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Midterm report
Centre of Clinical excellence in the Region of Southern Denmark

Grant: Odense Pancreas Center (OPAC)	
Grant holder: Michael Bau Mortensen	Grant-date:.June 2017 Start up: August 23, 2017
Location: Odense University Hospital	Report delivery date: February 15, 2020

Progress report

Summary of the Centre - History- purpose and activities:

OPAC was established and accepted as a *Centre of Clinical Excellence*, Region of Southern Denmark, 14.06.2017, and the grant award letter was approved on 23.08.2017.
OPAC is the first multi-disciplinary research and development centre in DK focusing on benign and malignant pancreatic diseases. In addition, **OPAC** is the first centre in DK to cover all aspects of pancreatic diseases from translational research to clinical practice and implementation of dedicated patient programs and education.
Short summary of activities and progress halfway through the grant period

- **OPAC** Board and Secretariat
- **OPAC** official logo
- **OPAC** Homepage (www.OPAC.nu)
- **OPAC** International Advisory Board
- **OPAC** participation in international Boards
- **OPAC** involvement of patient/relative groups and patient representatives
- **OPAC** scientific activities: 37 peer-review publications, 46 scientific oral presentations and 33 posters
- **OPAC** has 9 finished or ongoing PhD projects and several pre-graduate research projects
- **OPAC** initiated international multi-centre studies and **OPAC** participation in existing international multi-centre studies
- **OPAC** collaboration with other pancreatic centres of clinical excellence
- **OPAC** symposia (2 multi-disciplinary OPAC symposia (OUH, 2017 and 2018), 1 international **OPAC** Symposium Kolding (September 2019)

OPAC has generated **10.5** million DKK in co-financing so far (January 2020)

Progress in general:

OPAC has progressed as expected according to the final application and points addressed in the grant award letter.
Special focus areas according to the grant award letter were:

1. *Integration and coordination of the different work packages to achieve synergy and focus in the research program*
   This has been one of the focus areas in **OPAC** and the results of this improved synergy are visible on several levels: Increased number of projects and publications based on the integrated work and collaboration between at least two WPs, as well as several joint **OPAC** PhD students and projects (see below)

2. *Milestones in the research packages and across these*
   (For specific milestones please see WPs below) The majority of milestones are the result of

interaction between several WPs.

3. *Strengthen the organization of the center ("WP-5")*

Following the idea of easy, quick and broad access ("Open door policy") to patients, their relatives, different research groups, institutions, international contacts – as well as the exchange of ideas and research among different professional groups, **OPAC** has appointed a Board and a Chairman representing all aspects of pancreatic research and development. 1-3 person from each WP are represented in the Board which meets every month. To allow focusing on research and keeping formalities to a minimum, the Board meetings are open to all researchers apart from the first 15 minutes. Thus, the continuous involvement of key players from each WP at least one time every month ensures scientific support, discussions, progress reporting, financing, and updating on collaborative issues. This plan has succeeded in keeping problems and use of resources for organizational purposes on a very low level (see budget).
OPAC is working on additional minor improvements regarding the organization. This will be named "WP-5" and focus on improved inclusion of younger scientists, the **OPAC** NDP group (specialist nurses, dieticians and physiotherapists), the research bank, and representatives from patients/relatives and their organisations. Some of these improvements will be presented during the meeting with the Region of Southern Denmark in May 2020.

4. *Strengthen the international profile of the center*

OPAC is working with other international pancreas centers
(e.g. Department of Surgery, CLINTEC, Karolinska University Hospital, Sweden, Department of Surgery, Academic Medical Center, Amsterdam, the Netherlands, Department of Pathology, University of Oslo, Norway)

OPAC has initiated international multi-center studies
(e.g. FOLFIRINOX followed by local therapy (Resection, RT and/or IRE) in patients with locally advanced pancreatic cancer (LAPC): LAPC-03: A Nordic phase II study. Reproducibility of the Peritoneal Regression Grading Score (PRGS) for histological therapy response assessment in peritoneal metastasis)

OPAC is participating in international multi-center studies
(e.g. Pancreatic Cyst Follow-up, an International Collaboration, PACYFIC, Surgical and oncological outcomes after neoadjuvant FOLFIRINOX chemotherapy for borderline resectable and locally advanced pancreatic cancer: A pan-European cohort)

OPAC is participating in international boards, consensus meetings and publications
(International chronic pancreatitis guidelines: IAP, EPC, APA, JPS)(Dasiglucagon trials in congenital hyperinsulinism (ZP4207- 17103, ZP4207- 17106, ZP4207- 17109), Zealand Pharma / Children's Hospital of Philadelphia, PE, USA)(European Guideline on IgG4-related digestive diseases – UEG and SGF evidence-based recommendations)(International expert opinion on LAPC, ref.12)

