Yuhan Bi

Ph.D. (2018)

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Education:

2018-present	Postdoc, Immunology	Stanford University,
2013 - 2018	Ph.D., Pharmaceutical Sciences	University of Pittsburgh,
2010 - 2013	B.S., Biological Sciences	Georgia State University,

Work Experience:

2019- Present	Postdoc Scholar,	School of Medicine, Stanford University
2013- 2018	Research Assistant,	School of Pharmacy, University of Pittsburgh
2013- 2015	Teaching Assistant,	School of Pharmacy, University of Pittsburgh
2010- 2013	Lab Assistant,	Department of Biological Sciences, Georgia State University
2016-2017	Outreach Committee Lead,	AAPS Student Chapter of Pitt

Experimental Skills:

- **Animal work**: animal surgery (Liver perfusion, castration, and ovariectomy), animal treatment (i.p., i.v., gavage, s.c., etc), hydrodynamic plasmid tail injection, virus tail injection, cell adoptive transfer, animal husbandry (breeding and genotyping), tumor transplantation, tissue collection.
- **Cell biology**: Flow Cytometry, CyTOF, cell culture, primary cell isolation/culture (hepatocytes, BMDM, preadipocytes), stable cell line generation, Adeno/Lenti virus generation/ infection, Seahorse experiment, immunofluorescence (confocal), proliferation assay, cell toxicity, etc.
- **Molecular biology**: CRISPR Screening, CRISPR/Cas9 gene silencing, mutagenesis, plasmid construct clonal, IP, chip assay, EMSA, western blot, luciferase reporter assay, real-time PCR, etc.
- **Immunological Assays**: FACS, , Immune cell sorting (T, B, Monocyte, NK by FACS/Column), Immune cell generation from BM cells (DC, Basophil, Macrophage/Monocyte), Immune cell co-culture assay, Adoptive transfer, immune cell trafficking.
- **Histology**: IF (confocal), IHC, H&E staining, Oil red staining, Tunnel staining, etc.
- **Biochemistry**: Ligand and receptor interaction (photoprobe), non-targeted metabolomics, hydrolysis assay, enzymatic activity, ELISA (cytokines, adipokines, insulin, AST/ALT,) glucose and lipids isolation and measurement, glucose production/uptake assay, and etc.
- **Metabolic study related experiments**: Glucose/ lipid production assay, GTT, ITT, PTT, Clamp, GSIS, metabolic cages and MRI.
- **In vitro cell-based assay and PKPD study:** Metabolite stability assay in human/ mouse liver microsome and primary human/ mouse hepatocytes, In vitro ADME related assays (protein binding, transporter identification, permeability, intrinsic clearance, enzymatic activity, and etc.); Non- compartmental PK analysis (Phoenix/WinNolin), Analytical methods development with HPLC/MS.
- **Data analysis**: RNAseq, R programming, Pathon, statistics (GraphPad Prism, Excel, SPSS, SAS), imaging (Image J, Image Lab, Photoshop, Canvas, Illustrator), bioinformatics (CLC Genomics Workbench), etc.

Publications:

1. **Y Bi**, X Shi, J Zhu, Garbacz WG, Gao L, Yan*, Ren S, Liu Y, Ma X, Li S, **Xie W**. Regulation of cholesterol sulfotransferase SULT2B1b by HNF4a constitutes a negative feedback control of hepatic gluconeogenesis. *Molecular and cellular biology 38 (7), e00654-17*
2. **Y Bi,** M Jiang**,** W Guo, M Xu, S Ren, K. W Selcer, W Xie. Adipose tissue- and sex-specific role of steroid sulfatase in adipose inflammation and energy homeostasis. *Endocrinology 159 (9), 3365-3377*
3. L Gao, B Li, **Y Bi**, WG Garbacz, W Xie. NKT cell specific sensitizing effect of XX in Concanavalin A induced autoimmune hepatitis. (Manuscript in submission.)
4. **Y Bi**, Y Wang, W Xie. The interplay between HNF4α and cholesterol sulfotransferase in energy metabolism. *Liver Research*. https://doi.org/10.1016/j.livres.2019.09.004
5. Y AN, **Y Bi,** M Xu, S Ren, W Xie. Overexpression of cholesterol sulfotransferase sensitizes mice to acetaminophen induced acute liver injury. (Manuscript in preparation.)
6. J Yan, HC T, S Li, Y Niu, WG Garbacz, P Lu, **Y Bi**, etc, Xie W. Aryl Hydrocarbon Receptor Signaling Prevents Activation of Hepatic Stellate Cells and Liver Fibrogenesis in Mice. *Gastroenterology doi: 10.1053/j.gastro.2019.05.066*

