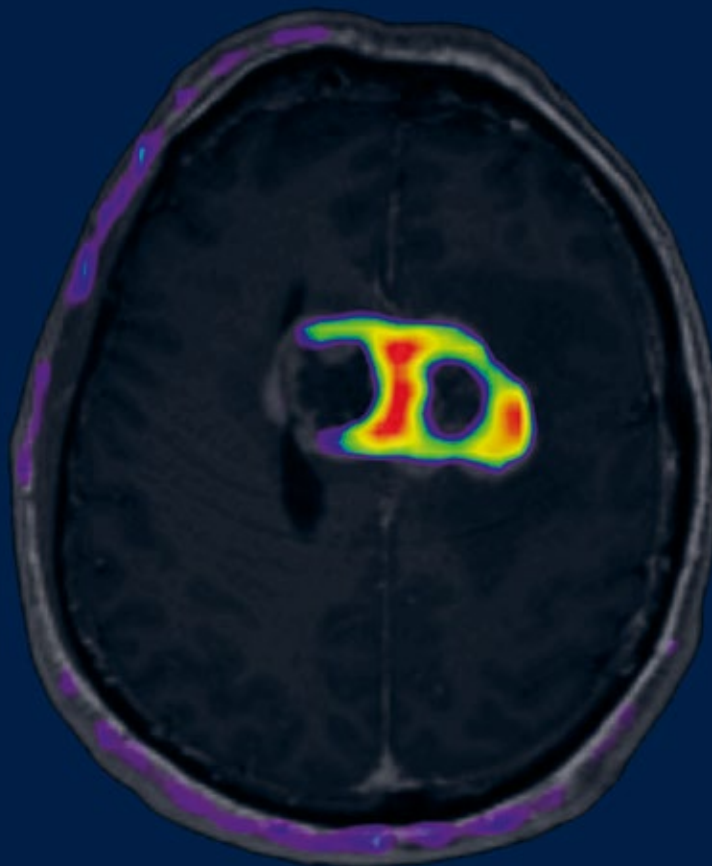


Department of Clinical Physiology, Nuclear Medicine & PET

Annual Report 2019





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



Rigshospitalet



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Preface

In 2019 we received a generous donation from the John and Birthe Meyer Foundation of 43,7 mio. DKK for a new PET/MRI scanner and research on artificial intelligence. It was an overwhelming gift, and we are honored, grateful and privileged. We would like to express our most sincere thank you. It will be implemented in 2020 in new premises in the Finsen building. It will be a major step forward for our department and most important for our patients and research. We got our first new digital PET/CT in Summer 2019, also donated by the John and Birthe Meyer Foundation. It is a whole new world for both patients and staff. Thank you very much to the John and Birthe Meyer Foundation for all the generosity.

The department had another busy year with a higher than ever number of patient investigations, 196,889 and 176 peer review publications. Research is a key activity and focus area of our department, and we have a comprehensive research program directed towards innovative solutions to solve unmet clinical needs in our patients. We adjust our research program to be clinically relevant and timely, and we have special focus on implementation of personalized or precision medicine in collaboration with Rigshospitalet's other research groups and international collaborators in Europe and the rest of the world. You can read more about our research endeavors in the various chapters in this little booklet. To all our research groups: a sincere thank you for the dedicated, impressive and important work. We

do research as an interdisciplinary effort and all groups are involved: Nuclear medicine physicians, radiologists, physicists, bioengineers, mathematicians and IT experts, radiochemists, nuclear medicine technologists, radiographers and many others.

In 2018 we reported problems with the newly implemented Agfa RIS/PACS ICT system for picture archiving and patient reporting. Unfortunately, it has been an uphill struggle also in 2019, as the problems continued with defect performance, stability and speech; the essentials of a well-functioning ICT system in a diagnostic imaging department. Thank you to everyone for patience and very long hours all year round due to the dysfunctional system. We would like to express a sincere thank you to all for the stamina, securing patient reports in time without any waiting list.

CAAI, Clinically Applied Artificial Intelligence, is our new research group with young people developing artificial intelligence for better imaging with improved image quality and lower radiation dose – already now applied in our routine clinical studies. This is very important for patients and for staff, as it reduces the burden of radiation to all. Artificial intelligence is also used to shorten the scan time for patients in our scanners, which is positive for both patients and the economy. CAAI leader is Postdoc Claes Nøhr Ladefoged, M.Sc., PhD together with Chief Computer Scientist Flemming Littrup Andersen.

2019 was a year with many celebrations; Linda M. Kragh, our Chief Nuclear Medicine Technologist celebrated her 40 years anniversary as nuclear medicine technologist at Rigshospitalet, and she was praised by all of us as a unique and wonderful leader. She also received the prestigious award from the hospital: “Årets bioanalytiker 2019”, or in English: “This year’s technologist 2019”.

In 2019 Professor Andreas Kjær obtained the prestigious Lundbeck Foundation Professorship and received a Knighthood for his impressive contributions in research and innovation. The department would like to congratulate Andreas Kjær with these major achievements.

Kate Pedersen Staff Technologist in PET celebrated her 40 years anniversary in Spring 2019, and we said thank you for her great efforts for the department throughout many years. She retired Fall 2019 and Maria Pejtersen is the new Staff Technologist in PET. A warm welcome. Maria Pejtersen has initiated a close collaboration with our section in Glostrup and KF to assure the best use of our competences and scanners.

In the Glostrup Section a new Staff Technologist Helle Møllegård Dahl took over February 2019 and is collaborating with Consultant Lotte Hahn Enevoldsen, who is head of Nuclear Medicine both at Blegdamsvej and in Glostrup. Warm welcome to Helle Møllegård Dahl and thank you to the whole section in Glostrup for working so diligently.

Thank you very much to Bettina Lundgren for 10 good years as our center director. Bettina Lundgren got a new prestigious job and left the hospital end of August 2019. Vice Director Lene Ørnstrup Christensen were then both acting director and vice director with two jobs for more than half a year. Thank you for all your work and the helpful collaboration. Thank you to the Department of Radiology, Head of Department Ilse Vejborg and Chief Radiographer Johnny Madelung. We appreciate the positive collaboration very much.

From November 2019 Head of Department, Professor Liselotte Højgaard was also acting head of Department of Pathology until March 2020. It has been quite a job to try and help the Department of Pathology, who were in a crisis situation. I would like to express a warm thank you to each and every one at the Department of Pathology for welcoming me so warmly and helping remedy the problems.

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.

Liselotte Højgaard
Professor, Head of
Department

Linda M. Kragh
Chief 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

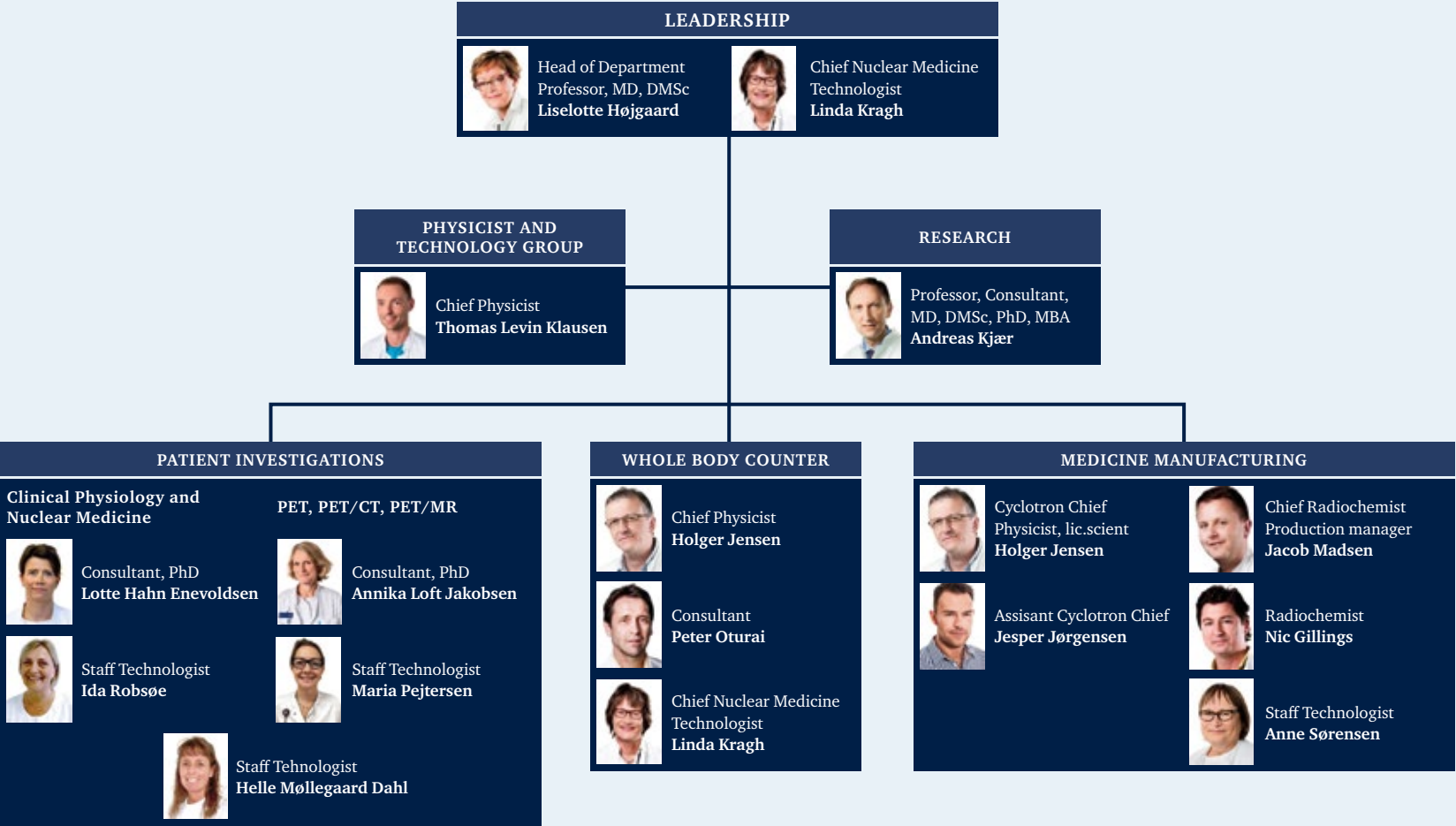
Organisation and staff 2019

Abrahamsen, Nynne Hejdemann, Technologist.
Agner, Elissaveta Castella, Radiographer.
Al-Atabi, Susan, Technologist.
Al-Hashemi, Ibtehal, Student.
Alfsen, Maria Zeiler, MSc Biomed., Research Assistant.
Ahangari, Sahar, Research Fellow.
Ahmadi, Amir, Radiographer.
Albers, Mia C. Hjorth, Teaching Technologist.
Albrecht-Beste, Elisabeth, MD, Consultant.
Allerslev, Kathrine Bøwig, Radiographer.
Alslev, Louise, MD, Consultant.
Amtoft, Annemarie Gjelstrup, MD, Consultant.
Anderberg, Lasse, Research Fellow.
Andersen, Ditte Lindbjerg, Radiographer.
Andersen, Flemming Littrup, MSc, PhD,
Computer Scientist.
Andersen, Jane, Technologist.
Andersen, Julie Bjerglund, MD, Senior Registrar.
Andersen, Kim Francis, MD, Consultant.
Andersen, Simon Surland, Student.
Andersen, Ulrik Bjørn, MD, Consultant.
André, Cecilie Dura, Student.
Asmar, Ali, MD, Staff Specialist.
Attauabi, Mohamed, Student.
Awwal, Zara Amalie Krog, Radiographer.
Azizi, Nadia, Radiographer.
Bashir, Asma, PhD Student.
Bay, Emma Therese, Student.
Bendtzon, Camilla Kuhre Vildrik, Medical Secretary.
Bentsen, Simon, MD, PhD Student.
Benzon, Eric von, MD, Consultant.
Berg, Ronan Martin Griffin, MD, Staff Specialist.
Berthelsen, Anne Kiil, MD, Consultant.
Beyer, Birgit Krindel, Staff Technologist.
Binderup, Tina, MSc Human Biology, PhD,
Senior Scientist.

Birch, Kirsten Junker, Technologist.
Bisgaard, Line Stattau, MSc Mol.Biomed., Postdoc.
Bisgaard, Sissel, MSc Med.Tech., Research Assistant.
Bjørling, Nina Louise, Medical Secretary.
Bobruk, Daniel Abdulla, Student.
Borgwardt, Lise, MD, PhD, Consultant.
Brakti, Inna, Student.
Brammer, Daniel, Student.
Brandt, Patrick Krøll, Student.
Brittain, Jane Maestri, MD, Senior Registrar.
Brun, Frederik Jager, Student.
Brus, Anja, MSc Biomedicine, PhD Student.
Calvo, Oriol Puig, MD, PhD.
Cappelen, Katrine Louise, Engineer.
Carlsen, Esben Andreas, MD, PhD Student.
Carstensen, Laura Stentoft, Student.
Choudhry, Aisha Bilal, Technologist.
Christensen, Anders, MD, Postdoc.
Christensen, Camilla Hell, MSc Chem., PhD Student.
Christensen, Camilla, Technologist.
Christensen, Esben, MSc Bio.Med., PhD student.
Christensen, Emil Nørgaard, Student.
Christensen, Jan Damgaard, Cyclotron Technician.
Christensen, Tine Nøhr, MD, PhD Student.
Clausen, Malene Martini, MD, PhD, Postdoc.
Clausen, Anne Skovsbo, DVM, PhD Student.
Clemmensen, Andreas Høeg, MSc Med.Tech.,
PhD Student.
Cold, Sigrid, Student.
Cortsen, Annette, Technologist.
Cramer, Stig Præstekjær, MD, Registrar, PhD.
Daghigh, Ata, Registrar.
Dahan, Daniel, Cyclotron Technician.
Dahl, Helle Møllegård, Staff Technologist.
de Nijs, Robin Vedel, Medical Physicist, MSc,
PDEng, PhD.