International **OPAC** Symposia
(e.g. the First Scandinavian Baltic Pancreas Symposium was held in September 2019)

OPAC as a brand
(e.g. OPAC is mentioned by name in all OPAC publications, OPAC is supported by the Region of Southern Denmark)

*Progress in **research** according to goals, the expected activities, the WPs and results etc. as described in the application and also including description of the points addressed in the grant award letter:*

Region Syddanmark

Research is a dynamic process reflected in changes in focus areas, conclusions, consensus and directions over time. Changes in research pathways (e.g. WPs) is a naturally part of this process, and **OPAC** has revised or refined part of their WPs in order to stay on track and comply with relevant scientific progress and discoveries in pancreas research.

OPAC WP status, February 2020. Important milestones are listed in green.

WP	Project	Status	Ref.
WP-1	1.1 Diagnosis, treatment and follow-up of an unselected cohort of adult patients with pancreatic cysts	*OPAC has decided to participate in international multi-center study, PACYFIC (see 1.4)* *Additional study awaits new local guidelines and implementation of new EUS-guided fluid analysis based on cyst fluid NGS analysis (e.g. KRAS, GNAS, TP53)*	
	1.2 Neo-adjuvant therapy for patients with resectable (rPC) and locally advanced pancreatic cancer (LAPC)	*Participation in international multi-center study, NorPACT1 (rPC)* *Participation in international study on MDT in pancreatic cancer evaluation* *Participation in national cohort study on the effect of adjuvant Gemcitabine in PC* *Participation in nationwide population-based cohort study on the impact of waiting time to surgery in PC* *OPAC randomized Phase-2 trial evaluating the effect of EUS and PET-CT during follow up after radical resection* *OPAC international multi-center study (LAPC-03) ongoing* *OPAC has participated in expert opinion publication regarding LAPC (ref.12)*	6-9, 12
	1.3 Optimal therapy for patients with metastatic pancreatic cancer disease (mPC): Efficacy and quality of life of combination therapy	*Ongoing* *First publication (worldwide) on PIPAC directed treatment of patients with mPC* *Preparation of new international multi-center study protocol in mPC*	*1, 10,11*
New WP-1 Trials	*1.4 PACYFIC*	*Participation in international multi-center study. Ethical and scientific approval. QoL questionnaires translated into Danish and validated. Inclusion start expected 01.01.2020*	
	1.5 Treatment of Peritoneal metastasis from pancreatic cancer with pressurized intraperitoneal aerosol chemotherapy (PIPAC)	*Prospective controlled phase II, single-center, one-arm open-label clinical trial investigating the effect of PIPAC in patients with biopsy proven peritoneal metastasis from gastrointestinal, ovarian or primary peritoneal cancer*	*1-5*
	1.6 Surgical and oncological outcomes after neoadjuvant FOLFIRINOX chemotherapy for borderline resectable and locally advanced pancreatic cancer: a pan-European cohort	*Inclusion finished. Awaiting first draft.*	

	1.7 DIPLOMA trial: ***Di**stal **p**ancreatectomy,* *Minima**l**ly invasive or* ***o**pen, for **ma**lignancy*	*OPAC certified for next study on laparoscopic distal resection* *OPAC national MIPS in DK*	

