BIOGRAPHICAL SKETCH

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NAME: Wang, Lianchun

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POSITION TITLE: Professor

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)	END DATE MM/YYYY	FIELD OF STUDY
Central South University Xiangya School of Medicine, Hunan, China	BS	07/1990	Experimental Medicine
Central South University Xiangya School of Medicine, Hunan, China	MS	07/1993	Physiology & Clin. Biochem.
Heidelberg University, Heidelberg, Germany	MD	12/1999	Med. - Hematology
University of California San Diego, USA	Postdoc. Fellow	07/2004	Cell Biology & Glycobiology

A. Personal Statement

Dr. Wang's research primarily focuses on understanding the biological functions and related structures of heparan sulfate (HS), particularly in areas such as vascular biology, stem cell biology, cancer biology, Alzheimer's disease (AD), and brain injury. Dr. Wang's active research programs have resulted in high-quality papers in prestigious journals, including but not limited to the *Journal of Clinical Investigation*, *BLOOD*, *Journal of Biological Chemistry*, *Nature Methods*, *Cellular & Molecular Proteomics*, *Laboratory Investigation*, *Angewandte Chemie International Edition*, *Journal of Cell Biology*, *Proceedings of the National Academy of Sciences* (*PNAS*) and *Science Advances*. Attracted by the strong vascular biology and neuroscience research programs, Dr. Wang relocated to USF in late 2018 and initiated to study the roles of HS in AD. This transition has been highly successful. Dr. Wang's AD research has been funded by NIA and the Florida State Department of Health. His AD study has published three reviews and four original papers in high-impact journals, including *Science Advances*, *Angew Chem Int Ed Engl*, *Carbohydr Polym and Journal of Am. Physiology*. Importantly, his ongoing studies have uncovered the critical roles of HS in cerebral Aβ clearance, suggesting that down-regulated HS expression in the AD brain may represent a major causative mechanism for Aβ accumulation in patients. He also discovered that the 3-O-sulfation is required for HS to bind and mediate Tau cellular uptake. Dr. Wang is deeply committed to mentoring students across different academic levels and guiding and nurturing them to achieve success in their respective careers.

<u>Ongoing NIH projects in Wang lab</u>:

1RF1AG069039 (Wang, Co-PI) 09/15/20 - 08/15/25
Heparan sulfate 3-O-sulfaiton in transcellular propagation of tauopathy in Alzheimer`s disease.

1RF1AG074289 (Wang, PI) 09/15/21 - 08/15/26
Heparan sulfate proteoglycan in the brain vascular clearance of amyloid-β and Alzheimer's disease

5 U01CA225784 (Wang, PI) 04/13/18 - 03/30/23 (NCE)
Heparan sulfate in prostate cancer

<u>Recent Publications related to Alzheimer`s disease:</u>

1. Zhao J, Zhu Y, Song X, Xiao Y, Su G, Liu X, Wang Z, Xu Y, Liu J, Eliezer D, Ramlall TF, Lippens G, Gibson J, Zhang F, Linhardt RJ, **Wang L***, Wang C*(2020). 3-O-Sulfation of Heparan Sulfate Enhances

Tau Interaction and Cellular Uptake. *Angew Chem Int Ed Engl.* 59(5):1818-1827. PubMed Central PMCID: PMC6982596. (*, co-corresponding author)

2. Zhu, Y, Gandy L, Zhang F, Liu J, Wang C, Blair L, Linhardt FJ, **Wang L** (2022). Heparan sulfate Proteoglycans in Tauopathy. *Biomolecules*. 12 (12): 1792. PMCID: PMC9776397. DOI: 10.3390/biom12121792.
3. Ozsan McMillan I, Li JP, **Wang L** (2023). Heparan Sulfate in Alzheimer's Disease: Aberrant expression and functions in molecular pathways related to amyloid-β metabolism. *Am J Physiol Cell Physiol*. 324(4):C893-C909. doi: 10.1152/ajpcell.00247.2022.
4. Wang ZJ, Patel VN, Song X, Xu Y, Kaminski AM, Doan VU, Su G, Liao Y, Mah D, Zhang F, Pagadala V, Wang C, Pedersen LC, **Wang L,** Hoffman MP, Gearing M, Liu J. (2023). Increased 3-O-sulfated Heparan Sulfate in Alzheimer's disease brain is associated with genetic risk gene HS3ST1. *Science Advances*. In press.

