Vetenskapsrådet

Ansökan

2019-00203	Sveriges lantbruksuniversitet	FI-IP

Information om ansökan

Utlysningsnamn: Infrastruktur av nationellt intresse 2019 (Forskningsinfrastruktur)

Bidragsform: Forskningsinfrastruktur

Sökt inriktning: Infrastruktur av nationellt intresse

Ämnesområde utlysning: FI

Projekttitel: Svenskt experimentellt klinisk centrum för innovativa stordjursmodeller

Projektstart: 2020-01-01 **Projektslut:** 2024-12-31

Sökt beredningsgrupp: FI-IP

Klassificeringskod: 30199. Andra medicinska och farmaceutiska grundvetenskaper

Nyckelord: Translational research, Large animal, Experimental surgery, Companion animal, Disease models

Sökta medel

År:	2020	2021	2022	2023	2024
Belopp:	15 001 632	21 135 844	18 307 044	17 762 605	17 677 753

Medverkande Organsationer*

Sveriges lantbruksuniversitet (SLU)
Uppsala universitet (UU)
Sveriges veterinärmedicinska anstalt (SVA)
Karolinska Institutet (KI)
Göteborgs universitet (GU)/Sahlgrenska universitetssjukhuset
Linköpings universitet (LiU)

Infrastrukturens namn (svenska)*

Svenskt experimentellt klinisk centrum för innovativa stordjursmodeller

Infrastrukturens namn (engelska)*

Swedish Experimental Clinical Center for Large-Animal Innovative Models (SWECCLIM)

Abstract (engelska)*

The Swedish University of Agricultural Sciences (SLU) together with Uppsala University (UU), the Swedish Veterinary Institute (SVA), Karolinska Institutet (KI), the University of Gothenburg (GU) / Sahlgrenska University Hospital and Linköping University (LiU) collaborate to create a new national infrastructure for clinical and experimental studies in large animal models. The proposed infrastructure will provide Sweden with a visible and well-coordinated university facility that can conduct long-term studies in large animals, open new research routes and facilitate the transfer of new treatments from "bench to bedside".

Animal experiments are expensive to perform and guarded by rigid legislation to ensure that only necessary and thoughtful studies are conducted. This makes it even more important to create environments where the best expertise in the field is gathered and that all aspects of competence are utilized. Through SWECCLIM, we create a transdisciplinary infrastructure that unites the best of expertise in human medicine in surgery, transplantation, anesthesia/intensive care and advanced diagnostic imaging together with specialists in veterinary medicine in corresponding areas. We also acknowledge the great importance of knowledge in animal health, animal welfare and ethology (behavior) by bringing together academic competence in these areas.

We will handle a wide range of projects, such as xenografts, infectious diseases, cancer, aging, orthopedics, soft tissue surgery, heart disease, nutrition, diabetes, stem cells, sepsis, osteoarthritis, lifestyle diseases, infections after surgery and development of new materials for prostheses. Thus, Sweden will have a state-of-the-art infrastructure for relevant research and development of new therapies for both animals and people that contribute to improved quality of life and prolonged survival.

Populärvetenskaplig beskrivning (svenska)*

Svenskt experimentellt kliniskt center för innovativa stordjursmodeller (SWECCLIM).

Sveriges lantbruksuniversitet (SLU) tillsammans med Uppsala universitet (UU), Sveriges veterinärmedicinska anstalt (SVA), Karolinska Institutet (KI), Göteborgs universitet (GU)/Sahlgrenska universitetssjukhuset och Linköpings universitet (LiU) går samman för att skapa en ny nationell infrastruktur för kliniska och experimentella studier i stordjursmodeller.

I den medicinska forskningen finns ett uttalat behov av studier i olika djurmodeller. Den stora volymen av djurexperiment görs i gnagare. Men det finns försök som lämpar sig bäst, eller är helt nödvändiga att utföra i större djur. På senare tid har det med all önskvärd tydlighet visat sig att behandlingar på människa, exempelvis med luftrörsimplantat, utförts utan att nödvändiga studier i stordjur först bekräftat lämpligheten av teknikerna och hur de skulle behöva optimeras innan man utsätter svårt sjuka människor för denna behandling. Djurexperiment är kostsamma att utföra och omgärdade av rigid lagstiftning för att tillse att bara nödvändiga och genomtänka studier utförs. Detta gör det än viktigare att skapa miljöer där den främsta kompetensen inom fältet samlas och att alla aspekter av kompetens tillvaratas. Genom SWECCLIM så skapar vi en transdiciplinär infrastruktur som förenar det bästa av kompetens inom humanmedicin i kirurgi, transplantation, anestesi/intensivvård och avancerad bilddiagnostik med experter inom veterinärmedicin på motsvarande områden. Vi lägger också stor vikt vid expertkunskap på djurvälfärd, djurskydd och etologi (beteende) genom att sammanföra akademisk kompetens inom dessa områden. Där kommer förutom den veterinärmedicinska kompetensen vid SLU även den gedigna kompetens som finns vid Göteborgs universitet (GU)/Sahlgrenska universitetssjukhuset samt Linköpings universitet (LiU) att komplettera. Allt detta är till för att skapa försök där informationen maximeras som förutsätter att djur stressas så lite som möjligt och att man anpassar studierna och miljön till rätt djurslag.

Universitetsdjursjukhuset (UDS) vid SLU ger tillgång till sällskapsdjur som under behandling kan fungera som spontana modeller för många sjukdomar som ses hos människa. Husdjuren delar levnadsmiljö, dricksvatten och vanor i stor utsträckning med sina ägare. Normalt åldrande sällskapsdjur som spontant utvecklar cancer och andra vanliga humana sjukdomar med gemensamt histologiskt utseende, genetik, biologiskt beteende, molekylära mål, svar på behandlingar kan fungera som en användbar brygga mellan traditionella prekliniska gnagarmodeller och kliniska prövningar i människa. Det här är en helt unik möjlighet, som inte finns i konventionella stora experimentella laboratorier.

Användning av spontana sjukdomar hos djur med ett fungerande immunförsvar reducerar också behovet av att framkalla sjukdomar hos friska laboratoriedjur och innehåller den nödvändiga komplexiteten vid sjukdomsförlopp, som ofta saknas i vanliga experimentella försök. Att använda djur med spontana sjukdomar lägger också till etiska värden och bidrar till att nå mål inom 3R (Reduce, Refine and Replace). Djuren ingår i studier samtidigt som de söker och får vård av veterinärmedicinsk expertis. Analyser görs på prover som ändå skulle tas för den normala diagnostiken eller behandling och tillför inget extra ”lidande” till patienterna, utan utförs i stort på överblivet material.

Den föreslagna infrastrukturen kommer att ge Sverige en synlig och väl samordnad universitetsanläggning som kan utföra långtidsstudier i stordjursmodeller, öppna nya forskningsvägar och underlätta överföringen av nya behandlingar från ”labbänk till säng”.

Vi kommer hantera ett brett utbud av projekt, tex xenotransplantationer, infektionssjukdomar, cancer, åldrande, ortopedi, mjukdelskirurgi, hjärtsjukdomar, nutrition, diabetes, stamceller, behandling av blodförgiftning, osteoartros, livsstilssjukdomar, infektioner efter operationer och utveckling av nya material för proteser. Således kommer Sverige att få en toppmodern infrastruktur för relevant forskning och utveckling av nya terapier för både djur och människor som bidrar till förbättrad livskvalité och förlängd överlevnad.

Område/Infrastruktur*

Infrastruktur för experimentell forskning på stora djur

Redogörelse för etiska överväganden*

Short summary of the legal framework for laboratory animals in Sweden and the ethic consideration for SWECCLIM

Within SWECCLIM we adhere to all of the far reaching legal framework regarding the animals that we use for scientific purposes in Sweden. The Directive 2010/63/EU (EU Directive) on the protection of animals used for scientific purposes has been implemented in the Swedish legislation, but Sweden maintained a definition of research animals which includes all animals in scientific procedures regardless of whether they are subjected to suffering or not. This means that all scientific projects have to meet several requirements, including an authorization issued by the competent authority (Swedish Board of Agriculture) that allows the researcher to perform studies on animals. The project must also pass an ethical evaluation for approval, by one of the six regional animal ethics committees (AEC) in Sweden. The project evaluation includes a harm-benefit analysis with regard to animal suffering and the predicted gain for society. Before an application can be submitted to the regional AEC, the principle investigator has to discuss the experimental plan with the animal care and welfare officer, the veterinarian and with the animal care takers to ensure good scientific practice and the best possible care and welfare for the animals. Research projects must be planned according to the principle of the 3Rs (Replacement, Reduction, and Refinement). This means that if there are no available alternatives to using animals, the number of animals should be kept to a minimum to still achieve statistically significant scientific results and that procedures should be performed in the most humane way possible. This is further strengthened by the requirement that all staff who perform research procedures and handle the animals must be adequately educated and trained for the species that they are working with. There is also a legal demand for all users of animals for scientific purposes to establish an animal welfare body that will give advice on matters related to the welfare of the animals and the application of the 3R:s. Furthermore, the animal welfare body shall promote animal welfare and therefore enhanced scientific outcomes by fostering a culture of care where all people involved with the animals constantly work together to improve animal welfare.

To highlight the importance of prudent use of research animals and adherence to the 3R principles, we have created a specific 3R/training module in this infrastructure. It ensure that a firm critical mass of expertise within this field has the responsibility to constantly monitor and advice on projects performed in SWECCLIM.

Use of personal data

Research projects involving companion animals will handle personal data on owners regulated by GDPR. We will push pseudo anonymized records from the electronic medical records to dedicated servers thereby removing sensitive owner data from the research records available to external partners. The data under control of SWECCLIM will be handled in accordance with the GDPR policy of SLU. Compliance with regulations will be controlled by the steering committee.

I projektet ingår hantering av persondata

Ja

I projektet ingår djurförsök

Ja

I projektet ingår humanförsök

Nej

Vetenskaplig plan*

Se nästa sida för bilaga.

Scientific plan

1 SWECCLIM – Swedish experimental clinical center for large-animal innovative models

Appropriate animal models for the evaluation of efficacy and safety of new drugs or therapeutic concepts are critical for the success of translational research – from molecule to bedside. Whereas biotechnological techniques have revolutionized manipulation of rodents to get more significant insights into human disease pathogenesis, these models often fail to reproduce the phenotypes of many human diseases. Disease models using animals that are more closely related to humans offer a much better route to understand disease mechanisms and evaluation of new therapies. Likewise, many of our livestock diseases are far from understood, with critical implications for food supply and human health. Access to facilities for experimental research and housing of large animals is imperative also for educational purposes. Management and clinical expertise within large animal species are primarily veterinary competences and because the collaboration between human and veterinary research has been relatively sparse, there is a lack of animal expertise outside veterinary settings. Furthermore, due to lack of resources and infrastructure in Sweden, many researchers and companies turn to facilities abroad to perform their studies. This fact hinders translational research in Sweden and will lead to a depletion of knowledge of large animal models in Sweden. Work with, and development of, large animal models require the integration between human and veterinary sciences. A platform for human and veterinary sciences to develop and validate models in large animal species, as well as facilitate the use of these models nationwide, is therefore urgently needed.

1.1 Prominent national and international research enabled by the infrastructure

The concentration of advanced large animal research in SWECCLIM that includes experimental models, natural models with spontaneous disease and research on primates, to one infrastructure is essential for development optimization and innovation. The modules are basic science and experimental models, Advanced diagnostic imaging, Spontaneous disease models in companion animals, Infectious diseases and 3R/Training.
In the experimental module Xenotransplantation, long-term studies of implants (such as artificial organs [e.g., trachea, aorta], pacemakers/defibrillators, orthopedic prosthesis, stents, implants to maintain hemostasis etc), long-term studies of bone-grafts and orthopedic implants in relevant large animal models are included.

Long-term studies of implants.
There have recently been some well-noticed drawbacks regarding implants for tracheal replacement and cardiac stimulators, partly due to insufficient studies in large animal models before the devices/implants were applied in patients. Hence, it is crucial for Sweden to have one facility that has the capacity for long-term studies of such implants in relevant-sized models. Today, several Swedish research groups perform their large animal studies in other countries. In this regard, it is important to note that implants such as pacemakers and prosthesis are not only used in humans but also in domestic animals and therefore such studies are also important from a translational perspective, for the development of veterinary medicine in itself and enhanced animal welfare.

Long-term studies of bone-grafts and orthopedic implants.
Most studies of bone regeneration and methods to improve bone grafting have been performed in rabbit models. However, to know the effect of bone grafting/regeneration it is important to study this during a longer period in models with adequate loading with similar stress and strain as in humans. Large animal models fulfill these requirements and the tradition is to use sheep models. These techniques are not only experimental, but also used today in state-of-the art veterinary oncological surgery where especially osteosarcoma in certain anatomical location (e.g. distal radius/ulna) are sometimes treated with limb-sparing techniques, where the tumor segment is excised and different implants are used to replace the tissue. These can be autologous with ipsilateral grafts and/or prosthetic devices of different materials, often 3D-printed from CT reconstruction/simulations of the patient's anatomy. Such treatments are ideal to also serve as models to study new techniques (materials and surgical techniques) in an immune competent model with similar complex etiology of the disease (osteosarcoma) with similar to identical tumor biology and histology.
Uppsala University has a strong track record within the material sciences and the area of bone regeneration. The ability to offer large animal models in the immediate proximity will strengthen the research area and also shorten the time frame for research treatments being made available to patients. The expertise at SLU within biomechanical measurements of animal movement will further enhance the quality of orthopedic research at SWECCLIM.

