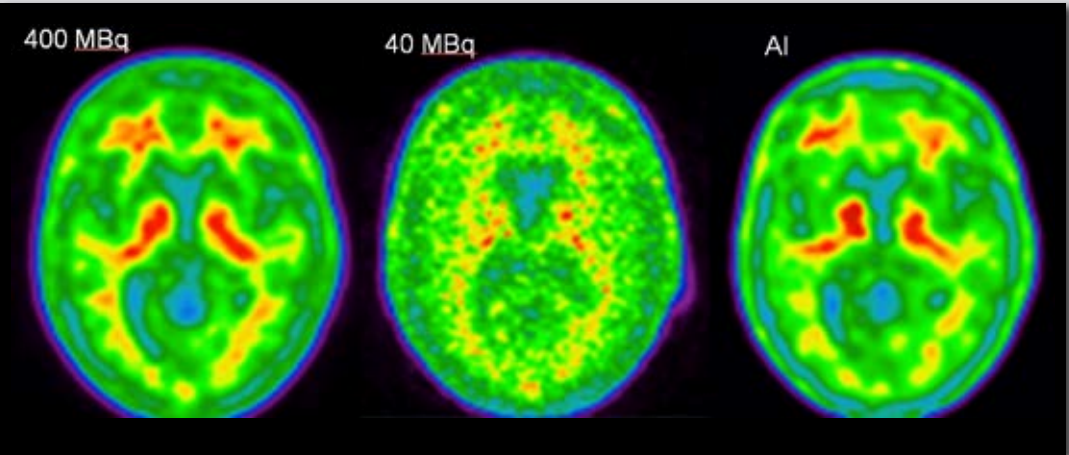
As Artificial intelligence (AI) continues to grow quickly the Physicist and Technology Group gets more and more involved in AI solutions for patient diagnosis and patient treatment. At our department we have formed a program for Clinically Applied Artificial Intelligence (CAAI) with the sole purpose of bringing AI into clinical routine in close dialogue with the clinicians. The group is led by Computer Scientists Flemming Littrup Andersen and Claes Ladefoged, and further comprises pre-graduate students, PhD students and post docs. The primary research areas have been directed towards data domain translation synthetic images generation, lesion segmentation and general noise reduction of image data. Noise reduction, which in medical imaging translates to lower radioactivity dose or shorter scan-

ning time both to great benefit for the patients, received a 2.5 million DKK grant from Danske Regioner, and several projects have been started within this area covering a number of organs. An example is shown in Figure 2 where a PiB amyloid imaging, used to diagnose Alzheimer’s disease, is reduced in dosis by a factor of 10 while still producing images of clinical quality.

With the installation of the new total body PET scanner (The Siemens Vision Quadra mentioned above), the focus has been to facilitate advanced analysis capabilities as well as data handling. A 10 Gbit fiber optic network has been installed serving storage of 0.7 PB of data with matching analysis computers capable of handling the huge amount of data produced by the scanner. Pipelines have been set up for kinetic analysis of glucose metab-

olism using FDG (See Figure 3) and of perfusion scans using ^{15}O -water, applied to clinical routine.

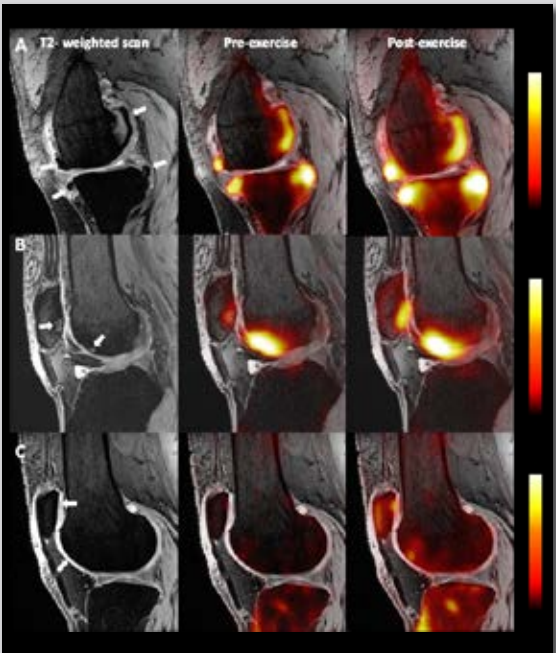
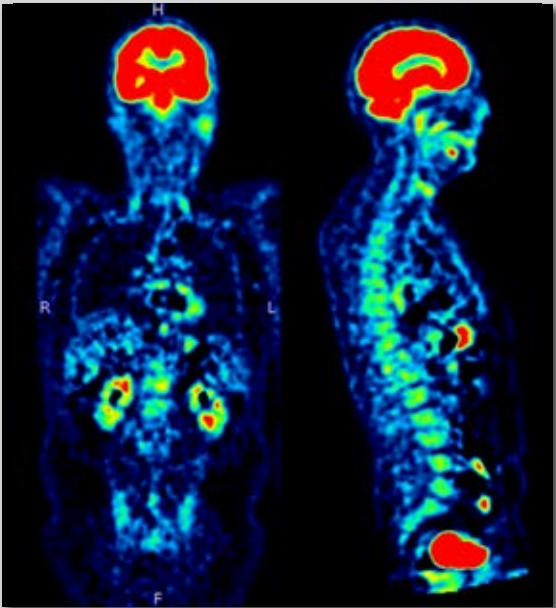
In 2021 the Physicist and Technology Group has continued its collaboration with the Department of Radiology at Stanford University to further develop the use of tracer kinetics in mapping bone physiology. The aim of the project is to enable an early diagnosis of bone pathology and provide a means to monitor response to treatment. In this work, higher $[^{18}\text{F}]\text{NaF}$ uptake after exercise was found to be predictive of onset of OA as opposed to current routine examinations. Areas without observed OA pathology that displayed focally large $[^{18}\text{F}]\text{NaF}$ increases after exercise were confirmed to be future locations of OA structural changes by means of a two-year follow-up study (see Figure 2).



▲ **Figure 2:** Positive PET scan at normal dose (left), simulated $1/10^{\text{th}}$ dose (center) and AI recovered image (right).

▼ **Figure 3** illustrates the unique capabilities of the Quadra scanner to visualize the local net influx rate (K_i) of glucose in one field of view. Here a Patlak plot is used showing high K_i in brain, heart, kidney and red bone marrow (spine).

► **Figure 4:** T_2 -weighted MR images (left), and SUV maps showing $[^{18}\text{F}]\text{NaF}$ uptake before exercise (center) and after exercise (right). ROIs with $\Delta\text{SUV}_{\text{max}} \geq 5$ corresponded to areas with elevated SUV at Scan 1 and structural features such as osteophytes (A) and bone marrow lesions (B). In some cases, bone areas that appeared unremarkable on MRI and SUV maps at Scan 1 (C) also displayed focally elevated uptake of $[^{18}\text{F}]\text{NaF}$. A follow-up study found these cases to be an early predictor of OA structural changes.



Neuro PET

Professor, Consultant Ian Law and Consultant Otto Mølby Henriksen

In the neuro PET group we continuously strive to improve the use and availability of PET and hybrid imaging in routine clinical brain imaging, and to further explore hybrid imaging of brain physiology in both the diseased and healthy brain. Collaborating with international and clinical research partners, a number of clinical and basic science projects explore the use of the most recent development in radiopharmaceuticals and MRI.

The glucose analog 2- ^{18}F Fluoro-2-deoxy-D-glucose (2- ^{18}F FDG) showing the functional integrity of the brain remains the backbone of clinical imaging of dementia and epilepsy. In the workout if neurodegeneration we further provide imaging with ^{11}C PIB for evaluation of cerebral amyloid in Alzheimer's disease, and ^{18}F FE-PE2I

for assessment of Parkinsonism. We are increasingly serving regional and extra regional memory and movement disorder clinics with imaging in this field. We use ^{15}O H_2O for quantification of cerebral blood flow reserve in patients with carotid occlusions and chronic ischemia. The total body PET/CT system has enabled this to be performed non-invasively with high precision and little discomfort for patients (Figure 1).

For brain tumors we supplement MRI with PET images using the amino acid analogue ^{18}F Flouro-Ethyl-Tyrosine (^{18}F FET) for gliomas, and the somatostatin II receptor ligand ^{68}Ga DOTA-TOC for meningiomas. The latter has expanded particularly in the identification of post-operative tumor remnants, not identifiable on MRI



Neuro PET



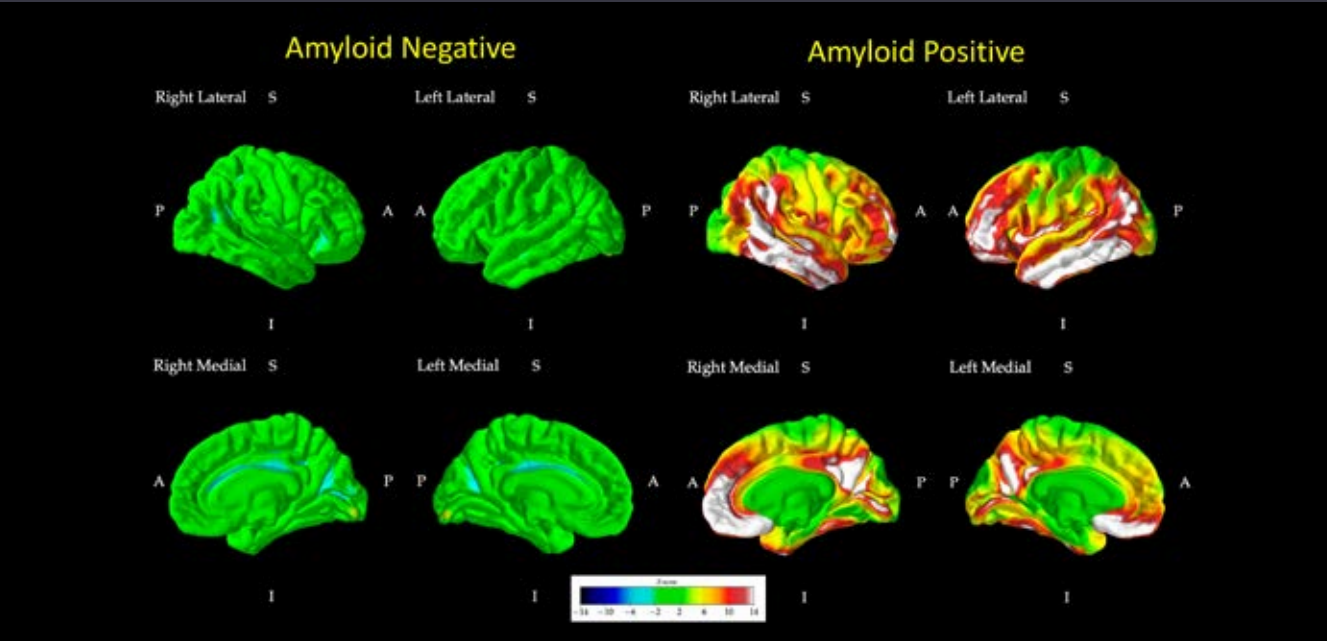
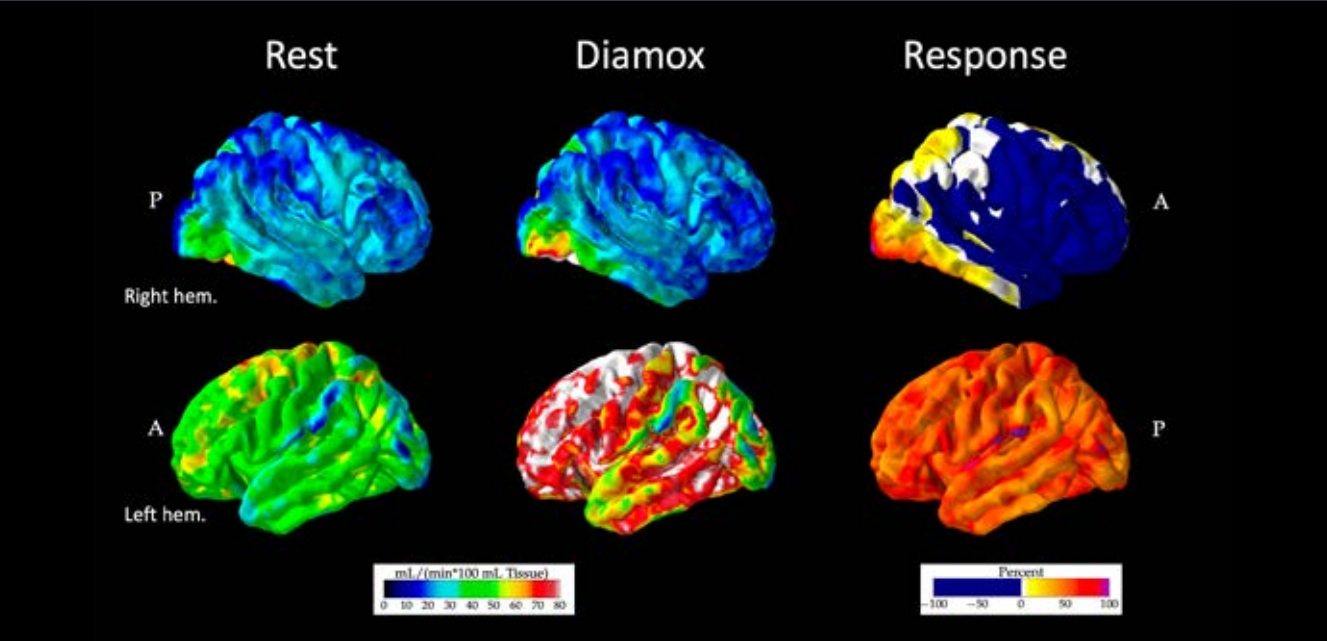
Our Siemens hybrid PET/MR scanners allow a comprehensive structural and functional evaluation of brain pathologies within a single imaging session, and is not only a powerful research tool, but now also fully implemented in routine clinical investigations of patients with dementia and brain tumors and in increasing use. This also allows us to evaluate the potential of various novel MRI techniques as supplements or alternatives to PET in patients referred for routine PET/MRI. The total body PET/CT system allows us to perform short scan sessions in patients, mainly children.

With the increasing demand of neuro PET examinations and increasing analytical complexity of particularly PET/MR studies, we have

implemented post-processing pipelines providing fully automated reports with standardized analyses of PET and MRI data supporting clinical interpretation and reporting. Reports are used routinely for hippocampal volumetric measurements showing reduction in Alzheimer’s disease, for identifying signs of Parkinsonism using [18F] FE-PE2I, for estimating the amyloid uptake found in Alzheimer’s disease using [11C]PIB and for identifying reduced cerebrovascular reserve using [15O]H2O (Figure).

► **Figure 1. Quantification of cerebral blood flow reserve**
A patient with right carotid occlusion and chronic ischemia prior to revascularizing surgery. Injections of [15OH2O] was used for absolute quantification of cerebral blood flow at rest (Left) and during vasodilation (Middle) with acetazolamide (Diamox™) non-invasively on the total body PET/CT system. While the response (right) is normal in the left hemisphere (bottom row), it is severely compromised in the right hemisphere (top row) showing a decrease in cerebral blood flow indicating a high risk of ischemic infarcts in these areas.

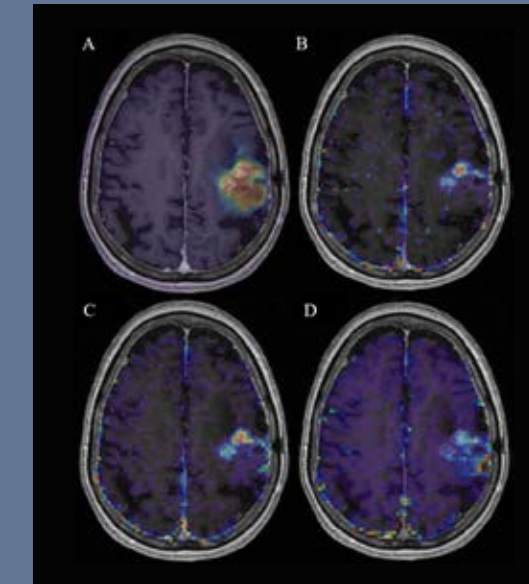
► **Figure 2. Automated quantification and presentation of cortical amyloid accumulation**
Two patients with memory impairment suspected of Alzheimer’s disease investigated with [11C]PiB PET scanning of the brain. A newly in-house developed automated analysis allows fast and standardized quantification of cortical amyloid accumulation, statistical analysis and presentation. Statistical surface projections of a typical amyloid negative patient (left), unlikely to have Alzheimer’s disease, and an amyloid positive patient (right), at increased risk of having Alzheimer’s disease. The projections aid the clinicians in the understanding of scan findings and in communicating these to the patient.