Research Projects (PhD Work):

Regulation of cholesterol sulfotransferase SULT2B1b by Hepatocyte Nuclear Factor 4 α (HNF4α) constitutes a negative feedback control of hepatic gluconeogenesis.

- Inject and infect Adeno virus expressing shHNF4α into SULT2B1b transgenic mice/primary hepatocytes to knockdown HNF4α.
    - Measure blood glucose level, hepatic glucose production, and gluconeogenic gene expression.
    - Demonstrate that SULT2B1b inhibits gluconeogenesis by antagonizing the HNF4α.
- Conduct gel shift assay, chip assay, luciferase reporter assay, mutagenesis to demonstrate SULT2B1b is the transcriptional target of HNF4α.
- Do IP, IF and subcellular fractionation to mechanically demonstrate that knocking out SULT2B1b increases acetylation and nuclear translocation of HNF4α.
- Synthesize a chemical derivative of SULT2B1b substrate Thiocolesterol and measure its ADME and gluconeogenic inhibitive effects *in vitro* and in mice.
- Do IP, IF and subcellular fractionation to mechanically demonstrate that Thiocholesterol inhibits HNF4α acetylation and nuclear translocation.

Sex-Dimorphic and Sex Hormone–Dependent Role of Steroid Sulfatase in Adipose Inflammation and Energy Homeostasis.

- Generate aP2-STS transgenic mice expressing STS specifically in adipose tissue.
- Assess the adipose tissue biology, metabolic functions and inflammation in obese and diabetic transgenic mice and wild type counterparts. In obesity, STS in adipose tissue is beneficial in female mice, but detrimental to male mice.
- Measure STS enzymatic product and substrate through LC-MS and ELISA in different tissues and serum.
- Conduct castration in male and overiactomy in female obese mice and demonstrate that STS effect in *male* is *androgen* dependent while in *female* is *estrogen* dependent.
- Reveal the novel role of STS in energy homeostasis in an adipose tissue- and sex- specific manner and illuminate the direct effects of androgen and estrogen in adipose tissue energy homeostasis. STS in adipose tissue a novel therapeutic target for obesity and type 2 diabetes.

The role of XX (a nuclear receptor) in autoimmune hepatitis.

- Measure body/ spleen weight, immune cell proliferation, apoptosis, liver histology and cytokine level in Concanavalin A (Con-A) induced autoimmune hepatitis using XXKI and XXKO mice.
    - Demonstrate that XX sensitized mice in Con-A induced hepatitis.

- Sort different types of immune cells responsible for the susceptibility of XX using flow cytometry, Cell specific depletion, NKT cell specific knockout (Cd1dKO) mice/ iNKT cell and hepatocyte specific XXKI mice.
- Conduct adoptive transfer of iNKT cells from XXKI mice and wild type mice to Cd1dKO mice.
- Use XX KI iNKT cells and apply anti-IFNg neutralizing antibody in XXKI mice to demonstrate that IFNg is required for XX induced susceptibility to immune mediated hepatitis.

Overexpression of cholesterol sulfotransferase SULT2B1b sensitizes mice to acetaminophen (APAP) induced acute liver injury.