The plan is to make all existing equipment and the unique veterinary diagnostic imaging specialist competence available for the needs of the researchers with animal models in SWECCLIM. A new large-bore Positron Emission/Computed Tomography (PET/CT) machine is in this regard an essential addition to the existing imaging infrastructure. It will be needed for experimental studies in inflammation, transplantation, and oncology in both experimental and natural models (see the different modules).

At SLU there is a unique constellation of specialists with research experience in several disciplines of veterinary medicine. There is a strong tradition in veterinary diagnostic imaging in Sweden going back to the late 1950s when one of the first professors in the subject in the world was located here. There are today more than 20 individuals specialized in veterinary diagnostic imaging working at SLU, several with a European specialization degree (DipECVDI), and the University Veterinary Hospital at SLU is an approved training center for veterinary radiology and currently has four residents doing this four years long post-graduate education. Finally, it is planned to further expand the excellence by increasing the collaboration with the imaging experts in radiology and nuclear medicine at the Uppsala University/University hospital and Karolinska Institutet/hospital.

The Uppsala University's Platform for Preclinical PET-MRI (PPP), has a long and successful track record of PET tracer validation within the field of biomedical research including neurology, oncology, inflammation, metabolic diseases and drug discovery and development. PPP has indeed the expertise to push translational projects all the way from radiolabeling to human clinical trials and will be a key player for providing the necessary PET tracers to the imaging facility at SLU as well as validation of new tracers.

Likewise, the PET Unit for imaging non-human primates (NHPs) at Karolinska Institutet is conducting pre-clinical imaging in NHPs since the ´80´s. The main focus of the research group has been on the development of new PET radioligands for brain imaging and development of new CNS drugs in collaboration with major pharmaceutical companies. Over several decades more than 150 PET radioligands for the CNS have been developed at Karolinska Institutet and evaluated pre-clinically in NHPs. PET imaging in NHPs is a key element of the translational molecular imaging chain from small animals to human subjects due to the genetic similarity between primate species and their similar metabolic pathways. The access to NHPs at the Astrid Fagreus Laboratory (AFL) provides a fully translational research platform for rapid implementation and validation of new PET probes for human studies.

The large large-boar PET-/CT at SLU will with its strategic place be an equipment used for both module 2 and 6 and with the possibility to also serve study objects from the infectious module at SVA only a couple of hundred meters away. Finally, it is planned that some investigations in NHPs will be performed using this unique device, primarily as the necessary access to a specialist in veterinary anesthesiology is always available at SLU Uppsala.

Companion animals develop many diseases in common with their owners. They share the same living condition, including drinking water, food and indoor and outdoor environment. Dogs are good cancer models because they are large outbred animals, have genetic similarities to humans, have naturally occurring cancers, are immune competent and syngeneic, have relevant tumor histology and genetics, receive relevant response chemotherapy, have compressed progression times, display heterogeneity and recurrence/resistance, and enable the study of metastasis biology. Dogs can be used in pre-clinical studies, prospective clinical trials (phase I and II), ADME studies (absorption, distribution, metabolism, and excretion), prognostic and predictive biomarker development. Due to shorter period of tumor development and time to relapse it is also easier to study biomarkers in longitudinal studies, as well as monitor ctDNA (including liquid tumor biopsies) with time in dogs.

Diabetes mellitus is a large concern in both dogs and cats. Common risk factors include overweight and gestation/pregnancy. It is suggested that dogs have a diabetes very similar to type 1 in man, whereas cats present with a type 2 variant, sometimes going into remission if diet and weight reduction is occurring at an early stage. Usually with a shorter time of concurrent insulin therapy. At SLU research on c-peptide in dogs and association of overweight and diabetes in cats have been performed. It is also discovered that certain breeds (in both dogs and cats) are predisposed to develop diabetes. This offers an interesting model to study genetic risk factors to develop both diabetes type 1 and 2. With a very strong competence within veterinary endocrinology and internal medicine at SLU coupled with stellar human diabetic knowledge from partners within SWECCLIM (such as Uppsala University and KI), there is a huge potential in discovering important pathways to interfere and reverse diabetic status in both animals and man. This would offer a big impact on society, as diabetes (especially type 2) is an emerging society catastrophe both concerning suffering and financial.

1.2 How the infrastructure addresses scientific and societal challenges

Animal research has been challenged in modern society. This fact could be partly due to lack of understanding and information of the importance of this kind of science, but also that the translation of results to human welfare of research in rodent models has been scarce. Indeed, extremely few promising rodent studies of malignant diseases, inflammation and trauma have been positive in patients. Therefore, it is crucial to have models of similar size and with similar physiology as in humans to be able to translate experimental results to patients with higher probability. This will, except benefit the patients and science, increase the societal acceptance of experimental animal research. The suggested infrastructure will have, as mentioned earlier, a capacity to perform long-term studies in relevant large animal models, and is in line with the recommendation from the Swedish Research Council in its recent scientific overview for medicine and health to strengthen the support of the animal research.

Natural disease models have the advantages to be very similar to humans' diseases since they develop in the same environment. Thus, pets live in the same houses, eat similar food, and importantly, are exposed for similar pollutants and chemical environment as humans and therefore develop the same diseases, e.g., cancer, chronic obstructive lung diseases and cardiopulmonary conditions as people. Thus, studies in the natural models have high relevance and could be translated not only to humans but also to domestic animals and therefore could, in the end, improve both human and animal health. The suggested infrastructure, where the University Animal Hospital is included will be the only site in Sweden where such studies could be performed.

The suggested infrastructure will have the highest concentration in Sweden of expertise in all veterinarian medicine fields and in animal welfare indicating that the 3R perspective will be of the highest possible standard. In addition to more relevant study results and excellent animal welfare, this will increase the societal understanding of the importance of animal research for medical progress.

1.3 Long-term significance of the infrastructure for the scientific field in relation to other national and international existing infrastructures

As indicated above, this kind of infrastructure is essential for the development of new therapies in humans such as xenotransplantation, implants (artificial organs [e.g., trachea, aorta], pacemakers/defibrillators, orthopedic prosthesis), bone-grafts and in both humans and animals using natural large animal models, e.g., cancer, pulmonary and cardiovascular diseases.

At the present local University animal research facilities, mostly terminal experiments are performed in large animals. At some facilities, e.g., CBR, Linköping, is it possible to house the animals to perform longer-term studies on e.g. skin transplantation in pigs, but at no Swedish facility, any major long-term experiments are performed on a large animal (pigs, sheep or cattle) or non-human primate models. Thus, there exists no facility for performing long-term experiments regarding, e.g., xenotransplants or implants. In addition, although education in some areas, e.g., trauma care, is performed diligently in many of the facilities in Sweden, the suggested infrastructure will be superior and unique for education in advanced interventions for both animal experimentalists, physicians and veterinarians. Since the infrastructure is associated with the Swedish Livestock Research Centre (Lövsta) at SLU, it will have full quality control of the research animals from breeding at the farm to the experiments at the laboratory. This fact guarantees that the animals are healthy, e.g., at Lövsta SLU only breeds SPF (specific pathogen-free) pigs. At the moment this is to study the positive impact of SPF status on production parameters, but with the possibility to also include these in medical research, where SPF animals are instrumental in certain research areas and expensive to produce and obtain. Using SLU Lövsta is hence both cost- and logistically efficient.

As stated above, the suggested infrastructure will be the only one in Sweden that can perform translational research in natural occurring spontaneous models. This is due to the immediate access to the University Animal Hospital (with veterinary academic expertise). Moreover, since the infrastructure includes the only research facility for non-human primates, studies in animals evolutionary close to humans will be feasible that will be highly relevant in e.g., immunological and xenotransplant research.

In Uppsala there are two specialized veterinary pathology labs, with the highest competence both within research and clinical specialization in the field. At SVA the possibility to serve the infectious module facility with direct examinations will be indispensable. Similarly, the pathology lab at SLU is in close vicinity to both the experimental animal unit as well as the University Animal Hospital. It is well known that rapid fixation and analysis of tissue is crucial to optimize research output. At SVA and SLU several molecular pathology techniques and expertise in interpreting results and changes from all species included in SWECCLIM is present, ensuring optimal support to the entire cross-disciplinary research team working within the infrastructure. Finally, the incorporation of veterinary pathology labs within SWECCLIM will minimize transportation of animals. Transportation is costly, imply biohazard potential and risk to compromise accurate interpretation of research performed if tissue degradation occurs before post mortem analysis is conducted.

1.4 Users

We presume, as mentioned, to have users from all academic medical centers in Sweden, SLU and many international medical or veterinarian institutions as well from the medico-technical and pharmaceutical industries. Since the planned infrastructure is new, it is not possible to give exact numbers. However, the infrastructure will consist of among the others the large animal laboratory (the Hedenstierna laboratory) presently located at Uppsala University campus. This laboratory, which now only perform terminal experiments, has users from Uppsala University (Anesthesiology and Intensive Care, Cardiothoracic Surgery, Neurosurgery, Infectious disease), SLU, as well as from Karolinska Institutet (Cardiothoracic Surgery, ECMO center), Gothenburg University (Anesthesiology and Intensive Care), Lund University (Cardiovascular surgery), the Universities in Magdeburg, Germany; Bonn, Germany; Lyon France; Grenoble, France; Madrid, Spain; Valencia, Spain; Milan, Italy; Ferrara, Italy; Bari, Italy; Sao Paolo, Brazil and Santiago de Chile. Thus, it is used by about 20 different research groups with more than 60 different scientists who mainly perform their experiments in collaboration with the groups at UU. Approximately about 40% of the researchers are women: Also, the laboratory is used at present by four medico-technical companies for development and education. The academic use covers about 80% of the about 250-300 experiments performed at laboratory per year. We anticipate that the number of experiments (short and long-term studies, studies in natural spontaneous models and NHP:s) at SWECCLIM will be 500-600 annually and that the national and international institutions will contribute as described above. In addition different companies within the drug development and medical technique and diagnostic sectors will be using SWECCLIM.

1.5 Novel research areas and user groups

Since it has been impossible to perform full-size xenotransplant research in Sweden, this will be a new research area. Furthermore, as long-term studies of implants, infection, immunology, bone research, wound healing etc. have not been possible in Sweden in large animals we expect that users from these areas will utilize the infrastructure. Indeed, we have a positive response from orthopedic and transplant surgeons and intensive care medicine researchers from KI, Universities of Uppsala, Lund, Linköping and Gothenburg. Although, research on spontaneous disease models in sports- and companion animals has been performed since long, the formation of such an intricate network of cross-disciplinary researchers and a state-of-the art infrastructure will enable completely new projects within this field. It will allow full use of the potential to study complex diseases in immunocompetent models sharing the same environment as their owners – humans. This type of research is highly regarded by the public and will contribute to highest ethical standards of the infrastructure at the same time as unmet needs in treatments of pets simultaneously informs human research about possibility of progress within, prevention, diagnostics and treatment of severe human conditions that currently cause individual suffering and generate high costs for the society.

