Curriculum Vitae

Yongmei Xu

Research associate professor

A. PERSONAL CONTACT INFORMATION

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B. EDUCATION

2009-2013 **Postdoctoral** research associate, University of North Carolina at Chapel Hill.

Mentor: Professor Jian Liu

2007-2008 **Visiting scholar**， University of North Carolina at Chapel Hill.

Mentor: Professor Jian Liu

2000-2003 **Ph.D. in Environmental Science**, Wuhan University, P. R.China,

1994-1997 **M.S. in Polymer Engineering**, Hubei University of Technology, P. R. China.

1988-1992 **B.S. in Light Chemistry Engineering**, Hubei University of Technology, P. R. China.

C. PROFESSIONAL EXPERIENCE

2019-current Research associate professor, University of North Carolina at Chapel Hill.

2014-2018 Research assistant professor, University of North Carolina at Chapel Hill.

2013-present CO-Founder and consultant, Glycan Therapeutics, LLC, Raleigh, NC

2004-2007 Associate professor, Wuhan University of Technology, P. R. China.

1997-2000 Assistant professor, Hubei University of Technology, P.R.China

1992-1994 Teaching executive administrator, Hubei University of Technology, P.R.China

D. HONOR

2006 Distinguished Faculty *from* Wuhan University of Technology, P. R. China
2005 Distinguished Faculty from Wuhan University of Technology, P. R. China

E. BIBLIOGRAPHY

Research Articles

1. Wander, R., Kaminski, A.M., Wang, Z., Stancanelli, E., **Xu, Y.**, Pagadala, V., Li, J.,

Krahn, J.M., Pham, T.Q., Liu, J., and Pedersen, L.C. (2021) Structural and substrate specificity analysis of 3-O-sulfotransferase isoform 5 to synthesize anticoagulant heparan sulfate *ACS Catalysis* minor revision.

2. Wang, Z., Arnold, K., Dhurandahare, V.M., **Xu, Y.**, Pagadala, V., Labra, E., Jeske, W., Fareed, J., Gearing, M., and Liu, J. (2021) Analysis of 3-*O*-sulfated heparan sulfate using isotopically labeled oligosaccharide calibrants. *Anal Chem*, submitted.

3. Stancanelli, E., Liu, W., Wander, R., Li, J., Wang, Z., Su, G., Kanack, A., Pham, T.Q., Pagadala, V., Padmanabban, A., **Xu, Y.** and Liu, J. (2021) Chemoenzymatic synthesis of homogeneous heparan sulfate and chondroitin sulfate chimeras. *Angew Chem Int Ed* under review.

