



This year we celebrate the 30-year anniversary of Ellegaard Göttingen Minipigs A/S. 30 years of collaboration, growth, and progress.

Collaboration lay the foundation of the entire company - and is one of our core values. In the 1980s and '90s a collaboration with the George-August University in Göttingen, made it possible to establish a company around Göttingen Minipigs - a close collaboration that remains strong today.

Growth throughout the years has been a confirmation of the potential and importance of Göttingen Minipigs in biomedical

research. But it has required investments, risks, and a lot of hard work to accomplish this.

Progress and development have defined Göttingen Minipigs in the world of science, but also Ellegaard Göttingen Minipigs' ability to adapt and meet market expectations in terms of animal welfare, health status, surgically prepared Göttingen Minipigs and an always high quality product. Opening of a Research Facility in 2016 and now offering genetically altered minipigs is just another testimony to our development.

This entire edition of the Göttingen Minipigs Magazine has been dedicated to celebrating these past 30 years. You will get the history behind the company, an article describing the importance of pigs in biomedical research today, and a selection of topics and papers that illustrate some of the areas in which Göttingen Minipigs have excelled through the years.

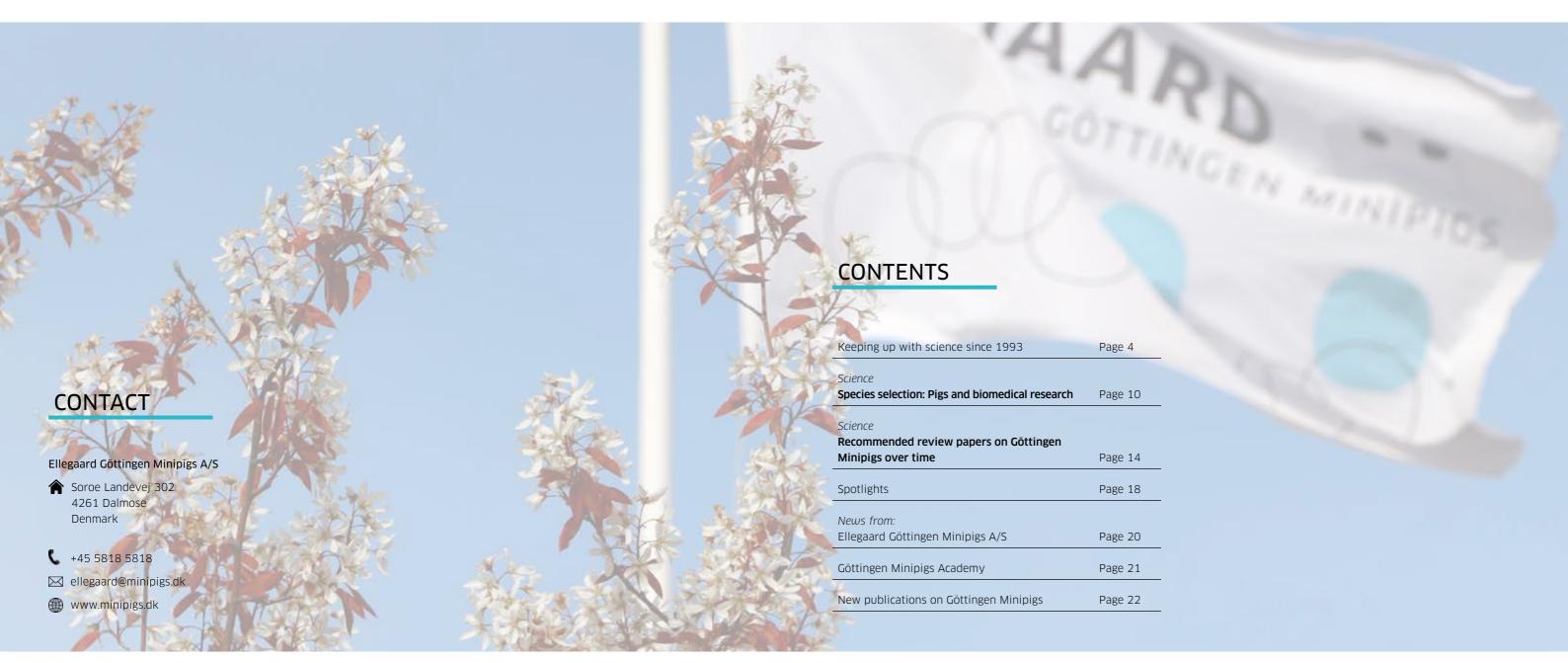
There is no doubt, that we have come far in our first 30 years, so I am excited to see where the next 30 will bring us. For the near future we have news of more progress, which I look very much forward to sharing with you. But until then, let's celebrate the period 1993-2023.

Congratulations to Ellegaard Göttingen Minipigs!



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Martin Windfeld Velin, CEO Ellegaard Göttingen Minipigs A/S



Keeping up with science since 1993

Over the last 30 years, Ellegaard Göttingen Minipigs has gone from being an agricultural enterprise with production of conventional pigs to a leading international supplier of microbiologically defined minipigs for biomedical research. A unique transformation, that has not been seen before at any other pig breeding facility.

The company Ellegaard Göttingen Minipigs was founded in 1993 to breed and distribute Göttingen Minipigs for the biomedical research industry. But the story begins decades before, and what happens in this period is essential for the history of the company.

Germany, the 1960s | The minipig that came to be

The George-August University in Göttingen, Germany is looking into how to meet the pharmaceutical industry's growing demand for a better non-rodent animal model, than what is already available. Such an animal model should have many similarities to humans, a high-quality health standard, well-defined genetics, and be small and easy to handle. They crossed the Minnesota Minipig with the Vietnamese Potbelly, attractive for their small size and reproductivity respectively, which resulted in small, multi-coloured offspring. The newly bred minipigs were then back-crossed with the German Landrace to introduce the light pigmented skin, and in 1969 the development of the new race was complete and named "Göttingen Minipigs".

Denmark, the 1970s | Eyeing new markets

In 1971 the SPF-system is established in Denmark and Lars Ellegaard, a Danish breeder of conventional pigs, rederivates



The Ellegaard farm before the foundation of Ellegaard Göttingen Minipigs.



2001 Ellegaard Göttingen Minipigs with office building, Barrier 1 and first part of Barrier 2

his herd to SPF status in the mid-seventies. Based on this new status, he receives an enquiry from Novo Nordisk about SPF pigs for insulin research. After a few years of positive cooperation, Novo Nordisk requests a minipig instead, as the conventional pigs grow too fast and are difficult to handle. After doing some research, he enters into dialogue with the George-August University about breeding and distribution of their recently developed minipig, which is the smallest known minipig breed in Europe.

