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Göttingen Minipigs
MAGAZINE

ELLEGAARD
GÖTTINGEN MINIPIGS

Dear reader

The beginning of a new year is always a special time. Personally, I look back on 2021 with reflection and lots of learning, and I look into the new year with both excitement and a bit of uncertainty.

Covid-19 is still a huge part of our daily life. Both personally and professionaliy, we are highly affected with restrictions and many activities are centered around Teams, Zoom and SoMe interactions. Let us hope that we will soon return to more usual interaction, scientific events, and social gatherings.

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One thing that has not changed is our corporate values: Animal Welfare, Quality, Respect and Collaboration – all part of our daily life and business. We define our animal welfare by living out a Culture of Care and maximizing the well-being for our animals. This is one of the pillars in our organisation. We are passionate about constantly improving and refining our animal welfare and adhering to a Culture of Care is a natural part of the process towards interaction and bonding between human-animal and human-human.

We focus on animal welfare in several aspects; not only as good science and animal welfare, which go hand in hand, but also as gratitude to all animals enabling us to develop safer and more effective medicines – you can read much more about this in the Magazine.

I hope you will enjoy reading the Magazine, and even more, I hope to see many of you in the coming year; maybe in May at the Minipig Research Forum (MRF) 2022, which will be hosted at our newly expanded and renovated breeding and research site in Dalmose, Denmark.

I wish you all a Happy New Year.

Lars Friis Mikkelsen, CEO
Ellegaard Göttingen Minipigs A/S

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A Culture of Care

By Kirsten Rosenmay Jacobsen, CSO, & Maja Ramløse, Laboratory Animal Veterinarian, Ellegaard Göttingen Minipigs A/S

Animal Welfare is one of the four core values at Ellegaard Göttingen Minipigs together with Quality, Respect, and Collaboration. The values were defined in the company years ago and are still the foundation of the daily work and an important part of the corporation's future strategy.

Good animal welfare can only be achieved with a continuous focus on Culture of Care. A Culture of Care is typically defined and used in the laboratory animal community to indicate a commitment to improving animal welfare, scientific quality, care of the staff and transparency for the stakeholders. Although, it is not directly mentioned in the Directive 2010/63, it is included in its guidance documents produced by the EU commission and recognized by several organizations such as EFPIA and RSPCA, as an important part of good animal science. Culture of Care is an establishment-wide commitment that goes beyond merely meeting legal requirements.

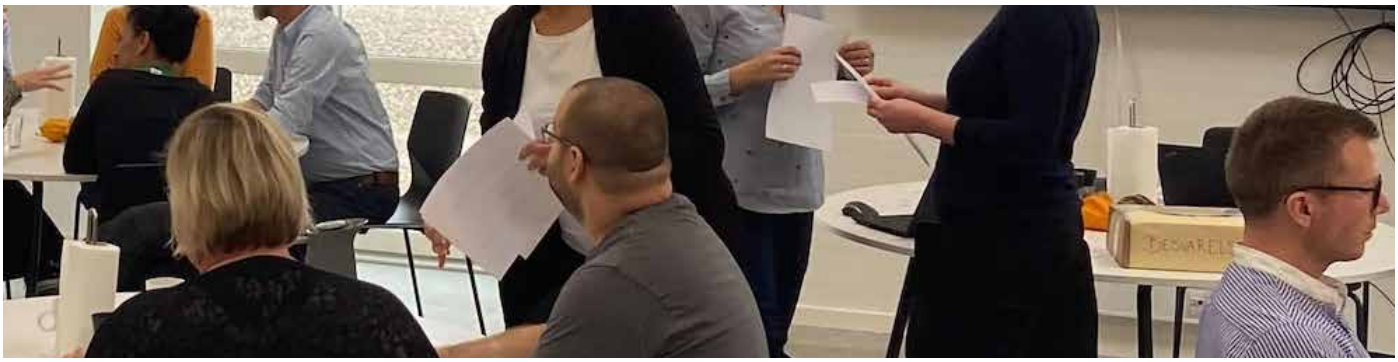
A Culture of Care is a Culture of Commitment

Ellegaard Göttingen Minipigs' ambition on animal welfare is indeed to go beyond regulatory requirements and thus, the company has adopted the Culture of Care principles. The concept is included in internal standard operating procedures (SOPs), and thus integrated in the handling and care of each individual animal.

In November 2021, all employees attended a workshop about Culture of Care, organized by Maja Ramløse, Laboratory Animal Veterinarian and Carina Christoffersen, Animal Welfare Technician at Ellegaard Göttingen Minipigs. The purpose of the workshop was to engage all levels of staff in a discussion on the current level of the Culture of Care and animal welfare, as well as to identify relevant focus points to continue working on in the future. And very importantly, how can it be implemented in all aspects of operations – from the daily work by the animal caretakers to the final delivery of the animals.

Furthermore, the workshop included a questionnaire to give insight into potential challenges and benchmark knowledge related to animal welfare, and possible future initiatives were discussed in small groups. The questionnaires and the results of the group discussions were presented afterwards and will be used actively by the Animal Welfare Body to further strengthen the Culture of Care within the company, and to form the basis of a new company-wide SOP on corporate values.

Image 1: Employees filling in questionnaire
Image 2: The enrichment room is an effective way to increase behavioural diversity of young Göttingen Minipigs



Maja Ramløse, Laboratory Animal Veterinarian says, “we work continuously on refining our housing and husbandry practices by taking the health, natural behaviour and needs as well as the affective state of the animals into consideration".

A positive Culture of Care is required for good animal science

Culture of Care and animal welfare are about more than caring for the animals out of ethical obligations. High animal welfare is a prerequisite for high scientific quality. Animals with compromised welfare have disturbed behaviour, physiology, and immunology, which may affect the scientific output. Thus, refinement of experimental procedures not only has welfare benefits for the animals involved, but also improves the data, decreases variation, and secures reproducibility between experiments and overall interspecies translatability to humans. At Ellegaard Göttingen Minipigs, several experimental procedures have been refined including blood sampling using a sling, positive reinforcement training of minipigs to participate in procedures (e.g., milking for lactation studies) and focus on non-invasive dosing methods whenever possible, just to mention a few examples.

Image 3: Sow performing nest building behavior prior to farrowing:

Replace, Reduce, Refine.

Culture of Care and animal welfare are related to the 3Rs (Replacement, Reduction and Refinement). The 3Rs in relation to animal experimentation are a widely accepted ethical framework and guiding principles for the ethical use of the laboratory animals. Refinement covers improvements which minimize actual or potential pain, suffering, distress, or lasting harm and/or improve animal welfare – including positive changes in the housing environment to stimulate natural species-specific behaviours.

The ability to express a natural behavioural profile is important to maintain good psychological and physiological wellbeing. At Ellegaard Göttingen Minipigs, the behavioural management and enrichment program is often reviewed, and new enrichment items and devices are implemented. Within recent years, this has resulted in the inclusion of long fibered hay to farrowing sows, stimulating the natural nest building behaviour seen prior to farrowing. To stimulate play, explorative and manipulative behaviour, an enrichment room was designed allowing young minipigs dedicated play time on a weekly basis. And to stimulate rooting behaviour, all animals are provided with straw twice daily and various enrichment devices are rotated regularly between the pens. And very importantly, all animals are housed in groups unless veterinary reasons suggest otherwise, to meet their social needs.

"Even though, we strive to do well, it will never be ´good enough´- and we should always aim to improve and refine by challenging status quo, current attitudes, and workflow”, says Maja Ramløse.

Utility of Göttingen Minipigs for translational model in dialysis evaluation

By Nihon Bioresearch Center

Chronic kidney disease (CKD) progresses to the end-stage renal disease (ESRD), in which renal function declines with aging, making it difficult to maintain homeostasis and eventually requiring dialysis. In dialysis patients with ESRD, abnormalities in the bone and parathyroid glands caused by mineral-bone-disorder (MBD) have a significant impact on life prognosis through vascular calcification1)2).

Introduction

Rodent models of adenine-induced renal injury have been used as animal models of dialysis, but they cannot be said to fully replicate the condition of dialysis patients because renal function cannot be completely impaired in rodents 3) 4).

Therefore, attempts have been made to establish dialysis models in dogs and monkeys, but even in these species, there have been no reports of long-term dialysis 5) 6).

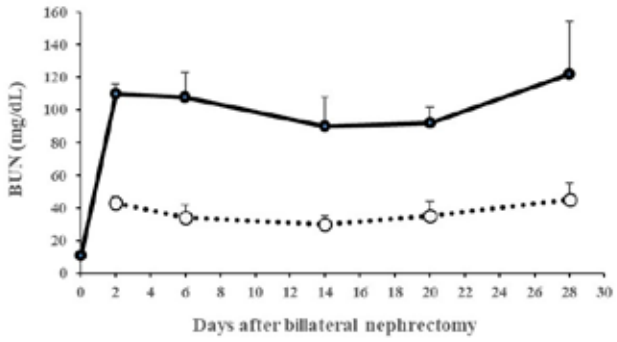
We thought that minipigs could be used as a dialysis model, because this species has a larger body size and blood volume compared to dogs and monkeys, and Hct, HGB, whole blood coagulation time are similar to those of humans, and can use human dialysis machines as they are.