B. Positions and Honors

Positions and Employment

2022 -	Member, American Physiological Society
2020 -	Affiliate Member, Florida International University, Translational Glycobiology Institute, Miami, FL
2018 -	Professor, University of South Florida (USF) Mosani College of Medicine, Dept. of Molecular Pharmacology & Physiology, Tampa, FL
2018 -	Professor and Endowed Chair of Neurovascular Research, USF Mosani College of Medicine, Byrd Alzheimer`s Research Institute, Tampa, FL
2018 -	Professor and Member, USF Mosani College of Medicine, USF Heart Institute, Tampa, FL
2018 -	Collaboration member, Moffitt Cancer Center, Tampa, FL
2017 - 2018	Professor, University of Georgia (UGA), Complex Carbohydrate Research Center and Dept. of Molecular Biology & Biochemistry, Athens, GA
2015 - 2018	Member, UGA, Center for Regenerative Bioscience, Athens, GA
2013 - 2018	Member, UGA, Cancer Center, Athens, GA
2012 - 2017	Associate Professor, UGA, Complex Carbohydrate Research Center and Dept. of Molecular Biology & Biochemistry, Athens, GA
2006 - 2012	Assistant Professor, UGA, Complex Carbohydrate Research Center and Dept. of Molecular Biology & Biochemistry, Athens, GA
2004 - 2006	Assistant Project Scientist, University of California San Diego (UCSD) School of Medicine, Cellular and Molecular Center, La Jolla, CA
2000 - 2004	Postdoc Associate, UDSD School of Medicine, Cellular & Molecular Medicine, La Jolla, CA
1995 - 1999	Research Assistant, Heidelberg University School of Medicine, Dept. of Hematology, Germany
1993 - 1995	Instructor, Central South University, Xiangya Med. School, China

Other Experience and Professional Memberships

2002 - 2004	Member, American Heart Association, Basic Science Council
2002 - 2005	Member, American Society of Hematology
2006 -	Manuscript reviewer, Developmental Cell, PNAS, BLOOD, J Biol Chem, EMBO J, FASEB J, ATVB, ACS Chem Biol., Angiogenesis, Plos One, Glycobiology, Scientific Reports, Neoplasia, Mol. & Cell Proteomics, Nature Communication, et al.
2006	Grant reviewer, Canadian Institutes of Health Research
2007 -	Member, North American Vascular Biology Organization
2007 -	Member, Society for Glycobiology
2007 - 2010	Member, American Association for Cancer Research
2010 -	Member, American Society of Biochemistry and Molecular Biology
2010 -	Member, Chinese Biological Investigators Society

2023 -	Member, Alzheimer`s Association International Society to Advance Alzheimer`s Research and Treatment (STAART)
2013 - 2018	Steering committee member, Cancer Center of University of Georgia
2010 - 2017	Editorial Board member, World Journal of Stem Cells
2021 -	Editorial Board member, Glycobiology
2022 -	Editorial Board member, Proteoglycan Research
2022 -	Editorial Board member, Frontiers in Neuroscience
2013	Grant reviewer, Canadian Foundation for Innovation
2014-	Grant reviewer, NIH Vascular Cell and Molecular Biology (VCMB) Study Section
2015	Grant reviewer, The Brain Tumor Charity UK
2016-	Grant reviewer, NIH Tumor Microenvironment (TME) Study Section
2017-	Grant reviewer, NIH Special Emphasis Panel/Vascular Biology and Hematology
2017-	Grant Reviewer, Georgia CTSA's Pilot Translational & Clinical Studies (PTCS) program
2020	Grant reviewer, Department of Defense Congressionally Directed Medical Research Program (
2020	Grant reviewer, National Research Foundation, Singapore
2021-	NIH ZRG1 F05-D Fellowships: Cell Biology, Developmental Biology and Bioengineering