Publications

1. Peritoneal metastasis from pancreatic cancer treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC). Graversen M, Detlefsen S, Bjerregaard JK, Pfeiffer P, Mortensen MB. Clin Exp Metastasis. 2017 May 17. doi: 10.1007/s10585-017-9849-7.
2. Prospective, single-center implementation and response evaluation of pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastasis. Graversen M, Detlefsen S, Bjerregaard JK, Fristrup CW, Pfeiffer P, Mortensen MB. Ther Adv Med Oncol. 2018 Jun 1;10:1758835918777036. doi: 10.1177/1758835918777036
3. Treatment of Peritoneal Carcinomatosis with Pressurized IntraPeritoneal Aerosol Chemotherapy – PIPAC-OPC2. Graversen M, Detlefsen S, Asmussen J, Mahdi B, Fristrup C, Pfeiffer P, Mortensen MB. Pleura and Peritoneum 2018;3(2):20180108.
4. Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) as an outpatient procedure. Graversen, M, Lundell L, Fristrup C, Pfeiffer P, Mortensen MB. Pleura and Peritoneum 2018;3(4): 20180128.
5. Detection of free intraperitoneal tumour cells in peritoneal lavage fluid from patient with peritoneal metastasis before and after treatment with pressurized intraperitoneal aerosol chemotherapy (PIPAC). Graversen M, Fristrup C, Kristensen TK, Larsen TR, Pfeiffer P, Mortensen MB, Detlefsen S. J Clin Pathol 2019;72(5):368-72.
6. Multicentre Study of Multidisciplinary Team Assessment of Pancreatic Cancer Resectability and Treatment Allocation. Kirkegård J, Aahlin EK, Al-Saiddi M, Bratlie SO, Coolsen M, de Haas RJ, den Dulk M, Fristrup C, Harrison EM, Mortensen MB, Nijkamp MW, Persson J, Søreide JA, Wigmore SJ, Wik T, Mortensen FV. Br J Surg. 2019 May;106(6):756-764
7. Waiting time to surgery for pancreatic cancer does not affect survival: A nationwide population-based cohort study. Jakob Kirkegård, Frank Viborg Mortensen, Carsten Palnæs Hansen, Michael Bau Mortensen, Mogens Sall, Henriette Engberg, Claus Fristrup. Eur J Surg Oncol 2019:45(10);1901-5
8. The effect of postoperative gemcitabine on overall survival in patients with resected pancreatic cancer: A nationwide population-based Danish register study. Louise Skau Rasmussen, Benny Vittrup, Morten Ladekarl, Per Pfeiffer, Mette Karen Yilmaz, Laurids Østergaard Poulsen, Kell Østerlind, Carsten Palnæs Hansen, Michael Bau Mortensen, Frank Viborg Mortensen, Mogens Sall, Sönke Detlefsen, Martin Bøgsted & Claus Wilki Fristrup. Acta Oncol 2019;58(6):864-871.
9. Phase-II randomized clinical trial of endosonography and PET/CT versus clinical assessment only for follow up after surgery for upper gastrointestinal cancer (EUFURO study). Ole S. Bjerring, Claus W. Fristrup, Per Pfeiffer, Lars Lundell, Michael B. Mortensen. Br J Surg 2019;106(13):1761-8.
10. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for the treatment of peritoneal metastases. Graversen M, Detlefsen S, Knudsen AØ, Pfeiffer P, Mortensen MB. Ugeskr Laeger 2019;181(20A). PMID 31610840
11. Winther SB, Bjerregaard JK, Schonnemann KR, Ejlsmark MW, Krogh M, Jensen HA, Pfeiffer P. S-1 (Teysuno) and gemcitabine in Caucasian patients with unresectable pancreatic adenocarcinoma. Cancer Chemother Pharmacol 2018; 81: 573-8.
12. Seufferlein T, Hammel P, Delpero JR, Macarulla T, Pfeiffer P, Prager GW, Reni M, Falconi M, Philip PA, Van Cutsem E. Optimizing the management of locally advanced pancreatic cancer with a focus on induction chemotherapy: Expert opinion based on a review of

	current evidence. Cancer Treat Rev 2019; 77: 1-10.

WP	Project	Status	Ref.
WP-2	2.1 Pancreatic core-needle biopsies obtained by endoscopic ultrasound (EUS): Role for the precise pre-therapeutic diagnosis of PD, and as tool to obtain tissue specimens for research	*Study has been completed and two papers have been published* *1,2*	1,2
	2.2 Pancreatic cancer-associated fibroblasts (PANCAF): Analysis of their value as prognostic markers and as targets for the development of stroma-modulating therapeutic strategies	*One study has been published and another study is in press* *Functional and prognostic role will be further evaluated in project 2.9 (see below)*	3,4
	2.3 Large scale genomic analysis of circulating tumor DNA and circulating tumor cells for non-invasive detection of early-stage pancreatic cancer, residual disease and recurrence		
New WP-2 Trials	2.4 Frequency of Mismatch repair protein deficiency in pancreatic ductal adenocarcinoma (PDAC)	*This is a MD thesis, based on tissue-microarrays (TMAs) of around 165 PDACs, all operated at OUH. Defended at the faculty of University of Southern Denmark in January 2020. Manuscript currently prepared for submission to an international peer-reviewed journal*	
	2.5 Typing and molecular pathology of intraductal-papillary mucinous neoplasms (IPMNs) of the pancreas	*A consecutive series of resected IPMNs from OUH. Histological, immunohistochemical and clinical follow-up data are completed. We now await results from IHC for MMR proteins. Afterwards, the manuscript will be finalized and submitted*	
	2.6 Mutational profiling and immunohistochemical analysis of a surgical series of ampullary carcinomas	*This study has just been published*	5
	2.7 Utility of the immunohistochemical panel pVHL, maspin, S100P, IMP-3 and Ki67 for the differentiation of autoimmune	*This study has been presented as poster at one national and one international scientific meeting. Manuscript has been submitted for consideration of publication. Status: Minor revision – will be re-submitted before end of February 2020*	

