BIOGRAPHICAL SKETCH

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NAME: GUY, JOHN

eRA COMMONS USER NAME (agency login): johnguy

POSITION TITLE: Professor

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Miami School of Medicine, Miami, FL	MD	1977	
Univ. Penn Graduate Hospital, Philadelphia, PA Residency Medicine (Neurology)		1978	
Temple Univ. Med. Ctr., Philadelphia, PA Residency Neurology		1979	
Georgetown Univ. Med. Ctr., Washington, DC Residency Ophthalmology		1982	
Wills Eye Hospital, Philadelphia, PA Fellowship Neuro-ophthalmology		1983	

A. Personal Statement

The PI has 148 publications in peer reviewed journals, most as either first or senior author. They reflect a spectrum of experience in 1) mitochondrial gene therapy 2) animal models of mitochondrial diseases and 3) clinic PI recruiting and retaining patients in multicenter clinical trials for optic neuritis, MS ischemic optic neuropathy (ONTT, CHAMPS, IONDT) and Leber Hereditary Optic Neuropathy 4). Currently my clinical and laboratory work is focused on developing novel gene based therapies for the blinding disease LHON and the fatal disease Maternally Inherited Leigh Syndrome (MILS). Both disorders share a mitochondrial basis for irreversible visual loss and optic neuropathy. Our study group is currently involved in a phase I gene therapy clinical trial for LHON (NCT02161380) using a nuclear based approach for the G11778A mutation in ND4 that was developed in the laboratory many years ago (Guy et al. Rescue of a mitochondrial deficiency causing Leber Hereditary Optic Neuropathy. Ann Neurol. 2002; 52:534-542). When we compared treated eyes to fellow eyes of all our patients with chronic (onset > 1year) and acute visual loss (onset < 1year) we found a statistically significant effect of treatment on visual acuity improvement. A post-hoc comparison found that at month 12, the difference between study eye minus untreated fellow eye improvement in acute patients of 0.53 logMAR was greater than that observed in our prior acute natural history patients of 0.21 logMAR ($p=0.053$) (Guy J, Feuer WJ, Davis JL, Porciatti V, Gonzalez PJ, Koilkonda RD, Yuan H, Hauswirth WW, Lam BL. Gene Therapy for Leber Hereditary Optic Neuropathy: Low- and Medium-Dose Visual Results. Ophthalmology. 2017 Nov;124(11):1621-1634; Feuer et al. Gene Therapy for Leber Hereditary Optic Neuropathy: Initial Results. Ophthalmology. 2015 Nov 19. pii: S0161-6420(15)01210-5). At month 18, the difference between study eye minus fellow eye improvement in our acute gene therapy patients of 0.96 logMAR was greater than that observed in our prior acute natural history patients (0.17 logMAR), $p<0.001$ (Lam et al 2014). OCT of treated eyes had an average temporal RNFL thickness of 54 µm prior to injection and 55 µm at month 12. For fellow eyes prior to injection it was 56 µm dropping to 50 µm at month 12, $p = 0.013$. Thus, OCT suggested treatment may also be neuroprotective.

While outcomes from 18 participants enrolled in our clinical trial thus far found no serious safety concerns two patients developed asymptomatic uveitis with low and medium dose allotopic P1ND4v2 gene therapy. One was treated with low dose and one with medium dose vector. One of them had a rise in neutralizing antibodies, whereas the other did not (Guy et al 2017). The low-grade cells and flare quickly resolved without treatment as we had observed in our primate preclinical studies (Koilkonda et al 2014). Moreover, we continue to develop novel laboratory technology to introduce mitochondrial DNA directly into the organelle and reverse visual loss (Yu et al. Gene delivery to mitochondria by targeting modified AAV suppresses

Leber's hereditary optic neuropathy in a mouse model. Proc Natl Acad Sci U S A. 2012 May 15;109(20):E1238-47 and "Longterm Reversal of Severe Visual Loss by Mitochondrial Gene Transfer in a Mouse Model of Leber Hereditary Optic Neuropathy" (Yu H, Porciatti V, Lewin A, Hauswirth W, Guy J Sci Rep. 2018 Apr 3;8(1):5587. doi: 10.1038/s41598-018-23836-) and germline (Yu et al. 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). It is also our goal here to develop this direct delivery technology as an effective therapy for visual loss caused by mitochondrial dysfunction associated with LHON (G11778A) Maternally Inherited Leigh Syndrome (T8993G) and Neurogenic Ataxia and Retinitis Pigmentosa.

B. Positions and Honors

Positions and Employment

1983 1989	–	Assistant Professor of Ophthalmology & Neurology;, University of Florida
1989 2000	–	Associate Professor of Ophthalmology & Neurology, University of Florida
2000 2004	–	Professor of Ophthalmology & Neurology, University of Florida
2004 2008	–	Dean's Distinguished Professor in Neuro-Ophthalmology, University of Florida
2008 present	–	Professor, Neuro Service, Bascom Palmer Eye Institute, University of Miami
2016-present		Rodgers Research Chair, Bascom Palmer Eye Institute, University of Miami

