CURRICULUM VITAE

PERSONAL INFORMATION

Name Haiyan Fu
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EDUCATION

03/1996-02/2000 Dept of Pediatrics, University of North Carolina at Chapel Hill (postdoc)
09/1995 Institute for Animal Health, UK, **Ph.D** (PhD student, virology)
08/1988 Chinese Acad. Prevent. Med., Beijing P.R. China, **MSc** (Medical microbiology)
08/1981 Shandong Med. Univ., Shandong, P.R. China. **Diploma** (Advanced epidemiology)
08/1979 Shandong Med. Univ., Shandong, P.R. China, Diploma (Medicine)

PROFESSIONAL POSITIONS

11/2004 – Principal Investigator, Center for Gene Therapy, The Research Institute at Nationwide Children's Hospital

05/2000–10/2004 Research assistant professor**,** Divisionof Genetics and Metabolism, Dept of Pediatrics, University of North Carolina at Chapel Hill

09/91-08/1092 Visiting Scientist, Robens Inst, University of Surrey, UK

09/88-08/1991 Research scientist, Institute of Microbiology. & Epidemiology. Chinese Acad. Prevent. Med., Beijing, P.R. China.

09/79-08/1985 Resident (physician) and instructor. Department of Infectious Diseases and Epidemiology. Taishan Medical School, Shandong, P.R. China.

PROFESSIONAL MEMBERSHIPS

General Microbiology Society (1992-1996)
American Society of Gene and Cell Therapy (1999-)
National MPS Society (2005-)
American Society of Human Genetics (2007-)
Global Organization for Lysosomal Storage Diseases (2008-)
Society for Neuroscience (2009-)
American Association of Immunologists (2009-)

RESEARCH EXPERIENCE

1998 – Gene therapy targeting the root causes for the treatment of neuropathic lysosomal storage diseases (LSDs):

- Optimization of AAV-mediated CNS gene delivery (1998-): development of 1) intracisternal AAV gene delivery, and 2) mannitol-facilitated AAV CNS delivery via systemic route.

- Systemic rAAV9-hNAGLU gene delivery for the treatment of MPS IIIB (1998-, PI): **Phase 1/2 gene therapy clinical trial** ongoing at Nationwide Children's Hospital. (IND#16671, NCT03315182).
- Systemic scAAV9-hSGSH gene delivery for the treatment of MPS IIIA (2011-): A **Phase 1/2 gene therapy clinical trial** is ongoing (IND#: 16850, NCT02716246) at Nationwide Children's Hospital.
- Systemic scAAV9-hIDS gene delivery for MPS II (2013-): IND has been approved by the FDA for a **Phase 1/2 gene therapy clinical trial** (IND#: 17838), wich will begin in 2nd quarter in 2018 at Nationwide Children's Hospital.
- Systemic scAAV9-hIDUA gene delivery for MPS I (2013-): Pre-IND request will be submitted to the FDA in the 3st quarter, 2018, for a **Phase 1/2 clincal trial,** in collaboration with Dr. Joseph Muenzer at UNC-CH.
- Systemic scAAV9-hGNS gene delivery for MPS IIID (2013-): We have made the therapeutic AAV-hGNS vector for the treatment of MPS IIID, and are seeing collaboration to move it forward towards clinical trial.
- Second generation AAV vectors for treating MPS IIIA and MPS IIIB (2012-, PI):
    - MPS IIIA: Awarded Orphan Drug Designation by the FDA. Pre-IND request was submitted to the FDA to schedule the Pre IND meeting, for a **Phase 1/2 clinical trial** at UNC-CH (PI: Muenzer).
    - MPS IIIB: Pre-IND request will be submitted to the FDA in 2017, to schedule the Pre IND meeting, for a Phase 1/2 clinical trial.

2015- Develop novel blood-brain-barrier-crossing AAV vectors by capsid modification.

1998- Mechanisms of neuropathology in neuropathic LSDs: neuro-inflammation, nurodegeneration, metabolic impairments.

2013- Overcome pre-existing anti-AAV antibodies for clinical application of AAV gene therapy in humans.

We have identified an effective immuno-modulation regiman for depleting pre-existing AAV antibodies in a mouse model. Further testing in non-human primates has been initiated.