Honors

2018 -	Endowed USF Chair of Neurovascular Research, USF Mosani College of Medicine
2013	Research Grant Award, Mizutani Foundation, Japan
2007	Georgia Cancer Coalition Distinguished Scholar, Georgia Cancer Coalition
1990	STAR Undergraduate, Central South University - Xiangyang Med. School, China

C. Contribution to Science

1. **HS in Alzheimer`s disease.** 3-O-sulfation is a rare modification that occurs along the HS chain and plays a pivotal role in creating highly specific and high-affinity HS structures for protein-ligand binding. In our recent research, we discovered that 3-O-sulfation significantly enhances the ability of HS to bind to tau and facilitate tau uptake (a-c). In cells where *HS 3-O-sulfotransferase-1* (*Hs3st1*) was knocked out, resulting in reduced 3-O-S levels of HS, both cell surface binding and internalization of tau were reduced (a, b). Moreover, the addition of a 3-O-S HS 12-mer resulted in a reduction in both tau cell surface binding and cellular uptake. NMR titrations revealed that the 3-O-S binding sites were located in the microtubule-binding repeat 2 (R2) and proline-rich region 2 (PRR2) of tau. Our findings demonstrate that the rare 3-O-sulfation enhances tau-HS binding and is likely to promote the transcellular spread of tau, making it a promising target for the development of disease-modifying treatments for AD and other tauopathies. Furthermore, our ongoing studies have revealed that vascular HS is critical for amyloid-β clearance in the brain (c), and increased 3-O-sulfation in AD is associated with the genetic risk gene HS3ST1 (d).
   a. Zhao J, Zhu Y, Song X, Xiao Y, Su G, Liu X, Wang Z, Xu Y, Liu J, Eliezer D, Ramlall TF, Lippens G, Gibson J, Zhang F, Linhardt RJ, **Wang L***, Wang C*. 3-O-Sulfation of Heparan Sulfate Enhances Tau Interaction and Cellular Uptake. *Angew Chem Int Ed Engl.* 2020 Jan 27;59(5):1818-1827. PubMed Central PMCID: PMC6982596. (*, co-corresponding author)
   b. Zhu Y, Gandy L, Zhang F, Liu J, Wang C, Blair LJ, Linhardt RJ, **Wang L** (2022). Heparan Sulfate Proteoglycans in Tauopathy. *Biomolecules*. 12(12):1792. doi: 10.3390/biom12121792.
   c. McMillan I.O., Li, J, and **Wang L** (2023). Heparan Sulfate in Alzheimer's Disease: Aberrant expression and functions in molecular pathways related to amyloid-β metabolism. *Am J Phy*siology, In press.
   d. Wang ZJ, Patel VN, Song X, Xu Y, Kaminski AM, Doan VU, Su G, Liao Y, Mah D, Zhang F, Pagadala V, Wang C, Pedersen LC, **Wang L,** Hoffman MP, Gearing M, Liu J. (2023). Increased 3-O-sulfated Heparan Sulfate in Alzheimer's disease brain is associated with genetic risk gene HS3ST1. *Science Advances*. In press.

2. **HS and axon guidance molecules in angiogenesis**. Through the generation and examination of serial gene knockout mice, we have uncovered a novel proangiogenic pathway involving the axon guidance Slit3-Robo4 signaling (a). Our subsequent studies have demonstrated that endothelial HS plays a crucial role in

promoting vascular development by facilitating the Slit3-Robo4 signaling (b). These findings have not only provided the first evidence of endothelial HS's essential role in modulating vascular development but also suggested a novel link between HS deficiency, disruption of Slit3-Robo4 signaling, and human disease, such as "congenital diaphragm hernia" (b). Moreover, our research has also revealed that endothelial HS is essentially required for tumor angiogenesis by enhancing VEGF signaling (c). We have further explored the potential of targeting HS as a multifaceted pro- or anti-angiogenesis therapeutic to treat related human diseases by demonstrating that endothelial HS may modulate additional angiogenic signaling, such as IGF-1 and hypoxia, via multiple pathways to promote angiogenesis (d). Overall, our studies have significantly advanced the understanding of HS proteoglycans' role in vascular development and angiogenesis. We have elucidated the related molecular mechanisms and highlighted the potential of targeting HS as a therapeutic approach to treat related human diseases.