	pancreatitis and pancreatic cancer		
	2.8 Mutation profiling of peritoneal metastasis from pancreatic cancer before and after pressurized intraperitoneal chemotherapy (PIPAC)	*This is a MD thesis that has been presented as poster at one international and orally at one national scientific meeting. Defended at University of Southern Denmark in June 2019. Manuscript will soon be submitted for consideration of publication*	
	2.9 Clinical value of standardized assessment of margin clearance and liquid biopsy in pancreatic cancer	*Planned ph.d. study – expected to start in 2020. A feasibility study will start on January 1, 2020*	
	2.10 Microscopic subtyping and RNA expression profiling of ductal adenocarcinoma of the pancreas	*Ongoing Master's thesis – will be submitted in 2020*	
	2.11 Reproducibility of the Peritoneal Regression Grading Score (PRGS) for assessment of response to therapy in peritoneal metastasis	*Published in 2019*	7
	2.12 Synchronous pancreatic serous cystic neoplasm and duodenal neuroendocrine tumor: case report and review of the literature	*Published in 2018*	8
	2.13 Whole-exome sequencing (WES) of pancreatic cancer and 3 other tumors developed in the same patient	*Ongoing study*	
	2.14 Tumor heterogeneity studied by whole exome sequencing of primary tumor and circulating tumor DNA in plasma	*For 3 patients multiple samples from primary tumor and plasma DNA have been whole exome sequenced at high coverage, 200X for tissue and 400X for plasma DNA. Data analysis ongoing.*	
	Publications 1. Detlefsen S, Joergensen MT, Mortensen MB: Microscopic findings in EUS-guided fine needle (SharkCore) biopsies with type 1 and type 2 autoimmune pancreatitis. Pathol Int 2017, 67:514-20. 2. Larsen MH, Fristrup CW, Detlefsen S, Mortensen MB: Prospective evaluation of EUS-guided fine needle biopsy in pancreatic mass lesions. Endoscopy international open 2018, 6:E242-e8. 3. Nielsen MFB, Mortensen MB, Detlefsen S: Typing of pancreatic cancer-associated fibroblasts identifies different subpopulations. World J Gastroenterol 2018, 24:4663-78. 4. Nielsen MFB, Mortensen MB, Sørensen MD, Wirenfeldt M, Kristensen BW, Schrøder HD, Pfeiffer P, Detlefsen S: Spatial and phenotypic characterization of pancreatic cancer-associated fibroblasts after neoadjuvant treatment. Histol Histopathol 2020; Jan 21: 18201 5. Harthimmer MR, Stolborg U, Pfeiffer P, Mortensen MB, Fristrup C, Detlefsen S: Mutational profiling and immunohistochemical analysis of a surgical series of ampullary carcinomas. J Clin		

	Pathol 2019. 6. Knudsen KN, Mortensen MB, Detlefsen S. Squamous cell carcinoma of the common bile duct: A case report with genomic profiling. Pathol Int 2019 Jul;69(7):427-431 7. Solass W, Sempoux C, Carr NJ, Bibeau F, Neureiter D, Jäger T, Di Caterino T, Brunel C, Klieser E, Fristrup C, Mortensen MB, Detlefsen S. Reproducibility of the Peritoneal Regression Grading Score (PRGS) for assessment of response to therapy in peritoneal metastasis. Histopathology 2019 Jun;74(7):1014-1024 8. Madelung AB, Detlefsen S. Synchronous pancreatic serous cystic neoplasm and duodenal neuroendocrine tumor: case report and review of the literature. Int J Surg Pathol 2018 Sep;26(6):551-557