4. Li J, Su G, **Xu Y**, Arnold K, Pagadala V, Wang C, Liu J. Synthesis of 3-*O*-Sulfated Heparan Sulfate Oligosaccharides Using 3-*O*-Sulfotransferase Isoform 4. ACS Chem Biol. 2021 Oct 15;16(10):2026-2035.
5. Wander R, Kaminski AM, **Xu Y,** Pagadala V, Krahn JM, Pham TQ, Liu J, Pedersen LC. Deciphering the substrate recognition mechanisms of the heparan sulfate 3-*O*-sulfotransferase-3. RSC Chem Biol. 2021 Aug 5;2(4):1239-1248.
6. Gao J, **Xu Y**, Liu J, Huang X. Convergent chemoenzymatic synthesis and biological evaluation of a heparan sulfate proteoglycan syndecan-1 mimetic. Chem Commun (Camb). 2021 Apr 7;57(27):3407-3410.
7. Horton M, Su G, Yi L, Wang Z, **Xu Y**, Pagadala V, Zhang F, Zaharoff DA, Pearce K, Linhardt RJ, Liu J. Construction of heparan sulfate microarray for investigating the binding of specific saccharide sequences to proteins. Glycobiology. 2021 Apr 1;31(3):188-199.
8. Wang Z, Arnold K, Dhurandhare VM, **Xu Y**, Liu J. Investigation of the biological functions of heparan sulfate using a chemoenzymatic synthetic approach. RSC Chem Biol. 2021 Feb 22;2(3):702-712.
9. Gunn KH, Gutgsell AR, **Xu Y**, Johnson CV, Liu J, Neher SB. Comparison of angiopoietin-like protein 3 and 4 reveals structural and mechanistic similarities. J Biol Chem. 2021 Jan 19:100312.
10. Yang W, Eken Y, Zhang J, Cole LE, Ramadan S, **Xu Y**, Zhang Z, Liu J, Wilson AK, Huang X. Chemical synthesis of human syndecan-4 glycopeptide bearing O-, N-sulfation and multiple aspartic acids for probing impacts of the glycan chain and the core peptide on biological functions. Chem Sci. 2020 May 11;11(25):6393-6404.
11. Liu J, Schleyer KA, Bryan TL, Xie C, Seabra G, **Xu Y**, Kafle A, Cui C, Wang Y, Yin K, Fetrow B, Henderson PKP, Fatland PZ, Liu J, Li C, Guo H, Cui L. Ultrasensitive small molecule fluorogenic probe for human heparanase. Chem Sci. 2020 Oct 20;12(1):239-246.
12. Arnold K, **Xu Y**, Liao YE, Cooley BC, Pawlinski R, Liu J. Synthetic anticoagulant heparan sulfate attenuates liver ischemia reperfusion injury. Sci Rep. 2020 Oct 14;10(1):17187.
13. Yi L, **Xu Y**, Kaminski AM, Chang X, Pagadala V, Horton M, Su G, Wang Z, Lu G, Conley P, Zhang Z, Pedersen LC, Liu J. Using engineered 6-*O*-sulfotransferase to improve the synthesis of anticoagulant heparin. Org Biomol Chem. 2020 Oct 7.
14. Wang Z, Arnold K, **Xu Y**, Pagadala V, Su G, Myatt H, Linhardt RJ, Liu J. Quantitative analysis of heparan sulfate using isotopically labeled calibrants. Commun Biol. 2020 Aug 4;3(1):425.
15. Li J, Sparkenbaugh EM, Su G, Zhang F, **Xu Y**, Xia K, He P, Baytas S, Pechauer S, Padmanabhan A, Linhardt RJ, Pawlinski R, Liu J. Enzymatic Synthesis of Chondroitin

Sulfate E to Attenuate Bacteria Lipopolysaccharide-Induced Organ Damage. ACS Cent Sci. 2020 Jul 22;6(7):1199-1207.
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17. Miller RL, Guimond SE, Schwörer R, Zubkova OV, Tyler PC, **Xu Y**, Liu J, Chopra P, Boons GJ, Grabarics M, Manz C, Hofmann J, Karlsson NG, Turnbull JE, Struwe WB, Pagel K. Shotgun ion mobility mass spectrometry sequencing of heparan sulfate saccharides. Nat Commun. 2020 Mar 20;11(1):1481.
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19. Nguyen TH, **Xu Y**, Brandt S, Mandelkow M, Raschke R, Strobel U, Delcea M, Zhou W, Liu J, Greinacher A. Characterization of the interaction between platelet factor 4 and homogeneous synthetic low molecular weight heparins. J Thromb Haemost. 2020 Feb;18(2):390-398.
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28. Thieker DF, Xu Y, Chapla D, Nora C, Qiu H, Felix T, Wang L, Moremen KW, Liu J, Esko JD, Woods RJ. Downstream Products are Potent Inhibitors of the Heparan Sulfate 2-O-Sulfotransferase. *Sci Rep.* 2018 Aug 7;8(1):11832.
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glucuronide by alkaline and Smith degradation. *Org Biomol Chem.* 2017 Feb 1;15(5):1222-1227.

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Heparin-like Hexasaccharides for the Analysis of Heparin–Protein Interactions (Chem. Eur. J. 28/2010). *Chemistry-A European Journal* 2010, *16* (28), 8218-8218.

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Book Chapter:

1. **Yongmei Xu** and Jian Liu, Synthetic Glycomes, CHAPTER 9 Chemoenzymatic Synthesis of Heparan Sulfate and Heparin, Pages 207 – 225, 23 Apr 2019, ISBN 978-1-78801-164-8

Entrepreneurship

Co-Founder of Glycan Therapeutics, LLC, a UNC spin-off start-up to devolop carbohydrate-based research reagents and pharmaceutical products.