a. Zhang B, Dietrich UM, Geng JG, Bicknell R, Esko JD, **Wang** L. Repulsive axon guidance molecule Slit3 is a novel angiogenic factor. *Blood*. 2009 Nov 5;114(19):4300-9. PubMed Central PMCID: PMC2774558.

b. Zhang B, Xiao W, Qiu H, Zhang F, Moniz HA, Jaworski A, Condac E, Gutierrez-Sanchez G, Heiss C, Clugston RD, Azadi P, Greer JJ, Bergmann C, Moremen KW, Li D, Linhardt RJ, Esko JD, **Wang L**. Heparan sulfate deficiency disrupts developmental angiogenesis and causes congenital diaphragmatic hernia. *J Clin Invest*. 2014 Jan;124(1):209-21. PubMed Central PMCID: PMC3871243.

c. Fuster MM, **Wang L**, Castagnola J, Sikora L, Reddi K, Lee PH, Radek KA, Schuksz M, Bishop JR, Gallo RL, Sriramarao P, Esko JD. Genetic alteration of endothelial heparan sulfate selectively inhibits tumor angiogenesis. *J Cell Biol*. 2007 May 7;177(3):539-49. PubMed Central PMCID: PMC2064806.

d. Qiu H, Jiang JL, Liu M, Huang X, Ding SJ, **Wang L**. Quantitative phosphoproteomics analysis reveals broad regulatory role of heparan sulfate on endothelial signaling. *Mol Cell Proteomics*. 2013 Aug;12(8):2160-73. PubMed Central PMCID: PMC3734577.

3. **HS in stem cell biology**. We unexpectedly found that HS is not necessary for embryonic stem cell (ESC) self-renewal. However, HS is essential for ESCs to commit to differentiation (a) and differentiate into mesoderm cell lineage (b). Our mechanism studies elucidated that HS facilitates FGF signaling to mediate cell differentiation commitment and modulates FGF and BMB signaling, not Wnt signaling, to promote ESC differentiation into mesoderm cells (a-c). In addition, we discovered that HS also modulates TGFβ signaling to regulate prostate stem/progenitor cell activities 9d). These findings highlight the significance of HS in regulating stem cell self-renewal and differentiation. Our study suggests that the manipulation of HS using heparinoids or inhibition of HS biosynthesis could be applied to control stem cell culture and differentiation for cell therapy.

   a. Kraushaar DC, Yamaguchi Y, **Wang L** (2010). Heparan sulfate is required for cell fate commitment of embryonic stem cells. *J Biol Chem*. 285(8): 5907-16. [PMID: 20022960]

   b. Kraushaar DC, Rai S, Condac E, Nairn A, Zhang SY, Yamaguchi Y, Moremen K, Dalton S, **Wang L** (2012). Heparan sulfate facilitates FGF and BMP signaling to drive mesoderm differentiation of mouse embryonic stem cells. *J Biol Chem.* 287(27): 22691-700. [PMID: 22556407]

   c. Kraushaar DC, K, Dalton S, **Wang L** (2013). Heparan sulfate: A key regulator of embryonic stem cell fate. *Biol Chem.* 394(6): 741-51. [PMID: 23370908]

   d. Rai S, Alsaidan OA, Yang H, Cai H, **Wang** L (2020). Heparan sulfate inhibits transforming growth factor β signaling and functions in cis and in trans to regulate prostate stem/progenitor cell activities. *Glycobiology*. 19; 30(6): 381-395. [PMID: 31829419].

4. **Heparin, HS and chondroitin sulfate in leukocyte trafficking/inflammation**. Our research has revealed that the primary molecular mechanism underlying the potent anti-inflammatory effect of heparin is the inhibition of P- and L-selectin functions (a). Furthermore, we have identified the specific heparin structures responsible for this effect (a). Through our examination of conditional Ndst1 knockout mice, we have determined that endothelial HS is crucial for neutrophil trafficking during inflammation through various molecular mechanisms, including interaction with L-selectin expressed in neutrophils, immobilizing chemokine on the endothelial luminal cell surface, and mediating abluminal-to-luminal chemokine transcytosis (b). This work has established the essential role of HS in innate immunity, which was highlighted in the esteemed journal, *Nature Immunology*. Our studies have also shown that fucosylated chondroitin sulfate is a potent inhibitor of selectin-mediated leukocyte trafficking and tumor cell metastasis. We have elucidated the cellular and molecular mechanisms underlying heparin-induced leukocytosis, a clinical