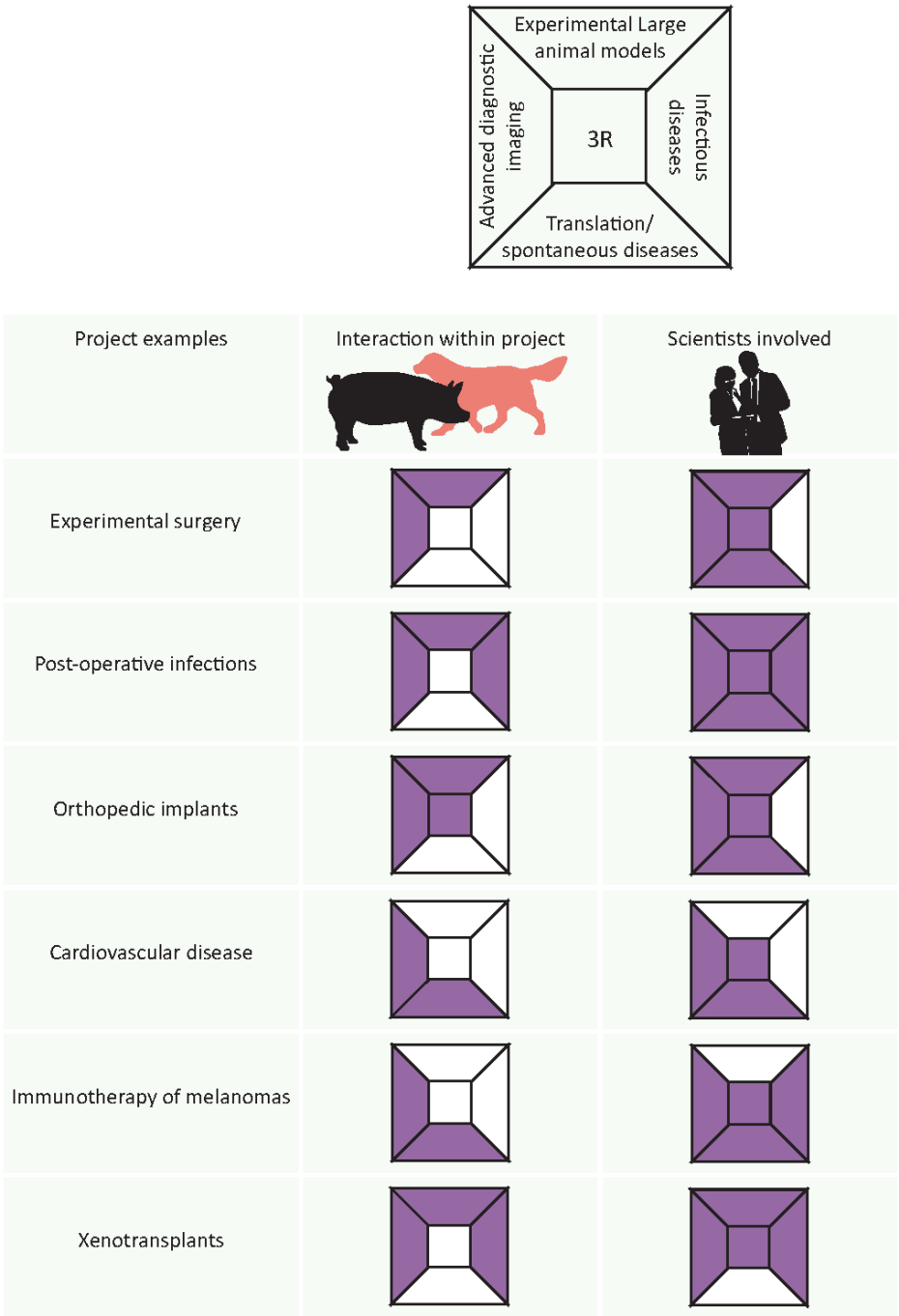

Figure 1. Integrations of modules within SWECCLIM. Both logistics/flow of animals as well as scientists are shown with a selection of projects mentioned in the application. In all mentioned projects several modules are well integrated, elucidating the use of interdisciplinary research. The idea with SWECCLIM is to improve knowledge transmission to optimize the use of research animals, create new clusters of competence and with state-of-the-art equipment perform research that in many instances hitherto has been impossible to conduct in Sweden.

1.6 Infrastructure's contribution to national capacity building and knowledge

Due to the substantial accumulation of animal research experts, academic veterinarians and advanced animal care personnel at one location, in addition to an excellent infrastructure and increased collaboration with other large animal research facilities in Sweden, the competencies in experimental methods, surgery, anesthesia and post-operative care of large animals, both research animals and animal "patients", will be improved. This increased competency will therefore not only benefit the infrastructure per se but all large animal research in Sweden. Furthermore, since the studies are aimed at improving medical therapies and basic knowledge of diseases of both human and animals, it will, eventually, improve both human and animal health care nationally and internationally. Notably, this facility is a requisite for the development of xenotransplants that may be an important step to reduce the lack of organs for human organ transplantations.

1.7 Policy of data sharing and national research competence development.

The increased collaboration between this infrastructure and other large animal facilities in Sweden will include data sharing and as indicated above, will also improve the overall large animal research competency. The included universities in this application are all in favor of Open Access publication. Within SWECCLIM we will support this approach and suggest all researchers to primarily publication in Open Access journals. This will also lead to that research data used for these studies will be more accessible to all researchers. The financial support for Open Access needs to be handled by respectively partner involved, as no special funds have been allocated in this application for Open Access publishing.

Research projects involving pets will handle personal data on owners regulated by GDPR. We will push pseudo anonymized records from the electronic medical records to dedicated servers thereby removing sensitive owner data from the research records available to external partners. The data under control of SWECCLIM will be handled in accordance with the GDPR policy of SLU. Compliance with regulations will be controlled by the steering committee.

2 Impact for society and innovation

The Swedish medical technology industry will benefit from such concentration of the medical/veterinarian expertise using models of relevant size and evolutionary development. At present, one of the applying parties, the Hedenstierna laboratory at UU has close collaboration with the medical-technical company, Getinge, and we anticipate that also pharmaceutical companies will have great use of long-term experiments and testing of new drugs in large animals.
Thus, the development of relevant and useful new therapies requires large animals. As mentioned above, although studies in rodents have shown important basic mechanisms, very few, if any, positive studies in small animals have been possible to translate to humans. Therefore, large animal research is the logical and essential intermediate step before testing new therapies in patients.
Large animal research is very expensive and therefore due to both economic and 3R-reasons this kind of research has to be concentrated to a site with the highest level of animal research and veterinarian expertise. This increased level will be of international interest and attract foreign researchers and companies.

The formation of SWECCLIM is one step assisting in meeting the WHO Sustainable Development Goals (SDGs) 3 “Good Health and Well Being” - *By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being.* In particular cardiovascular disorders, diabetes and cancer will need to significantly improve regarding diagnosis and treatment for SDG 3 to be realized. As an example, in 2012, the Globocan report estimated the number of new cancer cases to 14 million globally. Approximately 6.8 million, or 48 %, occurred in low- and middle-income countries. According to the same source, the number of new cancer cases is projected to have reached 24 million in 2035 and 54 % of these, or almost 13 million, will occur in low- and middle-income countries. Every approach to reach a better clinical implementation of pre-clinical research to actual progress in improved quality of life and cancer survival is important. The majority of cancer research this far is performed in rodent models and obviously the treatment success in man is still unsatisfying. With increased incomes and general standards the life expectancy will continue to increase and thus the cancer incidence and prevalence will continue to increase. With better use of large animal models, also including spontaneous occurring tumors in companion animals, it is suggested that a “new” optimized bridge between preclinical models and phase I-III trials in humans will enhance and hasten the development of more efficient cancer treatment. SWECCLIM has a strong collaborative competence within this field.
The perception that 3R and animal welfare and health is mandatory to optimize the output of the experiments necessary to perform is well acknowledge by society and academia. However, the attempts to manifest these visions into practice are rarely getting the deserved attention. Finally, the largest research focus on this has been within the rodent lab animal area. Within SWECCLIM we have gathered the highest competence both in ethics, social science and clinical implementation for large animal studies. We have also designed a separate module to secure that competence constantly is allocated to this focus area and showing that 3R should be a cornerstone in every single use of large animal for research purposes. The clear focus on 3R and training will lead to improved experimental planning and use of the research animals. Moreover, the signal out to the society is also important as it is a growing demand to ensure the highest standards in large animal experiments and motivate its use in comparison to alternative models.

Beskrivning av infrastrukturen och dess verksamhet*

Se nästa sida för bilaga.

Description of the infrastructure and its activities

1. The research infrastructure organization and management

Organization and management of the infrastructure

The infrastructure will be hosted by SLU, handling all administrative matters and act as the employer of the director. The main governing body of the infrastructure is the general assembly (GA) comprised of representatives of the consortium members. The general assembly will decide the general strategy, budget limits, composition of the steering committee, and other organizational matters.

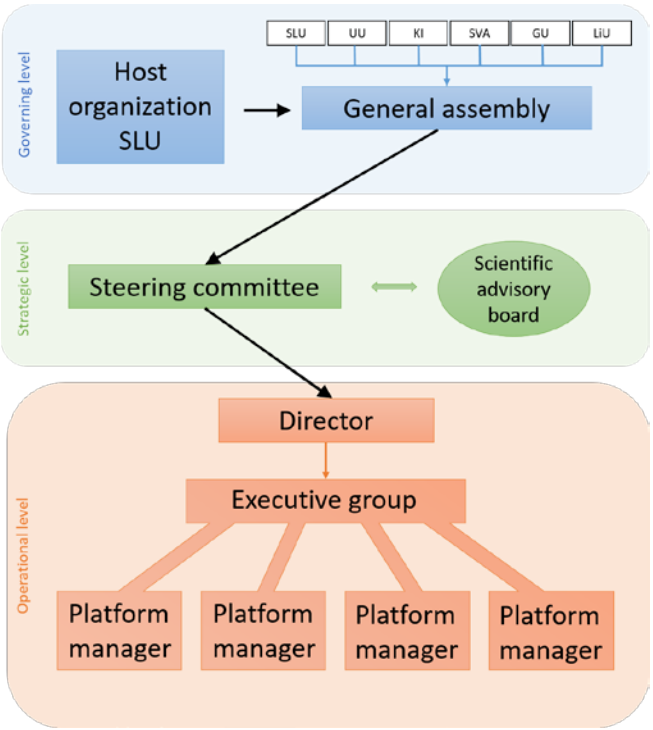

Figure 1. Management chart of SWECCLIM

The steering committee will be responsible for the budget, strategic planning within the framework decided by the GA, scientific leadership and continuous evaluation, including business intelligence analyses. A long-term plan for scientific objectives, funding and utilization, including support for and training of users, will be devised by the committee. To assist in the prioritization of access and scientific planning the committee will form a scientific advisory board.

The operational responsibility of the infrastructure is handled by the director implementing the decisions of the steering committee. An executive group consisting of the platform managers and headed by the director will be responsible for the operational planning and integration of the infrastructure sub-units. The present large animal laboratory at Uppsala University (the Hedenstierna laboratory) used for the invasive experimental procedures, will be relocated to SLU premises but remain a unit at UU and the laboratory manager will continue to be employed by the UU.

2. Infrastructure components and activity

2.1 Graphical overview of the infrastructure

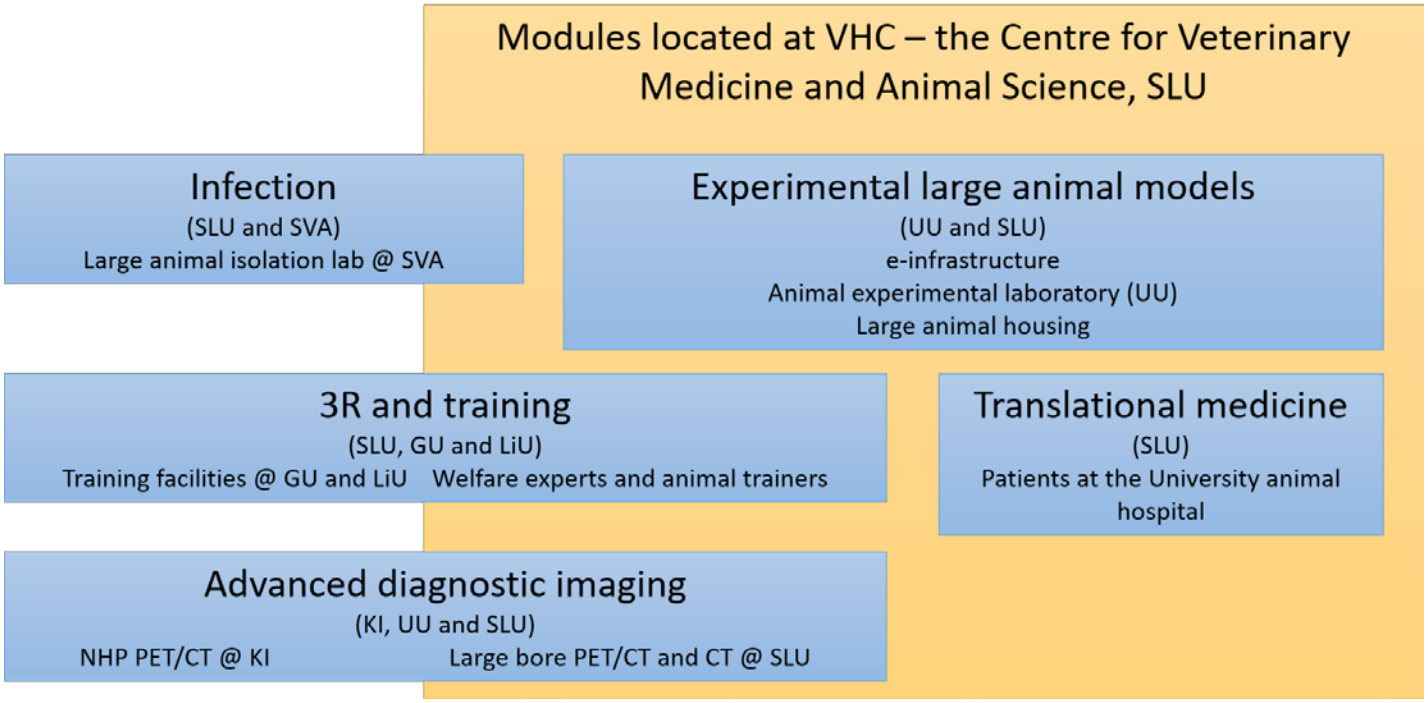

Figure 2. Physical localization and principal partners (in parentheses) of each module. This describe on a high level resolution how the different partners interact within the modules described.