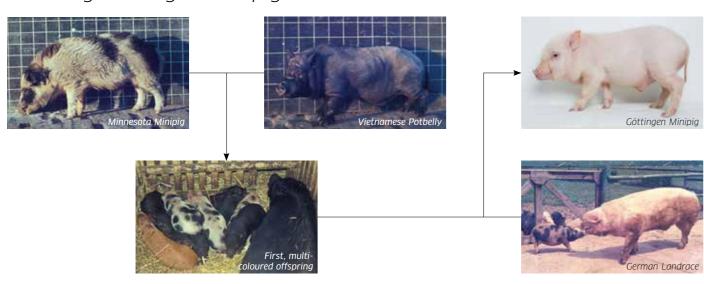
1980s | Early collaborations

Negotiations between Lars Ellegaard and the university in Göttingen are successful, and in December 1982 a small herd of conventional SPF health status is imported from Germany. The herd, consisting of 40 sows and 15 boars, allows Lars Ellegaard to become acquainted with and adapt to industry demands. Together with his wife, Bodil Ellegaard, he invests further in

the production and sales of Göttingen Minipigs to the Danish, Norwegian and Swedish markets, where he has now obtained exclusive rights. Though the industry is conservative and does not easily adopt a new animal species, Lars Ellegaard is persistent and has strong beliefs in the potential of the small minipigs.

Meanwhile, the health status at the university in Göttingen is declining and is starting to affect the reputation of Göttingen Minipigs. With his growing understanding of the industry's demands, Lars Ellegaard creates a new business model, which raises the bar significantly regarding expectations to health status and breeding. He enters into new negotiations with the university with the aim of separating commercial production from genetic management - and increasing the rights of his company: Ellegaard Forsøgsgrise (trans. Ellegaard Research Pigs).

Breeding Göttingen Minipigs





Mid-late 1980s Göttingen Minipigs of conventional SPF health status imported from Germany.



Mid-late 1980s Lars Ellegaard delivering Göttingen Minipigs from the back of his pick-up truck.



Prof. P. Glodek, Georg-August University, Göttingen hands over a plaque to Lars Ellegaard at the official opening of Barrier 1



The plaque still adorns the wall for everyone to see, as an important part of the company inheritance.



First caesarean section establishing the high health status and the herd still in breeding today.

Early 1990s | A new beginning

Late 1991, early 1992 an agreement is in place: Ellegaard Forsøgsgrise obtains exclusive rights for global production, sale, and distribution of Göttingen Minipigs, while the university in Göttingen is in charge of genetic management.

In order to increase the health status, Ellegaard Forsøgsgrise imports 36 pregnant sows from Göttingen to create the foundation of the new breeding strategy. The sows undergo caesarean sections under sterile conditions, and the around 230 new-born piglets create the basis for the herd still in breeding today.

At first, the new-born microbiologically defined Göttingen Minipig piglets are housed in customised dairy truck containers with filter ventilation, shower, air locks, and chlorinated water. They have an unprecedented high health status for pigs and Lars Ellegaard is determined to maintain the high health status.

14 May 1993 the company Ellegaard Göttingen Minipigs is founded. A board of directors is established with profiles specialised within finance, science, and sales.

The very first breeding barrier, Barrier 1, is constructed and ready to receive its new inhabitants in late 1993. The barrier has a comprehensive list of installations ensuring a clean, bio secure environment for the minipigs such as filtered air intake, irradiation of incoming water, slight positive pressure in case of leakage, and a procedure for the staff involving showering and complete change of clothes.

Late 1990s | New paths

The first scientific employee is hired. At the time, the tasks include much more than merely scientific work, but historically speaking, this turns out to be the first step in changing the company's path: Until then, Ellegaard Göttingen Minipigs had been a company focused on production and sales through breeding Göttingen Minipigs, but with this recruitment began the journey into the pharmaceutical industry, indicating an intention to engage and collaborate with scientists, not just supply.

In 1998 business is good. So good, that production is expanded by building an additional barrier, Barrier 2, and adding an office building to the facility. Until now, management has been conducted from the Ellegaard farm on the neighbouring land register, but at this point it makes sense to gather all functions in one location.

To emphasise the importance and quality of Göttingen Minipigs' health status, animal welfare, working environment and standardised production, Lars Ellegaard applies for the AAALAC accreditation. The accreditation is received in 1998 and has been maintained ever since.

At the same time, marketing activities are commenced in the USA and a quarantine station is established in Pennsylvania with the capacity of housing 100 imported Göttingen Minipigs at a time. Lars Ellegaard's son, Jens Ellegaard, becomes involved in developing the American market, but as it turns out the quarantine station does not provide a sufficient level of supply safety for the industry's high demands, the company is forced



Lars Ellegaard as the driveway is being paved to the new Barrier 1.



1994 The entire staff in front of the entrance to Barrier 1.

to look at alternative solutions. To accommodate the demand for local breeding and a certain consistency of supply, Jens Ellegaard starts looking for an American partner.

2000s | Rapid growth

In 2002 the first licensed breeding agreement is entered with Marshall Farms (later Marshall BioResources) for the American market. Marshall Farms is also a family-owned business with experience breeding ferrets and beagles for biomedical research since 1939.

In 2003, 175 sows and 25 boars are transported to Upstate New York, USA, to create the foundation of the new Göttingen Minipigs breeding herd. Jens Ellegaard remains with Marshall Farms to transfer knowledge and establish the new production and sales set-up based on experiences and instructions defined by Ellegaard Göttingen Minipigs.

Back in Denmark, business continues to grow, so the management building is expanded, and Barrier 2 is tripled in size. In 2004 Jens

Ellegaard returns to Denmark after 3 years in the USA to take over management of Ellegaard Göttingen Minipigs - a succession, which has been planned carefully and in consideration of the company's continued growth and development. Lars Ellegaard steps back but remains in the company with responsibility for sales.

The demand for Göttingen Minipigs continues to grow in Europe, so a few years later, in 2008, the construction of yet another barrier is commenced. With the new Barrier 3, Ellegaard Göttingen Minipigs can ensure a consistent supply to the industry as it has now doubled the facility's breeding capacity.

2010s | International and scientific focus

Now that Ellegaard Göttingen Minipigs has become well-established in Europe and is well on it's way in the USA, the time is now to look to the East. In 2010, a license breeding agreement is signed with Oriental Yeast Company in Japan and a breeding facility is established here as well. In 2014, Jens Ellegaard signs an agreement of distribution with WOOJUNGBIO in Korea. During the



The first AAALAC accreditation, which has been maintained ever since.



