BIOGRAPHICAL SKETCH

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NAME: Jean Bennett, MD, PhD

eRA COMMONS USER NAME): jebennet

POSITION TITLE: Professor, Ophthalmology; Cell and Developmental Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Yale University, New Haven, CT	BS	1976	Honors Biology
Univ. of California, Berkeley, Berkeley, CA	PhD	1980	Cell Biology/Zoology
Univ. of California, San Francisco; SF, CA	(postdoc)	1982	Radiobiology, Anatomy
Harvard Medical School, Boston, MA	MD	1986	Medicine
Yale University School of Medicine, New Haven, CT	(postdoc)	1987	Human Genetics
Johns Hopkins School of Medicine	(postdoc)	1989	Developmental Genetics

A. Personal Statement

I am a physician-scientist with experience/expertise in molecular biology, vector development and gene therapy translational studies. This experience is documented by >120 peer-reviewed publications on gene therapy (including the first publication to demonstrate proof-of-concept of retinal gene therapy) over the last 25 years. My lab has established a true "from bench to bedside" program, and thus I am familiar with steps necessary to go from proof-of-concept all the way to those necessary for testing of safety and efficacy in humans with blinding disease, including obtaining the appropriate molecular diagnoses. This work is supported by our Center for Advanced Retinal and Ocular Therapeutics (CAROT), of which I am director. Our work led to a gene therapy trial that demonstrated efficacy and enrolled both the first pediatric subject and the oldest person (44yo) to undergo gene therapy for a non-lethal disease. We have completed both a Follow-on (re-administration) trial and a Phase 3 registration gene therapy study for congenital blindness, the first and only randomized controlled gene therapy Phase 3 trial. This work could lead to the first approved gene therapy drug for retinal disease worldwide and the first approved gene therapy reagent in the USA. In the process we have gained experience in translational studies, moving projects from the laboratory into the clinic. We continue to expand the targets, and in the process, to train young investigators who will be able to accelerate the progress in developing treatments for inherited retinal degenerations.

B. Positions and Honors

1989-1990	Instructor	Johns Hopkins Med. School, Physiology
1990-1992	Instructor	Johns Hopkins Med. School,Wilmer Inst.
1992-2001	Asst. Prof	U Pennsylvania School of Medicine, Depts. Ophthalmology; Cell Bio
2001-2003	Assoc. Prof	U Pennsylvania School of Medicine, Depts. Ophthalmology; Cell Bio
2004-present	Professor	U Pennsylvania School of Medicine, Depts. Ophthalmology; Cell Bio
2005-present	Scientist	Children's Hospital of Philadelphia, Ctr Cellular & Molecular Therapeutics

Other Experience and Professional Memberships

2000-2003	Ad hoc Member, NIH Recombinant DNA Advisory Committee (RAC),
2001-present	Scientific Advisory Board, Foundation Fighting Blindness
2003-2008	Editorial Board Member, Investigative Ophthalmology Visual Science
2002-2007	Member and Chairman, Genetic Disease Committee; Board Directors, ASGCT
2008-present	Member, Nominating Committee, ASGT
2008-2012	Member, Gene and Drug Delivery Systems Study Section, NIH
2007-2010	Editorial Board Member, JCI
2011-present	Advisory Board Member, Science Translational Medicine

Honors (recent)

2007	Institute of Medicine, National Academy of Science, Washington, DC
2008	Cless Best of the Best Award, ARVO 2009, Chicago, IL
2009	Audrey E. Evans Award for Excellence, Philadelphia, PA
2010	ROPARD Vision of Children Award, Detroit, MI
2011	Pyron Award, American Assoc of Retinal Surgeons, Boston, MA
2012	Bressler Award for Vision Research, The Jewish Guild for the Blind, NY, NY
2013	Clinical Research Forum, Top 10 Clinical Research Achievement Award, Washington, DC
2015	American Academy of Arts and Sciences

C. Contribution to Science

1. Together with my team, I demonstrated long-term reversal of blindness in large and small animal models of a severe congenital blinding disease (Leber Congenital Amaurosis [LCA]). This led to several human clinical trials, including the human clinical trial she directed at The Children's Hospital of Philadelphia and Second Universitiy of Naples (Italy)– the first to report safe and sustained reversal of blindness in all 12 subjects. In that trial, each individual's worst-seeing eye received a subretinal injection of a recombinant virus carrying the wildtype version of their disease-causing gene (*RPE65*). The results showed efficacy in all twelve of the subjects, with the most dramatic results observed in the youngest individuals. The children enrolled in that study are now able to navigate independently and to participate in regular classrooms/sports without visual aids. The older participants also benefited and feel that the effects are life-changing. [See videos available at: http://www.uphs.upenn.edu/news/News_Releases/2009/10/gene-therapy-restores-sight/.]

