Volume 58, Number 4 Fall 2012 $4.95

Marin Medicine

The magazine of the Marin Medical Society

Healthcare Information Technology

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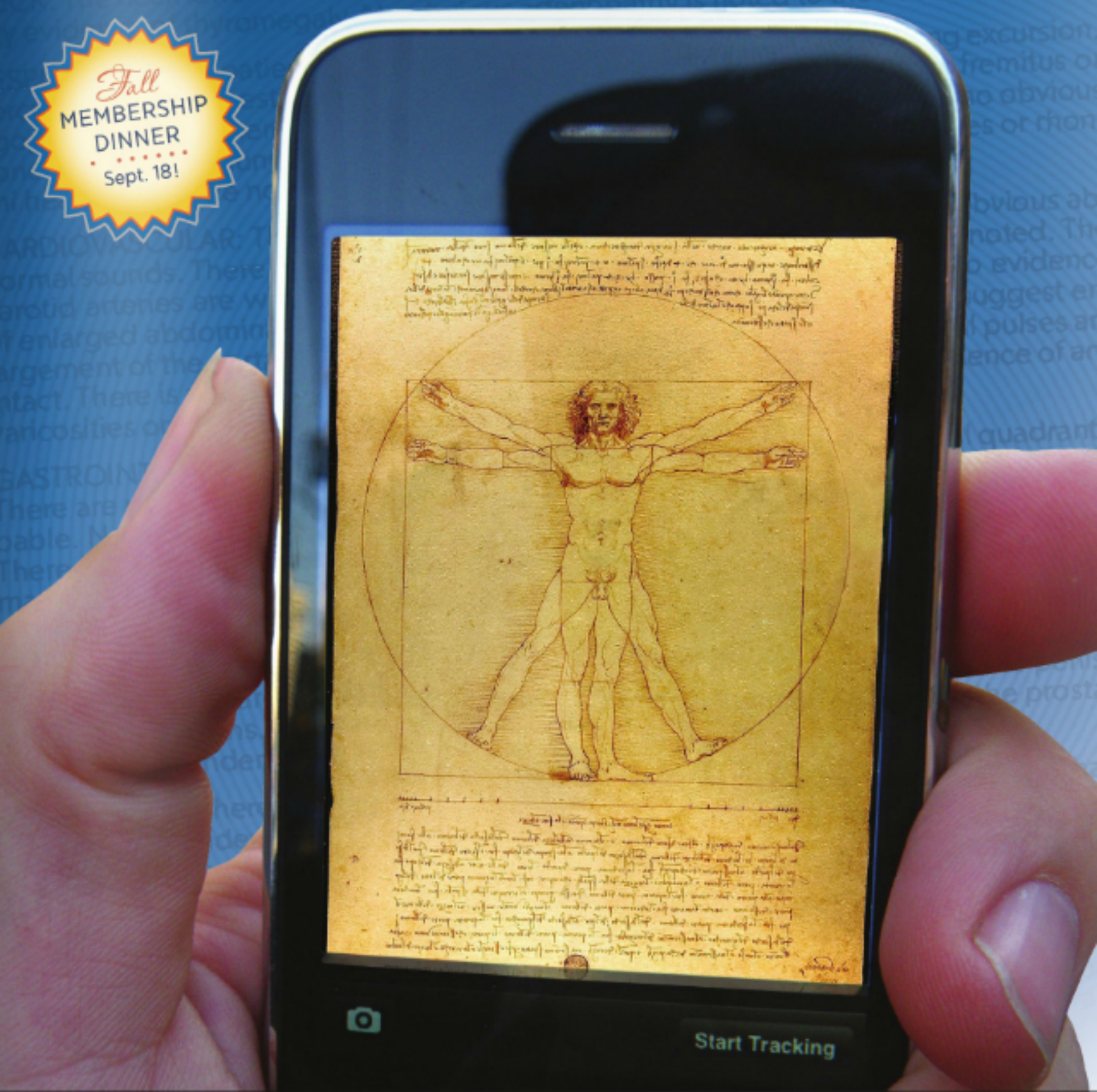