2003 Lars Ellegaard preparing transport boxes for the shipment of the breeding herd to the USA.



Lars Ellegaard officially handing over the management of Ellegaard Göttingen Minipigs to Jens Ellegaard.

2010s, Ellegaard Göttingen Minipigs expands their international presence further, through activity in India, Israel, and China.

8 years after Lars Ellegaard handed over management of Ellegaard Göttingen Minipigs to Jens Ellegaard, time has come to withdraw from the company completely, and thus Lars retires in April 2012. Jens remains CEO of the company until 2014, when he decides to hire a CEO to take care of daily business, while he focuses on the overall strategic work as Chairman of the Board of Directors. The board still consists of profiles within finance, science and sales, but profiles with knowledge of internationalisation and later sustainability and ESG also join the board.

Over the last two decades, Ellegaard Göttingen Minipigs' engagement in scientific research has increased steadily, and the potential grown correspondingly. The company starts engaging actively in research projects and through the establishment of the Ellegaard

Göttingen Minipigs Research Foundation in 2016 grants financial funding for scientific research based around Göttingen Minipigs. Taking the scientific engagement even further, the construction of a research facility has been in process for a while. In 2016 it is complete, offering a state-of-the-art surgical suite and housing facility for Göttingen Minipigs involved in research projects. It is the original Barrier 1 that has been reconstructed for the purpose and is now renamed Barrier 5. With the research barrier, Ellegaard Göttingen Minipigs is no longer only a breeder, but has now become a scientific partner, offering advanced services to facilitate research and collaborative efforts to support client studies, incl.: Development and characterisation of disease models, contract breeding of genetically altered minipigs, exploratory pharmacology studies, pre-implanted and neutered minipigs, diet and surgical induction, long-term housing of customer owned minipigs, and general open access to the surgical suite and scientific procedures.

2020s | Part of the future

In the early 2020s the activity level in the research barrier is increasing and now also include development of brand new transgenic Göttingen Minipigs models, in close cooperation with Danish and German universities and pharmaceutical companies: An Alzheimer's disease model; and the Humanized IgG Göttingen Minipigs carrying a mini repertoire of human Ig- $\gamma 1/\gamma 4$ heavy and the human κ light chain genes showing tolerance to a broad range of human or humanized IgG antibodies. Development continues and new promising models are on the way in the coming years, such as Göttingen Micropigs expected to be 60% the size of Göttingen Minipigs.

The management facility is, once again, expanded as there is a need for more office space and a place to host events. In 2021 this extension is finished, and Ellegaard Göttingen Minipigs now have a conference room with the capacity of housing up to 100 guests.

Focus on the American market and the potential to further develop the company's presence is increased. Therefore, in 2022,

the subsidiary Ellegaard Bioresearch Inc. is established, with the purpose of strengthening the knowledge of Göttingen Minipigs, the new transgenic models, and the scientific services available.

2022 is also the year for another new initiative: The Göttingen Minipigs Academy. The academy facilitates seminars and workshops based on a practical, theoretical, scientific, and hands-on approach and is conveyed by the experts employed at Ellegaard Göttingen Minipigs.

When expanding the facility over the years, sustainable and energy-saving solutions have always been a priority, and thus taking in the UN Global Goals for Sustainable Development is not unfamiliar. Examples include temperature regulation through geothermal heating and cooling, a straw-fired boiler as heat source and most recently planned investment in solar panels. However, in 2020 the company adopts a more structured approach and establishes four internal focus area groups to make sure sustainability is a joint responsibility for all employees.



2016 Fully equipped surgical suite in the research services facility at Ellegaard Göttingen Minipigs.



Examples of projects from the research barrier

Most studies are restricted by confidentiality clauses, but a few examples include:

An inhalation study performed at Ellegaard Göttingen Minipigs was part of the preclinical trials of a treatment of Covid-19 patients, which later moved on to clinical trials. In this treatment the patients would inhale an antimicrobial solution intended to treat infections, which helps the immune system to fight infections caused by bacteria or virus.

A diet-induced animal model of nonalcoholic steatohepatitis (NASH) in Göttingen Minipigs was developed a few years ago and have successfully been published. During recent years, the research facility has performed projects with NASH in Göttingen Minipigs, either as model validation or as pre-conditioning of minipigs with NASH, before delivering these to external partners. The large experience in diet-

induced models in the research facility combined with the possibility to harvest several liver-biopsies to monitor disease progression in NASH minipigs has been of high value for the projects.

A study looking to establish a new-born piglet hypoxia model to enable testing of the, to date unknown, juvenile pharmacology around new-born babies with hypoxia, who are treated with a mix of antiepileptics, sedatives, analgesics, and therapeutic hypothermia. The University of Antwerp needed a partner with the required facility and expertise, as the study must be performed within the first 24 hours of birth, and maintaining anaesthesia for 24 hours around the clock in new-born piglets was uncharted territory.

The laboratory and surgical suite has supplied numerous surgery services, such as neutering, pre-implanted Vascular Access Ports and Vascular Access Buttons, pre-implanted telemetric devices incl. Left Ventricular Pressure, but also training of the minipigs to walk/run on a treadmill or get accustomed to blood sampling.

Ellegaard Göttingen Minipigs anno 2023

Today Ellegaard Göttingen Minipigs is comprised of 3 barriers and a management building, and represent an international company serving as the global leader within the development, production and sale of Göttingen Minipigs for biomedical research and associated scientific services. This has been obtained by virtue of high health and quality standards, combined with high levels of knowledge, service, and trustworthiness.

The company remains focused on the four core values that lays the foundation for all activity:

Animal welfare, Quality, Respect and Collaboration This also forms the basis of the company's fundamental purpose:

Enabling development of safer and more effective medicines

This is obtained through belief in the value of scientific validity, research, background data and collaboration; investment in the development and accumulation of new knowledge about Göttingen Minipigs; and engagement in networking with scientists working actively with Göttingen Minipigs.

Species selection: Pigs and biomedical research

By European Animal Research Association (EARA).

This article is an extract from the article "Pigs and biomedical research" by EARA. The full article incl. quotations from prominent researchers can be found at eara.eu/pigs-and-animal-research.

There is a growing appreciation among the biomedical community of the value that pigs bring to research. Over the last decade, researchers and clinicians have increasingly seen how useful pigs are in many areas of research – for example, by providing organs for vital human transplants, improving our understanding of a range of diseases including cancer, and other applications like surgical training. The numerous similar characteristics of pigs to humans, such as the structure of their body, organs and genetics, also make them good choices for exploring and refining scientific techniques, and testing drugs for toxicity and safety, in both the lab and the clinic.