WP	Project	Status	Ref.
WP-3	3.1 Etiology and epidemiology in an unselected cohort of patients with chronic pancreatitis	*Inclusion in progress*	1
	3.2 Value of endoscopic drainage of the pancreatic duct in the treatment of chronic pancreatitis. A prospective randomized and sham controlled study	*The project is abandoned due to insufficient recruitment*	
	3.3 Establishing a reliable test of pancreatic exocrine function	*Considered less relevant and abandoned December 2019*	
	3.4 Prospective evaluation of EUS and EUS-FNA findings during screening for PDAC	*Ongoing* *(Oral presentation: Jørgensen MT, Mortensen MB. Clinical dilemma in in chronic pancreatitis. Danish Pancreas Forum Meeting, Copenhagen 2018)* *(Oral presentation: Jørgensen MT. Screening for pancreatic cancer in chronic pancreatitis: Should we do it at all - and how? UEGW Barcelona 2017)*	
	3.5 Progression at cellular level from precursor lesions to PDAC in patients detected with cancer during screening	*The study is ongoing, tissues data and blood-samples are almost collected.*	
New WP-3 Trials	Gene co-expression network analysis of precursor lesions in familial pancreatic cancer	*Oral presentation at UEGW 23rd of October 2019 in Barcelona.* *An article on the same study has been submitted*	
	Hereditary chronic pancreatitis	*Review article published 2020*	2
	Autoimmune pancreatitis	*Review article published 2019*	3
	3.6 Surgical treatment of complications in chronic pancreatitis. A national register	*Protocol drafted*	

	based study		
	Publications 1. Olesen SS, et al. Among authors: Jorgensen MT. The Scandinavian baltic pancreatic club (SBPC) database: design, rationale and characterisation of the study cohort. Scand J Gastroenterol 2017,52(8):909-15. 2. Hereditary pancreatitis. Tan M, de Muckadell OBS, Jørgensen MT. Ugeskr Laeger 2020;182:V11190676 3. Autoimmune pancreatitis. Petersen B, de Muckadell OBS. Ugeskr Laeger 2019;181:V07190398. 4. Thinesen MT, Schaffalitzky de Muckadell OB, Detlefsen S. IgG4 related sclerosing cholangitis involving intrahepatic bile ducts diagnosed with liver biopsy. Case Reports in Pathology 2018, article 2309203. 5. Detlefsen S, de Vos JD, Tanassi J, et at.. Value of antiplasminogen binding peptide, anticorbon anhydrase, innunoglobulin G4, and other serological markers in the differentiation of autoimmune pancreatitis and pancreatic cancer. Medicine 2018:97(31): article 11641 6. Detlefsen S, Klöppel G. IgG4-related disease - with emphasis on the biopsy diagnosis of autoimmune pancreatitis and sclerosing cholangitis. Virchows Arch 2018; 472(4):545-556 7. Detlefsen S. IgG4-related disease: Microscopic diagnosis and differential diagnosis [in German]. Pathologe 2019 Nov;40(6):619-626		

WP	Project	Status	Ref.
WP-4	4.1 Prospective description of new patients in terms of diagnosis, genetics, 18-F-DOPA PET/CT, surgery, histological type, and medical treatment.	*Completed and ongoing retrospective and prospective studies in CHI. Completed one PhD in 2017. Several single center and multi-center studies in progress.*	1,2,4,5,6,7, 11,13
	4.2 Exome trio scans and exome tissue scan is being performed to reveal new genetic causes to diffuse CHI and unexplained insulinoma.	*Completed one PhD in 2019; one paper accepted, two papers in review. One ongoing PhD (start April 2019) and one fully funded PhD to start February 2020.*	8,9,10
	4.3 Intraoperative high frequency ultrasound in addition to 18F-DOPA PET/CT to localize focal lesions and insulinomas; minimal invasive alcohol ablation/radiation; clinical outcome after surgery.	*Completed one retrospective study; one prospective study submitted on intraoperative ultrasound.*	3,14
	4.4 CRISPR/CAS genetic engineering to correct mutations in CHI. Preliminary studies in cell lines and rodents	*Only CRISPR Cas gene knock-outs have been successful. Further CRISPR Cas gene knock out studies to be performed in 2020-22 in cell lines, zebra fish and mice.*	
	4.5 Participation in a global trial of insulin receptor antibody treatment for severe, diffuse CHI	*Investigator site for the REZOLUTE Rice study Dec. 2019.*	