Other Experience and Professional Memberships

NIH Therapeutic Approaches to Genetic Diseases Study Section – TAG 10/25/18 - 10/26/18
ZEY1 VSN 02 NEI Mentored Career Development Award Applications. August 10 2017.
NIH DPVS Study Section - February 16-17, 2017
Special Emphasis Panel/Scientific Review Group 2016/05 NOMD 02/22/2016-02/23/2016.
NINDS R24/P30 programs Special Emphasis Panel ZNS1 SRB N (08) 2015/04/18
NOMD Neural Oxidative Metabolism and Death Study Section 2014/06
NOMD Neural Oxidative Metabolism and Death Study Section 2014/02
NIH ZRG1 BDCN-C (02) S Neuropsychiatric and Neuroimmunologic Studies 7/17/2013
NIH ZRG1 MDCN-E (03) Neurodegeneration, 06/12/2013
NIH ZRG1 BDCN-L(03) M– Brain Disorders and Clinical Neuroscience November 13, 2012
NIH DPVS Study Section – February 2012
NIH BDPE Study Section - October 2009.
NIH BDPE Study Section - October, 2008.
NEI Clinical Trials Review Panel (2007/ZEY1-VSN-05)
NEI Clinical Trials Review Panel, April 2008
NEI Clinical Trials Review Panel CB-G90 Retinopathy (2006/10 ZRG1 CB-G (90) (S)
NEI VSN07 Review Panel 8/2006
NEI Review Panel, ZEY1 VSN(02), 2005/12/01
NEI Small Grant for Pilot Research (R03) Applications, ZEY1 VSN(01), 2005/03/14
NEI Career Development Award Applications, ZEY1 VSN(05), 2004/11/01
NEI Novel Therapeutic and Pathogenetic Studies of Oculomotor Disorders, ZEY1 VSN(04), 2003/08/07

- Member, ARVO
- Member, NANOS
- Member, AAO
- Member, AAN

Honors

2001-18	America's Top Doctors, US News

2004	Dean’s Distinguished Professor in Neuro-Ophthalmology, University of Florida
2009	Cless Best of the Best Award 2009, UIC

C. Contribution to Science

1- Discovery of mitochondrial involvement in EAE animal model of multiple sclerosis (Qi et al. Mitochondrial protein nitration primes neurodegeneration in experimental autoimmune encephalomyelitis. J Biol Chem, 2006; 281:31950-31962).

2- MRI imaging (Guy et al. Enhancement and demyelination of the intraorbital optic nerve: Fat suppression magnetic resonance imaging. Ophthalmology, 99(5):713-719, 1992. Guy et al. Intraorbital optic nerve and experimental optic neuritis: Correlation of fat suppression magnetic resonance imaging and electron microscopy. Ophthalmology, 99(5):720-725, 1992.)

3- Novel laboratory technology to introduce mitochondrial DNA directly into the organelle (Yu et al. Gene delivery to mitochondria by targeting modified AAV suppresses Leber's hereditary optic neuropathy in a mouse model. Proc Natl Acad Sci U S A. 2012 May 15;109(20):E1238-47) and germline (Yu et al Consequences of zygote injection and germline transfer of mutant human mitochondrial DNA in mice. Proc Natl Acad Sci U S A. 2015 Oct 5. pii: 201506129) and reverse visual loss.

4- Translation of benchtop research to the clinic in a phase I gene therapy clinical trial for LHON (NCT02161380) using a nuclear based approach (Feuer et al. Gene Therapy for Leber Hereditary Optic Neuropathy: Initial Results. Ophthalmology. 2015 Nov 19. pii: S0161-6420(15)01210-5. Guy J, Feuer WJ, Davis JL, Porciatti V, Gonzalez PJ, Koilkonda RD, Yuan H, Hauswirth WW, Lam BL. Gene Therapy for Leber Hereditary Optic Neuropathy: Low- and Medium-Dose Visual Results. Ophthalmology. 2017 Jun 21. pii: S0161-6420(17)30495-5. doi: 10.1016/j.ophtha.2017.05.016. [Epub ahead of print] PMID: 28647203

D. Ongoing Research Support

1. U10 EY023558-05 – Guy, John (PI) 04/01/14 – 03/31/19 4.8 calendar months
   NEI/NIH
   Leber's Hereditary Optic Neuropathy: Gene Therapy Clinical Trial
   To conduct phase I trial testing the safety of gene therapy for Leber's hereditary optic neuropathy
   Role: PI

2. R01 EY017141-08 Guy, John (PI) 09/01/07-08/31/20 2.4 calendar months
   Modification of Adeno Associated Virus to deliver DNA directly to Mitochondria
   NEI/NIH
   Role: PI

3. 5R01 EY027414-02 Guy, John (PI) 04/01/07-03/31/21 2.4 calendar months
   Intravenous MitoTargeted AAV9 Gene Therapy for Treatment of Visual Loss and Encephalopathy in Leigh Syndrome and NARP
   NEI/NIH
   Role: PI

4. 1R24EY028785-01A1 Guy, John (PI) 03/01/2019-12/31/2023 2.4 calendar months
   Mito-Targeted AAV to treat Leber Hereditary Optic Neuropathy caused by ND4 mutations
   NEI/NIH
   Role: PI
   Pending Research Support
   Lebers Hereditary Optic Neuropathy:Gene Therapy
   NEI/NIH
   Continuation of U10

Pending

1. 2UG1EY023558-06 – Guy, John (PI) 04/01/2019-03/31/2023 4.8 calendar months

   Leber's Hereditary Optic Neuropathy: Gene Therapy Clinical Trial
   To conduct phase I trial testing the safety of gene therapy for Leber's hereditary optic neuropathy
   Role: PI

   OVERLAP
   If any Pending Grant(s) are funded, then efforts will be adjusted based on Scope of Work and agency requirements to accommodate new funding.
   The current pending award U10 award will be YR06 of the U10 on the ongoing support.