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Göttingen Minipigs
MAGAZINE

ELLEGAARD
GÖTTINGEN MINIPIGS

Dear reader

During the Covid-19 pandemic the importance of animal studies has been highlighted by many scientists, research institutions and even in many public media. The situation of today with increasingly fewer Covid-19 restrictions and increased “normalization” is due to collaborative efforts of scientists all over the world and the use of thousands of animals; to whom we should all be thankful.

Reliable and translatable animal models are crucial for high quality research, which is the main topic for this issue of our Magazine. Several papers discuss the importance of such animal models and in addition highlight the relevance of genetically altered Göttingen Minipigs based models.

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There is no doubt, that the development and use of genetically altered Göttingen Minipigs will increase in the coming years. More and more models become available, and more and more models are in the pipeline, including exciting models such as the very promising humanized Göttingen Minipigs, which will become commercially available within a few months.

I am also very pleased to invite all of you to our Minipig Research Forum meeting in May 2022. For the first time ever, the event will be hosted at our breeding and research site in Dalmose, Denmark – and as usual with lots of eminent, scientific presentations and lots of networking opportunities.

Finally, I am looking forward to meeting many of you in the coming months at various scientific events and hope you will enjoy reading the Göttingen Minipigs Magazine.

Lars Friis Mikkelsen, CEO
Ellegaard Göttingen Minipigs A/S

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The vital need for a reliable animal model

The Covid-19 pandemic and the urgency of developing safe and efficient treatments for critically ill patients and a successful vaccine program, have more than ever highlighted the crucial need for biomedical research and the availability of reliable and translational animal models.

Even though species selection has been an area of immense focus for decades, a major review published in 2016 based on almost 10,000 clinical transitions (phase 1, 2, 3, or filing), showed a success rate of only 10%. Efficacy constituted the biggest share of unsuccessful transitions, as lack of efficacy alone was responsible for more than 50% of all failures. This review critically highlights that the translational value of the used animal models is insufficient, as it must be presumed that both safety and efficacy were established and confirmed in animal models before entering clinical trials.

Such misalignments between the used animal models and the outcome of the clinical trials could be explained by lack of access to relevant large animal disease models – or in other words: Access to large animals with the same disease or clinical state as the humans intended for the final medicine or treatment. So far, only few actual disease models have been available in the most commonly used large animal species (non-human primates, dogs and (mini)pigs), as only a limited number of naturally spontaneous occurring disease models or induced disease models has been available for preclinical research, apart from induced viral or bacterial infectious disease models.

Did you know...

Ellegaard Göttingen Minipigs A/S offers the opportunity to use Göttingen Minipigs as background strain for the creation of genetically altered minipigs based on:

- a case-by-case assessment
- approval of your specified project plan
- a description of the specific sequence of the targeting construct

Furthermore, Ellegaard Göttingen Minipigs offers contract breeding of genetically altered Göttingen Minipigs in their AAALAC accredited state-of-the-art research facility.

Litter of genetically altered Göttingen Minipigs.

In recent years, and partly due to the development of new techniques like the CRISPR/Cas9 technology, especially more and more genetically altered minipig disease models have been created as a supplement to the already huge repertoire of genetically altered mice models. Hopefully, over time these will facilitate the development of new medicines against fatal and debilitating diseases like cancer, Alzheimer's disease, and a huge number of rare diseases still accounting for the suffering and deaths of millions of people.

"I trust that the development of and access to genetically altered Göttingen Minipigs disease models with a specific "human-like" disease, like the newly characterized and now commercially available SORL1 KO model with a known phenotype in humans causing Alzheimer's Disease, might direct and support preclinical research aiming at a much more translatable approach", says Lars Friis Mikkelsen, CEO at Ellegaard Göttingen Minipigs A/S.

For decades Göttingen Minipigs have been used in biomedical research, with their many anatomical, physiological, and pathophysiological similarities to humans, and as such play an important role as a large animal model in translational studies.

In recent years, the number of genetically altered Göttingen Minipigs has increased, as advanced genetic techniques have simplified the generation of animals with precisely tailored modifications, designed to replicate genetic alterations responsible for a variety of human diseases.

RECOMMENDED PAPERS

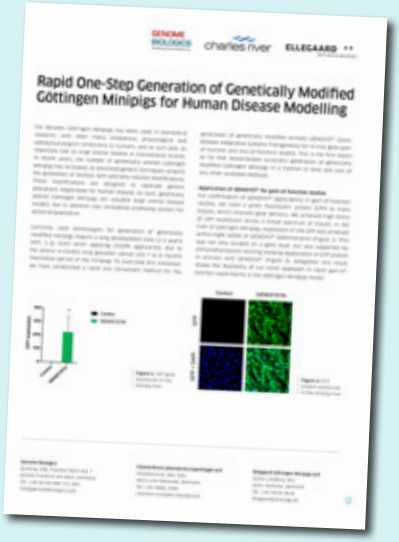
- *Andersen et. al:* In vivo evidence that SORL1, encoding the endosomal recycling receptor SORLA, can function as a causal gene in Alzheimer's Disease. Doi 10.1101/2021.07.13.452149
- *Berthelsen et. al:* The CRISPR/Cas9 Minipig–A Transgenic Minipig to Produce Specific Mutations in Designated Tissues. Doi 10.3390/cancers13123024
- *Habekost et. al:* Directly Reprogrammed Neurons Express *MAPT* and *APP* Splice Variants Pertinent to Ageing and Neurodegeneration. Doi 10.1007/s12035-020-02258-w
- *Maxeiner et. al:* Genomics Integrated Systems Transgenesis (GENISYST) for gain-of-function disease modelling in Göttingen Minipigs. Doi 10.1016/j.vascn.2021.106956

Whitepaper

Rapid One-Step Generation of Genetically Modified Göttingen Minipigs for Human Disease Modelling

One issue with the currently used technologies for the development of genetically altered minipig models, is the long term perspective due to the gestation and maturation period of minipigs. Therefore, a team of scientists has established an alternative and rapid method, called GENISYST®, for the generation of genetically altered animals.

Download the whitepaper: bit.ly/whitepaper-GENISYST



Göttingen Minipigs: A preclinical model to develop improved cell injection technologies

By Jasmin Knoll[1], Ruizhi Geng[1], Niklas Harland[2], Bastian Amend[2], Walter Linzenbold[3], Markus D. Enderle[3], Arnulf Stenzl[2], and Wilhelm K. Aicher[1,2]

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Urinary incontinence (UI) is a significant burden to the individuals affected. In Western countries 15% of the female and 10% of the male population suffer from UI. Based on distinct etiologies and pathologies, physicians discriminate between different forms of UI, stress urinary incontinence (SUI), urge urinary incontinence (UUI) and mixed forms. Clinically most important is SUI.

