

2020

DANISH 3R-CENTER
ANNUAL REPORT
2020



Danish 3R-Center
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ANNUAL REPORT

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RRR

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THE CHAIRWOMAN'S FOREWORD



READ MORE AT
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The Board of the Danish 3R-Center comprises Christine Nellemann, Peter Bollen, Axel Kornerup Hansen, Lisbeth E. Knudsen, Jan Lund Ottesen, Erwin Roggen and Adrian Smith. Further details about each board member are found on: en.3rcenter.dk/about-us/board/

DEAR EVERYONE

The COVID-19 pandemic made 2020 a different year for the Danish 3R-Center, as it has certainly done for everyone else as well. One of our most important purposes is to disseminate knowledge of the 3Rs to the wider world of interested stakeholders. Previously, we have successfully done this at our two annual events: the international 3R symposium and the annual meeting of animal welfare bodies. Both events were cancelled in 2020 due to the infection risk of COVID-19. As a result, dissemination in 2020 was largely based on our website and a series of online events.

Despite having to cancel the symposium, we managed to award the year's 3R Prize to Dorte Bratbo Sørensen, Associate Professor, University of Copenhagen. We, the members of the board, are deeply impressed by her presence in a profusion of laboratory-animal forums, by her activities for disseminating knowledge of laboratory animals and, obviously, by her research that benefits laboratory animals. I would like to take this opportunity to congratulate Dorte on the prize once again.

Another recurring event is the annual allocation of research funding for the 3Rs area where we always look forward to reading the host of applications we receive. The applications manifest the applicants' dedication to the field and give funding recipients an opportunity to present their research at our symposium and website, raising awareness of the projects beyond what they would have achieved otherwise.

Three new research projects were granted support by the 3R-Center again in 2020. Our website lists all the projects granted subsidy since the 3R-Center was founded in 2013, as well as an overview of the publications and knowledge generated by the projects.

In keeping with the past five years, we have invited an external institution to give an account of their 3R efforts in our annual report.

This year you can read about the 3R activities at Lundbeck.

I wish to express my gratitude to the Danish Animal Welfare Society, DOSO, LEO Pharma, Lundbeck, Novo Nordisk and the Ministry of Food, Agriculture and Fisheries for supporting the Danish 3R-Center in 2020. We experience excellent support from our financial backers during the year, which greatly benefits the centre.

I would also like to take this opportunity to extend my gratitude once again to my dedicated colleagues on the board and to the expert, conscientious secretariat for their brilliant efforts during 2020. It has been a pleasure working with you.

Drawing conclusions about 2020 inevitably looks forward to 2021, when we hope to host open in-person events once again for the benefit of both networking and knowledge-sharing.

2021 will also be a decisive year for the future of the Danish 3R-Center, as the Ministry and the above-mentioned supporters of the centre must decide whether they also want to continue supporting the centre going forward. If so, a new board must be appointed, effective on 1 November 2021. I would like to urge everyone with expertise within at least one of the 3Rs to consider participating in this interesting, rewarding work.

Personally, I am bowing out as chairwoman at the end of 2020 due to many other tasks, but I will continue as a board member under the chairmanship of Professor Axel Kornerup Hansen. In 2021, we will also publish a memorandum about the centre's activities and successes during the centre's almost eight years of existence, which the next board can choose to be inspired by. I look forward to this.

Best regards

Christine Nellemann
Chairwoman

The Danish 3R-Center (2013–2021)

1

RESEARCH

An important part of the Danish 3R-Center's work is to provide financial support to 3R research projects, on behalf of the Minister for Food. Once a year, the Danish 3R-Center calls for applications for research projects that in one way or another have the potential to improve the laboratory animal area through *Replacement*, *Reduction* or *Refinement*.

RESEARCH FUNDING

The 3R-Center manages the allocation of DKK 1.5 million a year to support research in one or more of the 3Rs – *Replacement*, *Reduction* or *Refinement*.

PRIORITY IS GIVEN TO THE PROJECTS'

- Quality
- Feasibility
- Relevance

WHO IS ELIGIBLE TO APPLY FOR SUPPORT?

Persons who are scientifically affiliated with an organization, institution or company in Denmark.

It is possible to apply for up to DKK 500,000.

RESEARCH FUNDING 2022

The call for the next round of applications (research funds for 2022) will take place in late summer 2021.

Stay up to date at the 3R-Center's website 3rcenter.dk or sign up for the Danish 3R-Center's newsletter en.3rcenter.dk/newsletter-subscription/

RESEARCH PROJECTS

SUPPORTED BY THE DANISH 3R-CENTER IN 2020

The Danish 3R-Center received 21 applications for support, of which the following three received a total of DKK 1.5 million.



READ MORE AT
[3RCENTER.DK](https://en.3rcenter.dk)

Did you know that...?

The Danish 3R-Center has supported a total of 22 projects since it was founded. You can find a list of all the projects in the appendix of the annual report, and further details about the projects are available on the 3R-Center's website en.3rcenter.dk/research/projects/

ESTABLISHMENT OF AN *IN VITRO* MODEL TO INVESTIGATE EXTRACELLULAR MATRIX AND VASCULAR MECHANICAL INTERACTIONS IN HUMAN ARTERIAL DISEASE

Julián Albarrán Juárez
University of Aarhus

Atherosclerosis is one of the leading causes of global death and a major threat to long and healthy lives in modern societies. Animal models of atherosclerosis have the potential to overcome many of the inherent restrictions of human research. Indeed, there have been many decades of research in mouse models that have led to more than 800 different ways of inhibiting atherosclerosis development. Yet, the translation of therapies designed to target molecular mechanisms of atherosclerotic plaques in mice has not made its way into routine clinical practice. This phenomenon may arise in part from the fact that atherosclerosis in mice is quite different from that in humans.

In healthy arteries, proper cell function is controlled tightly by the local microenvironment composed of a wide spectrum of proteins, signal molecules, and mechanical forces. During the development of atherosclerosis and other arterial diseases, vascular smooth muscle cells (SMC) located in the vessel wall react to the changes in their surroundings and become rapidly-dividing and disease-promoting cells. A similar shift in cell phenotype is observed when SMC are removed from their native environment and placed in culture.

How do they know the difference? Classical studies describing SMC function have been performed under standard culture conditions, in which cells adhere to a hard and static plastic plate. While these studies have contributed to the discovery of several molecular targets, they faced one limitation: the biochemical signals, such as extracellular matrix composition and mechanical cues, that control SMC function in arteries are not present. For that reason, SMC involvement in arterial diseases is today mostly studied in live animals.