Patents

1. Jian Liu, Katelyn Arnold, **Yongmei Xu**, Rafal Pawlinski, and Ding Xu SULFATED OLIGOSACCHARIDES HAVING ANTI-INFLAMMATORY ACTIVITY, US patent application **US 62/581,443**. Pub. No.:WO/2019/090203 International Application No.: PCT/US2018/059152
2. Jian Liu, Zhangjie Wang, Po-Hung Hsieh and **Yongmei Xu** SHORT ACTING SYNTHETIC HEPARIN, US patent application # **US 62/469,643;** WO/2018/165656, International Application No.:PCT/US2018/021986
3. Jian Liu, **Yongmei Xu**, Edward Harris and Robert Linhardt Reversible heparin molecules and methods of making and using the same, US Patent (**US 9,951,149B2**), date of patent: April 24, 2018
4. Liu, J., **Xu, Y.;** Chemoenzymatic synthesis of structurally homogeneous ultra-low molecular weight heparins. US patent serial # 61/426,921.
5. Liu, J.; Chen, J.; Jones, C.; **Xu, Y.,** Enzymatic synthesis of sulfated polysaccharides without iduronic acid residues, **US Patent 20090035787**. US patent serial # 12/178, 434

F. GRANT

Active

1. NIH STTR grant R42GM128484(04/2018 – 11/30/2021) Enzymatic synthesis of heparan sulfate and chondroitin sulfate; $1.95M. As a PI, design the project and coordinate with Glycan Therapeutics and Rensselaer Polytechnic Institute to finish the project.
2. NIH SBIR grant R44GM123792(04/2020 to 03/2022), Developing heparan sulfate glycan array, Co-PI, $668K. (PI Guowei Su, Glycan Therapeutics); synthesize the heparin sulfate library for Glycan Therapeutics to do microarray study.
3. NIH SBIR grant R43GM142304 (09/2021 to 06/2022), Quantitative analysis of heparan sulfate using 13C-labeled standards, Co-PI, $49K. (PI Vijay Pagadala, Glycan Therapeutics); synthesize 13C-labeled heparin sulfate standards for Glycan Therapeutics to do quantitative analysis.

Completed

1. Subcontract from Glycan Therapeutics LLC for NIH Small Business Innovation Research contract HHSN261201500019C. September 18 of 2017 to September 17 of 2018. Project title: "Chemoenzymatic synthesis of heparan sulfate oligosaccharides" Co-PI, Total cost $155,500. 50% effort. PI (Vijay Pagadala).
2. NIH Small Business Innovation Research contract HHSN261201500019C. September 18 of 2015 to September 17 of 2017. Project title: "Chemoenzymatic synthesis of heparan sulfate oligosaccharides" ($1M)(Principal Investigator; declined)

G. PROFESSIONAL SERVICE AT NATIONAL, INTERNATION

Journal Reviewer: International Journal of Pharmaceutics, International Journal of Biological Macromolecules, Journal of Biomedical Materials Research, The Journal of Carbohydrate Chemistry, Carbohydrate Polymer,
Grant reviewer: National Science Foundation Grants in China

F. Oral Presentations at Professional Meetings

1. Inserm workshop 256, Glycosaminoglycan Biology Conference, Bordeaux, France Jun 2019 . Title: "Chemoenzymatic synthesis of heparin and drug discovery"
2. 4th Glycobiology World Congress, Rome, Italy, Sep 2018. Title: "Chemoenzymatic synthesis of heparin and drug discovery".
3. 3th Glycobiology World Congress, Houston, USA, Sep 2017. Title: "Synthesis of oligosaccharides to replace animal-sourced heparins".

E. REARCH STATEMENT

Highlight

My research has been focused to develop an enzymatic method to synthesize structurally defined heparan sulfate(HS) and heparin. For the first time structurally defined heparin

analog was generated using chemoenzymatic means. This method demonstrates to efficiently synthesize a wide range of heparan sulfate oligosaccharides with diverse sizes and sulfate patterns. The method opens the good opportunity to develop HS based therapeutics. It was mentioned by more than 30 media including *New York Times, Chicago Tribune, Scientific American, Nature, Science, Chemical& Engineering News, a*nd et al. Here are highlights of my research achievement:

- Developed the chemoenzymatic method to synthesize heparin sulfate, published in *Science* (2011)
- Discovered a new heparin structure with reversible anticoagulant, published in *Nature Chemical Biology* (2014)
- Improve synthetic heparin to replace animal-sourced heparin, published in *Science Translational Medicine* (2017)
- Co-founder of Glycan Therapeutics LLC, received $13M non-diluted grant funding from NIH.