Dejanovic, Danijela, MD, Consultant.
Denholt, Charlotte Lund, MSc, PhD, Chemist.
Dibenedetto, Altea Paola, MSc Pharm.,
Research Assistant.
Do, Manh Tan, Student.
Dunbar, Douglas, Technologist.
Dähnhardt, Andreas, System Administrator.
Døssing, Kristina Benedikte Vangsted, MSc Biology,
Postdoc.
Einarsdóttir, Hrefna Sæunn, Registrar.
Elkington, Sakeena, Technologist.
Ellegaard, Andreas Høyby, Student.
Engel, Trine Bjørnbo, MSc Pharm Tech, Postdoc.
Enevoldsen, Lotte Hahn, MD, Consultant.
Erichsen, Laura Toft, Student.
Esmail, Mona Jasmin Ali, Technologist.
Federspiel, Marianne, Technologist.
Fischer, Barbara Malene, MD, DMSc, PhD, Consultant.
Fishekhxiu, Elida Sinik, Technologist.
Fliedner, Frederikke Petrine, MSc Biotech.,
PhD Student.
Foldager, Annette, Teaching Technologist.
Folkmann, Nanna Freja, Secretary.
Fonslet, Jesper, MSc Physicist, PhD, Postdoc.
Fosbøl, Marie Øbro, MD, Staff Specialist, PhD Student.
Frederiksen, Kåre Peter, Registrar.
Frederiksen, Mette Helene Borggreen,
Quality Coordinator.
Frost, Nadia, Technologist.
Fuchs, Annette Maria, Registrar.
Gelle, Liibaan Mohamed, Technologist.
Gillings, Nic, MSc, PhD, Chief Radiochemist.
Ginsborg, Lone Agervold, Medical Secretary.
Gram, Aurelie, DVM, PhD, Postdoc.
Grunwald, Nicolas Konrad Voigt, Student.
Gruszow, David Jakob, Student.

Department of Clinical Physiology, Nuclear Medicine & PET



Organisation and Staff 2019

Guldbrandsen, Kasper Foged, MD, Research Assistant. Gæde, Mathias, Engineer. Haddock, Bryan Thomas, Chief Physicist. Hag, Anne Mette Fisker, MSc Human Biology, PhD, Postdoc, Research Coordinator. Halldórsdóttir, Hölmfrídur Rósa, MSc Biochemistry, PhD Student. Hanel, Birgitte, Technologist. Hansen, Adam Espe, Physicist. Hansen, Anders Elias, DVM, PhD, Postdoc. Hansen, Camilla Josephine Teglgaaard, Technologist. Hansen, Caroline Rena Lind Hansen, Technologist. Hansen, Joachim Pries, Student. Hansen, Mathilde Bro, Student. Hansen, Naja Liv, MD, Staff Specialist. Hansen, Ole Michael Raun, Technologist. Hansen, Sofie Lindskov, Physicist. Hanson, Ida Grüner, Student. Hasbak, Philip, MD, DMSc, Consultant. Hassan, Mariam, Technologist. Haarbye, Martin Christian, Technologist. Haahr, Rasmus Primholdt, Scholarship. He, Yue, MSc Physicist, PhD Student. Hecht-Hansen, Marianne, Student. Henriksen, Frederikke Hurup, Medical Secretary. Henriksen, Otto Mølby, MD, PhD, Consultant. 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Larsen, Kristina, Technologist. Larsen, Lena Tina, Animal Technologist. Larsen, Mads Rud, Student. Larsen, Mette Fabiansen, Medical Secretary. Larsson, Henrik Bo Wiberg, MD, DMSc, Professor, Consultant. Law, Ian, MD, DMSc, PhD, Professor, Consultant. Lehel, Szabolcs, MSc Chemistry, PhD. Lejre, Daniel, Student. Lind, Camilla Louise Nordvig, Technologist. Linde, Elisabeth Specht, Student.	Lindbjerg, Rikke Xiao, Student. Lindberg, Ulrich, MSc Med.Tech, PhD. Lindell, Elin, Technologist. Linnet, Simone, Student. Ljunggren, Anna, Technologist. Loft, Mathias Dyrberg, MD, PhD Student. Lykke, Eva, MD, PhD Student. Lykkegaard, Magnus Rønne, Student. Lærke, Sonja Pedersen, Lab Technician. Löfgren, Johan, MD, Consultant. Lønholm, Emmy Marie, Medical Secretary. Madsen, Jacob, MSc, PhD, Chemist, Chief Production Manager. Madsen, Jasmine Melissa, Student. Madsen, Karine, MD, Staff Specialist. Marina, Simon Martin, MSc Mol.Bio.Med., PhD Student. Meeske, Kirsten Langberg, Technologist. 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Petersen, Ida Nymann, MSc Chem., PhD, Postdoc. Petersen, Lars Ringgaard, MSc Bio.Med., PhD, Postdoc. Petersen, Lotte Pia, Service Assistant. Philipsen, Frederik Ersø, Student. Poulsen, Constance Eline Grandjean, MSc Pharm., PhD Student. Poulsen, Jákup Martin, Radiographer. Qvist, Katrine, MSc Medicinal Biology & Molecular Biology, Technologist. Rasmussen, Thomas, MD, PhD, Postdoc. Reichkendler, Michala, MD, Staff Specialist. Rexhepi, Lume, Technologist. Ripa, Rasmus Sejersten, MD, DMSc, Consultant. Risør, Louise Madeleine, MD, PhD Student. Rossing, Jonas Hem, Student. Ryssel, Heidi, MD, PhD Student. Rønbirk, Lilian, Medical Secretary. Rønn, Vibeke, Head Medical Secretary, PA Professor Liselotte Højgaard. Sadikovic, Edin, Student. Salihu, Armend, Technologist. Sammour, Razan Abu, Technologist. Sandholdt, Michelle Windtberg, Technologist. Sass, Hjalthe Christian Reeberg, MD, PhD Student. Saxtoft, Eunice, NMT, Clinical Instructor. Schulze, Christina, Technologist. Segur, Liva, Student. Semitoje, Gudrun, Medical Secretary. Setterberg, Victoria, Technologist. Simonsen, Helle Juhl, Technologist. Sinik, Edita, Technologist. Skougaard, Kristin, PhD, Staff Specialist. Skovgaard, Dorthe Charlotte, MD, PhD, Postdoc.	Slipsager, Jakob Mølkjær, PhD Student. Sloth, Ane Beth, MSc Biomedicine, Research Assistant. Sommer, Niyan, Technologist. Stahlfest, Marianne, Medical Secretary. Stahr, Karin, Technologist. Stavnsbjerg, Camilla, MSc Mol.Bio.Med., PhD student. Sunde, Christine Høj, Technologist. Svalling, Susanne, Technologist. Svejstrup, Waldemar, Student. Svendsen, Nini Hvidtfeldt, Technologist. Sørensen, Anne, Staff Technologist. Sørensen, Louise Sørup Lendorf, Technologist. Sørensen, Maja Støvring, Technologist. Saaie, Hanan Rahim, Technologist. Tayyab, Mahvish, Technologist. Thalund, Mathilde Ørbæk, MD, PhD Student. Toft, Cecilie Grønkær, Student. Tolstrup, Britt Maria Jæger, Radiographer. Tornvig, Cecilie Maja, Technologist. Uzer, Sefika, Technologist. Vandel, Julius Scheel, Student. Veseli, Antigona, Technologist. Vestergaard, Mark Bitsch, PhD Student. Weihrauch, Per, Cyclotron Technician. Wessel, Mette Munk, MSc Human Biology, PhD, Postdoc. Westergaard, Michelle Kaijer, Technologist, PA Professor Andreas Kjær. Wieslander, Bente Krogsgaard, Consultant. Wiinberg, Martin, Student. Wiinholt, Mette Neiegaard, Msc. Human Biology, Technologist. Wikke, Tina, Technologist. Wittekind, Anne-Mette Nielsen, QA Pharmacist. Wittrup, Charlotte, Student. Zare, Soheil Naser, Radiographer. Aagaard, Christina Byrne Faurholt, MD, PhD, Postdoc.
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Highlights 2019



Linda M. Kragh, our Chief Nuclear Medicine Technologist received the prestigious annual award as Technologist of the Year 2019. The department is very proud of this fine achievement.



Professor Andreas Kjær was received in audience to thank Her Majesty Queen Margrethe II for the Royal Order of Dannebrog (Ridder af Dannebrogordenen).



A most generous donation from The John and Birthe Meyer Foundation to a new PET/MRI scanner and research on AI, artificial intelligence. We are truly grateful.



Professor Andreas Kjær received the 2019 Niels A. Lassen prize for his research within molecular imaging and targeted radionuclide therapy.



In 2019 Professor Andreas Kjær continued his work in the Science and Engineering Committee of the Danish Academy of Technical Sciences (ATV). The committee, together with a delegation of leaders from academia and industry, visited Delhi and Bangalore, some of the leading Science and Engineering regions in India. The work is described in the ATV report “India land of opportunity”.



Professor Liselotte Højgaard ist Mitglied ins Kuratorium die Robert Bosch Stiftung & Member of the Board of Directors of the Novo Nordisk Foundation”.



Our Head of Dept. Professor Liselotte Højgaard had a busy winter, as she was also Acting Head of Dept. of Pathology, from November 2019 to March 2020.



Linda M. Kragh had 40 years Anniversary as Nuclear Medicine Technologist, and the department celebrated with a reception with very many guests from Rigshospitalet and the rest of Denmark.

Clinical physiology and nuclear medicine

Section Head, Consultant Lotte Hahn Enevoldsen

Our department offers a variety of nuclear medicine and clinical physiological examinations of both routine patients and also for many research investigations in a broad spectrum of disciplines.

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).

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



PET/CT

Section Head, Consultant Annika Loft Jakobsen

In diagnosis and treatment monitoring of patients suffering from oncological or inflammatory diseases, personalized medicine plays an increasing role. PET/CT takes a natural part in this new paradigm in helping to depict the right patients for the right treatment. As part of our clinical every day work interpreting more than 15,000 PET/CT scans every year, we attend numerous multidisciplinary team conferences and tumor boards. This collaboration with our clinical colleagues is inspiring and definitely increases the quality of our interpretation of scan results and understanding of the importance of good communication as well as being updated and well trained.

The continuous involvement in research protocols and clinical trials testing new treatments as well as new PET tracers is an important part of the

daily work which improves our knowledge of the behavior of tumors. New indications and scanning procedures have been implemented as a result of this work.

^{18}F -FDG PET/CT is the work horse investigation in our daily clinical life, but the use of ^{68}Ga -Dotatoc and ^{64}Cu -Dotatate for patients with neuroendocrine tumors and ^{68}Ga -PSMA for prostate cancer patients is increasing tremendously due to the important information of disease behavior and extent necessary for the choice of treatment possibilities for these patients.

Radiotherapy planning with FDG PET/CT has been a clinical routine in our department for almost two decades now due to a fruitful collaboration with the Department of Radiotherapy and a unique set-up with specialists in radiology

working part time in PET and part time in Radiotherapy. By participating in research protocols in the use of FDG and other tracers for PET/CT radiotherapy planning we keep increasing our knowledge and expertise also in this field.

FDG PET/CT also plays an increasing role in the clinical set-up for infectious diseases in depicting involvement of organs as well as for treatment monitoring due to the unique possibility to detect even small active foci – a great help for the clinicians.

Incorporation of artificial intelligence in our clinical work is an ongoing and exciting new aspect we have great expectations for, when focusing on the improvement of image quality, radiation dose reduction and shorter scan time.



Artificial intelligence

Computer Scientists Flemming Littrup Andersen and Claes Nøhr Ladefoged

Since the installation of the first PET/CT in 2001, the department has grown rapidly, and is today performing more than 12,000 scans yearly. The vast majority of the data is only used to diagnose the single patient, and do not benefit the patients of tomorrow. With artificial intelligence (AI) this is about to change. AI will exploit the Big Data information to develop models that can aid the clinical decision-making and relieve the workload of some of the more tedious and time-consuming tasks. AI has recently shown great promise in analysis of medical imaging especially starting with the development of deep learning in general computer vision since 2012. The techniques have been rapidly adopted in medical imaging during the past few years with publications in the thousands and high publicity at medical conferences and workshops.

At our department we have formed a program for Clinically Applied Artificial Intelligence (CAAI) with the sole purpose of bringing AI into clinical routine. The group is led by Computer Scientists Flemming Littrup Andersen and Claes Nøhr Ladefoged, and further comprises 8 pre-graduate students, 4 PhD students, 2 postdocs and with links to various departments at Rigshospitalet, primarily Cluster for Molecular Imaging, Radiology and Oncology.

CAAI currently runs a number of projects spanning from bachelor to PhD level with a strong focus on pre-graduate supervision of computer scientist and engineer students. The primary research areas, defined in close dialogue with the clinicians, have been directed towards data domain translation i.e. converting MRI to synthetic CT images, lesion segmentation and noise reduction of image data.

Medical image segmentation is driven by the clinical needs; we have currently implemented automatic segmentation of PE2I brain images that visualizes availability of the dopamine transporter in the stratum. By deep learning based segmentation in a clinical implementation, a fast analysis is provided to the physician for diagnosis of Parkinson's disease. Another project has focused on multiple sclerosis (MS) using MR Flair images to implement white matter lesion segmentation. Here work is ongoing for prognostic tools for MS.

Correction for photon attenuation of PET images is critical for accurate quantitative image reconstruction and the fully integrated PET/MRI system (Siemens mMR) available at our department, but it is challenging to provide these images due to the lack of CT. We have shown that synthetic-CT

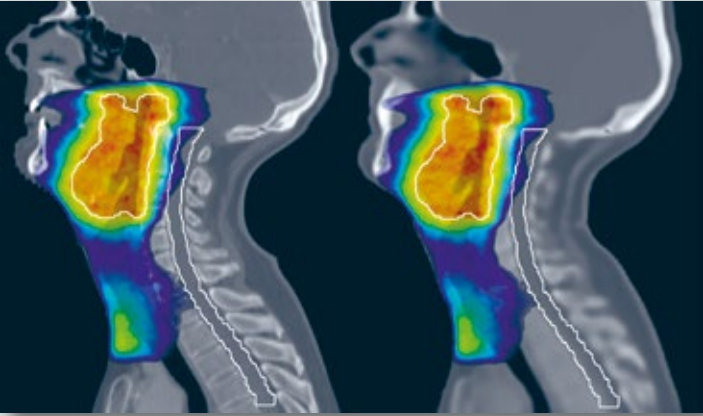
generation can be generated using deep learning networks, and these methods have recently been moved into clinical routine. Studies are ongoing to show feasibility for using synthetic-CT-derived dose plans for radiotherapy in head and neck cancer and cervical cancer with application to the PET/MR.

Noise reduction, which in medical imaging translates to lower radioactivity dose or shorter scanning time both to great benefit for the patients, received a 2.5 million grant from Danske Regioner, and several projects have been started within this area. A reduction of the PET tracer dose for brain scanning is ongoing with focus on dementia, where FDG PET scanning time for patient with Hodgkin's lymphoma has already been reduced from 2 minutes to 20 sec over the lungs, and is now possible in a single breath hold (see figure).

The programs translating AI into the clinical workflow are developed on high-end computer systems with Graphics Processing Units (GPU). CAAI currently operate a park of 7 servers with Nvidia TITAN V or RTX graphics cards (Nvidia Santa Clara) instrumental for the running projects, a supercomputer with 8 GPUs sponsored by IBM is under installation.



