PART I: General Information

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-	Assistant Professor, Department of Ophthalmology, Harvard Medical School
1998-2006	Assistant Scientist, Schepens Eye Research Institute, Harvard Medical School
2006-	Associate Scientist, Schepens Eye Research Institute, Harvard Medical School

Major Administrative Responsibility:

2002	Ad hoc reviewer, NIH Center for Scientific Review, the Molecular, Developmental, and Cellular Neuroscience Integrated Review Group
2004-	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
2005	Ad hoc reviewer, Glaucoma Research Foundation Grant
2005	Ad hoc reviewer, The Welcome Trust, Molecular and Cellular Neuroscience, Science program

Major Committee Assignments:

2000-2004	Chair, Safety and Use Committee for Gene Expression and Delivery System, Schepens Eye Research Institute
1999-	Member, Training committee, Schepens Eye Research Institute

2000-	Member, Curriculum committee, Training Program in Molecular Bases of Eye Disease, Harvard Medical School
2001-	Member, Research planning and review committee, Schepens Eye Research Institute
2004-	Member, Committee on Microbiological Safety, Harvard Medical School
2005-	Technology transfer committee, Schepens Eye Research Institute

Professional Society Involvement:

1989-1990	American Society for Anatomical Sciences, member
1989-	Society for Neuroscience, member
2000-	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

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 injures 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, Principle investigator, "Regulation of Neural Differentiation by Foundation Bcl-2"
2000-2006	NIH/NEI, principle investigator, "Molecular Mechanisms Underlying Optic Nerve Regeneration"
2001	Lilly Center, principle investigator, Inhibitory Effect of Myelin on CNS Regeneration
2001-2005	Juvenile Diabetes Research Foundation, "Neural and Glial Contribution to Early Research Foundation Diabetic Retinopathy"
2001-2002	Department of the Army, "Regeneration of the Damaged CNS"
2002-2003	PDA Foundation for Pharmaceutical Sciences, "Development of a Non-viral Gene Delivery Method for CNS Repair."
2002-2003	The Massachusetts Loins Eye Research Fund, Inc., "Promotion of Neural Graft Integration in the Retina by Mutating Vimentin/GFAP Genes in Mice."
2003-2005	Department of Defense, "Promoting Retinal Neuron Survival and Optic Nerve Regeneration with Lithium."
2004-2006	Department of Defense, "Novel treatments to controlling neural damage and inflammatory response in laser induced retinal injury."
2005-2007	Harvard Stem Cell Institute, "Neural stem/progenitor cell transplantation for retinal degeneration."

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

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

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

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 Invited speaker, Department of Neurobiology and Anatomy, MCP, Hahnemann University, Philadelphia, PA.
1999 Invited speaker, Department of Psychiatry and Neuroscience, Wayne State University, Detroit, MI.
2000 Invited speaker, Joslin Diabetes Center, Harvard Med. School, Boston, MA
2001 Invited speaker, Neuroscience Seminar Series, Children's Hospital, Department of Neurology, Harvard Medical School, Boston, MA.
2001 Invited speaker, 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
2004 Invited speaker, 4th Asian Pacific Symposium on Neural Regeneration, Osaka, Japan
2005 Invited speaker, Neuroscience Seminar Series, Massachusetts General Hospital, Boston, MA
2005 Invited speaker, Visiting Professor Lecture Series, New York Eye and Ear Infirmary, New York, NY
2005 Invited speaker, Tissue Bioengineering and Regenerative Medicine, Symposium at the 141st Annual Meeting for the American Ophthalmology Society; Sea Island, GA

2006 Invited speaker, “Seminar in Basic Ocular Science,” Department of Ophthalmology, Mount Sinai School of Medicine, New York, NY

2006 Invited speaker, Academic Seminar Series, the Vanderbilt Eye Institute, Vanderbilt University Medical Center, Nashville, TN

PART III: Bibliography

Original Articles

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).

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.

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.

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).

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.

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.

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.

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 tat striatum. ***Neuroscience*** 2001; 104, 397-405.

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.

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.

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.

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.

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.

Arroy 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.

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.

Arroy JG, Yang L, Bula D, and Chen DF. Photoreceptor apoptosis in human retinal detachment. ***Am J Ophthalmology.*** 2005; 139, 605-610.

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.

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.

Reviews, Chapters, and Editorials:

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.

Pekny M, Pekna M, Wilhelmsson U, & Chen, DF. Astroglial cells at the controls? (2004) ***Trends in Neurosci.*** 27, 243-244.

Patents

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

Chen, DF, Takeda M., & Cho K-S. (2003) Methods and composition for stimulating axon regeneration and cell replacement therapy. ERM-106.60 (pending).