

PART I: General Information

DATE PREPARED: November, 2011

Name: Dong Feng Chen

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Education:

1986 **M.D.** Peking University, Medical Center, Beijing, P. R. China

1992 **Ph.D.** Neurobiology, University of Louisville, School of Medicine, Louisville, KY

Postdoctoral training:

1992-1995 Postdoctoral Associate, Department of Brain and Cognitive Sciences,
Massachusetts Institute of Technology, Cambridge, MA

1995-1998 Senior Postdoctoral Associate, Center for Learning and Memory, Center for
Cancer Research, Massachusetts Institute of Technology, Cambridge, MA

Academic Appointments:

1998-2009 Assistant Professor, Department of Ophthalmology, Harvard Medical School

2009-present **Associate Professor**, Department of Ophthalmology, Harvard Medical School

1998-2006 Assistant Scientist, Schepens Eye Research Institute, Harvard Medical School

2006-present **Associate Scientist**, Schepens Eye Research Institute, Harvard Medical School

2009-present **Research Health Scientist**, VA Center for Innovative Visual Rehabilitation
RR&D Center of Excellence, Harvard Medical School

Major Administrative Responsibility:

2004-present Leader, Retinal laser injury research program, Schepens Eye Research Institute

2004-2005 Leader, Optic Nerve Club, Schepens Eye Research Institute and Massachusetts
Eye and Ear Infirmary, Harvard Medical School

2004-present **Scientific Advisor Board**, Glaucoma Research Foundation Grant

2006-present **Scientific Advisory Board**, New Jersey Commission on Brain Injury Research

2007-2010 Member and **Chair**, Retinal Cell Biology Program Committee, the Association
of Vision and Ophthalmology (ARVO)

2008-present **Editorial Board Member**, *Stem Cells*

2011-present **Editorial Board Member**, *Asia-Pacific Journal of Ophthalmology*

2011 **Advisory Board**, 5th Military Vision Symposium on Ocular and Brain Injury

Major Committee Assignments:

- 2000-2004 Chair, Safety and Use Committee for Gene Expression and Delivery System, Schepens Eye Research Institute
- 1999-2004 Member, Training committee, Schepens Eye Research Institute
- 2001-2004 Member, Curriculum committee, Training Program in Molecular Bases of Eye Disease, Harvard Medical School
- 2001-2006 Member, Research planning and review committee, Schepens Eye Res. Institute
- 2005-present Technology transfer committee, Schepens Eye Research Institute
- 2008-present Member, Harvard Stem Cell Institute Seed Grant Committee, Harvard Medical School
- 2009-present Member, Joint Committee on the Status of Women, Harvard Medical School/Harvard School of Dental Medicine
- 2010-present Chair, Seminar Committee, Schepens Eye Research Institute

Professional Society Involvement:

- 1989-1990 American Society for Anatomical Sciences, member
- 1989-present Society for Neuroscience, member
- 2000-present The Association for Research in Vision and Ophthalmology, member
- 2002-2003 American Society for Gene Therapy, member

Awards and Honors:

- 1997 Travel award for the Seventh International Neural Regeneration Symposium
- 1999 Junior Faculty Award, Charles H. King Foundation
- 2000 Lilly Center on Aging Fellowship through 50th Anniversary Program for Scholars in Medicine, Harvard Medical School
- 2005 Visiting Scholar, New York Eye and Ear Infirmary, New York, NY
- 2006 Sybil B. Harrington Scholar, Research to Prevent Blindness, New York, NY
- 2008 Outstanding Scientific Achievement Award, the Vision Awards, RP International

PART II: Research, Teaching, and Clinical Contributions

A. Narrative report (500 words or less) of Research, Teaching, and Clinical Contributions.

1. Major Research Interests

- Molecular mechanisms controlling optic nerve and CNS axon regeneration
- Neuroprotective mechanisms for retinal disease and injury
- Signaling events stimulating regeneration and neurogenesis of neural progenitor cells in the adult
- Astroglial barrier to neural integration in retinal transplantation

2. Description of Research

The research of my laboratory has been focused on the study of mechanisms that control neural differentiation, growth, and regeneration in the mammalian central nervous system (CNS). Elucidating the mechanisms regulating these processes is not only fundamental for our understanding of neural development, but also it may provide crucial information for the development of therapeutic strategies to treat developmental and degenerative disorders and injuries in the brain and the retina.

