FINAL PUBLISHABLE SUMMARY REPORT

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1 Executive summary

Hyperinsulinemic hypoglycaemia is a potentially lethal disease caused by overproduction of insulin by the beta cells of the pancreatic islets of Langerhans. Lethal hypoglycaemia and brain damage is a problem especially in infants born with the disease. The major challenge of current therapeutic approaches (partial/near total pancreatectomy combined with medical treatment) are the frequently observed severe side effects/morbidity (diabetes, exocrine pancreas insufficiency etc.) considered acceptable in relation to the lethal outcome of the disease itself although they massively reduce quality of life as well as life expectancy.

In order to significantly reduce the side effects of current therapeutic approaches and to increase quality of life and life expectancy, we develop an integrated simultaneous imaging/therapeutic ("theranostic") platform that allows targeted image guided surgery (IGS), targeted photodynamic therapy (tPDT) and radiopeptide therapy to detect, selectively resect or destroy diseased beta cells.

Congenital hyperinsulinism

Congenital hyperinsulinism (CHI) is a rare disease of infants characterized by presence of functionally defective non-neoplastic beta-cells with inappropriate (over-) secretion of insulin, leading to life-threatening hypoglycaemia. CHI is a major cause of hypoglycemic brain injury with mental retardation, epilepsy and cerebral palsy. CHI has an incidence of 1 in 50 000 live births and can be divided into two major subforms, a focal (40%-50%) and a diffuse one (50%-60%). While for the focal form cure is possible by surgical resection (if the focus can be identified), diffuse CHI is more difficult to treat as a consequence of the distribution of diseased beta cells throughout the pancreas.

If certain gene mutations are detected, the disease usually responds to diazoxide treatment. However, cases not responsive to medical treatment may require surgical intervention with near-total pancreatectomy (up to 98%) resulting in lifelong diabetes mellitus and pancreatic exocrine insufficiency.

PET (positron emission tomography) imaging with ^{18}F-DOPA is used to identify foci of hyperplastic beta cells; surgical resection is then performed by enucleation or partial pancreatectomy. Surgical treatment of CHI is accompanied by considerable morbidity (up to > 40%); however, in many cases surgery only helps to reduce hypoglycemia without achieving complete cure. This condition requires continued medical treatment which also has considerable side effects so that to date, cure without side effects or morbidity cannot be achieved for many if not most patients.

Adult hyperinsulinemic hypoglycemia

Insulinomas derive from pancreatic beta-cells and are the most common form of functional neuroendocrine tumors of the pancreas with an incidence of 1-4 newly diagnosed cases per 1 million per year. Most are benign and have a diameter of less than 2 cm. Resection is the therapy of choice and in many cases, the localization can be determined preoperatively (^{18}F-DOPA PET, MRI (magnetic resonance imaging), endoscopic ultrasound). Ultrasonography in combination with palpation is used to identify the lesion intraoperatively. Another cause of adult hyperinsulinemic hypoglycemia (AHH) is nesidioblastosis and it appears that in approximately 5% of the cases of AHH, nesidioblastosis may be the underlying pathology while insulinoma is responsible for the majority of cases.

Objectives of BetaCure

BetaCure aimed at developing individual patient-tailored treatment of CHI and AHH, aiming to reduce side effects while achieving high cure rate with low morbidity, improved quality of life and survival. We aimed to develop a theranostic platform utilizing tracer molecules as (intraoperative) biomarkers specifically targeting the beta-cells that allow

- preoperative non-invasive localization of foci in CHI and AHH with higher sensitivity and specificity than currently available imaging tracers
- intraoperative visualization of diseased beta cells for individualized image guided surgery allowing to reduce morbidity

- laparoscopic highly specific and quantitative treatment of diseased beta cells without requiring resection of large quantities of pancreatic tissue with potential for repeated treatment until cure is achieved
- non-invasive systemic treatment of diseased beta cells in selected patients

Achievements of BetaCure

- Development and clinical testing of an innovative highly sensitive open air fluorescence camera for real time imaging in image guided surgery has been finalized
- Extension of optical path through a coherent fibre bundle and inclusion of the coherent fibre bundle into a system suitable for simultaneous endoscopic image guided surgery and targeted photodynamic therapyExendin PET imaging shows excellent results detecting insulin producing tumors/focal beta cell hyperplasia in >40 patients, being the only imaging modality visualizing all lesions
- *In vitro* and *in vivo* experiments with Exendin labeled with fluorescent dyes and photosensitizers show highly promising tPDT and IGS properties
- An innovative F-18 labeled compound has been developed for optimized imaging of beta cell pathology and clinical trials are under preparation
- The kit labeling technology of ^{68}Ga-Exendin for clinical trials is established and has been successfully implemented in several centers,– this achievement forms the basis for market implementation
- Concepts for kidney uptake reduction of radiolabeled Exendin have successfully been tested in humans
- Training activities have covered GMP production and GMP product handling, data management, ethics, PET standardization, use of newly developed equipment, etc.
- A standard for quantitative SPECT imaging has been developed, independent of the camera vendor or the software package delivered with the camera
- Dissemination activities on international and national scientific and patient/family conferences
- Design and programming of the project website (http://betacure.eu/) and intranet

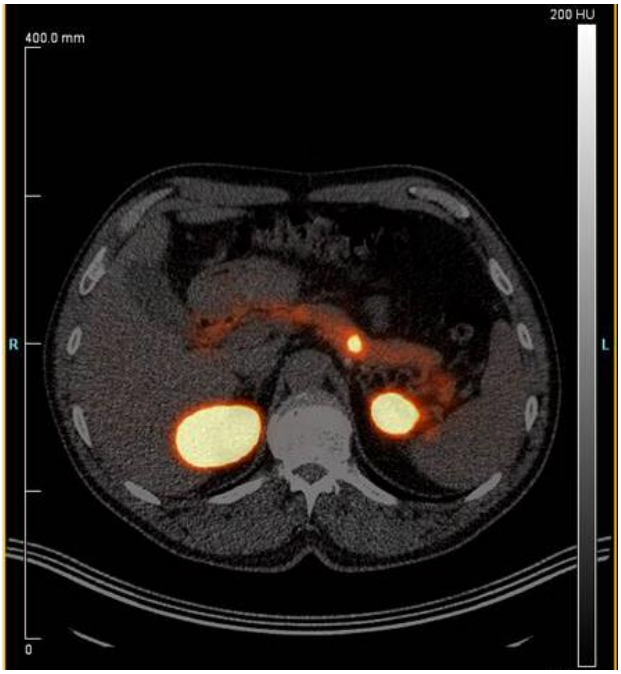

Figure 1. ^{68}Ga-NODAGA-evendin-4 PET/CT performed in a 65-year old man presented with symptoms of hypoglycaemia showed a clearly visible GLP-1 receptor positive lesion in the pancreatic body indicative for insulinoma.

2 Summary description of project context and objectives

Context

The fundamental goal of BetaCure was to develop innovative integrated imaging technologies combined with therapeutic properties into a theranostic platform allowing selective identification and treatment of diseased beta cells at a nearly cellular scale, enabling delivery of patient-individual tailored treatments for CHI and AHH. To achieve this, the project focused on the development of highly innovative equipment, imaging technologies (both radioactive and fluorescent) and therapy options.