In this project, we will establish a new *in vitro* model that more closely resembles the mechanical and physiological conditions from a native artery environment during healthy and disease conditions. Using this model, we seek to identify the specific mechanisms that regulate SMC phenotypic modulation to understand their relevance in human arterial disease. The goal is to establish techniques that can replace live animals for research in SMC function and to increase our understanding of the mechanisms that lead to the accumulation of unconventional SMC types atherosclerosis and other vascular pathologies.

INTRODUCTION OF NEW HUMAN *EX VIVO* MODEL SYSTEMS TO STUDY TUMORIGENESIS IN KIDNEY CANCER

Kirsten Madsen

University of Southern Denmark

Kidney cancer is a common disease with 400,000 new cases per year worldwide. In Denmark, 8-900 new patients are diagnosed per year making it the 9th most common cancer type. It is a high-risk cancer with a high mortality rate and a 5-year survival rate of only 40%. Patients with localized disease can be treated with surgery but for patients with advanced disease, the only treatment option is life prolonging medical treatment with tyrosine kinase inhibitors (TKIs). This treatment is associated with severe adverse effects, and the average survival time for this group of patients is only 1-2 years. Therefore, there is an evident need for identification of new therapeutic targets that can lead to the development of new treatment options for advanced kidney cancer.

Today, the discovery of new treatment targets mainly rely on the use of immortalized cell lines and animal studies. The aim of our project is to establish and validate new human *ex vivo* model systems that can be used to study kidney cancer biology. We will use freshly collected human kidney tumor tissue collected from nephrectomy specimens at Odense University Hospital. An array of *ex vivo* model systems will be tested including primary cell cultures, 3D spheroids and tissue slice culture models.

By the validation and implementation of these new test systems, we expect to be able to identify new treatment targets *ex vivo* that more clearly resembles human tumour biology *in vivo* and that the use of experimental animals within this field of research can be significantly reduced.



PHOTO: BIOMEDICAL LABORATORY,
UNIVERSITY OF SOUTHERN DENMARK

FIGHTING IRREPRODUCIBILITY IN PRECLINICAL MEDICINE USING A META-ANALYTICAL APPROACH FOR DETECTING FLAWS IN BEHAVIOR-BASED TESTING

Otto Kalliokoski

University of Copenhagen

One of the greatest problems with present-day medical research is irreproducible results. Frequently, the results from a study conducted in mice in one laboratory cannot be reproduced using the same mice, only in another laboratory. The implication, when results fail to replicate, is that the original findings were unreliable, or simply incorrect. "Double checking" studies in this manner takes time, however. In the meanwhile, therapies and drugs can be developed based on the original findings; drugs and therapies that will invariably turn out to be ineffective. In addition to the societal costs of failed investments in medicine and patients waiting in vain for therapies that were not effective in the first place, irreproducible findings are a major source of waste with respect to (laboratory) animal lives.

Neuroscience is the medical field that generates the fewest studies that can be successfully replicated. Laboratory animal studies in neuroscience often rely on testing behaviour – rats running mazes to test memory,

mice pressing levers in Skinner boxes to test motivation, etc. The irreproducible results in neuroscience can often be traced back to these behavioural tests. Some of the tests are half a century old, the theory behind them is murky, and they are often needlessly cruel.

We are looking to drive a move away from these outdated methods using meta-analytical investigations of historical data. It is important to explain how a method can be used for decades without measuring anything particularly useful if we want to avoid perpetuating the same mistakes. We need to clearly convey how primarily sharing results that conformed to expectations, and suppressing results that did not (what is known as "publication bias"), has given flimsy behavioral tests an air of legitimacy and reliability. Using modern statistical methods and clear no-nonsense communication, we aim to convey the message that many of the established behavioral tests are long overdue for a substitution.

2

THE DANISH 3R-CENTER'S 3R PRIZE

Each year, the Danish 3R-Center awards a prize to an individual or a group of individuals affiliated with a company, university or other institution entirely in Denmark who are distinguished by their outstanding efforts in the area of the 3Rs.

Winners of the Danish 3R-Center's 3R Prize

2014 Ellen Margrethe Vestergaard
Danish Medicines Agency

2018 Birgitte Kousholt
University of Aarhus

2015 Hanne Gamst-Andersen
Novo Nordisk

2019 Thomas Bertelsen
Novo Nordisk

**2016 QSAR-teamet v. Eva Bay Wedebye
og Nikolai Georgiev Nikolov**
Technical University of Denmark

2020 Dorte Bratbo Sørensen
University of Copenhagen

2017 Grete Østergaard
University of Copenhagen



READ MORE ON
3RCENTER.DK

Did you know that...?

You can nominate yourself or a colleague for the Danish 3R-Center's 3R Prize. Further details here:
3rcenter.dk/om-3r-centeret/3r-prisen

THE 3R PRIZE 2020



PHOTO: THE DANISH 3R-CENTER

Dorte Bratbo Sørensen, University of Copenhagen, was this year's highly deserving recipient of the Danish 3R-Center's 3R Prize. This made Dorte the seventh recipient of the prize.

The COVID-19 pandemic prompted the cancellation of the Danish 3R-Center's symposium in 2020, an event at which the 3R Prize is usually awarded to the winner. Therefore, the 3R-Center decided to surprise Dorte at her workplace instead, and she was definitely caught unaware when board chairwoman Christine Nellemann and Head of Secretariat Tom Bengtsen showed up with champagne, flowers and a certificate to give her the good news.

Christine gave a speech for Dorte in which she made it clear that Dorte is a well-deserving recipient of the 3R Prize. In fact, Christine started out by telling Dorte that it had never been a question for the Danish 3R-Center of *whether* Dorte should be awarded the prize but *when*, because the Danish 3R-Center had been aware of Dorte's enormous dedication to the field of laboratory animals ever since the centre was founded.

Next, Christine listed Dorte's impressive list of achievements in the area of laboratory animals:

"You are a member of the Animal Experimentation Council – and have been since 2009; you are a member of the institute's animal welfare body; you are a driving force at the Centre for Applied Laboratory Animal

Research (CALAR); you are chairwoman of CeLAT (Centre for Laboratory Animal Training), which, in our view, excellently embodies the Culture of Care – the fact that you attend to and are responsible for animal well-being that far exceeds what the law requires; your research primarily focuses on optimizing animal-model systems, (including blood sampling in the gentlest way possible, the use of natural behaviour as a well-being indicator, clicker training, all of which aim to improve conditions for laboratory animals); you co-authored a recently published book *Animal-centric Care and Management – Enhancing Refinement in Biomedical Research*, which notably involves widening the Refinement concept even further; you teach on the department's laboratory animal courses; and you are always available as a speaker for the Animal Experiments Inspectorate's mini-seminars; in recent years, you have organized the World Day for Laboratory Animals in cooperation with DOSO – I could go on and on."