Introduction

In some cases, pigs can be more appropriate than other more commonly used animals in research, such as mice, and they are an animal that humans have lived and worked with for centuries, with well-understood welfare needs.

Biomedical research is also increasingly making use of a specially bred type of pig called a minipig. The smaller size of these pigs, compared to larger farm pigs, makes them easier to manage in a lab setting, while possessing more fitting characteristics for research, such as their genetics and temperament. One of the most common breeds of minipig used in Europe, especially in pharmaceutical research, is Göttingen Minipigs, derived from the crossing of three different breeds – and the biggest supplier is Danish EARA member Ellegaard Göttingen Minipigs.

In this article, we will outline the growing use of pigs as a biomedical research animal in Europe, including the current and emerging areas of biomedical study in which they play an important role. We will also look at what the field of pig research might hold for the future, such as medical and clinical developments to benefit human health, and biotechnologies.

Why do we need pigs in biomedical research?

Pigs have a lot in common with humans at the level of organs, genetics, body function and the immune system, so using pigs in research studies can predict similar results in humans, compared to other large animals or the most common research mammal, the mouse (read our feature about mice in biomedical research). For instance, the heart of a pig is very similar to our own in terms of size and structure and so are relevant to human cardiovascular research and can be suitable to use for heart transplant research.

Modern gene editing technologies mean that pigs can be genetically altered to make them more 'human-like,' or humanised, allowing biomedical research that can more accurately mimic the human body. For example, in research at lowa State University, USA, humanised pigs were designed without essential parts of the immune system, allowing human cells to then be transplanted into their livers. This could then improve drug testing for diseases such as cancer, as well as to develop techniques like skin grafts.

Genetic modification of pigs can ensure the success of organ transplants that otherwise would not be possible, because standard pig organs are rejected by the human body. Additionally, genetically modified pigs can be made susceptible to diseases that wouldn't usually affect them in the wild, such as Covid-19, to shed light on severe symptoms that researchers cannot directly investigate in people.

Which areas of biomedical research use pigs?

Pigs are being used in more research fields than ever, for instance there is now more available genetic data on the pig genome. This growing awareness of the benefits of pigs to research, coupled with advances in technology, has meant that scientists have been able to make increasingly more discoveries in medicine and basic research using pigs. The most common areas of use are in general surgical training, for testing and assessment for drug toxicity and pharmacology (how medicines work), for studies of the skin (such as wound healing), and exploring new ways that treatments can be delivered to the body.

Pigs are also useful for analysing different devices and procedures to treat various diseases, such as injections into the eye for retinal diseases, and exploring optimal or improved ways to monitor body functions – researchers at the Massachusetts and California Institutes of Technology, both USA, recently developed an ingestible sensor that could be monitored as it travelled through the digestive tract of pigs, to potentially diagnose gastrointestinal disorders without the need for invasive surgery.

There is increasing evidence to suggest that pigs are also good models for vaccine research and development since their immune systems closely resemble ours by around 80%. Work at The Pirbright Institute, UK, for instance, has shown that pigs can model the effects of vaccination against human flu, and identified different routes to administering flu vaccines to provide better disease protection.

Pirbright has also conducted trials on pigs for new Covid-19 vaccines, while EARA members Sanofi Pasteur, France, and Ellegaard Göttingen Minipigs, Denmark, demonstrated the value of using minipigs to study the long-term effects of vaccines against whooping cough, which can be a particularly dangerous infection for babies and children.



Image 1
Minipigs, that have been 'humanised' through genetic editing, are increasingly being used for toxicological testing and safety assessment of therapeutic antibodies, as there is a growing interest in antibody-drug development to precisely target cells or molecules related to disease.

As well as this, research in pigs can provide benefits to the health of pigs themselves. For example, the global VACDIVA consortium, co-ordinated by Professor José Manuel Sánchez-Vizcaíno, at EARA member the Complutense University of Madrid, Spain, is currently developing and testing vaccines against African swine fever, a deadly disease affecting pigs and boars.

Skin disease studies

One of the major research areas that has involved pigs are studies of skin diseases, such as psoriasis, skin reactions (including allergies), understanding how wounds heal, the best way to give dermal treatments (such as an ointment or cream), as well as ways to administer non-dermal ones, for example through an injection into the bloodstream.

Pigs are beneficial to such studies because of the similarity of their skin to ours, in aspects like thickness and composition, allowing more accurate safety assessments to be carried out into chemicals and other potential skin toxicities. This also means pig skin can be used to help with injuries, with a group from Linköping University, Sweden, using pig skin to make human cornea implants, which successfully improved people's eyesight in a 2022 clinical trial.

Gene editing

Genetically modified pigs are very valuable in the study of many diseases, often providing a more accurate picture of human ones – for instance, better reflecting the complexities of what happens in the human body than a standard pig or some other genetically modified research animals.

Gene editing techniques, such as CRISPR-Cas9, allow researchers to introduce modifications into cells and organisms at specific sites to target areas of interest. Some of the diseases that have been studied using genetically modified pigs include Huntington's disease. In 2019 research led by the Emory School of Medicine, in Georgia, USA, successfully expressed in pigs one of the key genes that causes the disease - to model its neurodegenerative effects - to help study how Huntington's develops and identify possible routes to therapy.

Cystic fibrosis (CF), is another condition that has been well-studied in pigs thanks to gene editing. Pig and human lungs have a close resemblance, and pigs can be engineered to develop some of the same effects of CF, including all the symptoms of lung disease – the main cause of death from the condition. Gene editing in pigs also helps to refine and improve therapies for CF in humans, (since it is caused by a faulty gene) by using them to improve how efficiently the CRISPR-Cas9 gene-editing tool can be delivered to the right place in the body to carry out the gene editing.

Training for surgery

Due to the many similarities shared between the pig and human body - from the teeth and skeleton to organ and blood systems - pigs are one of the standard animals used to train surgeons in often crucial and complicated procedures.

In combination with technology such as simulated training environments and robotics, animals can allow for best performance and practices in surgery, while moving away from training on human patients altogether. This invaluable training is carried out by organisations such as EARA member the Orsi Academy, Belgium, where pigs are put under anaesthetic, with a team of animal caretakers and veterinarians to ensure that their welfare and ethical needs are being addressed and met.

Cancer, heart disease and other conditions

Pigs have helped in the understanding of cancer by mimicking how certain diseases and malignancies, such as heart disease and brain tumours, work or react to drugs in humans. Research led by the Technical University of Munich, for example, is using genetically edited livestock pigs to study a range of cancers, including colorectal cancer, osteosarcoma (a major form of bone cancer) and pancreatic cancer.