Test method

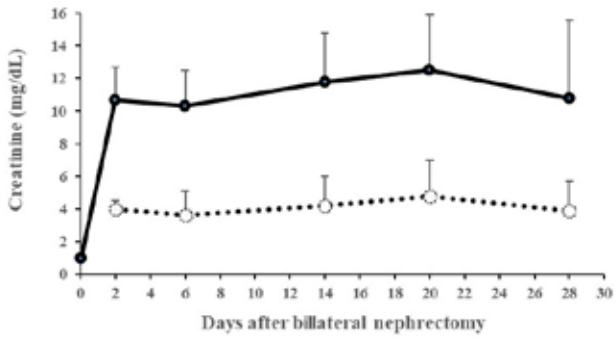
Göttingen Minipigs (male, 9-11 months of age) were used. Both kidneys were removed, and hemodialysis was performed every 2 days from 2 days after removal until 28 days after removal. Hemodialysis was performed for 5 hours per session using a dialysis machine with a blood circuit and hollow fiber dialyzer connected to a blood access catheter placed in the anterior vena cava. Hematological and blood chemistry tests were performed on days 2, 6, 10, 14, and 28 after nephrectomy. Echocardiography, angiography and intravascular ultrasonography of the coronary arteries were performed 28 days after nephrectomy, and then histopathological examination of the heart, aorta and lungs were performed.

Pre-emptive analgesia:
On the day of surgery, the animals were dosed with Meloxicam and Buprenorphine.

Postoperative care:
Ampicillin sodium was administered just after surgery. 6-8 hours after pre-emptive analgesia-dosing, buprenorphine hydrochloride was administered as post-operative analgesia.



(A) BUN



(B) Creatinine

Image 1 (A) and 2 (B)
The renal function parameters of hemodialysis minipigs. The data are presented as the mean + S.E. (n = 5-6.)

——— : Pre-dialysis
- - - - : Post-dialysis

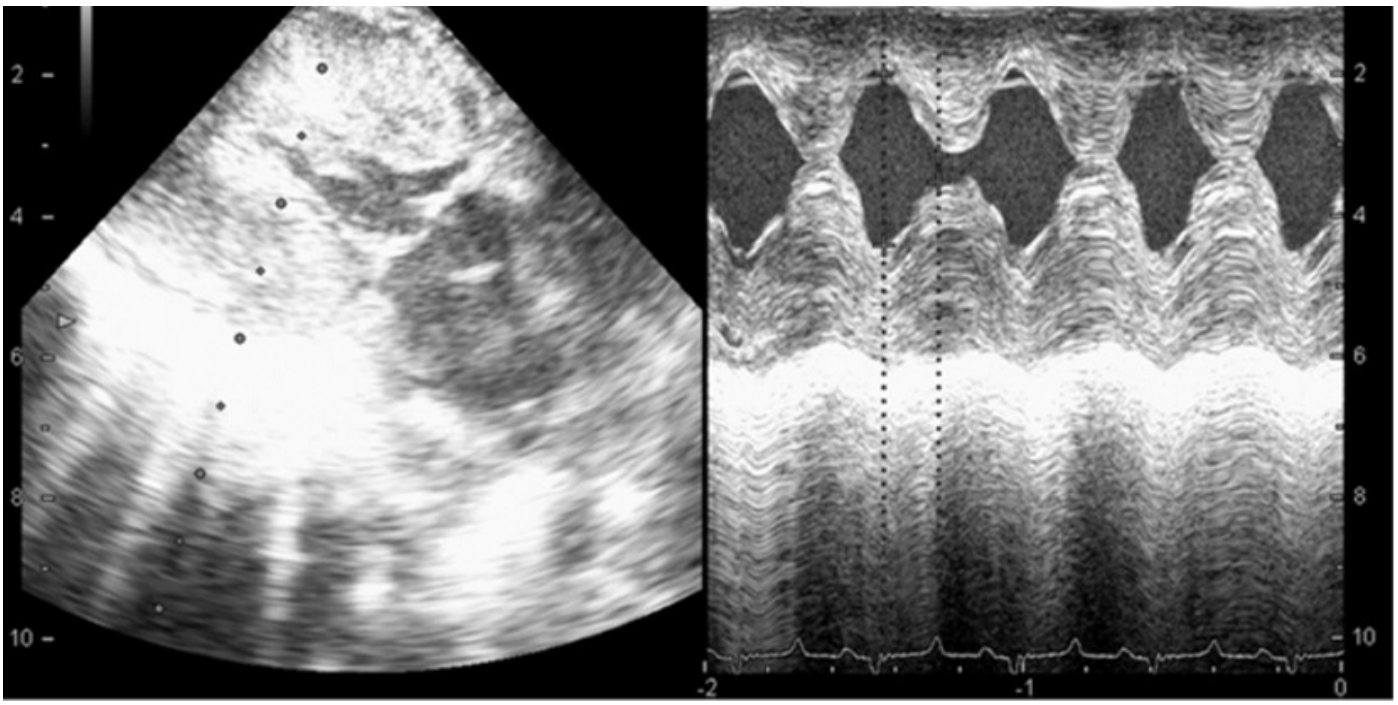


Image 3
Typical echocardiographic images in day 28 after bilateral nephrectomy of hemodialysis minipigs.

Meloxicam treatment was continued for 3 days after surgery.

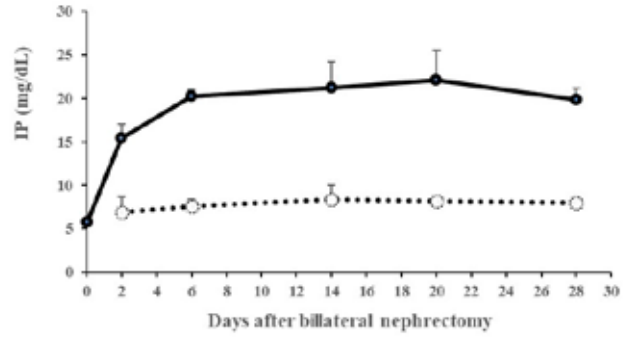
Characteristics of the minipig dialysis model

The levels of BUN and serum creatinine, which were elevated by nephrectomy to the level indicating uremia, clearly decreased after dialysis at all the time points and continued to increase to the same levels as at the time of nephrectomy before the next dialysis for 28 days. (Image 1)

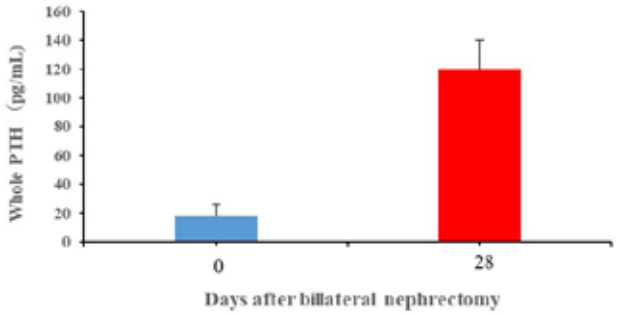
The serum phosphorus level also decreased to the level of pre-nephrectomy by dialysis, and repeatedly increased to a higher level than that of before dialysis, and the obvious increase in PTH and hyperphosphatemia were observed over 28 days. (Image 5)

Echocardiography showed cardiac hypertrophy due to thickening of the myocardium. Angiography showed coronary artery stenosis, and intravascular ultrasonography showed atherosclerotic calcification in the intima. Histopathological examination showed calcification in the heart and aorta as well. (Images 7, 8 and 9)

In addition, hypoalbuminemia, hyperkalemia, anemia, hypertension, and hyperparathyroidism were also observed.



(A) IP



(B) Whole PTH

Image 4 (A) and 5 (B)
The serum phosphate and whole PTH levels of hemodialysis minipigs. The data are presented as the mean + S.E. (n = 5-6.)

—— : Pre-dialysis
- - - - - : Post-dialysis

Discussion

We succeeded in creating a complete dialysis minipig model in which both kidneys were removed and animals were maintained by long-term hemodialysis for 28 days.

This was thought to be due to the fact that minipigs had a larger total blood volume than dogs and monkeys, were able to maintain extracorporeal circulation blood volume, and were able to secure a blood flow volume and dialysis time similar to those of human hemodialysis.

The situation of uremia developed by removal of bilateral kidneys and improved by dialysis could be maintained for 28 days. We also observed the development of hypoalbuminemia, hyperkalemia, anemia, hypertension, and cardiac hypertrophy seen in dialysis patients, as well as abnormal mineral metabolism (hyperphosphatemia) and elevated parathyroid hormone (PTH) as characteristic of hyperparathyroidism.

Thus, the dialysis model using Göttingen Minipigs was able to replicate the pathology of CKD-MBD in dialysis patients within a short period of 28 days after bilateral nephrectomy. These results suggest that Göttingen Minipigs are useful models for translational research in dialysis. We have evaluated many drugs and medical devices using this minipig hemodialysis model so far, and verified that it is a useful evaluation model.