Introduction

SUI is associated in women with mechanical load and stress to the lower pelvic muscles during pregnancy and vaginal delivery, changes in tissue elasticity upon menopause, and inflammatory processes of the lower urinary tract. In men, prostate cancer surgery is the predominant risk factor to suffer from SUI. On a molecular level one could state that loss of functional nerval and muscle tissue controlling the bladder closure complex (= urethral sphincter) is the cause for SUI.

To support regeneration of the urethral sphincter function after e.g. vaginal delivery or prostate surgery, gender specific exercises and regimen for pelvic floor training were developed. Also, pharmacological therapy may ameliorate symptoms of SUI. If such regimen yielded no satisfactory improvement or fail completely, surgical interventions are an option. Such surgeries include implantations of tapes to stabilize the tissue or will employ artificial sphincters. But considerable numbers of patients report with problems caused by such implants. Therefore, in preclinical and clinical studies, SUI cell therapies were investigated.

Cell therapy for stress urinary incontinence

The sphincter complex controls continence and voiding. This is a complex process. To maintain continence, the bladder muscle must relax and the sphincter muscle must close tight at the same time. For voiding the bladder needs controlled contraction while the sphincter muscle must relax. In addition, continence must work without conscious nerve control by the brain. This is made possible by an interaction of nerves, hormones, smooth muscle tissue and striated muscles. Accordingly, different cell-based pre-clinical and clinical studies intend to address these different components regulating continence. The injection of skeletal muscle cells in the sphincter complex targets the deficient striated sphincter muscle, called rhabdosphincter. This is the muscle we control actively while awake and in upright posture. Injection of mesenchymal stromal cells aims to support the self-healing of the injured sphincter. This may include improvement of vascularization, suppression of fibrosis, regeneration of peripheral nerves, the striated as well as smooth muscle tissues of the sphincter complex. The smooth muscle, called lissosphincter, is important for continence while asleep. In our preclinical animal study, we therefore investigate both arms of cell therapy.

Image 1 and 2
Göttingen Minipigs in their stable at about 9 months of age.

Image 3
Göttingen Minipig at about 9 months of age in the pre-clinical surgery setting for inducing experimental urinary incontinence in deep anesthesia under controlled respiration.

The Göttingen Minipigs SUI model to investigate cell therapies

Göttingen Minipigs inherit several well-known advantages as an animal model in biomedical research. Only the most important aspects merit mentioning in the context of our pre-clinical studies: At about 9 months of age Göttingen Minipigs are big enough to allow transurethral surgery with the normal instruments employed in patients' surgeries. This facilitates preclinical testing of real prototypes such as improved diagnostic tools to determine SUI or novel technologies to precisely apply novel active components, including cells. We therefore employ female Göttingen Minipigs to induce SUI-like symptoms mimicking female SUI by surgical dilatation of the urethra and mimicking male SUI by local injury of the sphincter muscle. Standard clinical instruments allow to measure the muscle strength in the urethra before and after SUI induction, as well as during follow-up by so called urodynamics. We can monitor severity of sphincter deficiency as well as spontaneous or therapy-induced functional tissue regeneration under conditions much closer to the clinical situation when compared e.g., to rodents, most popular animal models in biomedical research.

The Göttingen Minipigs SUI model is also very suitable to investigate cell therapy of SUI. The minipigs are big enough to target the small delicate sphincter muscle by transurethral route through an endoscope under visual observation. Again, the very same procedure – transurethral cystoscopy - is often used in clinical interventions in Urology. For injection of active components such as bulking materials, drugs and cells, needles are used routinely. We noted however, that upon needle injection cells are frequently not found in the region of interest. Therefore, a completely novel approach for cell injection was developed.

Development of a minimally invasive, needle-free, and precise cell injection technology

Patients often experience bruises after a blood draw from subcutaneous veins. The nurse or physician obviously has missed the vein even when looking and sensing at it. In adult women the sphincter muscle is only a few millimeters wide and thick. Therefore, intensive training and experience are required to precisely hit the tiny sphincter muscle in the urethra with a needle by aid of an endoscope. Surgeons have only limited control over the tissue penetration depth, when injecting cells or other medications by needles straight through an endoscope, despite visual observation. To evenly distribute cells in the tissue targeted, serial injections in close neighborhood were performed, thus increasing the risk of tissue damage and inflammation considerably. In addition, an injection needle always punches a hole in a tissue, facilitating outflow of the medication. This motivated us, to search for needle-free cell injection therapies.

Waterjet injections of isotonic liquids are routine in different disciplines of surgery. The waterjet technology is employed for instance to lift epithelial tissue from the mucosa or submucosa,

to separate connective tissue from blood vessels or nerves, to remove chronically inflamed tissues and thus facilitate wound healing. In all such applications an aqueous isotonic solution is used, possibly complemented by a dye, gel, polymer, or alike. The novelty of our approach is, to optimize the pumps, reservoirs, tubing, injection lance and nozzle to grant the injection of cells with high viability and efficacy not only ON but also IN tissues targeted. For injections of medication or cells by our novel waterjet technology, pressure and volume of the jet can be preset to the characteristics of the tissue targeted. We recently showed that cells can be delivered preferentially to the sub-mucosal connective tissue or closer the muscle layer of the porcine urethra. Other applications are currently under investigation. Göttingen Minipigs are an ideal candidate animal model in our future pre-clinical research for improved cell therapies.

Summary

Cell therapy of stress urinary incontinence is a promising regimen for patients that do not improve by current regimen. Many preclinical animal studies, employing mostly rodents, support the great potential of cell therapies for SUI. But in the past several clinical feasibility studies failed to provide clear evidence if cell therapies deliver superior outcome in human patients. By using Göttingen Minipig as a large animal SUI model we will bridge the contradictory outcome of preclinical and clinical studies. In addition, we investigate head-to-head the potential of both, stromal cells as well as striated muscle cells in a defined and controlled situation of urinary sphincter deficiency. Future studies include cell therapies employing different cells and targeting other organs.