Research into cardiovascular disease and heart conditions has made use of pigs to provide key insights into their management and treatment - such as in tackling heart failure by helping the heart muscle to repair itself, carried out by scientists at Baylor College of Medicine. in Texas. USA.

Infection and nutrition studies

Using common waste products from the livestock industry,

researchers have also been able to study infections. One example is a team at the University of Sheffield, UK, which investigated how bacterial, viral and fungal infections affected pig eyes and could lead to blindness, and serving as a guide to develop effective antibiotics.

Because what we eat can influence our risk of certain diseases like cancer, pigs can also provide vital clues to healthy (or unhealthy) lifestyles, and allow researchers to study conditions related to diet, such as obesity and diabetes. And as a large animal that can be fed a similar diet to humans, pigs are well suited to nutrition studies and research into the microbiome - the community of bacteria within us that is significantly impacted by diet and increasingly recognised as important in everything from digestion to a healthy immune system.

By studying the pig microbiome in the gut, the PIG-PARADIGM project, involving researchers from Denmark, the Netherlands and USA, is addressing the global health threat of antibiotic resistance by advancing understanding of how to prevent resistant bacterial infections in piglets and reduce the need for antibiotics.

Stem cells

In biomedical research, stem cells - which have the ability to develop into many different specialised cell types - are a promising technology that can be used to do everything from studying diseases to making regenerative medicine (replacing diseased cells with healthy ones). Pigs tend to have stem cells that are similar to humans, such as in the colon, again increasing the chance that they can be successfully applied to humans.



Image 2 Surgical training.



Image 3 Göttingen Minipigs at facility.

Researchers at the University of Maryland, USA, demonstrated for the first time in 2020 that pig stem cells, when injected into pig embryos, could solely lead to the development of the gut and liver - raising the possibility of growing human-specific organs in pigs. And in pig research carried out at the University of Georgia, USA, which provided new insights into stroke, transplanting stem cells into the brain was found to improve harmful stroke symptoms.

Stem cell research has the potential to benefit pigs too - 2022 research led by The Roslin Institute at the University of Edinburgh, UK, for example, showed that pig-derived stem cells can provide an almost limitless supply of the cells to help combat infectious diseases affecting pigs.

Although stem cell research has historically been more established in mice, monkeys and human cells in the lab, the increasing potential of pigs makes it likely that more efforts and practices to implement their use will emerge in the future.

Organ transplants and donation

Organ transplants are becoming increasingly possible, thanks to the dramatic advances in biomedical knowledge and medical expertise. However, a shortage of human organs available for patients needing a transplant is a growing concern.

It is now likely that animal-to-human transplantation (xenotransplantation), using genetically modified pig organs such as the heart, kidneys, liver and lungs, will be regularly possible in the near future, saving countless lives.

By modifying pigs to have a similar genetic background to humans, researchers can also prevent pig organs from being rejected during transplantations, increasing the availability of organs for crucial medical procedures and make transplants a reality for more people.

A kidney transplant (the most in-demand organ for transplants) was the first successful xenotransplantation from pigs to humans, in a surgery carried out by doctors at New York University (NYU) Langone Health, USA, in 2021.

The heart and blood system of pigs and humans work in a remarkably similar way, making hearts from pigs by far the most explored and used in these types of procedures, compared to other animal organs. Another major milestone in animal-tohuman organ transplantation was achieved using a genetically modified pig heart, with the patient surviving for two months following the procedure - longer than ever achieved before. This operation was conducted as a last treatment option for the patient, who would otherwise have died from terminal heart disease.

Researchers at Yale School of Medicine have also recently managed to revive hearts from dead pigs to further increase the amount of potential organs for transplants and donations, while 2016 work at the University of California, Davis, USA, developed pig embryos with human cells as a way to grow human organs in pigs.

The solutions that pig organs are now providing for organ transplant has led to plans for their regulatory approval, including for clinical trials of xenotransplantation by the US Food and Drug Administration (FDA). Clinical trials are needed to test and evaluate how well a medicine or therapy works in the general population, with the goal of establishing it as an approved treatment - provided it is shown to be beneficial and

Can pigs replace the use of dogs and monkeys in some research?

There is evidence that pigs are becoming more favoured over other types of large research animals, such as dogs, which have historically been used as a standard animal model in areas such as training for surgery and cardiovascular research. In brain research, scientists are increasingly using pigs to study brain diseases - sometimes instead of mice. Pigs are also being viewed as an alternative to monkeys in some areas of pre-clinical research, such as in the testing of treatments for therapeutic antibodies

As the use of pigs continues to grow and replace other animals in research across Europe and worldwide, it seems likely that they will open new doors to what researchers can study and achieve, particularly for human medicine and biotechnologies.

As with all species of animal used for research in Europe and elsewhere, consideration of their welfare is required by law to minimise any pain they experience during research, and the principle of the 3Rs (Replacement, Reduction, Refinement) is applied to lower the number of animals used where it is possible. In surgical training, for example, where pigs are commonly employed, measures such as organ harvesting after procedures can help to reduce the need for additional pigs in other training settings.

FULL ARTICLE

To read the full article go to <u>eara.eu/pigs-and-animal-research</u>.

Science

Recommended review papers on Göttingen Minipigs over time

Over the last 30 years, hundreds of scientific papers have been published about studies involving Göttingen Minipigs, proving the relevance of this non-rodent animal species in biomedical research. On the following pages, a selection of papers has been grouped in topics to illustrate areas in which Göttingen Minipigs have excelled. It is important to note, that the list of topics and papers is far from complete but includes an excerpt of papers with a more general approach, which have contributed to the general understanding and characterisation of Göttingen Minipigs as a large animal model.

Ellegaard Göttingen Minipigs strives at collecting all available knowledge and relevant publications about Göttingen Minipigs in biomedical research. If you are looking for something specific, or references to a topic not included on the list, please contact ellegaard@minipigs.dk.