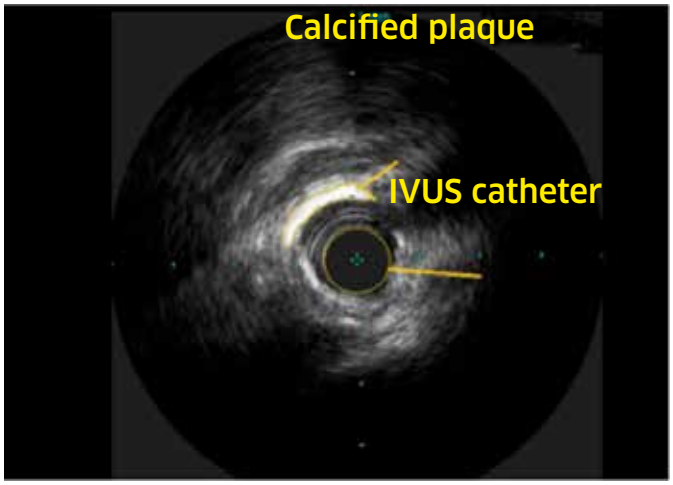
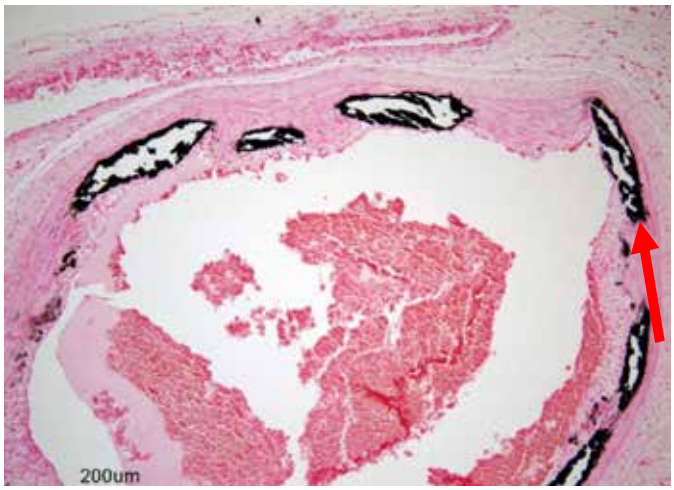
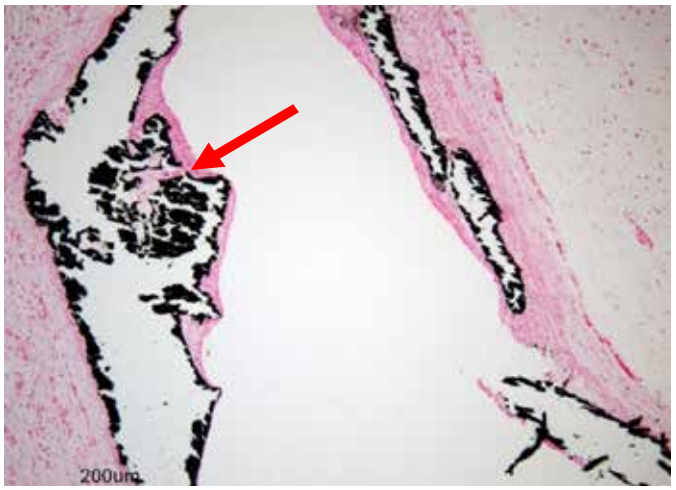


Image 6
Typical intracoronary ultrasound imaging in day 28 after bilateral nephrectomy of hemodialysis minipigs.





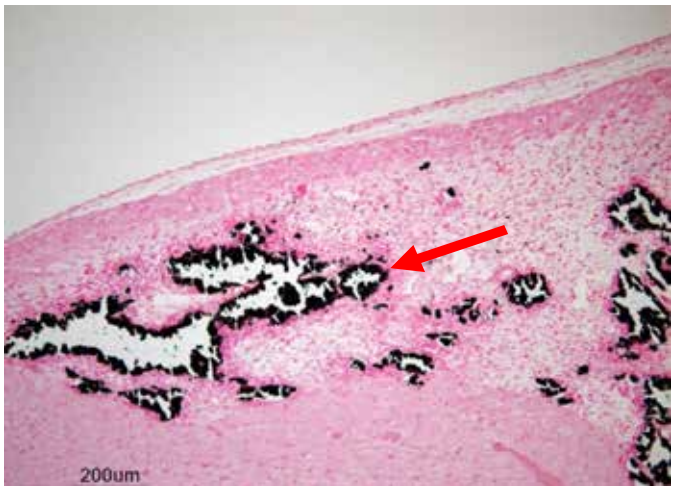


Image 7, 8 and 9
Representative von Kossa staining of aorta and heart of hemodialysis minipigs.

1. Left coronary artery
2. Mitral valve
3. Aortic root

The arrow indicates the calcification part

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Göttingen Minipigs: Modeling heart failure with preserved ejection fraction (HFpEF)

By Thomas E. Sharp III, Ph.D.[1,2]

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Heart failure with preserved ejection fraction (HFpEF) has become the most prominent form of HF in the world, accounting for more than 50% of all new HF diagnoses (1). HFpEF is a heterogenous, complex, comorbid-laden syndrome which has become the greatest unmet clinical need in cardiovascular medicine to date (2).

Introduction

The significant increase in the prevalence of HFpEF is due to an ever-growing older population which suffers from a multitude of comorbidities including hypertension, obesity and diabetes; this, coupled with a lack of efficacious treatments, exacerbates the severity of this public health problem. The extra-cardiac comorbidities, in concert with chronic and progressive cardiac remodeling, contribute significantly to the progression of HFpEF.

Current guideline directed medical therapy relies on symptom relief through neurohormonal modulators for blood pressure control (3), diuretics to relieve instances of volume overload (4) and other treatments for persistent comorbidities, such as diabetes mellitus (5). Entresto, a combination angiotensin II receptor blocker and neprilysin inhibitor, is the only US-FDA approved therapy for HFpEF (6), however hurdles of cost, compliance and adoption by clinicians has yet to see this treatment become the new standard.

Despite the heterogenous nature of the pathophysiology of HFpEF, clinical research has established aberrant vascular stiffening and cardio-vascular coupling, pulmonary hypertension, renal and skeletal muscle dysfunction, chronotropic incompetence, exertional intolerance and elevated left ventricular filling pressures in patients. Basic scientists are tasked with attempting to stratify these pathophysiological responses and developing models which produce several of these key clinical features.

The lack of advancements in novel therapeutic strategies and lack of current understanding in the underlying mechanism involved in HFpEF progression are not well defined due to an absence of reliable, reproducible translational large animal models. Models which reliably recreate the HFpEF syndrome need to have the capacity to layer multi-organ stressors in a single mammalian system which synergize to produce the clinical phenotype.

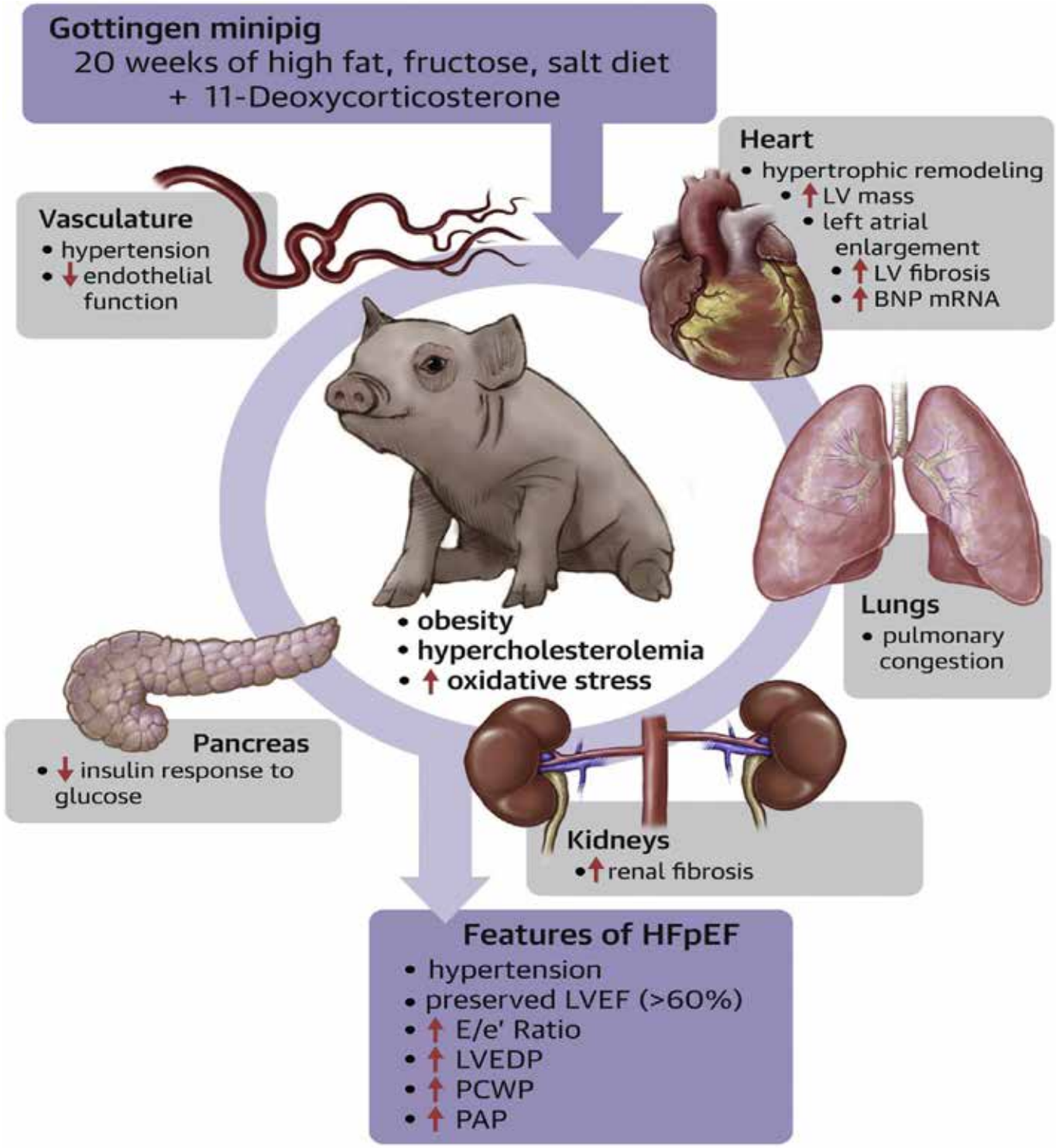
Swine models of HFpEF have previously been described (7,8) with varying results through induction of hypertension, obesity and/or diabetes mellitus. These comorbidities have been used as single insults or in two-hit approaches. Most models using hypertension as the sole driver of HFpEF are focused on cardiac remodeling alone. The hypertension is usually driven by anatomical manipulation of conduit arteries which produces a pressure overloaded system with which the heart must overcome in order to perfuse systemic organs.

Aortic banding or cuffing (7,9), stenting of arteries (10), as well as renal artery stenosis (11) have all been implemented, resulting in increased cardiac mass, stiffening of the myofilaments, and production of a fibrotic phenotype. These models recapitulate findings within the myocardium; however, are devoid of the extra-cardiac multi-organ pathophysiology which is present in human HFpEF.

