BENEFITS OF CROSS DISCIPLINE RESEARCH FOR HUMAN AND ANIMAL HEALTH

Executive summary

An interspecies approach offers opportunities over a spectrum of research (applications).

Cross species research leads to

- **the exchange of insights** on disease mechanisms, prevention and treatment of disease; discovery of novel diagnostic and therapeutic targets; innovative diagnosis and treatment methods; holistic data assembly; improvement of (animal) welfare.
- **facilitation of the transfer from preclinical to clinical research**: faster development of health applications and treatment optimization via complementary models.

The following research areas benefit animal as well as human health (non-exhaustive list of examples):

- Infectious disease: study of pathogens as well as their susceptibility/resistance to treatment and their prevention
- Non-infectious disease: study of prevention, disease mechanisms and treatment in cardiology, inflammatory disease, mental health issues, neurology, oncology, reproductive health

The cross pollination between the animal and human health sector stimulates innovation in animal health for a variety of technologies and creates development advantages and marketing opportunities in both sectors.

Support of this strategic research will contribute to the realization of the sustainable development goals (SDG): building public-private-partnerships (SDG17) to boost innovation (SDG9), supply of nutritious, safe and healthy food (SDG 2), reducing environmental impact, making better use of resources (SDG 12), respecting animal welfare and safeguarding human and animal (SDG 3) and environment (SDG 13 & 15) health thus responding to the requirements of the consumer/citizen.

“Humans and animals share so many of the same health and disease threats, so it stands to reason that they might also share the solutions.”

- Michael Francis[1]

The main goal of research is to find solutions for problems. To do so, researchers in theory make use of all research tools at their disposal. In reality, research is often conducted in species silo’s: research destined to benefit human or animal. However, humans and animals share more similarities than differences, and the study of these similarities and differences unlocks limitless research opportunities.

Both from an infectious and non-infectious point of view, humans are mammals and they share a great deal of disease targets with other species. By recognizing the possibilities inherent to interconnectedness of infectious diseases on the one hand and comparative medicine on the other, practices have been developed that have led to numerous medical breakthroughs.[2]

An interdisciplinary exchange of knowledge and insights speeds up discoveries and applications for multiple species and for a variety of health aspects. As such, cross species research can reinforce research and development for both the animal and human trajectory, as well as provide a better translation from preclinical to clinical research. These insights can cover disease presentations, prevention and treatment of disease, discovery of novel diagnostic and therapeutic targets, innovative diagnosis and treatment methods, holistic data assembly, improvement of (animal) welfare. The translational value manifests via a faster development of health applications and treatment optimization via complementary models.

This document promotes the benefits of a cross discipline research approach for human and animal health and is an invitation to contribute to a strategic research agenda towards improved health and monitoring and control of diseases across species.
A non-exhaustive list of examples of research opportunities in animal and human health is provided. The selected research areas include:

1. Infectious disease - pathogen

In addition to loss of life, epidemics and pandemics affecting human and/or animal devastate economies.

Estimated costs of past events in humans include: a loss of over €34 billion in productivity from the 2003 SARS epidemic; €45 billion loss from the economic and social impact of the 2014-2016 West Africa Ebola outbreak; and the €38-47 billion cost of the 2009 H1N1 influenza pandemic.[3] SARS-CoV2 will exceed these costs by far. Neglected tropical diseases (NTDs) are a diverse group of viral, bacterial and parasitic diseases, several of which are zoonotic or foodborne in nature. Worldwide, NTDs affect one in seven people, but have a disproportionate impact on the poorest communities in tropical countries. In 2015 these

1 Michael Francis, The Telegraph, June 3rd 2020, Animal medicine might play a crucial role in developing the sought-after coronavirus vaccine.
2 Osterhaus et al. Make science evolve into a One Health approach to improve health and security: a white paper. One Health Outlook (2020) 2:6
3 Strategic options for the co-ordinated development and manufacture of vaccine(s) protecting against COVID-19 by the European Commission and the Member States of the European Union

diseases resulted in about 24 million disability-adjusted life years, putting them in the top 10 of all infectious diseases.