Marin Medicine
Volume 58, Number 4 - Fall 2012

LOCAL FRONTIERS

Stem Cell Therapeutics for Retinal Degenerations

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The retina, like many other regions of the nervous system, is subject to various inherited and acquired degenerative conditions. One of the most common is age-related macular degeneration (AMD), a disease characterized by degeneration of the photoreceptors in the macula, the central part of the eye. AMD retinal changes are present in approximately 10% of people older than 65 and as many as one in three people older than 80. About 1.75 million people in the United States have advanced AMD with associated vision loss, and their number is expected to grow to almost 3 million by 2020. Apart from AMD, inherited retinal degenerations such as retinitis pigmentosa and Leber's congenital amaurosis have a prevalence of up to 1 in 4,000 and affect both the juvenile and young-adult populations.

In both AMD and inherited degenerations, the main cells affected are retinal photoreceptors and/or pigment epithelial cells. The inner retinal circuitry, however, is intact for many years following the loss of these cells. This persistence has led to the possibility of cell replacement as a potential therapy. Because the retina does not have an innate capacity to regenerate and replace lost cells, one potential way to help these patients is to replace the dead cells with new photoreceptors. Another possibility is to produce drugs that stop or at the least delay macular degeneration. Vascular endothelial growth factor inhibitors, for example, have already proved effective for stabilizing certain types of AMD.

Transplantation

The isolation of human embryonic stem cells has brought about a lot of hope and optimism for their future use in tissue engineering as well as a better understanding of human developmental biology. All cells and tissues of the body can trace their origins back to embryonic stem cells. Because stem cells are able to self-renew and to differentiate into any and all the cells in the body, they can potentially be used to treat several degenerative disorders, including those of the eye. Embryonic stem cells could provide replacement cells for degenerating retinas and help restore useful vision in these cases.

Recently, a new stem cell source has been discovered: induced pluripotent stem cells, also called iPS cells. These cells are produced by converting a patient’s somatic cells (e.g., skin fibroblasts, blood) to an embryonic stem cell-like cell.[1] The newly reprogrammed iPS cells have all the same properties as embryonic stem cells. They can be grown indefinitely in dishes and can form virtually any cell in the body, including retinal photoreceptors and retinal pigment epithelial cells. In addition to iPS cells, some labs are investigating adult stem cells. These cells have little capacity to regenerate, and their efficacy in making retinal cells for cell replacement purposes so far has been extremely limited.

My lab at the Buck Institute in Novato generates various retinal cells from both embryonic and induced pluripotent stem cells. Along with several other labs around the country, we have shown that it is possible to make both photoreceptors and the pigment epithelial cells in high enough number to be clinically useful in patients with various form of retinal degeneration.[2-8] We have spent the last seven years characterizing the cells and optimizing the protocols. The stem cell-derived retinal cells express the same genes expressed by fetal retinal cells,[9] and they can differentiate into all the different types of retinal neurons, including ganglion cells, amacrine cells, bipolar cells, and both rod and cone photoreceptors. The cells have minimal contamination of other cell types, and they show no tumor-forming potential in animal transplants.

Will stem cell-derived retinal cells actually work for cell replacement in patients? We tested the ability of both embryonic and iPS-derived retinal cells to integrate into normal mouse and rat retinas, and found they have the ability to move from the subretinal space (the site of their transplantation) and integrate with

normal retinal cells in both mice and rats. We also transplanted these stem cell-derived cells into several mouse models of human retinal degeneration, and again, the cells integrated into the degenerating retinas. The integrated photoreceptors make synaptic contacts with the host bipolar cells, the second-order neurons in the retina. These encouraging morphological results led us to test by electroretinogram (ERG) recordings whether the transplanted retinal cells were able to restore any light response to the animals, and we found that indeed we could detect an ERG signal (with appropriate latency and polarity of a b-wave) in the transplanted blind mice.[4]

Despite this encouraging data, there are still many regulatory and scientific challenges that could take several years to resolve. On the regulatory side, prior to any clinical trial, we need to show the safety of the cells to be transplanted. They cannot contain any contaminants that could potentially cause harm to patients--one of the most serious concerns being a teratoma. This regulation requires long-term survival studies.