PET/MRI

► **Figure.** Multiparametric PET/MR images using O-(2-[¹⁸F]fluoroethyl)-L-tyrosine (¹⁸F-FET) uptake in suspected recurrent high grade glioma with Dynamic Contrast-Enhanced T₁-weighted MRI A) PET/MRI fused ¹⁸F-FET uptake 20-40 min. p.i. on T1 weighted MPRAGE with Gd B) permeability, K_i C) Extra-vascular, extra-cellular volume, V_e D) Blood volume, V_b



Consultant Johan Löfgren and Physicist Thomas Lund Andersen

With a second state-of-the-art Siemens Biograph mMR installed, we had the capacity to escalate both clinical and research PET-MRI activity in 2021, but the Corona pandemic hit the world hard and we unfortunately had to pause many of our research projects and instead focus on mitigating the spread of COVID-19 by thorough hygiene procedures and reducing the pressure on the scanners and personnel.

Hopefully now seeing the end of the pandemic we will be able to take the full advantage of our scanner capacity and further underlining the Department of Clinical Physiology and Nuclear Medicine at Rigshospitalet as one the world leading sites of PET/MRI with two concurrent PET/MRI installations.

PET/MRI offers a unique simultaneous combination of molecular imaging with anatomic and

functional MRI. These capabilities are being exploited in clinical, translational, and basic research, as well as for clinical examinations. The types of PET/MRI examinations performed at the department range from clinical dementia exams including static ¹⁸F-FDG PET and anatomic MRI with a duration of 20 minutes to dynamic PET acquisitions with kinetic modeling and physiologic MRI measurements which may last 1-2 hours. In 2021 the number of examinations performed was 1,042, out of which a vast majority were clinical.

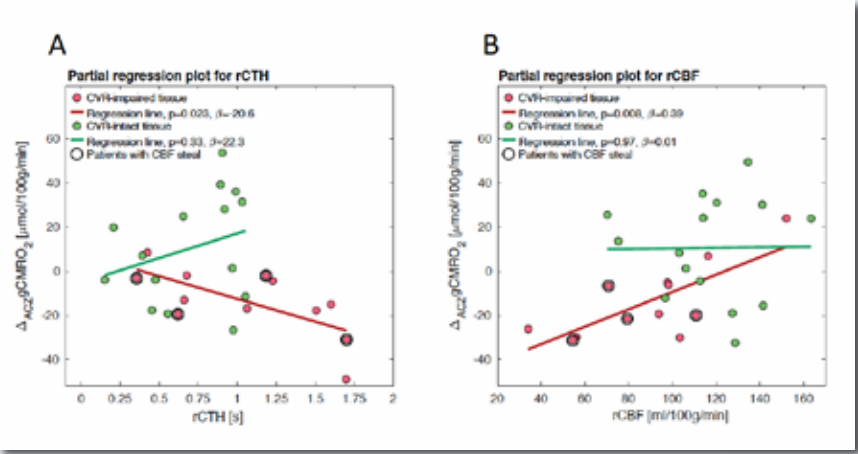
Clinical PET/MRI is undertaken primarily of patients with dementia, primarily Alzheimer’s disease, patients with brain tumors examined with ¹⁸F-FET PET and pediatric patients. Here, the simultaneous PET and MRI acquisition reduces the overall scan time and provides all indicated imaging within one session. Such a ‘one-stop-

shop’ examination provides a valuable logistic advantage for patients and relatives as well as for the diagnostic reading and minimizes PET/MRI misalignment. Since 2019 we have been using an Artificial Intelligence-based PET attenuation correction developed in the department in clinical routine for ¹⁸F-FDG PET brain examinations.

To further expand the clinical use of PET/MRI, many ongoing clinical research studies explore the utilization of PET and MRI in a synergistic fashion to improve patient management.

Indications investigated include lung cancer, head and neck cancer, gynecological cancer, neuro-oncology, dementia, pediatric oncology, and vascular and other inflammations. Finally, several clinical and pre-clinical research studies examine the utilization of combined PET and MRI to characterize the biology of disease.

MRI



Professor, Consultant Henrik BW Larsson

Brain oxygen consumption and brain capillary transit time heterogeneity.

Glucose and oxygen supply to brain tissue is governed by cerebral blood flow (CBF) – and especially by perfusion of brain capillaries, where transporter molecules extract glucose while oxygen is believed to passively diffuse into the neural tissue along an oxygen pressure gradient. The flux of these important compounds therefore relies on CBF.

In 1992 Kuschinsky and Paulson suggested that not only the level of perfusion per se was responsible for the delivery of nutrition to brain tissue, but also the perfusion pattern, i.e. the local distribution of capillary transit times along the capillary tree (1). This would be of relevance when the blood-brain barrier (BBB) is a hindrance for transport of the molecules into the brain tissue. A large variability of capillary transit times could result in a less efficient delivery of

substances over the BBB compared to a more even distribution of transit times. The capillaries with low perfusion will have insufficient delivery of substances whereas the highly perfused capillaries will contain sufficient substances but the diffusion across the BBB would be less likely due to the short transit time as described by the Crone-Renkin effect (2). This idea has been further theorized for oxygen delivery to brain tissue by Jespersen and Østergaard (3) and by mathematical models suggesting that a broad distribution capillary transit times, i.e. a large degree of capillary transit time heterogeneity (high CTH) will reduce oxygen delivery to the brain tissue even in highly perfused areas. However, direct verification of this idea is sparse in the literature.

We have experimental data, which directly shows that oxygen delivery is affected by CTH. A group of 34 patients with uni-lateral steno-occlusive disease, and typically also small vessel brain disease, clinically suspected of having reduced

cerebrovascular reserve capacity of brain vessels was clinically investigated by Single Photon Computed Tomography (SPECT) in conjunction with a acetazolamide (ACZ) test. As part of a research protocol all patients were additionally MRI scanned with Dynamic Contrast Enhanced (DCE) MRI using a conventional MR contrast agent, 20 minutes after infusion of ACZ. DCE was carried out simultaneous with injection of ^{99m}Tc -HMPAO. Global oxygen consumption, using the relation between susceptibility and concentration of deoxyhemoglobin measured in the sagittal sinus, was also measured before and after ACZ injection (4). Patients were then directly moved to a SPECT scanner, giving information about CBF. Patients were classified from SPECT imaging as having normal or reduced cerebrovascular reactivity as part of common clinical practise. By DCE MRI we estimate regional CBF, blood volume and mean transit time, and using advanced tracer kinetic modelling we also estimated regional distribution of capillary transit times, i.e., CTH (5).

Figure 1. Correlations between (A) capillary transit time heterogeneity (CTH) and (B) cerebral blood flow (CBF) obtained from DCE after administration of ACZ and change in cerebrometabolic rate of oxygen ($D_{ACZ}gCMRO_2$) before and after ACZ administration. In brain regions with impaired cerebrovascular reserve capacity (CVR) increasing CTH correlates with decreasing $D_{ACZ}gCMRO_2$. In contrast, CTH in CVR intact tissue did not correlate with $D_{ACZ}gCMRO_2$ (green line). Similarly, low rCBF in CVR impaired regions correlates with decreasing $D_{ACZ}gCMRO_2$. Overall, these results suggests that both low rCBF and high rCTH in hemodynamic limited tissue contribute to an inhibited oxygen metabolism.

Fifteen patients had impaired cerebrovascular reactivity and of these 5 patients demonstrated a steal phenomenon. Nineteen patients had intact reactivity. In this group oxygen consumption increased after ACZ injection, while the patient group with impaired vascular reactivity showed a decrease in global oxygen consumption. In this group we found a significantly elevated CTH along with a smaller CBF increase after ACZ, ipsilateral to the affected side of the steno-occlusive disease. A regression analysis showed that the decrease of oxygen consumption was significantly better explained by a decrease in CBF as well as an increase in CTH compared to only CBF, see figure 1. We conclude that in this group of patients with relative severe vascular brain disease not only CBF but also the capillary flow distribution have an impact on the resulting ability to extract and consume oxygen (6).



QUADRA



Professor, Consultant Malene Fischer

Total Body PET is a potentially game-changing innovation at the threshold of clinical implementation. The EXPLORER (EXtreme Performance LOng axial REsearch scanner) consortium launched a 194-cm-long PET/CT scanner (uEXPLORER) in 2018. This was followed by a 106-cm-long PET/CT scanner developed by Siemens (Biograph Vision Quadra PET/CT). Early experience has demonstrated very high sensitivity (by a factor 10 compared to current state of art PET/CT) enabling ultra-fast or low-dose scanning. Thanks to a generous and visionary investment from the Capital Region of Denmark (RegionH) one of the world's first total body PET systems was installed at the department in September 2021. The first patient was scanned on the Siemens Biograph Vision Quadra PET/CT on the 21st September and the scanner was officially opened by the CEO of RegionH Jens Gordon Clausen on the 25th October 2021. Since then, more than 300 patients have been scanned on the Quadra PET/CT in 2021.

The implementation of the Quadra PET/CT have been done by a multidisciplinary team consisting of nuclear medicine physicians, radiologists, physicist, technologists, radiographers and computer scientists led by Professor Malene Fischer and Data Manager Flemming Andersen. Early research on total body PET/CT systems promised significantly improved sensitivity and we have not been disappointed. Our experience from reading PET/CT scans performed on the Quadra, as well as a systematic evaluation of image quality confirms the improved sensitivity and signal-to-noise ratio. The image quality provided by the Quadra PET/CT is second to none and has opened up possibilities to significantly decrease scanning time or decrease radiation dose to the patient while maintaining high image quality.

Exemplar applications on the brink of implementation in daily clinical practice are 2-5 min scan time for a whole-body PET/CT, reduced dose to

pediatric patients and PET performed in breath hold. Combined with AI for image reconstruction we are working towards an ultra-low dose protocol enabling total body PET/CT performed with the use of less than 1mSv of ionizing radiation. This will enable research application and a broader clinical use of PET e.g. in otherwise healthy individuals and for screening purposes. We also envisage that the possibility for dynamic total body PET examinations will bring new life and research perspectives into the area of PET-kinetics. We are thus performing regular dynamic ^{18}F -FDG-PET as well as ^{15}O -H₂O studies, firstly to optimize the total body scan protocol and managing of the substantial amount of data, later to explore total body metabolism and perfusion and its potential impact on pathophysiology and patient outcome.

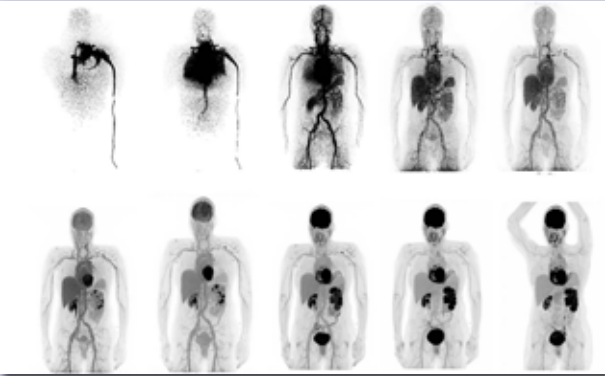
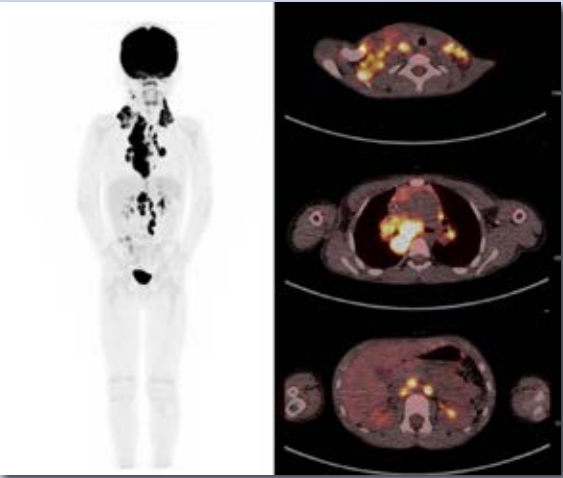
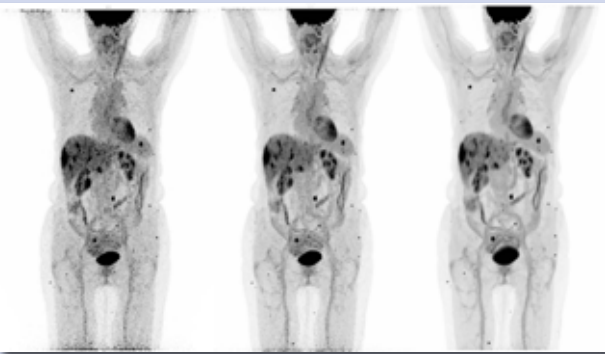


▲ **Figure 1** The Biograph Vision Quadra PET/CT installed at Rigshospitalet in September 2021.

► **Figure 2** Exemplar images from one of the first patients scanned on the Quadra PET/CT. Image reconstruction performed after 30, 90 (equals current clinical standard) and 600 seconds PET acquisition time. Note is made of the improved signal-to-noise, especially in the liver and pelvic region.

Figure 3 Pediatric patient with lymphoma. 5 minutes PET acquisition on Quadra PET/CT after injection of 1.5 MBq/kg FDG. Normal dose is 3 MBq/kg.

Figure 4 Dynamic whole-body FDG PET/CT scan with image reconstruction after 10, 20, 30, 60, 120 seconds (upper row) and 5, 10, 30 and 50 minutes (lower row). The far right image in the lower row is the clinical scan after 60 minutes performed on a Biograph Vision PET/CT.



Opening of our new Super-scanners



The new Super-scanners PET/MRI mMRI and QUADRA total body PET/CT were opened Monday, 26th of October with an opening speech by our Hospital Director CEO Per Christiansen and a scientific program with Consultant Annika Loft Jakobsen, Professor Malene Fischer, Professor Ian Law and Chief Computer Scientist Flemming Littrup Andersen. These “fabulous four” were the main initiators behind the acquisitions together with Chief Physicist Thomas Levin Klausen, who secured the project together with CEO Siemens Letitia Boatman, who gave a fine speech addressing the importance of providing the best diagnostic quality for all patients.

Head of Department, Professor Liselotte Højgaard said “Thank you very much” to all - The John and Birthe Meyer Foundation, Birthe Meyer, Gitte Meyer Brandt, Søren Drost-Nissen for the generous donations through more than 25 years since the opening of Denmark’s first PET scanner in 1991 donated by the foundation. We have

been immensely grateful for the support and interest.

Liselotte Højgaard said thank you to the hospital: CEO Per Christiansen, the previous CFO Thue Jensen, and our DIA leadership Center Director Helle Konradsen, Vice Director Lene Ørnstrup Christensen and many more for the new QUADRA. Thank you to Siemens’ Letitia Boatman, Jim Williams, Bernd Ohnesorg, Michael Palne and Peter Moos and his team installing and building the new section. To Steffen Boyhuus and Niels Broberg for their dedicated support.

The opening was finalized by MusikBeriget, the hospital orchestra, playing a suite of beautiful songs.

Guests and friends from Denmark and abroad celebrated together with the department and hospital, and it was truly a joyful day with reception and opening by Birthe Meyer and Gitte Meyer Brandt.

From the Foundation we have in the years obtained:

- 1991 Scanditronix 32 MeV,
- 1991 GE4096 PET Scanner
- 1993 NMR Spectrometer
- 1993 PET Advance Scanner
- 2001 PET/CT Scanner
- 2005 PET/CT Scanner
- 2005 Cyclotron 2
- 2007 HRRT Scanner
- 2009 Radiochemistry Synthesizer
- 2011 PET/MR Scanner
- 2017 PET/CT Scanner
- 2019 PET/MRI scanner and AI program
- 2021 Bilaco pediatric program

THANK YOU TO THE JOHN AND BIRTHE MEYER FOUNDATION.

THANK YOU TO THE STAFF OF THE PET- , CYCLOTRON- AND RADIOCHEMISTRY SECTIONS FOR A TREMENDOUS EFFORT





Merging of the Cyclotron and Radiochemistry sections

In 2021 the Cyclotron and Radiochemistry sections were merged into the Cyclotron and Radiochemistry Section, under the Department for Clinical Physiology and Nuclear Medicine. As the tasks in the Cyclotron and Radiochemistry sections were and are truly interdisciplinary, with a common goal of producing radiopharmaceuticals for patient investigations and research, it was felt to be a natural change in organisation. Thus, the new unit consists of a total of 18 employees managed by Tina Wikke Hallund, Nic Gillings, Holger Jensen and Jacob Madsen (Head of Section).



Radiochemistry

Chief Radiochemist Nic Gillings, Chief Radiochemist, Production Manager Jacob Madsen and Nuclear Medicine Staff Technologist Tina Wikke Hallund

Highlights

In October 2021 Staff Nuclear Medicine Technologist Anne Sørensen retired after 40 years in the department. Anne was a part of the radiochemistry team since the very beginning in 1990. We would like to express our sincere gratitude for the many years and wish her all the best in her well-deserved retirement.

In 2021 we received approval from The Danish Medicines Agency for production of [⁶⁸Ga]Ga-PSMA-11 for use in prostate cancer patients and to use the MedTrace P3 [¹⁵O]water system for patients. We have previously produced both these products; however, revalidation and renewed approvals were required due to changes in the production systems.