Cardiac investigations



◀ Synthetic-CT with superimposed dose plans for radiotherapy in head and neck cancer patients on PET/MR. Example shows original CT (left) and synthetic-CT (right). Delineation of planning target volume and spinal cord illustrated in white

Consultant Philip Hasbak

Cardiac Rubidium PET/CT

Rigshospitalet was the first hospital in Scandinavia and one of the first in Europe to introduce Rubidium PET/CT. 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.

Other cardiovascular nuclear medicine tests

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 inflammation.

A MUGA (Multigated Acquisition) scan is used to study the pumping function of the heart. It is generally used in patients with known heart disease or in those without heart disease but undergoing cancer treatment that can weaken the heart's pumping function.

Pyrophosphate imaging is used to assess the presence of amyloid in the heart. This test helps to differentiate the different types of amyloid in the heart.

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



Imaging of angiogenesis

The journey towards a broadly applicable clinical PET tracer

Professor Andreas Kjær

In 2012 we initiated development of a new angiogenesis PET tracer and identified ^{68}Ga -NOD-AGA-E[c(RGDyK)]₂ as a particularly promising candidate. The PET tracer went through in-depth preclinical testing both in cancer xenograft models (Figure 1) as well as in experimentally induced myocardial infarction in rats (Figure 2). In both diseases the tracer demonstrated high uptake and a close correlation to degree of angiogenesis as measured in the tissue by molecular ex vivo methods.

Based on the encouraging preclinical data we set forth to translate the PET tracer into human use. As part of this process, an important question was in which clinical applications we expect a value of angiogenesis-PET?

Neoangiogenesis, which is the target of our PET tracer, is involved both in cancer and cardiovascular disease as well as in other diseases. In tumor growth, the induction of neovessels through release of vascular endothelial growth factor

(VEGF) is essential in sustained tumor growth. Accordingly, one therapeutic principle in cancer is anti-angiogenesis therapy, e.g. bevacizumab (Avastin®). This therapy is a VEGF antibody that blocks the stimulatory effect of VEGF on angiogenesis and thereby hinders sufficient blood supply for tumor growth – the tumor is “starved”. Although a compelling strategy, the response to anti-angiogenesis therapy has been highly variable in many cancer types, e.g. glioblastoma and colorectal cancer. However, in responders the effect is often dramatic. One could therefore speculate whether the differences in response is caused by different levels of neoangiogenesis in the individual tumors and patients should be selected on basis of this. With angiogenesis-PET, it would be possible non-invasively to evaluate the individual patient’s tumor and metastases for level of neoangiogenesis and thereby to select cancer patients likely to be responders to anti-angiogenesis therapy. Moreover, angiogenesis-PET may be used to follow the effect on angiogenesis of the therapy.

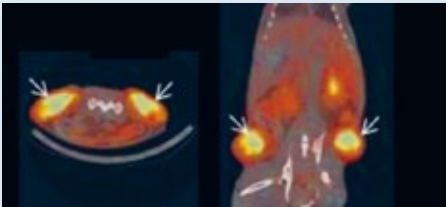


Figure 1.

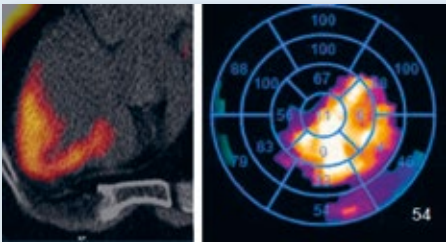


Figure 2.

In cardiovascular disease, the neoangiogenesis may be considered highly beneficial. If a myocardial infarction patient induces neoangiogenesis in the infarcted area, this may be seen as part of a healing process and the outcome may be more beneficial compared to patients where no or little neoangiogenesis is induced. The method may therefore predict final infarct size and be used for management strategy. In addition, the use of stem cell therapy or gene therapy in patients with ischemic heart disease has a major goal in inducing angiogenesis. Therefore, also within cardiovascular disease the future use of angiogenesis PET may be used for practicing precision medicine and preselect patients that are in need of angiogenesis-stimulating therapies.

Taken together, we believe our new angiogenesis PET tracer is broadly applicable in cancer and cardiovascular disease as shown in Figure 5. However, as angiogenesis is also a central element in other disease entities we expect to expand our list of probably applications in the future.

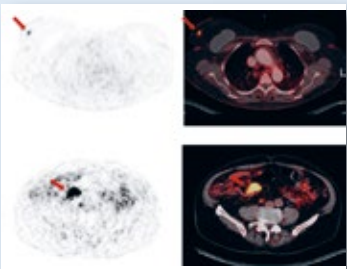


Figure 3.

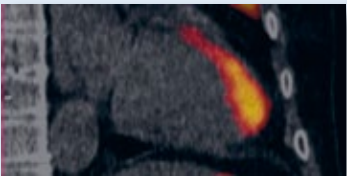


Figure 4.

Figure 1. First preclinical angiogenesis PET/CT study using ^{68}Ga -NODAGA-E[c(RGDyK)]₂ in cancer. Arrows indicate bilateral implanted human glioblastoma xenograft tumors (modified from Oxboel et al. Nucl Med Biol 2014).

Figure 2. Preclinical demonstration of induced angiogenesis 7 days after experimentally induced myocardial infarction in a rat using ^{68}Ga -NODAGA-E[c(RGDyK)]₂. The bulls eye plot to the right shows apical-antero-lateral neoangiogenesis corresponding to the site of infarction (Bentsen S et al.).

Figure 3. First clinical proof-of-concept showing angiogenesis PET (left) and PET/CT (right) with our in-house developed PET tracer in a patient with breast cancer (upper panel) and a patient with a neuroendocrine tumor (lower panel). Both tumors show high uptake of the PET tracer indicating induction of angiogenesis. In other patients with same types of tumors no or little angiogenesis was found (images not shown). We hypothesize that degree of angiogenesis as measured on PET, may

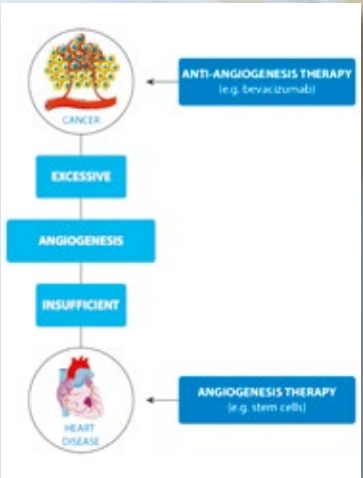


Figure 5.

be useful to select patients for anti-angiogenesis therapy, e.g. VEGF antibody-ies. Following a successfully completed phase I/IIa clinical trial, our angiogenesis tracer is now tested in several ongoing phase II studies (images provided by Carlsen E, Clausen M, Skovgaard D et al.).

Figure 4. First clinical data showing angiogenesis PET performed on day 7 after an acute myocardial infarction. It is clearly seen how angiogenesis is induced in the anterior myocardial wall of the heart in this patient. We hypothesize that strong induction of angiogenesis may predict favorable outcome. In contrast, if no or little neoangiogenesis is induced this may lead to poorer healing and angiogenesis-inducing therapies, e.g. stem cell therapy, may be relevant. The hypothesis is currently being tested in an ongoing phase II clinical trial (Image provided by Bentsen S et al.).

Figure 5. How angiogenesis is important both in cancer and cardiovascular disease and may become key in personalizing angiogenesis-modifying therapies.



Pediatric Nuclear Medicine

Head of Pediatric Nuclear Medicine, Consultant Lise Borgwardt

In 2019 we performed more than 3,000 pediatric nuclear medicine investigations. It is a special focus area for our clinic to perform children investigations at the highest level of excellence, and at the same time make it a positive experience for both the child and the parents.

This year we have been continuing the cooperation of the organizational work on preparing our new Children's Hospital Copenhagen. The project is very visionary and contains a large Diagnostic Unit where Paediatric Nuclear Medicine, among other diagnostic specialties, will be located. We have seen a virtual reality presentation of the Diagnostic Unit and it will be fantastic new facilities. The Children's Hospital Copenhagen will be finished 2024.

We already have a children's section integrated in our department with a children-friendly PET/128SliceCT, 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. Our 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. We conduct research protocols in children with acute and chronic liver diseases incl. translational piglet studies and a PhD in the field was defended this year. In order to develop this interesting area, we have developed protocols in pediatric non-oncological PET/MRI and also our data from the pediatric PET/MRI protocol for children with CNS tumors are being analyzed. We started up artificial intelligence projects in pediatric oncological diseases and a master was defended this year. In 2019 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 also part of the EpSSG in the Radiology Committee, participating in conducting the new European protocol.

BørneRiget Children’s Hospital



Head of Pediatric Nuclear Medicine, Consultant Lise Borgwardt

Rigshospitalet is building a Children’s Hospital. The vision behind the new hospital for children and families is encapsulated in the hospital’s Danish name, BørneRiget, which translated directly means Children’s Kingdom. The emphasis is on the first part of the name, Children (Børne), since the overarching theme of the user experience at the hospital will be the insight that kids will be kids. And, on a more general level, that users, whatever their age, do not stop being who they are when they step over the threshold of the hospital. The emphasis is also on kingdom (Riget), since the users should find themselves

in one kingdom, rather than a collection of small principalities. And lastly, of course, because BørneRiget (Children’s Hospital Copenhagen) is part of Rigshospitalet – known colloquially as Riget.

The vision for BørneRiget is simply to create a hospital for children and families that sets new standards in two key areas – patient care and the interplay between architecture, organization and operations. The new hospital will accord equal focus to treatment, research and training while striving to be the best in all three. We will estab-

lish an Academy where the hospital can share its professional competencies with educational institutions, research departments and the wider business community. We will invent and introduce a new continuity of patient care, bringing specialists to the patient rather than the other way round. We will make the hospital accessible to the outside world. In short, we will enhance the quality of Denmark’s best specialized hospital for children and family members a hundredfold. A grand ambition perhaps, so let us begin with the three main focus areas: Family, Technology and Effectiveness.

Family

The goal is to revolutionize the patient’s hospital experience before, during and after treatment, which also means taking into account the wider family experience. In addition to feeling secure, welcome and involved in the treatment process, families must help to shape, design and develop a hospital with a community focus.

Technology

Emotional well-being is only part of the picture. The new hospital complex will implement the highest technological standards – future-proofing

them for generations to come. Coordinated patient and medicine scanning, electronic medical records, electronic wayfinding and continual monitoring of individual bed locations are just some of the options already included in our planning.

Effectiveness

Logistics. Bed days. Incorrect treatment. Naturally, it would be self-defeating to create a hospital project of this caliber without enhancing treatment effectiveness. A key part of our vision is to revitalize and develop the entire Danish health service,

pioneering new, more effective working procedures that can be adopted elsewhere. Research. At the new hospital, we will create true synergy between treatment, research and education; a hospital where new knowledge about diagnostics procedures and treatment is created and shared with a view to achieving scientific breakthroughs. For this reason, education and research must be an integrated part of day-to-day clinical work.

The Diagnostic Centre within the BørneRiget will be at an international level, encompassing several inter-disciplinary areas of specialization,



Education

Professor, Consultant Jann Mortensen and Consultant Peter Oturai

The department contributes to the 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. physiology, nuclear medicine, and medical technology. In addition, regarding undergraduate education, nuclear medicine technologist students and radiography students receive part of their education at the department.

As goes for postgraduate education, seven educational positions for young physicians training to become specialists in clinical physiology and nuclear medicine are held by our facilities. Other roles in the specialist education of physicians are related to the dedicated courses in oncology-, cardiology-, lung-, and endocrinology- patho-

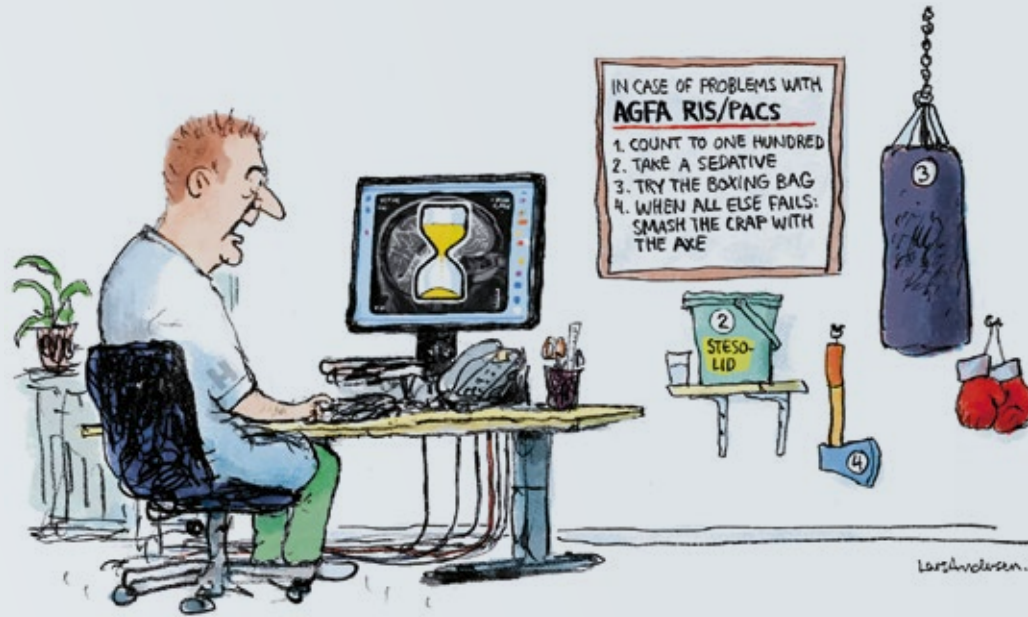
physiology, molecular imaging as well as more basic courses in methodology (MR and Kinetics), all held at our department and arranged by our professors and consultants. Furthermore, we contribute to the specialist education of physicians from other specialties such as urology, nephrology, radiology, oncology, hematology, 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, and we deliver training programs to staff from other nuclear medicine and radiological departments in Denmark and the Nordic countries.

The department's 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 Ivarsen and Professor Henrik Larsson are responsible for the undergraduate education of medical students in the department. Professor Liselotte Højgaard is responsible for under- and postgraduate education for bioengineers.

Agfa RIS/PACS



Consultant Johan Löfgren

In the beginning of 2018 Rigshospitalet implemented, as the last hospital the region, the new Agfa RIS/PACS system. A huge project initially started in 2009 where the radiology, clinical physiology and nuclear medicine departments in Region Hovedstaden, after a joint requirements analysis, agreed on shifting to a common RIS/PACS system.

Ever since the system was installed, we've been having huge problems with performance, stability and speech recognition. Thank you very much to our local system administrators, Maria Pejtersen, Martin Ravn Jensen, Katrine Cappelen, Mads Fjelbro Klavsén, Alexandra Hercman and Nanna Freja Folkmann helping the department to survive in this chaotic IT environment and thank you very

much also to all colleagues for hanging in there and putting extra effort and patience in their everyday work when the system is instable and slow.