Twenty percent of animal productivity or 60M ton meat and 150M ton milk are lost due to disease.[4]
The combined annual cost of helminth infections in 18 European countries in ruminal livestock was estimated at € 1.8 billion, which is similar or greater than the costs associated with some major epizootic diseases.[5]

To prevent such losses in the future, it is essential to share and invest in relevant insight in health across species.

2. Infectious disease - antimicrobial/parasitic resistance

Antimicrobial (including antiparasitic) resistance (AMR) is the result of many intertwined factors. Therefore, researchers in this field should be aware of the efforts needed across sectors and adapt accordingly: e.g. coordinate the use of antibiotic (type)s across species, align all stakeholders involved in antibiotic administration on correct antibiotic use. Factors that play a role in plants can be important for animals and humans and vice versa. Where the development of anthelmintic resistance is well known and studied in intestinal worms of animals, both the evidence and the diagnostic tools to assess anthelmintic resistance is lacking for human intestinal worms. Hence, the expertise in veterinary parasitology will be an important asset for public health. Environmental, pharmacological, transmission and behavioral factors for all involved actors should be considered.

[4] International Feed Industry Federation|FAOGlobalFoodOutlookNovember2012| FAO World agriculture towards 2030/2050 |Elanco presentation at EU Animal Health Innovation Summit, 2018

[5] Charlier et al. 2020. Initial assessment of the economic burden of major parasitic helminth infections to the ruminant livestock industry in Europe, Prev. Vet. Med. Volume 182 10.1016/j.prevetmed.2020.105103

3. Oncology, cardiology, inflammation/allergy, reproductive health issues, neurology and mental health

Similar fundamental principles apply across species in the development of diseases such as cancer, heart failure, inflammatory conditions, reproductive medicine and mental health issues.

Several animals develop the same disease as humans but have a less complicated **genetic** background. The study of the disease in these species offers bilateral opportunities: humans benefit from a faster identification of possible genetic causes, allowing a more rational and focused research afterwards and the concerned animal species can profit from the results of that knowledge. Likewise, animals may serve as **non-clinical animal model** in pharmaceutical and biomedical research and for optimizing surgical procedures (e.g. dogs with spontaneous tumors such as sarcoma and melanoma are ideal translational models for optimization of oncological surgery). The pig(let) has been increasingly demonstrated to be a suitable human surrogate large animal model in (paediatric) drug research, due to its similarities in terms of anatomy and physiology of major organ systems involved in the disposition processes of drugs and xenobiotics in general and a highly similar immune system. Furthermore, techniques of assisted reproductive technology (ART) such as intracytoplasmatic sperm injection (ICSI), pre-implantation genetic diagnosis and testing, freezing of oocytes and sperm, fertility preservation by testicular and ovarian tissue banking have progressed with great success, since the birth of the first test-tube baby after *in vitro* fertilization in 1978. All these procedures were first optimized and validated in animal models before they were applied in human clinical practice.

Furthermore, the **study of differences and similarities** of the same disease between species can reveal valuable research leads. When a species is not prone to develop a specific disease, research in this species can indicate which pathways offer protection against it, thus unraveling possible targets.

Some diseases are **rare in humans**, but common in other species. The greater availability of study material for rare diseases offers faster results for humans, all while benefitting the studied species as well.[6]

Finally, differences in **treatment approaches** among species offer opportunities to study (long-term) treatment effects and can result in practical insights across species.