2.2 Time plan by a Gantt chart

	2020	2020	2021	2021	2022	2022	2023	2023	2024	2024
SWECCLIM										
All part fully operational										
Module 1 - Management										
Staffing										
Fully operational										
Module 2 Experimental large animal models										
Staffing										
Remodeling, security and construction										
Relocation of experiments to SLU from UU										
Fully operational										
Module 3 Advanced diagnostic imaging										
KI unit - Primates										
Purchase PET/CT and CT										
PET/CT calibration										
Fully operational										
Uppsala unit - large animals										
Remodeling and construction planning										
Construction of CT bunker										
Purchase PET/CT and CT										
Staffing										
Calibration PET/CT										
Calibration CT										
Fully operational										
Module 4 Infectious diseases										
Remodeling for high P2 level, animals >5kg										
Fully operational										
Module 5 3R and training										
Staffing										
Equipment acquisitions										
Fully operational										
Module 6 Translational medicine										
Staffing										
Equipment acquisitions										
IT-integration										
Fully operational										

2.3 Users

Access to the infrastructure follows similar directions as set up by the Swedish Research Council, i.e., it is based on scientific excellence of the application and not, e.g., on organizational belonging. Furthermore, it is mandatory that the animal research ethics committee has approved the proposed study before it will be considered for evaluation. The Steering group is responsible for the evaluation of projects and can if they find it feasible, take advice from the Scientific Advisory Board. The managers at the modules used are responsible, in collaboration with the investigators, to implement a suitable protocol for any approved experiments.

A Communication Officer will be employed and be responsible for communication of research results and of the unique opportunity that the infrastructure provides to new users, e.g., by yearly information meetings at the Swedish universities and a selected number of foreign academic institutions as well as relevant industries. (This will be developed in the Strategic Communication and Dissemination Plan). Also, to increase the impact and use of the infrastructure, each publication will acknowledge SWECCLIM.
Particular in module 5 (3R and training) but also in module 2 (Experimental Large animals) new and experienced users will be educated/further educated in experimental setups. Also, Module 5 will have courses in collaboration with the FELASA (Federation of European Animal Science Associations) in experimental large animal research. Each module will have specialized expertise in experimental development and scientific support.

The deadline for the application for using the infrastructure will be scheduled to March for use during the autumn semester and to October for use during the spring semester. The application should include a well-prepared protocol, the length of the experiment, and the length of stabling/housing the animals. Some experiments will have an extended follow-up with intermittent controls that have to be considered. Thus, the approved studies have to wait 4-8 months. If any free slots occur, the director in collaboration with the module manager will decide whether this slot could be used for experiment. To allow vacations for the personnel the infrastructure is planned to operate from August 1 to the middle of December and from January 1 to June 30. Ongoing experiments and care of experimental animals will be handled the year around.

When using animals included in the Translational Spontaneous Disease module (#6) the same requirements regarding approved ethical applications are of course mandatory. As the caseload is continuous at the University Animal Hospital UDS) applications will be considered by the director in collaboration with the module manager at UDS on a regular basis and approval to initiate will be decided based on available clinical support and parallel studies using the same clinical phenotype and species.

The infrastructure has defined three different categories of users; 1. Academic users, 2. Veterinarian Clinical users and 3.Industrial users. The two latter users will pay fees according to a full cost model applied at the infrastructure. We intend that the Steering group develops a policy for subsidizing the fees for the academic users and that each academic user will be treated the same.

2.4 Design, development and operation of infrastructure

Module 1

Management – see above under 1.

Module 2

Experimental large animal models

The concentration of advanced large animal research in SWECCLIM that includes experimental models, natural models with spontaneous disease and research on primates, to one infrastructure is essential for development optimization and innovation. In the experimental module Xenotransplantation [1], long-term studies of implants (such as artificial organs [e.g., trachea, aorta], pacemakers/defibrillators, orthopedic prosthesis, stents, implants to maintain hemostasis etc) [2, 3], long –term studies of bone-grafts and orthopedic implants in relevant large animal models [4] are included.

Xenotransplantation
Development of xenotransplantation requires a major scientific organization and collaboration that is not presently available in Sweden. This kind of research demands front-line expertise in genetics, immunology, surgery, breeding, and animal care, as well as thorough, long-term studies in large animals and in primates before it can be translated to human care. Thus, it is essential to concentrate the efforts on one primary facility. The new facility at SLU combined with the research capabilities KI and UU with possible collaboration with other national and international institutions will have all infrastructure needed for such endeavor. The SPF pig unit at SLU Lövsta earlier mentioned is an asset that will be useful for this research area.

Long-term studies of implants.
There have been some well-noticed drawbacks regarding implants for tracheal replacement and cardiac stimulators, partly due to insufficient studies in large animal models before the devices/implants were applied in patients. Hence, it is crucial for Sweden to have one facility that has the capacity for long-term studies of such implants in relevant-sized models. Today, several Swedish research groups perform their large animal studies in other countries. In this regard, it is important to note that implants such as pacemakers and prosthesis are not only used in humans but also in domestic animals and therefore such studies are also important from a translational perspective, for the development of veterinary medicine in itself and enhanced animal welfare.

Long-term studies of bone-grafts and orthopedic implants.
Most studies of bone regeneration and methods to improve bone grafting have been performed in rabbit models. However, to know the effect of bone grafting/regeneration it is important to study this during a longer period in models with adequate loading with similar stress and strain as in humans. Large animal models fulfill these requirements and the tradition is to use sheep models. These techniques are not only experimental, but also used today in state-of-the art veterinary oncological surgery – where especially osteosarcoma in certain anatomical location (e.g. distal radius/ulna) are sometimes treated with limb-sparing techniques, where the tumor segment is excised and different implants are used to replace the tissue. These can be autologous with ipsilateral grafts and/or prosthetic devices of different materials, often 3D-printed from CT reconstruction/simulations of the patient's anatomy. Such treatments are ideal to also serve as models to study new techniques (materials and surgical techniques) in an immune competent model with similar complex etiology of the disease (osteosarcoma) with similar to identical tumor biology and histology.
Uppsala University has a strong track record within the material sciences and the area of bone regeneration. The ability to offer large animal models in the immediate proximity will strengthen the research area and also shorten the time frame for research treatments being made available to patients. The expertise at SLU within biomechanical measurements of animal movement will further enhance the quality of orthopedic research at SWECCLIM.

Module 3

Advanced diagnostic imaging

The plan is to make all existing equipment and the unique veterinary diagnostic imaging specialist competence available for the needs of the researchers with animal models in SWECCLIM. A new large- bore Positron Emission/Computed Tomography (PET/CT) machine is in this regard an essential addition to the existing imaging infrastructure. It will be needed for experimental studies in inflammation, transplantation, and oncology in both experimental and natural models (see the different modules).
At SLU there is a unique constellation of specialists with research experience in several disciplines of veterinary medicine. There is a strong tradition in veterinary diagnostic imaging in Sweden going back to the late 1950s when one of the first professors in the subject in the world was located here. There are today more than 20 individuals specialized in veterinary diagnostic imaging working at SLU, several with a European specialization degree (DipECVDI), and the University Veterinary Hospital at SLU is an approved training center for veterinary radiology and currently has four residents doing this four years long post-graduate education. Finally, it is planned to further expand the excellence by increasing the collaboration with the imaging experts in radiology and nuclear medicine at the Uppsala University/University hospital and Karolinska Institutet/hospital. Thus, the Uppsala University's Platform for Preclinical PET-MRI (PPP), has a long and successful track record of PET tracer validation within the field of biomedical research including neurology, oncology, inflammation, metabolic diseases and drug discovery and development. PPP has indeed the expertise to push translational projects all the way from radiolabeling to human clinical trials and will be a key player for providing the necessary PET tracers to

the imaging facility at SLU as well as validation of new tracers. Likewise, the PET Unit for imaging non-human primates (NHPs) at Karolinska Institutet is conducting pre-clinical imaging in NHPs since the ´80´s. The main focus of the research group has been on the development of new PET radioligands for brain imaging and development of new CNS drugs in collaboration with major pharmaceutical companies. Over several decades more than 150 PET radioligands for the CNS have been developed at Karolinska Institutet and evaluated pre-clinically in NHPs. PET imaging in NHPs is a key element of the translational molecular imaging chain from small animals to human subjects due to the genetic similarity between primate species and their similar metabolic pathways. The access to NHPs at the Astrid Fagreus Laboratory (AFL) provides a fully translational research platform for rapid implementation and validation of new PET probes for human studies.
The large-bore PET/CT at SU will with its strategic place be an equipment used for both module 2 and 6 and with the possibility to also serve study objects from the infectious module at SVA only a couple of hundred meters away. Finally, it is planned that some investigations in NHPs will be performed using this unique device, primarily as the necessary access to a specialist in veterinary anesthesiology is always available at SLU Uppsala.

Module 4

Infectious diseases

Several infectious models in cattle, sheep, pigs, and poultry are currently used at SLU for animal and human health purposes. For example, the bovine respiratory syncytial virus model in calves was developed to study the pathogenesis of RSV infections and to develop and evaluate vaccines and new treatments [5, 6]. Beyond the benefits to animal health, this model tackles translational medicine, through an ongoing collaboration with UU and Akademiska Sjukhuset. The approach was additionally applied to study influenza D, but since the Swedish facilities were not adapted to study emerging infections in large animals, this was performed in France.

Humans and animals are exposed to a variety of known and unknown infectious agents. At short and long term, infections impair human well-being and animal welfare, economy and agricultural sustainability, all of which are cornerstones in our society. The epidemiologic characteristics and the disease mechanisms that induce pathogenic effects are not always well understood. With the emergence of resistance against present treatments, new vaccines and therapeutic approaches are necessary, both to counteract infections and exaggerated immune responses. Since many infections in humans and animals are caused by the same or closely related pathogens, a coordinated strategy between the human and animal sector will maximize relevant outputs.
Due to the high health standard of conventional large animals in Sweden, animal experiments can be performed in high quality animals, which guarantee optimal research outcomes. Having access to well-equipped animal facilities for production animals will enable an onsite synergistic use of our animal models, laboratory platforms and centers of excellence. It will allow the continuous development of multicompetences, which are attractive for international collaborations and necessary for the identification of key biological features of infections. Synergistic work in a translational approach will benefit the society in a “One health” perspective through a better control of human and animal diseases.

In a collaboration between UU and SLU, sepsis models in sheep and pig are used, mainly with focus on acute kidney injury. However, for an optimal research, the facilities at SLU would need to get upgraded to allow more advanced surgical preparation and subsequent studies in conscious animals without the interference of anesthesia.
Other infectious models in pigs with the aim to document the clinical efficacy of different treatment substances and treatment strategies at pneumonia and diarrhea have been developed at SVA. Different models to study mammals, poultry and fish have also been developed at SVA

The upgrade to level 2 animal facilities will enable to use established and new infection models to get a better understanding of endemic and emerging diseases. The study of animal infections as model for human diseases will enable a faster development of effective control measures for animals and will contribute to help researchers to find innovate means to decrease the use of antibiotics.

Module 5

3R and training

The principles of the 3Rs (Replace, Reduce and Refine) provides a framework for performing more accurate and humane animal research. The 3R perspective will be present in all modules within SWECCLIM. It is a direct requirement from authorities to adhere to the 3R principles in all research including animals. It is also a promise to the society that we constantly strive to enhance the quality of life for research animals. Moreover we share a strong belief that the results from studies on organisms that are put under extreme artificial conditions with high stress and minimal resemblance of normal habitat and behavior will lead to biased results that could compromise the ability to translate findings into another species (i.e. man). High quality training before commencing large animal experiments are also fundamental to optimize output of investment.

Positive reinforcement training is becoming more and more in focus for laboratory animals and can enable collection of samples from conscious, unrestrained animals. Prices have been given out from EPAA (The European Partnership for Alternative Approaches to Animal Testing, a collaboration between the European Commission, trade associations, and industry) to technicians for handling and training mice and rats to give calmer animals during experimental procedures. If this can be achieved in laboratory rodents, it can be done also with larger animals. With unstressed animals, the results from a scientific study will be more relevant. If samples can be collected from unrestrained conscious animals, rather than from restrained, stressed or sedated animals, the data will not be compromised. Data on brain function can be obtained from awake unrestrained dogs with functional magnetic resonance imaging [7]. This demonstrates the possibility for training dogs to lie still for MRI and/or PET-CT scanning. With the PET-CT close to the animal facilities (as suggested in SWECCLIM), it facilitates daily training of the animals. Hence, studies conducted on conscious, unrestrained animals within SWECCLIM will be state-of-the-art and in part world unique in this context.

In parallel, competence training to ensure refinement of techniques before applying to large live animals are crucial to fulfill the goals of 3R. In SWECCLIM we have an excellent training module at University of Gothenburg that contributes with a south/west regional platform for large animal research within the national infrastructure. University of Gothenburg also provides unique training facilities with strong 3R benefits as outlined below and highly skilled staff.