In the past 5 years, a part of my work has been dedicated to study the molecular mechanisms that prevent CNS axon regeneration. At a certain point in development, axons in the mammalian CNS lose their ability to regenerate after injury. Using the optic nerve model, I have shown that this growth failure coincides with two developmental events: the loss of Bcl-2 expression by CNS neurons and the maturation of astrocytes. Before postnatal day 4 (P4), when astrocytes are immature, overexpression of Bcl-2 alone supported robust and rapid optic nerve regeneration over long distances, leading to innervation of brain targets in 4 days in mice. As astrocytes became more mature after P4, axonal regeneration was inhibited in mice overexpressing Bcl-2. Concurrent induction of Bcl-2 and suppression of reactive astrocytes by both pharmacological and genetic means were sufficient to reverse the failure of CNS axonal re-elongation and lead to rapid axonal regeneration over long distances and reinnervation of the brain targets by a majority of severed optic nerve fibers in mature mice. Therefore, these results demonstrate that the absence of intrinsic, Bcl-2-supported mechanisms of axonal growth and the induction of reactive astrocytes after injury are the two essential elements in adult CNS regenerative failure.

With recent progress in stem cell research, neural transplantation is emerged as another promising therapy for CNS injury and diseases. However, success of neural transplantation has long been limited by restricted ability of neural implants to integrate, grow neurites, or establish neuronal connections with the host. Recently, we have discovered that astroglial cells also contribute critically to the failure of neural integration and neurite growth after transplantation. The CNS of adult mice deficient in two intermediate filament proteins in astrocytes – glial fibrillary acidic protein and vimentin – provided a permissive environment for implanted neurons to extend neurites and migration in the host environment. This result demonstrates an essential role for astroglial cells in preventing neural graft integration and nerve regeneration after transplantation.

We believe that these findings present breakthroughs in CNS repair and regeneration. These results have important implications for the development of therapies to repair the CNS

after trauma, stroke, and other CNS insults, including damage and degenerative disease of the spinal cord. In addition, they may open up a door for using neural transplantation to cure blindness and CNS disorders.

B. Funding Information

1999	Charles H. Hood Foundation, PI ; "Regulation of Neural Differentiation by Foundation Bcl-2"
2000-2006	NIH/NEI, PI ; "Molecular Mechanisms Underlying Optic Nerve Regeneration"
2001	Lilly Center, PI ; "Inhibitory Effect of Myelin on CNS Regeneration"
2001-2005	Juvenile Diabetes Research Foundation, co-PI; "Neural and Glial Contribution to Early Research Foundation Diabetic Retinopathy"
2001-2002	Department of the Army, task PI; "Regeneration of the Damaged CNS"
2002-2003	PDA Foundation for Pharmaceutical Sciences, PI ; "Development of a Non-viral Gene Delivery Method for CNS Repair."
2002-2003	The Massachusetts Loins Eye Research Fund, Inc., PI ; "Promotion of Neural Graft Integration in the Retina by Mutating Vimentin/GFAP Genes in Mice."
2003-2005	Department of Defense, task PI; "Promoting Retinal Neuron Survival and Optic Nerve Regeneration with Lithium."
2004-2006	Department of Defense, task PI; "Novel treatments to controlling neural damage and inflammatory response in laser induced retinal injury."
2005-2007	Harvard Stem Cell Institute, PI ; "Neural stem/progenitor cell transplantation for retinal degeneration."
2007-2009	American Health Foundation, PI ; "Limiting Retinal Ganglion Cell and Axon Damage by Controlling Astroglial Responses in Glaucoma"
2007-2011	NIH/NEI R01, PI ; "Functional Restoration of the Optic Nerve after Disease and Injury"
2007-2011	Department of Defense, task PI; "Military Vision Research Program"
2008-2011	Alcon Fund, PI ; "A novel animal model of normal-tension glaucoma"
2009-2011	NIH/NIDA R21, PI ; "Glial modulation of cortical development and drug of abuse-induced brain damage"
2010-2011	Harvard Catalyst, PI ; "Longitudinal investigation of pathological changes of Glaucoma in mice by <i>in vivo</i> retinal imaging"
2010-2013	VA Medical Center Merit Award, PI ; "Biological Inquiry into Mechanisms and Neuroprotective Strategy for TBI"