The regional IT department in collaboration with the RIS/PACS vendor has used large resources trying to fix the problems without any major success. We had hoped for huge improvement with the three major updates planned to be implemented in autumn 2019. Unfortunately only one update was successful. One was postponed and the third failed and resulted in major problems the subsequent weeks.

In 2019 Denmark changed the national healthcare billing system which also effected the integration

between RIS/PACS and EPJ (Sundhedsplatformen). Unfortunately this integration is far from flawless, which has resulted in excessive extra work for our administrative staff during the last year.

Alongside struggling with the system and reporting issues, an expert group has evaluated our vendors next generation RIS/PACS system, actually the version our region originally purchased 10 years ago. The group has tried to find out if it would fulfill our functional needs of a modern RIS/PACS system. At the same time the regional IT department has looked into the new system's stability and performance. A decision regarding the future of RIS/PACS in our region will be taken in 2020 and we are hoping for a brighter future.





Neuro PET

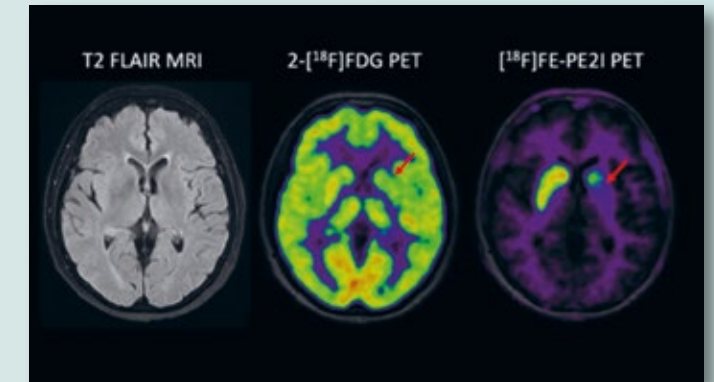
Consultant Otto Mølby Henriksen and Professor, Consultant Ian Law

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.

This year the new PET radiotracer [¹⁸F]FE-PE2I for assessment uncertain Parkinsonism was firmly established in clinical routine (Figure 1). The glucose analog 2-[¹⁸F]Fluoro-2-deoxy-D-glucose (2-[¹⁸F]FDG) showing the functional integrity of the brain remains the backbone of clinical imaging of dementia and epilepsy and is increasingly being used. Our non-2-[¹⁸F]FDG radiotracers comprise the amino acid analogue [¹⁸F]Flouro-Ethyl-Tyrosine ([¹⁸F]FET) for brain tumors, the somatostatin II receptor ligand [⁶⁸Ga]DOTATOC for meningiomas, [¹¹C]-PIB for evaluation of cerebral amyloid in Alzheimer's disease, and [¹⁵O]H₂O for quantification of cerebral blood flow reserve.

Our Siemens hybrid PET/MR scanner allows 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 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. For radiotherapy planning and the evaluation of recurrent meningioma we are employing [⁶⁸Ga]DOTATOC using our high-resolution research tomograph (HRRT) PET scanner, as the growth pattern of meningioma, and the small margins of the stereotactic radiation therapy used make a 2 mm resolution desirable.

With the increasing demand of neuro PET examinations and also increasing analytical complexity of in particular PET/MR studies, we are seeking to develop and apply post-processing pipelines providing fully automated reports and standardized analyses of PET and MRI data supporting clinical interpretation and reporting.



▲
Figure 1. Example of use of the new PET radiotracer [¹⁸F]FE-PE2I for assessment uncertain Parkinsonism in a patient with the “Dr. Strangelove syndrome”. The patient seen in the Memory Clinic had non-fluent aphasia, but not memory complaints, and the so-called “Alien Hand syndrome”, also called “Dr. Strangelove syndrome” after the movie. It is a category of conditions in which a person experiences their limbs acting seemingly on their own, without conscious control over the actions. This patient had left frontal lobe atrophy on MRI, but normal basal ganglia (left image), 2-[¹⁸F]FDG PET scanning with slight asymmetrical metabolic reduction in the left striatum (red arrow) and in the left frontal lobe (center image), and severe asymmetrically reduced [¹⁸F]FE-PE2I PET binding in the left striatum (red arrow) with normal conditions on the right side (right image). The image presentation is consistent with atypical Parkinsonism found in the neurodegenerative disease Corticobasal Degeneration (CBD) in which the “Alien Hand syndrome” is a known clinical expression.

MR imaging of muscle function

Professor, Consultant Henrik BW Larsson

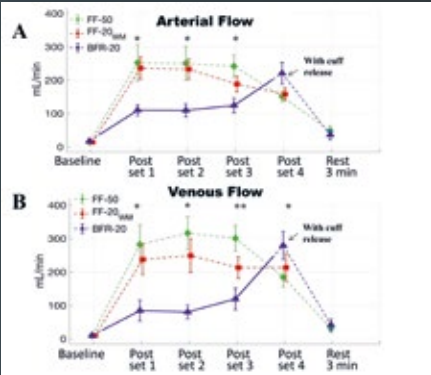
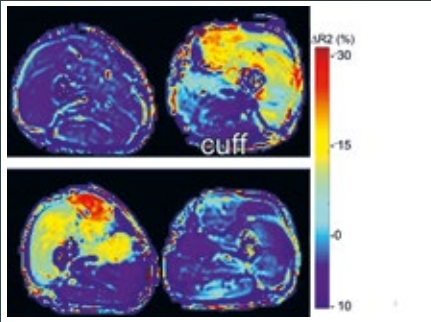
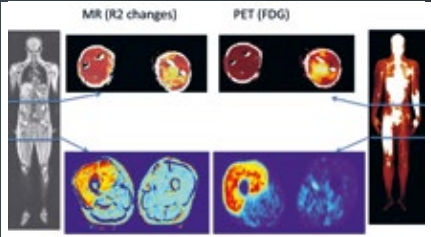
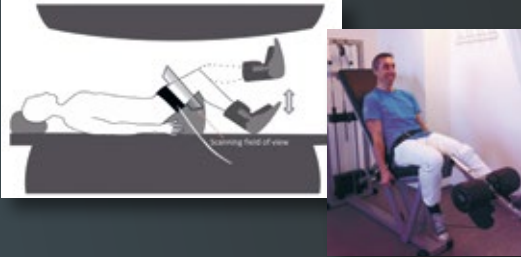
In patients with neuromuscular pathologies the evaluation of rehabilitation paradigms can be very challenging as the normal signaling between the brain and the muscles is partly or completely disrupted. An important milestone in developing successful interventions for these patient groups is to achieve the ability to detect the stimulation of muscle groups in the body and predict whether an intervention will help maintain or even improve muscle function. In 2019, we have worked with MRI scanning methods that map the distribution of skeletal muscle activation within both large and small muscle groups, in vivo, throughout repeated contractions, involving a set-up as shown in figure 1. Along with the distribution of activation, we acquire important physiological information regarding shifts in tissue fluids, blood flow and oxygenation.

Of particular interest, we have worked with a special training technique that has proven effective in helping patient groups regain muscle strength and muscle mass during rehabilitative muscle training. The technique involves applying compression during exercise via a cuff in a fashion similar to when measuring blood pressure. In

collaboration with researchers from University of Southern Denmark, Herlev Hospital and Bispebjerg Hospital, we have measured that similar responses in muscle tissue can be achieved when using this technique despite low loads and fewer repetitions.

Physicist Bryan Haddock, figure 2, completed a PhD thesis in 2019 using these MRI techniques to image muscle activity and evaluate differences between differing exercise strategies known to elicit skeletal muscle hypertrophy. The techniques applied include quantitative mapping of muscle activation (estimated using R_2 values), blood oxygen saturation (assessed via R_2^* values) along with mapping diffusion rates of tissue fluid and monitoring changes in blood flow, see figure 3, 4 and 5.

Collectively, the use of multimodal MRI to examine selected peripheral physiological variables represents a promising tool not only for decoding important mechanisms of adaptation, but also for optimizing the design of effective and personalized training strategies for patients with neuromuscular diseases.



► **Figure 1.** Functional imaging when using MRI of muscle tissue during exercise presents the challenge of creating a setup that allows the desired training of muscle groups in a fashion that is safe, respectful of scanning equipment and allows optimal data acquisition. The setup used to study the physiology of the quadriceps muscles during resistance training is shown here.

► **Figure 2.** Bryan Haddock exercising using some of the equipment used in this study.

► **Figure 3.** The distribution of muscle activity within muscle groups can be mapped by quantifying changes in MRI R2 relaxation rate values. Here, a subject having performed knee extension exercise with one leg and hand grip with one arm is scanned with $[^{18}\text{F}]\text{FDG}$ PET/MRI. Measured $[^{18}\text{F}]\text{FDG}$ uptake and changes in R2 values identify similar distributions of muscle activity.

► **Figure 4.** By applying a compression cuff during exercise, changes in R2 measured in muscle tissue were on average higher and more uniform even though the workload on the contracting muscle was reduced by more than half. Above is a map of R2 changes in muscles of the leg after performing repeated one-legged knee extension exercise lifting a load of 20% subjects maximum with the cuff applied. Below is a measure in the same subject (opposite leg) when the exercise was performed without the cuff using a load of 50% of the subject's maximum.

► **Figure 5.** Graphs show measures of relative arterial (A) and venous (B) blood flow in exercising muscle with the cuff applied (BFR-20) and without (FF-20wm and FF-50) over several sets of knee extension exercise. At recommended pressures, the cuff reduces blood flow by 50-60% compared to the same exercise without the cuff (FF-20wm) or the same exercise without the cuff and with a heavier load (FF-50). The augmented stimulation of muscle growth that occurs with the addition of a compressive cuff has been hypothesized to result from blood flow being reduced to a point where the metabolic demands of the active muscle cannot be met, initiating a cascade of alterations in metabolite concentrations and fluid shifts.



PET/MR

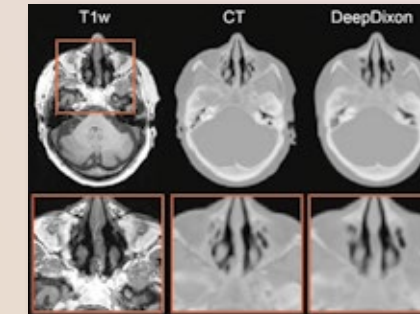


Figure 1. Example of deep learning PET/MRI brain attenuation correction. The Deep learning attenuation map ‘DeepDixon’ predicted from MRI matches closely the reference CT. Training, test and validation was done using a total cohort size of 1037 patients. PET bias was below 2% in any region of the brain. [C Ladefoged et al., submitted]

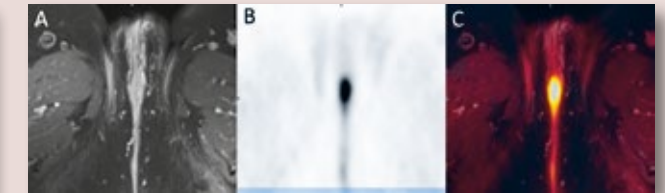


Figure 2. ^{18}F -FDG PET/MRI images from a project investigating the diagnostic value of PET/MRI in patients with newly diagnosed vulvar cancer, with special focus on localized spread of the tumour. A) Transverse contrast enhanced T1-weighted fat-suppressed Turbo spin echo MRI. B) FDG PET. C) PET/MRI fused image.

Physicist Adam Espe Hansen and Consultant Johan Löfgren

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 ^{18}F -FDG PET and anatomic MRI with a duration of 20 minutes, to dynamic PET with kinetic modeling and physiologic MRI measurements which may last 1-2 hours. In 2019 the number of examinations performed was approximately 800, out of which 70% were clinical.

Clinical PET/MRI is undertaken primarily of patients with dementia, primarily Alzheimer’s disease, patients with brain tumors examined with ^{18}F -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. In 2019 we implemented Artificial Intelligence – based PET attenuation correction in clinical routine, for ^{18}F -FDG PET brain examinations (Figure 1).

To further expand the clinical use of PET/MRI, a large number of 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 (Figure 2), prostate cancer, neuro-oncology, pediatric oncology, and vascular brain diseases. Finally, a number of clinical and pre-clinical research studies examine the utilization of combined PET and MRI to characterize the biology of disease.

Nuclear medicine technologists, radiographers and lab technicians

Chief Nuclear Medicine Technologist Linda M. Kragh

Nuclear medicine technologists, radiographers and lab technicians are together with medical secretaries and physicians crucial for our patient investigations and research.

The Radiochemistry Section have been busy, and we have increased the production of Gallium-68 Dotatoc and have extended the opening hours of the department to 6 PM on Tuesdays and 7 PM on Thursdays to secure that patients can be investigated and treated in time. This extension has been a challenge to plan, and it has led to a new dynamic in the department. It has after a run in period been evaluated positively. The number of staff in the section has been extended accordingly.

The work environment is in focus, and we have emphasized good manners, a polite, helpful and professional attitude with inclusion and acceptance. We have tried to reduce procedures with lifting of heavy patients and stuff, and we have installed lifts for patients in several of the scanners. Courses for staff in how to work smarter have been held throughout the year.

Thank you to each and every one of you for the helpful, professional and dedicated effort.

Masterplan

In the department we use the lean concept to adapt the increased number of patient referrals. PET/CT scans are used increasingly, and we have to plan carefully to secure slots for acute patients and for research. We have a new group working with a master plan to streamline the exploitation of our PET/CT scanners. Both nuclear medicine technologists, physicians, radiochemistry and medical secretaries are members of the group, and the whole procedure from production of PET tracer to reporting of PET/CT scans are carefully planned. This master plan is a dynamic document, updated after each meeting, chaired by Staff Nuclear Medicine Technologist Maria Pejtersen. Through constant updates and implementation of the new PET/CT scanner 5 it has been possible to reduce the scan time.

In May 2019 the old fashioned ^{99m}Tc myocardial perfusion SPECT studies were moved from the





*Content: Minimum 128 hours on several hospital departments.
ECTS: Minimum 20 ECTS points.*

Project with communication at the end. Point: Up to the total 40 ECTS.

The tuition should be minimum 40 ECTS, and the puzzle pieces can be put together as desired.

Glostrup Section to Blegdamsvej, where we do the cardiac studies for all patients using ^{82}Rb PET scans.

To reduce the number of no-show patients, we contact patients by phone to remind them on their appointment with us, as we previously saw that some patients either had forgotten or not received the invitation letter.

Professionalism

We are dedicated to a professional attitude by continuous education and participation in relevant courses and national and international symposia, workshop and congresses. We encourage that staff members present a poster or an oral presentation. We have focused on apprenticeships among colleagues and have specific training schemes with requirements concerning both theory and practice, so that staff members learn-

ing a new task can take responsibility for own progress. Focus has been on theory, patient safety, our ICT system, and how to perform their investigations. After training the staff nuclear medicine technologists have the responsibility for certifying the staff member and it is then documented in D4, our document management system.