Production for clinical and research PET investigations in humans

Production of [¹⁸F]FDG and krypton-81m generators along with [¹⁸F]FET, [¹⁸F]FE-PE2I, [¹¹C]PIB and ⁶⁸Ga-labelled ligands continued on a similar level compared to previous years. In 2021, we transferred the production of [¹⁸F]FE-PE2I to a synthesis cassette-based automated system which has resulted in a more reliable process. We continued to produce the uPAR imaging agent, [⁶⁸Ga]Ga-NOTA-AE105 and our angiogenesis tracer, [⁶⁸Ga]Ga-NODAGA-E[c(RGDyK)]₂ in 2021. Both are being evaluated in phase II clinical trials. There were 994 batches released for human use in 2021 comprising 14 different radiopharmaceuticals (see figure). Production of

neuroreceptor PET radioligands for human use for various research projects, conducted by The Neurobiology Research Unit at Rigshospitalet, continued as in previous years.

Radiopharmaceutical development

Oncology

The production of meta-[¹⁸F]fluorobenzyl guanidine ([¹⁸F]mFBG), for diagnosis and treatment monitoring of neuroblastoma patients (both children and adults), was set up and validated in 2021. An application to The Danish Medicines Agency was submitted in November 2021 and we expect to receive the final approval for patient production in early 2022.



Radiopharmaceutical	Batches	Usage/Target
[¹⁸ F]FDG	350	Oncology/glucose metabolism
Krypton-81m generator	149	Lung ventilation
[¹⁸ F]FE-PE2I	135	Neurology/dopamine transporter ligand
[¹¹ C]PIB	82	Alzheimer's Disease/ β -amyloid plaques
[⁶⁸ Ga]Ga-DOTATOC	68	Neuroendocrine tumors/somatostatin receptors
[¹⁸ F]FET	52	Oncology/amino acid transport
[¹¹ C]UCB-J	49	Brain research/synaptic density marker
[¹¹ C]SB207145	27	Brain Research/5-HT ₄ receptors
[⁶⁸ Ga]Ga-DOTATATE	24	Neuroendocrine tumors/somatostatin receptors (clinical trial)
[⁶⁸ Ga]Ga-NODAGA-E[c(RGDyK)] ₂	23	Oncology/angiogenesis imaging (clinical trial)
[⁶⁸ Ga]Ga-NOTA-AE105	15	Oncology/uPAR imaging (clinical trial)
[⁶⁸ Ga]Ga-PSMA-11	13	Oncology/prostate specific membrane antigen ligand
[¹⁵ O]Water	4	Cerebral blood flow
[¹¹ C]Cimbi-36	3	Brain Research/5-HT ₄ receptors
Total	994	

Radiopharmaceuticals produced for human use in 2021

Miscellaneous

Optimization of the production of [^{99m}Tc]technetium galactosyl human serum albumin ([^{99m}Tc]GSA), a radiopharmaceutical for the non-invasive assessment of liver function in a clinical setting, is ongoing and expected to be validated in 2022.

Quality Assurance

We are currently in the process of implementing a laboratory information management system (LIMS) which has been developed by LabLogic in the United Kingdom and is used in many PET centres throughout the world. This is an electronic system which will allow all production and quality control data to be automatically captured in a database, thus making the whole process more or less paperless. The system will be gradually implemented during 2022 and, although this will be a major undertaking, it will ultimately result in a more efficient and standardized production system and eliminate manual transcription errors.

Laboratory Technologists/Scientists

Following Anne Sørensen's retirement, Tina Wikke Hallund was appointed Nuclear Medicine Staff Technologist. Medical Laboratory Scientist Louise Sørensen, has been appointed as deputy for Tina Wikke Hallund and has also taken over from Charlotte Denholt as occupational health and safety representative for the Cyclotron & Radiochemistry section.

Education in radiopharmaceutical chemistry

The teaching program in radiopharmaceutical chemistry led by Associate Professor Matthias Herth, which was initiated in 2016 at the Faculty of Health and Medical Sciences, University of Copenhagen, continued in a similar format in 2021, with members of the radiochemistry section involved in lecturing and practical exercises. In addition, Matthias supervises several students engaged in radiopharmaceutical research.

Radiopharmaceutical research and PhD projects

- ▶ Troels Elmer Jeppesen has in 2021 been a visiting postdoctoral researcher at Massachusetts General Hospital, Harvard Medical School in Boston, US.
- ▶ Camilla Christensen returned from maternity in October 2021 and will continue her PhD. studies on the development of ⁸⁹Zr-labelled PET tracers for improved cancer immunotherapy. Camilla is currently preparing to validate site-specifically labelled [⁸⁹Zr]Trastuzumab for human use.
- ▶ Klas Bratteby successfully defended his PhD thesis, entitled Development of ¹⁸F-labelling strategies for base-sensitive precursors in March 2021.



Cyclotrons

Cyclotron Chief Holger J. Jensen and Deputy Cyclotron Chief Jesper Jørgensen

During the last 10 years we have experienced a relative stable number of productions at our two cyclotrons of 1250 ± 90 productions per year (Figure 1). In 2021 we had in total 1316 successful productions (670 and 646 for our Scanditronix MC32 and Siemens RDS Eclipse cyclotrons respectively) giving an average success rate of $99,5 \pm 0,5\%$ since 2012. Despite of the COVID-19 situation we have not seen a drop in our productions. As in the previous years we managed to keep the average radiation dose to the employee in the Cyclotron- and Radiochemistry Section at a low level (Figure 2).

Figure 3 shows the development in the controlled release via our chimney of low radioactive waste gas

produced in our Cyclotron- and Radiochemistry Section since 2012. Our permission from the authorities (SIS) allows us to release 10 TBq per year. In 2021 we ended at the very save side with a release of only 7,2% of this limit.

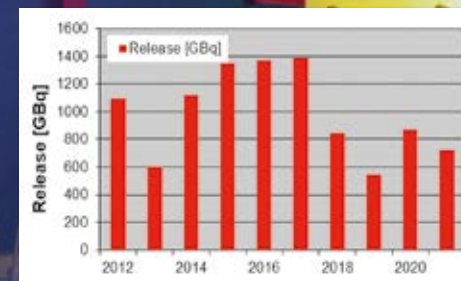
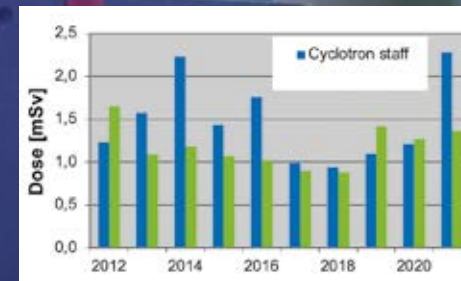
The authorities require the chimney designed, so no one in the general public can receive a radiation dose from our activities higher than 100 $\mu\text{Sv}/\text{year}$ (or approximately 40 times lower than the average background dose in Denmark). Figure 4 shows the estimated total dose distribution from the release last year illustrated for a 400x400 meter grid in the neighbourhood of the chimney. The example is given for a height of 20 m, where we have the highest concentrations. The highest

► **Figure 1.** Development in ^{18}F , ^{11}C and the total number of productions since 2012.

► **Figure 2.** Average received dose per year for employees in The Cyclotron- and Radiochemistry Section since 2012.

► **Figure 3.** Development in release of radioactive gas via our new chimney and filter system since 2012.

► **Figure 4.** Total dose distribution in the neighbourhood of the chimney for a total release of 0,87 TBq last year. Values are shown at a height of 20 m above ground level.



possible dose level is seen to be below 2,5 μSv and far from the release limit.

In former years we have invested in various upgrade projects for our Scanditronix MC32 cyclotron. This year we had a major upgrade for our Siemens RDS Eclipse cyclotron. The cyclotron is from 2005 and several subsystems of the cyclotron are no longer supported by Siemens. Consequently, the full RF- and SCADA systems were replaced in 2021 with the newest upgraded systems from Siemens.

Medical Secretaries

In the department we have highly competent medical secretaries important for referral of patients, organisation of the flow of patients through the department, writing the reports and sending them to the clinical departments. They do a dedicated effort. The medical secretaries master the complicated booking and secure that the waiting lists, the patient control examinations, and research scans can be done despite a high workload and a year with challenges due

to the Corona pandemic. A dedicated thank you to Marianne Stahlfest, Mette Fabiansen and Helle Højen Jensen in the KF Section, Gitte Hass and Sevil Durmus in the Glostrup Section and Tina Vikmann Nielsen, Gudrun Semitoje and Frederikke Hurup Henriksen in the PET Scanner section.

We would like to say a warm thank you to everyone for the high quality and performance.



Education

Consultant Peter Oturai and Professor, Consultant Jann Mortensen

The department of Clinical Physiology and Nuclear Medicine contributes to many of the pre-graduate activities of the Faculty of Health Sciences at the University of Copenhagen for medical students, human biology students and medicine & technology students in collaboration with DTU in various subjects, e.g. nuclear medicine, clinical physiology, respiratory physiology and medical technology. In addition, nuclear medicine technologist students and radiographer students and medical secretaries/SAK-students receive parts of their education at our department.

Regarding postgraduate education, seven educational positions for young physicians training to become specialists in clinical physiology and nuclear medicine are held by the facilities at Blegdamsvej and the Glostrup Section. Courses held and arranged by our professors, consultants and physicists are dedicated courses in oncology, and cardiological, pulmonary, endocrine pathophysiology and molecular imaging as well as courses in methodology such as MR, hybrid imaging,

and kinetics. Furthermore, we contribute to the specialist education of physicians from other specialities such as urology, nephrology, radiology, oncology, haematology, pulmonology, and thoracic surgery. A high number of PhD students are associated with the research activities in the department.

Colleagues and students from Denmark and abroad, have visited the department for educational and research purposes for periods ranging from weeks to months.

The department delivers training programmes to staff from other nuclear medicine and radiological departments in Denmark and the Nordic countries.

The departments educational activities have been accredited by the Accreditation of Nuclear Medicine Training Centres Committee of the Section of Nuclear Medicine of the European Union of Medical Specialists (UEMS) and The Danish Health Authorities.

Consultant Peter Oturai is responsible for the postgraduate education of physicians in the department. Professor Jann Mortensen, Professor Ian law, Professor Henrik Larsson, Professor Malene Fischer and associate professor Ronan Berg are responsible for the undergraduate education of medical students in the department and the medical faculty. Professor Liselotte Højgaard is responsible for under- and postgraduate education for bioengineers.

Technologist students and internal education

Clinical Teachers Mia Hjorth Albers, Torben Kirk Lehnkov and Annette Foldager

Our department contributes with a lot activities for our technologist students, biomedical laboratory scientists and radiographers at the University College Copenhagen. Throughout the year, 35 students have received clinical training and education in various subjects such as clinical physiology, nuclear medicine, communication etc. The clinical period in the department for the students is to inherit skills to plan and do the examinations and to profound insight in the selected examinations, develop competences to analyze, discuss and understand the complexity of those. The purpose of their education is to secure improvement of the patient's investigation and contribute to the innovation of our specialty.

Well-being

The COVID-19 pandemic has been a challenging time for our students learning and well-being.

National and international restrictions have challenged the framework and clinical outcome. Because of this a new project with the purpose of strengthening our department's learning environment was born. Through research we will attempt to apply clinical supporting interventions, based on Richard Ryan's and Edward Deci's "Self-Determination Theory". Our hope is to support the student's social integration, skills and increase participation in the department's work and the patients. All this is with the aim to expand the technologist students engagement, optimize their learning outcome and increase collaboration skills.

The future

To accommodate the challenge of the future a trainee-program has been developed in the department and will start in the summer of 2022. The trainees will rotate between our PET-, Radiochemistry- and Nuclear Medicine sections over a two-year period. Our goal is to recruit and maintain new employees and simultaneously strengthen the relations and interprofessional teamwork in our organisation.

Furthermore, we are aiming to improve and support our colleagues in many facets such as: professional and pedagogical competence, research, etc. In a national collaboration, we are working on an educational program for employees with years of practical experience. The purpose is targeted competence development to utilize the technological advances, for the benefit of the patient.

Medical Secretary and SAK Students

Medical Secretary Tutor Tina Vikmann Nielsen

In 2021 a new education was introduced: the SAK education. SAK stands for 'Health Administrative Coordinator' and is replacing the former medical secretary master teaching. It meant that the department in a period had both a student from the former education and a student from the new education on study stay.



Equipment

Chief Physicist Thomas Levin Klausen

Equipment	Product	Purchase year
Gamma cameras	Mie-Scintron	2004
	DDD Solo	2020
	Mediso N-TH45-D	2008
	DDD SoloMobile	2012
	DDD NephroCam System	2016
SPECT-cameras	Mediso Nucline X-Ring-R/HR	2009
	Symbia Evon	2017
SPECT/CT cameras	Siemens SymbiaT2	2006
	GE Discovery 670	2010
	Siemens Symbia 16-slice CT	2011
	Siemens Symbia Intevo Bold 16 slice CT	2017
PET scanner	Siemens Symbia Intevo Bold 16 slice CT	2020
	HRRT Siemens/CTI	2007
PET/CT scanner	Siemens Quadra	2009
	Siemens Vision (128)	2010
	Siemens Vision (64)	2011
	Siemens Vision (64)	2019
	Siemens Vision (64)	2019
	Siemens mCT-S (128)	2013
	Siemens mCT-S (64)	2016

Equipment	Product	Purchase year
PET/MR scanner	Siemens mMR	2011
	Siemens mMR	2020
	GE SPINlab MR Hyperpolarizer	2014
Lung function	Jaeger Masterscreen w/bodybox	2005
	Jaeger Masterscreen w/bodybox	2019
	Jaeger PFT pro w/bodybox	2007/13
	Jaeger Vyntus One PFT w/bodybox	2021
DXA scanner	GE Lunar Prodigy	2004
	GE Lunar Prodigy	2005
	GE Lunar Prodigy	2011
	GE Lunar iDXA	2014
Whole body counter	WBC w/Nal counting chamber	1977
	WBC w/plast counting chamber	1978
Cyclotrons	Scanditronix 32 MeV	1991
	RDS Eclipse cyclotron, CTI	2005