- Generate APAP induced liver injury model in SULT2B1b KO and SULT2B1b transgenic mice and assess liver toxicity by histology, Tunnel staining, cytokine levels, and AST/ ALT levels.
    - Demonstrate that SULT2B1b sensitizes mice to APAP induced hepatoxicity.
- Profile APAP metabolites by HPCL/MS in SULT2B1b KO and SULT2B1b transgenic after APAP injection to find out SUL2B1b substrates which are responsible the sensitization

Research Projects (Postdoc Work):

Molecular Machineries controlling endothelial specialization

I identified several transcription factors and pathways enriched in high endothelium (HEV) in comparison to flat walled capillary or non-high (flat) venular endothelium, based on the unpublished single cell RNAseq analyses of lymph node and GALT blood vascular endothelium in Dr. Eugene Butcher's lab. In this project, I mainly focus on the IRE1-Xpb1 pathway. Xbp1 mediates the unfolded protein response (UPR) and plays an important role in expansion of the endoplasmic reticulum (ER) for high level protein expression, for example in plasma cells. Like plasma cells, HEV are replete with ER and Golgi, which give them their unique cuboidal "high" phenotype. In addition to its role as a signaling molecule in the UPR, Xbp1 is a DNA binding transcription factor, and I have identified candidate Xbp1-binding motifs in several of the key genes that confer on HEV their ability to attract lymphocytes from the blood: CHST4 in peripheral lymph node HEV, and the mucosal vascular addressin MAdCAM1 in the GI tract, and the chemokine CCL21, important in both peripheral and gut associated lymphoid tissues, all have conserved Xbp1 motifs. I propose that Xbp1 is responsible for the "HEVness" of lymphocyte recruiting venules, effecting both ER expansion and transcriptional activation of genes for lymphocyte homing including MAdCAM1.

- Generating stable endothelial cell lines expressing HEV selective promoter-driven reporters including MAdCAM1.
- Generating stable endothelial cell lines expressing IRE1a (WT and Mutant).
- Generating EC specific knockout mice in the ablation of IRE1/ Xbp1/ Rank/ Relb and etc.
- Assessing the effects of IRE1 specific inhibitor in vivo by FACs, IHC, RT-PCR and etc, in inflammation models.
- Mastering a systems approach integrating transcriptomic (scRNA seq), proteomic (CyTOF) and phylogenomic to identify pathways for EC cell specification.

Molecular mechanism of mitochondrial carrier proteins mediated chemical uncoupling.

- Use LentiCRISPRv2 system to generate stable cell lines knocking out certain mitochondrial carrier protein candidates.
- Conduct Seahorse assay on those stable cells and wild type cells to measure uncoupler stimulated cell respiration in seahorse analyzer.
- Conduct JC-1/TMRM staining followed by FACS detection on those stable cells to interrogate the functional relevance of mitochondrial carrier proteins and chemical uncouplers in decreasing mitochondrial membrane potential.

- Mutagenize HEK293A cells with Brunello genome-wide CRISPR library to screen for uncoupler resistant cells.
- Use UV cross linkable NAA as photoprobe to label the C2C12 cells followed by Biotin-N3 click chemistry treatment and subject labeled cells to HPLC/MS analysis to find binding targets of NAAs.
- Heterogeneously express individual epitope-tagged mitochondrial carrier protein candidates and use photoprobe to assess the physical binding of these SLC25 candidates with NAAs through TAMRA in gel fluorescence detection and biotin pull down assay.
- Conduct mutagenesis to map the binding site(s) of chemical uncoupler on mitochondrial carrier proteins.

Conferences Presentations:

2018 ENDO 2018 Oral Presentation, Chicago, IN, USA
2017 9th AAPS Research Symposium, Pittsburgh, PA, USA
2016 7th Great Lake Nuclear Receptor Conference, Cleveland, OH, USA
2015 7th AAPS Research Symposium, Pittsburgh, Morgantown, WV, USA
2014 6th AAPS Research Symposium, Pittsburgh, PA, USA

Honors and Awards:

2018 Graduate Travel Award, Pittsburgh, PA, USA
2016 Best Poster Award, 7th Great Lake Nuclear Receptor Conference, Cleveland, OH, USA
2013 Honor Student in Dean's list, Atlanta, GA, USA
2013 Out-of-State Tuition Waiver Scholarship, Atlanta, GA, USA
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2010-2013 University Scholar, GA, USA