2010- Identification of effective biomarkers and novel therapeutic targets for neuropathic disorders and type 1 diabetes

- Blood-brain transcriptional links in neuropathic LSDs and Alzheimer's disease: biomarker potentials of blood transcriptional signatures.
- Blood transcriptional profiles and disease mechanisms of type 1 diabetes.
- Metabolomic impairments and biomarker potential of serum motabolomics profiling for neuropathic LSDs.

1996-1998: Potential of Epstin-Barr virus episomal vector for gene (UNC-CH: Postdoc project)

1992-1995: Mechanisms of bluetongue virus infection, dissemination and transmission in the vector, *Culicoides variipennis* (Diptera:Ceratopogonidae) (Institute for Animal Health, UK: PhD dissertation)

INTELLECTURAL PROPERTY

- **Patent applications:** Product and methods for delivery of polynucleotides by adeno-associated virus for lysosomal storage disorders (Pub. No.2010-014-02 and 2010-014-03; Pub. Date: Dec. 5, 2013)(under review)
- **Licensing:** NCH-RI licensed our AAV9 gene therapy products for MPS IIIA and MPS IIIB to Abeona Therapeutics Inc.

PUBLICATIONS

1. Fu, H, Meadows, AS, Pineda, RJ, Mohney, RP, Stirdivant, S, and McCarty, DM (2017). Serum global metabolomics profiling reveals profound metabolic impairments in patients with MPS IIIA and MPS IIIB. *Metabolic brain disease*. DOI: 10.1007/s11011-017-0009-1
2. **Fu H**, Meadows AS, Ware T, Mohney RP, McCarty DM (2017) Near complete correction of profound metabolomic impairments corresponding to functional benefit in MPS IIIB mice after IV rAAV9-hNAGLU gene delivery. *Mol Ther*. DIO: 10.1016/j.ymthe.2016.12.025 (in press)
3. Velazquez VM, Meadows AS, Pineda RJ, Camboni M, McCarty DM, **Fu H** (2017) Effective Depletion of Pre-existing anti-AAV Antibodies Requires Broad Immune Targeting. Mol Ther Clin Methods Dev. (in press)
4. **Fu H**, Cataldi PC, Ware TA, Zaraspe K, Meadows AS, Murrey DA, McCarty DM (2016) Functional correction of neurological and somatic disorders at later stages of disease in MPS IIIA mice by systemic scAAV9-hSGSH gene delivery. *Mol Ther,* 3:16036
5. Truxal KV, **Fu H**, McCarty DM, McNally KA, Kunkler KL, Zumberge NA, Martin L, Aylward SC, Alfano LN, Berry KM, Lowes LP, Corridore M, McKee C, McBride KL, Flanigan KM (2016) A prospective one-year natural history study of mucopolysaccharidosis types IIIA and IIIB: Implications for clinical trial design. Mol Genet Metab. 119(3):239-248.
6. **Fu H**, McCarty DM (2016) Crossing the blood-brain-barrier with viral vectors. Curr Opin Virol. 21:87-92.
7. Meadows AS, Duncan FJ, Camboni M, Waligura K, Montgomery C, Zaraspe K, Naughton BJ, Bremer WG, Shilling C, Walker CM, Bolon B, Flanigan KM, McBride KL, McCarty DM, **Fu H** (2015) A GLP-Compliant Toxicology and Biodistribution Study: Systemic Delivery of an rAAV9 Vector for the Treatment of Mucopolysaccharidosis IIIB. *Hum Gene Ther Clin Dev,* 26**,** 228-42.
8. Duncan FJ, Naughton BJ, Zaraspe K, Murrey DA, Meadows AS, Newsome DE, White P, **Fu H**, McCarty DM (2015) Broad functional correction of molecular impairments by systemic delivery of scAAVrh74-h*SGSH* gene delivery in MPS IIIA mice. *Mol Ther*. 23(4):638-47. DIO: 10.1111/php.12441