The concept of BetaCure originated from the problem that currently, although fundamental advances have been achieved in the last 20 years (including improved surgery and PET imaging), localizing and treating both AHH and CHI remains challenging. Many children with CHI remain dependent on medication for years with severe side effects, or they can only discontinue hyperglycemic medication after near-complete pancreatectomy, which comes at the price of an equally bad disease, diabetes. Based on genetic information and 18F-DOPA PET, patients will either be treated medically or operated on. Medical therapy has dramatically reduced the number of extensive surgical procedures necessary by the introduction of long-term treatment with octreotide, glucagon and intragastric dextrose and appears to help preventing severe hypoglycaemia and brain damage after a limited (50%-75%) resection of the pancreas. Despite the advances made in the last 20 years, therapy of CHI remains far from optimal. In case of nesidoblastosis in adults, the therapeutic challenges are comparable to CHI. Curative resection of insulinomas using endoscopic minimally invasive surgery is an attractive approach to further reduce morbidity. Endoscopic resection of insulinomas is currently performed in selected patients but the localization of the lesion needs to be determined with highest accuracy prior to endoscopic operation in order to avoid morbidity and the necessity to switch to open laparotomy. Currently used intraoperative examinations for localization of lesions (palpation, ultrasound) would require complementation by other techniques that are optimally suited for laparoscopic use. In open as well as laparoscopic surgical procedures, less partial pancreatectomies and lower morbidity could be achieved if the resection margins could be determined with higher accuracy. In case of malignant insulinoma, optimized surgical resection and highly specific systemic therapies in order to improve the prognosis are warranted.

Personalized therapy of patients with CHI and AHH would require optimized pre-therapeutic diagnostics combined with functionally optimized partial resection of the pancreas preserving exocrine pancreatic function as well as glycaemic control. As this aim may be difficult or impossible to obtain in patients with diffuse forms of CHI, alternative treatment strategies are warranted that may render partial pancreatectomy combined with medical treatment obsolete. The optimal treatment would be selective destruction of diseased beta cells while preserving the function of healthy islets as well as exocrine pancreatic function. Alternatively, diseased beta cells sufficient to retain glycaemic control should be preserved while avoiding hypoglycaemia; this approach, however, would most probably require repeated treatment. Therefore, innovative approaches for treating CHI and AHH should allow to reliably differentiate between focal and diffuse forms of the disease, they should allow to optimally guide surgical intervention and they should enable quantitative, controlled selective destruction of beta cells. In addition, side effects of treatment should be avoided.

Objectives reached

BetaCure partners have developed complementary technologies that, when combined with each other, appear to be optimally suited for personalized treatment of CHI and AHH. They have pioneered work in the fields of beta cell imaging and IGS. Several BetaCure partners have developed and optimized an imaging compound in a joint effort (EU FP7, contract no. 222980, BetaImage) that is targeting the GLP-1 (glucagon-like peptide-1) receptor (GLP-1R). This compound is based on the GLP-1 analog Exendin; its specificity for beta cells has been shown and a linear correlation of the beta cell mass and the signal obtained with this tracer has been established. Within the BetaCure project, this tracer has been used for optimized pre-operative imaging using Exendin (SPECT/PET) for identification of foci and for determination of the beta cell mass in order to allow guided quantitative therapy destroying the exact amount of beta cells required for achieving euglycaemia without causing diabetes.

This Exendin compound can be used for radiotracer imaging (PET and SPECT) but has in this project also been invested as an optical imaging tracer. Intraoperative life macroscopic visualization of diseased beta cells by near-infrared fluorescence labelled

Exendin (Exendin-800CW) guides therapy and allows exact determination of resection margins by IGS with high precision potentially reducing morbidity and side effects.

We have achieved differentiation of diseased and healthy tissue with a precision close to histopathological examination by xfOCM combined with contrast analysis for islet characterization, which in the future has the potential to reduce operation time by avoiding the need for intraoperative frozen section histology. This system will allow performing tailored surgical interventions which are more effective and have significantly fewer undesirable adverse effects in CHI and AHH patients.

As an alternative to surgical resection, we have developed highly specific compounds for endoscopic beta cell-selective tPDT using a targeted photosensitizer (Exendin-700DX) helping to avoid or reduce unnecessary resection of pancreatic tissue, expected to improve therapeutic outcome with further reduction of side effects. This is of major importance in children with CHI in whom diabetes mellitus and exocrine pancreatic insufficiency lead to impaired quality of life, increased morbidity and reduced life expectancy.

A hybrid laparoscope was developed compatible with both the Exendin-800CW and the Exendin-700DX tracer for intraoperative detection and irradiation of fluorescent labels for IGS and tPDT.

As systemic treatment, Exendin derivatives with low kidney uptake (in order to avoid toxicity) have been developed for PRRT in patients with metastasized insulinomas or patients that cannot undergo operation/IGS. Dosimetric calculations have shown a clear increase in the achievable radiation dose to beta cell derived tumours while avoiding renal toxicity.

Organization of the BetaCure project

The project comprised five scientific, one training / dissemination / quality control and one management work package (WP). Within the first WP we have developed, optimized and tested integrated imaging technology for intraoperative and endoscopic use for IGS as well as tPDT. The second WP's objective was to label and optimize GLP-1R targeting compounds such as Exendins with a) fluorescent dyes for IGS, b) a target-specific photo sensitizer based on a near-infrared phthalocyanine dye for tPDT, c) cleavable linkers or other structural modifications in order to reduce kidney uptake of the radiotracers for improved image quality and PRRT d) optimize protocols for imaging with DOPA and HTP by pharmacological improvement of islet specificity. The third WP focused on production and testing of GMP tracers for PET/SPECT, IGS, and tPDT. WP4 aimed at evaluation and optimization of quantitative pre-operative imaging for planning of IGS, which has allowed us to develop and optimize IGS strategies in adults and, in the future, CHI patients; in addition, the imaging technology developed in this WP allows us to determine the optimal pre-operative imaging strategy. In WP5, we have evaluated and optimized tPDT *in vivo* aiming to deliver the proof-of-principle in adult patients and subsequently in CHI. In WP6, we have transferred skills between imaging experts / endocrinologists / surgeons / engineers; achieved maximal synergy through broad availability of the partner´s specific competences; trained external medical doctors treating CHI and AHH; defined and implement standards for quantitative imaging in CHI and AHH; built up a data base for patients with AHH/CHI for imaging, IGS and tPDT; provided electronic case report forms and electronic documentation of all patient data (anonymized); made BetaCure achievements publicly available; created public awareness for CHI and AHH. WP7 ensured the proper functioning of the project in order to achieve the objectives, complete the milestones in time and to deliver the deliverables. In addition, an effective communication infrastructure was developed and this WP took care of management of intellectual property. Finally, we have submitted an application for recognition of Exendin as a PET tracer for improved diagnosis of AHH and CHI as an orphan drug to the European Medicines Agency (EMA) (recognition pending but expected in 2018) and are currently preparing for submitting an orphan drug registration using the data from the ongoing clinical studies.

