OMB No. 0925-0001 and 0925-0002 (Rev. 03/2020 Approved Through 02/28/2023)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

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|  |
| --- |
| NAME: Lewin, Alfred |
| eRA COMMONS USER NAME (credential, e.g., agency login): alewin |
| POSITION TITLE: Professor |

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

|  |  |  |  |
| --- | --- | --- | --- |
| INSTITUTION AND LOCATION | DEGREE(if applicable) | END DATEMM/YYYY | FIELD OF STUDY |
| University of Chicago, Chicago, IL | AB | 06/1973 | Biological Science |
| University of Chicago, Chicago , IL | PHD | 06/1978 | Biology |
| University of Basel, Basel, Basel Stadt | Postdoctoral Fellow | 01/1981 | Biochemistry |

### A. Personal Statement

My laboratory is developing both gene and pharmacologic therapies for diseases of the retina and optic nerve. These disease include autosomal dominant retinitis pigmentosa (adRP), X-linked retinitis pigmentosa (xlRP), Leber Hereditary Optic Neuropathy (LHON), age related macular degeneration (AMD), and uveitis. For example, in collaboration with investigators at the University of Pennsylvania, we tested gene therapy for adRP and xlRP in canine models of these diseases in preparation for clinical testing in human patients. In partnership with Dr. John Guy at the University of Miami, we have developed two different gene therapies for the mitochondrial disease Leber Hereditary Optic Neuropathy. A motivation of current research is to develop a gene therapy approach for the treatment of advanced dry age related macular degeneration. My group’s efforts have been focused on developing a mouse model that recapitulates some of the features of this disease, as closely as possible in an animal without a macula. We have tested the hypothesis that mitochondrial oxidative stress in the retinal pigment epithelium (RPE) contributes to RPE dysfunction and death, leading to localized retinal atrophy. In this model, we have tested both drug gene therapy vectors to block inflammation arising from oxidative stress. We have also used both gene therapy and topically delivered peptides for the treatment of the ocular inflammation known as uveitis. These approaches have proven extremely effective in mouse models of autoimmune uveitis and infectious uveitis.

1. Ahmed CM, Ildefonso CJ, Johnson HM, Lewin AS. A C-terminal peptide from type I interferon protects the retina in a mouse model of autoimmune uveitis. PLoS One. 2020;15(2):e0227524. PubMed PMID: [32101556](http://www.ncbi.nlm.nih.gov/pubmed/32101556/); PubMed Central PMCID: [PMC7043762](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC7043762/).
2. Ridley RB, Young BM, Lee J, Walsh E, Ahmed CM, Lewin AS, Ildefonso CJ. AAV Mediated Delivery of Myxoma Virus M013 Gene Protects the Retina against Autoimmune Uveitis. J Clin Med. 2019 Nov 29;8(12)PubMed PMID: [31795515](http://www.ncbi.nlm.nih.gov/pubmed/31795515/); PubMed Central PMCID: [PMC6947576](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6947576/).
3. Young BM, Jones K, Massengill MT, Walsh E, Li H, Lewin AS, Ildefonso CJ. Expression of a CARD Slows the Retinal Degeneration of a Geographic Atrophy Mouse Model. Mol Ther Methods Clin Dev. 2019 Sep 13;14:113-125. PubMed PMID: [31334304](http://www.ncbi.nlm.nih.gov/pubmed/31334304/); PubMed Central PMCID: [PMC6624323](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6624323/).
4. Brown EE, DeWeerd AJ, Ildefonso CJ, Lewin AS, Ash JD. Mitochondrial oxidative stress in the retinal pigment epithelium (RPE) led to metabolic dysfunction in both the RPE and retinal photoreceptors. Redox Biol. 2019 Jun;24:101201. PubMed PMID: [31039480](http://www.ncbi.nlm.nih.gov/pubmed/31039480/); PubMed Central PMCID: [PMC6488819](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6488819/).