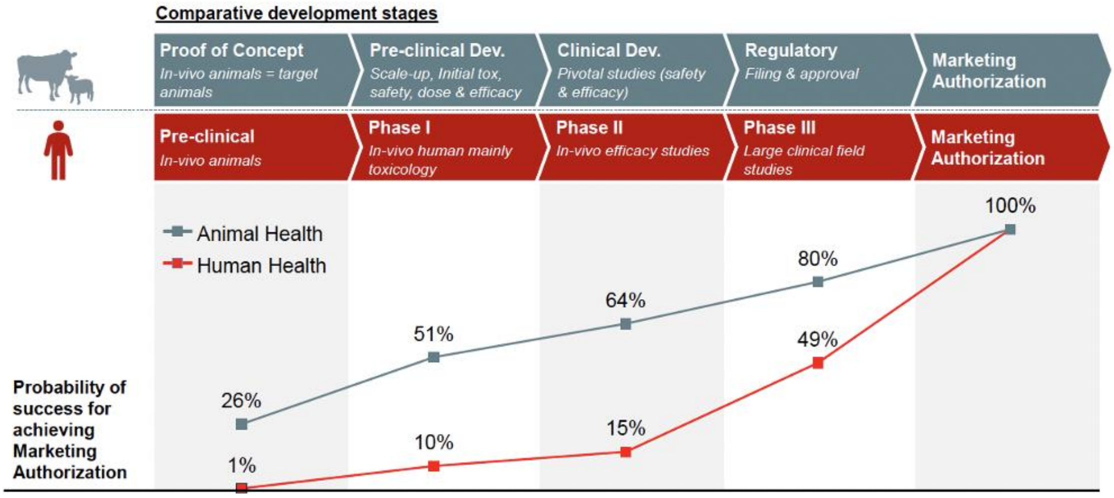
Some conditions occur more in animals than humans, such as osteosarcomas. This bone tumor affects dogs (4-15/100) more often than humans (5/1 000 000), depending on the dog race.
Therefore, more treatments can be tested via dogs with spontaneous tumors than via children alone. This approach is mutually beneficial as the dog receives a broader access to treatment opportunities.

- Joelle M. Fenger[9]

6 Fenger, et al. 2014. Canine Osteosarcoma: A Naturally Occurring Disease to Inform Pediatric Oncology, ILAR Journal, Volume 55, Issue 1, Pages 69–85

Market opportunities

Innovation in animal health can be stimulated by cross pollination between the animal and human health sector which is possible for various technologies such as drugs (e.g. alternative to antibiotics or antiparasitics), medtech, big data, etc.
Depending on the technology, the product (drug, diagnostic, wearable, IoT etc) could be marketed in both sectors (with first validation in animal care) or repurposed to the animal care sector.
Bioinformatics and biomarker development for diseases transcend species, uniting the biology of disease understanding across the animal kingdom. Solutions for newly emerging infectious diseases in animals may help protect the health of people.
One important driver is that the animal care sector is characterized by shorter development phases, lower development cost and lower risk profiles with higher probability of success in achieving marketing authorization when compared to the human care sector.



Animal health has a lower risk profile with higher probability of success in achieving marketing authorization – Stonehaven consulting, BioFIT 2018, Introduction to Animal Health

Furthermore, the veterinary field changes rapidly as the demand for veterinary specialists increases, pet insurance companies become more established and investment funds are investing in veterinary medicine. [7]

Entrepreneurial universities can play an important role in facilitating the route to market of new technologies and innovations and in the generation of ecosystems where researchers, innovators, industries and governments join forces to adopt a mission oriented and impact-focused approach to the health challenges faced across species.

"Founded in 2017, Vetigenics originally focused on development of immunotherapies for use in dogs with spontaneous diseases to accelerate the treatment of human cancers.
However, the start-up now also looks at the other end of the One Health spectrum and produces antibody therapeutics for the animal health market."- Joseph Harvey[8]

7 Jan De Schampelaere, Investeerders vechten om uw zieke hond en kat, De Tijd, 02/07/2020
8 Joseph Harvey, Vetigenics aims to solve challenges in canine immunotherapy discovery and development, IHS Markit, 21/07/2020

Examples of research opportunities

1. Infectious disease - pathogen

The following domains would benefit from cross-species integrated research:

Exchange of insights

- Infection prevention: biosecurity, immune-modulating nutrition and adapted housing represent mutual research areas of focus.
- Virology, bacteriology, mycology, parasitology:
  - Transfer of knowledge about mode of action and pathogenesis of a pathogen(‘s family members) across species (such as site of replication, relevant epitopes).
  - Cross-species pathogen discovery and mapping of the pathogen’s evolution
  - Interaction of gut microbiota and the immune system: the effects of feed additives and pathogens play an important role in humans and animals alike.
- Pathogens/micro-organisms and the toxins they produce: toxins produced by fungi or micro-organisms can be potent carcinogens, others exert nephrotoxic, hepatotoxic, immunotoxic, genotoxic or teratogenic effects. Insights into species-specific similarities and differences in the pathogenesis, toxicity, toxicokinetics and –dynamics, may contribute to improved food and feed safety, control measures and legislative frameworks. As for other diseases, suitable (large) animal models support research in this field.
- Immunology: similar immune mechanisms exist between animal and human for which the field could benefit from the vast complementary experience and technology available in human and veterinary medicine.
  - Share knowledge on critical cell populations, receptors and pathways involved in eliciting local immunity (oral, nasal, intestinal)
  - Value and explore the role of innate immunity which is more conserved between species than acquired immunity
  - Identify which biological differences result in resistance to infection/sensitivity to pathogen. This information can help identify possible targets on the pathogen or its host.
- Mathematical modelling, observational studies: map disease spread and/or detection of relevant epitopes via cross-species data, necessitating the collaborative input of epidemiologists, microbiologist, veterinarians, physicians etc. This approach allows for the exchange of insights on risk factors.
- Development of health decision algorithms to inform and optimize large-scale population-based interventions. For example, what would be the most-cost effective strategy to monitor anthelminthic resistance in both animals and humans.
- Diagnostics development such as user friendly and/or non-invasive sampling methods or tools; rapid and more precise diagnostics and tools for the monitoring of health and infection is useful across species.

Facilitate transfer from non-clinical to clinical research

- Vaccine development in animal and human follows the same process up until non-clinical studies. Through advances in veterinary medicine, the scientific community has a wide range of existing licensed novel vaccine technologies and associated know-how that do not need to be invented from scratch. Veterinary vaccine delivery technologies could also be leveraged in the development of human vaccines. Some poultry or swine vaccines for example are given through drinking water or as a spray, some dog vaccines are given intranasally, thus providing a painless, simple and rapid form of immunization. This kind of local administration could be particularly effective against respiratory and intestinal infections.
- Animal models offer results that can benefit the animal species as well as humans. Comparative data on pathogens will facilitate the identification of suitable animal models advancing vaccine and/or treatment development where the step from non-clinical to phase I is critical.

Different kinds of coronaviruses have long since affected animals including dogs, cats and livestock, and effective vaccines already exist to prevent some of them.

This means that the coronavirus family of diseases and their potential weaknesses are well studied by veterinary researchers, offering hope – and also valuable lessons – for the rapid development of a vaccine for people.

The current race to develop a Covid-19 vaccine is an important reminder not to ignore the lessons of veterinary medicine, which has already brought successful vaccines to market for several animal coronaviruses.

Over many years, researchers have expanded scientific knowledge of the virus and how to immunise against it. For example, it has been shown that the virus's "spike" proteins, which attach to cell receptors and allow the virus to infect and multiply, can be targeted using antibodies produced by the vaccination.

- Michael Francis[9]

9 Michael Francis, The Telegraph, June 3rd 2020, Animal medicine might play a crucial role in developing the sought-after coronavirus vaccine.

Veterinary vaccines have taught us a great deal already about the feasibility and efficacy of several vaccine administration routes, the role of humoral and cellular immunity and cross-species protection for several coronaviruses:

1. *Both killed (inactivated) and live (attenuated) whole virus vaccine strategies have been successfully employed to develop commercial coronavirus vaccines.*
2. *Virus-neutralising antibodies directed to the surface spike (S) protein play a major role in protective immunity.*
3. *T-cell responses may also be involved in protective immunity viral clearance, but they are unlikely to be the prime mode of protection for a vaccine.*
4. *Maternal antibodies and mucosal immunity play an important role in protection against enteric coronavirus infections.*
5. *Immune responses can be qualitatively improved by an oral prime and intra-muscular boost strategy.*
6. *Cross protective immunity can be developed by either combining vaccine strains within a vaccine or using a prime boost strategy with differing coronavirus.*
7. *Heterologous vaccines using a related coronavirus from one species can be used to vaccinate another species.*
8. *Vaccine-induced immunity is likely to last for at least 12 months and annual boosters are required in order to maintain protective levels of immunity.*

Those developing novel coronavirus vaccines should be aware of the potential risk of antibody-dependent enhancement induction leading to enhanced disease.