Others have attempted to incorporate metabolic syndrome by combining obesity and diabetes through western diet administration and additional pharmacological stressors yet fail to recapitulate critical features of the HFpEF syndrome (12).

Most animals utilized for basic research are biological resistant to many of the comorbidities which are necessary for the development of HFpEF, even after chronic exposure (13). The crossbreeding from which Göttingen Minipigs are derived has created a strain of pig that responds similarly to that of humans regarding the pathophysiological response to cardiovascular stressors. Bred specifically for research, Göttingen Minipigs are smaller and are easier to handle in the laboratory setting compared to other strains of pigs. It is well documented that Göttingen Minipigs can develop obesity, insulin resistance and glucose intolerance when exposed to a variety of high fat western diets and other stressors; and exhibits a tendency to develop hypercholesterolemia, vascular disease and atherosclerosis (14,15).

Given our limited understanding of the cofounding factors which seem to drive HFpEF development, coupled with the absence of a reliable and reproducible translational large animal model that incorporates several critical features of the syndrome, we at the Louisiana State University Health Sciences Center - New Orleans (LSUHSC-NO), Cardiovascular Center of Excellence embarked on a study to develop such a model in Göttingen Minipigs.



Sharp, T.E. et al. J Am Coll Cardiol Basic Trans Science. 2021;6(2):154-70.

Image 1
Illustration of Keys Findings in Göttingen Minipigs model of HFpEF.

Model of HFpEF in Göttingen Minipigs

At LSUHSC-NO, we felt Göttingen Minipigs were the most suitable strain for developing a model of HFpEF knowing the predisposition of the strain to many key risk factors of HFpEF.

After carefully searching the literature, it was apparent that a multiplicity approach was going to be necessary to better mimic the human syndrome. The model was published in the Journal of American College of Cardiology: Basic to Translational Science in February of 2021 (16). The model incorporated metabolic syndrome, which manifested as obesity, hypercholesterolemia and abnormal glucose metabolism through the administration of a high fat, fructose and salt western diet. Hypertension, the second insult, was derived through the administration of 11-deoxycorticosterone acetate (DOCA), a steroid hormone aldosterone precursor. The combination of this "two-hit" approach was maintained for a period of twenty weeks with serial measurements to monitor obesity, cholesterol levels, and cardiac systolic and diastolic function via transthoracic echocardiography.

Once there was establishment of significant cardiac diastolic dysfunction with preserve ejection fraction, and confirmation of the necessary comorbidities being manifested, we performed terminal procedures to measure clinically relevant cardiovascular hemodynamics that are used for diagnosis and as prognostic indictors of the severity of heart failure. Tissue samples from multiple organs were collected for ex vivo functional measures, biochemical and histological assessments.

Our data demonstrated that twenty weeks of high fat, fructose and salt diet, in combination with DOCA led to global elevation in oxidative stress, hypercholesterolemia and abnormal glucose metabolism (16). Within the vasculature, we observed hypertension and coronary vascular dysfunction, in an endothelial dependent manner. The pancreatic production of insulin was significantly reduced when an intravenous bolus of glucose was administered at twenty weeks (16), presenting similarly to a type I diabetes mellitus or a severe end stage type II diabetes mellitus.

Histologically there was an increased fibrotic response within multiple organs including the kidney and myocardium. When measuring adverse remodeling and functional deficits within the heart we observed progressive adverse concentric remodeling as measured by relative wall thickness, a preserved left ventricular ejection fraction, progressive diastolic function as measured by and elevated early mitral valve inflow velocity (E) over early diastolic tissue velocity (e') ratio (16). This pathophysiological response in the myocardium resulted in elevated left ventricular filling pressure, which is a hallmark of heart failure and key criteria under the diagnosis of HFpEF (1).

The observation of elevated filling pressure at rest would suggest a more well-developed form of the HFpEF syndrome in this model. Furthermore, pulmonary hypertensive phenotypes in human HFpEF have been previously described (5). Herein, after twenty weeks of western diet + DOCA we measured pulmonary pressures through right-sided heart catherization and found elevated pre- and post-capillary pulmonary pressures, suggestive of pulmonary and venous congestion despite a preservation of left ventricular ejection fraction (16). This novel model of HFpEF in Göttingen Minipigs presents a clear characterization which encompasses many of the abnormalities observed in human HFpEF.

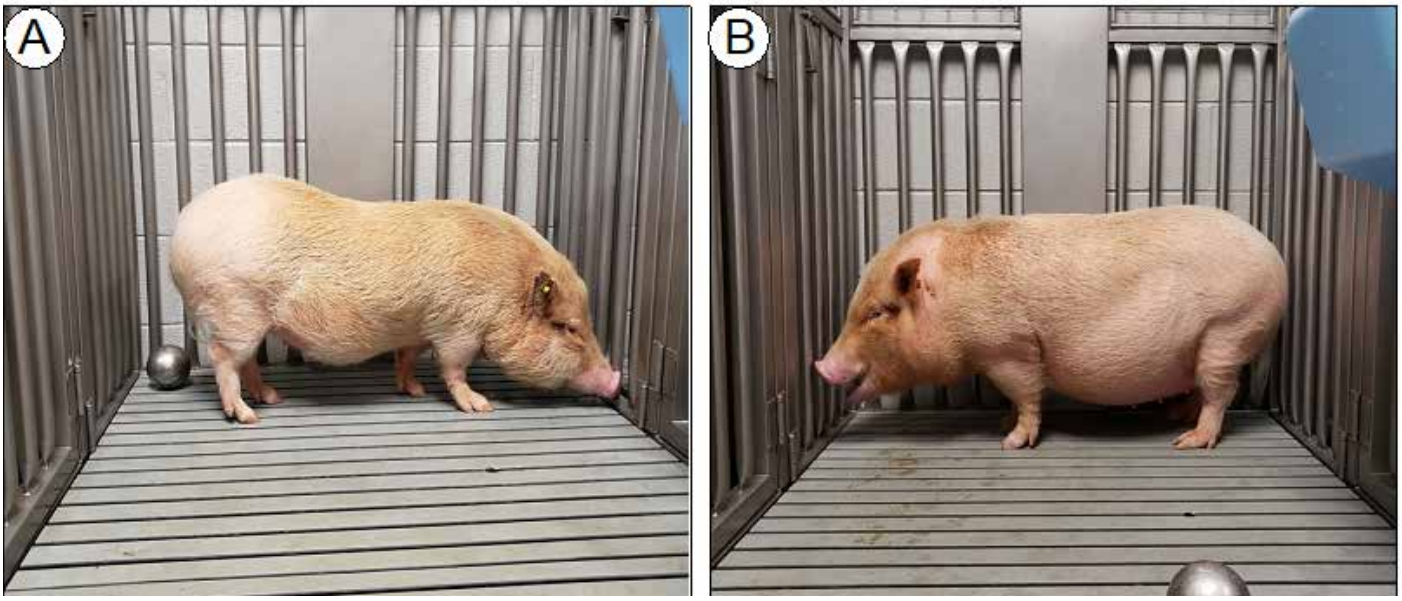


Image 2 (A & B)
Images of Göttingen Minipigs on (A) standard diet or (B) western diet + DOCA for 20-weeks.

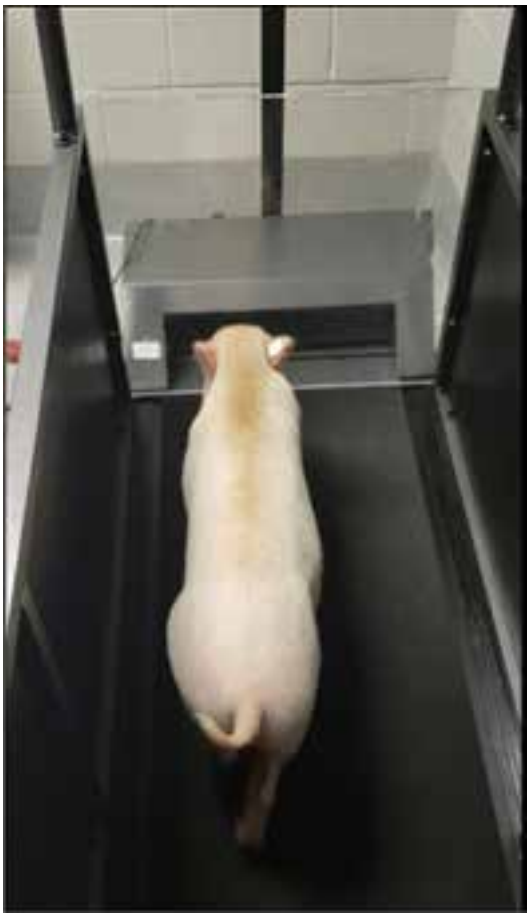


Image 3
Baseline treadmill exercise training of Göttingen Minipigs to examine exertional intolerance.

Summary

While previous pig models have been established (7,8), they lack critical features necessary for diagnosis of HFpEF (i.e. elevated left ventricular filling pressure), which were achieved in this model utilizing Göttingen Minipigs.

This model of HFpEF incorporates multiple comorbidities such as obesity, hypercholesterolemia, and a diabetic phenotype in concert with pulmonary and systemic hypertension. This model is the first, to our knowledge, to combine a "western diet" and a pharmacological mineralocorticoid excess (DOCA) in Göttingen Minipigs. This model has created a platform by which novel therapeutics, including device-based approaches can be tested in a clinically relevant translational large animal model. Ongoing studies are looking at titration of the insults to optimize the biomarkers and drivers of HFpEF to better mimic the human condition.