a. Acland, G.M.,Aguirre, G.D. Maguire, A.M., Zhang, Q., Aleman, T.S., Cideciyan,A.V., Pearce-Kelling, S.E., Anand, V., Zeng, Y., Ray, J., Jacobson, S.G., Hauswirth, W.W. and **Bennett, J**., "Gene Therapy Restores Vision in a Canine Model of Childhood Blindness," Nat Genet 29(1):92-95 (2001).PMID 11326284
b. Maguire, AM Simonelli, S, Pierce, EA, Pugh, EN, Mingozzi, F, Bennicelli, J, Banfi, S, Marshall, KA, Testa, F, Surace, E.M., Rossi, S., Lyubarsky, A., Arruda, V.R., Konkle, B., Stone, E, Sun, J., Jacobs, J, Dell''Osso, L, Hertle, R, Ma, J-X, Redmond, RM Zhu, Hauck, B, Zelenaia, O, Shindler, KS Maguire, MG, Wright, J.F., Volpe, NJ, McDonnell, J.W, Auricchio, A, High, K.A., **Bennett, J**., Safety and Efficacy of Gene Transfer for LCA, NEJM, 358(21):2240-2248 (2008).PMID 18441370
c. Maguire AM, High KA, Auricchio A, Wright JF, Pierce EA, Testa F, Mingozzi F, Bennicelli JL, Ying GS, Rossi S, Fulton A, Marshall KA, Banfi S, Chung DC, Morgan JI, Hauck B, Zelenaia O, Zhu X, Raffini L, Coppieters F, De Baere E, Shindler KS, Volpe NJ, Surace EM, Acerra C, Lyubarsky A, Redmond TM, Stone E, Sun J, McDonnell JW, Leroy BP, Simonelli F, **Bennett, J**, Age-dependent effects of RPE65 gene therapy for LCA: a phase 1 dose-escalation trial. Lancet 375(9701):1597-605 (2009) PMID: 19854499.
d. Testa, F, Maguire, AM, High, KA, Auricchio, A, **Bennett, J**, Simonelli, F, Three-year follow-up after subretinal delivery of AAV in patients with LCA 2, Ophthalmol S0161-6420(12)01168-2; PMID: 23474247
e. Russell S, **Bennett J**, Wellman JA, Chung DC, Yu ZF, Tillman A, Wittes J, Pappas J, Elci O, McCague S, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet.* Jul 13 2017. pii: S0140-6736(17)31868-8

2. I have been involved in all aspects of developing somatic retinal gene transfer, including development and characterization of novel viral vectors and nonviral gene delivery strategies for use in the eye, development of transgene regulatory systems to externally regulate levels of transgene expression after virus-mediated delivery, and use of gene transfer techniques to develop animal models of retinal/macular degeneration.

a. Auricchio A, Kobinger G, Anand V, Hildinger M,O'Connor, E., Maguire A. M., Wilson J. M., **Bennett J**. "Exchange of surface proteins impacts on viral vector cellular specificity and transduction characteristics: the retina as a model," Human Mol. Genetics 10: 3075-3081 (2001).
b. Lebherz, C, Maguire, A, Tang, W, **Bennett, J** and Wilson, JM, Novel AAV serotypes for improved ocular gene transfer, J. Gene Medicine, 10(4):375-82 (2008) PMID: 18278824.
c. Vandenberghe, LH, Bell, P, Maguire, AM, Cearley, CN, Xiao, R, Calcedo, R, Wang, L, Castle, MJ, Maguire,

AC, Grant, R, Wolfe, JH, Wilson, JM and **Bennett, J**, Dosage thresholds for AAV2 and AAV8 photoreceptor gene therapy in monkey; Sci Transl Med 3(88):88ra54 (2011) PMID 21697530.

d. Cronin, T, Vandenberghe, LH, Hantz, P Juttner, J, Reimann, A, Kacsó, A-E, Huckfeldt, R, Busskamp, V, Kohler, H, Lagali, PS, Roska, B, **Bennett, J**, Efficient transduction and optogenetic stimulation of retinal bipolar cells by a synthetic adeno-associated virus capsid and promoter, EMBO Molecular Medicine, e201404077 (2014). PMID 25092770.