### B. Positions and Honors

Positions and Employment

|  |  |
| --- | --- |
| 1981 - 1987 | Assistant Professor, Indiana University, Bloomington, IN |
| 1987 - 1994 | Associate Professor, University of Florida, Gainesville, FL |
| 1994 -  | Professor, University of Florida, Gainesville, FL |

Other Experience and Professional Memberships

|  |  |
| --- | --- |
| 1981 -  | Member, American Association for the Advancement of Science |
| 1982 -  | Member, American Society for Biochemistry and Molecular Biology |
| 1987 -  | Member, American Society for Microbiology |
| 1997 -  | Member, Association for Research in Vision and Ophthalmology |
| 2001 -  | Editorial Board Member, Mitochondrion |
| 2005 -  | Editorial Board Member, Molecular Vision |
| 2007 -  | Section Editor, PLoS One |
| 2009 -  | Member Macular Degeneration Research Review Panel, Bright Focus Foundation |
| 2010 - 2018 | Editorial Board Member, Experimental Eye Research |
| 2012 - 2016 | Regular member, NIH, DPVS Study Section |
| 2015 -  | Member, RNA Society |
| 2017 -  | Depurty Editor , Current Gene Therapy |
| 2017 -  | Member Scientific Advisory Board, Foundation Fighting Blindness |
| 2019 -  | Member, NIH, ZRG1 BDCN-R(02) Special Emphasis Panel |

Honors

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| --- | --- |
| 1987 - 1992 | Established Investigator, American Heart Association |
| 2002 | Shaler Richardson Professorship, University of Florida |
| 2003 | Jules Stein Living Tribute Award, RP International |
| 2005 - 2006 | Doctoral Mentoring Award, University of Florida |
| 2008 - 2009 | Exemplary Teacher Award, University of Florida |
| 2011 | Board of Directors Award, Foundation Fighting Blindness |
| 2015 | Elizabeth Anderson Macular Degeneration Rsearch Award, BrightFocus Foundation |
| 2018 - 2021 | University of Florida Research Foundation Professorship, University of Florida |
| 2019 | Fellow of ARVO, American Association for Research in Vision and Ophthalmology |