- Michael Francis[10]

2. Infectious diseases – antimicrobial resistance

The following research domains would benefit from interdisciplinary exchange:

Exchange of insights

- Infection prevention to reduce the need for antimicrobial use
- More efficient use of antibiotics: optimize dose and administration per species.
- Research towards resistance mechanisms in various relevant environments (such as hospital, retirement home, farm, slaughterhouse).
- Diagnostics:
  - Optimize the diagnostic flow from sampling to sample analysis.
  - Advances in the current diagnostic flow across species and monitoring of antibiotic resistance profiles of bacteria would allow less or a more targeted use of antimicrobials. The same applies for antiparasitic resistance.
- Coordination: a coordinated approach across species is necessary to halt the development and spread of antibiotic/parasitic resistance.
- Antimicrobial use: human, animal and plant research groups develop alternatives to antibiotic/antifungal/antiparasitic use. Applications for one species can possibly be translated to other species.
- Socioeconomics: identification of barriers and incentives for uptake of sustainable disease control measures by patients, animal owners, farmers and veterinarians. Development/improvement of communication strategies. Economic impact and context of disease (control measures).

3. Oncology, cardiology, inflammation/allergy, reproductive medicine, neurology and mental health issues

ONCOLOGY

Exchange of insights

- Genetics: several dog and cat breeds are known to be more susceptible to develop certain cancer types than others. The study of these specific breeds offers a more targeted approach -as opposed to humans- to i**dentify relevant targets and pathways**, which are often conserved across species. The identification of involved genes and pathways can lead to novel treatments, benefitting man as well as animal. Furthermore, more research on monogenetic diseases in animals may alter current breeding thus preventing occurrence of disease in future generations.
- Immunology: comparative research would greatly benefit from the development of more **species-specific markers and protocols**.
- As animals are likely to benefit from the extensive advances made in the field of human cancer, the targets identified in humans need to be explored to improve cancer **diagnostics and treatments** in animals.
- Cross-species **cancer registries** offer advantages to the species involved: as animals develop cancer faster than humans they can act as a sentinel for humans. Furthermore, registries of animal cancer cases will allow veterinary medicine to expand its knowledge on incidence, the success rate of different treatments, etc.

Facilitate transfer from non-clinical to clinical research

- Companion animals with naturally occurring cancer are an invaluable source of biological samples, not only to improve veterinary but also translational cancer research (i.e. for the human clinic). **Companion animals with cancer are a recognized, but still severely underexploited tool for advancing anti-cancer strategies**. [10] Indeed, cancers in pets display striking similarities to the human situation.
  - Intact immune system: tumors develop in animals with an intact immune system, and, as in human patients, metastatically spread, recur and/or become a drug-resistant disease over time.
  - Biology: companion animals share a similar histological, biological, and genetic cancer background with humans. These similarities are in general significantly higher than the relationship between rodents and man.
  - Clinical approach: corresponding diagnostic and treatment options are available for dogs and humans, while the progression of cancer in companion animals is faster. This allows results to be obtained within a reasonable period of time and/or allows innovative trial designs such as prophylactic cancer vaccine tests in a realistic setting.
  - Biology and pathology: the study of the behavior of rare diseases in human can be accelerated via the study of the same disease in animals.

10 LeBlanc et al., 2016 Defining the value of a comparative approach to cancer drug Development Clin Cancer Res. 22(9): 2133–2138