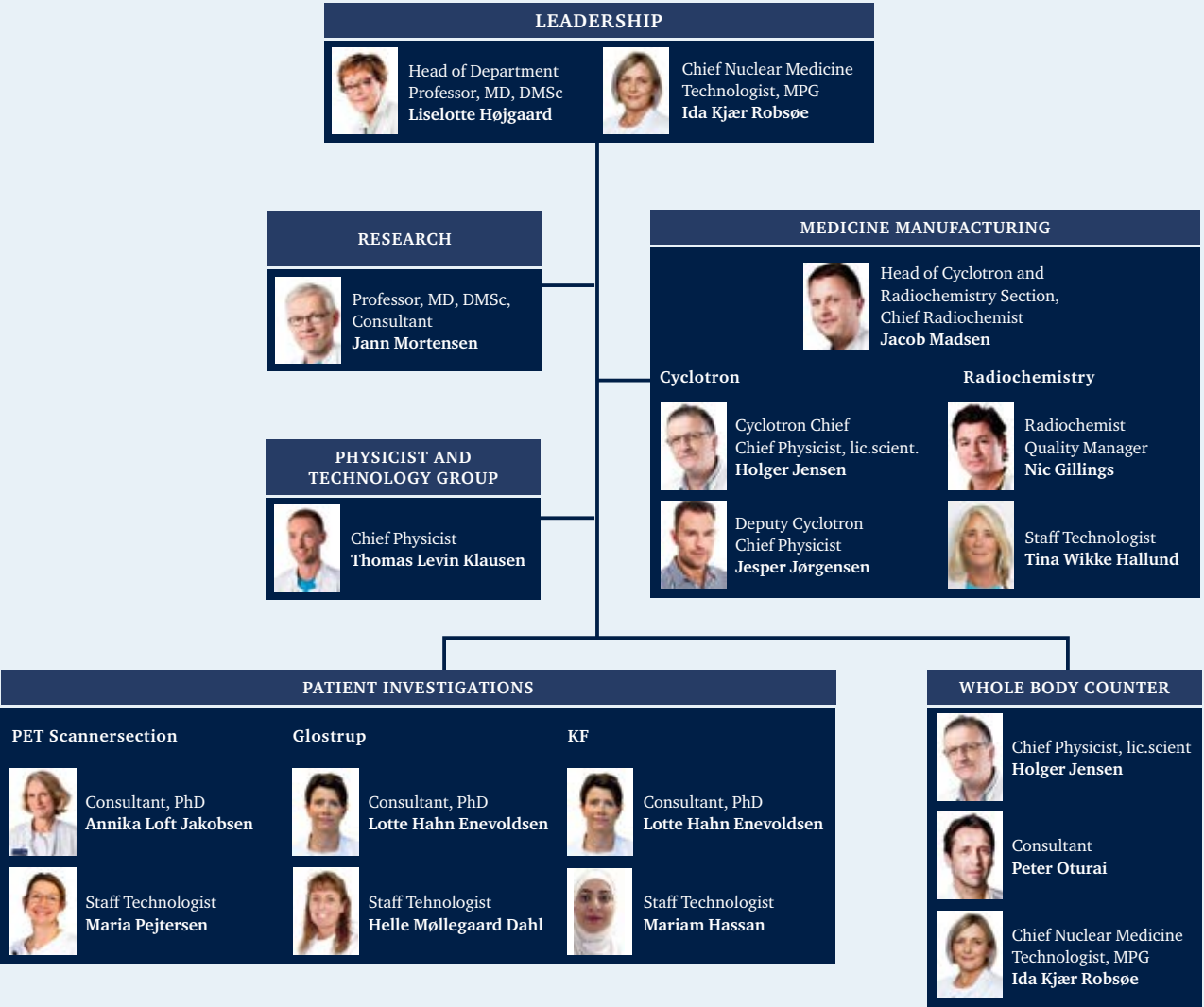
Organisation and Staff

Abrahamsen, Nynne Hejdemann, Technologist.
Afzai, Remshah, Technologist.
Agner, Elissaveta Castella, Radiographer.
Ahangari, Sahar, Research Fellow.
Ahlberg, Sofie, Technologist.
Ahmadi, Amir, Radiographer.
Al-Atabi, Susan, Technologist.
Albers, Mia C. Hjorth, Clinical Technologist.
Albrecht-Beste, Elisabeth, Consultant.
Alkaabi, Soha Nomas, Student.
Alexandrova, Alzhbeta, Technologist.
Amtoft, Annemarie Gjelstrup, Consultant.
Anderberg, Lasse, Research Fellow.
Andersen, Amanda Øster, student.
Andersen, Ditte Lindbjerg, Radiographer.
Andersen, Flemming Littrup, Computer Scientist, MSc, PhD.
Andersen, Jane, Technologist.
Andersen, Julie Bjerglund, PhD, Staff Specialist.
Andersen, Kim Francis, Consultant.
Andersen, Magdalena Bozena, Technologist.
Andersen, Thomas Lund, Physicist, PhD
Andersen, Ulrik Bjørn, Consultant.
Askløf, Mathias Gæde, MSc, Engineer.
Asmar, Ali, Staff Specialist.
Awwal, Zara Amalie Krog, Radiographer.
Azam, Aleena, MD, Researh Assistant.
Azizi, Nadia, Radiographer.
Bach, Mathias Jacobsen, Student.
Bak, Helle Østergren, Pharmacist.
Bakhshinejad, Babak, MSc Molecular Genetics, PhD, Postdoc.
Bardakci, Ayse, Technologist.
Bendtzon, Camilla Kuhre Vildrik, Medical Secretary.
Bentsen, Simon, MD, PhD, Postdoc.
Benzon, Eric von, Consultant.

Berg, Ronan Martin Griffin, Staff Specialist, Associate Professor.
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Bjørling, Nina Louise, Medical Secretary.
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Cappelen, Katrine Louise, Engineer.
Carlsen, Esben Andreas, MD, PhD Student.
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Christensen, Anders, MD, Postdoc.
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Christensen, Camilla, Technologist.
Christensen, Emil Nørgaard, Student.
Christoffersen, Anders, student.
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Elkington, Sakeena, Technologist.
Enevoldsen, Lotte Hahn, Consultant.
Engkebølle, Christian, Student.
Esmail, Mona Jasmin Ali, Technologist.
d’Este, Sabrina Honoré, Student.
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Gillings, Nic, MSc, PhD, Chief Radiochemist.
Grunwald, Nicolas Konrad Voigt, Student.

Department of Clinical Physiology and Nuclear Medicine



Organisation and Staff

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 Kikkenborg, Julie Bramstrup, Student.
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 Larsen, Kristina, Technologist.
 Larsen, Mads Rud, Student.
 Larsen, Victor, Student.
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Løyche, Thomas Asger, Nurse.
 Madsen, Jacob, Chief Production Manager, Chemist, MSc, PhD.
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 Madsen, Karine, Staff Specialist.
 Markova, Elena, Consultant.
 Martín, Marina Simón, MSc Mol.Bio.Med., PhD Student.
 McDaniel, Peter Nicolas, Student.
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 Montgomery, Maria Elkjær, Student.
 Mortensen, Jann, DMSc, Professor, Consultant.
 Mortensen, Julie van Krimpen, Student.
 Moustapha, Amani, Technologist.
 Mouritzen, Nanna Jung, Student.
 Murtezaj, Bardha, Student.
 Müller, Asger Raza, Radiographer.
 Müller, Felix, Registrar.
 Mønsted, Thormod Øgaard, Senior Registrar.
 Nielsen, Betina Sølvi, Technologist.
 Nielsen, Cora Schaumann, Technologist.
 Nielsen, Kasper With, Animal Technologist.
 Nielsen, Marcus Kristian, Student.
 Nielsen, Signe Maja Halstrøm, Radiographer.
 Nielsen, Sofie Hjerrild, Student.
 Nielsen, Susanne Weile, Technologist.
 Nielsen, Tina Vikmann, Medical Secretary.
 Okkels, Charlotte Holmgaard, Technologist.
 Olin, Anders Beck. Postdoc.
 Olsen, Paw Winther, Engineer.
 Ovesen, Karen Rosbjerg, Student.
 Oturai, Peter Sandor, Consultant.
 Oueiti, Ghena Nasser, Technologist.
 Pedersen, Cecilie Høeg, MSc Med.Tech., PhD Student.
 Pedersen, Karl Emil, Technologist.
 Pedersen, Katja Petrea Gissemann, Student.

Pedersen, Nanna Overbeck, Student.
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 Rasmussen, Thomas, MD, PhD, Postdoc.
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 Riedel, Casper Schwartz, Registrar.
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 Risør, Louise Madeleine, MD, PhD Student.
 Robsøe, Ida Kjær, Chief Nuclear Medicine Technologist, MPG.
 Ryssel, Heidi, MD, PhD Student.
 Rønn, Vibeke, Chief Secretary, PA.
 Salihu, Armend, Technologist.
 Sandholdt, Michele Windtberg, Technologist.
 Saribayir, Sirin, Technologist.
 Saxtoft, Eunice, Technologist, Clinical Instructor.
 Schulze, Christina, Technologist.
 Semitoje, Gudrun, Medical Secretary.
 Setterberg, Victoria, Technologist.
 Severinsen, Tino, Student.
 Simonsen, Helle Juhl, Research MR Technologist.
 Sinkjær, Anders Wilgaard, MSc Pharm., Research Assistant.
 Sjøstedt, Sannia, Senior Registrar.
 Skougaard, Kristin, PhD, Staff Specialist.
 Sloth, Ane Beth, MSc Biomedicine, PhD Student.
 Sommer, Niyan, Technologist.

Stahlfest, Marianne, Medical Secretary.
 Stavnsbjerg, Camilla, MSc Mol.Bio.Med., PhD, Postdoc.
 Stillits, Andreas, Student.
 Staudt, Markus, Msc. Chem., PhD, Postdoc.
 Svalling, Susanne, Technologist, Deputy Staff Technologist.
 Svendsen, Nini Hvidtfeldt, Technologist.
 Sørensen, Anne, Technologist.
 Sørensen, Louise Sørup Lendorf, Deputy Staff Technologist.
 Sørensen, Maja Støvring, Technologist.
 Tausen, Alice, Radiographer.
 Tayyab, Mahvish, Technologist, Deputy Staff Technologist.
 Teilmann, Laura Marie, Student.
 Toft, Cecilie Grønkær, Student.
 Tornvig, Cecilie Maja, Technologist.
 Uhrenholdt, Lukas, Student.
 Ullersted, Eva, Service Assistant.
 Urhammer, Gitte Marie, Technologist.
 Uzer, Sefika, Technologist.
 Vandel, Julius Scheel, Student.
 Varpe, Kristin, Technologist.
 Vestergaard, Mark Bitsch, PhD Student.
 Vijayakumar, Gidega, Student.
 Viknes, Vitusha, Student.
 Vindt, Lone Kjærshøj, Medical Secretary.
 Voldby, Christian Møller, Registrar.
 Weihrauch, Per, Cyclotron Technician.
 Wieslander, Bente Krosggaard, Consultant.
 Wiinholt, Mette Nieegaard, Msc. Human Biology, Technologist.
 Willumsen, Ida Vigdís, Student.
 Wittekind, Anne-Mette Nielsen, QA Pharmacist.
 Zare, Soheil Naser, Radiographer.

Studies 2021

Radiotherapy	
Treatment with ¹³¹ I, benign thyroid	65
Treatment with ¹⁷⁷ Lu-Dotatate	173
Treatment with ²²³ Ra-Dichlorid	73
Treatment with ¹⁷⁷ Lu-PSMA	0
Total	311
Peripheral vessels	
Systolic blood pressure, fingers	5
Systolic blood pressure, ancle and toes	340
Systolic blood pressure, ancle-brachial index after treadmill	98
Doppler ultrasound of the carotides	4,164
24 hours blood pressure measurement	372
Total	4,979
Blood and lymph system	
Sentinel node scintigraphy,	158
Sentinel node scintigraphy, head/neck SPECT,	187
Spleen scintigraphy,	7
Erythrocyt volume,	32
Plasma volume,	32
Peritumoral injection of	246
Total	662
CNS and peripheral nervous system	
CT scanning of cerebrum	408
Regional cerebral blood flow, ^{99m} Tc- HMPAO, pharm.prov.	9
Cerebral metabolism,	1,642
Cerebral receptor, ¹⁸ F-FE2PI	378
Cisternography,	2
Cerebral neuroreceptor,	270
Cerebral receptor,	163
Cerebral receptor,	56
Cerebral blood flow,	5
Regional cerebral receptor, ¹⁸ F-Florbetapir	0
MR scanning of cerebrum with and without contrast	1,698
MR scanning of hippocampus (MR-HCV)	590
Total	5,221

Other diagnostic procedures	
Image fusion (PET, SPECT, MRI, CT or planar)	15,534
Scintigraphy after	168
Whole body, contamination measurement	117
White blood cell scintigraphy,	0
White blood cell scintigraphy,	0
Neuroendokrine receptors, WB,	0
PET tumor scanning,	158
PET tumor scanning,	685
PET scanning	23
PET scanning,	7,073
PET tumor scanning,	23
PET tumor scanning,	7
CT head/neck SPECT/CT	315
CT lower and upper extremities SPECT/CT	15
CT abdomen SPECT/CT	322
CT pelvis SPECT/CT	128
CT wb PET/CT	2,009
CT wb PET/CT with contrast	6,727
CT wb SPET/CT	296
CT thorax SPECT/CT	950
CT thorax PET/CT breathhold	14
MR wb PET/MR	108
PET thorax PET/CT breathhold	14
Other investigations, incl. ¹¹ C-different tracers (NRU)	72
Supplementary/repeated imaging	2,747
Second opinions external PET, PET/CT, SPECT/CT, CT and MR	1,727
Extra tumor delineation	327
Total	39,559
Endocrine organs	
Adrenal marrow scintigraphy,	32
Tumorscintigraphy, ¹²³ I-Iodide	0
Iodine uptake test,	39
Parathyroid scintigraphy, ^{99m} Tc-Stamisis, SPECT	77
Thyroid scintigraphy,	77
Thyroid scintigraphy,	1,054
Thyroid ultrasound	1,145
Thyroid, fine needle aspiration biopsy	119
Parathyroid fine needle aspiration biopsy	0
Parathyroid ultrasound	0
Total	2,543

Gastric intestinal tract, liver, biliary tract and pancreas	
Bleeding scintigraphy (abdomen)	0
Biliary tract scintigraphy,	90
Meckels diverticle scintigraphy,	4
Salivary gland scintigraphy,	7
Liverperfusion ICG	31
Doppler ultrasound of splanchnic blood flow	547
Total	679

Heart and cardiovascular system	
Analysis of heart rate variability	284
Tilt table test	286
Isotope cardiography, LVEF, ^{99m} Tc-HSA	1,462
Myocardial calcium score	803
PET myocardial perfusion,	1,214
PET myocardial metabolism,	246
PET myocardial perfusion,	1,108
Myocardial perf. scintigr. gated,	1
Myocardial perf. scintigr. gated,	1
Myocardial scintigraphy,	84
Myocardial	0
Total	5,489

Bone and joint	
DXA, body composition	632
Bone scintigraphy,	1,163
Bone scintigraphy,	842
Bone scintigraphy,	45
Bone scintigraphy,	21
Osteodensitometri (DXA), columna lumbalis	4,31
Osteodensitometri (DXA) collum femoris	4,31
Osteodensitometri (DXA), lateral spine	289
Osteodensitometri (DXA), radius	182
MR scanning columna cervicalis	0
MR scanning columna thoracalis	0
MR scanning columna lumbalis	0
Total	11,794

Respiratory organs	
Lung perfusion scintigraphy, SPECT,	697
Lung ventilation scintigraphy, SPECT,	627
Lung function test, spirometry w/reversibility	86
Lung function test, diffusion capacity (CO)	4,054
Lung function test, diffusion capacity (NO/CO)	158
Lung function test, whole body plethysmography	2,978
Lung function test, whole body plethysmography w/reversibility	359
Lung function test, spirometry	0
Lung function test, spirometry w/reversibility	86
Lung ventilation scintigraphy, regional, ^{81m} Kr-gas	296
Lung ventilation scintigraphy, SPECT ^{99m} Tc-Technegas	70
Max. insp. abd expspir. muscle pressure	136
Mucociliary clearance,	10
Total	9,557

Kidneys and urinary tract	
Glomerular filtration,	0
Glomerular filtration,	2,014
Renal scintigraphy,	11
Renography,	2,179
Renography,	98
Renography,	3
Renography,	12
Doppler ultrasound of renal blood flow	528
Ultrasound of kidneys	528
Ultrasound of retroperitoneum	16
MR-scanning of kidneys	0
Total	5,464

In vitro analyses	
Affinity studies	134
Flow cytometry analyses	18,484
Gene expression analyses	6,211
Immunohistochemistry	1,185
Phage display	462
Plasma and protein analyses	6,679
Total	33,155

Studies

Animal studies

Rats	
⁶⁴ Cu-etelcalcetide	12
⁸² Rubidium	14
^{99m} Tc sestamibi	4
CT images for fusion	21
Mice	
¹¹ C-tucatinib	8
¹⁸ F-FDG	42
¹⁸ F-FET	10
¹⁸ F-tetrazine	6
⁶⁴ Cu-DOTATATE	26
⁶⁸ Ga-NOTA-nanoparticles	78
⁶⁸ Ga-xx	136
^{99m} Tc	51
¹¹¹ In-xx	267
Bioluminescence (luciferin)	316
Fluorescence (SMILE-NP)	184
Fluorescence (ICG-AE105)	112
Fluorescence (IRDye820)	8
MR	1,584
CT images for fusion	684
Ultrasound	36
Photothermal therapy	48
Radiotherapy, externally	296
Radionuclide therapy (α and β emitters)	231
Total	2,591

Total number of studies122,004

Invitation to collaboration

We invite to collaboration on patient studies, research, innovation and education in all aspects of Clinical Physiology and Nuclear Medicine.

Don’t hesitate to contact us.

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Publications 2021

Theses

Doctoral thesis

Knudsen, A. “Cardiovascular investigations in people living with human immunodeficiency virus”. April 16, 2021, virtual, University of Copenhagen.

PhD theses

Bentsen, S. PhD. “Preclinical investigation of ischemic heart disease based on molecular imaging”. December 12, 2021, virtual, University of Copenhagen.

Bratteby, K. PhD. “Development of 18F-labeling strategies for base-sensitive precursors”. March 26, 2021, virtual, University of Copenhagen.

Clausen, AS. PhD. “Development of positron emission tomography (PET) imaging and liposomal drug delivery systems for infectious and inflammatory diseases”. August 19, 2021, University of Copenhagen.

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Doctoral Thesis

Andreas Knudsen, PhD, DMSc (staff doctor)

Cardiovascular investigations in people living with human immunodeficiency virus



Defended
16.04.21, online

Chair
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Opponents
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Professor Won Yong Kim, Dept. of Cardiology & Dept. of Clinical Medicine, Aarhus University, DK

Defence leader
Professor Thomas Engstrøm, Dept. of Clinical Medicine, University of Copenhagen, DK

Abstract
Human immunodeficiency virus (HIV) is a chronic viral infection of the immune system which causes a gradual loss of T cells and – inevitably the patient’s death. Worldwide more than 37 million people are living with HIV (PLWH) of which approximately 6200 are living in DK. The highly efficacies combination of anti-retroviral drugs (ART) is provided free of charge in Denmark. When the patients adhere to this medication, they have a life expectancy approaching that of the general population. Along with this in-

crease in survival rate came a concern for non-AIDS co-morbidities such as cardiovascular disease (CVD). The apparent increased risk of CVD among PLWH has been subject to a lot of investigations of lifestyle (smoking, alcohol and drug abuse), other chronic conditions (hypertension and diabetes mellitus), co-infections (hepatitis and cytomegalovirus), and side effects of the ART. Recent research indicates an association between chronic inflammation driven by HIV infection and the different co-morbidities.