C. Report of Current Research Activities (bench research, clinical trials, outcome studies, efficacy studies as applicable)

Projects

1. Functional restoration of vision following optic nerve damage and regeneration using genetic mouse models.
2. Identification of glial cell-associated inhibitory proteins that block optic nerve regeneration in the adult CNS.
3. Uncovering the molecular signals stimulating neurogenesis in the adult retina and CNS from endogenous neural stem/progenitor cell pools.

4. Mechanisms controlling neural integration in retinal transplantation.
5. Effect of neuroprotective agents on retinal neurons in injury and disease

D. Report of Teaching

1. Local contributions

a. Medical School course

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| 1988 | Gross Anatomy, Teaching Assistant and Tutor, 150 medical students, 12 h/wk |
| 1988 | Neuroscience, Lecturer and tutor, 150 medical students, 6 h/wk |
| 1989 | Microanatomy / Histology, Teaching Assistant, 150 Medical students, 3 h/wk |

b. Graduate medical course

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| 1998 | “Neural Development and Regeneration”, MIT; organizer and lecturer for a literature reading course, 8 senior undergraduate students, 3 hr/wk |
| 2000 | Neuro 300 “Development and Regeneration of the CNS”, Harvard Medical School; organizer and lecturer for a literature reading course, 10 graduate students, 3 hr/wk. |
| 2004 | “Biological Bases of Ophthalmic Diseases,” Harvard Medical School; lecturer, 20 graduate students and postdoctoral fellows, 4 hr/wk |
| 2006 | “Nanocourse on CNS neuroregeneration,” Harvard Medical School; lecturer. |

2. Regional, national, or international contributions:

Regional contributions:

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| 2000 | Invited speaker, Seminar Series, Joslin Diabetes Center, Harvard Med. School, Boston, MA |
| 2004 | Invited speaker, Neuroscience Seminar Series, Massachusetts General Hospital, Boston, MA |
| 2007 | Invited speaker, Neuroscience Seminar Series, Massachusetts General Hospital, Harvard Medical School, Boston, MA |
| 2008 | Invited speaker, Neuroscience Seminar, Novartis Pharmaceuticals, Cambridge, MA |
| 2009 | Invited keynote speaker, Ophthalmology Retreat, Tufts University, Boston, MA |
| 2010 | Invited speaker, Military Symposium, Boston, MA |

National contributions:

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| 1997 | Invited speaker, International Business Communications’ (IBC’s) Conference on Neurodegenerative Disease; Philadelphia, PA |
| 1997 | Invited speaker, National Public Radio: “Talk to the Nation: Science Friday.” Boston, MA |
| 1999 | Department of Neurobiology and Anatomy seminar series, Hahnemann University, Philadelphia, PA. |
| 1999 | Invited speaker, Department of Psychiatry and Neuroscience, Wayne State University, Detroit, MI. |
| 2001 | Neuroscience Seminar Series, Neuroscience Center, University of North Carolina, School of Medicine, Chapel Hill, NC. |
| 2002 | Invited speaker, Wills Eye Hospital / Jefferson Medical College, Philadelphia, PA |
| 2002 | Invited speaker, NIH/NIMH, Bethesda, MD |