Also, to expand on relevant endpoints utilized in clinical trials, we are currently performing studies to measure exertional intolerance through exercise capacity testing and investigating molecular alterations in this model which recapitulate clinical findings. This model will provide a bridge to the gap between rodent HFpEF models and human HFpEF to allow for identification of key mechanistic insights and translation of novel therapeutic strategies to combat this most important unmet cardiovascular medicine public health concern.

CONTACT

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Furthermore, acknowledge our collaborator at the University of Pennsylvania, Dr. Dan P. Kelly. Drs. Thomas E. Sharp, Traci T. Goodchild and David J. Lefer has a pending patent on the composition and methods of modeling HFpEF in Göttingen Minipigs.

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Molecular imaging of Göttingen Minipigs

By Philip G. J. Pedersen[1], Frederikke P. Fliedner[1], Trine Starostka[1], Carsten H. Nielsen[1]
[1]Minerva Imaging, Ølstykke, Denmark

Most imaging modalities are available for small animals at Minerva Imaging and in spring 2021, we also installed a clinical SPECT/CT system to our facilities. This system enables on-site imaging of large animals including Göttingen Minipigs.

Introduction

Molecular imaging covers several non-invasive imaging techniques including ultrasound, magnetic resonance imaging (MRI), nuclear medicine techniques such as single photon emission computed tomography (SPECT) and positron emission tomography (PET), and X-ray computed tomography (CT). All techniques have profound impact on clinical health care solutions offered today within a broad variety of disease areas where they all support diagnostics, including monitoring of disease stage and progression. Furthermore, molecular imaging offers the possibility to interrogate biological processes at the cellular level as well as compound biodistribution in the intact living organism throughout the drug development process from preclinical research to clinical translation (Willmann et al. 2008).

With the use of molecular imaging there are numerous opportunities to increase the data output from each animal included in the preclinical test. Furthermore, the non-invasive approach opens the opportunity to reduce the number of animals needed and obtain valuable longitudinal read outs of endpoints which are also directly translational to the clinic setting. Having the imaging modalities in the animal facility also increases animal welfare as long transports and post examination recovery of the pig can be in the home pen.

Measuring renal blood flow, perfusion and filtration using CT

A CT scan combines a series of X-ray images taken from different angles around the body to create cross-sectional images of the body part at interest. This provides a more-detailed anatomical image than can be obtained using planar X-ray. A CT scan has many uses, but in the clinic, it is particularly well-suited to quickly examine people who may have internal injuries because of a trauma or to diagnose diseases and plan a relevant treatment.

The use of contrast agents which increases the density of the bloodstream shortly after an intravenous injection has been found to be useful during CT imaging as it enables a better visualization and delineation of organs and other soft tissues. Another elegant use of iodinated contrast agents during CT imaging is the ability to obtain detailed knowledge about the kidney function. This is possible since iodinated contrast agents are quickly and exclusively excreted via glomerular filtration. Hereby, the density changes in the blood pool and different compartments of the kidneys over time measured by CT can be used to estimate glomerular filtration rate (GFR), perfusion and renal blood flow in the different compartments of the kidneys (Krier et al. 2001). Compared to blood sample based GFR estimates where Inulin or Iohexol clearance is used, the CT based approach gives a much more detailed insight into the kidney function.

At Minerva Imaging we have successfully implemented this technique for determining regional kidney function in Göttingen Minipigs using our clinical Discovery NM/CT 670 SPECT/CT (GE Healthcare). Pigs are prepared with a central IV catheter with the tip placed under fluoroscopic guidance in the superior vena cava near the right atrium of the heart before the test. For the scan the anesthetized pigs are positioned in the CT scanner and with the use of localization scans a tomographic level containing the midhilar region of both kidneys and the abdominal aorta is identified. This level is selected for performance of the flow scan, which is performed repeatedly at a rapid rate to record density changes for 3 minutes after injection of contrast agent (0.5 ml/kg over 2 s, Ultravist®, 370 mg/mL, Bayer). Scan rate is kept at the lowest possible number to reduce the radiation dose. The flow scan will be followed by a volume scan. The volume scan commences 10 s after an injection of 0.5 ml/kg of contrast

agent over 5 s. The kidneys are scanned from pole to pole during peak enhancement to obtain contiguous tomographic levels for subsequent measurement of cortical, medullary, and whole kidney volume. The time-density curves showing the tissue enhancement in Hounsfield Units (HU) over time for the cortex and medulla of each kidney and the aorta are plotted for the regions of interest (Figure 1). By mathematical fitting of the curves (Figure 2) the variables of interest can be calculated. The simplest approach being the Patlak plot used to estimate whole kidney GFR (Granger et al. 2012).

Depending on the study design the scans can be repeated at different timepoints due to their non-invasive nature which enables longitudinal measurements of disease progression after a pharmacological intervention in a model of kidney disease.

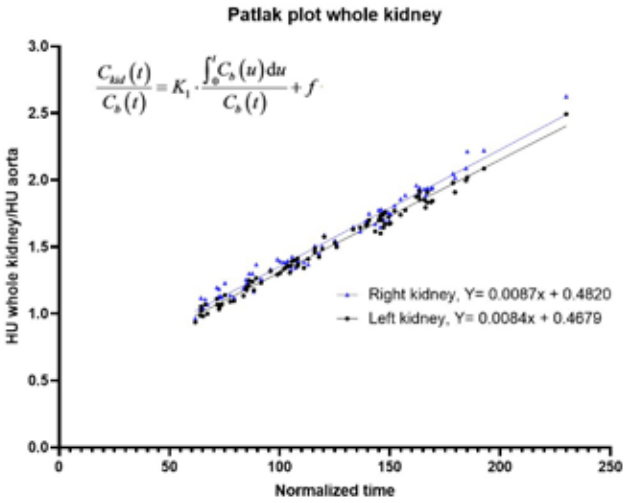
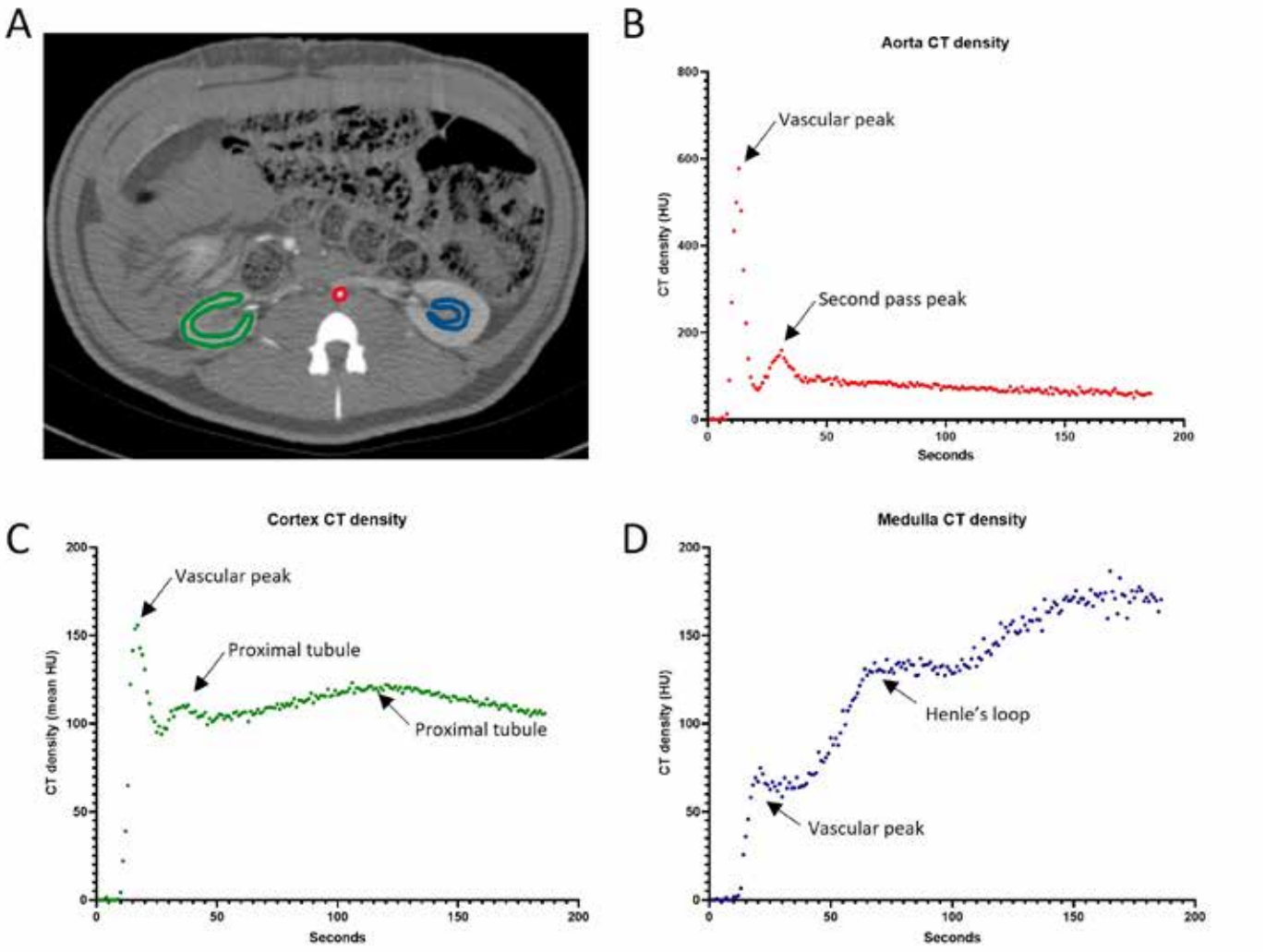


Figure 2 (above)
When contrast medium is accumulating within renal tubules and leaving the vascular compartment a Patlak plot can be used as a graphical analysis technique based on pharmacokinetic principles of a two-compartment model. Graphically, this equation represents a line whose slope is equivalent to whole blood clearance in ml/(sec × ml of renal tissue). The right renal volume was measured by CT to 66.9 ml and the hematocrit was determined using a hematology analyzer (IDEXX ProCyte One) to be 32.3%. Based on this the GFR of the right kidney could be calculated to 23.7 ml/min. Ckid(t) and Cb(t) is the concentration of contrast at time t in the kidney and blood respectively.