Transplantation research
Gothenburg has a long tradition of excellence in “bench-to-bedside” translational research. These discoveries have led to breakthroughs in medical treatments and implementation of novel methods into general clinical practice. As an example, EBM large animal resources were used to develop the methods to perform uterus transplantation, which has now, for the first time in the world, been successfully implemented in the clinic resulting in several births of children. A common key factor in such achievements has been the ability to progress experimental studies from simple organism to rodent models and further to pre-clinical testing in larger species preceding the safe testing and use in humans. Currently, research in Gothenburg is pioneering new methods to transplant artificial vessels. The research commonly involves both the University and the Sahlgrenska University Hospital. Further, there are strong links to Pharmaceutical companies (Astra Zeneca) and Research Institutes of Sweden (RISE). The high quality of the research methods developed in Gothenburg not only attracts national, but also international researchers, increasing the visibility of Sweden in the world.

The Scandinavian Microsurgery Academy (SMA - microsurgery.se) is a state-of-the-art, world-leading microsurgery training facility for both preclinical and clinical staff. It is a collaboration between the University of Gothenburg and the Sahlgrenska University hospital and affiliated with several international microsurgical training centers and international societies (ISEM - International Society for Experimental Microsurgery and ESSR - European Society for Surgical Research).

A full replacement (REPLACE) of use of animals in microsurgical training is implausible since the consensus is that at some stage in the training the trainee need to train in living models [8]. However, high quality, standardized training will contribute to improved data quality in preclinical research and results in a potential reduction in the number of animals used (REDUCE). If the person performing surgical interventions are well trained and qualified it leads to an improved welfare for the animals involved in the studies (REFINE).
Center for Biomedical Recourses at Linkoping’s University unique infrastructure is validated and approved for

large animal studies. Long-standing experience of collecting quantitative tissue data for the determination of organ composition (virtual biopsies), access to proprietary techniques for functional cardiac examinations using 4D flow with CT and MRI which can provide completely new knowledge of animal organ functions and replace invasive methods [9].

These provide completely new opportunities to produce data that can be used for teaching, provide functional information about animals and replace invasive procedures. Within SWECCLIM the best experts in all important field of training are at hand. We will focus investment in infrastructure at the site that already have a firm base and experience to host training to researcher both within and outside of SWECCLIM. The training span from artificial models in clinical training centers to exercises in cadavers to specific well planned courses in live animals regarding complex surgical intervention and anesthesia/intensive care.
SLU, often referred to as "the longest university in Sweden" with main campuses from Alnarp in the south to Umeå in the north have a vast experience on integrated education and research and has an IT-infrastructure designed for these demands.

Module 6

Translational medicine on spontaneous diseases in companion animals

SLU has several projects concerning various complex diseases, many of which also have a clear corresponding disease in humans. The purpose of this research is partly to identify genetic risk factors and to define how these interact with each other and with environmental factors [10]. In addition, to test new drug formulations in a disease model similar to human conditions, in a much more complex environment than in induced rodent models. Here immune competence, outbred genetic diversity, difference in diet and exercise comes into play – makes it much more similar to human studies. To reduce the complexity, different inclusion/exclusion criteria are made in the protocols to make the studies very stringent. Moreover, the high detail in diagnose (often on a molecular level), frequent monitoring with modern equipment and highly specialized personnel makes this a very attractive environment to perform research in for both pre-clinical drug candidates, medical devices as well as parallel studies to trim or confirm phase I-II drug studies in man [11].

There are several partners in this research, also internationally like an EU-funded project (LUPA) within the 7th framework [10]. The first complex disease in which we successfully managed to identify interesting candidate genes is the so-called Tollar disease, whose counterpart in humans is systemic lupus erythematosus (SLE), and studies are now being conducted to investigate how different genes interact in the onset of the disease. Following this discovery, BRACAI and II aberrations were found in dogs with increased risk for mammary tumors (Breast Cancer) [12]. As well as many loci in heritable dog osteosarcoma, including regulatory variants near CDKN2A/B with similar pathways as found in pediatric osteosarcoma in man with almost identical histology, anatomic locations and biological response on multimodal therapy including surgery, chemotherapy and radiotherapy [13]. Partly due to immune competence and histological and biological similarities to human malignant melanoma, an immunotherapy trial was conducted using a gene modified Adenoviral 5 vector expressing CD40L. The results were very encouraging and accelerated the introduction of this treatment into refractory high stage malignant melanoma in man, at the Uppsala University Hospital.

The Canine Biobank
The SLU/UU Canine Biobank was started in 2007 to support the European Consortium LUPA. It is primarily a collaboration between veterinary clinicians and molecular biologists at the faculty of Veterinary Medicine and Animal Sciences and Since (SLU) and the Department of Medical Biochemistry and Microbiology (IMBIM) at Uppsala University. Since then both LUPA investigators and other scientists have used the Biobank for studies spanning from monogenic traits to heart disease, cancer, immunological disease and behavior. More than 15,000 i samples, have been logged in the Biobank. They include mostly whole blood, but also plasma, serum and tissue samples providing possibility for functional analysis with RNA. All samples have been obtained from privately owned dogs with the owner's consent. The samples have been taken by veterinarians or animal nurses. The sample identities and associated clinical information is stored in the BC Samples platform and genetic data for the samples are stored in the BC Genome data base.

As samples come in they are appropriately aliquoted and stored until used in -80°C freezers. Research projects where the samples are used are both national and international collaborations in projects where we have ethical permits to use the samples and perform the projects. Samples or genetic data can often be used in multiple projects through collaboration. More than 110 papers have been published including samples from the Canine Biobank). Some examples include mammary tumors, Systemic Lupus Erythematosus (SLE) and Obsessive Compulsive Disorder (OCD). For both SLE and OCD, the identification of canine genetic risk factors have had strong comparative value and led to studies identifying novel human disease gene variants for the corresponding diseases.

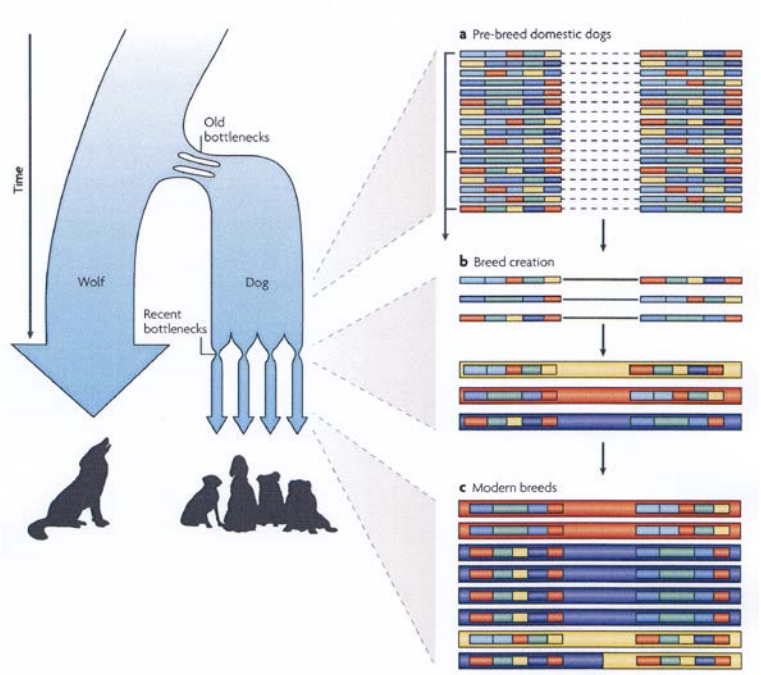

Figure 3. Haplotype structure of the dog. Two population bottlenecks in dog population history, 1 old and 1 recent, shaped haplotype structure in modern dog breeds. First, the domestic dog diverged from wolves ~ 15,000 years ago, probably through multiple domestication events. Within the past few hundred years, modern dog breeds were created. Both bottlenecks influenced the haplotype pattern and linkage disequilibrium (LD) of current breeds. A. Before the creation of modern breeds, the dog population had the short-range LD that would be expected given its large size and the long time period since the domestication bottleneck. B. In the creation of modern breeds, a small subset of chromosomes was selected from the pool of domestic dogs. The long-range patterns that were carried on these chromosomes became common within the breed, thereby creating long-range LD. C. In the short time since breed creation, these long-range patterns have not yet been substantially broken down by recombination. Long breed-haplotypes, however, still retain the underlying short ancestral haplotype blocks from the domestic dog population, and these are revealed when one examines chromosomes across many breeds. In conclusion the dog model offers both a "human-like" situation when comparing the dog population as a whole (with short LD) and at the same time "mouse-like" when investigating specific breeds (short LD), where specific disease traits sometimes are multiplied due to inbreeding as in rodent models. This figure is from *Molecular biological aspects on canine and human mammary tumors* [14].

In addition to the physical biobank, this canine disease genetics resource also includes a set of webpages (http://hunddna.slu.se) and a Facebook page (https://www.facebook.com/pages/Hundgenetikgruppen/494564477256862) informing the breed clubs, breeders and dog owners in particular and the public and society in general about ongoing research and how to enroll in the study. The webpage has >1000 visits a month, with 75% being repeat visitors. We now aim to update these to be able to collect much more detailed phenotyping information.

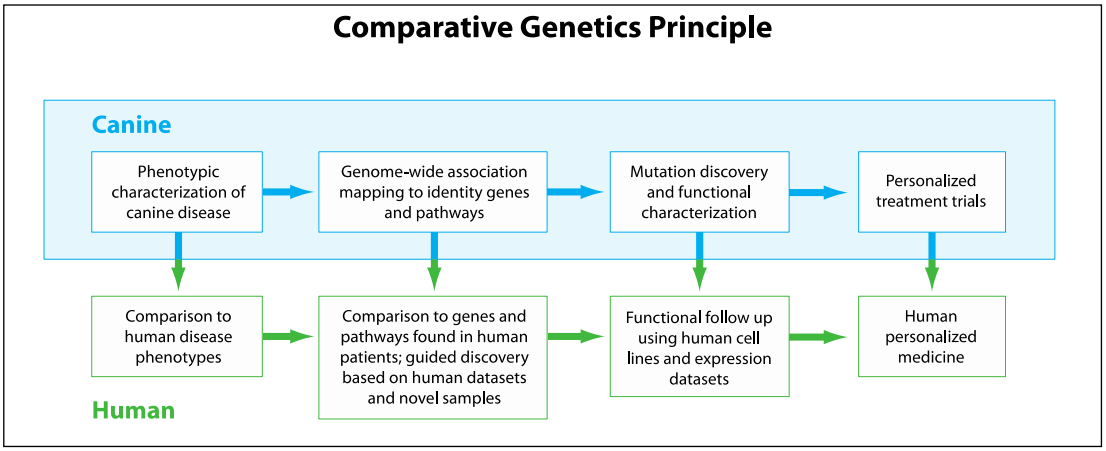

Figure 4. Comparative genetics principle. This figure depicts different steps necessary for developing personalized treatment strategies in dogs, including phenotypic characterization, sample collection, genome-wide mapping, mutation detection, functional analysis and personalized treatment trials. Throughout this process, comparison with human genetics is happening at all levels and hence informing human preclinical and clinical trials as well.

The scientists using the biobank also organize one-day conferences semi-annually to inform the public, breeders and breed clubs both about ongoing studies. The most recent event in October 2018 have had >100 participants from >80 breed clubs. We also frequently speak at different breed clubs. At these events we explain ongoing studies and how to interpret the results from canine and comparative studies.

Humans and companion animals share many types of cardiovascular diseases, the most important ones are different types of cardiomyopathy (dogs and cats), valvular heart disease (dogs), different types of congenital heart disease, and small vessel disease of the coronary arteries. Great advances have been made in recent years to delay the onset of signs of congestive heart failure (CHF) by clinical trial evidence of pharmacological interventions in dogs and cats affected by acquired heart disease [15]. Similar studies have not been conducted in people. The facility at SLU enjoys a good collaboration with the Swedish Kennel Club and specific dog and cat breed clubs (including PawPeds, which is a worldwide, and by far, the largest screening program against feline myocardial disease), which means that affected dogs and cats can readily be identified and examined. Furthermore, molecular genetical studies conducted at SLU have shown specific genomic loci associated with specific types of acquired myocardial and valvular heart disease in dogs and cats, and these loci are currently being investigated further by means of transcriptomic and proteomic studies of myocardial tissue of affected and normal dogs of specific breeds. The facility at SLU in the cardiovascular area includes a State of the Art cardiac clinic staffed by two European Specialists in Cardiology and equipped with the most recent diagnostic and therapeutic methodology. Furthermore, the cardiovascular unit at SLU enjoys the support of one of very few molecular genetic platforms for cats in the world. A new research opportunity is chronic pulmonary diseases since companion animals develop similar lung conditions as humans.

Inflammatory bowel disease (IBD) encompasses a very large proportion of the patients admitted to UDS. As in humans, a wide variety of etiologies is present. Sometimes, the conditions are diagnosed as idiopathic. We share this frustrating dilemma with human medicine. A multitude of studies are showing that the spontaneous model of IBD in companion animals are superior to the classical used rodent models, as they lack the complexity needed to fully understand pathophysiology. Moreover, the genetic similarity between humans and (especially) dogs are better than in rodents. The evolutionary development and selection of dogs to cope with human feed (through domestication of the wolves) have shown remarkable difference in the genome between wolf and dog in two specific areas, namely the ability to digest carbohydrates and the genes coupled to genes important in brain function, most of which belong to nervous system development pathways and potentially underlie behavioral changes central to dog domestication. Study on companion animal genetics and microbiome research are already performed at SLU and Uppsala University. Hence, the IBD model has a huge potential to reveal new diagnostic tools, treatment options and prevention benefit both man and animals, using the multitude of animal patients present at UDS.