- 2002 Invited speaker, The Glaucoma Foundation's 9th Annual Scientific Think Tank Meeting, Chicago, IL
- 2005 Visiting Scholar/Visiting Professor Lecture Series, New York Eye and Ear Infirmary, New York, NY
- 2005 Invited keynote speaker, Tissue Bioengineering and Regenerative Medicine, Symposium at the 141st Annual Meeting for the American Ophthalmology Society; Sea Island, GA
- 2006 Seminar in Basic Ocular Science, Department of Ophthalmology, Mount Sinai School of Medicine, New York, NY
- 2006 Invited speaker, Special Interest Group, "Cellular Response to Retinal Detachment: Strategies for Improving Visual Outcomes" Association for Research in Vision and Ophthalmology Annual Meeting, Ford Lauderdale, FL
- 2007 Academic Seminar Series, the Vanderbilt Eye Institute, Vanderbilt University Medical Center, Nashville, TN
- 2009 Invited speaker, Sixteenth Annual Optic Nerve Rescue and Restoration Think Tank, The Glaucoma Foundation, New York, NY
- 2009 Invited speaker, Mini-symposium "Optic nerve regeneration – a dream or approaching reality," Association for Research in Vision and Ophthalmology Annual Meeting, Ford Lauderdale, FL
- 2010 Invited speaker, Academic Seminar Series, Washington University School of Medicine at St. Louis, St. Louis, MO
- 2010 Invited speaker, Military Vision Research Symposium, Boston, MA
- 2011 Invited speaker, USAF DEW (lasers) Strategic Meeting, Crystal City, VA

International contributions:

- 2004 Invited speaker, 4th Asian Pacific Symposium on Neural Regeneration, Osaka, Japan
- 2006 Invited speaker, Peking University First Hospital, Beijing, P. R. China
- 2008 Invited speaker, the 4th Congress of the Asian Neuro-ophthalmology Society, Taipei, Taiwan
- 2008 Invited speaker, Stem cells and retinal repair session, The International Congress for Eye Research, Beijing, P. R. China.
- 2008 Invited keynote speaker, the 20th Anniversary Celebration of Beijing Society for Neurosciences, Beijing, P. R. China
- 2008 Seminar series, Eye & ENT Hospital of Fudan University, Shanghai, P. R. China
- 2009 Invited speaker, Tissue Bioengineering and Nanotechnology Symposium, the 24th Congress of the Asia-Pacific Academy of Ophthalmology, Bali, Indonesia
- 2009 Invited speaker, Hong Kong Nanosymposium, Hong Kong, P. R. China
- 2009 Invited keynote speaker, Forties International Society for Cosmetic Laser Surgeons, Boston, MA
- 2010 Moderator, Symposium "Genetic and Epigenetic Regulation of Eye Development and Disease – the Future of Vision Research", Association of Research in Vision and Ophthalmology Annual Meeting, Ford Lauderdale, FL
- 2010 Invited speaker, US-China Networking Lunch, Association of Research in Vision and Ophthalmology Annual Meeting, Ford Lauderdale, FL

- 2010 Invited speaker, "New frontiers in glaucoma neuroprotection", XIX Biennial Meeting of the International Society for Eye Research, Montreal, Canada
- 2011 Invited keynote speaker, Japanese Society of Ophthalmology Annual Meeting, Japan
- 2011 Invited speaker, Department of Ophthalmology Seminar, Eye and ENT Hospital, Shanghai, China