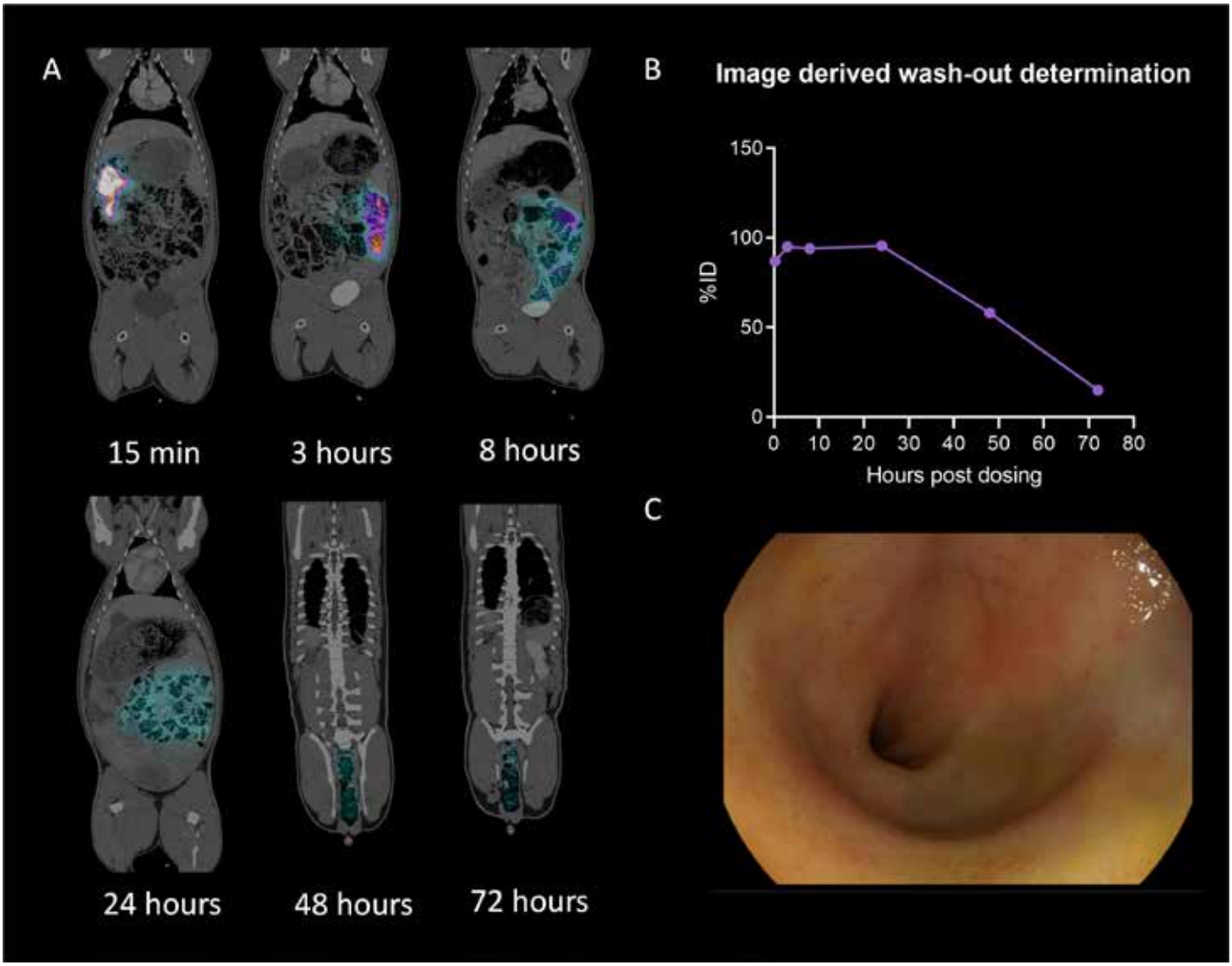
Figure 1 (below)
CT scan of the midhilar level of both kidneys and the abdominal aorta. The regions of interest including the aorta (red), the cortex (green), and the medulla (blue) are drawn over both kidneys (A). Time-density curves from the aorta (B), renal cortex (C), and medulla (D) of a normal Göttingen Minipig after a central venous bolus injection of contrast media. The labels and arrows indicate the tubular location of the bolus during its transit. HU, Hounsfield units..



SPECT/CT for in vivo tracking of a compound bound to the intestinal mucus

Combining SPECT and CT imaging open the opportunity to image physiological processes and to track the biodistribution of a molecule of interest in vivo. The scan procedure follows an administration of a low dose of a short-lived radiolabeled tracer molecule or test compound which emits gamma rays. The radioactivity is detected using a gamma camera to acquire multiple 2D image projections from different angles, that are reconstructed as 3D images to show the biodistribution of the radiolabeled compound in vivo. Combining the SPECT image with CT provides anatomical information for colocalization. The preclinical use of SPECT/CT imaging in Göttingen Minipigs are many and the interest from our sponsors are varied. In a recent collaboration, radiolabeled compound was delivered in the duodenum using endoscopic guidance with the aim of tracking its movement through the intestinal tract. The test compound was labeled with the diagnostic radioisotope In-111 (half-life 2.8 days) in our radiochemistry laboratory just before dosing. Longitudinal imaging was performed at the following timepoints: 15-minutes, 3-, 8-, 24-, 48-, and 72-hours post dosing. The quantitative SPECT data make it possible to calculate the wash-out period for the compound and to obtain comprehensive knowledge on the biodistribution and excretion route of the compound. In Figure 3 longitudinal images are shown depicting the compound distribution over time in one of the Göttingen Minipigs used for this study. From the images it is seen that the radioactive signal from the labeled compound is kept within the intestinal tract and excreted exclusively in the feces. and therefore, it could be concluded that the compound is not taken up from the intestinal tract and did not enter systemic circulation. The overall excretion can be calculated from the total activity found in the field of view over time and is presented in Figure 3.

Figure 3 (below)
Representative SPECT/CT images of the same animal showing the biodistribution of the In-111 labeled compound 15-minutes, 3-, 8-, 24-, 48-, and 72-hours post dosing (A). Images show the excretion of the compound in the GI tract. The graph depicts the quantitative output for the wash-out shown in percent injected dose (%ID) of the dosed compound (B). Quantitative measure is based on measuring the total amount of activity within the animal at each time point. (C) Representative image exemplifying the endoscopically guided dosing in the duodenum.



The expansion of Minerva Imaging will bring in further clinical imaging modalities and radiochemistry

The scientifically driven approach at Minerva Imaging is our key focus. Development of large animal imaging has high priority, and we seek to increase the catalogue of methods we can offer to our collaborators. In 2022, our facility in Ølstykke will be expanded to include a fully integrated GMP compliant radiochemistry laboratory, including a cyclotron for radioisotope production. Our expansion will further enable us to bring in other imaging modalities such as PET/CT and MRI, to obtain longitudinal read-outs in large animal models across disease areas supporting translational studies.

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Evaluating expression of messenger RNA of a target protein

ABOUT STUDY INSIGHTS: Göttingen Minipigs are increasingly selected for all aspects of pharmaceutical research and are fully recognized as a reliable and established animal model by all regulatory authorities worldwide. This section aims at providing an insight into the wide use of Göttingen Minipigs within biological research. If you know of an interesting study, you are welcome to reach out.

Insight provided by:
Jakob Bondo Hansen, Dan Ploug Christensen and Jeppe Hvidtfeldt Ekberg from Embark Biotech

What is the study about?
This study is about evaluating expression of messenger RNA of a target protein in a variety of different tissues from a handful of different species including young and adult Göttingen Minipigs.

What is the purpose of the study?
The purpose of the study is species qualification: To be able to qualify and select rodent and non-rodent species for performing nonclinical safety studies. As such, the dissection and RNA-preservation from various tissues from Göttingen Minipigs of different age are part of a bigger study.

Why is it important?
According to the U.S. Food & Drug Administration, the objectives of the nonclinical safety study is to define pharmacological and toxicological effects not only prior to initiation of human studies but throughout clinical development.

Both in vitro and in vivo studies can contribute to this characterization. Nonclinical safety testing should among others consider selection of the relevant animal species (species qualification) and its age, but also practical circumstances such as treatment regimen and route of administration. Thus, species qualification is paramount in the progress of nonclinical safety testing of novel therapeutics.

What makes this study particularly interesting?
With this study we are identifying relevant species for performing preclinical safety and as such the study will provide general biological information. The target protein and the biology that it entails are well-characterized in relation to the gastrointestinal tract. Our attention, however, is directed towards a novel role for the target biology and will therefore provide interesting biological information on the conservation of the novel target biology across species.

Which challenges have you met during the study?
As a small biotech company, we always keep an eye at the budget when initiating activities. Unfortunately, we have found it surprisingly difficult to obtain non-rodent tissue specimens in a cost-effective way, even though we would have liked to acknowledge the 3Rs by dissecting animals that find no more use.

More often than not, we have had a hard time coming to a common understanding of needs and economy. Ellegaard Göttingen Minipigs really helped us come up with a good solution where we were able to travel to the site to lend a hand in the dissection, connect with the friendly experts and learn a lot about Göttingen Minipigs while at the same time having fun and progressing our preclinical development.

How do you recommend going about species selection?
Species selection is a process not only entailing target protein tissue expression patterns from different species but also the biology of the target, which can vary between species. Careful attention and diligent searching will allow the selection of rodent and non-rodent species.