3 Description of the main S&T results/foregrounds

3.1 Summary of the main results/foreground of BetaCure

The central goal of BetaCure was to develop optimized individual patient-tailored treatment of CHI and AHH, aiming to reduce side effects while achieving high cure rate with low morbidity, and improved quality of life and survival. We aimed at developing a theranostic platform utilizing tracer molecules as (intraoperative) biomarkers specifically targeting the beta-cells.

For this purpose, in work package 1 (WP1), all technical equipment was developed required for the clinical studies in the project and future clinical use of Exendin in AHH/CHI. A fully functional hybrid laparoscope was developed compatible with both the fluorescent tracer used for IGS (Exendin-800CW) and the fluorescent tracer used for tPDT (Exendin-700DX). This endoscopic device allows simultaneous visible light, fluorescence imaging and tPDT and, due to its small diameter of only 3mm, can be used in adults as well as in babies with CHI. In addition, its sensitivity is by far higher (x100) than currently available comparable products. The device was successfully tested *in vivo*. In addition, a portable extended field Fourier domain optical coherence microscope (xfOCM) was developed. This device is fast, label-free and non-invasive and can be used for *ex vivo* analysis of removed pancreas tissue in the operation theatre for detection of resection margins, aiming at replacing frozen section histopathology. Also this device was successfully tested on human pancreatic tissue during surgery.

WP2 focused on optimizing both fluorescent and radioactive tracers for preparing their use in the clinics. Exendin-800CW was developed and successfully tested *in vitro* and *in vivo* for IGS. The combined use of Exendin-800CW and the laparoscope developed in WP1 was validated in an imaging experiment in minipigs. In addition, Exendin-700DX was developed and successfully tested *in vitro* and *in vivo* for tPDT. For radioactive imaging ^{68}Ga-NODAGA-Exendin-4 the islet absorbed radiation doses were calculated to be very low (with a maximum of 2,3mSv in babies/newborns reaching down to 0,7mSv in adults), enabling safe use of repeated imaging with this tracer. In addition, several new tracers with the same affinity for the receptor but with lower kidney uptake were developed: NOTA-MI-Exendin-4, biased agonists and albumin binders. The effect of Gelofusin uptake was investigated in a clinical study in 10 healthy volunteers and it was shown that this plasma expander substantially reduces the renal accumulation of ^{111}In-Exendin-4 in humans, enabling to achieve significantly higher doses in peptide receptor radiotherapy with Lu-177 labelled Exendin. The synthesis of F-18-labeled Exendin was successfully developed, characterized *in vitro* and *in vivo* and is ready for clinical translation (GMP production of the precursor is planned).

To translate the tracers developed in WP2 to the clinics, WP3 aimed at the GMP production of ^{68}Ga-Exendin for comparative imaging in AHH and CHI, Exendin-800CW for IGS and Exendin-700DX for tPDT. Both the Exendin-NODAGA precursor for labeling with Ga-68 and the Exendin-800CW were successfully developed under full GMP regulations, including toxicity testing and all required paperwork such as IMPD and IB. A long term stability testing program was also initiated. Considerable effort has been invested in the development of Exendin-700DX for clinical use, however, due to instability of the 700DX dye when exposed to physical forces (which was not known previously and has been discovered and characterized in this project); GMP production has not been reached. The GLP product did show excellent targeting of the receptor and high cell killing abilities when used for tPDT.

The compounds optimized and produced under GMP conditions in WP3 were used in WP4 for clinical studies. An important objective of the BetaCure project was the preoperative non-invasive localization of foci in CHI and AHH with higher sensitivity and specificity than currently available imaging tracers. Therefore, ^{68}Ga-Exendin was used in two clinical studies: one comparing ^{68}Ga-Exendin with the standard imaging methods ^{68}Ga-DOTA-TOC or ^{68}Ga DOTA-TATE (somatostatin imaging), endoscopic ultrasound and MRI or CT in AHH patients, and one comparing ^{68}Ga-Exendin with the standard imaging method ^{18}F-DOPA in CHI patients. For AHH, 33 patients have been scanned so far with excellent imaging results. For CHI, 6 patients have been scanned within the runtime of BetaCure, also with excellent results. Proof of concept is demonstrated to diagnose hyperinsulinemic lesions with ^{68}Ga-NODAGA-Exendin-4 PET in patients with AHH and CHI. All lesions identified on the scans and removed by surgery were confirmed by histopathology. Although both the AHH and CHI clinical study have not been finalized yet, ^{68}Ga-NODAGA-Exendin-4 PET clearly shows to be a reliable and valid diagnostic measure. A first clinical study using Exendin-800CW is expected to start in May 2018, and will evaluate the diagnostic value of the tracer in patients with pancreatic adenocarcinoma and / or insulinomas.

WP5's objectives were to develop and characterize the Exendin-700DX tracer for tPDT, finalize GMP production and validate the tracer in clinical studies: first in AHH patients, potentially also in CHI patients. The Exendin-700DX tracer was produced and fully evaluated both *in vitro* and *in vivo*. It shows excellent receptor targeting and impressive cell killing. With only 3 minutes of irradiation with near infrared light, *in vitro* cell death was shown up to 98%. These *in vitro* data indicate a high therapeutic potential for PDT with Exendin-700DX *in vitro.* These results have been validated *in vivo* demonstrating cell killing as well as improved survival in insulinoma bearing rodents. However, for further development into a GMP product, extensive HPLC analysis of the tracer was performed and showed instability of the dye when exposed to physical forces. This problem is already present in the dye itself and has previously not been identified. The producer of 700DX has been contacted and BetaCure partner piCHEM has helped to search for solutions for the problem. Several new conjugation, purification, lyophilisation and reconstitution strategies have been developed, but the issue of the instability has not been completely solved yet. Therefore, although therapeutic efficacy has not been impaired, pharmaco-legal requirements for purity of the product still hamper clinical translation.

Within WP6, scanners of all centres participating in BetaCure clinical studies have been included in the PET accreditation program and proved to perform correctly. In addition, the results of the EARL accreditation program demonstrated that the network of the scanners is suitable for multicentre studies involving both of the investigated radioisotopes, F-18 and Ga-68. All phantom scans with Ga-68 and F-18 performed at the different BetaCure hospitals have been analyzed and the results will be published in collaboration with the NKI/AvL hospital in Amsterdam. A multicenter collaboration between clinical physicists was set up to develop also accreditation guidelines for quantitative SPECT scanning aiming at delivering reliable reproducible results for camera-independent 3D dosimetry. Meetings and workshops were organised to disseminate BetaCure findings, and the website was launched, and updated on a regular basis.

WP7 was dedicated to project management, and took care of all administrative and coordinating tasks. In order to support the coordinator in monitoring the compliance of all beneficiaries with their obligations under the grant agreement, the project management office at concentris, together with the coordinator, kept a close eye on all partners' performance by ensuring that tasks were performed in a correct and timely manner, that reports were prepared and submitted according to the rules of the EC, that funds were used and claimed properly, that all partners fulfilled their obligations with regard to dissemination and funding acknowledgement, that changes to the work plan were communicated swiftly to the EC and compliant with ethical requirements and regulations. Mostly, the project management office at concentris functioned as a central node of communication between consortium members, and between the coordinator and the EC, regarding administrative and managerial issues, such as amendments, reportings and the contract agreement.