Scientific achievements

My recent 14 years research contribution is developing chemoenzymatic method to synthesize structurally defined oligosaccharides. Several key issues in synthesis were solved including labelling tag design, enzyme modification sequence, purification and scale-up. Comparing with traditional chemical method, the new method dramatically improves the synthesis efficiency and the product yield. We have accumulated several hundred of structures, which have been using in many research groups around the nation and world. HS has a wide range of important roles in mammalian physiology. New insights into the impact of their functions in disease processes as diverse as inflammation, cancer, and neurodegeneration are having underpinned exciting opportunities for exploitation in the development of novel therapeutics.

Chemoenzymatic method provides an efficient way to produce alternatives to conventional heparins with higher drug performance and safety. Worldwide sales of heparin are estimated at $4 billion annually. Heparins, a processed product sourced from pig intestine, are highly heterogeneous in size and structure. The long supply chain makes heparin difficult to monitor the quality control and safety. In 2008, several batches of contaminated heparin entered in the US market, killing 254 American. We designed a homogeneous heparin oligosaccharide that is amenable to scale-up chemoenzymatic synthesis. Nonhuman primate studies suggest the synthetic oligosaccharide can replace the animal-sourced heparin. The success in preparing synthetic heparin can absolutely eliminate the risk associated with animal-sourced heparin.

The representative publication covering this topic includes:

1. **Xu, Y**.; Chandarajoti,K.; Zhang, X.; Pagadala, V.; Dou, W.; Hoppensteadt ,D.M.; Sparkenbaugh, E.S.; Cooley,B.; Daily,S.; Key,N.; Severynse-Stevens,D.; Jawed Fareed,J.;Linhardt, R.J.; Pawlinski, R. and Liu, J., (2017), Synthetic oligosaccharides can replace animal-sourced low-molecular weight heparins. *Sci. Transl. Med.* eaan5954
2. **Xu, Y**, Moon, A.F., Xu,S., Krahn J.M., Liu, J. and Pedersan, L.C. (2017) Structure based substrate specificity analysis of heparan sulfate 6-O-sulfotransferase *ACS Chem. Bio.* 12(1):73-82.(PMC5331487)
3. **Xu, Y**, Cai, C., Chandarajoti, K, Li, L., Hsieh, P., Pham, T., Sparkenbaugh, E.M., Sheng, J., Key, N., Pawlinski, R., Harris, E., Linhardt, R.J., and Liu, J. (2014) Homogeneous and reversible low-molecular weight heparins with reversible anticoagulant activity. *Nat. Chem. Biol*. 10: 248-250 (PMID: 24561662).
4. **Xu, Y**.; Pempe, E. H.; Liu, J., (2012), Chemoenzymatic Synthesis of Heparin Oligosaccharides with both Anti-factor Xa and Anti-factor IIa Activities. *J. Biol. Chem.* 287 (34), 29054-61. (PMC3436553)
5. **Xu, Y.,** Masuko, S., Takieddin, M., Xu, E., Liu, R., Jing, J., Mousa, S., Linhardt, R.J. and Liu, J. (2011) Chemoenzymatic synthesis of structurally homogeneous ultra-low molecular weight heparins. *Science* 334: 498-501. (PMCID:PMC3425363)

F. Future Direction

Heparan sulfate have essential functions, including developmental processes, angiogenesis, blood coagulation and tumor metastasis. The key in developing HS-based drugs centers on the synthesis of HS having defined size and sulfation patterns. My future goal is to further improve the technology to synthesize structurally defined HS and heparin. Combing with chemical method and new isoforms of HS sulfotransferases, my effort will be to expand the coverage of the library to larger oligosaccharides and more diversified sulfated saccharide sequences resembling the authentic structures. Improving enzyme expression and purification, I will further develop the chemoenzymatic scale-up approach to accelerate the modernization of heparin drugs to eliminate side effect associated with animal-sourced heparn. With availability of large library, I will dissect the structure-biological function relationship and explore HS and heparin based therapeutics.