Christine expressed her admiration of Dorte's apparent ubiquity in the world of laboratory animals, after which Christine concluded her speech with the following words:

"We are convinced that your enormous efforts emanate from a genuine affection for the animals. The Danish 3R-Center can in no way take any credit for this quality, but we can acknowledge it, as we are doing today, by awarding you the 3R Prize. Congratulations, Dorte."

REFINEMENT: PUTTING THE LABORATORY ANIMAL FIRST

Dorte Bratbo Sørensen
University of Copenhagen

The 3Rs are by now a well-established concept: *Replacement* and *Reduction* deal with how to stop using living animals, whereas *Refinement* focuses on improving the living conditions of the animals that are used. In other words, *Refinement* is about finding methods that will optimize animal welfare. It is important that *Refinement* does not focus solely on preventing animals from experiencing discomfort, pain or suffering but also on enabling them to have positive experiences. At the same time, one must remember that *Refinement* applies throughout an animal's lifetime, i.e. also to transportation, housing and day-to-day care of the animals as well. Three *Refinement*-related points meriting special attention – and where there is in my opinion room for improvement – are presented in the following.

First of all, how animals are handled is important. Animals that are stressed by handling have poorer welfare than animals that are not stressed or afraid. Tunnel handling of mice was introduced by the British professor Jane Hurst in 2010, and subsequently introduced at several major animal testing facilities in Denmark. One of our projects involved designing a 'tunnel sampler' for use when taking blood samples from mice. The idea is that the mouse stays in the tunnel while a blood sample is taken from its tail. Mice that cannot be handled by hand and for example placed on a dish towel, for instance, while blood samples are taken can be put in the tunnel sampler for the blood-sampling process.

The tunnel sampler renders it unnecessary to lift the mouse out of the cage by the tail and into a 'tail holder' to take the blood sample. The development of the tunnel sampler was funded by the Danish 3R-Center and it is hoped that its use will be able to reduce the discomfort for mice that would otherwise be lifted by the tail. There is also a need for improving the handling of rats in many instances. I have seen animal keepers take blood samples from rats by lifting them out of the cage and putting them on a dish towel, for instance, and the rats remain calmly in place while the animal keeper takes the blood sample. Obviously, this requires both time and patience, but if the animal keeper has the skill-sets and willingness, and if the requisite time is set aside, this intensified focus on animal-friendly handling will vastly improve animal welfare. But it requires the management of the animal housing to allocate the resources required and demonstrably recognize employees who go the extra mile for the animals' sake.

Secondly, reward-based animal training can be crucial. Pigs can withstand substantial discomfort, such as injections if the pig is able to predict the situation and choose whether to participate. Annette Pedersen, animal training coordinator, Copenhagen Zoo, and I jointly organize courses in laboratory animal training, and we have gathered all the animal keepers and veterinarians who have taken the course in our Centre for Laboratory Animal Training, CeLAT (www.celat.dk).

3R Symposium 2021

The Danish 3R-Center's international symposium will be held in Charlottehaven, Copenhagen, on 16-17 November 2021.

The aim is to continue disseminating knowledge of the extent to which training can reduce stress in animals and thus improve animal welfare. This is why we have included several chapters about the training of animals in a recently published book, describing the different types of training for the different species.¹ The fact that using unstressed animals which cooperate with animal keepers and technicians will also improve experimental data almost goes without saying.

Last, but not least, animal welfare strategies and decisions on matters of principle applying to how animals are treated should take precedence over how trials and experiments are planned, by contrast with today where the reverse frequently seems to be true. In my view, there is still a widespread tendency for the planning of experiments to give first priority to the specific parameters to be measured and how this should be done and second priority to assessing the strain on the laboratory animal. The problem with this approach is that *Refinement* will always lag behind. Animal welfare will never be prioritized as actually envisaged by the EU directive, which states that "Animal welfare considerations should be given the highest priority in the context of animal keeping, breeding and use."² For instance, one can visualize the following steps in planning an experiment aimed at evaluating the efficacy of a drug on *E. coli*-induced diarrhoea in slaughter pigs. The study will comprise the inoculation of the pigs with *E. coli* bacteria and the daily taking of faeces samples over four days. The researcher plans to administer the dose via a gavage tube. The faeces samples are taken manually by fixating the pig with a snout snare.

If necessary, the pigs are dosed with a sedative before administering the tube. In other words, the *Refinement* of the experiment (administering a sedative) is the last thing to be planned – after the experiment design has been determined. I would prefer it if the management of animal housing gave much higher priority to establishing principles for optimizing animal welfare. Examples of this are carrying out oral dosing by mixing the test substance or inoculum into blended cat food or taking faeces samples primarily when the pigs defecate while being aired in the corridors. Within this framework, the researcher must plan his/her experiment and, not least, allow time for training, etc., in the experiment's time-line. This is obviously more costly, but in return, it shifts the primary focus to animal welfare, rather than it being just an add-on to an existing experiment design. In other words, if we really intend to promote animal welfare, we must adapt the experiments to the animals rather than the animals to the experiments.

Today, many laboratory animal facilities are already making a big effort to put animal welfare first as a separate, primary priority. I hope this trend will continue so that animals are given top priority in the future and that it becomes the gold standard to accustom mice and rats to procedures such as blood sampling without fixation and that pigs and other laboratory animals are trained to cooperate in a wide range of experimental procedures. I am convinced that Russell and Burch would feel the same way.

1 Animal-centric Care and management – Enhancing Refinement in Biomedical Research (2020).
Lead editor: Dorte Bratbo Sørensen. ISBN13: 9780367180836

2 Preamble 31 of Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010, on the protection of animals used for scientific purposes



PHOTO: BIOMEDICAL LABORATORY

3

DISSEMINATION OF INFORMATION

As the COVID-19 pandemic caused a series of laboratory animal events to be cancelled over the year – including the Danish 3R-Center’s symposium and the annual meeting of the Danish National Committee for the Protection of Animals used for Scientific Purposes – the Danish 3R-Center’s dissemination activities have primarily emanated from the website.

As the 3R-Center’s website primarily targets Danish researchers, we established a new website in 2020 for the Danish National Committee for the Protection of Animals used for Scientific Purposes, primarily targeting Denmark’s animal technicians.



READ MORE ON
3RCENTER.DK

NEWSLETTER

Sign up for the Danish 3R-Center’s newsletter so you don’t miss any news about the Danish 3R-Center’s research funding, symposium and similar. Subscribe on en.3rcenter.dk/newsletter-subscription/

THE DANISH 3R-CENTER'S WEBSITE **3RCENTER.DK**



READ MORE ON
3RCENTER.DK

An important aspect of the Danish 3R-Center's dissemination of knowledge on laboratory animals and the 3Rs is the centre's website 3rcenter.dk. Knowledge on the website is provided in Danish and English to members of the laboratory animal and alternative communities, as well as interested individuals.