3.2 Main results / foreground of the different work package

3.2.1 WP1: Development and evaluation of imaging technology

Partners involved SKU, SOP, UMCG, CHARITE, UCL, UL2, EPFL, and EXA

Total WP progress 100%

Background

Fluorescent Exendin tracers can be used in patients to lead the surgeon during surgery to find insulinomas (image guided surgery, IGS) and also to specifically irradiate insulinomas *in vivo* (targeted photodynamic therapy, tPDT). For this purpose, a laparoscope is required that can image visible light, 800CW and also irradiate 700DX in a patient. WP1 is a technical WP aiming at development, optimization and testing of integrated imaging technology for intraoperative and endoscopic use for IGS as well as tPDT. In addition, to be able to check resection margins during surgery, optical coherence microscopy is a very promising technology. It can be used to analyse human pancreas samples *ex vivo* in the operation theatre to check if tumour tissue has been removed and if resection margins are free of tumour tissue. In principle, there is no need for injection of a tracer and the technology is non-invasive. Within this WP, a fully functional OCM device was developed. This device is portable, enabling easy use in the operation theatre.

Objectives

1. To develop a clinical near-infrared fluorescence (NIRF) laparoscope, compatible with the beta-cell specific Exendin-800CW optical tracer developed in WP2.

2. To develop a fully integrated hybrid NIRF and photodynamic therapy compatible clinical laparoscope for theranostic purposes in combination with the Exendin-700DX tracer developed in WP2.

3. To design and build an optical coherence microscopy (OCM) system for label-free *ex vivo* pancreas and islet cell imaging for monitoring and optimizing the PDT therapy on established rodent models at a cellular level in conjunction with the hybrid laparoscope.

4. To develop a portable OCM desk-top device to be used as validation of resection margins *ex vivo* for image-guided histopathology purposes.

Results

- Hybrid NIRF/PDT/Colour laparoscopy system has been integrated and performance characterization experiments have taken place
- Live NIRF imaging of less than 3nM solutions of IRDye 800CW has been demonstrated, using an exposure time of 25 ms
- Through integration of a specifically developed optical splitter system, simultaneous imaging with visible light and fluorescence is feasible with this device as is laser activation of a photosensitizer at 690nm for tPDT
- *In vitro* and *in vivo* (mouse) experiments have validated the PDT capabilities of the device
- *In vivo* experiments on minipigs have validated the fluorescence imaging capabilities of the device
- Design of a fully functional portable OCM device for imaging of human pancreas samples *ex vivo*.
- Successful testing of the portable OCM device on more than 10 human pancreas samples, demonstrating the ease of use, precision, improved optical tissue penetration, and fast acquisition time.

Conclusions

WP1 has very successfully developed all required equipment to help the surgeon during the planned clinical studies within the remaining WPs. A hybrid laparoscope was developed compatible with both the Exendin-800CW and the Exendin-700DX tracer

and the device has successfully been tested both *in vitro* and *in vivo*. WP1 also developed a completely non-invasive, label-free, and fast OCM microscope, and tested the device on human pancreas samples. The average acquisition and reconstruction time of a 3D stack is possible in less than 15 seconds, islets are clearly identifiable (including islet structure, ducts and vascularisation), and penetration depth has been improved to up to 1 mm. The ease of use, an outstanding image quality and fast acquisition time are key assets for a much broader use in a clinical setting, promising time saving for the surgeon and pathologist.

3.2.2 WP2: Optimization and characterization of tracers

Partners involved SKU, SOP, UMCG, PSI, CHARITE, UHBS, UHE, UTU, and UL2

Total WP progress 100%

Background

Although Exendin is an optimal tracer as it targets very specifically the GLP-1 receptor and shows very high tumour to background ratios, it has the disadvantage to have very high kidney uptake due to the renal excretion pathway. Since the kidneys are located close to the pancreas, this hampers imaging of beta cells or insulinomas in the pancreas. In addition, high kidney uptake limits the maximum activity that can be safely administered for therapeutic purposes. Therefore, there is a need for the development of tracers with lower kidney uptake. Within this WP, 3 different tracers with lower kidney uptake were developed: MI-NOTA-Exendin, biased agonists and albumin binders. The work proposed includes the design, synthesis and *in vitro* as well as *in vivo* evaluation of optimized radiolabelled Exendin derivatives.

The high kidney uptake can also be reduced using the plasma expander Gelofusin. Within WP2, we evaluated the ability of Gelofusin to reduce the renal accumulation of radiolabelled Exendin in humans and we performed dosimetric calculations to estimate the maximum insulinoma absorbed dose that could be achieved when Exendin would be used for peptide receptor radionuclide therapy (PRRT).

Because of the longer half-life of the radionuclide that allows easier shipping compared to the Ga-68 compound, and because a slightly better image quality is expected based on the shorter positron range of F-18, the synthesis of F-18 labelled Exendin was developed in Turku, Finland.

For quantitative therapy planning and treatment of CHI and AHH, 3D dosimetric models including islet specific microdosimetry are required. This enables calculation of the dose to the specific organs and calculation of the dose that could be administered when developing Lu-177-labeled Exendin for treatment. These models were developed in WP2.

During surgery, locating insulinomas can be highly challenging, even when state-of-the-art preoperative imaging is available. Fluorescent tracers targeting the GLP-1 receptor expressed on insulinomas could greatly improve visibility of the lesions. Therefore, Exendin-800CW was developed in WP2 and fully characterized both *in vitro* and *in vivo*. In addition, Exendin can also be labelled with 700DX, a fluorescent dye that can be irradiated and will then release reactive oxygen species and specifically destroy GLP-1 overexpressing (insulinoma) cells. This tracer is very promising for tPDT in both AHH and CHI. This Exendin-700DX tracer was also developed and fully characterized *in vitro* and *in vivo* in WP2.

Objectives

1. Optimize tracers for PRRT, IGS and tPDT of CHI and AHH.

2. *In vitro* and *in vivo* evaluation of tracers in animal models and patients (cooperation with WP3).

3. Preparation of clinical studies through collecting of necessary preclinical data (cooperation with WP3).

4. Development of 3D dosimetric concepts based on beta cell specific microdosimetry in animals for planning and evaluation of PRRT and tPDT.

Results

- Exendin-800CW was completely and successfully evaluated and synthesized under full GMP regulations. The tracer shows specific and dose dependent targeting of the GLP-1R both *in vitro* and *in vivo*. Proof of principle of the combined use of the laparoscope developed in WP1 and the Exendin-800CW tracer developed in WP2 has been shown in experiments in minipigs. A fluorescent signal was observed and confirmed by scanning of sections of pancreatic tissue. Exendin-800CW was handed over to WP3 for GMP production and WP4 for clinical evaluation.