Education

We participate in the pregraduate education of biotechnologists and radiographers. This year one of the bachelor projects won the Bachelor Prize: “Optimering af ^{18}F -FE-PE2I scanning samt undersøgelse af tidspunkt for den optimale specifikke bindingsradio for ^{18}F -FE-PE2I”.

Specialist education for nuclear medicine technologists and radiographers

We have participated in a project in Region Hovedstaden, the Capital Region of Copenhagen,

to develop a new specialist education in clinical physiology and nuclear medicine for our nuclear medicine technologists and radiographers. The aim of the education is competence development to secure a high professional level in the future to improve patient investigations and support development and innovation in our specialty. At present we have held meetings with all the departments in Denmark in clinical physiology and nuclear medicine, and we collaborate as shown in the puzzle.

Our Nuclear Medicine Technologist Mia Hjorth Albers is leader of the project. Mia Hjorth Albers and the national group work to describe the curriculum of the education and plan the anchor-age of the education in the future.



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, and we have no waiting lists for patients or reports. The medical secretaries master the complicated booking and secure that the waiting lists, the patient control examinations and research scans can be done in spite of a high

workload. A dedicated thank you to Tina Vikmann Nielsen, Gudrun Semitoje, Frederikke Hurup Henriksen, Pia Kastrup, Marianne Stahlfest, Mette Fabiansen Larsen, Nina Bjørling, Camilla Kuhre Vildrik Bendtzon and Nanna Folkmann. Our Head Medical Secretary Vibeke Rønn is assistant to the leadership of the department.

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



*Gudrun Semitoje's 25 years Anniversary
September 6th, 2019*



Cyclotron Section

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

During the last 10 years we have experienced a relative stable number of productions at our two cyclotrons of 1.220 ± 120 productions per year, see figure 1. In 2019 we had in total 1.266 successful productions (553 and 713 for our Scanditronix MC32 and Siemens RDS Eclipse cyclotrons respectively) giving an average success rate of $99,4 \pm 0,5\%$ since 2010. As in the previous years we managed to keep the average radiation dose to the employees in the Cyclotron- and Radiochemistry Section at a low level, see 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 2010. Our permission from the authorities (SIS) allows us to release 10 TBq per year. In 2019 we ended at the very save side with a release of only 5,5% 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). At figure 4 we show the estimated total dose distribution from the release last year illustrated for a 400×400 meter grid in the neighborhood of the chimney. The example is given for a height of 20 m, where we have the highest concentrations. The highest possible dose level is seen to be below $2 \mu\text{Sv}$ and far from the release limit.

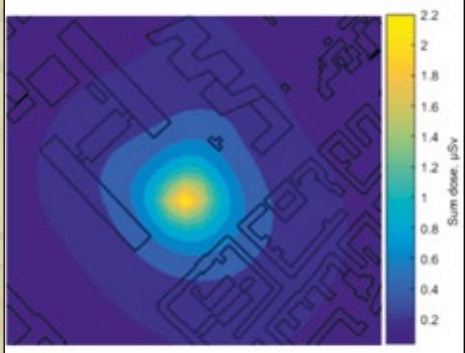
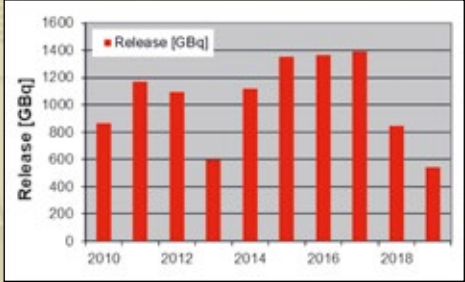
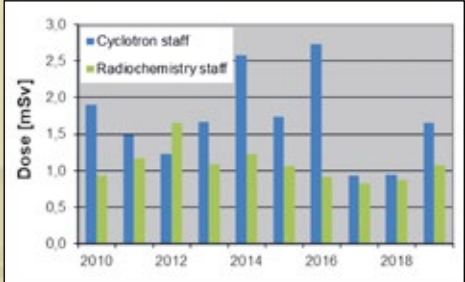
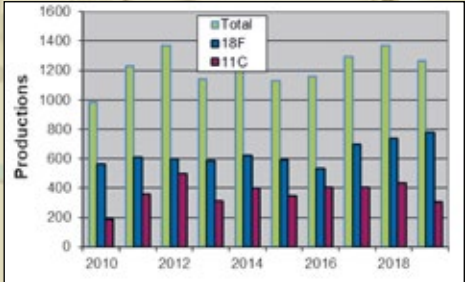
During the last few years, we have invested in various upgrade projects for our Scanditronix MC32 cyclotron. The machine is unique, and it is our ambition that the cyclotron should run for several decades more. One plan during the last few years has been to upgrade all electronics

► **Figure 1.** Development in ^{18}F , ^{11}C and the total number of productions since 2010.

► **Figure 2.** Average received dose per year for employees in the Cyclotron- and Radiochemistry Section since 2010.

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

► **Figure 4.** Total dose distribution in the neighborhood of the chimney for a total release of 0,55 TBq last year. Values are shown at a height of 20 m above ground level.



for the machine. Most part of the RF system has been replaced already and in 2018 we signed new contracts with the external companies “Wintek” and “Racetrack Microtron Systems AB” for replacements of the last parts of the RF system and other electronic boards respectively. In 2019 these projects were finalized and installed with success. See figure 5.

In 2019 we received very important spare parts for our CTI/Siemens Eclipse cyclotron from John Mallard PET Centre in Aberdeen. They decided to shut down their machine, that is almost identical to our, for a replacement with a GE PETTrace and we got the possibility to get all non-radioactive parts for free.



Radiochemistry Section

Chief Radiochemist, Production Manager Jacob Madsen and Chief Radiochemist Nic Gillings

Production for clinical and research PET investigations in humans

Production of [^{18}F]FDG and krypton-81m generators along with [^{18}F]FET, [^{18}F]FLT, [^{11}C]PIB and [^{15}O]water continued on a similar level compared to previous years. We continued to produce the uPAR imaging agent, [^{68}Ga]Ga-NOTA-AE105 and our angiogenesis tracer, [^{68}Ga]Ga-NODA-GA-E[c(RGDyK)]₂. Both are being evaluated in phase II clinical trials. There were more than 1,100 batches released for human use in 2019 comprising of 15 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

A phase I clinical trial to evaluate ^{18}F -labelled active site-inhibited factor VIIa ([^{18}F]ASIS), our first radiolabeled protein, was completed in 2019 and the results are under evaluation. This PET tracer binds to tissue factor, which, apart from playing a central role in the coagulation cascade, is up regulated in a number of cancer forms.

[^{68}Ga]Ga-OPS202 was produced for a multicenter, randomized, dose-confirmation, factorial phase II study to evaluate the optimal dose of [^{68}Ga]Ga-OPS202 as a PET imaging agent in subjects with gastroenteropancreatic neuroendocrine tumor (GEP-NET).

[^{68}Ga]Ga-PSMA-11 was produced as diagnostic agent for “The VISION trial”: An international, prospective, open label, multicenter, randomized Phase III study of [^{177}Lu]Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC).

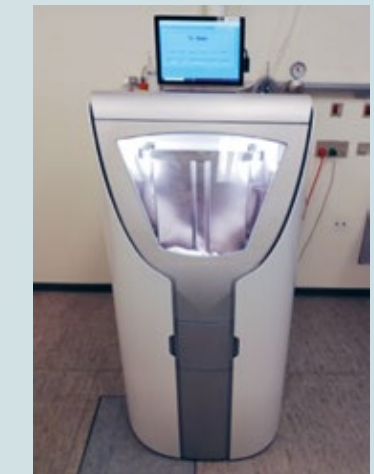
Neurobiology

Our collaboration with The Neurobiology Research Unit, Rigshospitalet and the Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen continued as in previous years. This work mainly focuses on development and evaluation of new PET ligands for brain research. Production of a promising synaptic density tracer, [^{11}C]UCB-J, has been set up and validated and an application for human use was submitted in 2019.

The dopamine transporter ligand, [^{18}F]FE-PE2I, which is used for the diagnosis of Parkinson’s

Disease is now produced routinely 3 or 4 times per week. Optimization of the production allowed for a more robust process and more stable radiochemical yields, and in 2019 151 batches were released for human use.

A system for production of O-15 water developed by the Danish company MedTrace Pharma A/S was installed during the last weeks of 2019. Validation and approval for clinical use is anticipated in 2020.



O-15 water production system

Radiopharmaceutical	Batches	Usage/Target
[¹⁸ F]FDG	354	Oncology/glucose metabolism
Krypton-81m generator	148	Lung ventilation
[¹¹ C]PIB	117	Alzheimer's Disease/β-amyloid plaques
[⁶⁸ Ga]Ga-DOTATOC	94	Neuroendocrine tumours/somatostatin receptors
[⁶⁸ Ga]Ga-NOTA-AE105	60	Oncology/uPAR imaging
[¹¹ C]SB207145	25	Brain Research/5-HT ₄ receptors
[⁶⁸ Ga]Ga-NODAGA-E[c(RGDyK)] ₂	77	Oncology/angiogenesis imaging
[¹⁸ F]FE-PE2I	151	Neurology/dopamine transporter ligand
[¹⁸ F]FET	53	Oncology/amino acid transport
[¹¹ C]Cimbi-36	5	Brain Research/5-HT _{2A} receptors
[¹⁸ F]FLT	6	Oncology/cell proliferation tracer
[¹⁵ O]Water	7	Cerebral blood flow
[⁶⁸ Ga]Ga-PSMA-11	21	Oncology/prostate specific membrane antigen ligand
[⁶⁸ Ga]Ga-OPS202	17	Neuroendocrine tumors/somatostatin receptors (clinical trial)
[¹⁸ F]ASIS	10	Oncology/tissue factor imaging
Total	1,145	

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 2019, with several members of the Radiochemistry Section involved in lecturing and practical exercises. In addition, Matthias Herth supervises a significant number of the PhD students listed below.

Radiopharmaceutical research and PhD projects

- ▶ Troels Elmer Jeppesen is employed as a post-doc and works on methods for rapid fluorine-18 labelling of peptides and labelling of optimized ligands for uPAR.
- ▶ Camilla Christensen started her PhD project in March 2018 where the focus will be to develop and validate novel radiolabeled an-

tibody-based positron emission tomography (PET) imaging biomarkers for immuno-PET and establish a platform for translation into clinical use.

- ▶ Klas Bratteby started a PhD project in January 2018 which is focused on investigation of ¹⁸F-fluorination methods for base sensitive labelling precursors. One aim of the project is to be able to improve the radiosynthesis of [¹⁸F]FE-PE2I and ¹⁸F-labelled tetrazines. Promising results regarding the optimization of the radiochemical yield of [¹⁸F]FE-PE2I have been achieved.
- ▶ Vladimir Shalgunov started as a postdoc in November 2017 and is working on the establishment of methods for the imaging of brain targets. Particular directions of his work are development of tetrazine-based radioligands for pre-targeted PET imaging of the brain and



Radiopharmaceuticals produced for human use in 2019

evaluation of PET radioligands for imaging of the serotonergic system.

- ▶ Ida Andersen started a PhD in December 2019 which focuses on ¹⁸F-labelled compounds targeting LAG3 for animal studies.
- ▶ Sara Lopes van den Broek started her PhD project in February 2019, which focuses on the development of blood-brain barrier penetrating *trans*-cyclooctene (TCO) modified antibodies (mAb) for pre-targeted PET imaging within the central nervous system. *In vitro* characterization and analyses of the TCO-mAb conjugates with ¹¹¹In- and ¹⁸F-labelled tetrazines have shown promising results and therefore *in vivo* studies are scheduled in the coming year for further evaluation of the TCO-mAbs.
- ▶ Rocío García Vázquez started her PhD in 2019. She is developing ¹⁸F-labelled tetrazines for pre-targeted imaging.



Academic and other activities

Andreas Kjær, Professor, Consultant, ERC advanced grantee, is member of the Oncology Committee of the European Association of Nuclear Medicine (EANM), member of the advisory board of the European Neuroendocrine Tumor Society (ENETS), national representative of the European Society for Molecular Imaging (ESMI), board member of the Cancer Research Foundation at University of Copenhagen, advisory board member of the Avatar Cancer Program, CPMC (Sutter Health), San Francisco. 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). International associate editor of Editorial board member of Journal of Nuclear Medicine (JNM) and European Journal of Nuclear Medicine & Molecular Imaging (EJNMMI). Leader of projects for development of theranostics for aggressive cancer and for project of hyperPET, funded by the Innovation Fund Denmark. Coordinator of an H2020 project on click-chemistry for PET. 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. Member of the Industrial Researcher Committee, Innovation Fund Denmark. Member of the Academy of Technical Sciences (ATV).

Anne Kiil Berthelsen, Consultant, is member of the International Lymphoma Radiation Oncology Group, Steering Committee (ILROG), “European Organisation for Research and Treatment of Cancer Lymphoma Group” (EORTC), the Danish Society of Radiology, the Danish and the Nordic Society of Gynaecological Oncology, British institute of Radiology (BIR), Billeddiagnostisk udvalg Ukendt Primærtumor (DAHANCA), National PET/CT Group, the Danish Society of Clinical Oncology, the Danish Society of Magnetic Imaging, Diagnostic Imaging Group under Danish Lymphoma Group, ERS European Society of Radiology and Sundhedsstyrelsens Udvalg for Kræft.

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

Annika Loft Jakobsen, Consultant, MD, 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 the Oncology Committee of the 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)) and pharyngeal/laryngeal cancer. Member of the National PET/CT Group. Board member of DGCG (Danish Gynecological Cancer 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 Scientists.

Bryan Haddock, MPE, MSC, 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.

Claes Nøhr Ladefoged, Postdoc, MSc, PhD, co-supervisor for PhD and MSc students in the department. Co-head of research group Clinically Applied Artificial Intelligence (CAAI) and academic secretary

to Rigshospitalets Research Strategy Council. Responsible for PET/MRI attenuation correction.

Elisabeth Albrecht-Beste, Clinical Associate Professor, Consultant, member of Danish Society of Radiology, chair of post-graduate radiology courses in Denmark, 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, MSc, PhD, Associate Professor, is involved in a number of clinical research protocols, supervisor for several PhD, master and bachelor students and involved in both pre- and post-graduate teaching. 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, member of Danish Society of Medical Magnetic Resonance Imaging and Danish Society for Good Clinical Practice.

Helle Juhl Simonsen, Research MR Technologist, Biomedical Laboratory Scientist. Board member in

ISMRM White Matter Study Group as SMRT representative. Vice Chair in the Local Chapters Committee, member of the Global Relation Committee, MR Safety Committee and Nominations Committee in International Society for Magnetic Resonance in Medicine (ISMRM)/Section for MR Technologists (SMRT). Board member of the Danish Society for Magnetic Resonance, member and service responsible.