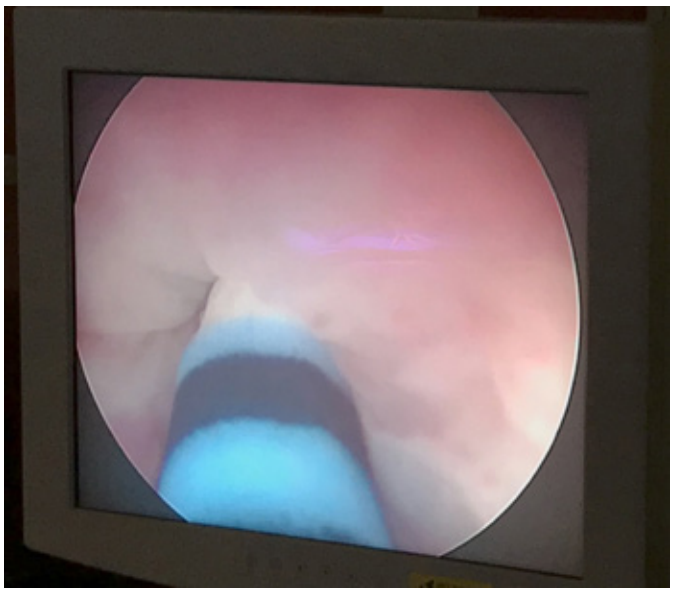

Image 4
Transurethral aspect by endoscope: Waterjet technology injecting cells in the porcine urethra. Injury and bleeding frequently observed after injections by Williams needles were reduced by injections of cells using the novel Waterjet technology. At the same time the precision of injection was elevated, and time for injection was reduced considerably.

Genomics Integrated Systems Transgenesis (GENISYST) for disease modelling in Göttingen Minipigs

By Jonathan Ward[1], Nemanja Ivanovski[1], Maria Duda[1], and Jaya Krishnan[1].

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For decades Göttingen Minipigs have been used in biomedical research. With their anatomical, physiological and pathophysiological similarities to humans, they have been successfully used in translational studies, for example as large animal models of human diseases[1,2]. Due to their small size, slow growth rate, genetic standardization, and superior health status, Göttingen Minipigs offer a cost-effective platform for disease modeling[3] and are therefore the preferred animal model as compared to domestic farm pigs.

Introduction

In recent years, the number of genetically altered Göttingen Minipigs has increased, as advanced genetic techniques have simplified the generation of animals with precisely tailored modifications. These modifications are designed to replicate genetic alterations responsible for human disease. On the flip side, modern genetic engineering technologies for generation of genetically modified Göttingen Minipigs, are cumbersome and typically require a 2 to 3 years development period[4,5], even with the application of novel Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) approaches. As such, there is a need to overcome these limitations in order to expand the use of Göttingen Minipigs.

Our approach

To address the unmet need in rapid disease modelling in Göttingen Minipigs, we have developed an adeno associated virus (AAV)-based method for a quick, convenient, and effortless generation of precisely modified transgenic animals, called Gene- Disease Integrative Systems Transgenesis (referred to as GENISYST®). This approach enables rapid in vivo modification(s) of one or more genes, all within a single animal. Whilst GENISYST® has already been successfully used in rodents for in vivo assessment of gain- and loss-of-function of coding and non-coding genes[6,7], here we present the application of this technology in successful generation of genetically modified Göttingen Minipigs. This proof-of-concept study opens the flood gates to complex human disease modeling in Göttingen Minipigs for in vivo drug and target validation. Thus, our data demonstrates the feasibility, efficiency, and utility of GENISYST® for generation of physiologically relevant transgenic large animal models in a fraction of time and cost, as compared to other available methods.

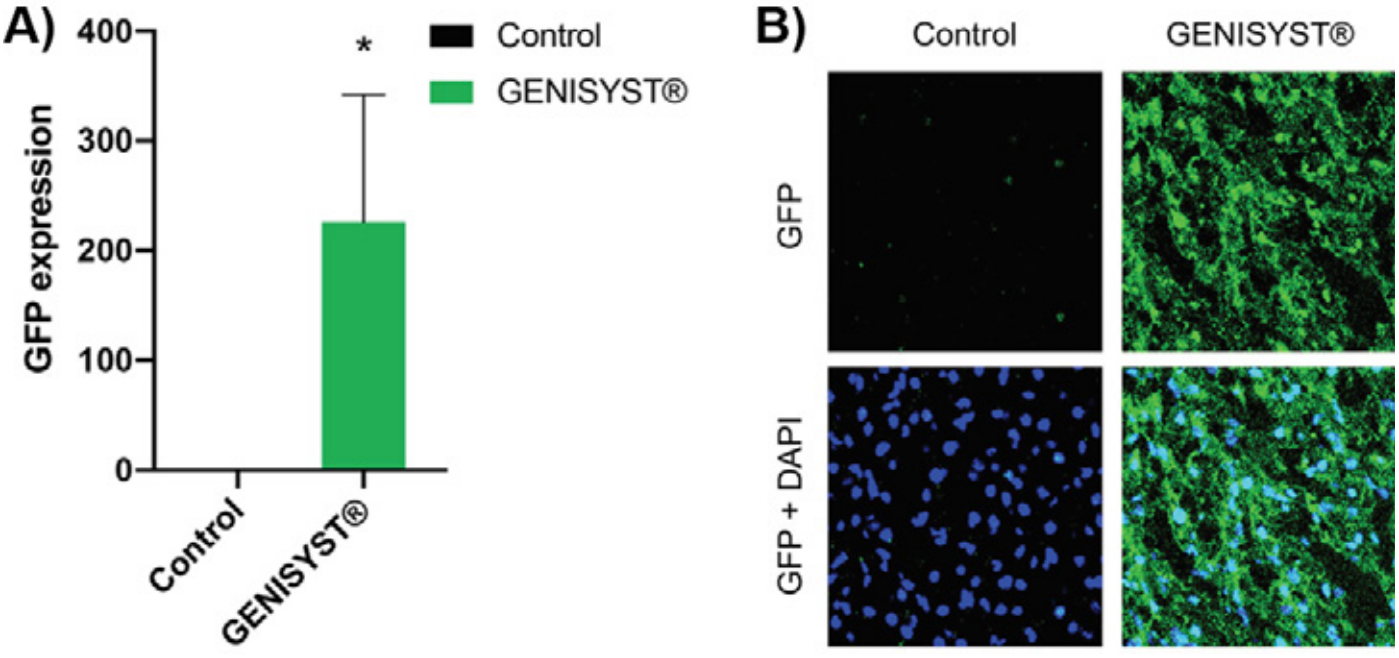

Figure 1
A) GFP gene expression, and B) GFP protein expression in the Minipig liver.

Results

Application of GENISYST® for gain-of-function studies

For confirmation of GENISYST® applicability in gain-of-function studies, we generated transgenic Göttingen Minipigs expressing green fluorescent protein (GFP) in multiple disease-relevant tissues including liver, heart, kidney, lungs, and the central nervous system (CNS). We have achieved high levels of systemic expression of GFP within weeks of GENISYST® administration across all tested tissues. This expression was evident on the gene level as well as on the protein level, as depicted in Figure 1. In conclusion, we have demonstrated the successful generation of gain-of-function Göttingen Minipigs model via an innovative and rapid GENISYST® approach. The detailed results from this study are now publicly available in the Journal of Pharmacological and Toxicological Methods[8].