On the scientific side, the biggest challenge seems to be integration. Currently, the percentage of cells able to integrate and make connections is low (approximately 0.05-0.2%). Since hundreds of thousands of photoreceptors will probably be needed to restore useful vision, the challenge for the cell replacement strategy will be to generate sufficient numbers of cells and identify methods to improve integration efficiency.

In contrast to retinal cells, the strategy for pigment epithelial transplantation is a lot easier because of the fewer number of cells required and simpler transplantation surgery. In 2010, Advanced Cell Technology received regulatory approval to use embryonic stem cell-derived pigment epithelial cells in a phase I/II clinical trial involving patients with Stargardt disease. This cohort was subsequently expanded to include patients with the dry form of AMD. Several eye institutes and hospitals throughout the United States and England are involved in the trial, which is ongoing.

Drug Discovery

The use of iPS cells allows for new approaches to studies of disease mechanisms, which could also allow us to find new drugs to slow disease progress. Patient-specific iPS cell lines have already been created from patients with Parkinson’s disease, Huntington’s disease and sickle cell anemia.

My lab is in the process of generating similar cells from patients with various forms of retinal degeneration. In vitro differentiated retinal cells from these patient lines can then be used for drug screening and discovery. Novel drugs or drugs already approved by the FDA could be screened to identify ones that will slow down or even stop the degenerative process. In addition, the cells can be used for toxicity screens that will provide safety data and help reduce the drug’s chance of failure in clinical trials.

Certain oral supplements currently used for retinitis pigmentosa and AMD are still not widely accepted in ophthalmology practices because the mechanisms of action are unknown. Using patient-derived cells will allow us to better understand the effects of these drugs. Patient-derived photoreceptors or pigment epithelial cells are the optimal model for novel drug discovery and pharmacological study.

Stem cell technology has opened up new avenues of therapeutic options for degenerative diseases, including those involving the retina. The research over the next several years should provide us with new treatment options for patients suffering from AMD as well as other degenerative disorders.

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References

1. Okita K, Yamanaka S, “Induced pluripotent stem cells: opportunities and challenges,”*Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences,*366:2198-207 (2011).

2. Lamba DA, et al, “Efficient generation of retinal progenitor cells from human embryonic stem cells,” *Proc Natl Acad Sci USA,* 103:12769-74 (2006).

3. Osakada F, et al, “Toward the generation of rod and cone photoreceptors from mouse, monkey and human embryonic stem cells,” *Nat Biotechnol,* 26:215-224 (2008).

4. Lamba DA, et al, “Transplantation of human embryonic stem cell-derived photoreceptors restores some visual function in crx-deficient mice,” *Cell Stem Cell,* 4:1-7 (2009).

5. Meyer JS, et al, “Modeling early retinal development with human embryonic and induced pluripotent stem cells,” *Proc Natl Acad Sci USA,* 106:16698-703 (2009).

6. Meyer JS, et al, “Optic vesicle-like structures derived from human pluripotent stem cells facilitate a customized approach to retinal disease treatment,” *Stem Cells,* 29: 1206-18 (2011).

7. Hambright D, et al, “Long-term survival and differentiation of retinal neurons derived from human embryonic stem cell lines in un-immunosuppressed mouse retina,” *Molecular Vision,*18:920-936 (2012).

8. Phillips MJ, et al, “Blood-derived human iPS cells generate optic vesicle-like structures with the capacity to form retinal laminae and develop synapses,” *Invest Ophthal Vis Sci,*53:2007-19 (2012).

9. Lamba DA, Reh TA, “Microarray characterization of human embryonic stem cell-derived retinal cultures,” *Invest Ophthal Vis Sci,* 52:4897-906 (2011).