Henrik B.W. Larsson, MD, DMSc, Consultant, 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, Professor in Medical Magnetic Resonance Imaging, Norwegian University of Science and Technology, Norway, 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, Management board of EU COST Action (BM1103): “Arterial Spin Labelling in Dementia”, Steering committee of the 7 Tesla project, Copenhagen, Denmark. Member of the Danish Multiple Sclerosis Research Council.

Ian Law, Professor, Consultant, is Chair of the Neuroimaging Committee, European Association of Nuclear Medicine (EANM), Member of the “PET Response Assessment in Neurooncology (RANO)

working group” under the European Association of Nuclear Medicine (EANM), European Association of Neuro-oncology (EANO), and Society of Neurooncology (SNO). Member of the Danish Neurooncology group (DNOG), responsible for the specialist training course in the central nervous system for nuclear medicine physicians.

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 Lungecancer Gruppe” (Danish Lung Cancer Group), the subcommittees for “Dansk Diagnostisk Lungecancer Gruppe” (Danish Diagnostic Lung Cancer Group) and “Lungecancer 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 the Danish spirometry course.

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.

Academic and other activities

Kim Francis Andersen, Consultant, is member of the Board of Danish Sarcoma Group (DSG). 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).

Linda Kragh, Chief Nuclear Medicine Technologist, is member of Sundhedsfagligt Råd i Klinisk Fysiologi og Nuklearmedicin i Region H, SFR, (the Speciality Advisory Committee in Clinical Physiology and Nuclear Medicine in the Capital Region), member of the DRG Committee of DSKFNM, and member of Uddannelsesudvalget på Radiografuddannelsen at Metropol (the Speciality Council for the Education of Radiographers at Metropol). Member of “Forum for uddannelse” på Rigshospitalet.

Lise Borgwardt, Consultant, Chief of Pediatric Nuclear Medicine at Rigshospitalet, Senior Advisor of the Paediatric Committee under EANM, Scientific Committee member of the EANM, boardmember of DAPHO, 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. 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 Tagea Brandt’s prize.

Louise Alslev, Consultant, teaches at the Bachelor’s Degree Program in Radiography at the University College Copenhagen (KP).

Malene Fischer, Associate Professor of Research, Consultant, is supervisor for several PhD, 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), 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. 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, 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 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 student 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.

Robin de Nijs, MSc, PDEng, PhD, Specialist 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 Danish and international students in a.o. Medicine & Technology and Medical Physics. Associated physicist for the SPECT brain scan section of the Neurobiology Research Unit at Copenhagen University Hospital.

Ronan M.G. Berg, MD, PhD, 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, of which he is board member in the latter. 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 EFO-MP’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, Chair of Danish Society for Medical Physics Educational Council, 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.

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. Responsible for the specialist course in cardiovascular circulation 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.



Equipment 2019

Chief Physicist Thomas Levin Klausen

Equipment	Product	Purchase year
Gamma cameras	Mediso Nucline X-Ring	2003
	Mie-Scintron	2004
	Mediso TH45	2007
	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	GE Infinia Hawkeye	2004
	Siemens SymbiaT2	2006
	Philips, Precedence 16-slice CT	2008
	GE Discovery 670	2010
	Siemens Symbia 16-slice CT	2011
	Siemens Symbia Intevo Bold 16 slice CT	2017
PET scanner	HRRT Siemens/CTI	2007
PET/CT scanner	Siemens Biograph TrueV 64-slice CT	2009
	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
	GE SPINlab MR Hyperpolarizer	2014
Lung function	Jaeger Masterscreen w/bodybox	2005
	Jæger Masterscreen w/bodybox	2019
	Jaeger PFT pro w/bodybox	2007/13
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
At Cluster for Molecular Imaging, Panum	Provivo/ ADAC mobile gamma camera	1990
	Siemens Micro-PET Focus 120	2006
	Phosphor Imager Perkin Elmer cyclone	2007
	Bruker preclinical MRI PharmaScan 7T	2013
	Siemens preclinical PET/CT Inveon	2013
	PX Inc. preclinical RT X-RAD 320	2013
	Mediso nanoScan SPECT/CT	2015

Studies 2019

CNS and peripheral nervous system		
Regional cerebral blood flow, DIAMOX, ¹⁵ O-H ₂ O	8	
Regional cerebral metabolism, ¹⁸ F-FDG	1,754	
Regional cerebral receptor, ¹¹ C-PIB	207	
Regional cerebral receptor, ¹⁸ F-FET	470	
Regional cerebral receptor, ¹⁸ F-FE2PI	452	
Regional cerebral blood flow, ^{99m} Tc- HMPAO, pharm. prov.	16	
Regional cerebral blood flow, ^{99m} Tc- HMPAO	15	
Regional cerebral receptor, ¹⁸ F-Florbetapir + FLP	17	
Regional cerebral receptor, ¹⁸ F-FLT	8	
Regional cerebral receptor, ⁶⁸ Ga-Dotatoc	74	
CT scanning of cerebrum	435	
MR scanning of cerebrum with and without contrast	2,560	
MR scanning of hippocampus (MR-HCV)	403	
Cisternography ^{99m} T c-DTPA	3	
Total	6,422	

Respiratory organs		
Lung function test, whole body plethysmography	2,717	
Lung function test, whole body plethysmography w/reversibility	384	
Lung function test, spirometry	824	
Lung function test, spirometry w/reversibility	246	
Lung function test, diffusion capacity (CO)	4,098	
Lung function test, diffusion capacity (NO/CO)	92	
Max. insp. abd. exspir. muscle pressure	3	
Lung perfusion scintigraphy, ^{99m} Tc-MAA	1	
Lung perfusion scintigraphy, SPECT, ^{99m} Tc-MAA	453	
Lung ventilation scintigraphy, ^{81m} Kr-gas	50	
Lung ventilation scintigraphy, regional, ^{81m} Kr-gas	266	
Lung ventilation scintigraphy, SPECT, ^{81m} Kr-gas	394	
Lung ventilation scintigraphy, SPECT ^{99m} Tc-Technegas	58	
Mucociliary clearance, ^{99m} Tc-Venticolloid	50	
CT thorax PET/CT breathhold	20	
PET thorax PET/CT breathhold	18	
Total	9,674	

Heart and cardiovascular system		
Isotope cardiography, LVEF, ^{99m} Tc-HSA	1,518	
Myocardial perf. scintigr. gated, ^{99m} Tc-MIBI, pharmacol. stress	50	

Myocardial perf. scintigr. gated, ^{99m} Tc-MIBI	43
Myocardial ¹²³ I- MIBG, sympaticus activity	3
Myocardial scintigraphy, ^{99m} Tc-PYP	12
Myocardial calcium score	733
Tilt table test	287
Analysis of heart rate variability	287
PET myocardial metabolism, ¹⁸ F-FDG	145
PET myocardial perfusion, ⁸² Rb, rest	843
PET myocardial perfusion, ⁸² Rb, pharmacological stress	771
Total	4,692

Peripheral vessels	
Doppler ultrasound of the carotides	4,002
Systolic blood pressure, fingers	1
Systolic blood pressure, ancle and toes	369
Systolic blood pressure, ancle-brachial index after treadmill	131
24 hours blood pressure measurement	248
Doppler ultrasound of abdominal vessels	386
Isolated limb perfusion leakage monitoring, ^{99m} Tc-erythrocyt	2
Total	5,139

Gastric intestinal tract, liver, biliary tract and pancreas	
Salivary gland scintigraphy ^{99m} Tc-Pertechnetat	18
Biliary tract scintigraphy, ^{99m} Tc-Mebrofenin	58
Bleeding scintigraphy (abdomen) ^{99m} Tc-erytrocytter	3
Doppler ultrasound of splanchnic blood flow	382
Meckels diverticle scintigraphy	3
Total	464

Kidneys and urinary tract	
Glomerular filtration, ⁵¹ Cr-EDTA	305
Glomerular filtration, ^{99m} TC-DTPA	2,182
Renal scintigraphy, ^{99m} Tc-DMSA	5
Renography, ^{99m} Tc-MAG, diuresis	25
Renography, ^{99m} Tc-MAG 3, ACE-inhibitor	142
Renography, ^{99m} Tc-MAG 3	2,224
Doppler ultrasound of renal blood flow	365
Ultrasound kidneys	362
MR kidneys	80
Total	5,139

Bone and joint	
Bone scintigraphy, ^{99m} Tc-HDP, regional, static	39
Bone scintigraphy, ^{99m} Tc-HDP, 2 phased	47
Bone scintigraphy, ^{99m} Tc-HDP, whole body, static	1,005
Bone scintigraphy, ^{99m} Tc-HDP, SPECT	798
Bone PET scanning ¹⁸ F-NaF	3
Osteodens. dual X-ray absorptiometri (DXA), columna lumb.	4,943
Osteodens. dual X-ray absorptiometri (DXA), lat.spine	173
Osteodens. dual X-ray absorptiometri (DXA), radius	182
Osteodensitometri, dual X-ray absorptiometri collum fem.	6,954
DXA, body composition	823
MR scanning columna	125
MR scanning columna thoracalis	30
MR scanning columna lumbalis	4
Total	15,126

Endocrine organs	
Thyroid scintigraphy, ^{99m} Tc-Pertechnetat	1,056
Thyroid scintigraphy, ¹²³ I-Iodide	79
Thyroid + ultrasound	1,134
Thyroid + fine needle aspiration biopsy	142
Iodine uptake test, ¹³¹ I-Iodide	50
Parathyroid scintigraphy, ^{99m} Tc-Stamisis, SPECT	78
Adrenal marrow scintigraphy, ¹²³ I-MIBG	26
Scintigraphy after ¹⁷⁷ Lu- Dotatate therapy	325
Total	2,890

Blood and lymph system	
Erythrocyt red blood celle survival, ⁵¹ Cr-erythrocytter	2
Erythrocyt volume, ^{99m} Tc-and ⁵¹ Cr erythrocytter	23
Plasma volume, ¹²⁵ I-HSA	17
Sentinel node scintigr. tumor drainage, ^{99m} Tc-Nanocolloid	239
Sentinel node scintigr. tumor drainage, SPECT ^{99m} Tc-Nanocolloid	202
Sentinel node scintigr. tumor drainage, head/neck SPECT, ^{99m} Tc-Nanocolloid	5
Peritumoral injection of ^{99m} Tc-Nanocolloid for sentinel node	623
Spleen scintigraphy, ^{99m} Tc-erythrocyte, heated	10
Total	1,121

Other diagnostic procedures	
Aprotinin scintigraphy ^{99m} Tc- aprotinin	1
PET scanning, ¹⁸ F-FDG	6,812
PET tumor scanning, ⁶⁸ Ga-Dotatoc	234
PET tumor scanning, ⁶⁸ Ga-PSMA	45
PET tumor scanning, ⁶⁴ Cu-Dotatate	610
White blood cell scintigraphy, ^{99m} Tc-white blood cell	17
White blood cell scintigraphy, ^{99m} Tc-white blood cell, SPECT	10
Whole body, contamination measurement	56
Image fusion (PET, SPECT, MRI, CT or planar)	14,576
CT head/neck SPECT/CT	321
CT wb SPET/CT	416
CT thorax SPECT/CT	567
CT pelvis SPECT/CT	148
CT abdomen SPECT/CT	315
CT lower and upper extremities SPECT/CT	24
CT wb PET/CT with contrast	6,440
CT wb PET/CT	1,693
MR wb PET/MR	28
Second opinions external PET, PET/CT, SPECT/CT, CT and MR investigations	2,192
Extra tumor delineation	268
Other investigations, incl. ¹¹ C-different tracers (NRU)	313
Supplementary/repeated imaging	2192
Total	37,278

Radiotherapy	
Treatment with ¹³¹ I, benign thyroid	99
Isotope treatment with ¹⁷⁷ Lu-Dotatate	172
Isotope treatment with ²²³ Ra-Dichlorid	83
Total	354

In vitro analyses	
Affinity studies	405
Flow cytometry analyses	69,674
Gene expression analyses	5,740
Immunohistochemistry	2,158
Plasma and protein analyses	25,021
Total	102,998

Studies 2019

Animal studies

Dogs	
HyperPET (RGD/ ¹³ Cpyruvat)	1
Rats	
¹⁵ O	4
¹⁸ F-FDG	210
⁶⁴ Cu-DOTATATE	67
⁶⁸ Ga-RGD	182
⁸² Rubidium	4
^{99m} Tc SPECT	61
²²⁴ Ra-Ca-CO3	18
Bioluminescens (luciferin)	2
MR	279
CT images for fusion	437
Ultrasound	216
Mice	
¹⁸ F-FDG	221
¹⁸ F-FHBG	5
¹⁸ F-tetrazine	160
¹⁸ F-tryptophan	4
⁶⁴ CuCl2	14
⁶⁴ Cu-anti-CD8a	49
⁶⁴ Cu-DOTATATE	226
⁶⁴ Cu-anti-CD4	66
⁶⁴ Cu-micelles	64
⁶⁴ Cu-tetrazine	8
⁶⁸ Ga-XX-AE105	7
⁶⁸ Ga-xx	4
⁸⁹ Zr-anti-CD3	40
⁸⁹ Zr-anti-PDL1	32
⁸⁹ Zr-Herceptin	9
⁸⁹ Zr-xx	96

^{99m} Tc SPECT	18
¹¹¹ In-Tetrazine	48
⁶⁴ Cu-TDM1	12
AI-18F-NOTA-AE105	36
AI-18F-XX-AE105	8
Bioluminescens (luminol)	60
Bioluminescens (luciferin)	1,229
Fluorescens (Cy5.5)	101
Fluorescens (ICG)	40
Fluorescens (ICG-AE105)	313
Fluorescens (IRDye800-AE105)	74
MR	1,332
CT images for fusion	902
Ultrasound	3
Photothermal therapy	68
Radiotherapy, externally	3,097
Radionuclide therapy (α and α emitters)	507

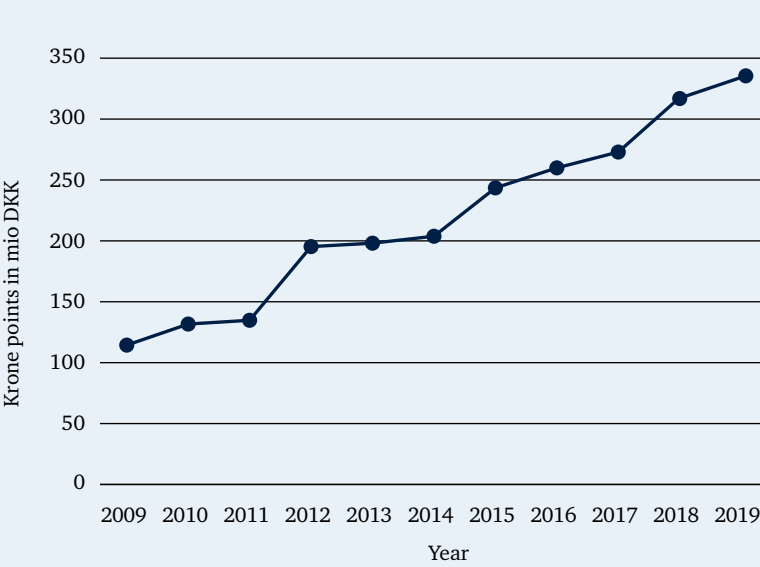
Rabits	
¹⁸ F-FDG	96
¹⁸ F-FET	1
¹⁸ F-NaF	23
⁶⁴ Cu-DOTATATE	61
⁶⁸ Ga-RGD	11
⁸² Rubidium	29
CT images for fusion	177

Pigs	
HyperPET (¹⁸ F-FDG/ ¹³ Cpyruvat)	-
MR	-
	-
Total	10,731

Total number of studies196,889

Finance

Turnover



The increase in activities measured in krone point* rose from 114.4 mio DKK in 2008 to 336.8 mio DKK in 2019.