Image1
Embark Biotech visiting Ellegaard Göttingen Minipigs in 2021.
The Embark dissection team, feeling content and fortunate to take part in the dissection of Göttingen Minipigs together with Adrian Zeltner from Ellegaard Göttingen Minipigs. Left to right: Jakob Bondo Hansen, Jeppe Hvidtfeldt Ekberg and Dan Ploug Christensen.

WOOJUNG Bio-Cluster for New Drug Development, Korea (WBNDD)

WOOJUNG BIO Cluster for New Drug Development (WBNDD), the headquarter of WOOJUNGBIO, is the first private-Bio-cluster in South Korea, and it is a groundbreaking open-innovation platform for new drug development. WOOJUNGBIO is Ellegaard Göttingen Minipigs' distributor in South Korea.

Benjamin Chun, CEO, Pharmacist, and Ph.D. established WOOJUNG Trading (current WOOJUNG Bio, Korea) in 1989. His initial business was supplying lab animal resources and has expanded to Engineering and Construction business; establishing facilities for animal lab, pre-clinical CRO business, and infection control business. Most recently, in September 2021, Chun completed the 100% privately-led WOOJUNG Bio-Cluster for New Drug Development (WBNDD).

WBNDD is a bio-cluster that provides a smart/one-stop platform for the drug development industry, ranging from non-clinical tests, proper planning of clinical trials to LO/LI (licence-out/-in), accelerating and investment. In particular, our focus is on optimizing facilities and activating R&D investment to expand various non-clinical testing services such as drug efficacy testing with animal models, pharmacokinetics, and toxicity testing whilst preparing to sell services for domestic and overseas sponsors.

In the 1980s, the driving force behind the new drug development was international trade pressures on introducing substance patents and the protection of intellectual property rights. Nevertheless, developing new drugs independently as a small-scale domestic pharmaceutical organization was nearly impossible. Chun, along with a few opinion leaders such as university professors as well as the head of the Pharmaceutical Research Institutes, joined forces to present a policy proposal to the government on the establishment of public drug development infrastructure that domestic pharmaceutical companies can utilize. The proposal emphasized the importance and role of shared laboratory animal centers and pre-clinical testing centers.

The importance of shared facilities led Chun to grow a vision to build a private bio-cluster, WBNDD, where various entities can gather and share the market-leading drug discovery facilities, realizing their innovative ideas. WBNDD will be a 'playground' for the entities to interact and brainstorm ideas, forming a collaborative and dynamic ecosystem.

WBNDD is a building of 15 stories above ground and six stories below ground, 23,194.87m2 (249,667ft2). It is located in Dongtan, Hwaseong-si, an optimal place for a dynamic ecosystem for new drug development to thrive. The building is equipped with state-of-the-art infrastructure such as a shared vivarium/lab/office, an analysis center, and services such as clinical planning/legal consulting, etc. In particular, the vivarium is composed of top-notch robots and automation systems. Drug discovery startups and organizations will gather and leverage the facilities and services, neither being required to build their own testing facilities (hardware) nor employ specialists (software).

Instead, WBNDD infrastructures are provided, and internal expert groups will be deployed as consortiums. In addition, other convenience facilities such as small- and large-sized conference halls and cafeteria are available.

With a mission to advance human well-being through drug discovery, WBNDD will play a pioneering role in supporting pharmaceutical companies and bio-ventures to join the WBNDD network and face unfathomable challenges in drug development together. We are actively expanding our network from government research centers, institutes, university labs to CROs to achieve our mission.

Working at Göttingen Minipigs

How did you get interested in working with animal welfare?
I have always liked animals and do have animals at home, but when I first started at Ellegaard Göttingen Minipigs in 2006, I did not have any work experience with animals. Previously, I worked in a shop, and therefore, working with animals and Göttingen Minipigs was a completely new territory for me.

At Ellegaard Göttingen Minipigs, I gradually increased my interest in animal welfare and especially the close co-operation between our veterinarians and me and their support was decisive for me to choose this path.

Why is animal welfare important to you?
Animal welfare is important, not just to me but for all my colleagues and a core value for us at a company level. The animals do not have a say; humans choose them as animal models, and therefore, it is our responsibility to secure their wellbeing, health, and welfare while they are in our care. It is all about taking responsibility and caring for the minipigs and relentlessly trying to refine the way we work and interact with the animals As an additional benefit, we also see better and more reliable research results when the animals are cared for in an optimal way.

I am also very pleased to have contributed actively to refining several animal husbandry procedures at Ellegaard Göttingen Minipigs and to see that my initiatives have been successfully implemented. As an example, I have worked with optimised care and refinement of new-born piglets in co-operation with our CSO, Kirsten Rosenmay Jacobsen. Furthermore, a refined method for blood sampling has been developed and implemented and today all animal caretakers have been trained to use this method.

About the Animal Welfare Committee
The Animal Welfare Committee within Ellegaard Göttingen Minipigs has 9 members. The committee is composed of representatives from all departments and consists of one chairperson, one representative from each housing facility, one veterinarian, one representative from research, one from production as well as two non-affiliated external members: a priest and a teacher respectively.

The purpose of the Animal Welfare Committee is to monitor our animal welfare with the aim of maintaining it at a high level. More issues are discussed: Competency development, and status of present and future projects are some of the fixed items on the agenda when the committee members meet every 3 months.

In focus

Name Carina Christoffersen
Function Animal Welfare Technician at Ellegaard Göttingen Minipigs A/S

Education Originally educated as sales assistant, Carina is currently participating in a customized educational programme based on her work experience and continued internal and external training to obtain the certificate as a trained animal caretaker

Background Carina has been employed at Ellegaard Göttingen Minipigs since 2006. In 2019, she applied for and got a new and dedicated position as Animal Welfare Technician at Ellegaard Göttingen Minipigs with a focus on improving animal welfare, but very importantly as well, developing, assessing and implementing improved housing conditions for our Göttingen Minipigs.

Personal information 46 years old, 3 children.
Carina lives together with John in a small town called Hyllested - close to Ellegaard Göttingen Minipigs.

Painting behind Carina: Susanne Ydo, ydoart.dk.

Which initiatives are you particularly proud of?
I am proud of many initiatives at Ellegaard Göttingen Minipigs. In particular, I am proud of the playroom, also known as the enrichment room, which now is implemented in two out of three housing facilities. It all started with the newly weaned minipigs, who got bored with the enrichment that we gave them in the pens and therefore needed to be stimulated in another way. I came up with the idea to design a playroom where the Göttingen Minipigs can be stimulated with colourful toys, water pools, and tunnels. In the playroom, I also equipped the playroom with toys with different scents and toys with sounds. Today, all animals aged 4 to 15 weeks benefit from approx. 20-30 minutes playtime on a weekly basis.

Describe your role in the Animal Welfare Committee?
I have been a member of the Animal Welfare Committee since 2016 and the Chairperson of the Committee since 2019. I am very happy with the work that we do in the Committee, which benefits the Göttingen Minipigs. I really feel that the accomplishments of the Committee with its diverse compilation of skills and mindsets have a positive impact on the conception of animal welfare at our facility.

What expectations do you have for animal welfare in future?
We must keep a high focus on animal welfare at all times and refine the housing and care of our Göttingen Minipigs. Further, we shall continue to work on refining the procedures related to the scientific use of the animals. At Ellegaard Göttingen Minipigs, a continuous training in animal welfare is mandatory for our employees: We can always learn more and improve ourselves, and we see it as an important part of our job to share our knowledge and experience with our customers and others who take an interest in the welfare of Göttingen Minipigs.

Spotlights

News

Export of Göttingen Minipigs to China approved

We are very pleased to annonce that in December 2021, Ellegaard Göttingen Minipigs succesfully completed a mandatory virtual pre-inspection from the General Administration of Customs of the People's Republic of China (GACC), which now allows us to ship Göttingen Minipigs to China. "This great achievement has been made possible through an intensive collaboration between our Chinese Country Manager, Jin Liu, and our dedicated team in Denmark and several stakeholders in China", says Lars Friis Mikkelsen, CEO at Ellegaard Göttingen Minipigs.

Winner of PwC´s Export Award 2021

In November 2021, Ellegaard Göttingen Minipigs A/S was presented with the PwC Export Award at a show hosted by our local muncipality, Slagelse.

Ellegaard Göttingen Minipigs received the award due to the constant development and growth for years and at the same time with strong financial results.

Jens Ellegaard, owner of Ellegaard Göttingen Minipigs A/S, pointed out the importance of being visionary and to look beyond borders both domestically and abroad.

Lars Friis Mikkelsen, CEO of Ellegaard Göttingen Minipigs A/S, underlined in his speech that export to a great extent is the foundation for Denmark's economy. Further, Lars emphasized that such an award only can be won by having the right knowledge, trust, and especially the right team.

HMR

Health Monitoring Report December 2021

Every 6 months the Health Monitoring Report (HMR), based on FELASA recommendations, is published for all three barriers at Ellegaard Göttingen Minipigs.

Laboratory Animal Veterinarian at Ellegaard Göttingen Minipigs, Maja Ramløse, who is responsible for reviewing the overall health monitoring plan, collecting, accumulating, and reporting the results, says: "In November/December we perform an extended analysis. For the latest report we are very pleased to confirm, that the December 2021 report shows no changes in the overall health status at our facility".