Diabetes mellitus is a large concern in both dogs and cats. Common risk factors include overweight and gestation/pregnancy. It is suggested that dogs have a diabetes very similar to type 1 in man, whereas cats present with a type 2 variant, sometimes going into remission if diet and weight reduction is occurring at an early stage [16]. Usually with a shorter time of concurrent insulin therapy. At SLU research on c-peptide in dogs and association of overweight and diabetes in cats have been performed. It is also discovered that certain breeds (in both dogs and cats) are predisposed to develop diabetes. This offers an interesting model to study genetic risk factors to develop both diabetes type 1 and 2. With a very strong competence within veterinary endocrinology and internal medicine at SLU coupled with stellar human diabetic knowledge from partners within SWECCLIM (such as Uppsala University and KI), there is a huge potential in discovering important pathways to interfere and reverse diabetic status in both animals and man. This would offer a big impact on society, as diabetes (especially type 2) is an emerging society catastrophe both concerning suffering and financial.

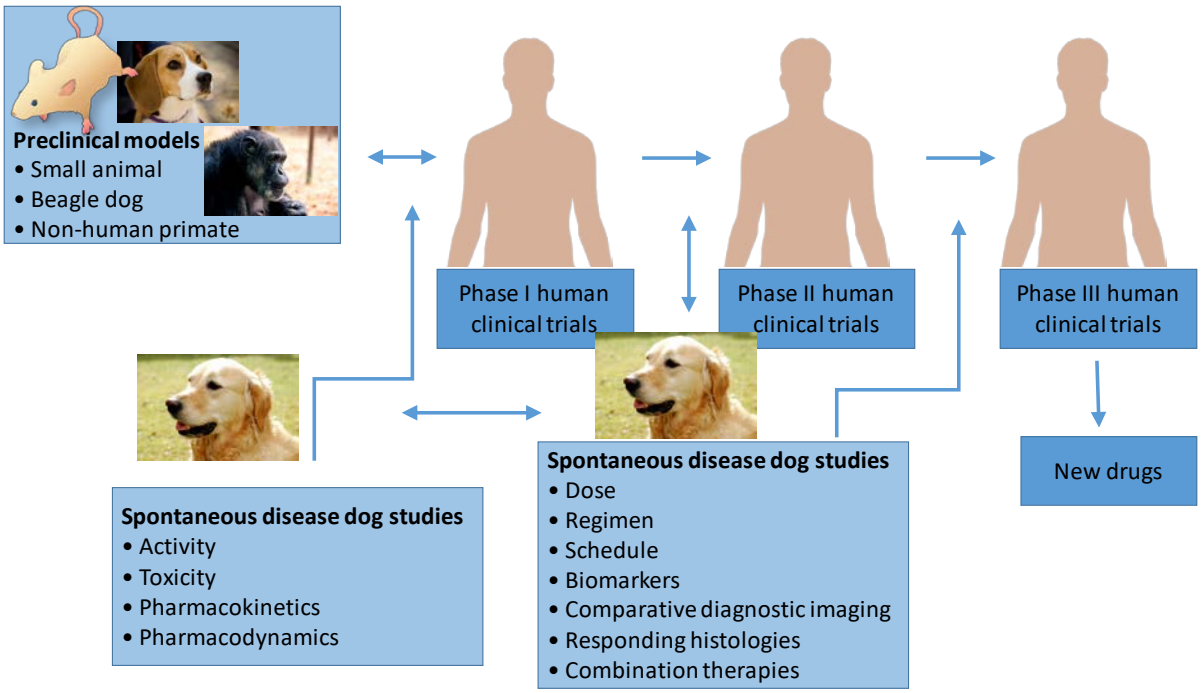

Figure 5. Integrated approach. Current drug development efforts are largely uni-directional and non-integrated. New drugs are evaluated in conventional preclinical models of efficacy and toxicity and then either succeed or fail in human clinical trials. An optimal drug development path would integrate both preclinical and clinical components of drug development so that questions that emerge in the human clinic could be answered in animals. Translational drug development studies in the pet dog with e.g. cancer, cardiovascular and endocrine diseases are optimal for such an integrated approach, being an intermediary between conventional preclinical models (mouse, research-bred dog and non-human primate) and the human clinical trial. The opportunity for this approach is now feasible on the basis of the recent completion of the canine genome sequence, the availability of tools to study disease biology and the biological consequences of therapy, and the urgent needs of the drug-development community for more effective models. Through this integrated approach it is likely that important questions about a new drug candidate can be answered before it enters human studies, for example, toxicity, dose, regimen, pharmacokinetics, pharmacodynamics and activity. Perhaps equally important are the questions that emerge following the completion of an early-phase human study (often left unanswered) as the agent moves into later stages of development. It is likely that the totality of information generated through this comparative approach will contribute to the success and reduce late attrition of e.g. new cancer therapeutics. It is important to note that the inclusion of the dog within this integrated approach will not be reasonable, feasible or valuable for all drugs, drug targets or disease conditions. Figure modified from [11].

Orthopedic diseases are the most common source of pain among man, horses and cattle [17, 18]. Because accumulation of micro-trauma is a prevalent cause of pathology in both humans and large animals, access to relevant large animal models and tissues has greatly advanced important topics of human disease, such as knowledge of tendon maturation and aging, determination of specific exercise effects (including early life), and definition of some of the earliest stages of subclinical pathology. It has therefore been proposed that the horse is a far more ideal model for human disease than for example mice, also justified on similarities of life span, lifestyle factor and general stress pathway evolution. Also, Swedish studies have shown that development of

osteoarthrosis and osteochondrosis display pathogenetic similarities between human and large animals.
SLU has world-renowned expertise within biomechanical measurements of animal movement, under clinical, fields and laboratory conditions. For all species, computer vision/ML systems that can automatically detect lameness or pain are of great interest and methodologies are emerging, but face validity of such systems need to be validated, both in terms of biomechanics and pain.
Medical, surgical, genetic and molecular genetic research projects are carried out include five different disease groups: cancer, neuropsychiatric diseases, inflammatory and endocrine diseases, cardiovascular diseases and orthopedic degenerative disease (arthrosis).
Already studies performed at SLU/UDS have been published in many of the highest ranked scientific journals including: Nature Genetics, Cancer Research, Genome Biology, PLoS Genetics, PLoS One and J of Immunotherapy.

The research infrastructure at the University Animal Hospital is generally well equipped with modern anesthesia, clinical chemistry, diagnostic imaging (improving this facility to state-of-the art standard is dealt with in the general module). However, to become sustainable, contemporary and also enable an increase in research construction of a new efficiently integrated a multi-disciplinary infrastructure is needed. Apart from what is described in the Large Animal module, with basic staff and center coordinator, the diagnostic imaging needs upgrades and implementation of a PET-CT to allow for non-invasive high-resolution imaging of functional/biological processes in situ and in vivo.
None of the infrastructure mentioned are former supported by the Swedish Research Council. The infrastructure is in principal financed from the University and in part from revenue out from the clinical services offered by the University Animal Hospital to the public.

2.4.1 Future expansion of SWECCLIM

Radiation therapy

Radiotherapy is one of the standard treatments for cancer in both humans and animals. A long history of experimental studies has led to successful protocols, achieving balance between acute and late side effects and optimal tumor response. Unfortunately, there are still several unsolved problems in human radiation therapy. Above all, there are radio-resistant tumors but in addition, increased knowledge is needed about how different pharmacology and immunotherapy could potentiate radiation (so-called radiosensitizers) leading to better survival and quality of life. Until now, preclinical research on tumors has been primarily performed via induced tumors on rodents. These models have problems since they do not have the same size as the tumors being treated in humans and furthermore, created in an immune-incompetent environment. The interaction with the immune system is extremely important when it comes to repair of radiation damage and the tendency to respond to antineoplastic therapy, regardless of type. Tumors in dogs and cats are of the same size as we find in humans. They often have identical or similar histology, polyclonal with built-in initial resistance, many molecular biological pathways are identified and they occur in an immunocompetent individual [19]. What is different is that today there are in principle no registered chemotherapy drugs or immunotherapy dedicated to dogs. It is therefore possible to treat completely treatment-naïve animal patients. This means that experimental protocols offered to humans as the 3rd or 4th line treatment when completely refractory to other treatment can be performed as the initial treatment in dogs and cats. Fewer resistance mechanisms are therefore induced and one can get a better picture of the real effect of new treatments.
In addition, the combined access to the PET-CT at SLU and the radiotherapy module would allow the characterization of the tumors with respect to several phenotypes known as being associated with poor response to chemo-radiotherapy such as high clonogening density, enhanced cellular proliferation and tumor hypoxia and the development of treatment strategies to overcome them. Special emphasis will be put on accounting for tumor hypoxia as one of the main factors responsible for the failure of radiotherapy.
It would actively contribute to strengthening the radiotherapy network locally (Uppsala-Stockholm) and complements the existing infrastructure. A newly installed facility for experimental treatment of small animals on exsist at the Department of Immunology, Genetics and Pathology (IGP). Two Nordic MR-Linacs with a built-in MR camera are installed in the accelerator at Akademiska University Hopsital in Uppsala and with the relocation to the “100-house”, in practice, the entire machine park is renewed for radiation treatment and preparatory imaging. The Skandion Clinic is right across the street from the 100-house. This excellent infrastructure combined with the cluster of RT companies in Uppsala-Stockholm and UU's strength in life sciences provides good conditions for research. The clinic at Akademiska mainly has equipment from Elekta, and uses Elekta's dose planning system, but also have a research system from RaySearch whose software is much better suited for

research. Among the other initiatives to strengthen the RT environment in Uppsala-Stockholm is a recent application submitted to Vinnova to start a competence center for superconducting accelerators in medicine. The initiative comes from the particle physicists at Ångström's FREIAlab and is about technology transfer from CERN to radiotherapy. If this comes about and a demonstration plant can be built, it would be an excellent complement for the treatment of larger animals.

2016 saw the creation of a National Cancer Institute (NCI) comparative brain tumor consortium with mission to inform the translation of new knowledge from canine to human brain tumor patients [20]. This is a continuation of the NCI:s Comparative Oncology Program (COP), a collaborative group, utilizing an extramural clinical trial consortium (Comparative Oncology Trials Consortium [COTC] within the entire USA. Something similar does not exist within the EU yet. The reason why CNS tumors are such an attractive comparative model between dogs (and also cat) and human are that they occur to a relatively large extent and have the same form of limitations regarding diagnostics and treatment. What makes dog even more interesting is that certain types of CNS tumors occur in specific breeds. This allows for parallel research on finding predisposing genetic risk factors for the development of these tumors, something that is more difficult in the complex genetic environment represented by humans as a whole group. Within the individual dog breed there is a genetic similarity and can more easily isolate whether differences within this group is linked to a clinical phenotype (in this case e.g., glioma). Thereafter, an identified genetic area in dogs can be more easily compared with clinical cases in humans and be investigated whether the same types of changes are present. Finally, steps can be taken to develop new improved treatment strategies and furthermore, in some cases to develop biomarkers enabling identification of early signs and recurrence of disease. This will improve monitoring and management of selected patient groups.