* Krone point: Price for each patient investigation multiplied with number of investigations, summarized for all patient studies performed during the year.

Balance 2019

Expenditure (DKK mio)	95
Receipts	13

Publications

Theses

Sabrina Khan, MD, MRI investigations of migraine without aura in an experimental human model. Defended February 8, 2019, University of Copenhagen.

Nelly Richard, M.Sc., Neurophysiological Correlates of Cognitive Decline. Defended November 18, 2019, University of Copenhagen.

Nielsen, J. PhD thesis. Pediatric Liver Disease. Exploring methods for assessment of the course of disease. Defended June 24, 2019, University of Copenhagen.

Byrne C. Ph.D thesis. Myocardial perfusion in patients with non-ischemic systolic heart failure and different additive factors: A cross-sectional study using rubidium-82 PET/CT. Defended January 19, 2019, University of Copenhagen.

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Podcasts



Liselotte Højgaards strålende kamp mod kræft
Rigshospitalets direktør Per Christiansen tager en snak med klinikchef og professor Liselotte Højgaard fra Klinik for Fysiologi og Nuklearmedicin om nuklearmedicinens kolossale betydning for kræftpatienter, om tåbeligt bureaukrati og kræftsyge børns som den bedste motivation i kampen mod cancer.



Linda Kragh og indsatsen
Ledende bioanalytiker Linda Kragh fra Klinik for Fysiologi og Nuklearmedicin har med sine fem årtier i sundhedsvæsenet været med til at sætte sit præg på bioanalytikeruddannelsen. Hendes kolleger på Rigshospitalet må ind i mellem løbe stærkt, der er kamp om at skaffe studerende nok til uddannelsen, men til gengæld er jobbet givende. Hør om at tjene menneskeheden, om pladsproblemer og om kyllingebein i gelé.



Kunstig intelligens skal hjælpe læger og ikke erstatte dem
Rigshospitalets direktør Per Christiansen besøger datalog Claes Nøhr Ladefoged, der arbejder med få kunstig intelligens til at hjælpe sundhedspersonale med at få hurtigere og mere præcise diagnoser, samt færre gener i processen for patienterne. Selv om der er en digital revolution på vej, så kan computere ikke erstatte læger, fortæller Claes Nøhr Ladefoged.

Cluster for Molecular Imaging

Professor Andreas Kjær

The paradigm of precision or personalized medicine, i.e. tailoring therapy to the 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. However, tissue sampling is prone to *sampling error*, i.e. the non-representativeness of a biopsy with regard to the disease due to heterogeneity. In contrast, molecular imaging allows for non-invasive studies at whole-body level in the intact organism and elegantly circumvents this potential error. Furthermore, because of the unsurpassed sensitivity of PET and the possibility to quantify tracer uptake, the use of specific PET tracers for molecular imaging of phenotypic characteristics as a basis for practicing *personalized medicine* holds great promise. Among characteristics, which can be visualized are the *hallmarks of cancer*, e.g. cancer aggressiveness, angiogenesis and cell proliferation. We foresee that such PET ligands for individual phenotyping will become game-changing within many diseases including cancer and

cardiovascular disease. Moreover, successful PET imaging ligands may be developed or “converted” into radionuclide therapies if labeled with alpha or beta-emitting isotopes or into optical imaging ligands for surgical navigation and guidance. The imaging companion may predict the distribution of the therapeutic ligand and thereby if the therapy is likely to work. Such imaging-therapy pairs are known as *theranostics*.

Currently, our molecular imaging and theranostics research program focuses on development and application of new molecular imaging/therapeutic ligands. Key application areas include, but are not limited to: 1) individual therapy planning including companion diagnostics), 2) therapy monitoring and early detection of non-responders, 3) drug development, and 4) targeted radionuclide therapy (theranostics) including alpha-emitting ligands. Diseases of particular interest in our translational research program include cancer, cardiovascular disease, infection/inflammation and metabolic disease.



▲ Figure 1. The major steps involved in PET tracer development: after identification of an unmet clinical need, selection of the key-process involved in the pathophysiology of the disease and a relevant molecular target is identified. Thereafter, a specific ligand is developed and labeled with a suitable radionuclide for imaging (or therapy). Target validation (specificity) is then initially evaluated in vitro followed by testing in vivo in relevant animal models where also the biodistribution is studied for calculation of radiation dosimetry. From animals used in vivo, tissue is excised, which then undergo ex vivo investigations, e.g. to confirm target binding and expression. Successful, lead candidates are then rigorously tested for possible toxicity according to European guidelines and biological and radiochemical data and procedures form the basis for the Investigational Medicinal Product Dossier (IMPD), which is part of the application for human use. Following approval by the health authorities, a first-in-humans phase I clinical trial may then be initiated. If successful, phase II studies of clinical utility are then pursued. This may be followed by commercialization to reach clinical use on a broader basis. Imaging ligands may also be used as a starting point for new targeted therapies, in particular radionuclide based therapies.



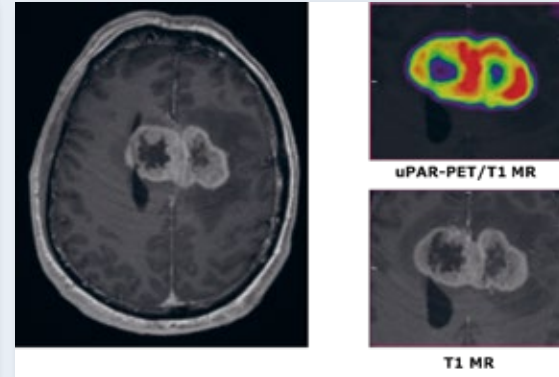
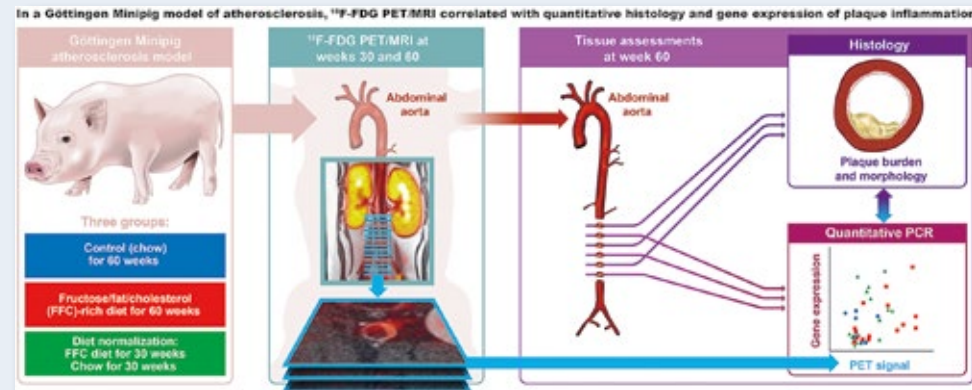


Figure 2. How we use a Göttingen Minipig model of atherosclerosis for non-invasive measurement of atherosclerosis by PET/MRI is longitudinal monitoring of therapies. The model may be used for studies of interventions, e.g. GLP-1 analogues. The imaging findings of the model have been validated by tissue assessment at the end of the study. For further details on the model system, which we developed in collaboration with Novo Nordisk A/S, please see Ludvigsen TP et al. Atherosclerosis 2019.

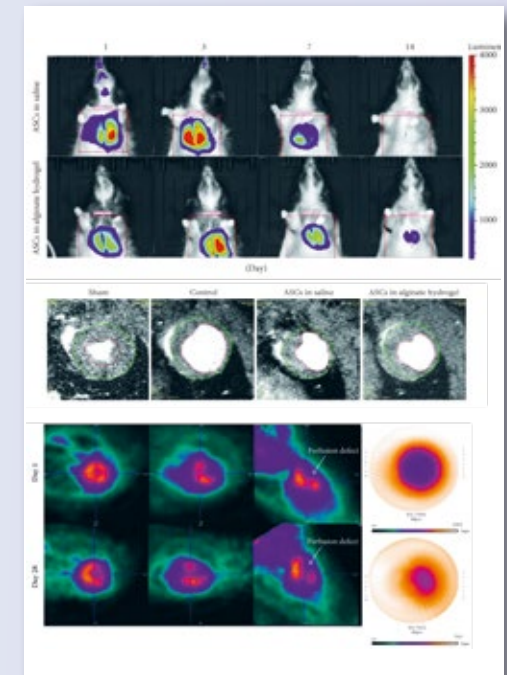
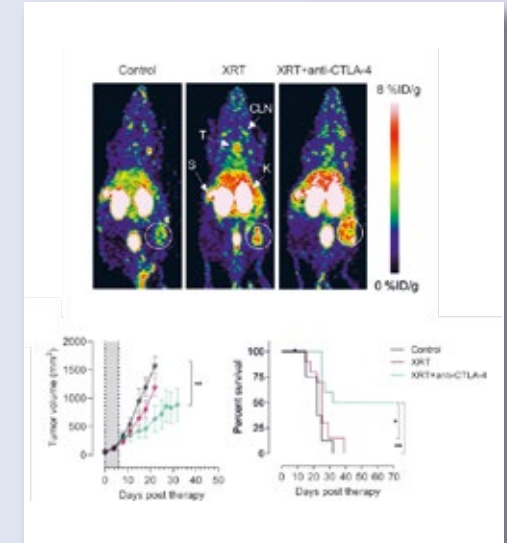
Figure 3. uPAR-PET in glioblastoma patient. Clear uptake of tracer in the tumor and very low background, which is encouraging for pursuing uPAR as a therapeutic target, e.g. with our uPAR-targeted radionuclide therapy (images from Kurbegovic S et al.).

apies. The goal is to help unfolding the immense potential of immunotherapies that are currently hampered by a low response rates. For this purpose, we have developed imaging ligands that can track the immune response, e.g. cytotoxic T-cells (CD8). With this platform, we have been able to predict the response to checkpoint inhibitor blockade in various cancers. This technology may serve for practicing personalized medicine and select likely responders to immunotherapy in cancer. In a recent publication, we were able to demonstrate how “priming” with external radiotherapy increased the T-cell (CD8) infiltration of the tumors and subsequent use of the checkpoint inhibitor thereafter further increased and sustained a T-cell response leading to increase in survival (Figure 4).

Within cardiovascular research, we have introduced and further developed animal models of cardiovascular diseases including models of atherosclerosis, myocardial infarction and heart failure (both with reduced and preserved ejection frac-

Figure 4. ^{64}Cu -NOTA-CD8a PET imaging of cytotoxic T-cells following external radiation therapy (XRT) and CTLA-4 checkpoint inhibition. Note the increased following XRT and further increase following checkpoint inhibition. The therapy led to inhibited tumor growth and increased survival (lower panel). This technology may be used to select patients eligible for checkpoint inhibition as well as monitoring of the induced immune response during therapy (Kellerman L et al. Mol Imaging Biol 2020).

Figure 5. Study performed in collaboration with the research group of Prof. Jens Kastrup on adipose-derived stromal cells administered in a rat model of acute myocardial infarction. The study used bioluminescence to track stem cells (top), cine MRI for measuring left ventricular ejection fraction (LVEF, middle) and ^{82}Rb -PET for measuring perfusion (bottom). The study revealed that stem cells improved perfusion as well as LVEF compared to control group (Follin B et al. Stem Cells Int).



Development of new molecular imaging tracers for PET is a complex process from definition of target to final use of the tracer in patients. We have focused on establishing competencies to support this workflow. The major steps involved in PET tracer development and translation into patients are shown in figure 1.

Cluster for Molecular Imaging, headed by Professor Andreas Kjær, was established in 2003 at the Faculty of Health and Medical Sciences, University of Copenhagen as a specialized facility at the Panum Institute for molecular imaging in animals with PET, SPECT, CT, MRI and optical imaging. This is a key component of our translational capabilities since it allows us to test new tracers and radionuclide therapies in animal models as basis for selection and translation into clinical use. Accordingly, we currently have a broad *pipeline* of PET tracers and radionuclide therapies in pre-clinical testing. We expect several of these candidates to be taken into clinical trials and become available for human

use over the next years. We continuously focus on use and development of more predictive animal models for PET tracer and radionuclide therapy development. This includes use of orthotopically implanted human xenograft tumors as well as metastatic cancer models using human cancer cell lines. Increasingly, we use patient-derived tumors (PDX) for orthotopic implantation (PDOX) to even better mimic the conditions in cancer patients regarding the tumor microenvironment, which is of great importance for tumorigenesis. For the study of immunotherapies in cancer, we use syngeneic and humanized preclinical models.

For more than a decade, we have worked on refining our translational platform for development of new PET tracers. With respect to cancer, the platform includes early use of promising PET tracers in companion dogs with spontaneous tumors scheduled for cancer therapy. This allows for testing in “full-size” as well as evaluation of tumor-stroma interaction due to the syngeneic tu-

mor environment. In this way, we bridge between xenograft models and first-in-human studies. This bridging is unique. Within cardiovascular disease, we use mice, rats, rabbits and (mini)pig models to develop new tracers. The pig model is our “full-size” model for myocardial infarction and atherosclerosis (Figure 2).

Studies of glioblastoma and use of our new uPAR-PET tracer has continued in animal models with orthotopically implanted human glioblastoma xenograft tumors as well as in glioblastoma patients (Figure 3).