- Exendin-700DX was completely and successfully evaluated and synthesized GLP grade. The tracer shows specific and dose dependent targeting of the GLP-1R both *in vitro* and *in vivo*. A strong tPDT effect was shown for Exendin-700DX both *in vitro* and *in vivo*.
- The albumin binding Exendin-4 has further been evaluated and the promising results for kidney reduction could be confirmed. Three different compounds with lower kidney uptake were developed: ^{68}Ga-NOTA-MI-Exendin-4, albumin binders and biased agonists. Few final experiments have to be done before the decision can be taken which compound is the best for a clinical study. Discussion with nuclear physicians about translation to the clinic has already started. A manuscript on ^{68}Ga-NOTA-MI-Exendin-4 is in preparation.
- The clinical study investigating the effect of Gelofusin infusion has been completed and shows a reduction of kidney uptake of radiolabelled peptide of approximately 20%. A manuscript on this work, including dosimetric calculations for PRRT with Lu-177, has been submitted.
- The dosimetric study has been finished and the calculations show that the existing compound can be applied to children and even new-borns without damage caused by radiation. This study has been published.
- The F-18 labelled compound is established and GMP production is planned at piCHEM. Toxicology studies will be performed.

Conclusions

WP2 has very successfully reached all objectives, milestones and deliverables. Exendin-NODAGA-Ga-68, Exendin-800CW and Exendin-700DX were successfully developed for comparative imaging, IGS and tPDT respectively, for the improved diagnosis, surgery and treatment of insulinomas. Tracers with lower kidney uptake were developed and Gelofusin was shown to lower kidney uptake of radiolabelled Exendin in humans. Dosimetry models were developed and showed the safety of repeated imaging with Exendin tracers. In addition, an F-18-labelled compound was developed and is ready for GMP production.

Note: For more details, please view the supplemental material-attachment no. 1 (confidential).

3.2.3 WP3: GMP production

Partners involved SKU, UMCG, PSI, CHARITE, UHBS, UTU, TRM, and piCHEM

Total WP progress 90%

Background

In order to guarantee for the seamless translation of novel tracer molecules into the clinics, this WP focused on production and delivery of clinical tracers according to all European and national guidelines and legislation. Within the BetaCure project both, the radioactive tracer ^{68}Ga-Exendin and fluorescent tracers for IGS (Exendin-800CW) and tPDT (Exendin-700DX) have been developed.

The Ga-68-Exendin-NODAGA as radiotracer for PET imaging has been prepared for use in clinical studies. The Exendin-NODAGA has been produced and vialed under full GMP conditions. ABX labelling kits and cassettes for the synthesizer have also been produced and released under GMP conditions. Alternative labelling process using various certified clinical grade Ga-68-generators and synthesis modules have been validated including the respective analysis methods. The required documentation (including IMPD, IB and protocols) have been written and approved. The production kits have been tested and validated according to EMA cGMP regulations. Exendin-NODAGA has been released for radioactive labelling with Ga-68 and injection into humans at SKU by a Qualified Person. Stability testing of the product has been initiated.

For the IGS tracer, the Exendin was conjugated, by partner PiChem, to a cGMP produced near-infrared dye IRDye800CW for first in-human use as Exendin-800CW. Together with the technical partner SurgVision, who developed the sensitive camera systems to detect the NIR tracer, a first in-human study has been initiated in the Netherlands in patients with pancreatic adenocarcinoma of the pancreas or insulinomas.

Prior to cGMP production, the compound was tested in animal models for its specificity and toxicity according to international ICH-GCP quality standards. Moreover, due to the progress in the GMP production of the radioactive Exendin imaging tracer, the development of Exendin-800CW could be supported by whole-body quantitative imaging data providing the necessary pharmacokinetic and biodistribution data, which are also relevant for the translation of an optical imaging agent like Exendin-800CW.

The image-guided surgery Exendin-800CW study in adult patients will serve as a step-up towards future application in patients with AHH and subsequently in paediatric patients with CHI. The simultaneous clinical translation of a targeting peptide for nuclear and also optical imaging clearly shows the strength of a multidisciplinary international collaboration in a difficult to treat and manage rare disease in paediatric patients. Obviously, precautious safety measures have been installed and a standardized analytical platform has been developed within the BetaCure WP3 to evaluate the optical imaging agent at the highest current standards.

Objectives

1. Production, translational testing and delivery of clinical grade (cGMP) produced Exendin-4 based radioactive tracers for pre-operative PET/SPECT/CT imaging in patients with AHH and CHI (cooperation with WP2).

2. Production, translational testing and delivery of cGMP produced Exendin-4 based optical tracer for intra-operative open-air and laparoscopic IGS in patients with AHH/CHI (cooperation with WP2).

3. Production, translational testing and delivery of cGMP produced Exendin-4 targeted imaging + photosensitizer (theranostics) for intra-operative beta-cell tPDT (cooperation with WP2).

Results

- Within WP3, the radioactive tracer ^{68}Ga-NODAGA-Exendin-4 has been produced, fully evaluated and tested according the international guidelines and EMA cGMP production regulations. The tracer is now evaluated in humans.

- Exchange of uniform production protocols has taken place, whereas the clinical protocols for inclusion of the first AHH patients have been submitted to the local IRBs and approved accordingly.
- The fluorescent tracer Exendin-800CW is produced under full GMP regulations and the animal toxicity study has been finalized. The IMPD and IB for this product are ready.
- *In vitro* and *in vivo* results of GLP produced Exendin-700DX are very promising with excellent tumour targeting and cell killing effect up to 100%, but due to currently unresolved production issues identified in the BetaCure project and formerly unknown (even by the producer), further GMP production of Exendin-700DX (including the animal toxicity study) was deemed not useful.
- As part of an ongoing technical and clinical feasibility study in pancreatic adenocarcinoma patients, it has been decided (as part of ethical requirements and safety measures) to evaluate the phase I studies of Exendin-800CW, but not Exendin-700DX (due to the aforementioned production issues), in patients undergoing surgery as a separate side-study. The primary endpoint will be beta-cell specific targeting of Exendin-800CW as determined intraoperatively and by *ex vivo* tissue analysis. Moreover, in a pilot study for *ex vivo* testing of Exendin-700DX, the selective beta-cell killing effect will be evaluated using *ex vivo* specimen irradiation and cell-death analysis.

Conclusions

Both the ^{68}Ga-NODAGA-Exendin-4 and the Exendin-800CW tracer were successfully developed, fully characterized and produced under GMP regulations, including all required documentation. Both tracers are being validated for use in humans at the moment. The Exendin-700DX tracer was also developed and successfully tested, however, an impurity in the dye has so far hindered to take the next step to GMP production.

3.2.4 WP 4: Clinical development and evaluation

Partners involved SKU, SOP, UMCG, CHARITE, UHBS, UCL, UHE, UTU, and UL2

Total WP progress 60%

Background

In WP4, the BetaCure consortium aimed at evaluation and optimization of quantitative pre-operative imaging for treatment planning including individual planning of IGS. The ^{68}Ga-Exendin tracer has been demonstrated to be an excellent tracer for imaging GLP-1R expressing lesions in AHH and CHI patients. The clinical studies in BetaCure define an optimal diagnostic approach for AHH and CHI and have identified an effective clinical approach for individualized planning of IGS and, in the future, also tPDT. IGS is an innovative means for the highly specific detection of diseased tissue which, by conventional macroscopic surgery, would not have been correctly identified or would have been challenging to identify. IGS relies on the principle of intraoperative imaging of fluorescent dyes specifically targeting certain tumour tissues. The fluorescent signal is visualized by optical systems displaying an image superimposing the fluorescent signal with visible light images. This technology therefore allows surgery of tumour tissue with hitherto unknown sensitivity and specificity and may revolutionize surgical treatment of cancer in the near future.