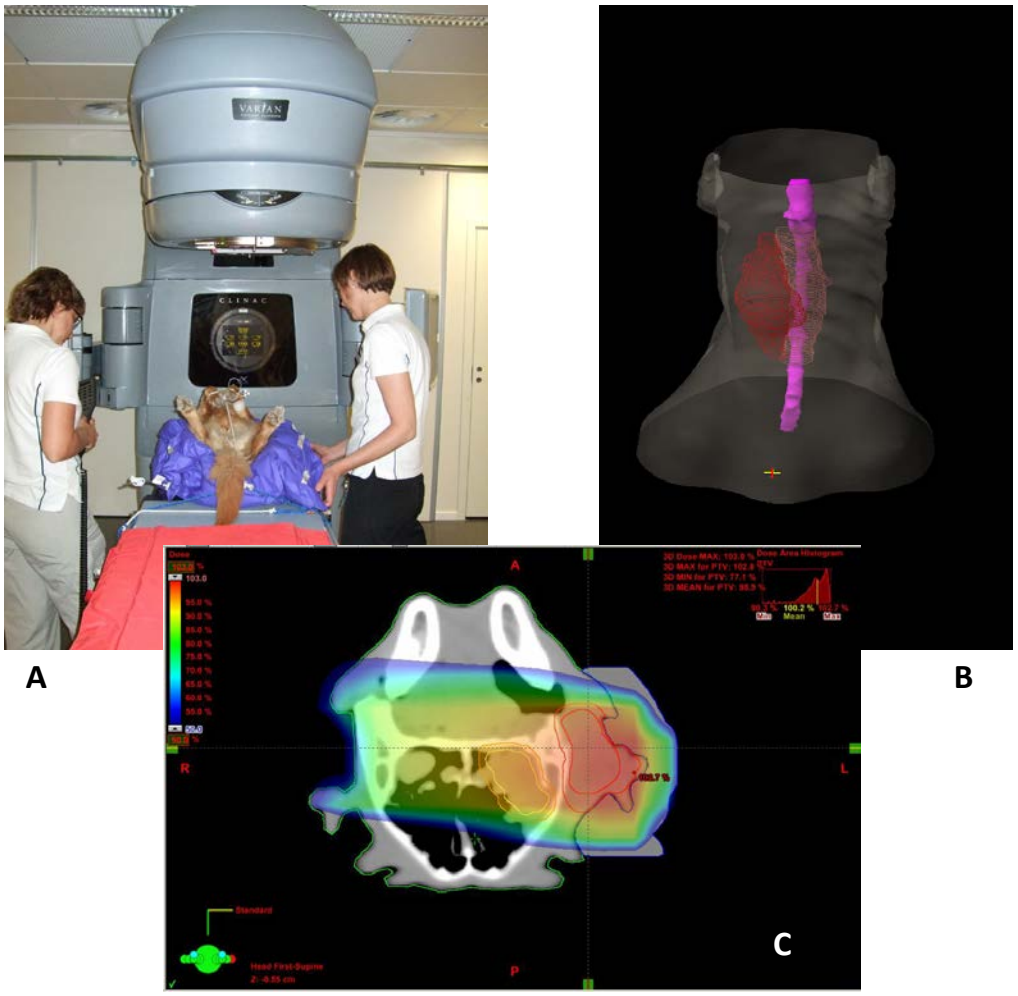

Figure 6. Example on previous experience with RT of dogs with spontaneous tumors at a human facility (Ray Clinic). The *Clinac system* was used from Varian and several dogs were treated with good results. **A** shows a dog with non-surgical removable highly malignant thyroid carcinoma. With efficient dose planning (**B**) highest radiotherapy dose could be delivered to the tumor while sparing sensitive tissue close to the target (e.g. trachea and esophagus). In **C** another dose planning of a nasal carcinoma is shown. In both these examples the tumor was impossible to surgically removed, the dogs' life were significantly extended and the treatments implied almost immediate improvement of quality of life, with little or no side-effects.

The unit in Sweden will be unique in Scandinavia. Earlier attempts have been present in Oslo at Rikshopitalet and at Copenhagen University. However, there is a high reluctance today to use cross species (man and animal) machines in the clinic and moreover, the increased numbers of cancer treatments prevents time for experimental research on clinical cases in dogs and cats. As education of the medical radiation physicist occurs in Stockholm within the Medical Radiation Physics division at the Stockholm University with participation from Uppsala University, the placement of a new modern facility at SLU is geographically optimal even for educational purposes. Thus, the clinical activities could be complemented by educational activities in radiation therapy equipment acceptance and commissioning - in the initial phase of designing the facility – followed by activities on quality control performed in collaboration with the Medical Radiation Physics group at SU and KI and the students following the educational program for becoming medical physicists. Further educational activities could be performed on treatment planning, optimization and verification as practical moments in the Radiotherapy course included in their education. This would strengthen the collaboration between SLU, SU, KI and UU.
The plan is to invest in the same system as used by KS and Uppsala, to provide an identical milieu and as little as possible of discrepancy from the clinical reality in human radio oncology.

The obvious interaction within SWECCLIM will be with the advanced diagnostic imaging module. Here the necessary dose planning will be conducted, as well as monitoring of treatment response with combined PET-CT. This will enable to investigate complicated CNS tumors and radio resistant hypoxia in e.g. CNS neoplasia as well as soft tissue sarcoma and malignant melanomas. Secondly, the cases treated with radiotherapy will primarily come from the University Animal Hospital (UDS) at SLU. Hence, a strong relation and dependence will be on the module for translational models with spontaneous diseases. At a lower priority, treatments on experimental animals will be conducted, especially if reactions on normal tissue after different forms/protocols of radiotherapy. Expertise from the general and spontaneous disease module will interact with the radiotherapy module, providing expertise in anesthesia, oncology and surgery. Finally, all treatments with radiotherapy will be within the 3R and educational model. Importantly, since dogs and cats with spontaneous diseases theoretically provide superior models over the current rodent models (see below), this could lead to a Refinement in models used and also Replace existing, less functional, models. In the end, better and refined models will lead to more information from each animal studied and hence a Reduction in the total number of animals needed to provide the same result as today.

2.5 Interaction with other infrastructures

There are no other similar national or Scandinavian infrastructures but, as mentioned, there are large animal research facilities at most of the major Swedish universities. The suggested infrastructure will establish an increased collaboration regarding research and education, and data sharing with these facilities. Finally, the uniqueness with access to spontaneous disease models at SLU, will provide researchers at other Universities in Sweden with a valuable source of novel research angles hitherto underused and with the creation of this novel infrastructure – available in a completely new organization.

With Kerstin Lindblad-Toh (https://www.scilifelab.se/researchers/kerstin-lindblad-toh/), former Co-director of SciLifeLab, SWECCLIM has a firm connection with SciLifeLab and will in many modules, e.g. Translational medicine on spontaneous diseases in companion animals continue the work already been performed within this infrastructure and with the new modalities suggested (e.g. advanced diagnostic imaging, experimental radiotherapy, experimental large animal models, infectious diseases and 3R and training) get completely new systems that will expand the interactions with SciLifeLab, both in Uppsala (UU) and Stockholm (KI).

2.6 Risk analysis

The most important risks in the project planning are summarized in the following list with the associated mitigation planning.

Description of risk	level of likelihood (Low / Moderate / High)	Proposed risk-mitigation measures
Problems with ethical approval.	Low	Each organisation in participating in the infrastructure has its own procedures on how to handle ethical

		approvals and are well experienced in handling approvals for the experiments that will be dealt with within in the infrastructure.
Change in the consortium, e.g. partner leaves.	Low	The procedure for how a partner leaves the consortium is described in the Consortium Agreement. Additional expertise will be recruited to the consortium if the members find it feasible at the time.
The number of scientists that utilize the infrastructure becomes lower than expected	Moderate	Different outreach activities will be performed early on. Information at relevant national conferences and recurrent meetings and updates with research secretaries at the different universities involved.
The estimated revenues from non-academic user fees in the budget becomes lower than expected.	Low	The revenues has been set fairly moderate from the beginning. Again, outreach to companies identified as potential users of SWECCLIM. This will be done by the coordinator/communicator at SWECCLIM but also in collaboration with the different trial centres at the partners within SWECCLIM, where natural contacts with industry and non-academic stake holders will raise the awareness of the included facilities within SWECCLIM
The data system and its databases has a failure	Low	The database that we use has a system for backup of all data
Dissemination of results not sufficient enough to create impact	Low	The infrastructure has a dedicated Communication Officer who will secure the dissemination processes. The infrastructure will develop a Strategic Dissemination and Communication Plan (SDCP).
The coordination and/or management of the infrastructure and its respective modules fails.	Low	The proposed director and members of the Steering Committee has extensive experience in managing and running large-scale research projects. Furthermore, sufficient resources has been set aside for a professional project management. This will lay the floor for a continuous and pro-actively monitoring of the infrastructure to avoid deviations and failures.
Insufficient communication or consensus within the consortium.	Low	We have designed a meeting structure and frequency that will enhance a good information flow within the consortium. Voting rules and dispute settling will be agreed upon in the Consortium Agreement.
Security threats from animal rights activists	High	The universities security divisions are contacted and are forming or updating already existing access controls. All partners within SWECCLIM already have access control systems with personal

		access cards and detailed plans are already made up to prevent unauthorized presence at the different infrastructures included within SWECCLIM.
Damage to brand due to negative publicity cause unwillingness among the general staff to participate in research.	Moderate	Careful development of materials that motivates the studies undertaken within SWECCLIM will be produced. Excellence within animal welfare and health works in the infrastructure and will ascertain that the understanding from the public is at the highest level. All complaints must of course be considered and the expertise within SWECCLIM will respond rapidly.
Lack of specialist veterinarians with key competences.	Moderate	As SLU and VHC is a central node within SWECCLIM the critical mass of veterinary specialists are high at the moments. The activity within SWECCLIM with gathering excellence is many disciplines of large animal experiments will yield more external grants and with a frequent communication with the management of SLU, the maintenance and increase of specialist veterinary competence will be guaranteed. If veterinary specialists occasionally lacks at units outside of SLU, competence within SWECCLIM can temporarily be relocated to pursue projects needing veterinary specialists.
Cross contamination of research animals and animal patients.	Low	This will primarily be a risk at SLU and the University Animal Hospital (UDS). Together with SLU Infra division, flow of different animal categories are already planned and need for re-build and changes in animal/patient flow is identified and are part of this infrastructure application. There is already a SOP in place at UDS considering flow of animals with suspect infectious disease and this SOP will be updated with research animals.
The facilities gets too crowded due to increased number of students.	Moderate	This is likely only a concern at SLU. The top management of SLU is already informed on the consequence analysis of expanding the number of students at SLU at its requirements to address these needs. This is promised by the vice chancellor to be considered. Careful logistic planning, as a central coordinator of SWECCLIM is employed will ensure optimal use of the infrastructure at SLU and avoid conflicts with parallel education.

3. Support e-infrastructure and data management plan

To accommodate the need for information retention and data interchange we intend to use the existing e-infrastructure of SLU and the university animal hospital (UDS). UDS is currently in the process of upgrading the electronic medical record (EMR) system to better meet the demands from clinicians and researchers without compromising GDPR compliance. We have been involved in this process to ensure that any further research activities can be accommodated. The supporting e-infrastructure at SLU is sufficient to handle the increased throughput and storage of research data. Although especially medical imaging can produce large images, the estimated data volume is in the gigabyte range for most projects, seldom reaching terabytes. The costs for storage and backup in included in the budget.

The distribution of research data collected from patients will require dedicated servers. Pseudo anonymized records from the EMR system can be pushed to these servers thereby removing sensitive owner data from the research records available to external partners. In the case of dedicated research animals the data can be stored directly on the research servers. All systems will be off the shelf systems minimising the need for dedicated software development, other than API-plumbing for system integration. As all software is commercially available, infrastructure specific knowledge is kept at a minimum and training will be available on demand.

We see the main challenges to be security related. As an animal facility we expect to experience sophisticated intrusion attempts which puts high demands on IT security standards both when designing the systems and during production to protect animal owner data and information connected to the researchers.

We intend to develop a data management plan based on the SLU guidelines with the help of SLUs data curation unit. Most data generated within the infrastructure is collected and stored in the LIM, EMR and research management systems at UDS. These systems use standard interchange formats making the transfer of data to the open access system under development at SLU, or to an external data repository, technically simple. As mentioned there are privacy and security concerns attached to the public dissemination of the data which we intend to solve with the help of the data curation unit and standard practice.

The responsibility of making the data findable by providing context lies with the researchers, but we intend to simplify the process by offering standard operating procedures for exporting data from our systems to public repositories at publication of the results or at the end of the project.

Table E1. The need of supporting e-infrastructure.

Our estimates, based on information from the scientists and SLUs IT services, is that the demand can be met using existing infrastructure with the addition of standard servers.

Year	2020	2021	2022	2023	2024
Calculation capacity (CPU hours)	N/A	N/A	N/A	N/A	N/A
Comment, need for special technical solution					
Storage (TB); online harddrive / tape	<10 TB	<10 TB	<10 TB	<10 TB	<10 TB
Comment, need for special technical solution	Mainly image data from CT and PET. No special solution is needed.				
Advanced user support (FTE)	N/A	N/A	N/A	N/A	N/A

Comment, need for special technical solution	We intend to use off the shelf systems including training.				
Network capacity	1Gb/s	1Gb/s	1Gb/s	1Gb/s	1Gb/s
Comment, need technical solution	SLU is currently considering increasing the bandwidth to the SUNET backbone. We do not anticipate a general lack of bandwidth, but rather rare burst transfers of large image projects.				

Table E2. Cost estimate of the needs stated in Table E1

Year	2020	2021	2022	2023	2024
Calculation capacity (SEK)	0	0	0	0	0
Storage (SEK)	300 000	300 000	300 000	300 000	300 000
Advanced user support (SEK)	50 000	50 000	50 000	50 000	50 000
Network capacity (SEK)					
Software licences (SEK)	250 000	250 000	250 000	250 000	250 000
Total (SEK), excl. OH	600 000	600 000	600 000	600 000	600 000

References (see section "Key references")

För infrastrukturer med pågående bidrag

Bilaga för befintlig infrastruktur

Ingen fil har laddats upp

Kostnader*

Driftskostnader	Beskrivning	2020	2021	2022	2023	2024	Totalt
1 Drift	Personalkostnader och övriga direkta kostnader	10 769 697	15 173 459	13 142 659	12 751 805	12 690 889	64 528 509
Totalt		10 769 697	15 173 459	13 142 659	12 751 805	12 690 889	64 528 509

Total budget*

	Specificerade kostnader	2020	2021	2022	2023	2024
1	Driftskostnader	10 769 697	15 173 459	13 142 659	12 751 805	12 690 889
2	Delsumma	10 769 697	15 173 459	13 142 659	12 751 805	12 690 889
3	Indirekta kostnader	4 231 935	5 962 385	5 164 385	5 010 800	4 986 864
4	Total projektkostnad	15 001 632	21 135 844	18 307 044	17 762 605	17 677 753

	Totalt, sökt	Total kostnad
1	64 528 509	64 528 509
2	64 528 509	64 528 509
3	25 356 369	25 356 369
4	89 884 878	89 884 878

Budgetunderlag för ansökan*

Filnamn: INFRA_SWECCLIM_190218_Prisma.xlsx - **Storlek:** 25 kB
INFRA_SWECCLIM_190218_Prisma.xlsx

Förklaring av budget*

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Budget explanation SWECCLIM

The SWECCLIM budget is divided into six modules, however due to the interdisciplinary nature some investments and personnel are shared by several modules. These have been placed in the second module “Experimental large animal models” which forms the core of the proposed infrastructure.