CARDIOLOGY
Exchange of insights

- Veterinary cardiologists and human cardiologists harbor vast complementary knowledge. The **comparison of cardiovascular pathophysiology** across species and broader access to autopsy in animals for research cases lead to new insights across species. E.g. aortic rupture in (Friesian) horses is often an unfortunate, fatal event. The underlying pathophysiology of aortic rupture, aorta-pulmonary fistula (and mega-oesophagus which can be of interest to the gastro-enterologists) has not been elucidated yet and is a field of active study. Comparison with aorta pathology in humans could help to better understand the potential underlying mechanism of the aorta pathology/ rupture.
- The study of cardiac **electrophysiology and arrhythmias** in dogs, cats, and horses generates opportunities to translate existing techniques from human medicine towards animals, based on a multidisciplinary approach (collaboration between engineers, material specialists, human specialists and veterinarians). On their turn, animals serve as a unique model for fundamental and clinical translational research.
  - Due to their susceptibility to spontaneous **atrial fibrillation** and because of a complete absence of associated thrombo-embolic events, horses provide an excellent model to study atrial fibrillation pathophysiology.
  - Ventricular and supraventricular heart rhythm disturbances in dogs and cats associated with **cardiomyopathies** such as dilated, hypertrophic or arrhythmogenic right ventricular cardiomyopathy occur frequently. These diseases share many pathophysiological characteristics with their human counterparts, and their benefit as a spontaneous animal model has been highlighted in several review papers, one even specifically advocating for a "one health approach" to feline hypertrophic cardiomyopathy.[11, 12] Not only clinical signs and phenotype of arrhythmias are similar, but interestingly, also genetic causes, for both cardiomyopathies as well as **primary inherited arrhythmias**.[13, 14, 15]
  - Many procedures (catheterization, implants, …) can be performed on the standing **awake horse** which **overcomes the effects of sedation and general anesthesia**.
- Dogs and cats frequently present with **congenital cardiac abnormalities** similar to those in people e.g. persistent ductus arteriosus, pulmonic stenosis, atrial or ventricular septal defects, tetralogy of Fallot etc. Because of their small size they are ideal candidates to develop/test new diagnostic tools, interventional or hybrid surgical techniques.

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11 Duncker et al., 2015. Animal and in silico models for the study of sarcomeric cardiomyopathies. Cardiovascular Research 105, 439–448
12 Stern and Ueda, 2017. A One Health Approach to Hypertrophic Cardiomyopathy. YALE JOURNAL OF BIOLOGY AND MEDICINE 90, pp.433-448
13 Hamlin et al., 2007. Animal models of ventricular arrhythmias. Pharmacology & Therapeutics 113 (2007) 276–295
14 Simpson et al., 2015. Genetics of Human and Canine Dilated Cardiomyopathy. International Journal of Genomics Volume 2015, Article ID 204823, 13 pages
15 Meurs et al., 2019. A QIL1 Variant Associated with Ventricular Arrhythmias and Sudden Cardiac Death in the Juvenile Rhodesian Ridgeback Dog. Genes, 10, 168

Facilitate transfer from non-clinical to clinical research

- **Interventional tools** in cardiology are mainly designed for human adults.
    - **Companion animal**. The smaller heart sizes of companion animals allow development of pediatric tools applicable in both children and small animals.
    - **Horse**. On the other hand, the large size of the equine heart, allows to better assess the impact of myocardial wall thickness, chamber size and quantity of blood flow on applied techniques.
    - **Cow**. Left ventricle (LV) assist devices used to support people with end stage heart failure are often tested in cows.
    - **Swine** and **sheep** are also often used in the research of human cardiovascular diseases. Structurally, the swine heart anatomy is similar to the human heart. The coronary microvasculature is even nearly identical to that of humans. Physiologically, resting heart rates and left ventricular pressures are comparable to humans. Pigs have been used in the development and testing of numerous cardiac devices & procedures e.g. intravascular stents, valve replacement, cardiac transplant, and cardiac assist devices. Pharmacological agents, stem cell therapy (in acute coronary syndromes/ myocardial infarction to decrease size of infarction and to improve LV function) and gene therapy have been tested in swine (heart failure models). Research on the renal pressure/perfusion relationship in pigs allows to better understand the mechanism of arterial hypertension due to renal artery stenosis and the secondary renin-angiotensin-aldosterone system activation. Such results could be translated to and be helpful for human patients to improve the management of hypertension due to renal artery stenosis; specifically, to better define the criteria for the potential usefulness of renal artery stenting.
    - **Mice/zebra fish:** Rare genetic conditions of the aorta, such as Marfan syndrome, occur both in humans and horses. Modelling of this disease in mice/zebra fish models allows a better insight into the pathophysiology/effect of specific genetic variants/sex/drug compounds across species.

- Human cardiologists train advanced interventions for specific diseases on healthy animals which is expensive and associated with ethical concerns. On the other hand, sick animals requiring such an advanced intervention often cannot receive the treatment because of financial constraints. Combining both under a **medical need program** would create a win-win situation for both the human and veterinary field. The success of a human-veterinary collaboration has already been shown in multiple PhDs and major breakthroughs in equine cardiac electrophysiology.

