National Career Development Consortium for Excellence in Glycosciences

2nd Annual National Meeting
January 11, 2021

SCHOLAR PROFILES

HARVARD SCHOLARS

Kevin Brown Chandler, Ph.D.

Assistant Professor, Dept. of Translational Medicine &
Translational Biology Institute of FIU (TGIF)

Florida International University

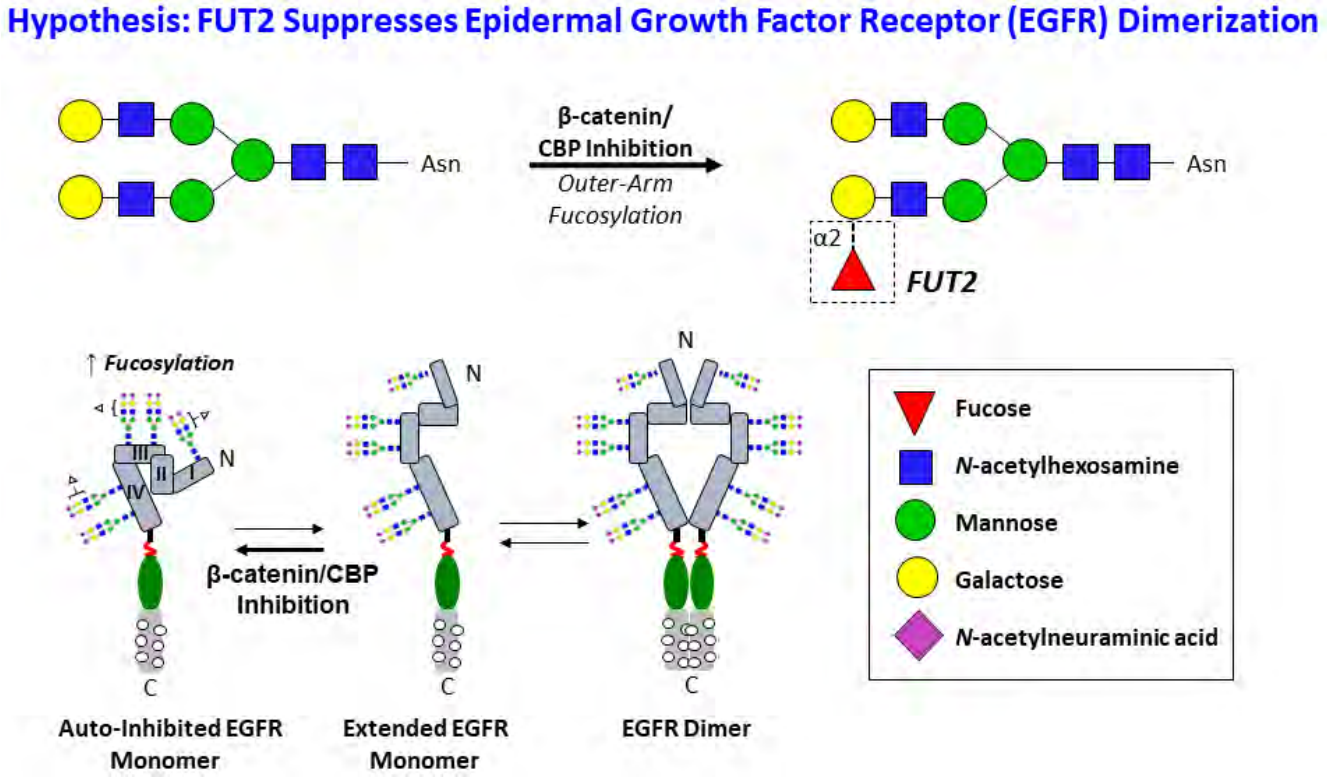
FIU

Herbert Wertheim
College of Medicine

kchandle@fiu.edu

The Role of FUT2 in Repression of EGFR Signaling

Graphical Abstract:



Summary/Highlights:

Treatment with ICG-001, a small molecule inhibitor of the interaction between β-catenin/CBP, led to increased expression of FUT2 in metastatic HSC-3 tongue squamous carcinoma cells, increased EGFR fucosylation, and decreased protein levels of EGFR.

Jiaxuan Chen, Ph.D.