phenomenon that occurs upon heparin application (c). Additionally, we have determined that endothelial HS is critical for regulating inflammation and fibrosis in diabetic nephropathy (d). These findings provide valuable insights for ongoing clinical drug development, particularly in the development of non-anticoagulant heparin as an anti-inflammatory or anti-tumor metastasis drug.

a. **Wang L**, Brown JR, Varki A. and Esko JD (2002). Heparin's anti-inflammatory effects require glucosamine 6-O-sulfation and are mediated by blockade of L- and P-selectins. *J Clin Invest* 110:127-36. [PMCID: PMC151027].

b. **Wang L**, Fuster M, Sriramarao P, Esko JD. Endothelial heparan sulfate deficiency impairs L-selectin- and chemokine-mediated neutrophil trafficking during inflammatory responses. *Nat Immunol*. 2005 Sep;6(9):902-10. [PMID: 16056228]

c. Zhang S, Condac E, Qiu H, Jiang J, Gutierrez-Sanchez G, Bergmann C, Handel T, **Wang L**. Heparin-induced leukocytosis requires 6-O-sulfation and is caused by blockade of selectin- and CXCL12 protein-mediated leukocyte trafficking in mice. J Biol Chem. 2012 Feb 17;287(8):5542-53. PubMed Central PMCID: PMC3285330.

d. Talsma DT, Katta K, Ettema MAB, Kel B, Kusche-Gullberg M, Stegeman CA, van den Born J, **Wang L** (2018). Endothelial heparan sulfate strongly contributes to inflammation and fibrosis in murine diabetic nephropathy. *Lab Invest*. 98:427-38 [PMID: 29330473]

5. **The anticoagulant heparin and other novel anticoagulant drug studies**. During my MSc and MD studies, I conducted research that led to several discoveries. Firstly, I found that histidine-rich glycoprotein, a plasma protein, exhibits procoagulant activity by competitively inhibiting heparin binding to antithrombin (a). Secondly, I developed a new method for the rapid diagnosis of heparin-induced thrombocytopenia patients (b). Thirdly, I reported, for the first time, that recombinant hirudin has a high antigenicity in heparin-induced thrombocytopenia patients, and the antibodies generated in response can potentially inhibit the anticoagulant activity of recombinant hirudin (c). This novel clinical observation also highlighted the unique immunity possessed by these patients, a mystery that still remains unsolved. Additionally, I discovered that the axon guidance molecule Slit3 strongly binds heparin, and its C-terminal fragment has the potential to neutralize heparin's anticoagulant activity, suggesting the development of the C-terminal fragment as a heparin blocker for clinical use (d).

   a. **Wang L**, He S, Chen Z. Purification of histidine-rich glycoprotein and its procoagulant activity. Bull Hunan Med Univ. 1995; 21(4):315-8.
   b. **Wang L**, Huhle G, Malsch R, Hoffmann V, Song XL, Harenberg J. Determination of heparin-induced IgG antibody in heparin-induced thrombocytopenia type II. Eur J Clin Invest. 1999 Mar;29(3):232-7. PubMed PMID: 10202380.
   c. Song X, Huhle G, **Wang L**, Hoffmann U, Harenberg J. Generation of anti-hirudin antibodies in heparin-induced thrombocytopenic patients treated with r-hirudin. Circulation. 1999 Oct 5;100(14):1528-32. PubMed PMID: 10510056.
   d. Condac E, Strachan H, Gutierrez-Sanchez G, Brainard B, Giese C, Heiss C, Johnson D, Azadi P, Bergmann C, Orlando R, Esmon CT, Harenberg J, Moremen K, **Wang L**. The C-terminal fragment of axon guidance molecule Slit3 binds heparin and neutralizes heparin's anticoagulant activity. Glycobiology. 2012 Sep;22(9):1183-92. PubMed Central PMCID: PMC3406619.

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