Barbara Natterson-Horowitz is a human cardiologist at the David Geffen School of Medicine at UCLA. She's also on the medical advisory board for the Los Angeles Zoo. In 2005, the vets at the zoo asked her to come by to take a look at an emperor tamarin suffering from heart failure.

As Natterson-Horowitz examined the monkey, she did what she usually does with her human patients: she gazed into her eyes to put her at ease. Immediately she felt the vet's hand on her shoulder.

"Please stop making eye contact," the vet said. "You'll give her capture myopathy."

She knew very well that myopathy refers to heart muscle damage, but in her 20 years as a cardiologist, she had never heard of capture myopathy. Later she did some research and discovered that it's a form of heart damage experienced by many animals. It occurs when animals are chased or captured by predators. A surge of hormones floods their body and ravages the heart. Some species—including small primates—can even die as a result. Even the gaze of a predator can cause capture myopathy.

It existed in humans, under the name of Takotsubo cardiomyopathy. Intense emotional stress can cause a hormone surge in humans, which can cause serious damage to the heart. Cardiologists discovered Takotsubo cardiomyopathy just a few years ago. But veterinarians knew about its animal version decades ago.

- Barbara Natterson-Horowitz[16]

16 Barbara Natterson-Horowitz, author of "Zoobiquity"

INFLAMMATION/ALLERGY

Exchange of insights

- Mechanisms of inflammatory **disease pathogeneses** as well as the **protective effects** of fecal transplants, bacterial strains and bacterial metabolites on gut homeostasis and their influence on inflammatory intestinal disease. These data can be used for the rational development of control measures against pathogen colonization or intestinal disease, including vaccines, feed additives and diagnostic tools.
- The exchange of knowledge on inflammatory mechanisms in **chronic wound** management; risk factors for **airway or bowel inflammation**.
- The identification of pivotal **immune cell subpopulations** (or conserved receptors on said cells) involved in inflammatory cascades in one species can lead to novel anti-inflammatory applications in other species.

Facilitate transfer from non-clinical to clinical research

- Allergy is not only increasing in prevalence in humans, but also occurring earlier in live. The mechanisms are not well understood. Diagnoses and treatment of allergy form a continuous challenge. **Also in dogs allergy is an increasing problem and similar questions are posed on etiology, diagnosis and treatment.** The dog is thus an excellent model for human **allergies** as dogs share many of the same allergies to foods and environmental allergens. It is possible to control for several factors in pet dogs with spontaneous allergies: e.g. diet, hormonal status, placebo effect to obtain insight in these derailed immune responses and strategies **to correct them**.
- **Metabolic inflammation**: the human metabolic syndrome (HMS) shows many similarities with the overconditioned cow syndrome. In accordance with the HMS, it is supposed that the adipose tissue provokes a derailment of the normal physiological processes in obese animals, thereby rendering them more susceptible to different health problems. Overconditioned cows are insulin resistant, the adipose tissue of dairy cows is also capable of producing different adipokines, the disease susceptibility of dairy cows is associated with a pro-inflammatory state, the immunity of overconditioned cows is attenuated, and overconditioned dairy cows are overall more susceptible to a variety of diseases. Dairy cows can act as spontaneous animal models to provide valuable insights on obesity, ageing and metabolic inflammation.

NEUROLOGY AND MENTAL HEALTH

Exchange of insights

- Several neurological and mental health diseases such as epilepsy and anxiety disorders in human and dog are very similar and joint research provides broader opportunities towards the unravelling of their **neurobiology**. Animals with neurological and mental health diseases benefit from the translation of human treatment protocols. In turn, this can further finetune treatments and identify biomarkers for both species.
- Preclinical testing of implantable devices for neuromodulation, is often impossible in rodents due to incompatible dimension of the technologies. Therefore, dogs are an ideal testing model. Neuromodulatory devices could allow unsupervised treatments imposing less efforts to the owner of the animal.
- The study of animal behavior informs how improvements can be made in **animal welfare** for e.g. housing and cohabitation measures ultimately benefitting the species, farmers and families involved.