Module 1. Management

The cost for the manager is calculated based on 75% salary of a professor. Depending on the requirements, this may be divided into a 50% manager and a deputy manager at 25%. In addition, an administrator employed at 50% responsible for logistics and economy is needed. We anticipate the need of a communications officer to handle internal and external communication of the infrastructure. Although most of the meetings will be held via Skype/Video, a reasonable budget for meetings and travel has been set aside for straightforwardmanagement of the infrastructure.

Module 2. Experimental large animal models

In addition to the module manager, core animal personnel eg veterinary nurses, veterinary supervisor, stable manager, surgical support staff and access to clinical chemistry and pathology are also located in this module. IT-costs such as file storage, purchase and support for the electronic medical records systems and the integrated research storage systems in addition to costs associated with securing the premises are also collected here.

The core infrastructure will be located at the VHC (the Centre for Veterinary Medicine and Animal Science) and within this also the University Animal Hospital (UDS). As described in our risk analysis, we have the challenges of managing patient and student flow in close proximity of the research sections in the building. We therefore need to reinforce doors, install cameras as well as installing additional alarms and card systems to secure the premises from intrusion and accidental contamination. Most of the scientific staff of this module comes from the Hedenstierna laboratory at Uppsala University but the facilities are located at VHC and UDS at SLU, Uppsala.

Module 3. Advanced Diagnostic Imaging

The third module consists of three different integrated nodes. The first node is the functional PET on nonhuman primates at Astrid Fagreus laboratory (AFL) at KI. The scientific staff of this module consists of a manager, nurse, senior lecturer and professor. In addition to the cost of a multiscan PET/CT camera, support staff consisting of a radiochemist, data analyst, and physicist is needed.

The node at the UDS consists of a large bore PET/CT camera, which will be used for medium sized animals. For large animals, such as horses, a separate large-bore CT is needed since the PET/CT only can be used on distal limbs due to the depth the camera. A table for standing horses used for head and neck CT is therefore included. This CT can also be used for positioning dogs and pigs in conjunction with the possible addition of a LINAC for the possible expansion of SWECCLIM with experimental radiotherapy in the same building. The scientific staff consists of a veterinary radiologist, veterinary nurse, and a PET technician.

The last node is the facilities for producing PET tracers at Uppsala University. The increased production require extension of the preclinical PET platform by a radiochemist, manager and coordinator.

Module 4. Infectious disease

The main investment in this module is the upgrade of the animal facilities to level 2 for animals weighing more than 5kg. In addition to this some monitoring equipment needs to be acquired and a support staff consisting of a technician, manager, and veterinarian.

Module 5. 3R and training

The 3R and training module is composed of three different but integrated nodes located at SLU, GU and LiU. The node will be involved in assisting scientists' submitting project proposals to the infrastructure to refine and reduce the use of animals, and to maximize animal welfare and consists of: a veterinary professor, welfare specialist and an animal trainer. The facilities at GU and LiU will handle surgical training for the refinement of experiments and method development aiming to replace animals in selected procedures. To this end laboratory and surgical equipment will be acquired and support staff needed including veterinarian and lab animal specialists.

Module 6 Translational medicine on spontaneous diseases in companion animals

The physical location of this module is UDS in Uppsala. As UDS is a modern and well equipped veterinary hospital very little is needed in new physical equipment. Therefore the main investment is in a dedicated veterinary research nurse coordinating and assisting research projects involving animal patients.

The already existing collaboration between the dog genetics group at SLU and groups at Uppsala University and ScilifeLab will be strengthened by an investment in genetic and molecular biology competence at SWECCLIM in the form of a lab technician and a specialist in bioinformatics.

Nyckelreferenser

Se nästa sida för bilaga.

Key references

*** Example of key references describing scientifically prominent research enabled by the infrastructure**

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Stödbrev*

Se nästa sida för bilaga.

Stödbrev till ansökan forskningsinfrastruktur av nationellt intresse (medverkande organisationer inklusive medelsförvaltaren)

SVERIGES LANTBRUKSUNIVERSITET stödjer ansökan om bidrag till " Swedish Experimental Clinical Center for Large-Animal Innovative Models" (SWECCLIM). Om ansökan beviljas av Vetenskapsrådet är SVERIGES LANTBRUKSUNIVERSITET beredda att

- ingå i det föreslagna konsortiet
- ta ansvar för den verksamhet som beskrivs i ansökan samt göra de finansiella och/eller andra åtaganden som anges för SVERIGES LANTBRUKSUNIVERSITET i ansökan.

Om Vetenskapsrådet beslutar att bevilja ansökan på en lägre nivå än vad som anges i ansökan avser SVERIGES LANTBRUKSUNIVERSITET att i god anda föra konstruktiva diskussioner med Vetenskapsrådet och de övriga medverkande organisationerna för att SWECCLIM ska bli en infrastruktur till gagn för svensk forskning.

Genom att underteckna stödbrevet bekräftas att innehållet i ansökan och budget är korrekt och att den beskrivna verksamheten sker i enlighet med gällande lagstiftning.

Karin Holmgren, rektor

2019-02-08
Datum

Sveriges lantbruksuniversitet

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Datum 2019-02-12 Dnr 2018/2334

Rektor
Sveriges lantbruksuniversitet

Stödbrev till ansökan forskningsinfrastruktur av nationellt intresse (Sveriges lantbruksuniversitet, Karolinska institutet, Sveriges veterinärmedicinska anstalt, Linköpings universitet, Göteborgs universitet, Uppsala universitet)

UPPSALA UNIVERSITET stödjer ansökan om bidrag till " Swedish Experimental Clinical Center for Large-Animal Innovative Models" (SWECCLIM). Om ansökan beviljas av Vetenskapsrådet är UPPSALA UNIVERSITET beredda att

- ingå i det föreslagna konsortiet
- ta ansvar för den verksamhet som beskrivs i ansökan samt göra de finansiella och/eller andra åtaganden som anges för UPPSALA UNIVERSITET i ansökan.

Om Vetenskapsrådet beslutar att bevilja ansökan på en lägre nivå än vad som anges i ansökan avser UPPSALA UNIVERSITET att i god anda föra konstruktiva diskussioner med Vetenskapsrådet och de övriga medverkande organisationerna för att SWECCLIM ska bli en infrastruktur till gagn för svensk forskning.
Genom att underteckna stödbrevet bekräftas att innehållet i ansökan och budget är korrekt och att den beskrivna verksamheten sker i enlighet med gällande lagstiftning.

Eva Åkesson
Rektor
Uppsala universitet

Organisationsnr:
202100-2932

Stödbrev till ansökan forskningsinfrastruktur av nationellt intresse (medverkande organisationer inklusive medelsförvaltaren)

KAROLINSKA INSTITUTET stödjer ansökan om bidrag till " Swedish Experimental Clinical Center for Large-Animal Innovative Models" (SWECCLIM). Om ansökan beviljas av Vetenskapsrådet är KAROLINSKA INSTITUTET beredda att

- ingå i det föreslagna konsortiet
- ta ansvar för den verksamhet som beskrivs i ansökan samt göra de finansiella och/eller andra åtaganden som anges för KAROLINSKA INSTITUTET i ansökan.

Om Vetenskapsrådet beslutar att bevilja ansökan på en lägre nivå än vad som anges i ansökan avser KAROLINSKA INSTITUTET att i god anda föra konstruktiva diskussioner med Vetenskapsrådet och de övriga medverkande organisationerna för att SWECCLIM ska bli en infrastruktur till gagn för svensk forskning.

Genom att underteckna stödbrevet bekräftas att innehållet i ansökan och budget är korrekt och att den beskrivna verksamheten sker i enlighet med gällande lagstiftning.

Karin Dahlman-Wright
Prorektor vid Karolinska Institutet

2019-0207
Datum

GÖTEBORGS UNIVERSITET

Stödbrev till ansökan forskningsinfrastruktur av nationellt intresse

Göteborgs universitet stödjer ansökan om bidrag till "Swedish Experimental Clinical Center for Large-Animal Innovative Models" (SWECCLIM). Om ansökan beviljas av Vetenskapsrådet är Göteborgs universitet beredda att

- ingå i det föreslagna konsortiet
- ta ansvar för den verksamhet som beskrivs i ansökan samt göra de finansiella och/eller andra åtaganden som anges för Göteborgs universitet i ansökan.

Om Vetenskapsrådet beslutar att bevilja ansökan på en lägre nivå än vad som anges i ansökan avser Göteborgs universitet att i god anda föra konstruktiva diskussioner med Vetenskapsrådet och de övriga medverkande organisationerna för att SWECCLIM ska bli en infrastruktur till gagn för svensk forskning.

Genom att underteckna stödbrevet bekräftas att innehållet i ansökan och budget är korrekt och att den beskrivna verksamheten sker i enlighet med gällande lagstiftning.

Göteborg 2019-02-14

Mattias Goksör
Ställföreträdande rektor Göteborgs universitet

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031 786 10 00
www.gu.se

REKTOR
HELEN DANNETUN

Stödbrev till ansökan forskningsinfrastruktur av nationellt intresse (medverkande organisationer inklusive medelsförvaltaren)

Linköpings universitet stödjer ansökan om bidrag till " Swedish Experimental Clinical Center for Large-Animal Innovative Models" (SWECCLIM). Om ansökan beviljas av Vetenskapsrådet är Linköpings universitet beredda att

- ingå i det föreslagna konsortiet

- ta ansvar för den verksamhet som beskrivs i ansökan samt göra de finansiella och/eller andra åtaganden som anges för Linköpings universitet i ansökan.

Om Vetenskapsrådet beslutar att bevilja ansökan på en lägre nivå än vad som anges i ansökan avser Linköpings universitet att i god anda föra konstruktiva diskussioner med Vetenskapsrådet och de övriga medverkande organisationerna för att SWECCLIM ska bli en infrastruktur till gagn för svensk forskning.

Genom att underteckna stödbrevet bekräftas att innehållet i ansökan och budget är korrekt och att den beskrivna verksamheten sker i enlighet med gällande lagstiftning.

Helen Dannetun 2019-02-11
Rektor

Linköpings universitet

Stödbrev till ansökan forskningsinfrastruktur av nationellt intresse (medverkande organisationer inklusive medelsförvaltaren)

Statens veterinärmedicinska anstalt (SVA) stödjer ansökan om bidrag till " Swedish Experimental Clinical Center for Large-Animal Innovative Models" (SWECCLIM). Om ansökan beviljas av Vetenskapsrådet är Statens veterinärmedicinska anstalt (SVA) beredda att

- ingå i det föreslagna konsortiet
- ta ansvar för den verksamhet som beskrivs i ansökan samt göra de finansiella och/eller andra åtaganden som anges för Statens veterinärmedicinska anstalt (SVA) i ansökan.

Om Vetenskapsrådet beslutar att bevilja ansökan på en lägre nivå än vad som anges i ansökan avser Statens veterinärmedicinska anstalt (SVA) att i god anda föra konstruktiva diskussioner med Vetenskapsrådet och de övriga medverkande organisationerna för att SWECCLIM ska bli en infrastruktur till gagn för svensk forskning.

Genom att underteckna stödbrevet bekräftas att innehållet i ansökan och budget är korrekt och att den beskrivna verksamheten sker i enlighet med gällande lagstiftning.

Underskrift rektor/myndighetschef Datum 190214

Lärosäte/myndighet med forskningsansvar

STATENS VETERINÄRMEDICINSKA ANSTALT

CV

Publikationer

Registrera

Villkor

Ansökningar där en organisation är sökande signeras automatiskt vid registrering av ansökan av den ansvarige för organisationsansökan vid medelsförvaltaren.

Signering av den sökande innebär en bekräftelse av att

- uppgifterna i ansökan är korrekta och följer Vetenskapsrådets instruktioner
- kostnadsberäkningen i ansökan godkänns
- den beskrivna forskningen eller forskningsstödjande verksamheten kan beredas plats vid medelsförvaltaren under den tid och i den omfattning som anges i ansökan
- de tillstånd och godkännanden som krävs finns innan forskningen påbörjas, exempelvis tillstånd från Läkemedelsverket eller godkännande från etikprövningsnämnd respektive djurförsöksetisk nämnd
- sökande kommer att följa samtliga övriga villkor som gäller för bidraget.