With the increasing use of immunotherapies, in particular checkpoint inhibitors, that support the immune system to fight cancers we have established numerous models of syngeneic cancers as well as humanized (with regard to the immune system) animal models. Only by using such models, is it possible to study the interaction between cancer and the immune system as well as immunother-

Research

Professor Andreas Kjær

A continuous focus on research and development is a key activity and focus area of our Department. We have over the years build a comprehensive research program directed at developing innovative solutions to solve unmet clinical needs. We constantly adjust our research program to be clinically relevant and timely. Our research program is built on our strong in-house competencies as well as on strategic collaborations with leading international and national research groups with complementary competencies and capabilities. The focus of our research program is development of new tracers for PET, PET/MRI hybrid imaging, radionuclide therapies (*theranostics*), clinical evaluation of new diagnostic methods, the use of methods from clinical physiology and nuclear medicine to study pathophysiology and application of machine learning and artificial intelligence in imaging. Translational research in molecular imaging is given special attention in order to accelerate translation of new tracers into clinical use in patients. Current major research areas are briefly described below.

New tracers

Numerous projects aimed at development of new PET tracers for non-invasive tissue characteriza-

tion and phenotyping are ongoing. These novel tracers will be used for diagnosing, staging, risk stratification, and therapy planning and monitoring. Tracers developed at our department, and taken first-in-humans by us, include ⁶⁴Cu-DO-TATATE, ⁶⁴Cu-DOTA-AE105, ⁶⁸Ga-NOTA-AE105, ⁶⁸Ga-NODAGA-RGD₂ and ¹⁸F-ASIS. Once taken successfully first-in-humans, we study in phase II clinical trials the utility of the tracers in the clinical setting to establish where they may be of particular value to the patients. Accordingly, ⁶⁸Ga-NOTA-AE105, which is a marker of cancer aggressiveness and metastatic potential (the invasive phenotype) has been tested in two completed and 7 ongoing phase II trials in various cancer types (Figure 1). Likewise, ⁶⁸Ga-NODAGA-RGD₂, an angiogenesis PET tracer, is currently tested in Phase II clinical trials.

Over the years, we have build a comprehensive platform for validation of new tracers, including cell laboratory, molecular biology (proteomics and genomics), histology and biomarker laboratory. We currently have additional promising new PET tracers in our developmental pipeline and expect a continuous translation of the best of these into clinical use over the next years.

PET/MRI

Being one of the first departments to install a combined PET/MRI scanner, we established a comprehensive research program on PET/MRI with focus on the added value of combining molecular imaging with PET and multiparametric MRI. 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) and magnetic resonance spectroscopy (MRS). With access to matching preclinical PET and 7T MRI, we can work translational in developing and evaluating new methods. As an example, the use of PET/MRI for radiation therapy planning and response monitoring is being evaluated both preclinically and clinically. Also, the added value of multiparametric imaging combining information from both PET and MRI is currently studied.

hyperPET

Our department was the first to install a dynamic nuclear polarized (DNP) for hyperpolarization of



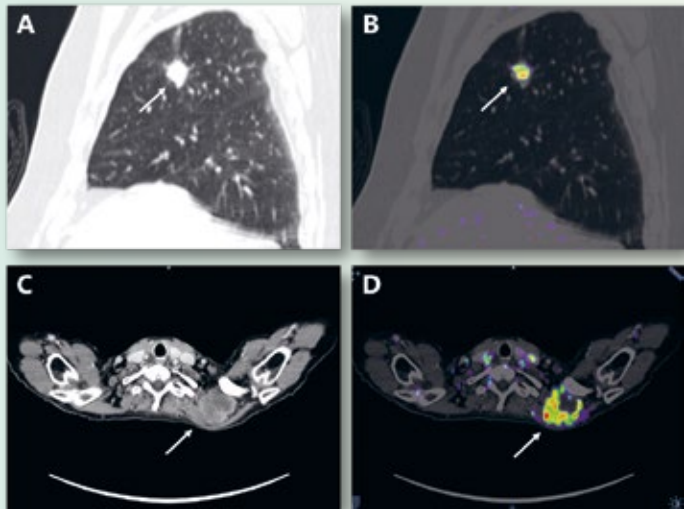
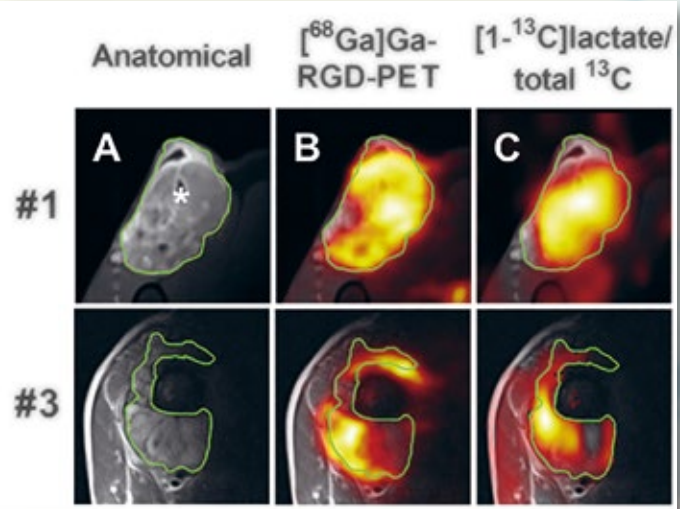


Figure 1 showing uPAR-PET/CT (B, C) and CT (A, C) imaging in 2 patients with neuroendocrine carcinomas from an ongoing phase II clinical trial. Upper row (A, B): Bronchopulmonary NEC. Lower row (D, D): Large subcutaneous metastasis from primary colon G3/NEC (Images from Carlsen EA et al.) formation may allow for better cancer phenotyping and be used for personalizing therapy (Images from Clemmensen A et al.)

Figure 2 showing first non-FDG hyperPET combining angiogenesis ⁶⁸Ga-RGD-PET (B) with hyperpolarized ¹³C-pyruvate magnetic resonance spectroscopy (MRS) imaging of metabolism (B) in two canine sarcoma cancer patients. Tumor delineation drawn on basis of anatomical MRI (A) are shown in green. Combined angiogenesis and metabolic information may allow for better cancer phenotyping and be used for personalizing therapy (Images from Clemmensen A et al.)



¹³C-labeled compounds next to a PET/MRI scanner. We have used this set-up for development of and research in the combination of hyperpolarized ¹³C-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 ¹³C-pyruvate, we have continued our studies of the Warburg effect and its relation to glucose uptakes as measured by FDG. We have found, that FDG only in part reflects the Warburg effect. Recently, we also combined ¹³C-pyruvate with a non-FDG PET tracer, e.g. the angiogenesis tracer ⁶⁸Ga-NODAGA-RGD₂. In addition, we also studied non-pyruvate ¹³C-compounds, e.g. ¹³C-fumarate, and indicator of necrosis, in hyperPET studies. Based on our results obtained so far, hyperPET may be superior in cancer phenotyping and response monitoring and has the potential for future clinical use.

Clinical PET/CT in oncology

A large number of prospective clinical protocols aimed at evaluation of the diagnostic and prognostic value of PET/CT using various tracers, including the ones developed in-house, are currently undertaken. The studies are performed in various types of cancer and both in children and in adults. Head-to-head comparison of new PET tracers and established imaging methods is also an area of interest. The use of PET/CT for the planning of radiation therapy (“dose-painting”) and the use of respiratory gating are also currently being evaluated. Many of these studies also include PET/MRI to study the added value compared to PET/CT.

Pediatric nuclear medicine investigations

The department undertakes many pediatric investigations including participation in an array of prospective studies. These research protocols, us-

ing of PET and SPECT, are carried out in cooperation with clinical departments, particularly within oncology and function of the hepato-biliary system. Also 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 studies.

Neuro PET

Brain tumor studies are currently undertaken using PET/MR, PET/CT and HRRT PET. Brain tumors are in particular studied with the amino acid tracer FET but also with several of our novel in-house developed tracers, e.g. uPAR-targeting ligands. Studies of brain perfusion using PET or DCE-CT are also performed. In addition, attention is given to imaging of dementia using various new tracers. In cooperation with Neurobiology Research Unit and Centre for Integrated Molecular Brain Imaging, neuroreceptor ligands have been developed and

used for research in neurobiology. The focus has mainly been on the serotonergic system.

Functional MR

Many brain studies using functional MR are undertaken in close collaboration with clinical departments including neurology and psychiatry. A particular area of interest is development of new methods and clinical application of new functional and molecular MR methods. Methods are aimed at obtaining information on tissue physiology, organ perfusion, and molecular biology.

Atherosclerosis

Visualization of atherosclerosis non-invasively and prediction of plaque vulnerability in atherosclerosis using PET/MRI and PET/CT is intensive-ly studies both preclinically and in clinical studies. In particular, the quantification of low-grade vascular inflammation has become a focus area



Research

and is now used in several clinical trials on cardiovascular risk and mode-of-action studies in GLP-1 therapies. 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 ⁶⁴Cu-DOTATATE. Clinically, our ambition is to provide image-based risk stratification to select patients that will benefit from vascular surgery. Also, we were the first to publish data showing advantage of PET/MRI over PET/CT for carotid artery imaging and we continue to refine and develop vascular imaging using PET/MRI with novel PET tracers.

Nuclear cardiology
Taking advantage of the ability to quantify myocardial perfusion in absolute terms and myocardial flow reserve by ⁸²Rb PET, we study these parameters in various cardiovascular diseases. This includes studies on how interventions as stem cell therapy, gene therapy and pharmacological treatment affects myocardial perfusion and integrated vasomotor function. With the use PET/CT, the development of ischaemic heart diseases is studied in selected groups of patients, e.g. patients with diabetes, HIV, CMV infection and hepatitis. On basis of this, better screening algorithms for early detection of ischaemic heart disease are developed.

Lung studies
A large number of studies using lung function testing and lung scintigraphy in different patient groups are ongoing, e.g. studies in lung

transplantation and endobronchial stenting for emphysema, are performed. Accordingly, we have previously demonstrated the increased value of combined use of SPECT/CT for diagnosing pulmonary embolism compared to CT only. Continuous research is also being conducted into mucociliary clearance, a method pioneered at the department, of the nose and lungs. Finally, the department is 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 and nuclear medicine as well as molecular analyses, muscle function, bone density, and body composition are studied. The current focus is on the effect of exercise, immobilization, and aging. In addition, data are collected on the same parameters from a population-based study. These data will serve as a reference database and elucidate markers to predict aging-related diseases.

Immune cell tracking
At present, we strongly focus on development of non-invasive imaging tools for visualizing the immune response and tracking immune cells. These methods will be used in studies of inflammation, infection, rejection and immune oncology. In some studies, the added value of MR-derived parameters of PET/MR is also studied. Our department is a partner in the PERSIMUNE program, personalized medicine of infection complications in immune deficiency. Currently, special attention

is given to development of new PET ligands for specific imaging of the immune response, e.g. macrophage, CD4 and CD8 imaging. These tracers will also be applicable within immune oncology, where they can serve to better understand the mechanisms behind immune response during tumorigenesis and as a tool to select patients eligible for 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 labeled 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
Optical guided cancer surgery is a relatively new concept. In collaboration with several surgical departments, we develop our most promising PET ligands targeting cancer specific targets into

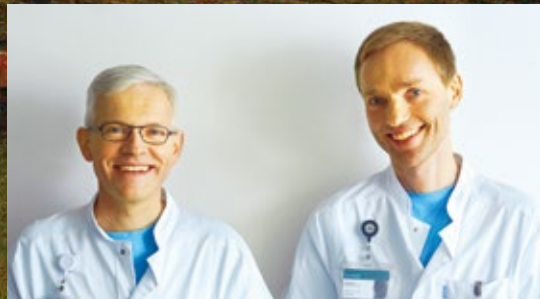
near-infrared (NIR) optical probes to be used for intraoperative delineation of cancer. The methods ensure to a larger extent negative margins and spare functional tissue that may be critical, e.g. in the brain. The optical guidance is expected to lead to better patient outcome, including overall survival and quality of life. The methods will work in synergy with PET, as a preoperative PET scan of the same target will predict whether use of optical imaging is feasible. We expect the technology to become an enabler of performing semi-automated robotic surgery where robots can be guided by these imaging signals.

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
In a number of projects we currently study how to exploit artificial intelligence/machine learning in medical imaging. These studies cover most of the imaging modalities and disease areas we currently work with, e.g. oncology, brain and cardiovascular. Examples of studies performed include how to generate synthetic CT attenuation maps from MR scans, how radiotracer doses may be reduced and how to perform automated image interpretation from segmentation to clinical outcome. Increasingly, also non-imaging data will be integrated in the studies.



Collaboration with The National Hospital of the Faroe Islands



Professor Jann Mortensen and Chief Physicist Thomas Levin Klausen

Landssjúkrahúsið was founded in 1924 in Tórshavn. It was originally named Dronning Alexandrines Hospital after the Danish Queen. 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 51,000.

The National hospital has 850 employees and 120 beds. The 9,000 in-patients and 60,000 out-patients annually are taken care of by 29 medical specialties, of which 9 are via consultant collaborations, including collaboration in clinical physiology and nuclear medicine with our department at Rigshospitalet.

Second opinion on scintigraphies and lung function measurements is provided via a direct telemedicine connection. The responsible physician and physicist for nuclear medicine in Tórshavn is Consultant, Professor, DMSc Jann Mortensen and Chief Physicist Thomas Levin Klausen.

In 2019, the Department of Clinical Physiology and Nuclear Medicine in Tórshavn performed around 500 scintigraphies of lungs, bones, thyroid, kidneys and renographies on the department's 2-headed Skylight camera. Nearly 500 lung functions tests were performed with the Jaeger whole body plethysmograph and close to 600 routine and research DXA studies 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 Innovation Fund Denmark Center for Experimental Medicine NeuroPharmacology (NeuroPharm). The research focus of NRU is neurobiology, physiology and pathophysiology, molecular imaging and neuroreceptor ligands with focus on the serotonergic system.

nru.dk | cimbi.dk | neuropharm.eu

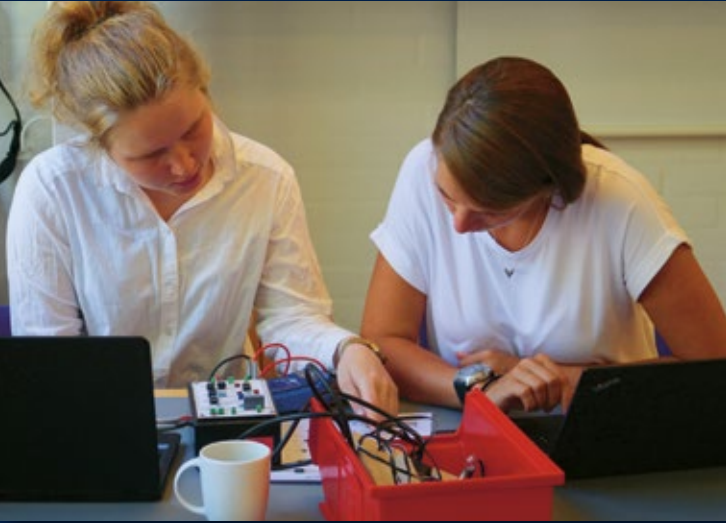


Bioengineer in Medicine and Technology



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 these 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

