Everyday ethical considerations

The ethics of animal testing should be a consideration that is woven into the everyday business of researchers

Let's put it straight from the very beginning: no living, ordinary person could be enthusiastic about using animals for research and making them suffer in the laboratories of the world to advance medicine. But the serious researchers among us know that we cannot find new insights and new therapies for humans and animals without using them, and this is for several reasons. Among them are basic insights to studying disease mechanisms and thereby understanding where the chain of events is broken in cases of pathology. Cell and organ cultures can tell us a lot and are widely used, however, they cannot explain everything. For this, living organisms are too complex to just be quickly mimicked in cell culture wells or bioreactors. Therefore, animal experiments cannot be avoided, since on the other side of the coin weighs the suffering of both human and animal patients desperately awaiting cures for their diseases.

Although we divide research into basic and applied research, in reality these borders are not so clear and distinguishable – it's a transient business. How can we find good strategies for therapeutic regimens if we don't know where to intervene? To give you a sample: millions of animals give their lives to study cartilage resurfacing with very limited success and why? Certainly hyaline cartilage is a tricky thing to repair to start with. However, one of the main reasons is that nobody has yet found out what the normal regeneration and repair mechanisms of hyaline cartilage are, and how this is connected to the underlying subchondral bone.

Granted, this is difficult to find out, but if we can't understand this fundamental physiology of our joints, there is little hope that we will ever be able to regenerate new cartilage after a defect occurred on the surface. This is true for humans and animals. Dogs and horses have a lot of joint problems and wait for new therapy strategies as humans do. For horses this is one of the most common reasons to be euthanised or slaughtered. This shows impressively that animal experiments are not just for humans but also for animals – to save their lives.

Ethics and philosophy

The ethical and philosophical aspects of why animal experiments can be justified in science are widely discussed and are not the focus of this essay. There is also the issue of the famous 'three Rs' (3Rs), which stand for Reduce, Replace and Refine, leading to more conscious use of animals in research, and this issue is mainly left to the philosophers. One of the main problems, however, is very often neglected, but is instrumental for animals in research and directly connected to the individual animal's wellbeing or suffering. It's about the quality of how animal experiments are conducted and who conducts them. Some aspects are covered by legislations within the different countries. They are mainly related to infrastructure and environment of animal facilities. It also includes personnel with their training and very rudimentary documentations.

Most of the FELASA accredited laboratories nowadays include veterinarians for staff members. However, these are often not veterinary specialists for either small rodent facilities or large animal surgery, respectively anaesthesia. Nowadays, this should be unacceptable in all laboratories. It should be required by law that veterinary specialists with Board Certifications of the European or American Colleges of Laboratory Animals (ECLAM/ACLAM) are leaders of such facilities. It should also be the law that specialists of the European or American Veterinary Colleges of surgery (ECVS/ACVS) and of anaesthesia and analgesia (ECVAA/ACVAA) must be involved in every single surgery for experiments with larger animals like sheep, goats, pigs, calves, heifers, dogs and cats or primates.

Medical doctors, biologists or other basic scientists should not be allowed to be alone at the table in future when surgeries on these animals are conducted. Surgeries should only be permitted in

collaboration with veterinary specialists which, in the case of larger animals, should have both ECVS/ACVS and ECVAA/ACVAA diplomas. The latter are just as important for conducting correct anaesthesia and analgesia regimens. Too many serious errors happen and have been witnessed around surgeries and aftercare by the author, when specialists are not involved.

Quality

If ethical concerns are taken seriously, it starts right there: with the quality of the experiments performed at the table with each individual animal, and not only at the drawing board or with administrative legislation. Involving true specialists would reduce incidents that include administration of wrong human dosages to sheep for instance with muscle relaxants, heparin, or other incompatible drugs leading to experiment-unrelated death of hundreds of experimental animals in the world, some including serious suffering of animals (bleeding or suffocating to death).

Quality in animal experiments also includes their standard documentation and considerations of regulatory affairs if therapeutic approaches are studied and are part of the project. This goes hand in hand and should be part of initial planning in animal experiments to avoid repeating them later. This is imminent for reducing animal numbers right from the start (3Rs). Regulatory affairs relate to accreditation of preclinical experiments by either European agencies (TUV) or the FDA (Food and Drug Administration) in the United States, a prerequisite for allowance of clinical trials, Phase I-III and later registration of any medication, medical devices or combination products. Depending on the study and the technology tested, preclinical experiments should comply with Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP).

Once clinical studies are attempted these have to be conducted according to Good Clinical Practice (GCP). Different to the United States, where projects can be conducted according to GLP given the correct audits, in Europe the facility has to be officially acknowledged by the authorities (e.g. Swissmedic in Switzerland) prior to any GLP experiment being conducted. In most countries GLP or GMP approved facilities are private companies without the academic background of universities and other academic institutions (e.g. Fraunhofer institutes in Germany), where the expertise for most projects would be considerably broader.

This major gap between academia and later industrial needs is responsible for many animal experiments that have to be repeated, or are not accepted by the regulatory bodies due to the animal model used and missing or incomplete documentation. Therefore, it is advisable to include companies that should be involved in production and upscaling of test items, and contact regulatory bodies right from the start. To include these considerations in scientific translational and also basic projects means applying ethical considerations for animal experiments in everyday business of researchers.

Roadmaps of Horizon 2020 consider regulatory affairs in connection with animal experiments an important aspect for translation from bench to bedside.

The official Competence Center for Applied Biotechnology and Molecular Medicine (CABMM) is a unique professional network at the University of Zürich, Switzerland, for translational medicine where medical problems are investigated literally from "bench to bedside" (see http://www.cabmm.uzh.ch/index.html). The expert members of the CABMM deal with either: A) experimental medicine or surgery; B) molecular medicine; C) regenerative medicine; or D) applied biotechnology. Basic researchers focus on molecular regulation mechanisms, and material scientists place their emphasis on developing new (intelligent) scaffolds/matrices used for tissue engineering, one of the modern backbones of modern regenerative medicine. *In vitro* generated tissues are studied in preclinical experimental animal studies, where biocompatibility, integration and functionality tested before clinical trial phases in humans can be initiated.

The main strategic goal of the CABMM is the promotion of translational research based on excellent interaction between basic research and clinics, academic institutions and industrial partners. Through consolidation and optimisation of an already excellent infrastructure, the methodical knowhow is continuously improved and the expertise of all members and their national and international research partners allows the development of products and appropriate technology transfer. Through the uniqueness of the CABMM, the University of Zürich is the only European university with official accreditation in Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP). These are required to get products registered at the FDA for clinical application.

Brigitte von Rechenberg, Prof Dr med vet, Dipl ECVS
Head of the Musculoskeletal Research Unit (MSRU), Head of the Competence Center for Applied Biotechnology and Molecular Medicine (CABMM)
Dean of the Vetsuisse Faculty
University of Zürich, Switzerland

tel: +41 4463 58410

bvonrechenberg@vetclinics.uzh.ch
http://www.cabmm.uzh.ch/index.html