### C. Contribution to Science

* 1. As a predoctoral student at the University of Chicago I helped make the first physical map and transcript map of mitochondrial DNA and characterized the consequences of the petite mutant of yeast on mitochondrial DNA. These were the early days of eukaryotic molecular biology and mitochondrial DNA was the first type of eukaryotic genome to be well characterized. As a postdoctoral fellow at the Biocenter in Basel, I characterized the import pathway of nuclear encoded subunits of cytochrome oxidase and F1 ATPase from the cytoplasm into mitochondria, and the PNAS paper arising from this work remains one of my most cited papers. I continued this line of research as an Assistant Professor at Indiana University and at the University of Florida and expanded into the synthesis of peroxisomal proteins in yeast. One of my trainees from this period, Dr. KK Singh, is now a full professor at UAB at the Editor-in-Chief of the journal Mitochondrion.
	2. Singh KK, Small GM, Lewin AS. Alternative topogenic signals in peroxisomal citrate synthase of Saccharomyces cerevisiae. Mol Cell Biol. 1992 Dec;12(12):5593-9. PubMed PMID: [1448089](http://www.ncbi.nlm.nih.gov/pubmed/1448089/); PubMed Central PMCID: [PMC360498](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC360498/).
	3. Burns DJ, Lewin AS. The rate of import and assembly of F1-ATPase in Saccharomyces cerevisiae. J Biol Chem. 1986 Sep 15;261(26):12066-73. PubMed PMID: [2875070](http://www.ncbi.nlm.nih.gov/pubmed/2875070/).
	4. Lewin AS, Gregor I, Mason TL, Nelson N, Schatz G. Cytoplasmically made subunits of yeast mitochondrial F1-ATPase and cytochrome c oxidase are synthesized as individual precursors, not as polyproteins. Proc Natl Acad Sci U S A. 1980 Jul;77(7):3998-4002. PubMed PMID: [6254007](http://www.ncbi.nlm.nih.gov/pubmed/6254007/); PubMed Central PMCID: [PMC349755](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC349755/).
	5. Lewin A, Morimoto R, Rabinowitz M. Restriction enzyme analysis of mitochondrial DNAs of petite mutants of yeast: classification of petites, and deletion mapping of mitochondrial genes. Mol Gen Genet. 1978 Jul 25;163(3):257-75. PubMed PMID: [355853](http://www.ncbi.nlm.nih.gov/pubmed/355853/).
	6. In collaboration with Bill Hauswirth and investigators at the University of California and the University of Pennsylvania, my group described the use of RNA enzymes and small interfering RNAs to block the expression of mutant rhodopsin animal models of autosomal dominant retinitis pigmentosa. My group has continued this research by using an allele-independent approach to adRP gene therapy. In the course of these studies we determined that gene augmentation alone, without RNA knockdown, may be sufficient to treat some dominant RHO mutations. We also explored the role of the unfolded protein response in adRP pathology caused by RHO mutations, and Dr. Marina Gorbatyuk is pursuing this line of inquiry as an independent investigator (Associate Professor) at UAB.
	7. Cideciyan AV, Sudharsan R, Dufour VL, Massengill MT, Iwabe S, Swider M, Lisi B, Sumaroka A, Marinho LF, Appelbaum T, Rossmiller B, Hauswirth WW, Jacobson SG, Lewin AS, Aguirre GD, Beltran WA. Mutation-independent rhodopsin gene therapy by knockdown and replacement with a single AAV vector. Proc Natl Acad Sci U S A. 2018 Sep 4;115(36):E8547-E8556. PubMed PMID: [30127005](http://www.ncbi.nlm.nih.gov/pubmed/30127005/); PubMed Central PMCID: [PMC6130384](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6130384/).
	8. Mao H, Gorbatyuk MS, Rossmiller B, Hauswirth WW, Lewin AS. Long-term rescue of retinal structure and function by rhodopsin RNA replacement with a single adeno-associated viral vector in P23H RHO transgenic mice. Hum Gene Ther. 2012 Apr;23(4):356-66. PubMed PMID: [22289036](http://www.ncbi.nlm.nih.gov/pubmed/22289036/); PubMed Central PMCID: [PMC3327607](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3327607/).
	9. LaVail MM, Yasumura D, Matthes MT, Drenser KA, Flannery JG, Lewin AS, Hauswirth WW. Ribozyme rescue of photoreceptor cells in P23H transgenic rats: long-term survival and late-stage therapy. Proc Natl Acad Sci U S A. 2000 Oct 10;97(21):11488-93. PubMed PMID: [11005848](http://www.ncbi.nlm.nih.gov/pubmed/11005848/); PubMed Central PMCID: [PMC17227](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC17227/).