3. My colleagues and I were the first to report that readministration of the vector in the contralateral eye was not only safe but also effective. The concern with re-administration was that previous exposure could "vaccinate" the individual and result in an inflammatory response upon repeat exposure. There had heretofore been no indication of success in studies involving systemic gene therapy readministration and further, there had been signs of immunologic toxicity. Although we had collected data showing that delivery of gene therapy vectors to the retina is benign immunologically, we proceeded cautiously and only initiated a human readministration study after they had carried out investigations in large animal models to demonstrate the safety of this approach. The large animal studies were designed to test the worst-case scenario: administration to a subject that had been "immunized" with the vector and re-administration at a time when immune response was likely at a peak.

The excellent safety and efficacy data from the animal studies provided the justification for moving forward with human studies, studies which were designed to proceed slowly and cautiously in the event that humans might respond differently than the animals. The first individuals to be enrolled were thus those who had the most advanced disease. Enrollment of each of these first subjects was separated by two months and immunologic responses were evaluated thoroughly, along with functional responses. What was particularly exciting was the demonstration that each of these "second" eyes became far more sensitive to dim light as evidenced not only by retinal function testing but also by evaluations of activation of the visual cortex. The reactivation of the visual cortex proceeded over a period of about 3 months. The dogma had been that even if one could correct the retinal dysfunction, it would be impossible to reactivate cortical function in adults who had been severely visually impaired since birth. This readministration study therefore also demonstrated the plasticity of the central nervous system with respect to the ability to respond to sensorineural input. Besides the safety and efficacy data, the results provide data relating to the unique immunologic responses of the eye that are of general interest to basic scientists as well as clinicians. These results also aided in establishing the readministration approach that is being used in the only Phase 3 gene therapy trial that is currently in progress.

a. Amado, D, Mingozzi, F, Hui, D, Bennicelli, JL, Wei, Z, Chen, Y, Bote, E, Grant, RL, Golden, JA, Narfstrom, K, Syed, NA, Orlin, SE, High, KA, Maguire, AM, **Bennett, J**, Safety and efficacy of subretinal re-administration of a viral vector in large animals to treat congenital blindness, Sci Transl Med 2, 21ra16, (2010) PMID:20374996

b. **Bennett, J**, Ashtari, M., Wellman, J, Marshall, KA, Cyckowski, LL, Chung, DC, McCague, S, Pierce, EA, Chen, Y, Bennicelli, J, Zhu, X, Ying, G-s, Sun, J, Wright, JF, Auricchio, A, Simonelli, F, Shindler, KS, Mingozzi, F, High, KA, and Maguire, AM, AAV2 Gene Therapy Readministration in Three Adults with Congenital Blindness, Sci Transl Med 4, 120ra15 (2012).PMID 22323828.

c. Ashtari, M, Cyckowski, LL, Monroe, JF, Marshall, KA, Chung, DC, Auricchio, A, Simonelli, F, Leroy, BP, Maguire, AM, Shindler, KS, **Bennett, J**, Human visual cortex response to gene therapy-mediated recovery of retinal function after prolonged sensory deprivation, J Clin Invest, 121(6):2160-8 (2011) PMID 21606598.

d. **Bennett, J**, Wellman, J, Marshall, KA, McCague, S, Ashtari, M, DiStefano-Pappas, J, Elci, OU, Chung, DC, Sun, J, Wright, JF, Cross, DR, Aravand, P, Cyckowski, LL, Bennicelli, JL, Mingozzi, F, Auricchio, A, Pierce, EA, Ruggiero, J, Leroy, BP, SImonelli, F, High, KA, Maguire, AM. Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutations: a follow-on phase 1 trial. Lancet 388:661-72 (2016) PMID:27375040.