The Danish 3R-Center's website

Researchers:

News from the 3R world

Information about relevant events (symposiums, mini-seminars, animal welfare bodies' annual meetings, etc.)

Newsletters

Research funds

Research projects

The 3R Prize

Resources for improving your research (e.g. PREPARE)

Articles about laboratory animals and animal testing

Presentations from 3R symposiums organized by the 3R-Center

Guidelines for implementing EU Directive 2010/63/EU

Links to teaching resources (for future users of laboratory animals)

Links to tissue-sharing services

Annual reports

Individuals/schoolchildren:

Teaching materials on laboratory animals and the 3Rs Factual and basic information about laboratory animals

- What are laboratory animals used for?
- How many laboratory animals are used?
- Which species are used in research?

Politicians and stakeholders:

Goals and goal-achievement forms for the Danish 3R-Center

Minutes of board meetings

Annual reports

DISSEMINATION OF INFORMATION



Did you know that...?

The Danish 3R-Center has developed teaching materials about laboratory animals and the 3Rs for lower and upper secondary school classes. The class set can be ordered free of charge on the 3R-Center's website, and fifteen schools dispersed all over Denmark ordered the materials in 2020.

PHOTO: BIOMEDICAL LABORATORY, UNIVERSITY OF SOUTHERN DENMARK

One of the most essential features of the 3R-Center's website is the dissemination of news. On the website, it is possible to follow national 3R initiatives and events held by the Danish 3R-Center, the Danish National Committee for the Protection of Animals used for Scientific Purposes, and the Animal Experiments inspectorate and thus stay up to date on the latest news about laboratory animals and the 3Rs. For this purpose, the website disseminates national and international research information that can inspire the website visitor's own research.

Another important task managed by the Danish 3R-Center is the dissemination of knowledge about laboratory animals to interested individuals, including schoolchildren. It is definitely in the interest of the Danish 3R-Center that the public debate on laboratory animals and how they are used is conducted on an informed basis, which is why much of the website's content is intended to serve this purpose. At the website, visitors can find information about experiment targets, the number and species of laboratory animals used, and visitors can also find information on the level of strain laboratory animals are subjected to.

WEBSITE OF THE DANISH NATIONAL COMMITTEE FOR THE PROTECTION OF ANIMALS USED FOR SCIENTIFIC PURPOSES: **NATUD.DK**

The committee's new website went live in 2020 and will be finished during 2021. The website must meet the needs of Denmark's animal technicians in the best possible way, which is why this goal will be achieved together with representatives from the target group.

On the website, it must be possible for Denmark's animal technicians to find materials that can inspire them in terms of handling and housing laboratory animals so the animals live under the best conditions possible. In this context, it is worth mentioning that due to increasingly closer cooperation with NC3Rs (the British 3R centre), the Danish 3R-Center has received NC3Rs' permission to have the materials it developed for animal technicians translated into Danish so that a wide range of welfare-optimizing materials become more readily available to animal technicians in Denmark.

Annual meeting of animal welfare bodies, 9 June 2021

The first session, which is for members of Denmark's animal welfare bodies only, will deal with the handling of laboratory animals in transit.

If you are not a member of one of Denmark's animal welfare bodies, you can take part in the meeting's afternoon session which opens its doors to all interested parties with a professional interest in laboratory animals. The meeting is highly relevant to animal keepers who can be inspired to try new housing and handling methods for laboratory animals at the meeting's so-called marketplace (display of 3R initiatives).

Note: The programme is being prepared and at the time of writing it is still uncertain whether the meeting can be held in person. Keep an eye on the committee's website (natud.dk) where the programme will be announced in the near future.

Ideas for the website

In the view of the Danish National Committee for the Protection of Animals used for Scientific Purposes, Denmark's animal technicians need their own website. If you have any ideas and/or comments concerning the website's contents, the secretariat is very interested in hearing from you. Send an e-mail to: **info@3rcenter.dk**



READ MORE ON
NATUD.DK

4

3R ACTIVITIES AT EXTERNAL RESEARCH INSTITUTIONS

In recent years, we have asked researchers from a number of external research institutions to describe their 3R-related activities to get an impression of the widespread efforts in Denmark to improve the area of laboratory animals. In recent years, the University of Aarhus, Novo Nordisk, the Technical University of Denmark, the University of Copenhagen and LEO Pharma have assisted in this.

This year, Lundbeck has provided a valuable contribution to our annual report.