Objectives

1) Clinical validation and comparison of the developed/improved pre-operative imaging methods in patients with AHH/ CHI in order to determine the optimal pre-operative imaging strategy for planning IGS.

2) Optimizing quantitative pre-operative imaging in patients with focal/diffuse CHI/AHH and correlation with surgical outcome and reduction of radiation exposure.

3) Clinical validation, optimization and comparison of the newly developed intra-operative imaging methods (IGS) in patients with AHH/CHI and correlation with surgical outcome.

Results

During the course of the project, WP4 has achieved the following results:

- Preoperative imaging in AHH patients was set up at 8 different hospitals. In 5 of them, the study is open. Scanning of the first patient with ^{68}Ga-Exendin for the AHH study was performed in January 2016. So far, 33 patients have been included in the study with ^{68}Ga-NODAGA-Exendin PET imaging. Additionally, 5 patients were scanned with ^{111}In-DTPA-Exendin SPECT at partner UL2.
- Scans with ^{68}Ga-Exendin in these patients show not only the proof-of-principle for insulinoma imaging: The image quality is very high and tumour-to-background ratios are clearly improved compared to the standard ^{68}Ga-DOTA-TOC imaging.
- For preoperative imaging in CHI patients, the first 6 children have been scanned with ^{68}Ga-Exendin-NODAGA PET imaging at UCLH. The preliminary data are promising and indicate towards a benefit of ^{68}Ga-NODAGA-Exendin 4 PET over ^{18}F-DOPA PET.
- At SKU, a database (eCRF) has been successfully set up to include all data from the AHH and CHI study from all centres. Logins were provided to all partners.
- Protocols for centralized analysis of tissue samples from clinical studies were developed and are being used.
- The medical ethics committee has given approval for the protocol for the Image Guided Surgery study at UMCG. The study is expected to open in June 2018.
- Proof of principle was shown for intraoperative detection of a lesion in a CHI patient within a compassionate use setting. A manuscript on this work is written at the moment.

Conclusions

Within this WP, a radioactive imaging tracer has been developed and produced under full GMP regulations and the radioactive labelling of this compound has been set up at 8 different hospitals. Preoperative imaging of AHH and CHI patients has successfully been set up and has shown excellent results. Exendin imaging so far has proven to be better as compared to the standard imaging methods. This radioactive Exendin tracer has shown to have the potential to become the new imaging method for both AHH and CHI patients, replacing all other imaging modalities. In addition, a fluorescent tracer has been developed and produced under full GMP conditions. All preparations for a clinical study have been performed and the study is ready to start.

Note: For more details, please view the supplemental material-attachment no. 2 (confidential).

3.2.5 WP5: Targeted Photodynamic Therapy (tPDT)

Partners involved SKU, SOP, UMCG, PSI, CHARITE, UCL, and UL2

Total WP progress 40%

Background

This WP aimed at evaluation and optimization of tPDT, finally delivering the proof-of-principle in adult patients and possibly also in CHI patients. tPDT combines a photosensitizing agent with the physical energy of nonionizing (usually near infrared) light to kill cells. The disadvantage of current concepts is the lack of specificity of the non-targeted photosensitizer for the tumour cells resulting in uptake in normal tissues causing serious side effects. Furthermore, current small molecule photosensitizers have a tendency to accumulate in epithelial cells including the skin, resulting in further unwanted phototoxicity. Lately, a novel photosensitizer has been developed for targeted PDT that avoids the disadvantages of current photo sensitizers, i.e. low extinction coefficients and lipophilicity. This photosensitizer (700DX) was conjugated to antibodies allowing specific delivery of the compound to tumour cells *in vivo* which were subsequently destroyed by excitation of the photosensitizer. Cell kill was achieved with internalized 700DX as well as 700DX bound to the cell membrane only. Therefore, 700DX is a highly promising compound for tPDT. In BetaCure, we used 700DX as the optimal photosensitizer for coupling to Exendin allowing to retain the hydrophilicity of the compound in order to achieve highly specific cell killing of GLP-1R expressing lesions in AHH and CHI while preserving healthy tissue.

Objectives

1. Determine the *in vitro* and *in vivo* efficacy of tPDT by (Exendin-4)-700DX.

2. Execute a full evaluation for clinical translation of cGMP synthesized (Exendin-4)-700DX (includes cGMP

production, testing (animal toxicity testing) and IMPD writing).

3. Execute small smart feasibility study in adult patients with pancreatic cancer and AHH.

4. Feasibility study of tPDT in paediatric patients with CHI.

Results

- First *in vitro* PDT trials with the new photosensitizing agent Exendin-700DX showed that GLP-1 overexpressing CHL cells are efficiently destroyed by the therapy, without causing relevant islet or cell death by Exendin-4, Exendin-700DX itself, or laser irradiation itself. Exendin-700DX is highly efficient for tPDT when bound to the GLP-1 receptor (more than 97% cell death).
- Subsequently, *in vivo* tPDT experiments were executed in insulinoma-bearing mice, demonstrating efficient cell killing and improved survival.
- The first in-human pancreatic cancer phase I/II safety/dose-finding study using an antibody-based IRDye800CW tracer has been approved by the local IRB at the UMCG and is on-hold for an interim-analyses of 3 dosing groups. Currently 9 patients are included and neither (S-) AEs nor any technical difficulties (using the IRDye800CW tracer in this extreme high-risk patient population) were observed.
- The intraoperative camera has been shown repeatedly to be safe in its technical performance, and is shown in a comparative study to be 100-times more sensitive than other cameras in the field.
- Moreover, the *ex vivo* specimen analytical methodology and an SOP are established, using so-called Multiplexed Advanced Pathology Imaging (MAPI, Clin Cancer Res 2016, Nature Communications, under revision). This investigator protocol and IB is the blue print for using cGMP produced Exendin-IRDye800CW for IGS.
- After safe application of Exendin-800CW in adult patients, the final stage will be application in paediatric patients extending beyond the end of the BetaCure project.

Conclusions

The Exendin-700DX tracer was produced and fully evaluated both *in vitro* and *in vivo*. It shows excellent receptor targeting and impressive cell killing. With only 3 minutes of irradiation, *in vitro* cell death was shown up to 98%. These *in vitro* data indicate a high therapeutic potential for PDT with Exendin-700DX *in vitro*. However, for further development into a GMP product, extensive HPLC analysis of the tracer was performed and showed instability of the dye when exposed to physical forces. This problem is already present in the dye itself. Several new conjugation, purification, lyophilisation and reconstitution strategies have been developed, but the issue of the instability has not been solved yet. Therefore, clinical translation has been hampered. The producer is currently working on a solution for the problem, supported by BetaCure partner piCHEM.

