BIOGRAPHICAL SKETCH

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NAME: Seiji B. Shibata

eRA COMMONS USER NAME (credential, e.g., agency login): sbshibata

POSITION TITLE: Assistant Professor of Otolaryngology

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)*	Completion Date MM/YYYY	FIELD OF STUDY
Kansai Medical University, Hirakata, Japan	MD	04/2002	Medicine
Otolaryngology Residency, Kansai Medical University Hospital		03/2007	Otolaryngology
Kansai Medical University Graduate School	PhD	04/2007	Basic medical science in Otolaryngology
Postdoctoral fellowship, University of Michigan Dept. of Otolaryngology		03/2011	Oto-pathology
Otolaryngology Residency, University of Iowa Hospital and Clinics		06/2018	Otolaryngology
Neurotology Fellowship, University of Iowa Hospital and Clinics		06/2020	Neurotology

A. A. Personal Statement

I am a surgeon-scientist trained in neurotology/skull base surgery and molecular biology. My long-term research goal is to elucidate the mechanism of various forms of hearing loss and develop novel molecular therapies to treat deafness. Our lab investigates cellular reprogramming of cochlear glial cells to generate induced SGNs and the glial cell response to acute spiral ganglion neuron (SGN) degeneration. This work investigating the processes of SGN degeneration and regeneration may provide the groundwork for future translational research to treat human auditory neuropathy and neural deafness. My background is unique in that I have finished an Otolaryngology residency and Ph.D. in Japan and have done extensive research in nerve regeneration and auditory gene therapy as a postdoctoral fellow and research investigator at the University of Michigan with Dr. Yehoash Raphael (*Exp Neurol 2010* and *Sci Rep 2015*). I further chose to pursue an Otolaryngology residency at the University of Iowa to become a surgeon-scientist in the USA. Drs. Richard Smith and Marlan Hansen were my research mentors at Iowa. Dr. Smith and I demonstrated that viral-mediated miRNA gene therapy could attenuate hereditary hearing loss in the *Beethoven* mouse, which is the murine model for human hearing loss DFNA36. This miRNA gene therapy was effective in neonatal and adult mutant mice (AJHG 2016, *MT 2019,* and *LSA 2022*). Dr. Hansen and I investigated the effects of NeuroD1 on the proliferation of Schwann cells (Laryngoscope 2020). Since moving to the University of Southern California, I assembled a mentorship committee with expertise in regenerative neuroscience and developmental and stem cell biology, which suits my current research and career development goals. As a practicing neurotologist, I encounter patients with profound deafness daily and am passionate about improving their treatment outcomes through my research. My track records demonstrate my capability of starting and accomplishing productive research and my commitment to science. With the guidance of my research committee and the supportive research environment at USC, I am ideally set to pursue my research aspirations and goals.

B. Positions, Scientific Appointments, and Honors

Employment

03/2011-06/2011 Research Investigator, Kresge Hearing Research Institute University of Michigan
Dept. of Otolaryngology-Head & Neck Surgery, Ann Arbor, MI
08/2020-present Assistant Professor, University of Southern California
Dept. of Otolaryngology Head & Neck Surgery, Los Angeles, CA

Other Experience and Professional Memberships

2002-present Japanese National Medical Board, permanent - Japanese National Medical Board
2007-present Board Certified, Otolaryngology - ORL Society of Japan (Certificate#0145193)
2007-present Member, Association for Research in Otolaryngology
2009-present Educational Commission of Foreign Medical Graduates Certification
2018-present State of Iowa Medical License (Certificate# MD-45151)
2019-present Board Certified, Otolaryngology - American Board of Otolaryngology (Certificate#23268)
2020-present State of California Medical License (Certificate#168954)

Honors

2006 Sakurane Hiroko Award, Kansai Medical University Alumni Association, Moriguchi, Japan
2007 Tomiko Fujiwara Award, Kansai Medical University Alumni Association, Moriguchi, Japan
2009 Sakurane Hiroko Award for best scientific publication
2013 Travel Grant Award, ARO Mid-Winter Meeting, Baltimore MD
2013 Alfreda Van Wart Resident Research Award (First place), Resident Research Day, Iowa City IA
2013 AAO-HNSF Resident Research Award
2014 Travel Grant Award, ARO Mid-Winter Meeting, San Diego CA
2014 Alfreda Van Wart Resident Research Award (First place), Resident Research Day, Iowa City IA
2016 First Place Temporal Bone Dissection, Iowa City IA
2017 First Place Temporal Bone Dissection, Iowa City IA
2017 University of Iowa Inventor Award
2018 First Place Temporal Bone Dissection, Iowa City IA
2018 University of Iowa Inventor Award
2022 Clinician-Scientist Award, American Otological Society Research Foundation, FL, USA
2024 Joseph Gordon-Levitt Award, University of Southern California, Los Angeles, USA

C. Contributions to Science

1. Nerve maintenance and regeneration in the damaged cochlea. The retraction of afferent innervation follows the degeneration of auditory hair cells. Cochlear implantation is the only therapy currently available for cases with severe or complete loss of hair cells. To enhance the therapeutic benefits of a cochlear implant, it is necessary to attract nerve fibers back into the cochlear epithelium. We demonstrated that forced expression of the neurotrophin gene BDNF or NTF in epithelial or mesothelial cells that remain in the deaf ear induces robust regrowth of nerve fibers towards the cells that secrete the neurotrophin and results in re-innervation of the sensory area. The process of neurotrophin-induced neuronal regeneration is accompanied by significant preservation of the spiral ganglion cells. The ability to regrow nerve fibers into the basilar membrane area and protect the auditory nerve will enhance the performance of cochlear implants and augment future cell replacement therapies such as stem cell implantation or induced transdifferentiation.