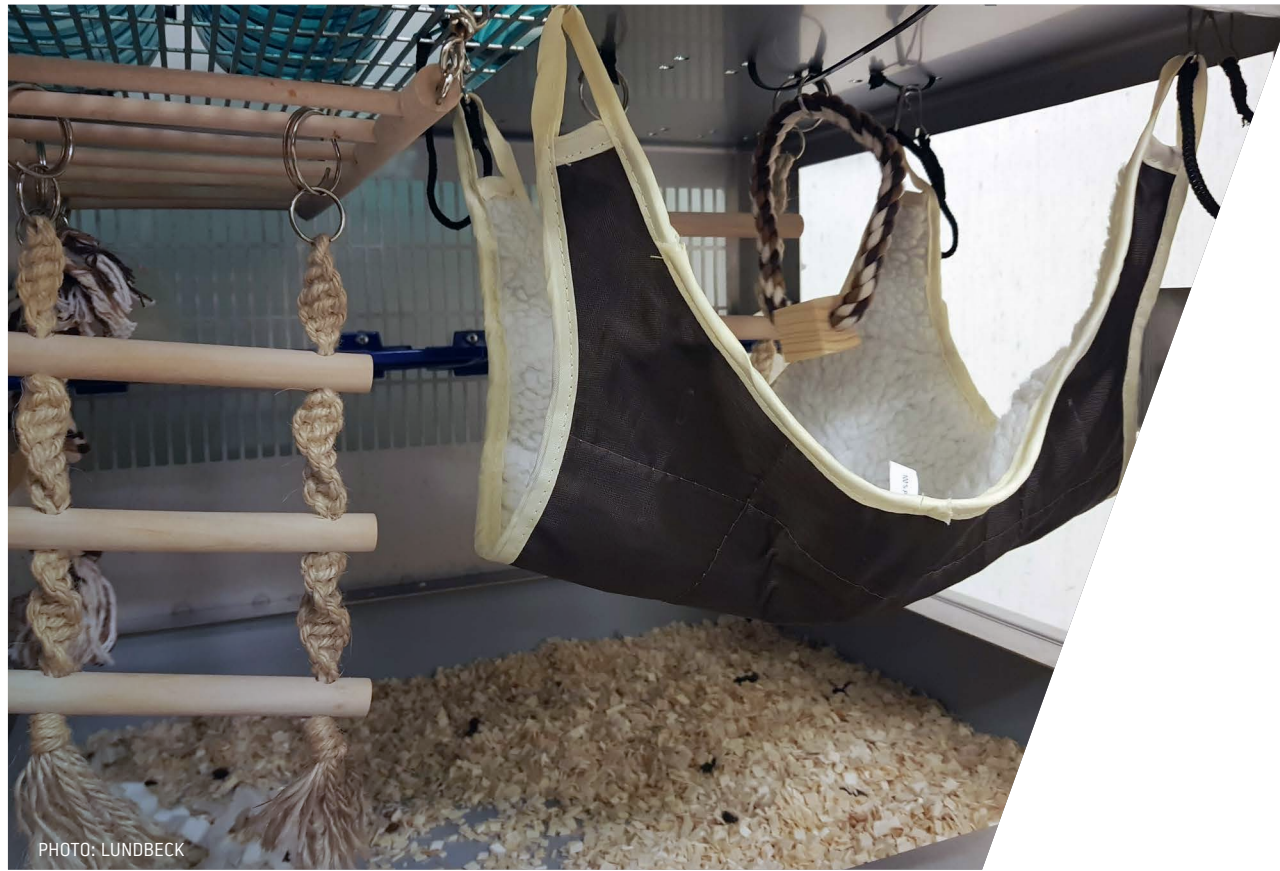


PHOTO: LUNDBECK

THE 3Rs AT LUNDBECK

By **Mia Trein Andersen**, **Helle Northeved** and **Tina Brønnum Pedersen**

Lundbeck is a global pharmaceutical company dedicated to improving the quality of life for sufferers of brain diseases. For this purpose, Lundbeck is involved in research and development of drugs, as well as their production and sales, all over the world. In our search for new, innovative and safe drugs, it is an indisputable necessity (and a requirement of the health authorities around the world) to use laboratory animals for testing new medicines. Efforts involving live laboratory animals imposes a duty on us, as a company, to take ethical responsibility for the entire value chain. This is described in Lundbeck's *Code of Conduct*, which is our fundamental set of values.

It also describes the mutual obligation incumbent on Lundbeck and each employee to comply with legislation and the expectation to act with care and observe ethical considerations relating to the use of animals for testing.

To Lundbeck, the 3Rs (*Replacement*, *Reduction*, and *Refinement*) are essential principles. It is paramount for us to maintain good animal welfare and to properly house, handle and use the animals in a manner that minimizes animal stress, as a needlessly stressed animal can affect experimental data and lead to an incorrect assessment of a test substance's efficacy.

Replacement

In the initial stages of drug development, the presumed efficacy and toxicity are assessed *in silico* in computer-based models, whereby the lead candidates are selected. Next, these candidates are tested and screened *in vitro* in cell cultures, to ensure that the substance interacts with the right receptor, for instance. This is done by means of high throughput screening, in which a large number of test substances are screened and only relevant substances continue to the selection process. Depending on the test substance's expected efficacy, other *in vitro* tests are conducted in which cells constitute a disease model, for instance. It is also necessary to test whether new prospective drugs cause local irritation so we can prevent discomfort when they are administered. We have previously used animals for this type of testing, but we have replaced them with test tube experiments.

Due to technological developments and the growing number of alternative methods, we have been able to reduce the number of animals by 70% over an eight-year period from 2003. Whether this is actually 'replacement' is debatable (as the key driver of drug development is to use the most ideal model), but it has significantly reduced in the number of laboratory animals that would otherwise have been used in experiments. In other words, both the motivation to reduce the number of laboratory animals and the development of technology have prompted this sharp reduction.

Reduction

It is possible to assess several test substances' potential adverse effects *ex vivo* by using tissue and organs from a single animal. For example, we use a *Langendorff heart* in which a wide variety of substances can be tested in one removed heart when assessing the efficacy of new drugs on the heart's contractile activity.

First, experiments are conducted on live animals *in vivo*, once new test substances have been assessed in test tube experiments and tested to see whether they have had the desired effect on cells and cell components. This applies both to efficacy testing and testing for adverse effects. After this, the next step is to study the test substances' pharmacokinetic metabolism, absorption, excretion, etc., as well as efficacy. This requires an organism that is still intact and, generally, only a few animals are studied before a more comprehensive experiment is set up. In 2019, we introduced ultra-microsampling, which enabled us to get a complete pharmacokinetic profile using minute (20 µl) blood-samples.

This made the procedure less invasive for the individual animal but also sharply reduced the number of animals needed, as the blood volume needed could be taken from a single animal instead of several.

We discuss and challenge ideas and treatment concepts before we initiate the animal testing. We conduct experiments with animals only if no alternatives are available and only after attempting to minimize the number used in every instance. We do this by means of various experiment designs and by calculating the minimum number of animals required to obtain usable, valid data.

Refinement

Our animal keepers handle and cuddle our rats as much as possible before the experiment starts so the rats are accustomed to and feel secure about being handled when the experiment begins. This reduces the rats' stress level and is instrumental in obtaining more robust experiment results as well.

Another refinement example is the housing of our mice where we have installed shelves in their boxes to give them a larger area to explore and a platform to jump up on. We also mix a little muesli into our rodents' bedding whenever their boxes are changed to encourage foraging behaviour. New forms of nesting material are continuously being tested to see which type they prefer, also individually for the various mice species.

Recently, we also tried out new super-enrichment cages for our rats. The cages consist of two interconnected ferret cages with space for about 10 rats, filled with toys, hammocks, tubes and ladders. It was a big success which resulted in noticeably more active and sociable rats. Our studies have also shown that it is also possible to house a group of rats (such as rats with head implants) in this type of cage. Accordingly, it is a housing option we will further develop and try to implement as standard in the near future.

At the same time, our animal keepers have successfully used clicker training with our minipigs to get them to follow a target stick, step up onto scales and to stand still for clinical examination and blood-sampling. The minipigs have also been trained to walk up a ramp onto the examination table by themselves where they can be handled and dosed. Clicker training has eliminated the need for heavy lifting and needless fixation of the pigs. It has led to a situation where the pigs want to cooperate with the animal keepers. With input from both animal keepers and researchers, new toys and enrichment materials for minipigs are regularly being tried out.