	4.6 Participation in an international study on novel tracers in PET/CT for detection of focal CHI and insulinomas.	*Applied for EU European Research Network (ERN / ENDO) on rare glucose disorders Dec. 2019.*	
	4.7 Improved diagnostic evaluation and management of adults suspected of malignant/non-malignant insulinoma and other endocrine tumors of the pancreas	*Case report published*	12
New WP-4 Trials	4.8 Multicenter study on Kabuki Syndrome Hyperinsulinism	*Submission of manuscript pending*	
	4.9 Multicenter study on HNF1A/HNF4A hyperinsulinism	*Data collection phase ended, manuscript in writing phase*	
	4.10 Multicenter study on glucagon treatment in CHI	*Planning phase*	
	4.11 Collaborative study on ABCC8-CHI (Switzerland)	*Writing phase*	
	4.12 Multicenter studies on rare glucose disorders, other	*Awaiting ERN/ENDO decision*	
	4.13 Performance of a high-sensitive insulin immunoassay in diagnosing CHI	*Writing phase*	
	4.14 Transient hyperinsulinism cohort	*Writing phase*	
	4.15 Atypical CHI cohort	*Data collection phase*	
	Publications 1. Both Low Blood Glucose and Insufficient Treatment Confer Risk of Neurodevelopmental Impairment in Congenital hyperinsulinism: A Multinational Cohort Study. Helleskov A, Melikyan M, Globa E, Shcherderkina I, Poertner F, Larsen A-M, Filipsen K, Brusgaard K, Christiansen CD, Hansen LK, Christesen HT Frontiers Endocrinol, 2017;8:156 2. A Multicentre Experience with Long-Acting Somatostatin Analogues in Patients with Congenital Hyperinsulinism. van der Steen I, van Albada ME, Mohnike K, Christesen HT, Empting S, Salomon-Estebanez M, Greve Rasmussen A, Verrijn Stuart A, van der Linde AAA, Banerjee I, Boot AM. Horm Res 2018;89:82-89 3. Intraoperative Ultrasound: A Tool to Support Tissue-sparing Curative Pancreatic Resection in Focal Congenital Hyperinsulinism. Julie Bendix Dichmann, Mette Østergaard Laursen, Michael Bau Mortensen, Maria Melikyan, Evgenia Globa, Sönke Detlefsen, Lars Rasmussen, Henrik Petersen, Klaus Brusgaard and Henrik Thybo Christesen. Frontiers Endocrinol 2018:22:478 4. Performance of 18F-DOPA PET/CT and 68Ga-DOTANOC PET/CT scan in predicting focal vs. non-focal type of congenital hyperinsulinism.Christiansen CD, Petersen H, Nielsen AL, Detlefsen S, Brusgaard K, Rasmussen L, Melikyan M, Ekström K, Globa E, Rasmussen AH, Hovendal C, Christesen HT. Eur J Nucl Med Mol Imaging, 2018, 45, 250-261. 5. Tissue variations of mosaic genome-wide paternal uniparental disomy and phenotype of multi-syndromic congenital hyperinsulinism. Christesen HT, Christensen L, Löfgren Å, Brøndum-Nielsen K, Svensson J, Brusgaard K, Samuelsson S, Elfving M, Jonson T, Grønskov K,		

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	Rasmussen L, Backman T, Hansen LK, Larsen AR, Petersen H, Detlefsen. Eur J Med Genet. 2019 Feb 20. pii: S1769-7212(18)30932-7 6. The difficult management of persistent, non-focal congenital hyperinsulinism: A retrospective review from a single, tertiary centre. Greve Rasmussen A, Melikian M, Globa E, Detlefsen S, Lars Rasmussen L, Petersen H, Brusgaard K, Rasmussen AH, Christesen HT. Pediatr Diabetes 2020 Jan 29. Doi: 10.1111/pedi.12989 7. Clinical, genetic and radionuclide characteristics of the focal form of congenital hyperinsulinism. Diliara Gubaeva, Maria Melikyan, Daria Ryzhkova, Lubov Mitrofanova, Bairov, Syhockaya, Poida, Sokolov, Henrik Christesen, Irina Nikitina. Проблемы Эндокринологии (Problems of Endocrinology, Russian Journal)(Accepted, dec 2019) 8. A novel gene in congenital hyperinsulinism: *ADCY7* knock-out using CRISPR/Cas9 upregulates insulin genes and glucose-stimulated insulin secretion pathway leading to excessive insulin secretion. Alhaidan Y, Christesen HT, Lundberg E, Al Balwi M, Brusgaard K. Hum Mol Gen *(reviewers replied Oct 2019)* 9. Exome sequencing revealed DNA variants in *NCOR1, IGF2BP1, SGLT2* and *NEK11* as potential novel causes of ketotic hypoglycemia in children. Alhaidan Y, Larsen MJ, Schou AJ, Stenlid MH, Al Balwi M, Christesen H, Brusgaard K. Sci Rep 2020, 201,2114. Doi.org/10.1038/s41598-020-58845-3. 10. A novel gene in early childhood diabetes: *EDEM2* knock-down downregulates *SLC2A2* and *PXD1* expression leading to impair insulin secretion. Alhaidan Y, Christesen HT, Højlund K, Al Balwi M, Brusgaard K. Mol Genet Genom *(Submitted Nov 2019)* 11. A novel pseudo-syndrome of transient congenital hyperinsulinism and conjugated hyperbilirubinaemia due to Rhesus D prophylaxis failure. Riis, SST, Jørgensen MH, Rasmussen KF, Husby S, Hasselby JP, Borgwardt L, Brusgaard K, Fagerberg C, Christesen HT. J Clin Res Pediatr Endocrinol *(resubmitted Nov 2019)* 12. Occult insulinoma, glucagonoma and an endocrine pancreatic pseudotumour in a patient with Multiple Endocrine Neoplasia Type 1. Erichsen TD, Detlefsen S, Andersen KØ, Pedersen H, Rasmussen L, Gotthardt M, Pörksen S, Christesen HT. Pancreatology 2019, Dec 24. pii: S1424-3903(19)30814-2. doi: 10.1016/j.pan.2019.12.017. 13. Update of variants identified in the pancreatic beta-cell KATP channel genes *KCNJ11* and *ABCC8* in individuals with congenital hyperinsulinism and diabetes. Elisa De Franco, Cécile Saint-Martin, Klaus Brusgaard, Amy E. Knight Johnson, Lydia Aguilar-Bryan, Pamela Bowman, Jean-Baptiste Arnoux, Annette Rønholt Larsen, May Sanyoura, Siri Atma W. Greeley, Raúl Calzada-León, Bradley Harman, Jayne A. L. Houghton, Elisa Nishimura-Meguro, Thomas W. Laver, Sian Ellard, Daniela del Gaudio, Henrik Thybo Christesen, Christine Bellanné-Chantelot and Sarah E. Flanagan. Hum Mut 2020, February 4, doi:10.1002/humu.23995. 14. Intraoperative Ultrasound Characteristics during Surgical Treatment of Congenital Hyperinsulinism: A Prospective and blinded Single-centre Analysis. Bjarnesen AP, Dahlin P, Christesen HT, Rasmussen L, Detlefsen S, Mortensen MB. Br J Surg *(Submitted February 2020)*