Facilitate transfer from non-clinical to clinical research

- Anatomy: the dog's anatomy offers greater access to the cerebrospinal fluid (CSF) than in humans, which facilitates research of biomarkers in CSF and serum.
- Radiation: as companion animals will undergo less medical imaging than humans throughout their lifetime, more research with nuclear tracer imaging is possible. Expensive research imaging equipment can be shared among species.

REPRODUCTIVE HEALTH

Exchange of insights

- The efficiency and safety of currently used methods of assisted reproductive technology have first been addressed in several animal models before clinical practice in human. An important concern with developments in medically assisted reproduction is that new techniques or add-ons to existing ones are often introduced without sufficient preclinical **safety and efficacy** studies, and also without meaningful efforts to collect follow-up data. Popular animal models for this are mice, cow, pig and non-human primates. For example, the formulation of culture media to support the growth of embryos *in vitro* has been largely optimized in several animal models. Also, routinely used techniques such as freezing by vitrification have been first validated in different animal models. Vice versa, newly developed techniques in human assisted reproductive technology (ART) have also been applied in animal, to increase for example the reproduction rate of some valuable animal models, to preserve certain endangered species, to perform semen sexing.

- New methods are currently arising with some of them already reaching the clinical phase: such as the application of assisted oocyte activation during intracytoplasmatic sperm injection (ICSI), the three-parent baby using nuclear transfer technology transplanting the nucleus of a diseased egg into a recipient donor egg, CRISPR/Cas9 gene editing in the germline. It is paramount that these newly developed technologies are first tested and validated in appropriate animal models before extrapolation to the human clinic.
- Finally, more fundamental cross-species research is needed to better understand early human embryo development and human stem cell biology, to reveal differences between species and to obtain more insight in the early stages of human development. The latter still represents a black box due to the inaccessibility of *in vivo* derived human material because of ethical constraints.

Facilitate transfer from non-clinical to clinical research

Animal models offer huge advantages to test new techniques or diagnostic tests for human assisted reproductive technology as human reproductive material is very scarce and comes with ethical limitations. In the context of the study of female reproductive biology, the analysis of knock-out and transgenic mice has strongly contributed to clarify the underlying processes leading to follicular development, oocyte maturation, fertilization events or embryo implantation. However, research cannot be limited to rodent models.

- Reproductive processes: the **rodent** is not as effective a model as other species in translating to human pathologies. For example, rodents are considered poly-ovulatory while women are considered mono-ovulatory. Additionally, the onset and development of folliculogenesis is very different between rodents and women. The rodent reproductive cycle is also very short (i.e., 4 d) when compared with 28 d in women. Finally, rodents have a gestation length of 21 days compared with 9 months in women and it is very difficult to collect sufficient quantities of blood samples from rodents to obtain dynamic patterns of endocrine, metabolic or steroid hormones for comparison to women. Several different domestic livestock and nonhuman primate models are more beneficial to understanding these human biological processes. **Pig**s and humans have anatomical and physiological similarities that make the pig a good model to study human infertility. The pig is a litter-bearing species with a shorter generation interval, so trans-generational questions may be answered in shorter timeframes. The **bovine** model system is well suited to understand reproductive disorders in women. Secretion of hormones during the reproductive (estrous) cycle in cattle is very similar to the menstrual cycle in women and both species have multiple follicular waves that result in ovulation of a single ovarian follicle. Cows can be maintained in large groups of genetically similar females under consistent environmental conditions to reduce sources of phenotypic variation. Thus, cattle are valuable models to elucidate the endocrine and local mechanisms controlling both early and terminal stages of ovarian follicular development in mono-ovulatory species. Experiments conducted in the cow can have direct relevance to ovarian reproductive disorders in women.

- New techniques of ART, e.g. the application of Nuclear Transfer (r-parent baby) to overcome the transmission of certain genetic diseases, for example mitochondrial DNA mutations, need to be studied first in mice and non-human to test its efficacy and safety. These optimized techniques can benefit breeding practices in other species as well.
- Pluripotent stem cell biology: important insight was first obtained in mice, before embryonic stem cells could be generated from human embryos. In addition, artificial embryos can be made from different cell types in mouse, and now several research groups try to reproduce these findings in human enabling the study of the early stages of human development (implantation, gastrulation).

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