Importance of Animals in Vision Research

> Virtually every major medical advance for both humans and animals has been achieved through biomedical research using animal models to study and find a cure for disease, and through animal testing, to prove the safety and efficacy of a new treatment.
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> Former U.S. Surgeon General, Dr. C. Everett Koop

Background

ARVO's Animals-in-Research Committee prepared this resource to share with colleagues and students, who are joining animal research labs for the first time. They noted a lack of available resources on animal research, specifically targeted for vision research. This resource is intended as a brief introduction to why animals are used in vision research, along with examples of how such research translates to better therapies for human and animal eye conditions. It also provides links to existing resources from other organizations, put into a vision context.

Virtually all medical advances over the past century have required animal research and this is particularly true of advances in eye and vision research. Research with animals is crucial for understanding vision and for the diagnosis, treatment and prevention of human and animal eye diseases. Examples include dry eye, age related macular degeneration, diabetic retinopathy, corneal disease, uveitis, cataracts, glaucoma and retinal degeneration.

Vision facts

Worldwide, 38 million people are blind and 110 million are vision-impaired. In the U.S. alone, the economic impact of vision loss is estimated by the National Eye Institute to be $68 Billion per year (not taking into account the loss in wages for individuals with vision loss). In many developed countries, aging of the population is expected to increase the burden of vision in the near future. Meanwhile, eighty percent of vision loss and impairment are found in developing countries.

Seventy five percent of vision loss is preventable and treatable with advances made from prior vision research studies. Better treatment and prevention of eye disease reduces economic burdens to society and communities and also contributes to better safety. Vision impairment in drivers is a safety hazard for the community, while vision impairment in affected individuals is a risk factor for premature death.

Although many vision problems are related to aging and degenerative diseases, congenital and childhood eye diseases are also debilitating from the perspective of time living with the condition, long-term cost of treatment and impact on development. In fact, childhood blindness is expected to rise in areas with ready access to processed foods, as the incidence of child hood diabetes is rising.

The relevance of this childhood blindness was highlighted in 1967 and 1981, when researchers received Noble Prizes for research related to understanding visual pathways and the critical period of vision development in children.

Additional facts about vision loss are found under vision advocacy resources on the ARVO advocacy resources website.

Facts about animal research

Experimental studies in animal models provide information about mechanisms, how eye diseases occur, and the safety and efficacy of potential treatments.

- Vision scientists use other models, such as cells or bio-engineered material, to reduce and replace animals whenever possible. Nevertheless, there are no complete alternatives to vision research with animal models.
- Many cells present in the visual system and body can be cultured in the lab (*in vitro*). In initial studies, researchers observe cellular responses to treatments in these cultured cells.
- Selection of drugs and doses are obtained from *in vitro* studies prior to testing in animal models. However, *in vitro* studies cannot replicate the complex structures, connections and interactions that underlie visual system function. For example, events downstream of treatments affecting an animal's systemic immune system cannot be replicated *in vitro*. Understanding diseases where complex interactions between the immune system and visual system occur can only be done in animal models with intact immune systems.
- Non-mammalian research animals can also be beneficial. However, the behavioral and developmental stages of these animals do not approach the complexities of those in mammals. Non-mammalian models can be utilized in vision research to help scientists understand basic behavioral responses to images, and basic

mechanisms of development in flies and invertebrates, as well as in vertebrates.

- Most laboratory animals (95%) are rodents (rats and mice) that are bred for this purpose. Reasons why rodents are utilized include the following:
  - Rodents are small, easily bred and relatively inexpensive to house.
  - A variety of genetically altered rodents (knockout and transgenic models) are available for scientists to study eye diseases.
- Dogs, cats and non-human primates account for less than 0.5% of all laboratory animals.
- Use of animal models is regulated and supervised by veterinarians to ensure the fewest number of animals are used, that their treatment is humane, and to minimize discomfort or distress. Prior to conducting animal research, scientists have to prepare proposals that are reviewed by animal care and use committees, who oversee the ethical use of animals in federally funded research. Also, scientists have to comply with local regulations in order to present their work at scientific meetings and to be able to publish results of studies in peer-reviewed journals.
- ARVO scientists are required to comply with the ARVO Statement for the Use of Animals in Ophthalmic and Visual Research and any applicable local laws.