3.2.6 WP6: Training, dissemination, quality control

Partners involved SKU, TRM, EARL, and concentris

Total WP progress 100%

Background

This work package plays a central role in the interaction of BetaCure partners aiming at building up intersectoral expertise, training of experts within and outside of the consortium and definition and implementation of standards for personalized diagnostics and treatment in CHI and AHH patients. In addition, in order to obtain quantitative SPECT and PET data of the highest quality, all scanners used for the clinical studies have been calibrated and certified. A certified program for PET scanner calibration is already available and is coordinated by EARL for F-18. In addition, in WP6 we also performed phantom scans with the radionuclide Ga-68 that is used in BetaCure clinical studies for insulinoma imaging. Scans from many hospitals within and also outside the BetaCure project have been analyzed and a publication is under preparation. For SPECT imaging, a program for scanner calibration is not available yet. Therefore, within this WP guidelines for SPECT scanner calibration have been developed in a multicenter setting, including different brands and types of SPECT scanners.

Objectives

1. Training of scientists including training for clinical studies (task 3).

2. Definition and implementation of standards for the clinical studies including scanner calibration and data management (task 1).

3. Dissemination of BetaCure results towards the scientific community and the general population with a focus on contact with patient organizations (task 2, 4).

4. Training of physicians and scientists outside of the consortium (task 2, 3).

Results

- Scanners of all centres participating in BetaCure clinical studies have been included in the PET accreditation program and proved to perform correctly
- The results of the EARL accreditation program demonstrated that the network of the scanners is suitable for multicentre studies involving both of the investigated radioisotopes, F-18 and Ga-68.
- All phantom scans with Ga-68 and F-18 performed at the different BetaCure hospitals have been analyzed and the results will be published in collaboration with the NKI/AvL hospital in Amsterdam.
- A multicenter collaboration between clinical physicists was set up to develop also accreditation guidelines for SPECT scanners.
- Meetings and workshops were organised to disseminate BetaCure findings, and the website was launched.

Conclusions

PET scanner accreditation was successfully applied for F-18 and developed for Ga-68 for all clinical PET scanners in the consortium. Also, guidelines for SPECT scanner accreditation were developed in a multicentre initiative.

Note: For more details, please view the supplemental material-attachment no. 3 (confidential).

3.2.7 WP7: Project management

Partners involved SKU and concentris

Total WP progress 100%

Background

Work package 7 was dedicated to project management to take care of all administrative and coordinating tasks. In order to support the coordinator in monitoring the compliance of all beneficiaries with their obligations under the grant agreement, the project management office at concentris, together with the coordinator, kept a close eye on all partners' performance

Results

WP7 ensured the following:

- that tasks assigned to the beneficiaries were performed correctly and in a timely manner
- that reports were submitted according to the guidelines and in time
- that funds were used and claimed according to the rules
- that the partners fulfilled their obligations regarding dissemination and funding acknowledgements
- that any changes to the work plan were communicated to the EC swiftly
- that any changes were compliant with the ethical requirements and regulations

Conclusions

The Project management office acted as a helpdesk for all participants. It was the central node of communication on a day-to-day basis and communicated with the European Commission on behalf of the Coordinator regarding administrative and managerial issues (i.e. contract, amendments, reportings etc.).

4 Potential impact and the main dissemination activities and exploitation of results

4.1 Socio-economic impact and the wider societal implications of BetaCure

BetaCure has developed a theranostic platform which combines molecular biomedical imaging with simultaneous therapeutic capabilities. This theranostic platform is based on technology that could only be developed because BetaCure partners have previously relied on combining complementary expertise spread throughout Europe in cooperative efforts in previous joint projects. We have established, validated and clinically implemented novel strategies for personalized treatment of different rare diseases related to insulin-producing pancreatic beta cells (congenital hyperinsulinism and adult hyperinsulinemic hypoglycaemia). Tailored medical interventions using this theranostic platform will lead to improved outcome of treatment combined with fewer adverse effects, especially in new-borns and infants, which has already been demonstrated in the ongoing clinical studies. The theranostic platform developed in BetaCure will facilitate the uptake of personalized healthcare in clinical CHI and AHH therapy in the near future.

This platform will allow easy adaptation for use in other diseases, including the use in cancer, by the choice of a suitable alternative ligand; it is therefore expected that the development of this platform will have a tremendous effect on the competiveness of European research and industry in the field of personalized healthcare. Indeed, the principle demonstrated in BetaCure has for example already been translated to PSMA ligands targeting metastatic prostate cancer.

The BetaCure project clearly advanced research and patient care in personalised medicine. Finally, the BetaCure project has successfully contributed to the goals of the International Rare Diseases Research Consortium (IRDiRC): 200 new therapies and a diagnostic tool for the majority of rare diseases by 2020.

As described previously, CHI is a debilitating disease requiring treatment associated with side-effects that are only considered acceptable because of the morbidity of the disease, including irreversible brain damage and early death. The same is basically true for AHH, although the morbidity is lower. As both disease entities belong to the group of rare diseases, they are not in the focus of (commercial) interest of the pharmaceutical industry, and share this fait with other rare diseases. Also, the socioeconomic impact of CHI and AHH is limited if compared to diseases such as diabetes with alarmingly increasing numbers of patients world-wide. However, the impact on the patients and their families is enormous, ranging from delayed diagnosis because of unspecific symptoms and insufficient awareness of healthcare professionals for the disease (especially in AHH) to difficulties in finding adequate local healthcare support or specific revalidation. In addition, the side effects of therapy in combination with frequent visits to specialised hospitals require continuous efforts of the families of CHI patients. Therefore, CHI and AHH have massive negative consequences on the life of the patients and their families. BetaCure already has a tremendous positive impact on quality of life of patients and their families by improved diagnosis leading to efficient therapeutic interventions. In the future, BetaCure technology will improve the situation of AHH and CHI patients with respect to the psychosocial consequences of the disease and help to avoid long-term complications of the therapy.

Within the BetaCure project, three highly innovative technologies have successfully been developed and tested in humans/humans tissue:

- An integrated optical system for simultaneous intraoperative visible light and fluorescence imaging 100 times more sensitive than any other currently available system. Through integration of a specific optical splitter developed for this purpose in BetaCure, simultaneous activation of photosensitizers by near infrared light of 690nm is also feasible. The diameter of the endoscopic system is only 3mm while providing excellent image quality, allowing even the use in babies.
- A mobile xfOCM system for examination of resected tissue in the operation theatre during ongoing operations has been developed and tested in fresh human pancreatic tissue. This device allows the timely evaluation of resection margins, potentially replacing fresh frozen section histopathology.
- Ga-68-NODAGA-exendin is currently under scrutiny for orphan drug designation at the European Medicines Agency (approval expected in 2018) and with the results of the ongoing studies in AHH and CHI, we strive to obtain marketing authorization after finalization of the clinical study in AHH.