*Progress in **education** according to the set up in the application (e.g. Each participating department is strategically planned to host and supervise at least one pregraduate research student and one Ph.D. student):*

Ongoing or finished OPAC PhD student projects

1. Ole Steen Bjerring (WP-1, WP-2) (Thesis defended 02.02.18, University of Southern Denmark)
2. Michael Friberg Bruun Nielsen (WP-2, WP-1) (Thesis defended 08.04.19, University of Southern Denmark)
3. Martin Graversen (WP-1, WP-2) (Thesis defended 31.01.20, University of Southern Denmark)

4. Ming Tan (WP-1, WP-2, WP-3) (ongoing)
5. Kristina Magaard Koldby (WP-2, WP-1) (ongoing)
6. Yazeid AlHaidan (WP-4) (Thesis defended May 2019, University of Southern Denmark)
7. Trine Aaquist (WP-1, WP-2) (ongoing)
8. Annette Rønholt Rasmussen (WP-4) (ongoing)
9. Kirstine Øster Andersen (WP-2, WP-4) (Fully financed, expected start April 2020)

All WPs and participating departments have at least one pre-graduate research student, and this includes collaboration between several WPs.

*Progress in **clinical functions and outcome** according to the set up in the application:*

A list of goals for clinical functions and outcome was presented in the application. The majority of these goals has been achieved – or are work in progress.

Neoadjuvant treatment of patients with resectable pancreatic cancer (PC): OPAC has joined the Scandinavian multi-centre study NeoPACT1 which will probably stop inclusion within one year. OPAC will work with the Scandinavian HPB group to ensure a "NeoPACT2" protocol before ending NeoPACT1

Multi-modal treatment of LAPC and metastatic PC: Ongoing international LAPC protocol initiated by OPAC. New protocol for metastatic PC in preparation.

Scandinavian centre for PIPAC treatment of peritoneal metastasis and "prophylactic" PIPAC treatment before definitive surgery: OPAC and Odense PIPAC Center (OPC) have started this only centre in Scandinavia. Patients with metastatic PC have been treated with remarkable results. OPC has presented >10 PIPAC publications in close collaboration with OPAC, and more PC protocols are in progress

Personalized PC treatment strategies based on translational research - The role of pancreatic stellate cells and pancreatic cancer-associated fibroblast (biomarkers), circulating tumor DNA and cancer cells in the peripheral blood, and cancer cells in peritoneal washings: Several published and ongoing trials. One finished PhD project and one ready to include patients.

National centre for diagnosing and treatment of premalignant pancreatic lesions: Ongoing work on optimizing pancreatic cyst fluid analyses (NGS) as part of new diagnostic strategy based on EUS guided FNB/FNA.