Toxicology and Safety

The minipig as a platform for new technologies in toxicology

Roy Forster, Philippe Ancian, Merete Fredholm, et al. *Journal of Pharmacological and Toxicological Methods* Published: May 2010

DOI 10.1016/i.vascn.2010.05.007

The RETHINK project on minipigs in the toxicity testing of new medicines and chemicals: conclusions and recommendations

Roy Forster, Gerd Bode, Lars Ellegaard, et al. *Journal of Pharmacological and Toxicological Methods* Published: May 2010

DOI 10.1016/i.vascn.2010.05.008

The utility of the minipig as an animal model in regulatory toxicology

Gerd Bode, Peter Clausing, Frederic Gervais, et al. *Journal of Pharmacological and Toxicological Methods* Published: May 2010

DOI 10.1016/j.vascn.2010.05.009

The RETHINK project: Minipigs as models for the toxicity testing of new medicines and chemicals: an impact assessment

Roy Forster, Gerd Bode, Lars Ellegaard, Jan Willem van der Laan Journal of Pharmacological and Toxicological Methods

Published: June 2010

DOI 10.1016/j.vascn.2010.05.003

Regulatory acceptability of the minipig in the development of pharmaceuticals, chemicals and other products

Jan Willem van der Laan, John Brightwell, Peter McAnulty, et al. Journal of Pharmacological and Toxicological Methods

Published: June 2010

DOI <u>10.1016/j.vascn.2010.05.005</u>

A shortened study design for embryo-fetal development studies in the minipig

Céline Pique, Edward Marsden, Paul Quesada, et al. *Reproductive Toxicology* Published: June 2018

DOI 10.1016/j.reprotox.2018.06.009

Perspectives From the 12th Annual Minipig Research Forum: Early Inclusion of the Minipig in Safety Assessment Species Selection Should be the Standard Approach

Keith Jones, Joanna Harding, Andy Makin, et al. Toxicologic Pathology Published: July 2019

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Cardiovascular

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Implantation of telemetric blood pressure transmitters in Göttingen Minipigs: Validation of 24-h systemic blood pressure and heart rate monitoring and influence of anaesthesia

Michelle Fischer Carlsen, Berit Østergaard Christoffersen, Rikke Lindgaard, et al.

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Electrocardiography and heart rate variability in Göttingen Minipigs: Impact of diurnal variation, lead placement, repeatability and streptozotocin-induced diabetes

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Anne Smits, Pieter Annaert, Steven Van Cruchten, Karel Allegaert Frontiers In Pharmacology

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Neuro

The d-amphetamine-treated Göttingen miniature pig: an animal model for assessing behavioral effects of antipsychotics

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Published: January 2021

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A systematic review of porcine models in translational pain research

Suzan Meijs, Martin Schmelz, Sigal Meilin, Winnie Jensen Lab Animal

Published: October 2021

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Ocular

Göttingen Minipigs in Ocular Research

Stephanie M Shrader, William F Greentree Toxicologic Pathology

Published: April 2018

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Luis Fernando Negro Silva, Christian Li, Paula Juliana Brizuela de Seadi Pereira, et al.

International Journal of Toxicology

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POLYRETINA restores light responses in vivo in blind Göttingen minipigs

Paola Vagni, Marta Jole Ildelfonsa Airaghi Leccardi, Charles-Henri Vila, et al.

Nature Communications
Published: June 2022

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Novel modalities

The genomic organization and expression pattern of the low-affinity Fc gamma receptors (Fc γ R) in the Göttingen minipig

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Pharmaceutical Research
Published: September 2020

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The CRISPR/Cas9 Minipig—A Transgenic Minipig to Produce Specific Mutations in Designated Tissues

Martin Fogtmann Berthelsen, Maria Riedel, Huiqiang Cai, et al. Cancers

Published: June 2021

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Published: September 2022

DOI 10.1038/s41551-022-00921-2

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Published: October 2022

DOI 10.3389/fcell.2022.1031812

Investigating the effect of obesity on adipose-derived stem cells (ASCs) using Göttingen Minipigs

Maria Meyhoff-Madsen, Esben Østrup, Merete Fredholm, Susanna Cirera

bioRxiv

Published: February 2022

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Online histological atlas of the Göttingen minipig brain

Dariusz Orlowski, Andreas N Glud, Nicola Palomero-Gallagher, et al. *Helivon*

Published: March 2019

DOI <u>10.1016/j.heliyon.2019.e01363</u>

The minipig intraoral dental implant model: A systematic review and meta-analysis

Marta Liliana Musskopf, Amanda Finger Stadler, Ulf Me Wikesjö, Cristiano Susin

PloS One

Published: February 2022

DOI <u>10.1371/journal.pone.0264475</u>

Selecting the Best Animal Model of Parkinson's Disease for Your Research Purpose: Insight from in vivo PET Imaging Studies

Caroline Cristiano Real, Karina Henrique Binda, Majken Borup Thomsen, et al.

17

Current Neuropharmacology Published: February 2023

DOI <u>10.2174/1570159X21666230216101659</u>

Spotlights

Straw boards

To maintain a high level of animal welfare, pigs must be supplied straw in copious amounts, and hence straw in the slurry is unavoidable. Unfortunately, this results in weekly clogged drainage systems and the staff use a considerable amount of time removing slurry blockages. In conventional pig breeding, mechanical solutions remove used straw and other waste, but this is not a solution for Ellegaard Göttingen Minipigs A/S, as the pens always have residents. Also, straw is replaced much more frequently due to health standards and animal welfare.

Therefore, the staff at Ellegaard Göttingen Minipigs has been working on a solution that will keep the straw away from the drainage system and has come up with a very simple yet effective solution. "We have mounted boards of around 10 cm in height - high enough to hold back the straw from the drainage system, but also low enough to avoid creating a trip hazard for the minipigs. There is a gap of 1 mm between the board and the floor to allow water to run through to the drainage system, and while cleaning the boards are lifted to allow easy access" explains Nicolai Dyhr Rothmann, Maintenance Assistant at Ellegaard Göttingen Minipigs A/S.

The gain of this implementation is many-folded. Kim Pagel, Animal Caretaker at Ellegaard Göttingen Minipigs, concludes that "after the implementation of the straw boards, we use 15% less straw, because we are able to keep it inside the pens for longer. This also means, that the straw is available as enrichment for a longer time. Also, we save a lot of time spreading extra straw and handling slurry."





25 years with AAALAC

In 1998 the first AAALAC International Accreditation was issued to Ellegaard Göttingen Minipigs - an achievement, which the company has now received for the 9th consecutive time.

In the report, the council highlighted:

"Especially noteworthy were the very positive attitude of team members at every level of the organisation; the appearance, in general, of healthy and relaxed looking animals; the competent handling of animals resulting in calm and quiet animals; the culture of care workshop to raise awareness of the company's commitment; the post-approval monitoring system for study evaluation; and the outreach provision to clients to help promote best practice."









Tech Week 2023

In the 5th week of 2023, Ellegaard Göttingen Minipigs joined in celebrating the International Laboratory Animal Technician Week, to pay tribute and officially recognise the skills and hard work of Laboratory Animal Technicians caring for animals in biomedical research. "It is important to remember and acknowledge the vital contribution to scientific research brought by Laboratory Animal Technicians every day. Not just this week, but all year round, as Animal Technicians create the best possible environments for laboratory animals, and thereby clear the path for optimal scientific results" explains Maja Ramløse, Principal Laboratory Animal Veterinarian at Ellegaard Göttingen Minipigs.

