A Model for Inter-Institutional 3Rs Cooperation – Sharing In Vivo Research Resources
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Summary
In keeping with ethical research using animals as codified in the philosophy of the 3Rs (Reduce, Refine, and Replace), our corporate enterprise entered into an inter-institutional agreement to make ferret trachea tissue available to a nearby academic institution to enable them to carry out in vitro research work without having to obtain additional live animals. The purpose of this communication is to emphasize that, while many new developments involving sophisticated computer modeling and in vivo imaging are doing their part to reduce and refine research animal use, a simple common sense idea involving communication, awareness, time, and attention also can result in immediate reduction in research animal use. Keys to the successful effort described here were communication within the laboratory animal sciences community, institutional recognition of the importance of the 3Rs in ethical research, and the willingness to engage in a collaborative process beyond one’s own immediate interests in order to reduce and refine research animal use where possible.

Keywords: 3Rs, ferret, trachea, cooperation

1 Introduction

Animal use reduction is one of the cornerstones of the 3Rs – the “Reduce, Refine, Replace” approach to live animal use in research, teaching, and product testing. To this end, work has been ongoing to replace live animal use, when possible, with sophisticated technical tools such as computer models. Similarly, reduction and refinement have been achieved with such approaches as imaging modalities, which do not require the animal to be sacrificed in order to monitor disease response to treatments. There are, however, other underutilized “low- to no-tech” ways to reduce animal use substantially. The purpose of this paper is to showcase the positive outcome of a simple tissue sharing agreement entered into in 2008 to formally allow ferret tracheas harvested from animals being euthanized at a commercial biotechnology company for federally mandatory product safety testing to be shared with a neighboring academic institution to enable them to carry out in vitro research work without having to obtain additional live animals. The intent of this communication is to highlight the notion that simple measures can result in immediate and substantial reductions in animal use. While awaiting the development of the high tech equivalent of the “virtual animal” or “virtual person,” researchers and their host institutions can forge ahead using common sense to reduce animal use. The key to success, however, is institutional awareness and support for such ethical undertakings that may not have a direct “pay off” and personnel who are willing to take the extra steps needed to engage across responsibility lines.

Background
Ferrets are the best model for influenza research and vaccine efficacy and safety testing (Belser et al., 2011; Maher and DeStefano, 2004). In the mid-1990’s, a biotechnology company called Aviron was formed in Mountain View, California to investigate and produce a modified live influenza vaccine for people based on a new technology that allows for genetically engineering an attenuated influenza virus scaffold to incorporate the immunogenic surface proteins of the annual circulating influenza virus to make a safe, effective vaccine aimed at the most likely circulating influenza virus strains coming up for the year – every year (Murphy and Coelingh, 2002). This technology, known as reverse genetics, proved very successful (Hoffmann et al., 2000; Neumann et al., 1999). The company was able to start commercial production of this vaccine in 2003. However, since the vaccine is a live, attenuated, product the FDA mandates that it must be tested every year in animals to verify its safety. Since ferrets are completely susceptible to human influenza viruses and exhibit clinical signs of fever, lethargy and upper respiratory symptoms of coughing and sneezing, they are the best animal model available for this purpose.

Stanford University is located nearby in Palo Alto, California. The university has a diverse and extensive medical and basic research mission. One of its laboratories focuses on cystic fibrosis (CF) (Rowe et al., 2005), a genetic defect that results in serious respiratory disease that affects young children and for which no cure is yet available. CF is debilitating and often
deadly by young adulthood. A key defect in CF is abnormal mucous production and cilia movement, which leaves the victims unable to adequately clear bacteria and other microbial agents out of their airways. The inability to rid the respiratory tract of many commonly encountered microbes leads to repeated lung infections and bouts of pneumonia, which causes scar tissue to build up in the lung. Fibrotic scar tissue replaces normal air-exchanging lung tissue and is less compliant, such that breathing becomes increasingly difficult and inefficient. All of these detrimental outcomes from chronic pneumonia lead to an eventual inability to breathe, leading ultimately to death over the course of stressful and painful years in the youngster’s life. Stanford’s CF lab was established to research this disease. A better understanding of the genetic defect and its effect on cilia and mucous cell function will surely lead to better treatments and perhaps eventually even a cure.

As it happens, the ferret is one of the few good animal models for studying CF. The ferret trachea has a histology similar to the human’s – one of the reasons ferrets also are so well suited for human influenza research. In order to study cilia movement and tracheal mucous production in detail, the Stanford CF lab developed a system to study the isolated trachea (Joo et al., 2001; Wine and Joo, 2004) – and observe the mucous production of a single tracheal cell. Therefore, they needed ferrets only to provide fresh tracheas for their laboratory in vitro system.