National centre for screening and treatment of patients with high-risk of developing pancreatic ductal adenocarcinoma and focusing on results from translational research: Ongoing inclusion and screening of national Danish cohort. PhD project on translational part has been initiated.

Improved evaluation and treatment strategy in patients with congenital hyperinsulinism, insulinomas and other endocrine pancreatic tumours: New treatment methods in the surgical management of focal CHI have been investigated along with translational efforts regarding diagnosis, classification and medical treatment. A clinical/paraclinical setup including regular conferences among OPAC members has secured optimal diagnostic and treatment related pathways in non-malignant (endocrine) tumours of the pancreas.

*Progress in **budget** including status for the mandatory target: Equivalent funding from external and internal sources 2x7.5 mio. DKK and including description of points addressed in the grant award*

letter:

OPAC is obliged to provide external funding for at least 7.5 mio. DKK during the five years of support from the Region of Southern Denmark.

At the time of this Midterm report **OPAC** has raised a total of **10.517.031 DKK**.

*Progress in **organisation**, collaboration and participation of partners and patients as described in the application and also including description of points addressed in the grant award letter:*

Patients and relatives
The national group for patient and relatives treated for pancreatic cancer ("*Pancreasnetværket*", www.pancreaspatient.dk) is an integrated part of **OPAC** and *Pancreasnetværket* has participated with posters in several **OPAC** meetings and symposia

OPAC is also involved in patient and relatives information on the website of the largest private founder of cancer research in DK ("Kræftens Bekæmpelse", www.cancer.dk)

OPAC works with a named representative for patient and their relatives during design and information on research projects

OPAC is involved in national guidelines regarding pancreatic cancer, chronic pancreatitis, CHI, pancreatic cysts, and pancreatic neuroendocrine tumours

OPAC is involved in international guidelines regarding IgG4-related disease / autoimmune pancreatitis

*Progress in **dissemination**, publicity and communication including launch of a website:*

The **OPAC** Website was established in 2017 and is regularly updated.

Available information includes **OPAC** organization, trials, publications, meetings & symposia, and info to the patient

OPAC projects and achievements have been exposed in television and other media on several occasions (e.g. https://www.tv2fyn.dk/odense/livsforlaengende-kemobehandling-af-bughinden-afproves-pa-ouh, https://www.tv2fyn.dk/nyheder/27-12-2019/1930/sydfynske-forskere-med-succes?autoplay=1#player, erfaringer fra et center of clinical excellence: https://www.tv2fyn.dk/fyn/kamerapille-faar-rygstoed-paa-millioner) (https://www.sdu.dk/da/om_sdu/fakulteterne/sundhedsvidenskab/nyt_sund/lavt_blodsukker_hos_boern?utm_source=Nyheder+fra+Det+Sundhedsvidenskabelige+Fakultet%2C+Syddansk+Universitet&utm_campaign=c17cfe515d-SUND_10_07_2017_COPY_01&utm_medium=email&utm_term=0_95b5fd2684-c17cfe515d-361707581) (https://www.eurekalert.org/pub_releases/2020-02/uosd-uul020720.php) (https://medicalxpress.com/news/2020-02-unexplained-blood-sugar-children-variation.html) (https://via.ritzau.dk/pressemeddelelse/uforklaret-lavt-blodsukker-hos-born---svaret-findes-maske-i-generne?publisherId=12056383&releaseId=13587751)

OPAC has arranged meetings with patient organisations (e.g. "Pancreasnetværket I Danmark. Konference for patienter og pårørende", Odense April 11, 2019) (One-day meeting with Julie Raskin and Davelyn Hood, USA, the leaders of Congenital Hyperinsulinism International, Odense February 10, 2020)

OPAC has hosted several meetings and one international symposium. A second international symposium will be arranged prior to the end of the grant period

*Progress regarding the **advisory board**:*

The **OPAC** Advisory Board has been used continuously in the dynamic interplay between **OPAC** members and their different focus areas. Advisory Board members have provided opinions and suggestions to specific projects covering (across) several WPs.
Other issues and news to highlight:
OPAC has inspired two Danish institutions to create similar centres but with focus on acute and chronic pancreatitis, only. **OPAC** has collaborated with Odense PIPAC Center (OPC) in performing the first (worldwide) PIPAC directed treatment of patients with pancreatic cancer and peritoneal metastases
List the attachments to this progress report such as Ph.D. – and postgraduate projects, revised budget, lists of disseminations etc.: 1. OPAC Publication List 2. OPAC Budget signed by grant holder and Deputy Head of Finance and Planning OUH