These achievements demonstrate that BetaCure technology may be a major asset for the competiveness of European healthcare research and may foster future development of European cutting edge technology in this field. As stated above, although the socioeconomic impact of BetaCure achievements will be limited in respect to the number of patients that will directly profit from the innovative theranostic platform, the development of the platform in itself will be an achievement with relevant consequences for European research and industry as the principle of the platform has a large potential for translation to other diseases, including diseases with high incidence and millions of patients in Europe. Theoretically, the principle of the BetaCure theranostic platform can be applied to every disease fulfilling the following criteria: (a) the disease is caused by functionally defective cells and/or (malignant) cells growing in clusters or locally replicating, (b) a ligand exists specifically binding to the target cells with low accumulation in the surrounding tissue, (c) the cell clusters are difficult to differentiate from healthy tissue macroscopically and residual disease after operation causes recurrence, (d) the target cells can be reached for activation of the photosensitizers by near-infrared light (may require invasive or minimally invasive treatment). Thus, many kinds of cancer diffusely spreading in the peritoneal cavity or in connective tissue belong to the group of diseases that can potentially be diagnosed and treated with the technology proposed here, as well as chronic inflammatory diseases.

European researchers have been strong in the development of specific ligands for molecular imaging. Partners of BetaCure have been involved in the development of innovative PET/SPECT tracers and new labelling strategies. Together, we have developed new imaging technology and improved existing technologies opening new fields for molecular imaging research. BetaCure SMEs have successfully designed and developed highly sophisticated strategies for optical imaging, putting the project in a world leading position in the specific field. The BetaCure project therefore supports the European position in a very competitive field, where transformation of frontier scientific discoveries into exploitable products may have a profound impact on public health and European economy.

4.2 Main dissemination activities of BetaCure

Yearly DGN Summer School

One of the key educational and professional networking accomplishments of BetaCure was the organisation of the yearly "DGN Summer School" by the BetaCure beneficiary CHARITÉ. Many of the young and several of the experienced researches had a chance to participate, connect, learn about advances in medical imaging technology, discuss issues, and present their data during these annual summer schools of the German Society for Nuclear Medicine (Deutsche Gesellschaft für Nuklearmedizin, DGN e.V.).

Workshops

In addition to the broader setting of the DGN summer schools, some very topic-specific workshops were held in order to teach and distribute important technical protocols and work-procedures, and to ensure that equally high standards of quality and quality control were applied in all centres and of all members of the consortium. In 2014 and 2015, for example, SKU organised a total of 3 workshops in Nijmegen that targeted specifically the members of the BetaCure consortium.

- The first workshop addressed all requirements for meeting the worldwide accepted standards of the so called Good Manufacturing Practice (GMP) production, or, more specifically, clinical grade Good Manufacturing Practice (cGMP) production.
- A follow-up workshop was tailored even more towards the objectives of the BetaCure project in that it presented GMP-compliant Ga-68 labelling procedures of the Exendin-NODAGA tracer.
- A third workshop developed and discussed the specifics of a standardized clinical protocol to improve the diagnostic procedure of congenital hyperinsulinism (CHI), especially in small children

Articles published in the popular press

Three articles in the popular press are worth mentioning:

- In April 2014, the official magazine of the SKU Radboud University Medical Centre published a detailed article about different types of diabetes, hyperinsulinism, and the BetaCure research team and scientific approach in the article "Stop op suikervreters".
- In November 2016, the Dutch journal "Endocrinologie" actively promoted the BetaCure project and encouraged patients to participate in the study. The article was entitled "Gezocht: patiënten met verdenking op insulinoom".
- The Dutch Endocrinologist Association also published a print article about the BetaCure project in December 2016.


OVERLEVEN OP COLA

'Onderzoek naar de behandeling van diabetes vergt veel uithoudingsvermogen'

VAN TECHNIEK NAAR BEHANDELING

Figure 2. Excerpt from the article "Stop op suikervreters" in the official magazine of the Radboud University Medical Centre.

Video and multimedia

In a publicly available video by the European Association of Nuclear Medicine (EANM) from February 2014, BetaCure coordinator Prof. Dr. Martin Gotthardt announces the beginning of the EU-funded international study, explains the project's research objectives, and stretches the importance of helping patients suffering from CHI or adult endogenous hyperinsulinemic hypoglycaemia (AHH). Feel free to follow this link to view the video: **https://youtu.be/2owsWHG8yes**. In addition, two technical videos were circulated in 2015 within the consortium for educational and informative purposes, one about the "labelling of Exendin-NODAGA" and another one on "Quality Control (QC) procedures for EANM/EARL accreditation".

The first success of the EARL Taskforce EU-grants: BetaCure Project

Figure 3. YouTube video about BetaCure, provided by the European Association of Nuclear Medicine (EANM)

Oral presentations to a wider audience

The BetaCure consortium also ensured to organise presentations and event for the general public and a wider audience in general. The following outreach activities and presentations were made possible by SKU and CHARITÉ:

- June 2015, German Association for Congenital Hyperinsulinism: affected parents meet the experts in Berlin, Germany
- April 2016, DGN Meeting: presentation on the results of targeted photodynamic therapy (tPDT) in Dresden, Germany
- Sept 2016, Highlights of Medical Engineering 30th Meeting: „PET/CT & PET/MR in Men and Mice" in Berlin, Germany
- Sept 2017, The BetaCure Project: "Optimizing diagnosis of CHI using beta cell imaging with Exendin" in Paris, France

Oral presentations and posters presented at scientific events

In total, more than 22 oral presentations and posters were disseminated amongst experts within the field at scientific events all over Europe (e.g. Athens, Barcelona, Turku, Rome, Vienna, Oxford, San Sebastián, Nijmegen and Noordwijkerhout), such as the European Neuroendocrine Tumour Society (ENETS) Conference or annual meetings of DGN, EANM, the Dutch Endocrinologist Association, hot topics in molecular imaging (TOPIM), the International Pancreas and Islet Transplant Association (IPITA) or the European Society for Pediatric Endocrinology (ESPE).

4.3 Exploitation of results of BetaCure

The main exploitable foreground of BetaCure is the development of a research device for fluorescence imaging and photodynamic therapy excitation during laparoscopic surgery. The development of this interactive imaging device falls under the category of "general advancement of knowledge", serves as a proof-of-concept, and will ultimately set novel standards for pancreatic surgery once it has advanced into a commercially available medical apparatus. The device is expected to be brought to the market by SurgVision (SOP), and further research into production details will be ongoing. This also means that the scientific details leading to this exploitable foreground are strictly confidential until a patent license or commercial product exists.

5 Address of the project's public website and relevant contact details

Public Website: **http://www.betacure.eu**

Figure 4. Excerpt from the official website of the BetaCure project.

Below is a list of all beneficiaries and contact details of the team leaders at each of these institutions. Contact details for each beneficiary can also be found on the BetaCure website under "ABOUT => PARTNERS".

Beneficiary	Title	First Name	Last Name	Email
01 SKU	Prof.	Martin	Gotthardt	martin.gotthardt@radboudumc.nl
01 SKU	Mrs.	Annemarie	Eek	Annemarie.Eek@radboudumc.nl
02 SOP	Mr.	Stefan	Schorling	stefan.schorling@surgvision.com
03 UMCG	Prof.	Gooitzen	van Dam	g.m.van.dam@umcg.nl
04 PSI	Dr.	Martin	Béhé	martin.behe@psi.ch
05 Charité	Prof.	Winfried	Brenner	winfried.brenner@charite.de
06 UHBS	Prof.	Damian	Wild	damian.wild@usb.ch
08 UCL	Dr.	Pratik	Shah	Pratik.Shah@ucl.ac.uk
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