Application of GENISYST® for loss-of-function studies

For confirmation of GENISYST® applicability in loss-of-function studies, we used a well-characterized disease model that results from the inactivation of PCSK-9 gene (Proprotein convertase subtilisin/kexin type 9)[9]. PCSK-9 is an enzyme of medical importance because of its activity in lipoprotein homeostasis[10]. Agents that block the action of PCSK-9, yield lower plasma concentrations of cholesterol, thus reducing the risk of liver and cardiovascular disease, including inflammatory Non-Alcoholic Steatohepatitis (NASH)[11]. Within six weeks of GENISYST® administration in Göttingen Minipigs, we have achieved a consistent reduction of PCSK-9 levels in the liver (Figure 2A).

Administration of GENISYST® has led to physiological changes in the affected animals that recapitulate previously reported hallmarks of PCSK-9 inactivation, such as significant reduction in blood cholesterol levels (Figure 2B)[9]. This data thus confirms the successful applicability of GENISYST® in disease modelling in Göttingen Minipigs for genetic loss-of-function studies.

Conclusions

The GENISYST® approach is a pioneering approach that demonstrates successful generation of genetically modified Göttingen Minipigs. GENISYST® facilitates accelerated generation of gain- or loss-of function human disease models in a broad spectrum of tissues, all while leading to a reduced number of animals being used. Altogether, the GENISYST® platform offers significant cost and time savings over traditional methods, while at the same time, reduces the ethical burden of animal experimentation.

GENISYST® technology is part of Genome Biologics integrated platform, where when combined with an AI-driven in silico analysis and a complementary validation platform that includes human cardiac organoids (TrueCardium™), offer an unprecedented hit-to-lead toolkit for a de-risked target and drug discovery and validation.

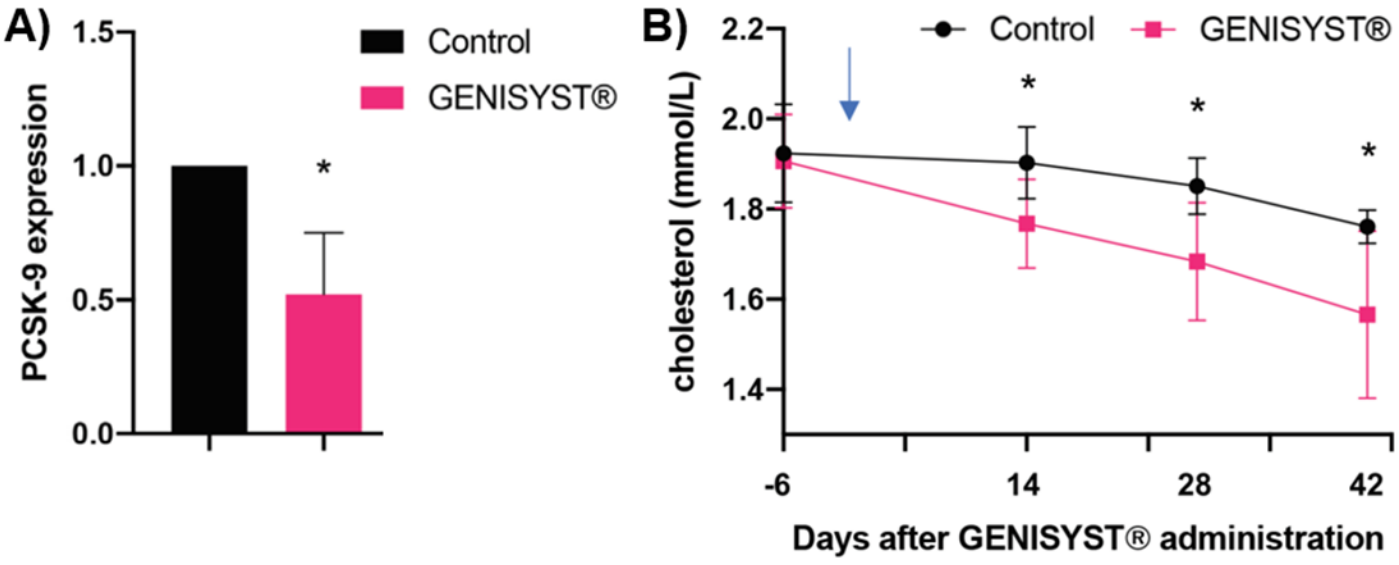

Figure 2
A) PCSK-9 gene expression the Minipig liver, and
B) cholesterol levels in the Minipig blood.

Image 1
Litter of genetically altered Göttingen Minipigs.

CONTACT

If you are interested in more information or discussing potential collaborations, please contact info@genomebiologics.com.

ACKNOWLEDGEMENTS

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Genetically modified Göttingen Minipigs for studying cellular mechanisms of age-related neurodegenerative disorders such as Alzheimer's disease

By Mette Habekost[1,2]

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Genetically modified animals and reprogramming technologies to obtain neurons from accessible cell types are useful tools for studying human neurodegenerative disorders such as Alzheimer's disease. In this regard, pigs may have the molecular advantage when compared to rodents in capturing specific features of the ageing human brain.

The neuropathological process of Alzheimer's Disease includes increased extracellular deposition of amyloid-ß (Aß) in so-called plaques and development of intraneuronal neurofibrillary tangles (NFT) of tau, which are linked to neuronal death (Grundke-Iqbal et al., 1987; Masters et al., 1985). Tau exists in six isoforms in the adult human brain, which are generated by alternative splicing of *MAPT* and differ by presence or absence of protein domains encoded by exon 2 and exon 3 in the N-terminal part (0N, 1N, 2N), and inclusion (4R) or exclusion (3R) of a microtubule-binding repeat encoded by exon 10 in the C-terminal part of tau. Genetically modified animal models of Alzheimer's disease are often generated in rodents, but a shortcoming of such models has been their lack of NFT formation, which may be explained by the absence of 3R tau isoforms in the adult rodent brain (Goedert et al., 1992; Dinkel et al., 2011). In our work recently outlined by Habekost et al. in Molecular Neurobiology we compared the expression of tau and Amyloid Precursor Protein (APP) isoforms during porcine and murine brain development and related these expression patterns to porcine neurons generated by direct reprogramming (Figure 1). In the following paragraphs, the highlights of this work are described.