Vision therapies from animal research

Researchers use animal models because of the complex biological interactions occurring in the intact animal. Therefore, tests for new therapies are ultimately performed in animal models. Animal models of acquired and inherited disease are an important resource for understanding the pathophysiology of disease and for developing novel therapies to restore normal function. Below are examples ARVO's Animals-in-Research Committee compiled. Such examples show how researchers used animal models to translate basic research to clinic application, improving the eye health of animals and humans.

Vision research restores vision in vision impaired animals. Shown in the photo is the first dog to receive a successful gene therapy for Leber Congenital Amaurosis.

Leber Congenital Amaurosis gene therapy. Leber Congenital Amaurosis (LCA) is a rare, inherited degenerative disease of the retina that causes severe loss of vision or blindness in children. ARVO scientists found mutations in the RPE65 gene that account for the majority of LCA cases. Later, vision scientists found that Briard dogs can inherit congenital LCA similar to the condition in humans.

Using their knowledge of naturally-occurring RPE65 mutations in Briard dogs, vision scientists generated a mouse model using gene knockout technologies. This model was valuable for understanding the role of RPE65 in normal retinal development and function and how mutations cause photoreceptor degeneration. The mouse model also helped researchers develop a gene-replacement therapy, which they later used to reverse blindness in Briard dogs. After that, successful clinical trials restored vision in children. For more information on LCA and gene therapy, visit the resources below.

- From Bench to Bedside. Resource from the National Eye Institute, covering animal models used in developing gene therapy for LCA Clinical Trials. Visit resource.

- What is Leber Congenital Amaurosis? Foundation Fighting Blindness (FFB) resource that covers symptoms, cause, diagnosis and prospects for treatment. Visit FFB website.

- Cure for blindness? Good Morning America coverage of how young adults have improved vision from gene therapy. Watch video.

- New hope for gene therapy. Video of a nine year-old boy whose vision was restored with gene therapy. Learn more.

Gene therapy for color blindness. In humans, defects in color vision affect ~8% of males and ~0.4% of females worldwide. Some people are unable to distinguish certain shades of colors. For example, the most common form of color blindness is the inability to distinguish certain shades of red or green. Other people with color blindness have complete absence of ability to see any colors (called achromatopsia) and only see shades of grey. Color vision can be inherited, or color detection deficits can accompany other disease processes, medications, aging or exposure to harmful chemicals. Recently gene therapy in animal models has been effective for treating red-green color blindness. Visit the resources below for more information on color blindness.

- Simulations of color deficiency,

- Consumer information on color deficiency, from Medline Plus,

- American Optometric Association information on color deficiency,

- Therapy for color blindness in squirrel monkeys. California Academy of Sciences video that covers how viruses can be used to deliver gene therapies for treatment of color blindness. Watch video.

Therapies for macular degeneration and neovacularization. Age-related macular degeneration (AMD) is a disease that causes central vision loss. There are two forms of macular degeneration, wet and dry AMD. The more severe form, wet AMD is associated with new blood vessel growth at the back of the eye, called neovascularization. The blood vessels can leak fluid; hence the name "wet" AMD. A variety of situations also can cause neovascularization at other locations in the eye, which also impairs vision.

In 1989, researchers discovered that vascular endothelial growth factor (VEGF) promotes new blood vessel growth. Studies in animal models subsequently showed that VEGF is vital for normal development of the vasculature during embryonic development. The development and validation of VEGF blockers for treating neovascularization provided the foundation for the current anti-VEGF drugs used to treat neovascular age-related macular degeneration, as well as macular edema due to central retinal vein occlusion. Clinical trials are underway to evaluate anti-VEGF therapy for other neovascular diseases of the eye, including proliferative diabetic retinopathy, diabetic macular edema, retinopathy of prematurity, corneal neovascularization and choroidal melanoma. Additional information about AMD is found in an AMD fact sheet.

Therapies for diabetic retinopathy. Diabetic retinopathy is a significant cause of vision loss. About 25 million people in the U.S. suffer from diabetes and up to 24,000 lose their eyesight yearly from diabetic retinopathy. Incidence of diabetic retinopathy is projected to increase because diabetes is being diagnosed in children at earlier ages than ever before. For the first time, children are expected to have shorter lives than their parents because of the incidence of child hood diabetes. Animal models of diabetic retinopathy have proven valuable in efforts to unravel the pathogenesis of the disease and to identify therapies to inhibit disease development.