We studied the association of different biomarkers and myocardial infarction (MI) in PLWH and found that while MI did seem associated with inflammation, an association was found even before the patients started ART – years before the MI which indicates that the MI is possibly not related to neither HIV nor ART.

Across several studies we looked at the possible influence of cytomegalovirus (CMV) on early CVD as assessed with ultrasound of the carotid arteries, coronary calcium score, and quantification of the blood flow to the heart muscle in both PLWH and healthy controls. In PLWH we found an association between both the enlargement of the arterial wall, the deposit of calcium in the arterial wall and the level of antibodies against CMV, which was not found among healthy controls [...]



PhD Thesis

Simon Bentsen, MD, PhD

Preclinical investigation of ischemic heart disease based on molecular imaging



Defended
02.12.21, online

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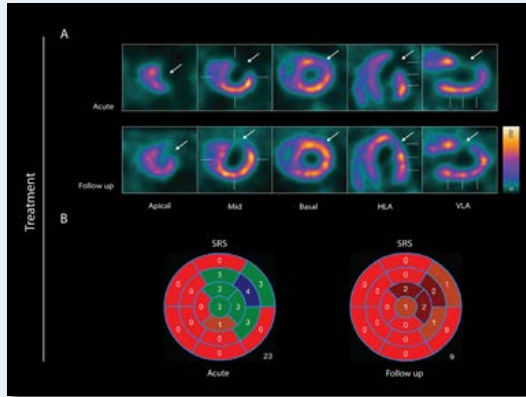
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Professor Lars Gormsen, Dept. of Clinical Medicine Nuclear Medicine and PET, Aarhus University Hospital, DK

Professor Henrik Engblom, Dept. of Molecular Medicine and Surgery, Karolinska Institute, SE, University of Edinburgh, Edinburgh, UK.

Abstract
Cardiovascular disease (CVD) is still one of the leading causes of death worldwide. In Europe, alone, nearly four million people die from CVD each year. Ischemic heart disease is the most common cause of death from CVD, and the most acute and severe form of ischemic heart disease is myocardial infarction (MI). MI occurs as a result of temporary or permanent occlusion of the coronary artery, which can be initiated by the rupture of a vulnerable plaque. The impaired blood flow to the myocardium, leading to ischemia, causes necrosis of the myocytes. The healing of the myocardium after an MI is complex, and poor healing is associated with remodeling of the myocardium, which leads to congestive heart failure. Therefore, the continuous research into diagnosis, treatment and risk assessment in patients with ischemic heart disease is a vital part of reducing short-term and long-term mortality

The overall aim of this PhD project was to evaluate certain aspects of CVD using molecular imaging in preclinical setups. The objectives were: 1) to investigate if certain drugs used to treat CVD increase or decrease the uptake of 82Rb into the heart; 2) to eval-

uate the cardioprotective effects of a new treatment “α-calcitonin gene-related peptide” analogue called SAX, following MI; and 3) to investigate a novel PET tracer [68Ga]Ga-RGD in the detection of angiogenesis following MI.



Myocardial perfusion imaging analysis after myocardial infarction. A: The acute scan (2 hours after myocardial infarction) shows that a large perfusion defect is present in the anterior and apical wall and a reduction in size at follow-up (three weeks after myocardial infarction) in a SAX treated rat. B: Polar map using the AHA 17 segment model, showing a clear reduction in perfusion defect from acute to follow-up scan.

PhD Thesis

Klas Bratteby, PhD

Development of ¹⁸F-labeling strategies for base-sensitive precursors

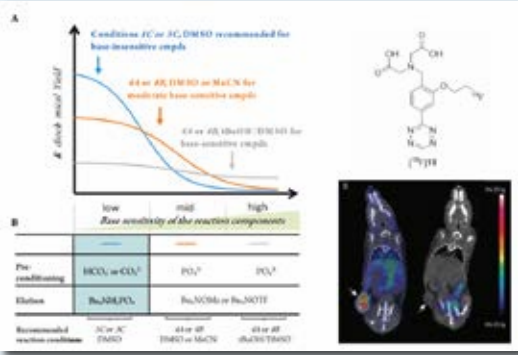


Defended
26.11.21, online

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Abstract
Functional molecular imaging has a significant impact e.g. on diagnoses or treatment planning within state-of-the-art clinical care. Positron emission tomography (PET) is usually the method of choice for functional imaging. It provides the highest sensitivity and spatial resolution compared to other functional imaging modalities. The radionuclide fluorine-18 (18F) is the most commonly used radionuclide for PET. Despite numerous tracers being developed in recent years, often with thorough optimization, the process of trapping and eluting 18F-fluoride on a QMA has historically been overlooked. Since this process is commonly the only source of base in the reaction this is essential for the reaction conditions, especially for aliphatic labelling. Through a thorough screening of the elution process using different preconditioning and eluting anions, a good map of conditions was obtained that could be tailored depending on the precursor. This was later applied to increase the radiochemical yield by up to 166% for different clinical tracers, including the popular Parkinson’s tracer [18F]FE-PE2I. Furthermore this also allowed us for the first time to aliphatically 18F-fluorinate a highly reactive tetrazine that later showed higher tumor uptake in a mouse tumour model compared to previous tetrazines.



Mapping of conditions for aliphatic ¹⁸F-fluorinations resulted in conditions that could be adapted depending on the structure of the precursor (left). This could then enable the first ever aliphatic ¹⁸F-fluorination of a highly reactive tetrazine. This gave us the freedom to design a novel structure (top right) that could then be evaluated in an in vivo mouse tumor model. The results showed an increased uptake in the tumor using pretargeted imaging and presents a new promising tool in the effort to proceed to clinical translation of ¹⁸F-tetrazines.

PhD Thesis

Anne Skovsbo Clausen, DVM, PhD

Development of positron emission tomography (PET) imaging and liposomal drug delivery systems for infectious and inflammatory diseases



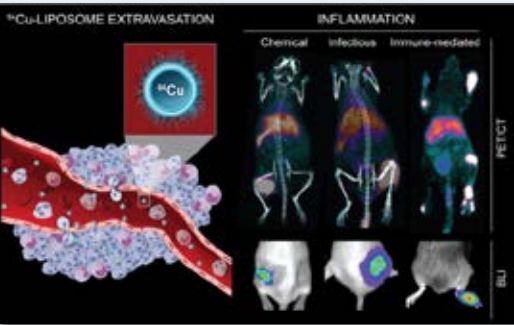
Defended
19.08.21, Nielsen Nielsens Auditorium, Panum Institute

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Abstract
► Infectious and inflammatory diseases represent therapeutic and diagnostic challenges in terms of lack of efficacy, adverse effects and delayed treatment initiation. In the clinic, new methods for earlier detection, monitoring of disease activity and optimizing drug delivery are highly warranted. For this purpose, molecular imaging and nanoparticle-based drug delivery systems would be highly valuable.
► In this thesis, the potential of the non-invasive imaging modality positron emission tomography (PET) to convert molecular knowledge about the cellular and vascular changes during inflammation into a specific, targeted tool for diagnostics and monitoring of treatment response was assessed. Additionally, liposomes were investigated as a potential nanoparticle-based theranostic system meaning a system for drug delivery and with diagnostic capabilities.
► With the focus on immune-mediated disorders including autoimmunity, inflammatory and infectious diseases, we assessed different preclinical mouse models. Included are two bacterial-induced infectious models with Staphylococcus aureus (S. aureus) and Borrelia burgdorferi sensu stricto (Bb), respectively. Subsequently, focal inflammatory models induced by turpentine and lipopolysaccharide (LPS), and a collagen-in-

duced arthritis (CIA) inflammatory model of rheumatoid arthritis (RA) were included
► In paper I, radiolabeled polyethylene glycol (PEG)-coated liposomes accumulated to a promising degree in inflammatory and infectious lesions throughout different inflammatory and infectious mouse models. As these long circulating 64Cu-liposomes showed great inflammatory and infectious targeting properties, we suggest that they can improve drug delivery and be used as a promising theranostic system for future clinical expansion. [...]



Graphical abstract of the article Quantitative determination of 64Cu-liposome accumulation at inflammatory and infectious sites: Potential for future theranostic system. Published in Journal of Controlled Release 2020.

PhD Thesis

Frederikke Petrine Fliedner, MSc Bio-Biotech, PhD

Liposomal drug delivery and early treatment monitoring in cancer - Advanced molecular imaging in rodent cancer models

Defended
25.03.21, online

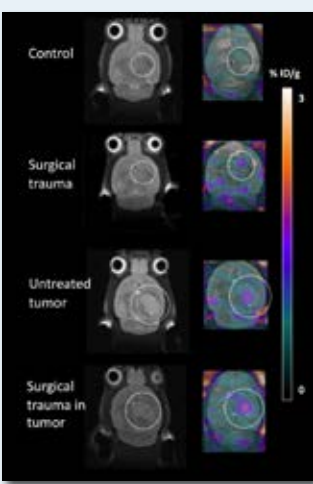
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Abstract
Decades of extensive cancer research has led to improvements in patient care and overall survival of patients across cancer types. However, the incidence

rate is estimated to increase in the coming years. The tumor microenvironment has proven highly heterogeneous, both within cancer types and between these, creating difficulties in disease management. Expanding the knowledge of the mechanisms of cancer pathogenesis, of treatment delivery, and of treatment responses can potentially give rise to further improvements of survival rates and quality of life for cancer patients. The overall objective of this thesis was to investigate the tumor microenvironment in relation to treatment delivery and treatment response monitoring. Liposomal drug delivery has been investigated intensively since the first cytotoxic drug encapsulated in passively delivered liposomes was approved in 1995. However, the potential of liposomal drug delivery has not met its expectations yet. Within this thesis, passive liposome accumulation was investigated by noninvasive molecular imaging. We wanted to obtain a better understanding of the mechanisms underlying liposome accumulation in tumors and how these could be optimally exploited for adjuvant therapy in combination with either radiation therapy or tumor resection. Project I investigated how the tumor microenvironment of two different cancers responded to radiation treatment and how the response affected liposome accumulation. Liposome accumulation was found to be affected by radiation doses, which regulated the vascularity within tumor [...]

To explore ⁶⁴Cu-liposome accumulation properties in brain cancer (xenograft orthotopic glioblastoma model, U87-MG) in connection with surgical intervention, animals were divided into four groups: a non-tumorous control of normal brain, surgical trauma site in normal brain, untreated tumor, and lastly surgical trauma in tumor area. In the figure, representative T2-weighted MR imaging from each group showing tissue structure and co-registered PET/MRI images are seen. Contrast difference between tumor site and surgical site was seen on the MRI images. On the co-registered PET/MR, accumulation of liposomes in the region of interest (marked with white circles) were visible. Increased contrast in the surgical trauma in normal brain was observed, which correlated with results from a subcutaneous model.



PhD Thesis

Lotte Kellemann Kristensen, MSc Human Biology, PhD

Development and evaluation of novel immune-PET radiotracers for optimized immunotherapy in cancer

Defended
02.12.21, online

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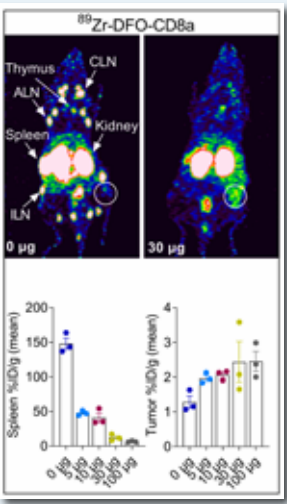
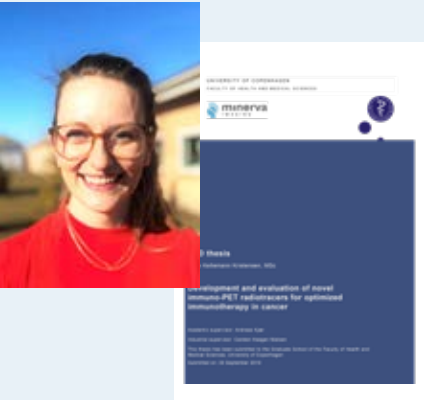
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Chief scientific officer Tina Bøndsorff, Oncoinvent AS, NO

Abstract
Cancer immunotherapy has revolutionized the way we treat multiple types of cancer. In particular, therapeutic strategies to block immuno-inhibitory signals by targeting immune checkpoints have shown significant clinical success. Although durable responses are

observed among many patients, the overall response rate is low and exceedingly variable. Thus, accurate companion diagnostic methods for selecting the patients most likely to benefit and assessing therapeutic response are essential to spare patients from ineffective treatments with potentially severe side effects and to improve overall survival.

Based on this unmet clinical need, this thesis covers the development of antibody-based positron emission tomography (immuno-PET) imaging biomarkers (PD-L1, CD4 and CD8) of the immune response established towards cancers cells. Throughout Manuscript I-III, the synthesis and optimization of these radiotracers for PET imaging is described. Furthermore, they are evaluated for their potential as non-invasive in vivo biomarkers of response to therapeutic blockade of various immune checkpoints.

Collectively, we developed immuno-PET tracers specific for whole-body detection and quantification of PD-L1, CD4 and CD8a. These radiotracers may be powerful tools to evaluate response to novel immunotherapeutic candidates in preclinical drug development. Furthermore, clinical translation of the developed probes may serve as an attractive approach to non-invasively identify cancer patients eligible for immune checkpoint therapy in the future.



PET imaging of CD8 T cells in tumor-bearing mice injected with one of the developed radiotracers, 89Zr-DFO-CD8a. To improve image contrast “cold” unlabeled CD8a (range; 0-100 ug) was injected along with 89Zr-DFO-CD8a. Co-dosing with >30 ug CD8a blocked endogenous signal from CD8a T cells in the spleen and lymph nodes and increased availability for tumor accumulation and visualization. Circles designate the tumor. ALN: axillary lymph node; CLN: cervical lymph node; ILN: inguinal lymph node.

PhD Thesis

Anders Beck Olin, MSc.Eng., PhD

Enabling multiparametric PET/MR imaging for radiotherapy planning in head and neck cancer patients

Defended
23.06.21, Auditorium 1, Rigshospitalet

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Associate Professor Flemming Littrup Andersen, Dept. of Clinical Physiology and Nuclear Medicine, Rigshospitalet, DK
Professor Adam Espe Hansen, Dept. of Diagnostic Radiology, Rigshospitalet, DK
Dr. Jacob Højgaard Rasmussen, Dept. of Otorhinolaryngology, Head & Neck Surgery and Audiology, Rigshospitalet, DK

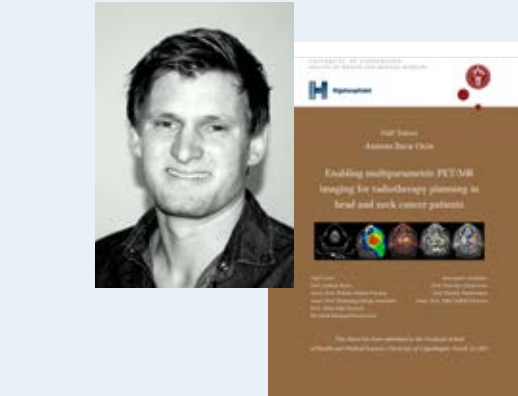
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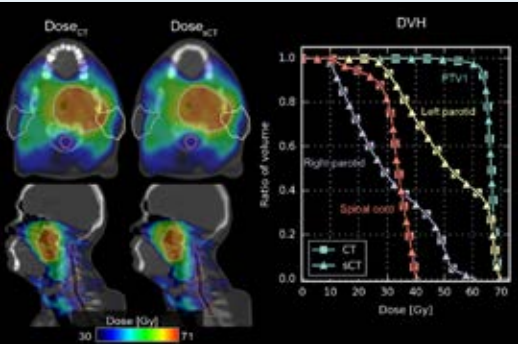
Abstract
Radiotherapy aims to deliver a high radiation dose to the target, while sparing the healthy surrounding tissues as much as possible. Despite advanced dose delivery technique and the use of planning CT images, treatment still fails for almost half of head and neck cancer patients. Therefore, attention is directed towards using improved imaging techniques such as PET and MRI for radiotherapy planning. The combined PET/MRI scanner offers simultaneous acquisition of images with excellent soft tissue contrast and functional information of great value for accurate target delineation and more individualized treatment strategies, such as dose painting.

The aim of this PhD project was therefore to enable the use of the multiparametric PET/MRI scanner as a one-stop shop for radiotherapy planning in head and neck cancer patients.

First, we designed a radiotherapy setup for PET/MRI and demonstrated the clinical feasibility of performing multiparametric PET/MRI of patients in radiotherapy treatment position.