We began our experiments by isolating RNA and protein from fetal and adult mouse and porcine cerebral tissues. To

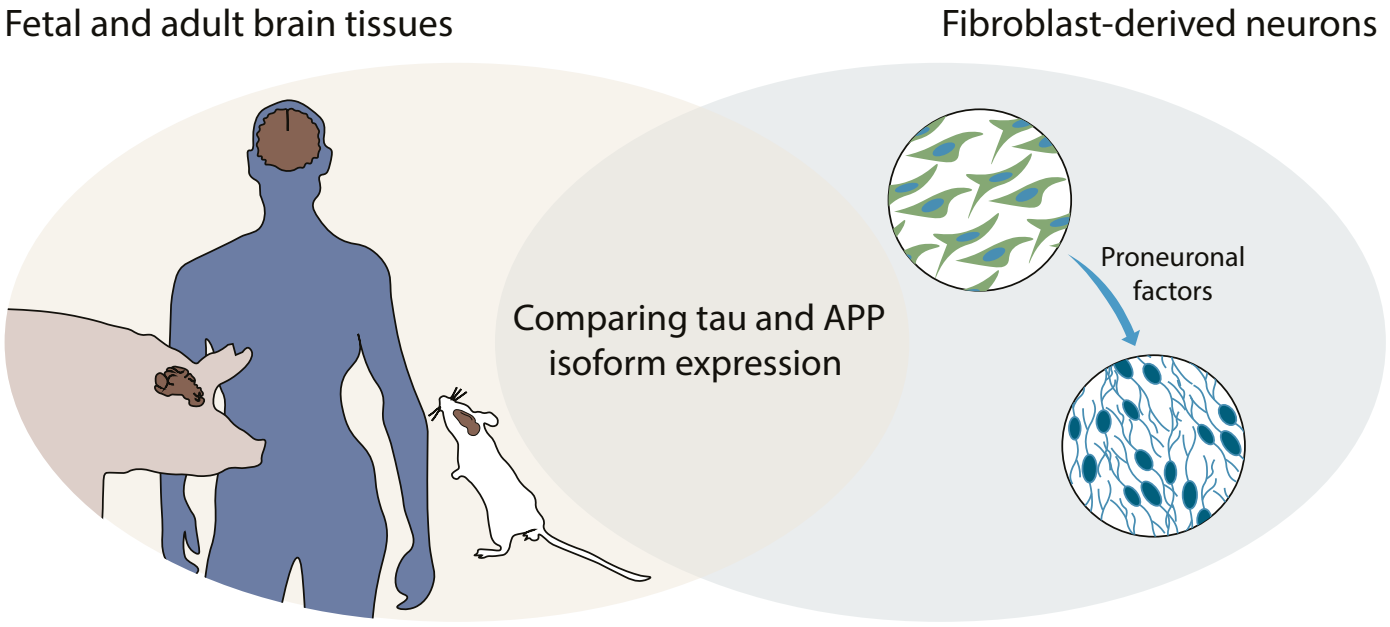

Figure 1
Schematic overview of the study reported by Habekost et al., 2021 in Molecular Neurobiology.

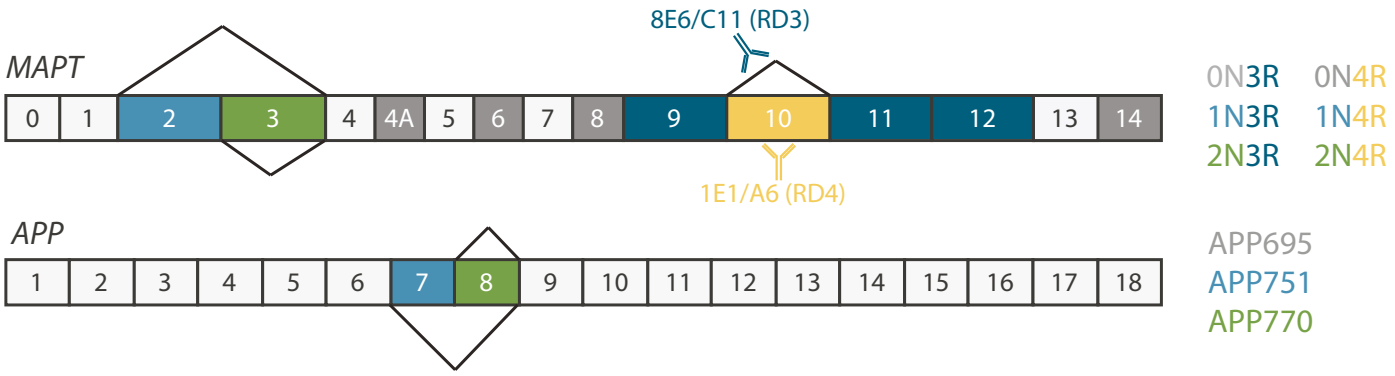

Figure 2
Schematic illustration of *MAPT* and *APP* exon structure.

capture the dynamics of *MAPT/Mapt* and *APP/App* alternative splicing in these tissues, we designed species-specific RT-PCR primers and used 3R- and 4R-specific antibodies to detect the expression of the three (APP770, APP751, APP695) and six (0N3R, 1N3R, 2N3R, 0N4R, 1N4R, 2N4R) main isoforms of APP and tau respectively (Figure 2). We found that the expression of 3R tau isoforms was conserved during brain development in mouse and pig, as in human (Goedert et al., 1989). By contrast, the adult mouse brain predominantly expressed the 4R tau isoforms, whereas the porcine brain with its composition of both 3R and 4R tau isoforms was more similar to the isoform expression in the adult human brain (Goedert and Jakes, 1990). Regarding *APP/App*, the shorter transcript representing APP695 was the main transcript being expressed in both species, consistent with its cell-type-specific distribution in neurons (De Silva et al., 1997).

These findings raised an intriguing question regarding which tau isoforms are expressed in reprogrammed neurons. It has been demonstrated that neurons derived from iPSCs are juvenile compared to the transcriptomic and epigenetic signatures of the starting cells. In contrast, directly reprogrammed neurons generated from fibroblasts by forced expression of transcription-factors, microRNAs or small molecules retain the ageing signatures present in the parental cells (Mertens et al., 2015). In publicly available RNA sequencing data, we found that human neurons generated from direct reprogramming of fibroblasts express the same *MAPT* transcripts as the adult human brain. To relate this finding to porcine cells, our group established a protocol for reprogramming porcine fibroblasts (obtained from skin biopsies from Göttingen Minipigs) directly into neurons that display several characteristics of postmitotic neurons (Habekost et al., 2020). We characterized the isoform expression of *APP* and *MAPT* and found changes in alternative splicing events during reprogramming of fibroblasts to neurons. Whereas the general gene expression level of *APP* did not change, the predominant transcript switched from APP770 in fibroblasts to APP695 in neurons. The expression level of *MAPT* increased during reprogramming, and the transcripts representing 3R and 4R tau were present in the reprogrammed neurons as in the adult porcine brain. In contrast, reprogrammed neurons generated from embryonic (E35) Göttingen Minipig fibroblasts mainly expressed 3R tau, supporting the notion that this methodology preserves the ageing signatures of the fibroblasts.