PART III: Bibliography

Original Articles

1. **Chen DF**, Jhaveri S & Schneider GE. Intrinsic changes in developmental retinal neurons result in regenerative failure of their axons. *Proc. Natl. Acad. Sci.* 1995; 92, 7287-7291. (see comments on *Science* 1995; 269: 925).
2. Wu M, **Chen DF**, Sasaoka T & Tonegawa S. Neural tube defects and abnormal brain development in F52-deficient mice. *Proc. Natl. Acad. Sci.* 1996; 93: 2110-2115.
3. Tsien JZ., **Chen DF**, Gerber D, Tom C, Mercer EH, Anderson DJ, Mayford M, Kandel ER & Tonegawa S. Subregion- and cell type- restricted gene knockout in mouse brain. *Cell* 1996; 81, 1317-1327.
4. **Chen DF**, Schneider GE, Martinou J-C & Tonegawa S. *Bcl-2* promotes regeneration of severed axons in mammalian CNS. *Nature* 1997; 385, 434-439 (see comments on *Nature* 1997; 385, 391-392).
5. Shen J, Bronson TB, **Chen DF**, Xia W, Selkoe DJ & Tonegawa S. Skeletal and CNS defects in *Presenilin-1* deficient mice. *Cell* 1997; 89, 629-640.
6. Iwasato T, Erzurumlu RS, Huerta PT, **Chen DF**, Sasaoka T, Ulupinar E & Tonegawa S. NMDA receptor-dependent refinement of somatotopic maps. *Neuron* 1997; 19: 1201-1210.
7. Zhou, L., Connors, T., **Chen, DF**, Murray, M., Tessler, A., Kambin, P. & Saavedra, R. A. Red nucleus neurons of *Bcl-2* overexpressing mice are protected from cell death induced by axotomy. *Neuroreport* 1999; 10: 3417-3427.
8. Holm, K. H., Cicchetti, F., Bjorklund, L., Boonman, Z., Tandon, P., Costantini, L. C., Deacon, T. W., Huang, X., **Chen, DF**, Isacson, O. Enhanced axonal growth from fetal human *Bcl-2* transgenic mouse dopamine neurons transplanted to the adult rat striatum. *Neuroscience* 2001; 104, 397-405.
9. Huang X, Wu D-Y, Chen G, Manji H, and **Chen DF**. Support of retinal ganglion cell survival and axon regeneration by lithium via a *Bcl-2*-dependent mechanism. *Invest. Ophthalmol. Vis. Sci.* 2003; 44, 347-354.
10. Lu C, Huang X, Ma HF, Gooley JJ, Aparacio J, Roof DJ, Chen C, **Chen DF**, and Li T. Normal Retinal Development and Retinofugal Projections in Mice Lacking the Retina-Specific Variant of AbLIM. *Neuroscience* 2003; 120, 121-131.
11. Kinouchi R, Takeda M, Yang L, Wilhelmsson U, Pekny M, and **Chen DF**. Robust neural integration and nerve regeneration from retinal transplants in mice deficient in GFAP and vimentin. *Nature Neuroscience* 2003; 6, 863-868.
12. Yang L, Bula D, Arroyo JG, and **Chen DF**. Preventing retinal detachment-associated photoreceptor cell loss in *Bax*-deficient mice. *Invest. Ophthalmol. Vis. Sci.* 2004; 45, 648-654.
13. Cho KS, Yang L, Ma HF, Lu B, Huang X, Pekny M, and **Chen DF**. Re-establishing the regenerative potential of CNS axons in adult mice. *J Cell Sci.* 2005; 118, 863-872.
14. Arroyo JG, Yang L, Bula D, and **Chen DF**. Retinal biopsy techniques for the removal of retinal tissue fragments. *Ophthalmic Surg Lasers Imaging.* 2005; 36, 76-78.
15. Jiao J, Huang X, Feit RA, Snider WD, and **Chen DF**. *Bcl-2* signaling Ca^{2+} to stimulate the intrinsic regenerative capacity of CNS axons. *EMBO J.* 2005; 24, 1068-1078.
16. Arroyo JG, Yang L, Bula D, and **Chen DF**. Photoreceptor apoptosis in human retinal detachment. *Am J Ophthalmology.* 2005; 139, 605-610.