9. Naughton BJ, Duncan FJ, Murrey DA, Meadows AS, Newsom DE, Stoicea N, White P, Scharre DW, McCarty DM, **Fu H** (2015) Blood genome-wide transcriptional profiles reflect broad molecular impairments and strong blood-brain links in Alzheimer's disease. *J Alzheimer's Dis* 43(1):93-108, DOI: 10.3233/JAD-140606
10. Murrey DA, Naughton BJ, Duncan FJ, Meadows AS, Ware TA, Campbell KJ, Bremer WG, Walker CM, Goodchild L, Bolon B, la Perie K, Flanigan KM, McBride KL, McCarty DM, **Fu H** (2014) Feasibility and Safety of Systemic rAAV9-hNAGLU Delivery for Treating Mucopolysaccharidosis IIIB: Toxicology, Biodistribution, and Immunological Assessments in Primates. *Hum Gene Ther Clin Dev* 25(2):72-84.
11. McCarty DM, **Fu H** (2014) Gene therapy for neurodevelopmental disorders. *eLS*, John Wiley & Sons, Ltd (DOI: 10.1002/97804700 15902.a0025276).
12. Naughton BJ, Duncan FJ, Murrey D, Ware T, Meadows A, Mccarty DM, **Fu H** (2013). Amyloidosis, Synucleinopathy, and Prion Encephalopathy in a Neuropathic Lysosomal Storage Disease: the CNS-biomarker Potential of Peripheral Blood. *PLoS One*, 2013. **8**(11): p. e80142.
13. **Fu H,** McCarty DM (2013) Treating Lysosomal Storage Diseases that Affect the Central Nervous System: Overcoming the Blood-brain Barrier. *Current Medical Literature – LSD*, 11(2):33-41
14. Rosas LE, Grieves JL, Zaraspe K, La Perle KM, **Fu H**, McCarty DM (2012) Patterns of scAAV Vector Insertion Associated With Oncogenic Events in a Mouse Model for Genotoxicity. Mol Ther. Doi: 10.1038/mt.2012.197
15. **Fu H**, Bartz JD, Stephens RL Jr, McCarty DM (2012) Peripheral Nervous System Neuropathology and Progressive Sensory Impairments in a Mouse Model of Mucopolysaccharidosis IIIB. *PLoS ONE* 7(9): e45992. DOI:10.1371/journal.pone. 0045992
16. **H. Fu**, J. DiRosario, S. Killedar, K. Zaraspe, DM. McCarty (2011) Correction of Neurological Disease of Mucopolysaccharidosis IIIB in Adult Mice by Trans-Blood-Brain-Barrier Gene Delivery. *Mol Ther* 19(6):1025-33
17. DM McCarty, J DiRosario, K Gulaid, S Killedar, A Oosterhof, TH van Kuppevelt, PT Martin, **H Fu** (2011) Differential distribution of heparan sulfate glycoforms and elevated expression of heparan sulfate biosynthetic enzyme genes in the brain of mucopolysaccharidosis IIIB mice. *Metab Brain Dis.* 26(1):9-19
18. S. Killedar, J. DiRosario, E. Divers, PG. Popovich, DM. McCarty, **H. Fu (**2010) Mucopolysaccharidosis IIIB, a lysosomal storage disease, triggers a pathogenic CNS autoimmune response. *J Neuroinflammation* July 16, 7(39)(DOI: 1742-2094-7-39)
19. **H Fu**, J DiRosario, L Kang, J Muenzer, DM McCarty (2010) Restoration of CNS α-*N*-acetylglucosaminidase activity and therapeutic benefits in mucopolysaccharidosis IIIB mice by a single intracisternal rAAV2 vector delivery. *J Gene Med*, 12(7):624-33.
20. DM McCarty, J DiRosario, K Gulaid, J Muenzer, **H Fu** (2009) Mannitol-facilitated CNS entry of rAAV2 vector significantly delayed the neurological disease progression in MPS IIIB mice. *Gene Therapy* 16(11):1340-52
21. J DiRosario, E Divers, C Wang, A Charrier, P Jukkola, J Etter, H Auer, V Best, DL Newsom, DM McCarty, **H Fu** (2009) Innate and adaptive immune activation in the brain of MPS IIIB mouse model. *J. Neuroscience Res*, 87(4):978-990
22. **H Fu,** L Kang, JS Jennings, SS Moy, A Perez, J DiRosario, DM McCarty, J Muenzer (2007) Significantly increased lifespan and improved behavioral performances by rAAV gene delivery in adult Mucopolysaccharidosis IIIB mice. *Gene Therapy*, 14:1065-1077. (corresponding author: **Fu**)