In a final set of experiments, we explored the applicability of the reprogrammed neurons as a disease model. We reprogrammed neurons from transgenic Göttingen Minipigs carrying the Alzheimer's disease-causing mutations *APPswedish* and *PSEN1M146I* (Jakobsen et. al., 2016). Fibroblasts from these animals express high protein levels of APP and ß-CTFs indicative of abnormal Aß production. The reprogrammed neurons derived from the transgenic fibroblasts showed no changes in reprogramming rates or neurite lengths but had significantly fewer neurites per neuronal cell compared to neurons reprogrammed from wildtype fibroblasts. In addition, we observed that the endogenous *APP* mRNA was spliced normally during the time-course of reprogramming (i.e. shifts to APP695). Quantification of Aß in the culture media detected increased Aß42/40 ratio compared to wildtype cells consistent with the effects of the *APPswedish* and *PSEN1M146I* transgenes, which indicates that the initial steps in the Alzheimer's disease pathogenesis are modelled in these neurons.

Our results demonstrate that the adult porcine brain and not the rodent brain expresses both 3R and 4R tau isoforms similar to the adult human brain. Thus, the porcine brain may have the molecular mechanism to produce NFTs upon stimulation, and future studies using porcine models of the disease are needed to examine this potential. We show that reprogrammed neurons generated from porcine fibroblasts recapitulate the age-dependent and cell-type-specific isoform expression of tau and APP, which highlights the use of this strategy for modelling specific ageing-related features on a cellular level, and we anticipate that this method may promote the use of the pig in neuroscience.

For more information see: Habekost, M., Qvist, P., Denham, M., Holm, I.E., Jørgensen, A.L., 2021. Directly Reprogrammed Neurons Express MAPT and APP Splice Variants Pertinent to Ageing and Neurodegeneration. Mol Neurobiol, 58(5), 2075-2087. doi: 10.1007/s12035-020-02258-w.

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Ellegaard Göttingen Minipigs Research Foundation: Donations in 2021

Supporting and participating in scientific research activities involving Göttingen Minipigs is a fundamental part of the business foundation at Ellegaard Göttingen Minipigs. Therefore, the Ellegaard Göttingen Minipigs Research Foundation was founded in 2016 to actively support these activities, and holds the main objective of providing financial funding for scientific research based around Göttingen Minipigs.

Criteria for funding

In 2021, the Ellegaard Göttingen Minipigs Research Foundation grants in total up to €50,000 to support activities that aim at characterizing Göttingen Minipigs or promoting the development of Göttingen Minipigs based disease models. In addition, projects that intend to improve animal welfare, focus on the 3Rs, and/or optimize handling or research techniques as well as educational and communication activities in relation to Göttingen Minipigs use may receive funding, as long as the project will generate significant background data and/or ensure knowledge dissemination and promote the use of Göttingen Minipigs in scientific research.

Supported projects in 2021

During 2021, the Ellegaard Göttingen Minipigs Research Foundation has supported three exciting and very diverse research projects:

- Multi-tissue RNAseq gene expression atlas in Göttingen Minipigs and the qualification of the model in toxicology and pharmacology.
- Liver status of adult female Göttingen Minipigs as a model for NFALD.
- In vivo evidence that SORL1, encoding the endosomal recycling receptor SORLA, can function as a causal gene in Alzheimer's Disease.

The outcome of all three funded research project will be presented in later editions of the Göttingen Minipigs Magazine.

Apply for funding

To learn more about the Ellegaard Göttingen Minipigs Research Foundation or apply for funding, please visit minipigs.dk or contact CSO at Ellegaard Göttingen Minipigs, Kirsten Rosenmay Jacobsen on krj@minipigs.dk.

Working with Göttingen Minipigs

How did you become aware of Ellegaard Göttingen Minipigs?
Having no direct experience within the area of biomedical research, I did not become aware of Ellegaard Göttingen Minipigs until a head-hunter recommended that I applied for the position as COO.

Why did you decide to apply for the position as COO?
I was looking specifically to join a Danish SME with international operations. Though I was not looking particularly for a family-owned business, it was important to me that it was a company with a strong set of values. After a bit of research, it became clear to me that this was a company of integrity, loyalty, and with a profound belief in their values.

What was your initial impression after your first day(s) at work?
My very first impression was extremely positive and reflected a clean, decent, and highly professional company. There is no doubt that welcoming the person to fill this position had been looked forward to with great anticipation, and I immediately felt welcome and expected. I quickly felt that working at Ellegaard Göttingen Minipigs is becoming part of a team - not "just" another headcount. Everyone has been so open-minded and willing to share knowledge from each of their areas of expertise. What I found likewise impressive is that this is a company who really understands what it takes to breed research animals for biomedical research and has a state-of-the-art facility to accomplish this.

Did your impression change when you experienced the minipigs up front and barriers from the inside?
On the contrary. Getting to see the barriers from the inside only confirmed the professional impression from the outdoor surroundings and seeing the surgery and research facility along with meeting the people who work there every day was

About the Operations Department
The Operations Department at Ellegaard Göttingen Minipigs has been subject to some recent organisational changes, incl. the creation of a new COO-position. The changes have been implemented to further strengthen the existing business but also to support future strategic initiatives.

The Operations Department includes all functions that relate to operational business functionalities, incl. order management, IT, finance, and the breeding facility. It thereby constitutes the biggest department at Ellegaard Göttingen Minipigs and counts around 40 employees.

In focus

Name Martin Windfeld Velin
Function COO at Ellegaard Göttingen Minipigs A/S

Education
MBA and Master in Military Studies

Background
After spending 18 years as an officer in the Danish army incl. 4 deployments, Martin decided it was time for a change of career. He then joined the Maersk organisation, first Maersk Drilling and later Maersk Supply Service.

Experience
Martin has a lot of experience working internationally, both during his time in the Danish army, but also while working within the international organisation of Maersk where he has been posted to both Ghana and Mexico.

very impressive. These are very professional and competent people. Experiencing the minipigs was also very affirmative: They were extremely happy, wagged their tales all the time, ran around playing - no doubt animals from an environment with a very high level of welfare. Also, the Animal Caretakers had a very calm and unstressed approach to the minipigs, and I am convinced that this is the result of a successful animal welfare programme that benefits both minipigs and staff.

What fascinates you the most about Göttingen Minipigs?
Their joyful, curious, and playful nature. Of course, a lot of work is put into facilitating this behaviour through their surroundings and animal welfare initiatives, but if you have ever experienced a conventional pig farm, you will recognise the contrast immediately. At Ellegaard Göttingen Minipigs the minipigs have a playroom and are only paired with other minipigs with whom they get along - to name a few initiatives from the huge animal welfare program.

What do you look forward to the most in your new role?
I look very much forward to further developing the international presence of the company. The process has already been started years ago, but I'm excited to contribute to the next steps of the journey. Learning about the potential within genetically altered Göttingen Minipigs and xenotransplantation has also been a very motivating factor, and even though my knowledge within these areas is limited, the knowledge and drive from my new colleagues have been a huge inspiration and I am excited to now become part of this adventure.