2 The 3R’s idea

The initial idea to share the ferret tracheas came from members of the laboratory animal veterinary community in California informally known as CLAMS (California Lab Animal Medicine Specialists). The group meets once per year to conduct business and exchange news and ideas. Awareness of ongoing work involving research animals at member institutions is central in helping to implement best practices without “reinventing the wheel” for every issue that may arise. In this case, the veterinarians from both the academic and the biotech company were able to discuss the possibility of being able to share the ferret tracheas from animals that required euthanasia for influenza work to be used for the CF in vitro system. The idea made sense. Would each institution, with its associated researchers, Institutional Animal Care & Use Committees (IACUC) and legal systems support this exchange?

3 Bureaucracy and perceived risk

At the time the initial idea occurred, Aviron had been acquired by MedImmune. By the end of the agreement process, the mature biotechnology company had itself been acquired by AstraZeneca.

The academic institution, Stanford University, is of course a world renowned research powerhouse.

Both institutions have potentially formidable processes and inertias to overcome. Although the institutions have differing mandates, in this case, the stakes for both were similar and high. Specifically, these included the need to guard against liabilities and protect intellectual property, investigators, personnel, and reputations.

4 IACUC engagements and support

Key to success on the corporate side of this tissue sharing agreement was the initial engagement and support of the IACUC chairperson. This individual had a strong in vivo background in basic research and had risen to become a senior executive with an appreciation for the importance and ethics of animal use.

Equally essential to the continued progress of the tissue contract negotiation was the understanding and support of Public Affairs, Regulatory, and legal staff at corporate headquarters.

On the academic end of the process, the IACUC also needed to review and approve the animal care and use protocol, even though no live animals would be procured. When fresh animal tissue is acquired and used in research, its source, transport and location of use must be reviewed to ensure that the tissue is acquired legally and humanely, and that it does not pose any risk of infection to personnel or other research animals that might be exposed.

Legally, both institutions needed to ensure that the tissue transfer did not impose any intellectual property liability on either’s research work. The initial step was to submit a contract request and Confidentiality Agreement. Proprietary angles and ownership were clarified during this process.

Also of significant importance was that both institutions had the highest quality animal care and use programs to ensure healthy animals were obtained and used in accordance with appropriate regulations and ethical considerations. Both are accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International and have had successful research partnerships and relations with each other in the past.

5 Culture of the 3Rs

Non-research employees of academic and even pharmaceutical/biotechnology companies may not be aware of the role that animals have in their research mission. It is vital that society at large understands this, but even more important that the personnel involved in companies and educational/research institutions are aware of and understand the basis of their research and the ethical considerations implicit in their work. Thus, the basic understanding must be widespread regarding how research breakthroughs occur, how the safety of many medical and consumer products is assured, and how critical the live animals are to this mission. Equally essential is an appreciation and awareness of the ethical underpinnings of animal-related work throughout the institution – even in those functions quite distant from the research arena and laboratories, such as the legal and contracting departments.
In this situation, key personnel at each institution were in place to assist in support of the process. Thus, the goal of providing the tissue was enabled while allowing each institution the ability to review and protect against possible adverse consequences.

6 What success looks like

In the end, the tissue sharing agreement was implemented, actual tissue was shared, and research was conducted. The process of implementing the agreement was time consuming and took more than six months to complete. First, both IACUCs had to review and approve their respective protocols. The corporate institution has a tissue sharing protocol, under which this request was introduced and which helped streamline the approval process. Next, the legal departments at each institution had to prepare and approve a contract that finally consisted of a 15-page document to describe the procurement and sharing of “certain fresh ferret tracheas…”

Over the course of the three years since this agreement has been in place, more than 270 ferret tracheas have been provided for in vitro testing. In addition to several scientific publications, one early and exciting outcome of this collaboration was the development of a unique test system that holds promise for the evaluation of novel human therapies (Cho et al., 2010; Sun et al., 2010).

On a more intangible level than publications and possible treatments, an important outcome has been the collaboration itself. Staff at both institutions, in research, animal care, and legal and administrative departments as well, have had the opportunity to implement ethical practices into their daily work stream, of seeing each institution look beyond its immediate self-interest – even taking on some unnecessary exposure risk – to “walk the talk” of using research animals as humanely as possible for important lifesaving work while cooperating to minimize unnecessary use.

References


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