23. **H Fu,** J Muenzer, RJ Samulski, G Breese, J Sifford, X Zeng, DM McCarty (2003) self-complementary adeno-associated virus serotype 2 vector: global distribution and broad dispersion of AAV-mediated transgene eExpression in mouse brain. *Mol. Therapy*. 8(6):911-7
24. DM. McCarty, **H Fu,** PE Monahan, CE Tolson, P Naik, RJ Samulski. (2003). Adeno-associated virus terminal repeat (TR) mutant generates self-complementary vectors to overcome rate-limiting step to transduction *in vivo. Gene Therapy*, 10(26):2112-8.
25. **H Fu,** R.J Samulski, TJ McCown, J Picornell, D Fletcher, J Muenzer (2002) Neurological correction of lysosomal storage in mucopolysaccharidosis IIIB knock-out mouse model by adeno-associated virus-mediated gene delivery. *Mol. Therapy*. 5(1):42-9
26. **H Fu,** CJ Leake, PPC Mertens, PS Mellor (1999) The barriers to bluetongue virus infection, dissemination and transmission in the vector, *Culicoides variipennis* (Diptera:Ceratopogonidae). *Arch. Virol.* 144:747-61
27. ZT Kelleher, **H Fu,** E Livanos, B Wendelburg, S Gulino, J-M Vos (1998) First-generation of mouse artificial episomal chromosomes for shuttling 100 kb of self-replicating human DNA. *Nature Biotechnology*. 16(8):762-8.
28. LA Martin, AJ Meyer, RS O'Hara, **H Fu,** PS Mellor, NJ Knowles, PPC Mertens (1998) Phylogenetic analysis of African horse sickness virus segment 10: sequence variation, virulence characteristics and cell exit. *Arch. Virol-Supplementum.* 14:281-93
29. PP Mertens, JN Burroughs, A Walton, MP Wellby, **H Fu,** RS O'Hara, SM Brookes, PS Mellor (1996) Enhanced infectivity of modified bluetongue virus particles for two insect cell lines and for two Culicoides vector species. *Virology.* 217(2) 582-93
30. **H Fu,** R Cai, M Jia (1991) The distribution of serotypes and biotypes of *Campylobacter jejuni/coli* isolated from ten provinces/cities in China. *Chinese J Epidemiol*. 1:25-28
31. **H. Fu** (1987) *Campylobacter* and Guillain-Barr syndrome *Chinese Zoonosis*

ORAL PRESENTATIONS (2011-)

1. **Fu H,** DiRosario J, Killedar S, Zaraspe, K, McCarty D. Correction of Neurological Disease of Mucopolysaccharidosis IIIB in Adult Mice by rAAV9 Trans-Blood-Brain-Barrier Gene Delivery. ASGCT 15th Annual Meeting. Seattle, WA. May 18-21, 2011 (invited by Sanfilippo Foundation, Switzerland)
2. **Fu H,** DiRosario J, Killedar S, Zaraspe, K, McCarty D. Treating MPS IIIB by rAAV9 trans-blood-brain-barrier gene delivery. MPS 2011 International Congress. Geneva, Switzerland. December 8-10, 2011 (invited speaker)
3. McCarty D (invited speaker), Zaraspe K, Murrey D, Ware T, **Fu H,** Systemic self-complementary AAV9 and AAVrh74 CNS gene delivery in MPS IIIA mice. MPS 2011 International Congress. Geneva, Switzerland. December 8-10, 2011
4. Ware T, Murrey D, McCarty DM, **Fu H.** Normalized survival and permanent restoration of NAGLU activity in the CNS, PNS and somatic tissues in MPS IIIB mice after a single intravenous rAAV9-hNAGLU gene delivery. ASGCT 15th Annual Meeting. Philadelphia. May 16-19, 2012
5. Murrey D, Ware T, Naughton B, Duncan FJ, Campbell K, Walker C, Goodchild L, Flanigan K, McCarty DM, Fu H. Systemic delivery of rAAV9-hNAGLU in adult non-human primates:

efficient CNS and somatic transduction with no detectable toxicity. ASGCT 15th Annual Meeting. Philadelphia. May 16-19, 2012