a. **Shibata SB**, Cortez SR, Beyer LA, Wiler JA, Di Polo A, Pfingst BE, et al. Transgenic BDNF induces nerve fiber regrowth into the auditory epithelium in deaf cochleae. Exp Neurol. 2010;223(2):464-72. PMID: 20109446

b. **Shibata SB**, Budenz CL, Bowling SA, Pfingst BE, Raphael Y. Nerve maintenance and regeneration in the damaged cochlea. Hearing Research. 2011 Nov; 281(1-2):56-64. PMID: 21596129

2. RNAi gene therapy for Hereditary Hearing loss. Hearing impairment is the most common sensory deficit, often caused by the expression of an allele carrying a single dominant missense mutation. We demonstrated that a single intracochlear injection of an artificial microRNA carried in a viral vector could slow the progression of hearing loss for up to 35 weeks in *Beethoven* mouse, a murine model of non-syndromic human deafness caused by a dominant gain-of-function mutation in the *Tmc1* (transmembrane channel-like1) gene. We also elucidated whether this therapeutic approach is feasible in the mature *Beethoven* murine cochlea since the successful restoration of hereditary hearing

thus far has been limited to treatment during the neonatal stage. RNAi-mediated gene therapy prevents progressive hearing loss and morphological degeneration within a defined temporal window in the adult *Beethoven* mouse. This was the first report of successful gene therapy in mature mice with inherited deafness, leading to substantial hearing preservation for 20 weeks.

a. **Shibata SB,** Ranum PT, Moteki H, Pan B, Goodwin AT, Goodman SS, Abbas PJ, Holt JR, and Smith RJH. RNA interference prevents autosomal dominant hearing loss. The American Journal of Human Genetics. 2016 Jun 2;98(6):1101-13. PMID: 27236922

b. Yoshimura H, **Shibata SB**, Ranum PT, Hideaki Moteki and Smith RJH. Targeted Allele Suppression Prevents Progressive Hearing Loss in the Mature Murine Model of Human TMC1 Deafness. Molecular Therapy 2019 Jan 7; PMID: 30686588

c. Iwasa Y, Klimara MJ, Yoshimura H, Walls, WD, Omichi R, West CA, **Shibata SB**, Ranum PT, and Smith RJH. Mutation-agnostic RNA interference and engineered replacement rescue *Tmc1*-related hearing loss. Life Sci Alliance 2022 Dec 27 PMID:36574989

3. Development of atraumatic inner ear vector delivery in adult mice. A critical step of inner ear gene therapy is the ability to deliver transgenes to target tissue without inducing additional inner ear trauma or hearing loss. Due to its high safety profile, the adeno-associated virus has recently become the inner ear gene delivery workhorse. Historically, murine inner ear delivery has been challenging secondary to poor transduction efficiency and minimal distribution of the viral vector throughout the cochlear duct. We established an injection method that addresses these previous issues. Adding a vent fenestration in the posterior semicircular canal and injecting through the round window membrane allows a wide distribution of the viral vector and enhances conventional AAV vector-mediated hair cell transfection. Also, in the neonatal murine model, we were the first to identify inner transduction with the AAV9 serotype vector following systemic injection through the temporal vein. This method allows bilateral transduction without manipulation of the inner ear.

a. **Shibata SB**, Yoshimura H, Ranum PT, Goodwin AT, and Smith RJH. Intravenous rAAV2/9 injection for murine cochlear gene delivery. Scientific Reports. 2017 2017 Aug 29;7(1):9609 PMID: 28852025

b. **Shibata SB**, Yoshimura H, Ranum PT, and Smith RJH. Enhanced viral-mediated cochlear gene delivery in adult mice by combining canal fenestration with round window membrane inoculation. Scientific Reports. 2018 Feb 14;8(1):2980 PMID: 29445157

4. Establishing neonatal deafening model with aminoglycosides. Animal models are essential to a better understanding of the pathophysiology of deafness and developing therapeutics to restore hearing. In this project, we demonstrate a method to inject neomycin locally into the scala media space of neonatal mice. This single direct injection protocol results in profound hearing loss with rapid total hair cell ablation, immediate auditory neurite damage, and SGN density loss occurring as early as two weeks. This method allows us to study a near-complete severe lesion across the sensory epithelium and secondary nerve damage in neonatal and adult mice.

a. Cutri RM, Lin J, Nguyen NV, Shakya D, **Shibata SB**. Neomycin-induced deafness in neonatal mice. J Neurosci Methods 2023 Apr7 PMID 37031766.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/seiji.shibata.2/bibliography/public/

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

Ongoing Research Support
American Otological Society Clinician Scientist Award (PI) 2021-2024
Role: Principle Investigator
Cellular reprogramming of peripheral glial cells to generate auditory neurons.

Triological Society Career Development Award (PI) 2023-2024
Role: Principle Investigator

Optimizing Targeted Delivery of AAVs into Cochlear Glial Cells

NIDCD K08DC021750-01 Award (PI) 2024-2029
Role: Principle Investigator
Cellular reprogramming of peripheral glial cells to generate auditory neurons

Completed Research Support

Japanese Ministry of Education, Culture, Sports, Science, and Technology (Grant-in-Aid for Young Scientists (B) 40373112) Toshio Yamashita (PI) 2005-2007
Role: Resident, Graduate Student

NIH-NIDCD T32DC005356 Marci Lesperance (PI) 2007-2010
Role: Postdoctoral fellow

AAO-HNSF Resident Research Award Seiji Shibata (PI) 2013-2014
Role: Principle Investigator
Using RNA-interference to rescue progressive hearing loss in the Tmc1 mouse

NIH-NIDCD DC002842 Richard Smith (PI) 2013-2020
Role: Research fellow
Autosomal Dominant Non-Syndromic Hearing Loss