Second, we developed a deep learning network for deriving synthetic CT from MRI and evaluated it for radiotherapy dose calculations and PET attenuation correction, while keeping the real planning CT as the reference [...]



Right: Comparison of a CT-based dose distribution ($Dose_{CT}$) and the dose distribution for the corresponding synthetic CT derived from MRI using deep learning ($Doses_{CT}$). Left: The cumulative dose volume histograms for different organs at risk and the planning target volume (PTV1) are shown for both calculation methods ($CT = squares$; synthetic $CT = triangles$). Note that the curves are on top of each other indicating a very high similarity between dose calculations performed using the real CT and the synthetic CT.

PhD Thesis

Jakob M. Slipsager, Software Engineer

Markerless Motion Correction For Better Image Quality in Brain MRI

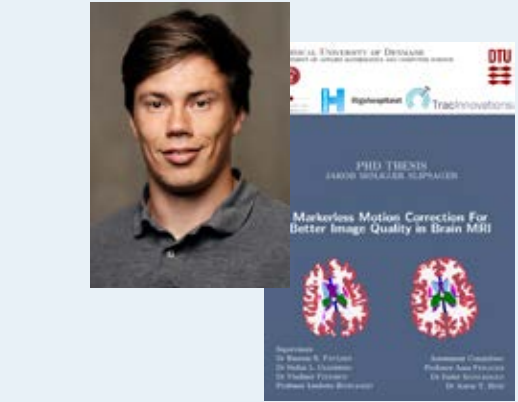
Defended
19.11.21, Department of Applied Mathematics and Computer Science, Technical University of Denmark

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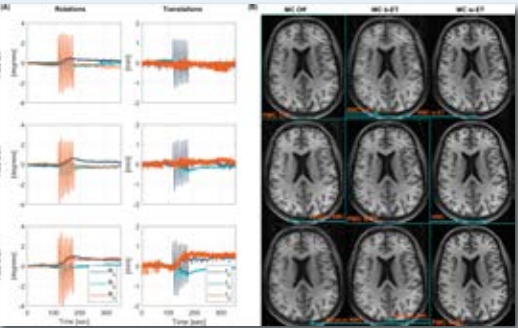
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Abstract
Diagnostic imaging such as X-ray, CT, and MRI are major players in modern diagnostic to obtain accu-

rate and correct diagnoses of diseases to provide the most effective treatment of patients. Magnetic resonance imaging (MRI) is a sophisticated technique developed in the 1970s using strong magnets and radio waves to create images of a patient's internal structures. MRI offers excellent soft-tissue contrast compared to CT, making MRI a powerful tool for neuroanatomical scans of the brain. However, the acquisition of MRI images is time-consuming, and during the data acquisition, the patient needs to lie still in a narrow and often loud scanner tunnel. The uncomfortable environment and lengthy examinations increase the risk of patient motion during the scan. Today, patient motion is a significant concern in clinical and research scans because even small motion can cause artifacts in the image, making it more challenging to interpret for the radiologist. Repeating low-quality scans and using anesthesia are commonly used to mitigate the motion problem, but these methods substantially increase the examination's cost. In this industrial Ph.D. thesis, we estimated the financial expenses of unintended patient motion and found that the annual cost can be more than \$370,000 per scanner. We calculated repayment periods of motion correction solutions with variable implementation cost and performance based on the estimated cost. Here, we found that a motion correction solution with a total installation cost of \$100,000 is financially viable after one year if it can



correct at least 50% of the unusable images. Thus, our estimate shows that motion correction can substantially reduce the expenses of patient motion (...)



In vivo comparison of MC OFF, PMC, and RMC during periodic continuous motion (large amplitude, subject 2). (a) Recorded motion parameters of the performed motion. (b) The MPRAGE images along the diagonal were acquired with PMC off, Before echo train PMC (PMC b-ET), and Within echo train PMC (PMC w-ET). Images outside the diagonal are retrospectively corrected or reverse corrected versions of the highlighted image along the same row (indicated by the arrows). These images include RMC, reverse RMC (r-RMC), and HMC. From Slipsager et al. [32]

Academic and other activities

Ali Asmar, Staff Specialist, PhD, Secretary of Danish Society of Clinical Physiology & Nuclear Medicine (DSKFNM) and member of the board in Danish Hypertension Society (DaHS).

Andreas Kjær, Professor, Consultant, ERC advanced grantee, is member of the advisory board of the European Neuroendocrine Tumor Society (ENETS) and board member of the Cancer Research Foundation at University of Copenhagen. Past President of the Scandinavian Society of Clinical Physiology and Nuclear Medicine (SSCPNM) and member of the Scientific Committee of the Danish Cancer Society. Founding Editor-in-Chief of Diagnostics (Basel) and International Associate Editor of Journal of Nuclear Medicine (JNM). Leader of several multi partner projects for development of compounds to visualize aggressive cancer and click-chemistry funded by the Innovation Fund Denmark and EU. Head of the Cluster for Molecular Imaging and Director of the PhD Program for Medical & Molecular Imaging at the Faculty of Health and Medical Sciences, University of Copenhagen. Co-chair of the Lundbeck Foundation Danish American Research Exchange (DARE) Program. Co-chair of Clinical Academic Group – Image-Guided Cancer Surgery. Member of the Industrial Researcher Committee, Innovation Fund Denmark. Member of the Academy of Technical Sciences (ATV).

Anne-Mette N. Wittekind, MSc. Pharm., Deputy Qualified Person, is member of Dansk Standard.

Annika Loft Jakobsen, Consultant, PhD, is involved in a various number of clinical research protocols, teaching at national and international courses pre- and postgraduate for medical doctors, technologists, radiographers and nurses and is invited speaker at national and international meetings and congresses. She is supervisor and opponent for several PhD students and responsible for the specialist course in oncology for nuclear medicine physicians. She is member of the “European Organization for Research and Treatment of Cancer” (EORTC). Member of European Association of Nuclear Medicine (EANM) and member of BIR, Danish Society of Oncological Radiology and Danish Society of Clinical Physiology and Nuclear Medicine. Member of Regional Working Groups for implementation of clinical guidelines for: lymphoma, malignant melanoma, lung cancer, cancer of unknown primary, and suspicion of severe disease. Member of National Working Groups for lymphoma (Chair of the Diagnostic Imaging Group under Danish Lymphoma Group (DLG)). Member of the National PET/CT Group.

Birgitte Hanel, Biomedical Scientist, DMSc. Member of the committee, Dansk Lungefunktions Standard. Member of the Spirometry Committee, ERS. Teaching in specialist course in “Clinical Respiratory Physiology” for Nuclear Medicine physicians and Respiratory Physicians. Teaching in course of spirometry and quality control organized by PLO. Board member of the Foundation of Biomedical Laboratory Scientist.

Bryan Haddock, Physicist, MPE, MSC, Board member of both the Danish Society for Clinical Physiology and Nuclear Medicine (DSKFNM) and the Danish Society for Medical Physics (DSMF). Supervisor for several master- and bachelor students.

Camilla Bardram Johnbeck, Staff Specialist, PhD, Chairman of the board of Young Doctors in Nuclear Medicine in Denmark (YNK), member of the board in Danish Society of Clinical Physiology and Nuclear Medicine (DSKFNM) and member of the European Neuroendocrine Tumor Society (ENETS).

Claes Nøhr Ladefoged, Postdoc, MSc, PhD, co-supervisor for PhD and MSc students in the department. Co-head of the research group Clinically Applied Artificial Intelligence (CAAI). Responsible for PET/MRI attenuation correction.

Elisabeth Albrecht-Beste, Clinical Associate Professor, Consultant, member of Danish Society of Radiology, chair of post-graduate education committee of Danish Society of Radiology, chair of the Regional Advisory Board in postgraduate education in radiology and member of the Danish Society of Oncoradiology.

Flemming Littrup Andersen, Head of IT, MSc, PhD, Associate Professor at Department of Clinical Medicine, Copenhagen University, is involved

in a number of clinical and pre-clinical research protocols, supervisor for several PhD, master and bachelor students and involved in both pre- and postgraduate teaching. Joint head of the research program CAAI for Clinically Applied Artificial Intelligence at the department. Member of the HYBRID Network; a collaboration for research and training of young researchers in the field of hybrid imaging, funded as a Marie Skłodowska-Curie Innovative Training Network under EU Horizon 2020.

Helle Hjorth Johannesen, Consultant, is member of Danish Society of Radiology, member of Danish Society of Oncoradiology and member of Danish Society of Medical Magnetic Resonance Imaging.

Helle Juhl Simonsen, Research MR Technologist, Biomedical Laboratory Scientist, member in International Society for Magnetic Resonance in Medicine (ISMRM)/Section for MR Technologist (SMRT) MR safety committee. Board member of the Danish Society for Magnetic Resonance, member and service responsible. Member of RegionH’s MR safety committee, MR safety education group and MR contrast group. Board member of the Danish MR safety group, working with Danish guidelines for MRI safety.

Henrik B.W. Larsson, Professor, Consultant, DMSc, Head of Functional Imaging Unit. Professor in Clinical and Comparative Physiology, Institute of Clinical

Medicine, The Faculty of Health and Medical Science, University of Copenhagen, Denmark. Responsible for specialist course in tracer kinetic theory, math, and statistic for nuclear medicine physicians. Responsible for specialist course in functional imaging (MRI, PET-MRI, UL) for nuclear medicine physicians. Member of the Danish Multiple Sclerosis Research Council.

Julie Bjerglund Andersen, Staff Specialist, PhD. Board member in Society for Junior Physicians in Nuclear Medicine, a part of the Danish Society of Nuclear Medicine and Clinical Physiology. Staff representative for Junior Physicians in the Department.

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Jann Mortensen, Clinical Professor, Consultant, is responsible for the specialist course in “Clinical Respiratory Physiology” for nuclear medicine physicians and respiratory physicians. Responsible physician for Nuclear Medicine in the Faroe Islands. Member of the steering committee of “Dansk Forskningscenter for lungekræft” (Danish Research Center for Lung Cancer), Dansk Lunge-

cancer Gruppe” (Danish Lung Cancer Group), and its subcommittees “Dansk Diagnostisk Lungcancer Gruppe” (Danish Diagnostic Lung Cancer Group) and “Lungcancer Screeningsgruppen” (Screening of Lung Cancer Group), member of the steering committee and the quality subcommittee for creating Danish reference values for lung function, and member of the steering committee of Danish spirometry courses..

Johan Löfgren, Consultant, teaches at specialist courses for oncologists, endocrinologists, radiologists and nuclear medicine specialists. Member of the Diagnostic Imaging Group under Danish Lymphoma Group. Involved in clinical research protocols with special focus on PET/MRI and is an invited speaker at national and international meetings and congresses. Involved as a clinical expert in RIS/PACS and HIS on a local and regional level.

Kim Francis Andersen, Consultant, is Chairman of the Danish Sarcoma Group (DSG). He is member of Scandinavian Sarcoma Group (imaging subgroup), European Osteosarcoma Consortium (FOSTER - imaging subgroup) and Danish Pediatric Hematology Oncology Group (DAPHO - solid tumor subgroup). He is involved in various clinical research protocols. He teaches at specialist courses for medical doctors and is supervisor for students at the Medicine and Technology programme (Biomedical Engineering), Technical University of Denmark (DTU).

Academic and other activities

Lise Borgwardt, Consultant, PhD. Chief of Pediatric Nuclear Medicine at Rigshospitalet, Senior Advisor of the Paediatric Committee under EANM, Scientific Committee member of the EANM, Boardmember of DAPHO for Diagnostic Imaging, Boardmember of BørneRigets Project Steering Group, Member of Radiology Committee EpSSG, Member of NM Committee SIOPEN, member of the Paediatric Imaging Harmonization Group EANM/ SNM, member of the Tumourboard for Paediatric Solid Tumours at Rigshospitalet, Chair of Danish Association of Paediatric Nuclear Medicine, Chair of the Paediatric Focus Group at the Department of Clinical Physiology, Nuclear Medicine and PET and member of the Process Group for the development of the Children’s Hospital at Rigshospitalet. Involved in clinical research protocols, supervisor for PhD students, teaching at national and international courses pre- and postgraduate for medical doctors, and invited speaker at national and international meetings and congresses.

Liselotte Højgaard, Professor, Head of Department, member of the Board, Die Robert Bosch Stiftung, Germany. Member of the Board of Directors, The Novo Nordisk Foundation. Member of the ERC Scientific Council. She represents the University of Copenhagen, Rigshospitalet in the Medicine and Technology Bioengineer program, the Technical University of Denmark (DTU), where she is also adj. professor. Elected member of the Royal Danish Academy of

Sciences and Letters, elected member of ATV, “the Danish Academy of Technical Sciences”, member of the Olav Thon Foundation, Science Advisory Board, member of the Board of the Crown Prince Frederik and Crown Princess Mary’s Foundation and member of the Board of Arvid Nilsson’s Foundation and Chair of Tagea Brandt’s prize.

Malene Fischer, Professor, Consultant, DMSc, PhD, is supervisor for several PhD Students, master- and bachelor students and involved in both pre- and postgraduate teaching. Member of the European Association of Nuclear Medicine (EANM), European Society of Hybrid Imaging (ESHI) where she is treasurer and member of the board, the Danish Society of Clinical Physiology and Nuclear Medicine (DSKFNM) and the Danish Society of Clinical Oncology. Affiliated to the Centre of Excellence for Personalized Medicine of Infectious Complications in Immune Deficiency (PERSIMUNE). Work package leader in the HYBRID Network; a collaboration for research and training of young researchers in the field of hybrid imaging, funded as a Marie Skłodowska-Curie Innovative Training Network under EU Horizon 2020. MF is a member of the ”Hybrid, Molecular and Translational Imaging” committee for the European Conference of Radiology 2022. Since June 2018 holding a joined position as Senior Clinical Lecturer and honorary Consultant at the PET Centre, Guy’s & St Thomas Hospital, Kings College London in UK.

Maria Helene Pejtersen, Staff Nuclear Medicine Technologist, is member of the Symposiagroup for Technologists at Rigshospitalet.

Nic Gillings, MPhil, PhD, Chief Radiochemist, Qualified Person (QP) is vice chair of the EANM Radiopharmacy Committee, member of the editorial board of EJNMMI Radiopharmacy and Chemistry, member of the Society of Radiopharmaceutical Sciences and member of the Royal Society of Chemistry. He also acts as coordinator for the joint supplier audit program for all manufacturers of PET radiopharmaceuticals in Denmark and Southern Sweden.

Otto Mølby Henriksen, Consultant, PhD, is member of the DRG Committee in Danish Society for Clinical Physiology and Nuclear Medicine (DSKFNM) and member of the Danish Epilepsy Surgery Team. He is co-supervisor of two PhD students and teaches at PhD courses as well as pregraduate courses for Medicine and Technology Bioengineers.

Peter Oturai, Consultant, is responsible for the postgraduate education of physicians in the department. He is head of the Doctors Clinical Physiology and Nuclear Medicine (CPNM) Training Committee affiliated to DSKFNM. He is responsible for the specialist course in Endocrine Pathophysiology for CPNM physicians in Denmark.

Rasmus Sejersten Ripa, Consultant, DMSc, Supervisor for several PhD students. Member of the Danish Health Authority’s Committee for Heart Disease. Board member of the Society for Theoretical and Applied Therapy and member of American Society of Nuclear Cardiology. Editorial Board Member “Diagnostics”, Section editor “Frontiers in Endocrinology”.

Robin de Nijs, MSc, PDEng, PhD, Medical Physicist, is member of the Danish Society for Medical Physics and lecturer at the Technical University of Denmark, Copenhagen University and for the association of physics teachers. Supervisor for under- and post-graduate students in a.o. Medicine & Technology and Medical Physics. Associated Medical Physics Expert for the SPECT brain scan section of the Neurobiology Research Unit at Copenhagen University Hospital.

Ronan M.G. Berg, MD, DMSc, Staff Specialist and Associate Professor of respiratory physiology at the University of Copenhagen, Visiting Professor at the University of South Wales, UK, scientific co-editor at the journal Physiology News (London, UK). Member of several scientific societies including the Physiological Society (UK) and the Danish Society of Medical Philosophy, Ethics and Methodology. He has previously received the prestigious Pfizer Prize from the Physiological Society for his contributions to the physiological sciences. He teaches physiology, nuclear medicine and medical ethics at both

pre- and postgraduate levels, and handles scientific supervision on bachelor, master, and PhD levels both in Denmark and in the UK.

Sune Høgild Keller, Computer Scientist, PhD, is involved in various clinical and preclinical research protocols and scientific development in PET/CT, PET/MR and neuro-PET (HRRT). He teaches at a variety of courses for medical doctors, PhD students, technologists and MSc students. He is supervisor for students at the Medicine and Technology program (Biomedical Engineering), Technical University of Denmark (DTU) and co-supervises PhD students in biomedical engineering and computer science.