During the week, several initiatives and events were conducted, all with the purpose of giving insight into the routines and tasks of an Animal Caretaker:

Monday

Kicking off the week, Animal Caretakers in the research team welcomed colleagues for a tour inside the research facility. Visitors got to see Göttingen Minipigs of all ages and even the new Humanized IgG Göttingen Minipigs, and finally stopping by the impressive operating theatre.

Tuesday

Employees attended a presentation about the key role Animal Caretakers at Ellegaard Göttingen Minipigs play during customer projects, all the way from initial enquiry, through project set-up, until project follow-up and evaluation. Animal Caretakers are always consulted, as they hold the expertise on handling and caretaking, and are the ones who are in closest contact with the minipigs on a daily basis.

Wednesday

The two breeding barriers invited colleagues to visit inside the barriers, to give insight into their daily activities. After the mandatory showering, disinfection and other biosecurity measures (according to applicable standard operating procedures), visitors got to see the Animal Caretakers' working environment and not least the ever curious and playful Göttingen Minipigs, who were very interested in their guests.

Thursday

Taking good care of Göttingen Minipigs takes proactivity, innovation and a desire to always find new ways of further improving animal welfare. Animal Caretakers presented examples of their work in the conference room and explained all the preceding considerations and actions to target training, development of new hay racks, and habituation to blood sampling in a sling. Finally, a video showed what it's like to grow up as a minipig at Ellegaard Göttingen Minipigs from birth to shipping.

Friday

Rounding off the week, Animal Caretaker of the year was announced based on internal voting. Congratulations to Michael Jensen for the announcement!

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NEWS FROM

Ellegaard Göttingen Minipigs A/S

Ellegaard Göttingen Minipigs A/S is a leading international company supplying Göttingen Minipigs for biomedical research around the world. From our AAALAC accredited facility in Denmark we breed Göttingen Minipigs and enable the development of safer and more effective medicines, all based on our core values; Animal welfare, quality, respect, and collaboration.

New appointments



In March, John Cameron joined as new Regional Business Development Director representing the subsidiary in North America, Ellegaard Bioresearch.

John will be the point of contact in North America regarding research services and genetically modified Göttingen Minipigs incl. the new Humanized IgG Göttingen Minipigs.



In March, Ofer Doron started a new position as Sales Representative in Israel for Ellegaard Göttingen Minipigs A/S.

Ofer is a well-known profile within the Israeli biomedical research community and will be a great resource to the company with his many years of experience within the industry and the Israeli market.

Visit from the Ministry

28 March the Danish Minister for Food, Agriculture and Fisheries, Jacob Jensen, visited Ellegaard Göttingen Minipigs A/S along with the Mayor of Slagelse Municipality and Director of Business, Retail and Technique in Slagelse.

CEO, Martin Windfeld Velin, and Chairman of the Board, Jens Ellegaard, gave the prominent guests a tour of the facility and enjoyed inspiring and interesting discussions about Göttingen Minipigs in biomedical research.







Great interest for Humanized IgG Göttingen

Humanized IgG Göttingen Minipigs, which were made commercially available end of 2022, after the publication of "A humanized minipig model for the toxicological testing of therapeutic recombinant antibodies" in September 2022, have received a warm welcome in the pharmaceutical industry.

"We experience great interest and currently have several promising dialogues with both pharmaceutical and biotech companies and CROs" says Peter Vestbjerg, Head of International Sales at Ellegaard Göttingen Minipigs A/S.

Humanized IgG Göttingen Minipigs carry a mini repertoire of human Ig- $\gamma 1/\gamma 4$ heavy and the human κ light chain genes and show tolerance to a broad range of human or humanized IgG antibodies.

Contact Peter Vestbjerg at pve@minipigs.dk if you consider using the Humanized IgG Göttingen Minipigs for your study.

Where to meet us in 2023

CONFERENCE	DATE	LOCATION
International Pain Conference: Bench to Bedside	8-9 Mar	Ness Ziona, Israel
SOT and ToxExpo	19-23 Mar	Nashville, Tennessee, USA
IAT Congress	21-24 Mar	United Kingdom
Janssen Juvenile Tox Symposium	20-21 Apr	Beerse, Belgium
Scand-LAS	25-28 Apr	Uppsala, Sweden
AFSTAL	7-9 Jun	Bordeaux, France
GV-Solas	6-8 Sep	Mainz, Germany
EUROTOX	10-13 Sep	Ljubljana, Slovenia
SPS	18-21 Sep	Brussels, Belgium
STP-I	27-29 Oct	Ahmedabad, India
ACT	12-15 Nov	Orlando, Florida, USA
EALAS	22-24 Nov	Rome, Italy
LASACON	TBA	TBA

GÖTTINGEN MINIPIGS ACADEMY

Ellegaard Göttingen Minipigs is all for sharing and believe that openness creates trust, enriches, and clears the path for new opportunities. We create fora for networking and knowledge sharing about Göttingen Minipigs in biomedical research. We support scientific research through our Research Foundation. And we educate through the Göttingen Minipigs Academy.

19 June 2023 Veterinary Management, Welfare and Culture of Care

Are you a veterinarian or an experienced animal caretaker with interest in animal welfare? Then you will benefit from this course and improve your professional skills.

On 19 June 2023, Göttingen Minipigs Academy is holding the course "Veterinary Management, Welfare and Culture of Care" at our breeding and research site in Dalmose, Denmark.

You will be introduced to topics like health monitoring and the veterinarian's toolbox including the most common disease cases. Learn how we apply culture of care at Ellegaard Göttingen Minipigs and bring it to life at your own workplace. Enrichment is important when working with Göttingen Minipigs and in a practical session you get to explore how to design the best enrichment settings. You will also go on a guided tour at our premises and see our Göttingen Minipigs from the viewing lofts.

To register, go to minipigs.dk/events.

Other courses in 2023

22 May and 25 September 2023 Hands-on course: Handling and dosing

Göttingen Minipigs Academy conducts a Handling and Dosing course at our breeding and research site in Dalmose, Denmark.

On this course you get an introduction to Göttingen Minipigs and you learn how to take care of, train and handle the animal in the best possible manner.

Moreover, you get to try different practical procedures like lifting and carrying the minipig, dosing the animal via various routes, and establishing vascular access. We also briefly touch upon anaesthesia and euthanasia.

Book your participation soon, only limited number of seats.

Follow Ellegaard Göttingen Minipigs on LinkedIn, for ongoing announcements on new









For questions about course content or the Academy in general, please contact Laboratory Animal Research Veterinarian and Academy Facilitator, Susi Søgaard at sso@minipigs.dk.