Moreover, in 2020 we have been working on using a gelatinous mixture for peroral doses which our minipigs voluntarily ingest instead of having to place them in a restraint device and dose them through a gavage tube. The procedural challenges are getting the pigs to eat something that doesn't necessarily taste good and making sure that the gel doesn't detract from or adversely affect the intake of the test substance and that its texture is appetizing to the pigs. These efforts have been successful, to the great delight of animal keepers and minipigs alike. The pigs voluntarily ingest the gel containing the test substance, saving both time and labour. Voluntary peroral administration with gel promotes the pigs' training, because they no longer have to be restrained for dosing. It is also beneficial in terms of research results by making it possible to more accurately time the administration, as minipig handling does not have to be considered to the same extent. The purpose of using the gelatinous mixture is eventually to replace all gavage-tube dosing of our minipigs.

We also use voluntary peroral dosing for post-operative pain relief of our rodents. Instead of subcutaneously injecting the animals with pain relievers, they are given so-called MD pellets. The MD pellets are specially developed for administering pain-relief agents to rodents, and make it easy to ensure that the animals ingest enough carprofen to provide pain relief. This was implemented to reduce pain-relief-related handling and optimize the pain reduction. The individual research departments are continuously working to improve procedures and similar initiatives so we improve animal welfare and achieve better research results at the same time.

The lab-animal veterinarians examine and treat the animals if necessary, and read through and help in the wording of animal-testing applications to ensure that the applications take account of the 3Rs. Also, the veterinarians regularly inspect and evaluate experiments to ensure that these conform to the procedure described in the permit.

3R prize

Lundbeck's Animal Care & Use Committee (LACUC) constitutes Lundbeck's animal welfare and ethics body. LACUC draws up and maintains Lundbeck's animal welfare and ethics policy and serves in an advisory capacity for researchers, animal keepers and veterinarians.

To recognize the efforts made by our employees relating to 3R, LACUC awards a 3R prize to one or more employees who have made an outstanding effort to reduce

the number of laboratory animals, to improve animal welfare or to replace the use of animals with other *in vitro*, *ex vivo*, or *in silico* options. The prize is primarily awarded for initiatives that have already been implemented, but it can also be awarded for the best idea.

Training and education

We also ensure that all employees involved with laboratory animals have the requisite skill sets by verifying their achieved, documented expertise, such as FELASA training certificates. For this, we organize an extensive in-house training programme to ensure compliance with Lundbeck's animal welfare and ethical guidelines and standards. This includes a mandatory course in animal ethics, which all employees must complete before they are allowed to work with the animals and a course in basic surgery if the employee is expected to perform surgery.

External cooperation projects

Some of Lundbeck's animal testing is performed by external partners. The minimum requirements for this are the EU Directive, and the same requirements apply all over the world where animals are used on behalf of Lundbeck. The lab-animal veterinarians make a big effort to ensure that the animal welfare of our external partners is on a par with the animal welfare in our own facilities.

We often share ideas with these partners and have fortunately experienced that the vast majority are interested in engaging in dialogue and are responsive to improvement proposals. Particularly for experiments involving large animals, such as non-human primates (NHP), minipigs and dogs, we take great interest in promoting the benefits of clicker training which we ourselves deem indispensable in experiment settings.

Lundbeck is also represented on steering committees for CALAR and the Danish Association of the Pharmaceutical Industry, and we support the Danish 3R-Center in promoting animal welfare in general.

The 3R principles are also found in a wide variety of aspects of Lundbeck's involvement with laboratory animals, and we consider the principles as the foundation for responsible research involving animals. We are convinced that the 3R principles not only improve animal welfare but also improve research-data quality and, not least, heighten job satisfaction for all our employees who are involved with animals.

5

INTERNATIONAL COOPERATION

The Danish 3R-Center has focused on international cooperation again this year, because the relatively modest size of our centre makes it logical to cooperate with others to disseminate knowledge of the 3Rs. Besides our vast networking efforts which – circumstances permitting – take place at various meetings and conferences attended by the Danish 3R-Center, more specific collaboration efforts are ongoing or taking shape.

EUROPEAN NETWORK OF 3R CENTRES – EU3RNET

One of the most interesting cooperation initiatives is our ongoing efforts to establish tangible cooperation among a wide range of European 3R organizations. In fact, a total of 24 European 3R organizations – so far – are involved in this cooperation (EU3Rnet does not yet have a website, but Norecopa has made an interactive map showing all the centres, which you can find here: norecopa.no/3REurope).

Since 2018, the number of network members has grown, clearly indicating that it is not only the Danish 3R-Center which regards cooperating with other centres as essential, because the individual centres’ national 3R improvements are obviously interesting internationally as well.

To establish a foundation – a frame of understanding – for this cooperation, it was decided in 2019 to formulate a consensus statement for the network, as the origins of the individual 3R organizations are vastly different in terms of tasks and organizational set-up. The Danish 3R-Center formulated a draft memorandum for this purpose, which, after incorporating input from the other centres, has now been adopted with the following wording:



PHOTO: NORECOPA

CONSENSUS STATEMENT

ALTEX preprint published 19 October 2020 doi:10.14573/altex.2010061

EU3Rnet embraces all of the 3Rs (*Replacement, Reduction and Refinement*) throughout its work, since the 3Rs are the foundation of improved conditions for research animals and for better science.

EU3Rnet also considers it important to focus on non-animal methods¹ as part of its collaborative efforts. Non-animal methods have largely been developed further after the introduction of the 3R concept by Russell and Burch² in 1959, thanks to technological advances in *in vitro* and *in silico* methods. EU3Rnet will therefore endeavour to promote this approach, so that researchers do not consider animal models by default when answering research questions, and instead consider the range of non-animal methods available, in order to avoid the unnecessary use of animal experimentation. When a relevant non-animal method or an alternative *Replacement* method³ to an animal model does not exist, the possibilities for *Reduction* and *Refinement* of the model must be examined.

EU3Rnet considers it important that internationally relevant national efforts to develop and promote the 3Rs and non-animal methods are disseminated within the network. The network will disseminate such information to its members, who in turn will disseminate the information further through their communication channels (which include websites, newsletters, symposia, training activities, annual reports and other channels).

EU3Rnet will emphasize the importance of involving all members of the research animal community in these efforts to develop and disseminate 3R resources. These include animal carers, technologists, veterinarians, teachers, lecturers and scientists.

All of the 3R centres in EU3Rnet pledge themselves to prioritization of their dissemination efforts. Whenever possible, they will use publicly available platforms to disseminate this knowledge, in order to maximize exposure.

1 Non-animal methods are defined as totally animal-free methods, not using any animal component.
2 Russell, W. M. S. and Burch, R. L. (1959). The Principles of Humane Experimental Technique. <https://caat.jhsph.edu/principles/the-principles-of-humane-experimental-technique>
3 Replacement methods like *in vitro* methods might still be dependent on animal components such as foetal bovine serum or Matrigel.