Søren Holm, Senior Physicist, is chair of the EANM Radiation Protection committee. He is a delegate for the Danish Medical Physics Society (DSMF) to the European and International organizations for Medical Physics (EFOMP and IOMP), assessor for EFOMP’s Examination Board (EBB), member of an IAEA advisory group concerned with QA/QC of non-imaging nuclear medicine equipment and member of ICRP Task Group 117 for radiation protection in PET and PET/CT. He is member of Sundhedsfagligt Råd i Klinisk Fysiologi og Nuklearmedicin in the Capital Region, (the Specialty Advisory Committee (SFR) in Clinical Physiology and Nuclear Medicine) and external lecturer at University of Copenhagen.

Thomas Levin Klausen, Chief Physicist, MSc, Specialist Medical Physicist, member of the Danish Society for Medical Physics (DSMF) and the Danish Society of Clinical Physiology and Nuclear Medicine (DSKFNM). Responsible Physicist for Nuclear Medicine at the Faroe Islands.

Thomas Lund Andersen, MSc, PhD., Medical Physicist, is member of the Danish Society for Medical Physics (DSMF) and the Danish Society for Medical Magnetic Resonance (DSMMR). Involved in various clinical and preclinical research protocols and the scientific development of PET/MRI.

Ulrik B. Andersen, Consultant, Co-supervisor for PhD students in the department. Member of European Society of Hypertension and acknowledged hypertension specialist by this society. Expert in vascular ultrasound and responsible for the specialist course in vascular ultrasound for nuclear medicine physicians in Denmark. Member of the Danish Society of Clinical Physiology and Nuclear Medicine, Danish Society of Cardiology and Danish Society of Diagnostic Ultrasound.

Research



Professor Jann Mortensen, Associate Professor Ronan Berg and Research Coordinator, Ursula Hartmann

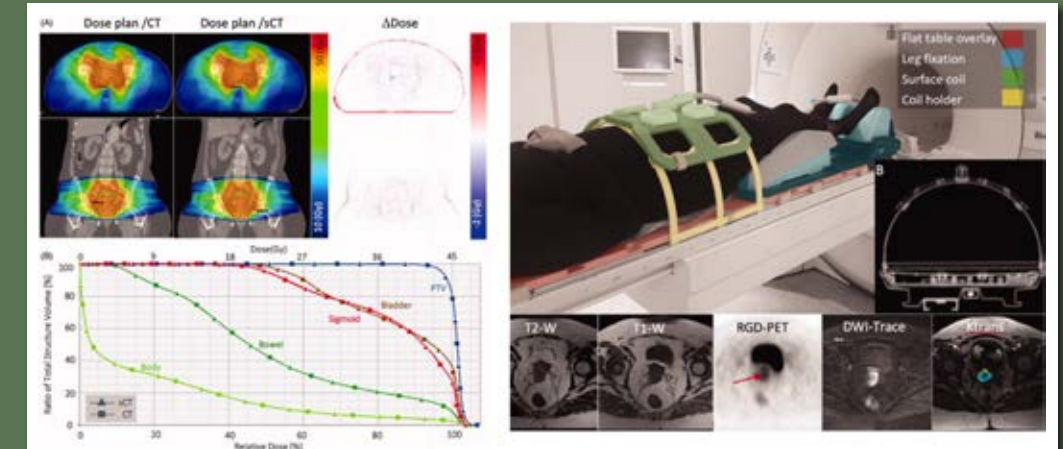
Year 2021 was the second year of scientific research in the COVID-19 era, which has continued to affect the conduct of science in all the Department's research groups. Despite these irrefutable challenges, our dedicated scientists have maintained our comprehensive research program directed at developing innovative solutions to solve unmet clinical needs, including research specifically directed at understanding the pathophysiology and identifying potential treatment targets in COVID-19 and its long-term sequelae. Furthermore, we have expanded the Department's research team, so that it now also includes our new in-house research coordinator, Ursula Hartmann, who assists the Department's many researchers in coordinating and administering various projects and related funding. Our research program is built on our strong in-house com-

petencies as well as on strategic collaborations with leading international and national research groups with complementary competencies and capabilities. Although challenging in many ways, the year 2021 ended on a high with the installation of a total-body PET/CT scanner. Direct access to this new technology will not only improve our clinical service and current research portfolio, but also enable us to explore completely new areas of research areas. Studies across all our current major research themes are highlighted below.

New tracers

Several projects aimed at developing new PET tracers for non-invasive tissue characterization and phenotyping are ongoing. These novel tracers will be used both for diagnosing, staging and risk stratification as well as for therapy planning

Figure 1. Radiotherapy planning in patients with cervical cancer on PET/MR: (A) The calculated dose plan for CT and synthetic CT (sCT) images and the error map representing the dose distribution difference. (B) Dose volume histograms comparing the planned dose of target volumes (PTV) and different organs at risk for CT and sCT. (C) Example of a patient in radiotherapy position using dedicated MRI compatible positioning equipment, with AC map of the radiotherapy set-up and representative multi-parametric PET/MRI image dataset with simultaneous RGD-PET/MRI of a cervical cancer patient. (Reproduced from Ahangari, S et, *Acta Oncologica* 2021 Aug;60(8):1045-1053).



and monitoring. Tracers developed and already taken first-in-humans at the Department include ^{64}Cu -DOTATATE, ^{64}Cu -DOTA-AE105, ^{68}Ga -NOTA-AE105, ^{68}Ga -NODAGA-RGD₂ and ^{18}F -ASIS. Some of these tracers have now moved into phase II clinical trials to investigate and establish their clinical utility. Accordingly, ^{68}Ga -NOTA-AE105, a PET tracer targeting uPAR, which is a marker of cancer aggressiveness and metastatic potential, has been tested in three completed and six ongoing phase II trials in various cancers. Likewise, ^{68}Ga -NODAGA-RGD₂, an angiogenesis PET tracer, is currently tested in Phase II clinical trials within both cancer (see Figure 1) and cardiovascular disease.

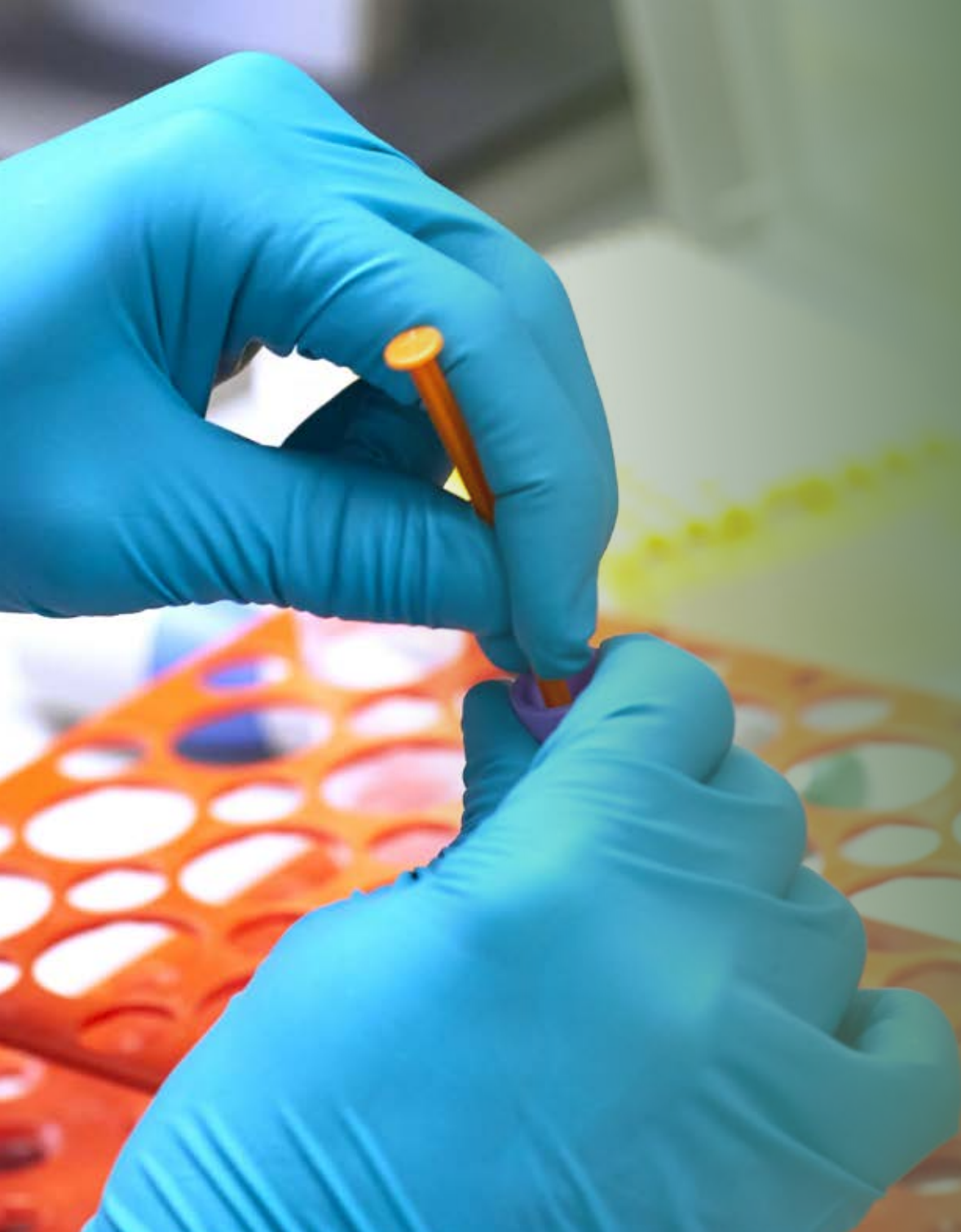
To facilitate development and clinical translation of new PET tracers, we have built a comprehen-

sive platform for validation of novel tracers, including facilities for cell work, molecular biology (proteomics and genomics), histology, biomarker measurements and predictive relevant animal models. We have other promising new PET tracers in our developmental pipeline and expect a continuous translation of the best of these into clinical use over the coming years.

Clinical PET/CT

The department is among the largest clinical PET-facilities in Europe and have a strong focus on delivering up-to date excellent clinical quality. One of the key means to fulfil this goal is clinically embedded research. This includes a large number of prospective clinical protocols aimed at evaluating the diagnostic and prognostic value of PET/CT in different clinical scenarios, from phase 1 and 2 trials

testing new tracers to larger studies aiming at clinical implementation. An example of the latter being the on-going national randomized trial, anchored at the department, testing the value of FDG-PET/CT in the surveillance of patients with lung cancer. We also conduct or are involved in a number of retrospective research projects as well as projects focused on quality development, e.g. related to implementation of the new total body PET/CT scanner. Based on previous and on-going research and in close collaboration with the Radiotherapy department, we have been pioneering the use of respiratory gating in PET/CT. Many of these studies also include PET/MRI to study the benefit compared to PET/CT (see Figure 1). An area of growing interest is the use of PET/CT for non-malignant indications, i.e. inflammation and infection, and a number of studies are currently on going within this field.



PET/MRI

Being one of the first departments to install a combined PET/MRI scanner in 2011/2012 and a second one in 2020, we have established a comprehensive research program on PET/MRI with focus on the benefit of combining molecular imaging with PET and multiparametric MRI. As an example, the potential of PET/MRI as a ‘one stop shop’ for radiation therapy planning has been demonstrated in patients with oropharyngeal respectively cervical cancer (see Figure 1). A large number of clinical trials have been finalized or are ongoing with this purpose. The ambition is to improve tissue characterization and response monitoring ability in cancer treatment, pediatric studies, brain studies and atherosclerotic plaque characterization. Focus of MRI includes the use of diffusion-weighted images (DWI)/apparent diffusion coefficient (ADC), perfusion imaging (DCE-MRI) and magnetic resonance spectroscopy (MRS) especially with the use of hyperpolarized molecules. With access to matching preclinical PET and 7T MRI, we can work translational in developing and evaluating new methods.

HyperPET

The Department was the first to install a dynamic nuclear polarized (DNP) for hyperpolarization of ^{13}C -labeled compounds next to a PET/MRI scanner. We have used this set-up for development of and research in the combination of hyperpolarized ^{13}C -MRS and PET, a combination we named *hyperPET*. So far, we have focused on the use of

HyperPET for tissue characterization in cancer, cardiovascular disease and inflammation/infection. Using ^{13}C -pyruvate, we have continued our studies of the Warburg effect and its relation to glucose uptake as measured by FDG. Recently, we also combined ^{13}C -pyruvate with a non-FDG PET tracer, i.e. the angiogenesis tracer ^{68}Ga -NODAGA-RGD₂. In addition, we studied non-pyruvate ^{13}C -compounds, e.g. ^{13}C -fumarate, which is an indicator of necrosis. Based on our results obtained so far, HyperPET is superior in cancer phenotyping and response monitoring, and has the potential for future clinical use.

Pediatric nuclear medicine investigations

The Department undertakes many pediatric investigations, and is involved in a wide array of prospective clinical trials using both PET and SPECT in collaboration with clinical pediatric departments. These ongoing studies particularly focus on diagnostics and treatment of pediatric cancers and infections with FDG-PET, as well as functional assessments of the hepato-biliary system and renal function. In addition, targeted radionuclide therapy for cancer in children is currently an area of intense interest. Finally, the use of PET/MRI in children to save radiation dose is studied.

Neuro-PET

Over the past year, the research focus has mainly been on clinical method development in brain tumors, dementia classification, as well as

non-invasive assessments of the molecular characteristics and growth of meningioma, and the detection of small tumor remnants after treatment. Furthermore, we have been engaged in tumor perfusion mapping using predominantly PET/MRI in order to identify a multiparametric potential. The total-body PET/CT system has been implemented for use in pediatric neurooncology and non-invasive estimation of cerebral perfusion for assessment of cerebrovascular disease. In cooperation with the Neurobiology Research Unit and Centre for Integrated Molecular Brain Imaging, neuroreceptor ligands in the serotonergic system have been developed and used for research in neurobiology.

Functional MRI

Magnetic Resonance Imaging (MRI) is useful for studying physiological brain function, and we have over the years developed methods. We currently have a major focus on the brain’s glycolysis and lactate production, and have indeed contributed to a new understanding of the brain’s metabolism, where oxygen consumption is related to the steady on-going energy ‘household’ while transient increases in local neural activity relies on a fast but less efficient energy production from lactate-producing glycolysis. Indeed, it seems that the level of neural information generation is very dependent on the capability of fast aerobic glycolysis. The perspective is that the capability of local and fast lactate production is a prerequisite for neural information generation, and thus assessing

lactate production indicates the level of neural information possible. This hypothesis links neural activity and metabolism directly and gives new perspective for improving or ameliorating cognitive decline during aging, mild cognitive decline and neurodegenerative diseases as Alzheimer’s dementia.

Atherosclerosis

Non-invasive visualization of atherosclerosis and prediction of plaque vulnerability in atherosclerosis using PET/MRI and PET/CT is intensively studied both in preclinical and clinical trials. The quantification of low-grade vascular inflammation has become a focus area and is now used in several clinical trials on cardiovascular risk and mode-of-action studies of different therapies, like GLP-1 antagonists. In addition, patient groups at risk are studied and special focus is on the value of new specific PET tracers, e.g. for the study of macrophage activation by ^{64}Cu -DOTATATE. Clinically, our ambition is to provide image-based risk stratification to select patients that will benefit from vascular surgery. We continue to refine and develop vascular imaging using novel PET tracers.

Nuclear cardiology

Taking advantage of the ability to quantify myocardial perfusion in absolute terms and myocardial flow reserve by ^{82}Rb PET, we study these parameters in various cardiovascular diseases. This includes studies on how interventions as stem cell therapy, gene therapy and pharmacological treat-

ment affect myocardial perfusion and integrated vasomotor function. The development of ischaemic heart diseases is studied in selected groups of patients, e.g. patients with diabetes. In addition we study the value of new specific PET tracers, e.g. for the study of myocardial angiogenesis by ⁶⁸Ga-NODAGA-E[c(RGDyK)]₂. On basis of this, better screening algorithms for early detection of ischaemic heart disease are developed.

Lung studies

A major theme has been the sequelae of COVID-19, so-called 'long COVID'. Thus, we have completed the SECURE (Sequelae COVID-19, Copenhagen University Hospital, Rigshospitalet) study, focusing on the long-term impact of COVID-19 on lung function and structure, and conducted randomized clinical trials on rehabilitation efforts after COVID-19 using either aerobic training or inspiratory muscle training. We have also continued our studies on the innate and adaptive pulmonary immunology of COVID-19. A large number of other studies using lung function testing and lung scintigraphy (VQ-SPECT/CT) in different patient groups are ongoing, e.g. studies in lung transplantation, and lung volume reduction treatment of emphysema, thus taken advantage of the superior diagnostic performance of VQ-SPECT/CT compared to CT alone as previously demonstrated by us. Furthermore, several studies on mucociliary clearance of the nose and lungs, a method pioneered at the Department, have been conducted. Finally, we are participating in a large study

collecting data for a lung function test reference database.