Follow for information on new courses

courses or keep an eye on minipigs.dk/events



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.

Gilljam KM, Stenlund P, Standoft S, et al.

Alginate and Nanocellulose Dressings With Extract From Salmon Roe Reduce Inflammation and Accelerate Healing of Porcine Burn Wounds

Journal of Burn Care & Research | 2023 Jan 14 DOI: 10.1093/jbcr/irad006

Iachina I, Eriksson AH, Bertelsen M, et al.

Dissolvable microneedles for transdermal drug delivery showing skin penetration and modified drug release

European Journal of Pharmaceutical sciences | 2023 Mar 1 DOI: 10.1016/j.eips.2023.106371

Jhelum H. Grand N. Jacobsen KR. et al.

First virological and pathological study of Göttingen Minipigs with Dippity Pig Syndrome (DPS)

bioRxiv | 2023 Jan 26

DOI: 10.1101/2023.01.26.525667

DeMitchell-Rodriguez EM, Shen C, Nayak VV, et al.

Bone Tissue Engineering in the Growing Calvaria: A 3D Printed Bioceramic Scaffold to Reconstruct Critical-Sized Defects in a Skeletally Immature Pig Model

Plastic and Reconstructive Surgery | 2023 Feb 1 DOI: 10.1097/prs.000000000010258

Feller LE, Sargeant A, Ehrhart EJ, Balmer B, Nelson K, Lamoureux J. et al.

Cardiac Rhabdomyoma in Four Göttingen Minipigs

Toxicologic Pathology | 2023 Feb 1 DOI: 10.1177/01926233221148393

Haubold J, Jost G, Theysohn JM, et al.

Contrast Agent Dose Reduction in MRI Utilizing a Generative Adversarial Network in an Exploratory Animal Study

Investigative Radiology | 2023 Jan 12 DOI: 10.1097/rli.0000000000000947

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Selecting the Best Animal Model of Parkinson's Disease for Your Research Purpose: Insight from in vivo PET Imaging Studies

Current Neuropharmacology | 2023 Feb 16 DOI: 10.2174/1570159x21666230216101659 Yu Y, Tham SK, Roslan FF, et al.

Large animal models for cardiac remuscularization studies: A methodological review

Frontiers In: Cardiovascular Medicine | 2023 Mar 15 DOI: 10.3389/fcvm.2023.1011880

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Effects of Sex on the Susceptibility for Atrial Fibrillation in Pigs with Ischemic Heart Failure

Cells | 2023 Mar 23

DOI: 10.3390/cells12070973

Li K, Cardoso C, Moctezuma-Ramirez A, Elgalad A, Perin E

Evaluation of large animal models for preclinical studies of heart failure with preserved ejection fraction using clinical score systems

Frontiers In: Cardiovascular Medicine | 2023 Mar 23 DOI: 10.3389/fcvm.2023.1099453

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The incidence of spontaneous arrhythmias in telemetered beagle dogs, Göttingen Minipigs and Cynomolgus non-human primates: A HESI consortium retrospective analysis

Journal of Pharmacological and Toxicological Methods | 2023 Mar 22 DOI: 10.1016/j.vascn.2023.107266

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Sensitive and rapid method for the quantitation of amoxicillin in minipig plasma and milk by LC-MS/MS: A contribution from the IMI ConcePTION project

Journal of Pharmacological and Toxicological Methods | 2023 Mar 22 DOI: 10.1016/j.vascn.2023.107264

Chen S, Darby

Inter-implant distance and buccal bone thickness for a novel implant design: a preclinical study

Clinical Oral Investigations | 2023 Mar 22 DOI: 10.1007/s00784-023-04942-2

Moons CP, Spiri AM, Boxall J, et al.

Survey among FELASA members about rehoming of animals used for scientific and educational purposes

Laboratory Animals | 2023 Mar 24 DOI: <u>10.1177/00236772231153747</u> Uno Y, Morikuni S, Murayama N, Yamazaki H

2-Oxidation, 3-methyl hydroxylation, and 6-hydroxylation of skatole, a contributor to the odour of boar-tainted pork meat, mediated by porcine liver microsomal cytochromes P450 1A2, 2A19, 2E1, and 3A22

Xenobiotica | 2023 Apr 5

DOI: 10.1080/00498254.2023.2197037

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Cardiovascular Response to Intraneural Right Vagus Nerve Stimulation in Adult Minipig

Neuromodulation | 2023 Mar 29 DOI: 10.1016/j.neurom.2023.03.002

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Platelet Activation by Antisense Oligonucleotides (ASOs) in the Göttingen Minipig, including an Evaluation of Glycoprotein VI (GPVI) and Platelet Factor 4 (PF4) Ontogeny

Pharmaceutics | 2023 Mar 31

DOI: 10.3390/pharmaceutics15041112

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Nanopore sequencing reveals methylation changes associated with obesity in circulating cell-free DNA from Göttingen Minipigs

Epigenetics | 2023 Apr 10

DOI: 10.1080/15592294.2023.2199374

Christoffersen BØ, Kristensen CA, Lindgaard R, et al.

Functional and morphological renal changes in a Göttingen Minipig model of obesity-related and diabetic nephropathy

Scientific Reports | 2023 Apr 12 DOI: 10.1038/s41598-023-32674-6

Landau AM, Jakobsen S, Thomsen MB, et al.

Combined In Vivo Microdialysis and PET Studies to Validate [11C] Yohimbine Binding as a Marker of Noradrenaline Release

Biomolecules | 2023 Apr 14 DOI: 10.3390/biom13040674

Bolon B

Toxicologic Pathology Forum Opinion: Interpretation of Gliosis in the Brain and Spinal Cord Observed During Nonclinical Safety Studies

Toxicologic Pathology | 2023 Apr 14 DOI: <u>10.1177/01926233231164557</u> Fallegger F, Trouillet A, Lacour SP, et al.

Subdural Soft Electrocorticography (ECoG) Array Implantation and Long-Term Cortical Recording in Minipigs

Journal of Visualized Experiments | 2023 Mar 31 DOI: 10.3791/64997

Kleinbongard P, Lieder H, Skyschally A, Heusch G

Diazoxide is a powerful cardioprotectant but is not feasible in a realistic infarct scenario

Frontiers In: Cardiovascular Medicine | 2023 Apr 19

DOI: 10.3389/fcvm.2023.1173462

Flisikowska T

Humanized minipigs to assess drug safety

Nature Reviews: Cancer | 2023 Apr 19 DOI: <u>10.1038/s41568-023-00573-7</u>





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