Participants of EU3Rnet, who agreed to the consensus statement

- 3Rs Center Czech Republic
- 3Rs-Centre of Utrecht University, The Netherlands
- BB3R - Freie Universität Berlin, Germany
- Centro3R: Italian Interuniversity Center for the Promotion of the 3Rs Principles in Teaching and Research, Italy
- Charité 3R - Charité - Universitätsmedizin Berlin, Germany
- CMCiB-IGTP - Comparative Medicine and Bioimage Centre of Catalonia, Germans Trias i Pujol Research Institute, Spain
- Comparative Medicine, Trinity College Dublin, Ireland
- EUSAAT - European Society for Alternatives to Animal Testing Europe
- ICAR3R - Interdisciplinary Center for 3Rs in Animal Research, Germany
- Innovation Centre - 3R Alternatives (IC-3Rs), Belgium
- Leibniz Alternatives at IUF - Leibniz Research Institute for Environmental Medicine, Germany
- LIST - Luxembourg Institute of Science and Technology, Luxembourg
- MUI animal Free Research Cluster, Austria
- Norecopa, Norway
- R2N - "Replace" und "Reduce" aus Niedersachsen, Germany
- ROCAM - Romanian Center for Alternative Test Methods, Romania
- Slovak National Platform for 3Rs in Research, Development and Education, Slovakia
- Swiss 3RCC
- TARCforce 3R - Medical University Mainz, Germany
- The Danish 3R-Center
- The National Centre for the 3Rs (NC3Rs), UK
- The RepRefRed society / Austrian 3R Center
- The Swedish 3Rs Center
- Unit Ethics and Human-Animal Studies, Messerli Research Institute, Vienna Austria



PHOTO: NOVO NORDISK

COOPERATION INVOLVING SIX EUROPEAN 3R CENTRES

THE DANISH 3R-CENTER / NC3RS / 3RS-CENTRE UTRECHT LIFE SCIENCES / THE SWEDISH 3RS CENTER / CHARITÉ 3R / SWISS 3R COMPETENCE CENTRE

In 2020, the Danish 3R-Center was involved in cooperating with the above-mentioned 3R centres. The group was established after NC3Rs inquired about the possibility of joining forces to hold a webinar, as the COVID-19 pandemic had rendered physical meetings impossible. The webinar was held with great success, which is why the group participants decided to continue cooperating.

In contrast with the above-mentioned cooperation (European Network of 3R Centres), this team of centres have decided that it does not need a framework of understanding, but will work as an informal group on the basis of shared interests.

The cooperation will occur as monthly meetings at which the centres keep one another informed of current areas of work and future plans to identify possible collaboration options in specific areas, and the individual centres can also submit ideas for one another's tasks.

The above-mentioned webinar was held on 22–24 September 2020 under the title *The 3Rs across Europe*, for which each of the six 3R centres provided two speakers: Jorid Sørli (National OHS Research Centre, Denmark) and

Eva Bay Wedebye (Technical University of Denmark), both of whom have received support for their research from the Danish 3R-Center, gave a webinar presentation on, respectively, *An in vitro method to predict sudden adverse lung effects* and *QUSAR modelling of chemical substances' possible interference with the thyroid hormone system*.

The attendance at all three webinar days was impressive with more than 600 viewers.

In the view of the Danish 3R-Center, this profoundly boosts the cooperation with other countries' 3R centres in the planning of such events. The fact that all the centres jointly promote the event undoubtedly generates higher attendance figures than if each individual centre had planned a separate event. As the Danish 3R-Center is modest in size, such collaborative ventures are crucial for our efforts to raise awareness of the Danish 3R-Center's work and the projects supported by the centre.

The team of centres will continue its efforts to organize similar webinars, as least as long as the pandemic renders physical conferences impossible.

The 3Rs across Europe

You can find video recordings of all the webinar presentations on: nc3rs.org.uk/3rs-across-europe-webinar-series-recordings



READ MORE AT
NC3R.ORG.UK

“The success of efforts to advance the 3Rs is dependent on having the right connections and collaborations in place. The new alliance between six European 3Rs centres was a real highlight for me in 2020. The benefits are obvious. We have all widened our networks and by pooling our knowledge and expertise we can collectively increase our impacts on the 3Rs.”

Dr Vicky Robinson
Chief Executive, NC3Rs

COLLABORATION WITH THE SWEDISH 3RS CENTER

Ever since the Swedish 3Rs Center was formed, the Danish 3R-Center has sought close collaboration. During 2020, this cooperation developed into quite close collaboration primarily based on the two centres' communication tasks. Roughly once a month, the two centres' two communication officers meet to keep one another up to date on current tasks and future plans. These meetings are very rewarding due to the two centres' keen focus on communication, as well as the similar

tasks shared by the two communication officers – such as tasks relating to organizing events, websites, annual reports, social media, etc.

Besides giving one another feedback on their many common tasks, both centres focus on disseminating one another's news on social media, primarily Twitter, spreading the two centres' good stories even further.

“Our rewarding cooperation is due to the fact that both Denmark and Sweden have a 3R centre and that they have engaged a communication officer. To me, as a solitary communication officer among experts in totally different fields, such as biomedicine or animal testing science, it is incredibly valuable to have a colleague who I can talk to on the other side of the Sound. We can truly learn from one another's experiences. We share ideas, proposals, thoughts and reflections from a communications perspective. We also give each other a heads up about what's happening in the 3Rs area in the respective countries and disseminate one another's information and activities.

Obviously, Denmark and Sweden work together in other areas as well, most recently in November when the Swedish 3Rs Center organized a webinar on non-animal methods and replacement, to which Denmark contributed expert knowledge and lecturers.”

Lisa Andersson
Communication Officer, Swedish 3Rs Center



PHOTO: BIOMEDICAL LABORATORY

APPENDIX

The following is an overview of all the projects that have received support since the Danish 3R-Center was founded in 2013.