17. Feit-Leichman RA, Kinouchi R, Kern TS, Mohr S, and **Chen DF**. The Mouse Model of Diabetic Retinopathy: Vascular Damage without Müller Glial Cell Activation and Neuronal Loss. *Invest. Ophthalmol. Vis. Sci.* 2005; 46, 4281-4287.
18. Koprivica V, Cho KS, Park JB, Yiu G, Atwal J, Gore B, Kim JA, Lin E, Tesser-Lavigne M, **Chen DF**, and He Z. EGFR Activation Mediates Inhibition of Axon Regeneration by Myelin and Chondroitin Sulfate Proteoglycans. *Science* 2005; 310,106-10.
19. Nakazawa T, Matsubara A, Noda K, Hisatomi T, She H, Skondra D, Miyahara S, Sobrin L, Thomas KL, **Chen DF**, Grosskreutz CL, Hafezi-Moghadam A, Miler JW. (2006) Characterization of cytokine responses to retinal detachment in rats. *Mol Vis.* 12, 867-878.
20. Nakazawa T, Takeda M, Lewis GP, Cho K-S, Jiao J, Wilhelmsson U, Fisher SK, Pekny M, **Chen DF***, Miller JW*. (2007) Attenuated Glial Reactions and Photoreceptor Degeneration after Retinal Detachment in Mice Deficient in Glial Fibrillary Acidic Protein and Vimentin. *Invest. Ophthalmol. Vis. Sci.* 48:2760-2768 (*co-corresponding authors).
21. Takeda M, Takimiya A, Jiao J, Cho KS, Trevion SG, Matsuda T, and **Chen DF**. (2008) Alpha-aminoadipate induces Photoreceptor Regeneration and Progenitor Cell Properties of Muller Glia in Adult Mice. *Invest Ophthalmol Vis Sci.* 49(3):1142-1150.
22. Tukker B, Klassen H, Yang L, **Chen DF**, and Young MJ. Elevated MMP Expression in the MRL Mouse Retina Creates a Permissive Environment for Retinal Regeneration. (2008) *Invest Ophthalmol Vis Sci.* 49, 1686-1695.
23. Verardo M, Lewis GP, Takeda M, Linberg KA, Byun J, Luna G, Wilhelmsson U, Pekny M, **Chen DF**, Fisher SK. Abnormal Reactivity of Mueller Cells After Retinal Detachment in Mice Deficient in GFAP and Vimentin. (2008) *Invest Ophthalmol Vis Sci.*; 49(8):3659-3665.
24. Cho K and **Chen DF**. Promoting optic nerve regeneration in adult mice with pharmaceutical approach. (2008) *J Neurochem Res.* 33(10):2126-2133.
25. Jiao J and **Chen DF**. Niche Astrocytes Stimulate Neurogenesis from Dormant Neural Progenitors in Non-conventional Neurogenic Regions of the Adult CNS. (2008) *Stem Cells.* 26(5):1221-1230.
26. Jiao J, Feildheim D, and **Chen DF**. Ephrins as negative regulators of adult neurogenesis in diverse CNS regions. (2008) *Proc. Natl. Acad. Sci.* 105(25):8778-8783.
27. Rao RC, Tchedre KT, Fang Y, Coleman N, Marquez VE, and **Chen DF**. Dynamic Patterns of Histone Lysine Methylation in the Developing Retina. (2010) *Invest Ophthalmol Vis Sci.*; 51(12): 6784-6792.
28. Chen H, Wei X, Cho K-S, Chen G, Sappington R, Calkins DJ, and **Chen DF**. Optic Neuropathy Due to Microbead-Induced Elevated Intraocular Pressure in the Mouse. (2011) *Invest Ophthalmol Vis Sci.* 52(1):36-44.
29. Gregory MS, Hackett CG, Abernathy EF, Lee KS, Saff RR, Hohlbaum AM, Moody SL, Hobson MW, Jones A, Kolovou P, Karray S, Giani A, John SWM, **Chen DF**, Marshak-Rothstein A, and Ksander BR. Opposing roles for membrane bound and soluble fas ligand in glaucoma-associated retinal ganglion cell death. (2011) *Plos One* 6(3):1-13.
30. Wei X, Yu Z, Cho K-S, Chen H, Wang X, and **Chen DF**. Neuroglobin: Endogenous Neuroprotectant for Retinal Ganglion Cells against Glaucomatous Damage. (2011) *American J Path.* In press.

Reviews, Chapters, and Editorials:

1. **Chen DF** & Tonegawa, S. Why do mature CNS neurons of mammals fail to re-establish connections following injury – functions of bcl-2. (1998) *Cell Death and Differentiation*. 5, 816-822.
2. Pekny M, Pekna M, Wilhelmsson U, & **Chen, DF**. Astroglial cells at the controls? (2004) *Trends in Neurosci*. 27, 243-244.
3. **Chen DF** and Cho K-S. Optic neuropathy and ganglion cell degeneration in glaucoma – Mechanisms and therapeutic strategies. (2008) *Mechanisms of the Glaucomas*. Eds. Barnstables C.; Shields M.B., Tink J.T.; Human Press.
4. Rao RC and **Chen DF**. Nanomedicine and optic nerve regeneration – implications for ophthalmology. (2011) *US Ophthalmic Rev*. 4(1): 110-114.

Patents:

Schneider, G. E., Chen, DF, Tonegawa, S., & Jhaveri, S. Methods of controlling axonal growth. MTE-199CP.

Chen, DF, Chen J, & Chen H. Therapeutics that target autoimmunity for treating glaucoma and optic neuropathy. US provisional application 61/447.379

Chen, DF Composition for controlling axonal outgrowth. US provisional application 61/447.314