	10. Lewin AS, Drenser KA, Hauswirth WW, Nishikawa S, Yasumura D, Flannery JG, LaVail MM. Ribozyme rescue of photoreceptor cells in a transgenic rat model of autosomal dominant retinitis pigmentosa. Nat Med. 1998 Aug;4(8):967-71. PubMed PMID: [9701253](http://www.ncbi.nlm.nih.gov/pubmed/9701253/).
1. With John Guy and Bill Hauswirth, I have helped develop AAV vectors for the treatment of Leber Hereditary Optic Neuropathy (LHON), one of the most common diseases caused by mitochondrial DNA mutations. We took two approaches: The first is to transfer mitochondrial genes to the nucleus, changing the genetic code and adding a targeting peptide for import of the proteins into mitochondria. This approach has led to the first gene therapy clinical trials for a mitochondrial disease. The second approach is to delivery wild-type mitochondrial genes to the mitochondria using an AAV capsid that has a mitochondrial targeting peptide attached to some of its subunits. This technology has powerful implication for the treatment of mitochondrial diseases for the development of animal models for these diseases. I find this research particularly rewarding because it makes practical application of discoveries I helped to make as a graduate student and postdoc.
	1. Yu H, Porciatti V, Lewin A, Hauswirth W, Guy J. Longterm Reversal of Severe Visual Loss by Mitochondrial Gene Transfer in a Mouse Model of Leber Hereditary Optic Neuropathy. Sci Rep. 2018 Apr 3;8(1):5587. PubMed PMID: [29615737](http://www.ncbi.nlm.nih.gov/pubmed/29615737/); PubMed Central PMCID: [PMC5882860](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5882860/).
	2. Yu H, Koilkonda RD, Chou TH, Porciatti V, Mehta A, Hentall ID, Chiodo VA, Boye SL, Hauswirth WW, Lewin AS, Guy J. Consequences of zygote injection and germline transfer of mutant human mitochondrial DNA in mice. Proc Natl Acad Sci U S A. 2015 Oct 20;112(42):E5689-98. PubMed PMID: [26438859](http://www.ncbi.nlm.nih.gov/pubmed/26438859/); PubMed Central PMCID: [PMC4620890](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4620890/).
	3. Koilkonda R, Yu H, Talla V, Porciatti V, Feuer WJ, Hauswirth WW, Chiodo V, Erger KE, Boye SL, Lewin AS, Conlon TJ, Renner L, Neuringer M, Detrisac C, Guy J. LHON gene therapy vector prevents visual loss and optic neuropathy induced by G11778A mutant mitochondrial DNA: biodistribution and toxicology profile. Invest Ophthalmol Vis Sci. 2014 Oct 23;55(12):7739-53. PubMed PMID: [25342621](http://www.ncbi.nlm.nih.gov/pubmed/25342621/); PubMed Central PMCID: [PMC4249950](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4249950/).
	4. Yu H, Ozdemir SS, Koilkonda RD, Chou TH, Porciatti V, Chiodo V, Boye SL, Hauswirth WW, Lewin AS, Guy J. Mutant NADH dehydrogenase subunit 4 gene delivery to mitochondria by targeting sequence-modified adeno-associated virus induces visual loss and optic atrophy in mice. Mol Vis. 2012;18:1668-83. PubMed PMID: [22773905](http://www.ncbi.nlm.nih.gov/pubmed/22773905/); PubMed Central PMCID: [PMC3388991](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3388991/).
2. We have used conditional knockout technology to create a mouse model of RPE oxidative stress that recapitulates certain cardinal features of geographic atrophy, including damage to Bruch’s membrane, RPE hypertrophy followed and atrophy of the RPE and death of photoreceptors in regions of RPE atrophy. This model has been useful in testing pharmacological therapy and gene therapy for dry AMD and in studying the importance of autophagy in the RPE. I believe that it will be of importance in testing gene therapy to prevent the development of advanced AMD.
	1. Young BM, Jones K, Massengill MT, Walsh E, Li H, Lewin AS, Ildefonso CJ. Expression of a CARD Slows the Retinal Degeneration of a Geographic Atrophy Mouse Model. Mol Ther Methods Clin Dev. 2019 Sep 13;14:113-125. PubMed PMID: [31334304](http://www.ncbi.nlm.nih.gov/pubmed/31334304/); PubMed Central PMCID: [PMC6624323](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6624323/).