Download the full report from minipigs.dk/health-status

We enable development of safer and more effective medicines

At Ellegaard Göttingen Minipigs we are all for sharing and believe that openness creates trust, enriches and clears the path for new opportunities. ***We share knowledge*** *about Göttingen Minipigs for biomedical research, both our own knowledge but also learnings from scientists around the world.* ***We create fora*** *for networking and knowledge sharing amongst scientists.* ***We support scientific research*** *through our Research Foundation.* ***We educate*** *through webinars and practical courses.*

WEBINARS 2022

Topic	Date	Guest speakers	Register
Live Webinar Event: Why you should consider Göttingen Minipigs as your large animal model	25 January 2022 3 pm CET*	**Steven Van Cruchten,** Professor, Comparative Perinatal Development, University of Antwerp, Belgium: *Drug metabolism in the Göttingen Minipig: key information for species selection in safety testing of pharmaceuticals* **Edward Marsden**, Associate Director, ERT, DART & Juvenile Toxicology, Charles River Laboratories, Lyon, France: *Recent updates in the use of Göttingen Minipigs as a relevant model in drug development* **Susanne Mohr**, Senior Toxicology Project Lead, F. Hoffmann-La Roche, Basel, Switzerland: *Non-rodent species selection from a pharmaceutical company point of view*	https://campaigns.minipigs.dk/events/webinar-consider-gottingen-minipigs/
Training of minipigs to ensure stressfree handling, and better science	3 March 2022 3 pm CET*	**Stine Drent Larsen**, Animal Caretaker Novo Nordisk **Mie Berthou Johansson**, Animal Caretaker, Novo Nordisk	More information to come
Genetically modified SORL1 Göttingen Minipigs as a model for Alzheimers' Disease	3 May 2022 3 pm CEST**	**Charlotte Brandt Sørensen**, Lecturer, cand. scient, Ph.D., Aarhus University **Olav Michael Andersen**, Associate Professor, Department of Biomedicine, Aarhus University	More information to come.

* *Central European Time*
** *Central European Summer Time*

New publications on Göttingen Minipigs

Ellegaard Göttingen Minipigs gives high priority to collaborative projects that aim to better characterize and validate Göttingen Minipigs as a translational animal model and which facilitate and refine the use of Göttingen Minipigs in research projects and safety testing. Do you have an idea for such a collaborative project? Please contact ellegaard@minipigs.dk.

Allan Valenzuela, Claire Tardiveau, Miriam Ayuso, et al.
Safety Testing of an Antisense Oligonucleotide Intended for Pediatric Indications in the Juvenile Göttingen Minipig, including an Evaluation of the Ontogeny of Key Nucleases
Pharmaceutics 2021, 13(9), 1442
Doi: 10.3390/13091442
https://mdpi.com/1999-4923/13/9/1442

Simon Bentsen, Andreas Clemmensen, Mathias Loft, et al.
[68Ga]Ga-NODAGA-E[(cRGDyK)]2 Angiogenesis PET/MR in a Porcine Model of Chronic Myocardial Infarction
Diagnostics 2021, 11(10), 1807
Doi: 10.3390/diagnostics11101807
https://mdpi.com/2075-4418/11/10/1807/htm

Cláudia Correia, Qing-Dong Wang, Gunilla Linhardt, et al.
Unraveling the Metabolic Derangements Occurring in Non-infarcted Areas of Pig Hearts With Chronic Heart Failure
Front. Cardiovasc. Med., 13 October 2021
Doi: 10.3389/fcvm.2021.753470
https://frontiersin.org/articles/10.3389/fcvm.2021.753470/full

Yuval Ramot, Michal Steiner, Yossi Lavie, et al.
Safety and efficacy of sFilm-FS, a novel biodegradable fibrin sealant, in Göttingen minipigs
J Toxicol Pathol 2021 Oct;34(4):319-330
Doi: 10.1293/tox.2021-0030
https://pubmed.ncbi.nlm.nih.gov/34629733/

Søren Østergaard, Johan F. Paulsson, Jacob Kofoed, et al.
The effect of fatty diacid acylation of human PYY3-36 on Y2 receptor potency and half-life in minipigs
Scientific Reports volume 11, Article number: 21179 (2021)
https://nature.com/articles/s41598-021-00654-3

Laura Tvilling, Mark J. West, Andreas Glud, et al.
Anatomy and histology of the Göttingen minipig adenohypophysis with special emphasis on the polypeptide hormones: GH, PRL, and ACTH
Brain Structure and Function volume 226, pages 2375–2386 (2021)
Doi: 10.1007/s00429-021-02337-1
https://link.springer.com/article/10.1007%2Fs00429-021-02337-1

Suzan Meijs, Martin Schmelz, Sigal Meilin, and Winnie Jensen
A systematic review of porcine models in translational pain research
Lab Anim (NY), November 2021
Doi: 10.1038/s41684-021-00862-4.
https://pubmed.ncbi.nlm.nih.gov/34650279/

Daniel Overhoff, Gregor Jost, Michael McDermott et al.
Low kV Computed Tomography of Parenchymal Abdominal Organs—A Systematic Animal Study of Different Contrast Media Injection Protocols
Tomography 2021, 7(4), 815-828
Doi: 10.3390/tomography7040069
https://mdpi.com/2379-139X/7/4/69/htm

Aravind Sundaramurthy, Vivek Bhaskar Kote, Noah Pearson, et al.
A 3-D Finite-Element Minipig Model to Assess Brain Biomechanical Responses to Blast Exposure
Front. Bioeng. Biotechnol., 17 December 2021
Doi: 10.3389/fbioe.2021.757755
https://frontiersin.org/articles/10.3389/fbioe.2021.757755/full

Sabrina Halecker, Julia Metzger, Christina Strube, et al.
Virological and Parasitological Characterization of Mini-LEWE Minipigs Using Improved Screening Methods and an Overview of Data on Various Minipig Breeds
Microorganisms 2021, 9(12), 2617
Doi: 10.3390/microorganisms9122617
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Haagdorens, M., Edin, E., Fagerholm, P, et al.
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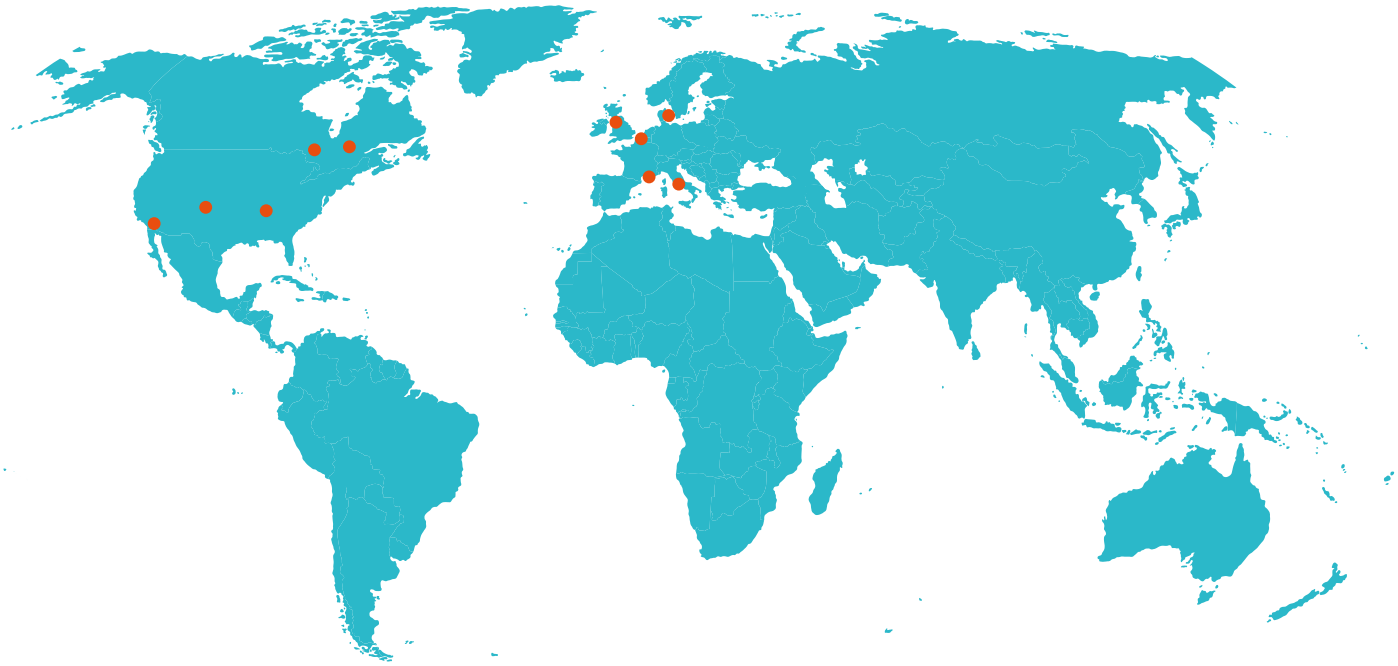
Doi: 10.1007/s40883-021-00220-3
https://plantscience.agri.huji.ac.il/publications/plant-recombinant-human-collagen-type-i-hydrogels-corneal-regeneration

Johannes Bech Steinmüller, Carsten Reidies Bjarkam, Dariusz Orlowski, et al.
Anterograde Tracing From the Göttingen Minipig Motor and Prefrontal Cortex Displays a Topographic Subthalamic and Striatal Axonal Termination Pattern Comparable to Previous Findings in Primates
Front. Neural Circuits, 26 November 2021
Doi: 10.3389/fncir.2021.716145
https://frontiersin.org/articles/10.3389/fncir.2021.716145/full

Where to meet us in 2022



CONGRESS / CONFERENCE	DATE	LOCATION
SOT 2022	27-31 March	San Diego, USA
IAT Congress 2022	29 March - 1 April	Harrogate, UK
Minipigs Research Forum (MRF) 2022	18-20 May	Dalmose, Denmark
Swine in Biomedical Research Conference 2022	10-14 June	Madison, Wisconsin, USA
FELASA 2022	13-16 June	Marseille, France
SPS Annual Meeting 2022	11-14 September	Montreal, Canada
EUROTOX + ICT 2022	18-21 September	Maastricht, Holland
AALAS National Meeting 2022	23-27 October	Louisville, Kentucky, USA
ACT Annual Meeting 2022	13-16 November	Denver, Colorado USA

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