OVERVIEW OF SUPPORTED PROJECTS, 2014-2020

PROJECT	R	PROJECT MANAGER	STATUS	PUBLICATION
2014				
‘Artificial blood vessels’ – a model for investigating diabetic arterio-sclerosis	Replacement	Mette Bjerre University of Aarhus	Completed	To be published once additional studies have been done and more results achieved
Standardizing gut microbiota in mice as a tool for reducing the number of animals in the individual experiments	Reduction	Axel Kornerup Hansen University of Copenhagen	Completed	Published in Scientific Reports in March 2017 (link at the Danish 3R-Center’s website)
Refinement of animal models of pain: Development of methods to limit pain in laboratory rats used in pain research	Refinement	Klas Abelson University of Copenhagen	Completed	Publication expected in the near future (link on the Danish 3R-Center’s website)
Pathological and immunological consequences of murine blood sampling	Refinement	Dorte Bratbo Sørensen University of Copenhagen	Completed	Published in the Journal of the American Association for Laboratory Animal Science in May 2019 (link at the Danish 3R-Center’s website)
2015				
Developing an <i>in vitro</i> method to predict acute pulmonary toxicity from aerosol proofing products	Replacement	Jorid Birkelund Sørli (previously Søren Thor Larsen) National OHS Research Centre	Completed	Published in ALTEX Online First in August 2017 (link at the Danish 3R-Center’s website)
Can chickens be immunized with an aerosol combined with vaccination? Investigating a non-invasive method for producing antibodies	Replacement	Otto Kalliokoski University of Copenhagen	Completed	Not published (negative results) (Link to the report on the Danish 3R-Center’s website)
Artificial skin in a Petri dish as an alternative to laboratory animals	Replacement	Mette Elena Skindersø (June Lissa Hansen) Statens Serum Institut	Completed	Publication expected in the near future (link on the Danish 3R-Center’s website)
2016				
Development of computer models for predicting chemicals’ impact on thyroid hormones	Replacement	Marianne Dybdahl DTU-FOOD	Completed	Published in Computational Toxicology in January 2017 and Computational Toxicology in 2017 (link at the Danish 3R-Center’s website)
Using cell cultures to minimize the need for laboratory animals in developing and manufacturing vaccines for farmed fish	Reduction/ Refinement	Niels Lorenzen University of Aarhus	Completed	Supplementary experiments must be conducted to enable publication
Towards better treatment of brain cancer with new cell-based models and less animal testing	Replacement	Bjarne Winther Kristensen University of Southern Denmark	Completed	Published in the Journal of Neuro-Oncology in August 2016 and PLOS ONE in May 2016 (link at the Danish 3R-Center’s website)

PROJECT	R	PROJECT MANAGER	STATUS	PUBLICATION
2017				
The use of primary kidney isolates from humans for studying the molecular aspects of blood-pressure regulation	Replacement	Henrik Dimke University of Southern Denmark	Completed	No plans for publication
Implementation of pain-treatment methods for rats used as a model for inflammatory arthritic pain	Refinement	Klas Abelson University of Copenhagen	Completed	Publication expected in the near future (link on the Danish 3R-Center’s website)
Development of cell-based assays for measuring antibody-mediated protection against the chlamydia bacterium	Replacement	Jes Dietrich Statens Serum Institut	Completed	Published in the Journal of Quantitative Cell Sciences in March 2018 (link at the Danish 3R-Center’s website)
2018				
Murine Passport	Reduction	Axel Kornerup Hansen University of Copenhagen	Completed	
New advanced blood-infection model	Replacement	Thomas Emil Andersen University of Southern Denmark	Completed	Publication expected in the near future (link on the Danish 3R-Center’s website)
Transport and metabolism of fungicides in the human placenta	Replacement	Bjarne Styrihave University of Copenhagen	Forventes afsluttet primo 2021	Publication expected in the near future (link on the Danish 3R-Center’s website)
2019				
The significance of cage enrichment for protein metabolic experiments	Refinement	Helle Nygaard Lærke University of Aarhus	Completed	Publication expected
Genetic modification of mice without a need for extensive breeding	Reduction	Per Svenningsen University of Southern Denmark	Expected in early 2021	
Study and analysis of the internal validity in the field of Danish pre-clinical research	Reduction	Birgitte S. Kousholt University of Aarhus	Expected to be completed in August 2021	
2020				
Establishment of an <i>in vitro</i> model to investigate extracellular matrix and vascular mechanical interactions in human arterial disease	Replacement	Julián Albarrán-Juárez University of Aarhus	Expected to be completed in late July 2021	
Introduction of new human <i>ex vivo</i> model systems to study tumorigenesis in kidney cancer	Replacement	Otto Kalliokoski University of Copenhagen	Expected to be completed in late April 2023	
Fighting irreproducibility in preclinical medicine using a meta-analytical approach for detecting flaws in behavior-based testing	Replacement	Kirsten Madsen University of Southern Denmark	Expected to be completed in late November 2021	

THE DANISH 3R-CENTER IN BRIEF



READ MORE ON
3RCENTER.DK

The Danish 3R Center is a collaboration involving the Ministry of Food, Agriculture and Fishery, the Danish Animal Welfare Society, DOSO, LEO Pharma, Lundbeck and Novo Nordisk. The Danish 3R-Center works to promote the 3Rs in Denmark to bring focus to bear on alternatives to animal experimentation and create even better conditions for laboratory animals.

THE DANISH ANIMAL WELFARE SOCIETY

“In the view of the Danish Animal Welfare Society, the use of laboratory animals must be restricted wherever possible. This is why the Danish Animal Welfare Society actively supports the Danish 3R-Center’s efforts to replace, reduce and refine the use of laboratory animals. In particular, we have great confidence that efforts to promote the development and knowledge of alternatives to laboratory animals will contribute to realizing DAWS’ ambition to phase out the use of laboratory animals.”

DOSO (COOPERATION ORGANISATION OF ANIMAL WELFARE BODIES)

“The overarching aim of DOSO is to abolish animal experimentation. Towards this end, DOSO is actively engaged in promoting the development, validation and implementation of alternatives to animal testing based on the 3R principles. Making an active effort and supporting the Danish 3R-Center provides a good opportunity to achieve this goal.”

LEO PHARMA

“Many of our tests and testing models in the development of pharmaceuticals for treating skin disorders have been replaced in part by laboratory testing.

However, we still need to use laboratory animals in the development of medicine to reliably assess the efficacy of medicines and comply with regulatory requirements. At LEO Pharma, our animal welfare policy revolves around on the 3Rs, and we have ongoing initiatives to reduce, replace and refine the use of laboratory animals wherever possible. It is consequently a natural element of this policy to support the national 3R-Center to increase resources within the 3Rs.”

LUNDBECK

“To facilitate the development of safe and effective medicinal products, we have to use laboratory animals at Lundbeck. We continuously seek to optimize the conditions for these animals, and we use alternative methods wherever possible. For this reason, it was a natural choice for us to support the Danish 3R-Center so that we can stay abreast of 3R developments. With this collaboration, we support the continued development of all 3Rs while staying up-to-date on new ideas and initiatives that can benefit our laboratory animals.”

NOVO NORDISK

“It is still not possible to develop medicine that is efficacious and safe for patients without using laboratory animals. Novo Nordisk and the Danish 3R-Center share the same wish to promote the development of alternatives to animal testing, reduce the use of laboratory animals, improve conditions for laboratory animals and disseminate knowledge about alternatives to animal testing. Novo Nordisk actively works to achieve these goals, which is why we also actively support the Danish 3R-Center.”