4. We used induced pluripotent stem cells (iPSCs) generated from blood samples donated by individuals affected with choroideremia to develop proof-of-concept data. Data from these "personalized models" showed that delivery of the normal Choroideremia gene resulted in reversal of the cellular pathology. The iPSC data was used to form the basis of an Investigational New Drug (IND) filing with the US Food and Drug Administration, an approach that may blaze a quicker pathway in developing treatments for inherited

conditions. The Phase 1 trial was initiated in January 2015 and is evaluating safety and efficacy of the intervention in adults with choroideremia. Ultimately, the goal is to prevent progression of the disease by treating individuals early in the course of the disease.

a. Vasireddy, V, Mills, JA, Gaddameedi, R, Basner-Tschakarjan, E, Kohnke, M, Black, AD, Alexandrov, K, Zhou, S, Maguire, AM, Chung, DC, Mac, H, Sullivan, L, Gadue, P, Bennicelli, JL, French, DL, **Bennett, J**, AAV-mediated gene therapy for choroideremia: Preclinical studies in personalized models, PLoS ONE 8(5): e61396. doi:10.1371/journal.pone.0061396 (2013). PMID:23667438

5. Plans are now also underway to test additional gene intervention strategies developed in the Bennett lab as precision medicine for other blinding diseases. One target is Leber's congenital amaurosis due to CEP290 mutations. In order to develop a strategy to treat this disease, we characterized the cell biology of the large CEP290 protein. We also characterized the cell biology and disease pathogenesis of the lebercilin-encoding gene, LCA5.

a. Drivas TG, Holzbaur ELF, **Bennett J**, Disruption of novel CEP290 microtubule/membrane binding domains causes retinal degeneration. JCI 123(10):4525-4539 (2013), PMID 24051377,
b. Boldt, K, Mans, DA, Won, J, van Reeuwijk, J, Vogt, A, Kinkl, N, Letteboer, SJF, Hicks, WL, Hurd, RE, Naggert, JK, Texier, Y, den Hollander, A, Koenekoop, RK, **Bennett, J**, Cremers, F, Gloeckner, CJ, Nishina, PM, Roepman, R, Ueffing, M, Disruption of intraflagellar protein transport in photoreceptor cilia causes Leber congenital amaurosis, J Clin Inves 121(6):2169-80 (2011) PMID 21606596.

D. Research Support

List both selected ongoing and completed research projects for the past three years (Federal or non-Federally-supported). *Begin with the projects that are most relevant to the research proposed in the application.* Briefly indicate the overall goals of the projects and responsibilities of the key person identified on the Biographical Sketch. Do not include number of person months or direct costs.

Current:

Spark Therapeutics Maguire (PI) 3/1/13 – 12/31/17 <0.1 calendar
Clinical Trial Agreements
To serve as the Scientific Director for follow-up studies of Phase I/II and Phase III gene therapy clinical trials for LCA due to RPE65 mutations and for a Phase I Trial for Choroideremia due to CHM mutations.

C-CL-0607-0389-UPA01 Bennett (PI) 9/1/13 – 8/30/18
Foundation Fighting Blindness 1.0 calendar
"CHOP-Penn Center for Pediatric Retinal Degenerations" –
Phenotype/genotype studies for inherited retinal degeneration and development of treatments

1R24 EY019861-01A1 Bennett (PI) 8/1/11-7/31/17
NEI/NIH "Therapeutic approaches for ABCA4-associated disorders. 1.0 calendar
To develop trans-splicing and small molecule approaches for treating ABCA4 disease.

Biogen Wilson, Bennett (Co-PIs) 8/1/16 – 9/1/18 5.0 calendar
Scientific Research Agreement
To serve as the Scientific Director for preclinical gene therapy studies aiming to bring two retinal disease targets to clinical trial.

Limelight Biologics Bennett (PI) 12/1/16 – 11/311/18 1.0 calendar
Scientific Research Agreement
To serve as the Scientific Director for preclinical studies aiming to develop gene therapy for diseases currently unamenable to gene therapy.

Completed:

8 DP1 EY023177-02 Bennett (PI) 9/30/11-7/31/16
NEI/NIH "Broad spectrum molecular therapy for blinding retinal disorders" 6.12 calendar

To develop optogenetic therapy for end-stage retinal blindness

3-RO1-EY10820 Bennett (PI) 3/1/03-2/28/09
NEI/NIH "Gene therapy for inherited retinal degeneration" 2.0 calendar
To develop proof-of-concept and safety data for gene therapy for inherited retinal degeneration

1U10EY013729 Bennett (PI of module) 9/30/01-7/30/06
NEI/NIH "Gene therapy for Leber congenital amaurosis" 2.0 calendar
To develop proof-of-concept and safety data for gene therapy for Leber's congenital amaurosis due to RPE65 mutations.