	2. Biswal MR, Ahmed CM, Ildefonso CJ, Han P, Li H, Jivanji H, Mao H, Lewin AS. Systemic treatment with a 5HT1a agonist induces anti-oxidant protection and preserves the retina from mitochondrial oxidative stress. Exp Eye Res. 2015 Nov;140:94-105. PubMed PMID: [26315784](http://www.ncbi.nlm.nih.gov/pubmed/26315784/); PubMed Central PMCID: [PMC4624518](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4624518/).
	3. Mao H, Seo SJ, Biswal MR, Li H, Conners M, Nandyala A, Jones K, Le YZ, Lewin AS. Mitochondrial oxidative stress in the retinal pigment epithelium leads to localized retinal degeneration. Invest Ophthalmol Vis Sci. 2014 Jul 1;55(7):4613-27. PubMed PMID: [24985474](http://www.ncbi.nlm.nih.gov/pubmed/24985474/); PubMed Central PMCID: [PMC4112607](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4112607/).
	4. Seo SJ, Krebs MP, Mao H, Jones K, Conners M, Lewin AS. Pathological consequences of long-term mitochondrial oxidative stress in the mouse retinal pigment epithelium. Exp Eye Res. 2012 Aug;101:60-71. PubMed PMID: [22687918](http://www.ncbi.nlm.nih.gov/pubmed/22687918/); PubMed Central PMCID: [PMC3419481](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3419481/).
3. Over 100,000 people in the United States have uveitis, and ten percent of these patients with uveitis can expect to become blind. The current mainstay of treatment is corticosteroids, leading to an increased risk of blindness because of this therapy, though increased IOP or cataracts. We have found that gene therapy or peptide therapy targeting inflammation effectively inhibit infiltration of inflammatory cells and damage to the retina in mouse models that recapitulate autoimmune uveitis (EAU) or infectious uveitis (EIU). We hope to translate these approaches to therapy for patients.
	1. Ahmed CM, Ildefonso CJ, Johnson HM, Lewin AS. A C-terminal peptide from type I interferon protects the retina in a mouse model of autoimmune uveitis. PLoS One. 2020;15(2):e0227524. PubMed PMID: [32101556](http://www.ncbi.nlm.nih.gov/pubmed/32101556/); PubMed Central PMCID: [PMC7043762](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC7043762/).
	2. Ahmed CM, Massengill MT, Brown EE, Ildefonso CJ, Johnson HM, Lewin AS. A cell penetrating peptide from SOCS-1 prevents ocular damage in experimental autoimmune uveitis. Exp Eye Res. 2018 Dec;177:12-22. PubMed PMID: [30048621](http://www.ncbi.nlm.nih.gov/pubmed/30048621/); PubMed Central PMCID: [PMC6528831](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6528831/).
	3. Ildefonso CJ, Jaime H, Biswal MR, Boye SE, Li Q, Hauswirth WW, Lewin AS. Gene therapy with the caspase activation and recruitment domain reduces the ocular inflammatory response. Mol Ther. 2015 May;23(5):875-884. PubMed PMID: [25698151](http://www.ncbi.nlm.nih.gov/pubmed/25698151/); PubMed Central PMCID: [PMC4427880](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4427880/).
	4. Ildefonso CJ, Jaime H, Rahman MM, Li Q, Boye SE, Hauswirth WW, Lucas AR, McFadden G, Lewin AS. Gene delivery of a viral anti-inflammatory protein to combat ocular inflammation. Hum Gene Ther. 2015 Jan;26(1):59-68. PubMed PMID: [25420215](http://www.ncbi.nlm.nih.gov/pubmed/25420215/); PubMed Central PMCID: [PMC4303190](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4303190/).

### D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1R01EY026268-01, NIH/NEI

Lewin, Alfred (PI)

08/01/16-07/31/21

Testing Gene Therapy in Mouse Models of Geographic Atrophy

This is a translational research project to develop gene therapy for the advanced dry form of (AMD) using viral vectors to deliver genes for antioxidant and anti-inflammatory proteins in two independent mouse models of this disease.

Role: PI

7R01EY026999-04, NIH/NEI

Yan, Chen (PI)

08/01/19-07/31/21

mTORC1-TFEB pathway in degeneration of the RPE

This is a subcontract of a grant to Dr. Yan Chen at the University of Oklahoma HSC, We generated AAV-TFEB vector for testing the functional roles of mTOR in controlling RPE trafficking and helped Dr. Chen analyze the data resulting from her experiments.

Role: Co-Investigator