How can you make a difference in the company?
My skills will be no help within the breeding or research areas. But I can create the best possible settings, an economy and operation that works smoothly, so my colleagues can focus on practising their professional and technical knowledge, and abilities. Creating a secure framework around our core business is what I am good at.

Which of your experiences do you expect will benefit you the most?
That will have to be my experience from Mexico. I was stationed there with Maersk Supply Service with the goal of establishing the local department from scratch. I arrived with nothing but a credit card and left a fully functioning office set-up, meaning I know every detail of what is necessary to have a functional and thriving site.

How do you see the potential for Ellegaard Göttingen Minipigs?
Seen in the light of our high-quality products and services, this is a company of huge potential. Especially China, which might be one of the markets with the greatest potential and I look forward to being able to accommodate the demand from this market.

Spotlights

Publication

"Species selection for nonclinical safety assessment of drug candidates: Examples of current industry practice"

This newly published paper on species selection is an important and valuable read highlighting the importance of minipigs as an equal consideration as a large animal model for preclinical studies based on best practices within the industry.

Read the open access paper: Doi 10.1016/j.yrtph.2021.105029

Characterization of a genetically altered Göttingen Minipigs SORL1 knockout model for Alzheimer's disease

The Ellegaard Göttingen Minipigs Research Foundation has financially supported a project at Aarhus University in Denmark with the aim of developing and characterizing a genetically altered Göttingen Minipigs model expressing Alzheimer's disease.

The outcome of the characterization has recently been published (Doi 10.1101/2021.07.13.452149) and the model is now commercially available for scientists with an interest in studying the understanding of Alzheimer's disease and the potential treatment.

For more information about the SORL1 knockout model or information about the development of other genetically altered Göttingen Minipigs models, please contact CEO at Ellegaard Göttingen Minipigs, Lars Friis Mikkelsen at lfm@minipigs.dk.

Publication

"Safety Testing of an Antisense Oligonucleotide Intended for Pediatric Indications in the Juvenile Göttingen Minipig, Including an Evaluation of the Ontogeny of Key Nucleases"

Recent paper shows that Göttingen Minipigs are a promising nonclinical model for safety assessment in human pediatric treatment. This is an important paper, which yet again highlights the importance of Göttingen Minipigs as a translational non-rodent animal model.

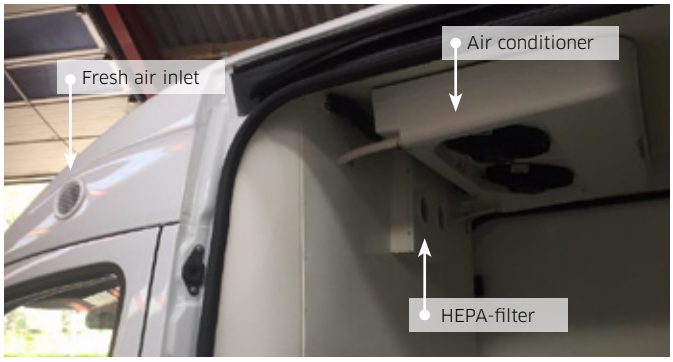
Read the paper: Doi 10.3390/pharmaceutics13091442

High transportation standards of Göttingen Minipigs

"We are used to explaining and documenting the isolated barrier facilities at Ellegaard Göttingen Minipigs. But the fact is that it does not stop there." Søren Vangsgaard, Head of Production and Facility Management at Ellegaard Göttingen Minipigs knows everything about the facility and conditions under which Göttingen Minipigs are bred and handled - from farrowing to delivery.

When the minipigs leave the facility, it is still with the aim to keep them as isolated as possible. Søren Vangsgaard explains: "Our cars have air filters installed, meaning only fresh HEPA-filtered air enters the cargo room where the minipigs are kept." Adding to this, the temperature in the cargo room remains constant under the entire transportation, and there is a slight positive pressure to make sure no unfiltered air enters through the air outlet. From the cabin, the driver can monitor and check that ventilation and temperature is within the required ranges, and if it changes, the vans have an alarm system, which immediately notifies the driver and the office.

Göttingen Minipigs are social creatures, so to make sure they feel safe and comfortable during transportation, they are only kept in transport boxes with "friends" from their own pen, and they always have water and plenty of bedding material at their disposal. The drivers attend to the minipigs every 4 hours and refill water, food, and bedding when needed. "Animal welfare is essential. Not only at our facility, but also during transportation. Therefore, we monitor the conditions in the cargo rooms and prioritise opening the doors frequently - even though this means letting in a bit of unfiltered air. This is the only way we can ensure the minipigs' well-being," Søren Vangsgaard says and elaborates: "We are very transparent about the transportation conditions, meaning the customer can always receive a copy of the temperature report and documentation of the inspections from the drive."



Health Monitoring Report: July 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: "We monitor the health of our colonies twice a year for a wide range of pathogens. In May/June we screen for selected agents, and in November/December we perform an extended analysis. For the latest report we are very pleased to confirm, that the July 2021 report shows no changes in the overall health status at our facility."

Download the full report from minipigs.dk/goettingen-minipigs/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.*

Subscribe to news and invitations

Receive invitations to webinars and scientific meetings, new Göttingen Minipigs Magazine publications and other news directly in your inbox, by subscribing to news from Ellegaard Göttingen Minipigs: minipigs.dk/sign-up-for-news

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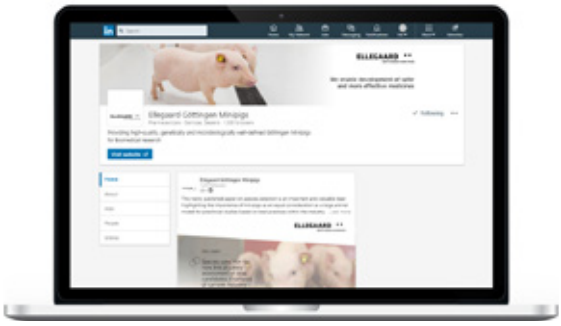
Add Ellegaard Göttingen Minipigs to your feed and be notified of:

- Scientific meetings
- Webinars
- Publications and research results
- Health status incl. Health Monitoring Reports, health screenings, accreditations etc.
- Project call-outs from Ellegaard Göttingen Minipigs Research Foundation



Attend webinars

If you are interested in specific topics, or you would like to share your knowledge or experience with Göttingen Minipigs in one of our webinars, please contact us on events@minipigs.dk

Topic	Date	Guest speaker	Register
Refinements in Minipig Inhalation Toxicology	26 October 2021 2 pm CEST*	Alice McNamara | Labcorp, UK	bit.ly/EGMweb211026
The Göttingen Minipig - a new model for gut microbiome	16 November 2021 3 pm CET**	Christian Kabel, University of Copenhagen, Denmark	More information to come.