For more information on diabetic retinopathy, get facts from the National Eye Institute. Get the facts.

Therapies for ocular infections. Each year, a significant number of people suffer vision loss and blindness due to ocular infections. There are many infections that affect vision. Corneal infections on the eye surface can result from contact lens misuse, contamination of contact lens solutions or from eye trauma. Infections can also enter the eye following surgery, trauma or systemic infection. Organisms that affect the eye include bacteria, fungi, viruses and

parasites. Researchers use animal models to analyze the mechanisms by which organisms damage the eye, as well as how the ocular immune response fights infection. They also use these animal models to evaluate novel anti-infective and anti-inflammatory agents specifically developed for the eye. This is a critical step for the clinical application of new and more powerful drugs, designed to eliminate ocular inflammation and infections and preserve vision.

Understanding dry eyes. Dry eye is one of the most common eye diseases. Over 9 million Americans suffer from dry eyes, and tens of millions more have less severe symptoms that are notable during exposure to factors such as dry air. It is an important public health problem, causing increased risk of ocular infections and bothersome symptoms including discomfort, fatigue and visual disturbances that can interfere with activities such as reading, working on a computer and driving a car. Animal models mimicking dry eyes revealed that the dryness of ocular surface not only causes the breakdown of the protective tear film, but also causes subsequent immune responses. These findings give insight into novel treatment strategies.

Additional resources

Other scientific societies, associations and advocacy groups have additional animal resources as indicated below.

- The American Physiological Society (APS). Visit their animal research site to find answers to questions about animal research and animal welfare. Animal Research: Finding Cures, Saving Lives.
- Federation of American Societies for Experimental Biology (FASEB). Find teaching and advocacy materials including power point presentations, posters and answers to FAQs. Learn more.
- Americans for Medical Progress (AMP). Find information to bolster public opinion regarding animal-based research, animal research benefits, patient stories, FAQs, materials for advocacy and news analysis for researchers. Learn more.
- Foundation for Biomedical Research (FBR). Educators can locate resources for students. Visit FBR.
- ResearchSaves.org. A great location for videos, podcasts and FAQs on the benefits of animal research for patients, including stories from researchers with their personal connections between their research and disease. ResearchSaves.org
- AnimalResearch.Info. Locate essays by scientists about research, articles about how animals contribute to progress in medicine, why animals are used in research, animal models and information on regulations and legislation regulating animal research. AnimalResearch.Info
- Understanding Animal Research. Find information, videos, news and interactive learning activities that promote the importance and value of animals for biomedical research and human health. Understanding Animal Research
- States United for Biomedical Research (SUBR). Promotes health through science and education by promoting public understanding and increased appreciation of the value of biomedical research. Learn more.
- Alternatives to animal research
  - Bibliography on alternatives to animal testing: ALTBIB
  - Global clearing house for information on alternatives to animal testing: AltWeb
  - Animal use alternatives terminology (National Agricultural Library): USDA Thesaurus
  - Information Resources for adjuvants and antibody production: USDA Antibodies
- Additional organizations that promote proper and ethical use of laboratory animals
  - Asian Federation of Laboratory Animal Science Associations (AFLAS),
  - Canadian Association for Laboratory Animal Science (CLAS),
  - American Association for Laboratory Animal Science (AALAS),
  - Federation of European Laboratory Animal Associations (FELASA),

- International Council for Laboratory Animal Science (ICLAS),
- American College of Laboratory Animal Medicine (ACLAM).

About ARVO

ARVO is the largest and most respected vision research organization in the world. Members include more than 12,600 researchers from over 80 countries. The membership is multidisciplinary and consists of both clinical and basic scientists who contribute to the quality of life by increasing knowledge about sight.

The Association encourages and assists members in research, training, publication and dissemination of knowledge in vision and ophthalmology, and in the ethical and humane use of animals in vision research.

Continued progress in many areas of vision inquiry requires research with animals to investigate complex systems and functions.

Learn more at www.arvo.org/animals.

Feedback

To provide feedback on this resource, please e-mail advocacy@arvo.org.