Studies of muscle function

With the use of methods from clinical physiology, nuclear medicine, MRI and molecular analyses, muscle function, bone density, and body composition have been studied with a current focus on the effects of exercise, immobilization, and aging. Data collected on the same parameters form a population-based study, that serves as a reference database and which may elucidate markers to predict aging-related diseases.

Immune cell tracking

At present, a particular focus is on development of new imaging tools for non-invasive visualization of the immune response and for tracking immune cells. These methods will be used in studies of inflammation, infection, rejection and in particular immune oncology. The Department is a key participant in the PERSIMUNE program funded by the Danish National Research Foundation. Currently, special attention and support from the PERSIMUNE program is given to development and use of new PET ligands for specific imaging of the immune response, e.g. CD4, CD8 and macrophage imaging. Within immune oncology, these tracers will serve to better understand the mechanisms behind immune responses in cancer and as a tool to select patients eligible and likely to respond to specific immunotherapies.

Radionuclide therapy and theranostics

An ever-increasing attention is directed towards development and use of targeted radionuclide therapy using both beta- or alpha-emitting specific ligands targeting relevant cancer characteristics. The Department takes part in research within this area by testing new ligands and producing relevant therapeutic isotopes. Most notably, we also in-house develop new theranostics based on promising imaging ligands, which are then labelled with beta or alpha emitting radionuclides. Cancers that are currently being targeted clinically include glioblastomas, neuroendocrine tumors, prostate and colorectal cancer. Development of therapeutic radioligands is largely based on imaging with the same ligand as the therapy (theranostics). The concept of a tracer that visualizes the target prior to starting therapy is also known as companion diagnostics.

Image guided surgery

Image-guided cancer surgery using optical probes is a relatively new concept. In collaboration with several surgical departments, we develop our most promising PET ligands targeting cancer specific targets into near-infrared (NIR) optical probes. These are used for intraoperative delineation of cancer to better ensure negative (free of cancer cells) surgical margins and to spare critical functional tissue, e.g. during brain surgery. The technology of image-guided cancer surgery is expected to lead to better patient outcome, including overall survival and improved quality of

life. Within this field, the Department participates in the Clinical Academic Group – Imaging-Guided Cancer Surgery (CAG-IGCS). We expect the optical methods to work in synergy with PET, as a pre-operative PET will predict whether use of optical imaging of the same target is feasible. We expect the optical technologies to become enablers of performing semi-automated robotic in the future.

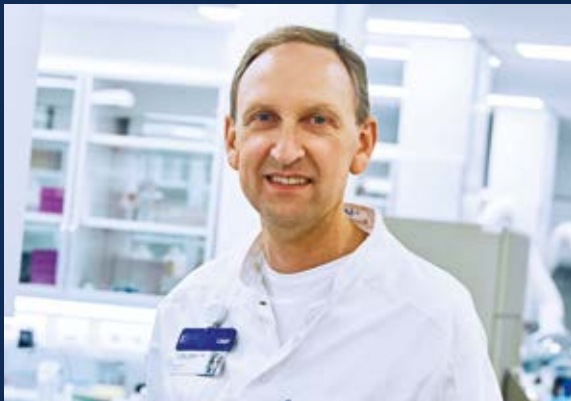
Whole body counting

Together with external collaborators, we apply whole body counting for precise measurements of body composition. Moreover, studies on the absorption of certain minerals from the gastrointestinal tract are undertaken.

Clinically applied artificial intelligence

We study how to exploit artificial intelligence in medical imaging. These studies cover most of the imaging modalities and disease areas in the Department, e.g. oncology, brain, cardiovascular and radiation therapy. Examples of studies performed includes generation of synthetic CT from MR scans for PET attenuation correction and RT dose planning (see figure 1), noise reduction applied to reduction of radiotracer doses, or outcome prediction, segmentation, and classification in order to support image reading including artificial intelligence-driven image derived biomarkers.





Cluster for Molecular

Cluster for Molecular Imaging

Professor Andreas Kjær

Precision medicine, i.e. tailoring therapy according to disease characteristics of the individual patient, has caused a need for diagnosing at the molecular level. Standard molecular biology methods rely on tissue sampling for in vitro and ex vivo analyses and are prone to not being representative, e.g. when a biopsy does not characterize the aggressiveness of a tumor. In contrast, molecular imaging allows for non-invasive studies at the whole-body level and elegantly circumvents *sampling error*. Due to the unsurpassed sensitivity and quantitative nature of PET, the technology holds great promise for molecular imaging of phenotypic characteristics as a basis for practicing *personalized medicine*. Among characteristics, which can be visualized are the *hallmarks of cancer*, e.g. cancer aggressiveness, angiogenesis, and interaction with the immune system. We

predict that such PET ligands will become game-changing within many diseases including cancer and cardiovascular disease. Moreover, successful PET imaging ligands can be “modified” into targeted radionuclide therapies if labeled with α - or β -emitting isotopes or into optical imaging ligands for guiding surgery.

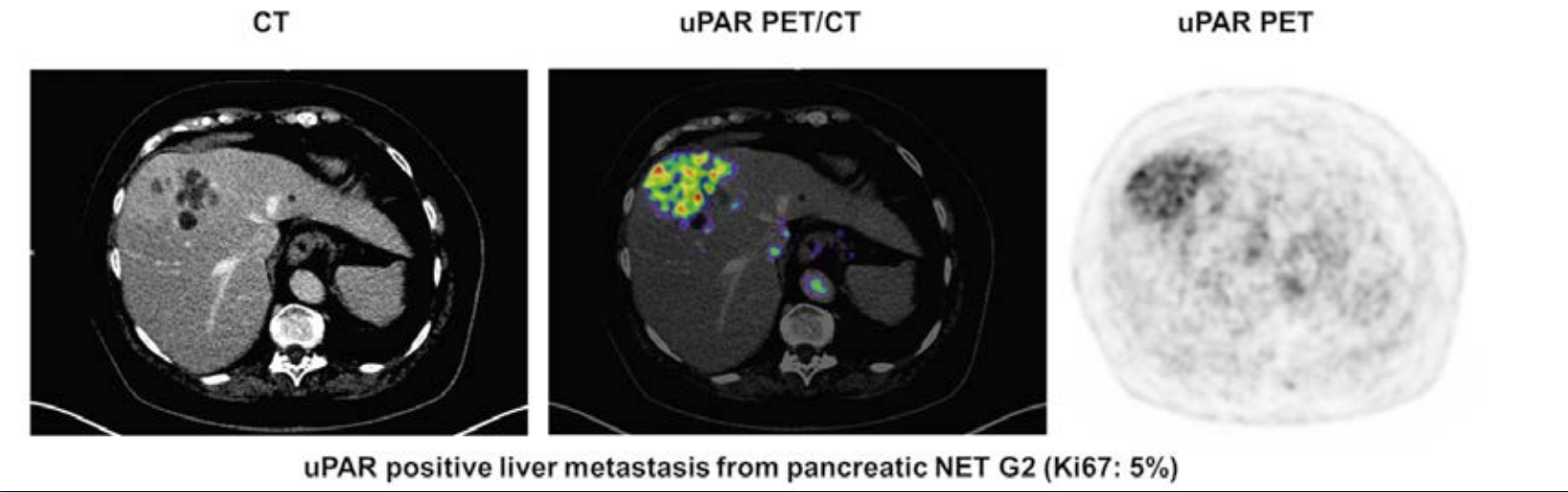
At present, our translational molecular imaging and theranostics research program focuses on the development and application of new molecular imaging and therapeutic ligands to support *precision medicine*.

Cluster for Molecular Imaging was established in 2003 at the University of Copenhagen (Panum Institute) and started out as a specialized facility for molecular imaging in animals using

PET, SPECT, CT, MRI and optical imaging. Over the years, it was further developed into a comprehensive translational platform to support the discovery and development of new PET tracers and radionuclide therapies. Testing in relevant animal models forms the basis for ligand selection and translation into clinical use. The development of *predictive animal models* across disease entities, e.g. orthotopically implanted human xenograft tumors as well as metastatic cancer models is a core competence.

We currently hold a broad *pipeline* of PET tracers and radionuclide therapies in pre-clinical development and expect several of these candidates to be taken into clinical testing and human use over the next years.



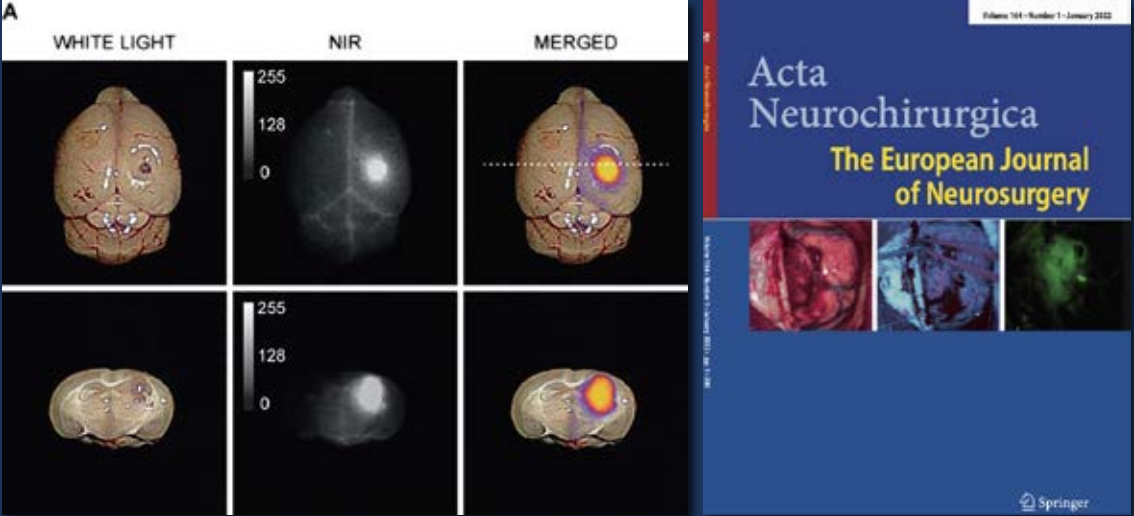


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Figure 1. uPAR-PET of a neuroendocrine tumor patient using our in-house developed radiotracer ^{68}Ga -NOTA-AE105. Transverse CT, PET/CT and PET images demonstrate clear uPAR tracer binding to a liver metastasis in a patient with a WHO grade 2 (Ki67: of 5%) tumor. (images provided by Carlsen EA et al.).

▶

Figure 2. Translation of an optical uPAR-targeting probe for brain tumor surgery. On the left, experimental proof-of-concept studies where the probe was administered to a mouse with an orthotopically implanted human xenograft brain tumor. The delineation of the brain tumor in white light is unclear whereas once near-infrared light (NIR) is turned on and the uPAR-probe lights up (yellow) it is easy to delineate the tumor. On the right, first clinical data using the probe in a human brain cancer patients made it to the front cover. (Images provided by Kurbegovic S, Juhl, K et al.).



Immunotherapies, in particular checkpoint inhibitors that support the immune system to fight cancers, are increasingly being used. However, the response rates are still relatively low. To unfold the potential, we have a focus on development of *immune cell imaging* ligands, e.g. targeting T-cells (CD4) or cytotoxic T-cells (CD8). With this platform, we have demonstrated that we are able to predict the response to checkpoint inhibitor blockade in various cancer models and we are convinced that this technology may serve for identifying likely responders to immunotherapy. In addition, we have demonstrated how “priming” with radiotherapy increased the T-cell infiltration of tumors and improved survival after use

of checkpoint inhibitors. PET tracers that track immune cells may also be used outside immune oncology, e.g. in *inflammation and infection*. Accordingly, we recently demonstrated how imaging of CD4 T-cells could be used for visualization of collagen-induced arthritis and infectious Lyme disease (borreliosis).

We have established relevant animal models of atherosclerosis, myocardial infarction and heart failure, with reduced or with preserved ejection fraction. These models are used for studies of *cardiovascular disease* and the effect of intervention with novel therapies, e.g. stem cell and GLP-1 therapy. Many of the models include advanced

surgical procedures. We apply various PET tracers for the study of different aspects of cardiovascular disease and for prediction of outcome that may be used in a clinical setting for tailoring therapies.

A particular focus is the targeting of uPAR, a marker of *cancer aggressiveness* that can both be used for prognostication but also as a target for radionuclide therapy. We have studied the uPAR-PET tracer in various cancers and most recently demonstrated in a clinical phase II study, that it is highly prognostic in head-and-neck cancer. In another clinical trial, we demonstrated that most neuroendocrine tumors are uPAR positive (Figure 1) and that uPAR-PET is highly prognostic.

Recently, we have extended our studies of use of uPAR imaging to atherosclerosis, where uPAR is also involved.

Our interest of imaging of *angiogenesis*, which is important both in cancer and cardiovascular disease, has continued. We believe angiogenesis PET may become game-changing in management and personalization of angiogenesis-modifying therapies. In cancer, the goal is to inhibit angiogenesis whereas the goal in cardiovascular disease, in general, is to stimulate neoangiogenesis, e.g. by stem cells following myocardial infarction. Several Phase II studies have recently been concluded or underway.

Optical imaging has recently gained traction for guidance in cancer surgery. We have developed our promising ligands used for PET into optical probes. Accordingly, the peptide used for uPAR binding in PET has demonstrated the ability to delineate tumor margins in several orthotopic xenograft tumor models. Most recently, our first uPAR-targeting ligand (Figure 2) has been tested successfully in more than 30 brain cancer patients.

Finally, an increasing focus is currently on developing new *radionuclide therapies*. Using small animal SPECT, it is possible to visualize, e.g. ^{177}Lu -labeled radionuclide therapy ligands to

investigate biodistribution and binding to tumors. We obtained approval from the authorities to perform animal experiments using α -emitting therapy, which is more effective due to the high linear energy transfer (LET). The efficacy of several such therapies is currently being tested in relevant, predictive human tumor models.



Collaboration with The National Hospital of the Faroe Islands

Professor Jann Mortensen and Chief Physicist Thomas Levin Klausen

The National hospital was founded in 1924 in Tórshavn. It was named Dronning Alexandrines Hospital after the Danish Queen. Now, it is called Landssjúkrahúsið. In the 1960's the hospital was expanded and officially declared the National Hospital of the Faroe Islands. Recently it merged with the two smaller hospitals in Klaksvík and Tvøroyri into one hospital system with joint leadership. The National Hospital of the Faroe Islands serves the Faroe Islands population of 53,664.

The National hospital was accredited by The Danish Healthcare Quality Programme, DDKM in February 2017. The National hospital has 900 employees and

120 beds. Yearly, about 1,700 patients are referred for overseas treatment, whereas 9,500 in-patients and 115,000 out-patients visits are taken care of by the 29 medical specialties, of which 9 are via consultant collaborations, including collaboration in Clinical Physiology and Nuclear Medicine with our department at Rigshospitalet.

Reporting of the scintigraphies and lung function tests is provided via a direct telemedicine connection. The responsible physician and physicist for Nuclear Medicine in Tórshavn is Professor, Consultant, DMSc Jann Mortensen and Chief Physicist Thomas Levin Klausen.

In 2021, the Department of Clinical Physiology and Nuclear Medicine in Tórshavn performed 1,388 (1,296 in 2020) patient examinations even though it was the second COVID-19 year: 499 (477 in 2020) scintigraphies of lungs, bones, thyroid, kidneys and renographies with the department's old 2-headed Skylight camera; 260 (232 in 2020) lung function tests (spirometry, bodyplethysmography and diffusion capacity for CO) were performed with the Jaeger whole body plethysmograph; and 629 (587 in 2020) routine and research DXA studies (BMD and body composition) were performed with The Norland DXA 840 scanner.



Neurobiology Research Unit

We appreciate the excellent collaboration with Professor Gitte Moos Knudsen, Head of the Neurobiology Research Unit (NRU) at Rigshospitalet, University of Copenhagen and also Director of the Lundbeck Foundation's Center for Integrated Molecular Brain Imaging (CIMBI) and BrainDrugs as well as Innovation Fund Denmark Center for Experimental Medicine NeuroPharmacology (NeuroPharm). The research focus of NRU is neurobiology, neuropharmacology, functional and molecular neuroimaging.

nru.dk | cimbi.dk | neuropharm.eu





Alexander Foss Gold Medal

Liselotte Højgaard, Professor and Head of Department, member of the ERC Scientific Council, received the Alexander Foss Gold Medal from DTU, The Technical University of Denmark.

Bioengineer in Medicine and Technology

In cooperation with the Technical University of Denmark (DTU) and the University of Copenhagen (KU), the department represented by Professor Liselotte Højgaard is involved in the Bioengineer program in Medicine and Technology at bachelor and master level. You can read more about the program at dtu.dk/bme.

At present several of the bioengineers are seconded to the department as PhD students, and we have numerous students working with bachelor and master reports in collaboration with DTU.



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Going green