6. Duncan FJ, Naughton B, Zaraspe K, Murrey D, Ware T, Meadows A, **Fu H**, McCarty DM. Broad correction of molecular impairments by a single systemic rAAVrh74-hSGSH gene delivery in a mouse model of MPS IIIA: links between the brain and peripheral blood. ASGCT 16th Annual Meeting. Salt Lake City, Utah. May 15-19, 2013

7. Naughton B, Duncan FJ, Ware T, Murrey D, Meadows A, McCarty DM, **Fu H.** Peripheral blood white cells present molecular signatures of neurodegeneration and respond to a single intravenous rAAV9-hNAGLU gene delivery in MPS IIIB mice. ASGCT 16th Annual Meeting. Salt Lake City, Utah. May 15-19, 2013

8. **Fu H**, Duncan FJ, Naughton B, Zaraspe K,[1] Murrey D, Ware T, Meadows A, White P, McCarty DM. Correction of broad molecular impairments in a mouse model of MPS IIIA by systemic rAAVrh74-hSGSH gene delivery. WORLDSymposium 2014 - 10th World Symposium on Lysosomal Diseqses. San Diego, CA. Feb. 10-13, 2014

9. **Fu H**, Meadows AS, Duncan FJ, Montgomery C, Waligura K, Camboni M, Bremer WG, Walker CM, Bolon B, Flanigan KM, McBride KL, McCarty DM. An IND-enabling GLP-Toxicology and Biodistribution Study Assessing Systemic rAAV9-hNAGLU Gene Delivery for Treating MPS IIIB: Genotype- and Sex-specific Dose-limiting Acute Liver Toxicity in Male Wild Type C57BL/6 Mice. ASGCT 18th Annual Meeting. New Orleans, LA. May 13-16, 2015

10. Hoffman R, Duncan FJ, Naughton BJ, Meadows AS, Wetzel A, White P, **Fu H.** Broad blood transcriptional abnormalities and complexity of pathophysiology in patients with Type I diabetes. Brisbane, Australia. Oct. 7-10, 2015

11. **Fu H** (invited speaker) CNS Gene therapy approaches for treating neuropathic lysosomal storage diseases. Neurotech 2015. San Francisco, CA. April 7-8, 2015

12. Meadows A, Camboni M, Waligura K, Murrey D, McCarty DM, **Fu H**. Functional Correction of Mucopolysaccharidosis I in Adult Mice by a Systemic rAAV9-IDUA Gene Delivery. WORLDSymposium 2016 - 12th World Symposium on Lysosomal Diseqses. San Diego, CA. Feb. 29- March 4, 2016

13. **Fu H**, Zaraspe K, Meadows A, Murakami N, Camboni M, McCarty DM. Functional benefits of systemic rAAV9-hIDS gene delivery in MPS II mouse model WORLDSymposium 2016 - 12th World Symposium on Lysosomal Diseqses. San Diego, CA. Feb. 29- March 4, 2016

14. **Fu H** (invited speaker) Intravenous gene therapy for MPS IIIA/B. 14th International Symposium on MPS and Related Diseases. Bonn, Germany. July 14-17, 2016

INVITED LECTURES AND SEMINARS (2010-)

1. Mucopolysaccharidosis (MPS) IIIB: CNS Gene Delivery, Neuropathology and Neuroautoimmunity**.** Gene Therapy Center, UNC-CH, Chapel Hill, NC. April, 2010

2. Neuropathic lysosomal storage diseases and CNS gene delivery. Powell Gene Therapy Center, University of Florida. Gainesville, FL. April, 2013

3. Gene therapy for neuropathic lysosomal storage diseases. Gene Therapy Center, UNC-CH, Chapel Hill, NC. October, 2015
4. CNS Gene delivery targeting the root cause of neuropathic lysosomal storage diseases. Translational Science Seminar Series, Nemours Biomedical Research, Alfred I DuPont Hospital for Children. October 3, 2016
5. Gene therapy targeting the root cause for the treatment of neuropathic lysosomal storage diseases. USC Genetic Counseling Fall Symposium, University of South Carolina, Colombia, SC. November 10-11, 2016