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

The 14th Minipig Research Forum

Facility of Ellegaard Göttingen Minipigs A/S

Dates and venue | Mark your calendar:

18-20 May 2022
at Ellegaard Göttingen Minipigs A/S in Dalmose, Denmark

REMIND ME, WHAT IS MRF ABOUT?

The Minipig Research Forum is a unique opportunity for Göttingen Minipigs users to meet, discuss and share knowledge and experiences within all areas of minipig use related to biomedical research. Mark your calendar for this 3-day conference packed with scientific lectures, poster presentations and the opportunity of networking with minipig users from all over the world.

NOTICE

Stay updated on the full scientific program and for registration opening in January 2022 at the MRF website and the LinkedIn group.

WHY NOT A VIRTUAL MEETING?

A highly valued part of the MRF meeting is the chance for members to get acquainted, to meet in person, and talk to fellow scientists and users. This is a very important reason why we refrain from arranging a virtual MRF meeting. The MRF Steering Committee will continue to monitor the COVID-19 situation and of course hopes to conduct the physical meeting as planned in May 2022.

The MRF is one of my favourite conferences: Not too big, great people and networking.

Good mixture of science, practical topics, animal welfare and networking/ discussions.

My first MRF: Loved it totally and found everything to be very well organized.

ABOUT THE LOCATION

The event will be facilitated by and hosted at the site of Ellegaard Göttingen Minipigs A/S, located only 1½ hours outside the city of Copenhagen and Copenhagen Airport, in the beautiful Danish countryside. During the MRF conference you will also get a unique opportunity to visit the breeding and research facilities of Ellegaard Göttingen Minipigs.

The MRF Steering Committee has pre-booked a number of hotel rooms within 15-20 minutes' drive from Ellegaard Göttingen Minipigs and will arrange shuttle busses during the conference days. You can book your hotel room when registering for the conference on a first come, first served basis.

The MRF is a non-profit organization with more than 500 members worldwide working with minipigs in industry, academia, and regulatory bodies. Participation in the annual MRF conference requires membership (membership is free of charge). Read more and apply for membership at www.minipigresearchforum.org

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.

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Doi: 10.3390/ijms22063286
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Front Hum Neurosci. 2021 Feb 3;15:618626
Doi: 10.3389/fnhum.2021.618626
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Genomics Integrated Systems Transgenesis (GENISYST) for gain-of-function disease modelling in Göttingen Minipigs
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Doi: 10.1016/j.vascn.2021.106956
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Doi: 10.3389/fimmu.2021.613810
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Doi: 10.1016/j.toxrep.2021.04.005
https://pubmed.ncbi.nlm.nih.gov/33996503/

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Nutrients. 2021 May 6;13(5):1560
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Doi: 10.1371/journal.pone.0256208
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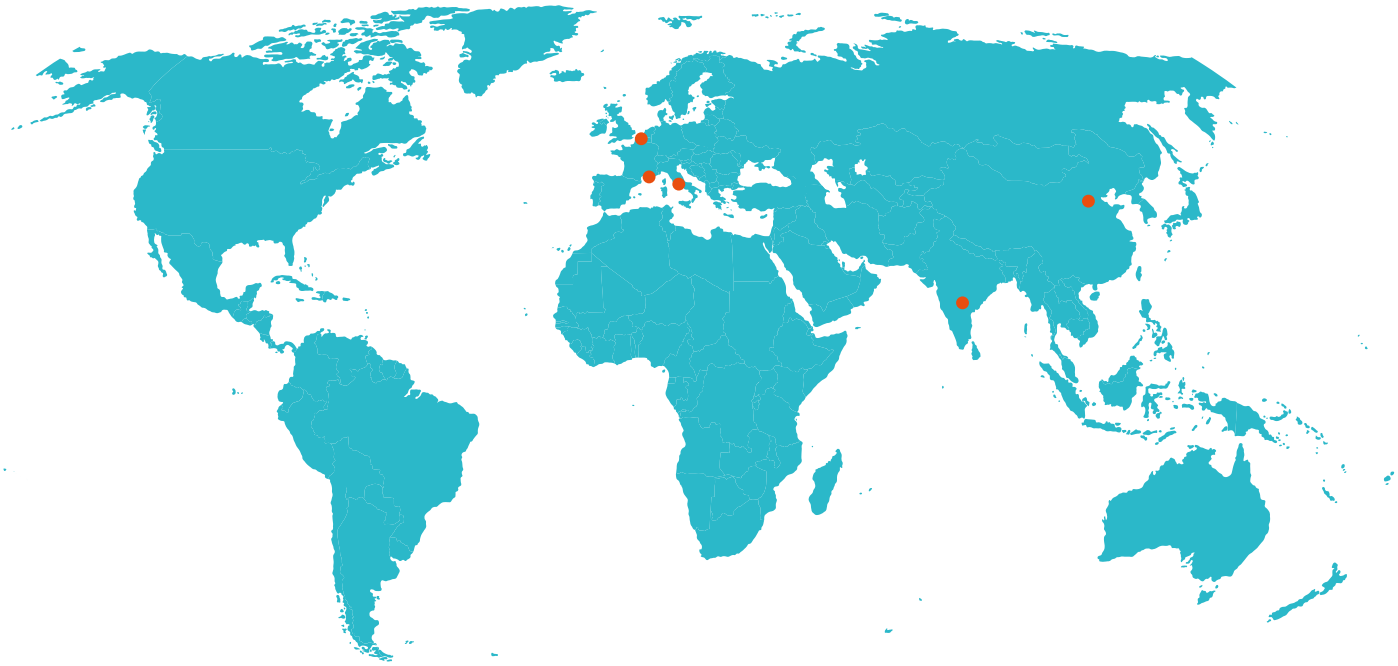
Where to meet us in 2021



CONGRESS / CONFERENCE	DATE	LOCATION
IAT	9-25 March	*Online event*
SOT and ToxExpo	15-25 March	*Online event*
Tierschutz-Tagung Travemünde	8-9 June	*Cancelled*
AFLAS	21-27 June	*Cancelled*
SBR	10-14 July	*Postponed to 2022*
World Congress (WC11)	22-26 August	*Online event*
GV-Solas IGTP	22-24 September	*Online event*
EUROTOX	26-29 September	*Online event*
Flanders Vaccine: Immunity for Health	14 October	Ghent, Belgium
STP-I	22-24 October	*Online event*
Joint Scientific Symposium (ERBC and Ellegaard Göttingen Minipigs)	28 October	Rome, Italy
CALAS	2-5 November	Taiyan, China
3R's Research and Progress	18-19 November	*Online* / Hyderabad, India
AFSTAL	30 November - 2 December	Marseille, France
LASACON	TBA	TBA

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