The Evolution in Medical Research

Human tissue is rapidly replacing animal models for evaluating age-related macular degeneration therapy.

BY GERALD J. CHADER, PhD

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly in developed countries. Yet so much about this disease—the etiology, pathology, and natural history of progression—is still unknown. I believe we are on the brink of much greater understanding and progress in identifying better therapies for AMD, thanks to changes in how research can be conducted.

One of the challenges is that basic research and preclinical studies of AMD are very difficult to conduct. The best animal models we have are rodent models, but these leave much to be desired, both physiologically and pathologically. For starters, mice and rats do not have a macula, the specific area that sustains damage in AMD. Their retinal photoreceptor cells are predominantly rods, rather than the cone cells that predominate in the human macula. What cones the rats do have are dispersed throughout the retina, rather than concentrated around the fovea as they are in humans.

A faithful representation of neovascularization, the archetypal sign of wet AMD in the human, is nearly impossible to produce in any animal model, and even the drusen that characterize dry AMD are difficult to induce. Murine models such as the rat and mouse models have been widely used in ophthalmic research. Because they are relatively cheap, plentiful, and easily reproduced and manipulated, they have been very useful for studying such things as wound healing and drug safety. They are, however, a poor surrogate for the human eye when it comes to studying drug efficacy and age-related diseases. A rodent with a 2-year lifespan provides little insight into the very slow, degenerative processes that affect human eyes over an 80- or 90-year lifespan.

Other animals are also dissimilar; there are few workable models for studying the posterior segment in rabbits, pigs, or other lower-order animals. There is one good monkey model for AMD but it requires working with specific monkeys from a colony in Japan that are few in number and expensive. Most researchers are also loath to conduct research in primates for ethical reasons. So we have largely been left with the rat—and with the reality that extrapolation of findings from rodents to humans is little better than wishful thinking.

Benefits and Challenges of Human Tissue

Human cadaver tissue would be far superior to animal models for in vitro experimentation. To date, AMD research with human tissue has been very limited, but what has been done has been fruitful. For example, Gregory Hageman, PhD, who is now at the Moran Eye Center in Utah, has spent the past decade researching the composition of drusen (Figure 1). That research could not have been conducted reliably in animal eyes because of potential species differences and the paucity of recoverable murine drusen. Early on, studies by Hageman and his coworkers pointed to the prevalence in drusen of proteins associated with inflammation and immune-mediated processes, which led AMD researchers towards entirely new hypotheses about the pathogenesis of AMD.1,2
This kind of research can also help us identify the gene mutations that increase risk for AMD and devise therapies to target those mutations. It is a prime example of how human tissue research can propel us forward toward a more robust understanding of diseases that are specific to human eyes. However, there have been significant barriers to human tissue research.

Eye banks were established and have historically been organized primarily to provide corneas for transplant, with research being a secondary consideration. There is growing recognition of the value of research tissue today, but there are still challenges in obtaining high quality retinal tissue. The retina is a thin layer of delicate cells that is difficult to dissect under the best of conditions. Unlike the “privileged,” largely inert cornea, it is highly subject to proteolytic attack and far more susceptible to cell death. Although properly preserved corneas are still viable days or even weeks after enucleation, the metabolically active tissue of the retina is difficult to preserve in anything approaching a naturally functioning state for more than 6-10 hours after death.

This temporal imperative makes shipping difficult, traditionally limiting researchers only to fresh specimens from their nearest eye bank. In my prior research experience, 9 out of 10 eyes provided for retinal research had already deteriorated too much or were otherwise unusable for research.

**THE LEITR MODEL**

A new model of eye banking, the Lions Eye Institute for Transplant and Research (LEITR), has the potential, I believe, to overcome many of these limitations. LEITR, on whose Scientific Advisory Board I serve, is the world’s first combined eye bank and ocular research facility. Located in Tampa, FL, the Institute draws from a large population (many elderly) with high rates of AMD, glaucoma, diabetes and other conditions of interest to ocular researchers. Donor tissue is available for immediate use in its high-technology research and tissue culture facility, where specialized laboratory services and even sleeping quarters are available to visiting researchers.

LEITR is far more research-focused than a typical eye bank. It allocates about half the donor tissue it collects annually to research purposes and takes extra steps to log each donated eye into a comprehensive database with extensive information about the donor’s clinical and familial medical history. Whole globes, corneas, lenses, sclera, retinas and retinal pigment epithelium, trabecular meshwork, optic nerves, endothelial cells and other components of diseased and healthy human eyes are available, often within 4-6 hours after death.

**EXPANDING THE POTENTIAL OF AMD RESEARCH**

I can now imagine the potential of being able to request multiple pairs of fresh donor eyes with the same disease—or even the same stage of that disease. Research that required years of waiting for enough suitable eyes can now be initiated much more quickly. This model changes how we might think about designing AMD research studies as well as studies on other retinal diseases.

Much work now focuses on retinal pigment epithelial cells since these cells are affected very early on in diseases such as AMD and some forms of retinitis pigmentosa. My own work over the years would have benefitted greatly from the availability of good human specimens for both biochemical analyses and tissue culture as now available at LEITR.

Henry F. Edelhauser, PhD, who serves with me on the LEITR Board, has been going to LEITR in Tampa to repeat drug delivery studies that have been done in animal eyes on human tissue. He is evaluating the distribution of various drugs and antibodies that can potentially be used in the treatment of AMD following microneedle injection into the suprachoroidal space. This work will be very important in understanding how drug delivery in humans may be similar to or different from that in animal eyes—and it would be much more difficult without a dedicated research facility with access to fresh donor eyes.

For the first time in history, it is becoming possible to conceive of and conduct research on viable human retinal tissue. I believe this will be absolutely critical to understanding the pathology, genetics, etiology, and progression of AMD. What causes 10% of those with the dry form of the disease to progress to the neovascular stage? What is the initiating event that leads to photoreceptor cell death in AMD? These mysteries will probably not be unraveled with animal studies. Only human tissue holds the clues that we need to answer these questions.

Gerald J. Chader, PhD, is Chief Scientific Officer at the Doheny Retina Institute and Professor of Ophthalmology at the University of Southern California in Los Angeles. He serves on the Board of the Lions Eye Institute for Transplant and Research. Professional editorial assistance for this article was provided by Jan Beiting of Wordsmith Consulting. Dr. Chader can be contacted at +1 323 442 6767 or gchader@doheny.org.