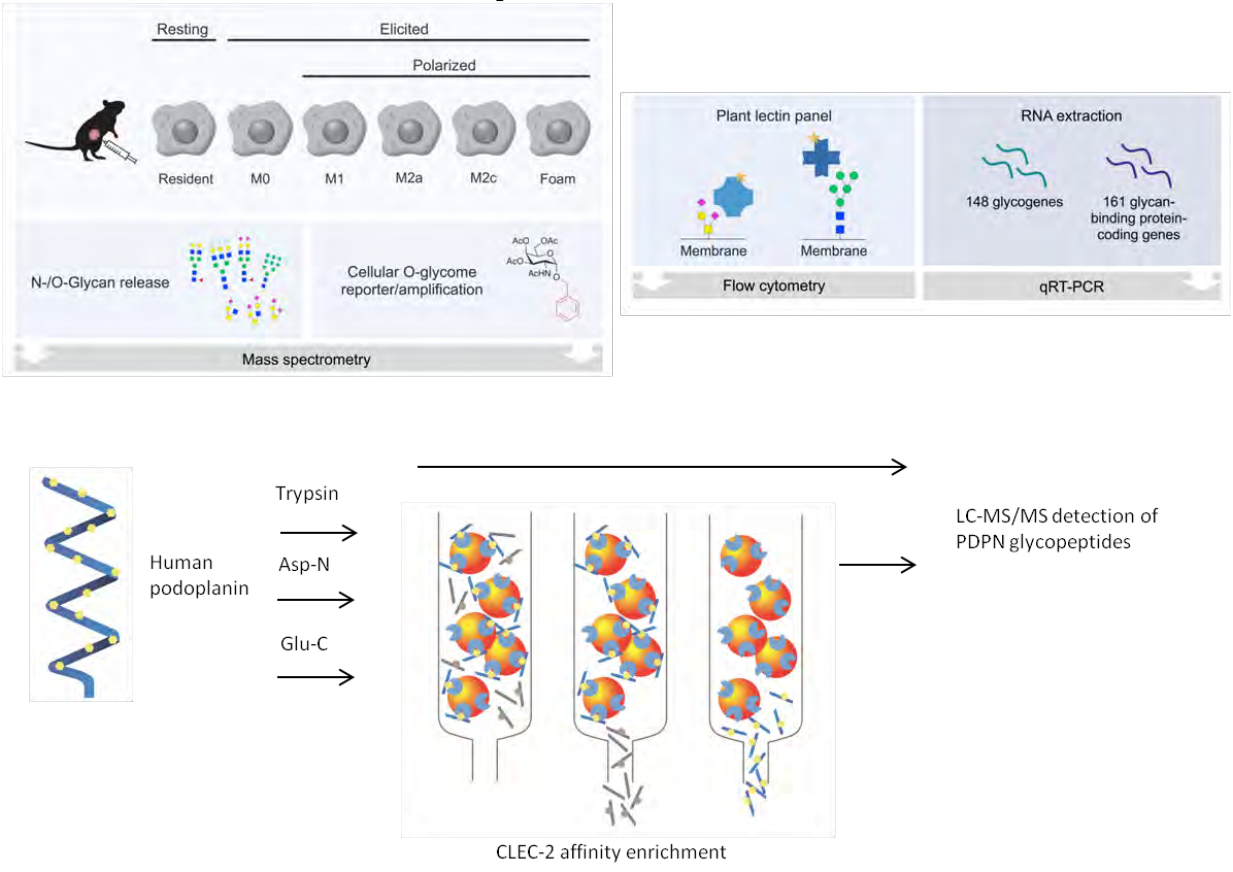
Research Scientist

Beth Israel Deaconess Medical Center

jchen13@bidmc.harvard.edu

Glycan analysis of macrophages and podoplanin

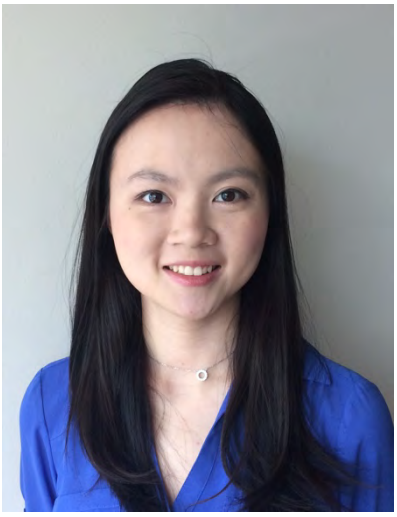
Graphical Abstract:



Summary/Highlights:

1) Resident macrophages exhibit a less heterogeneous glycan profile than elicited cells (Cell Chemical Biology 28, 2021).

2) Performed comprehensive site-specific glycosylation analysis of functional human podoplanin and established a method to enrich CLEC-2 interacting motifs.



Jane Cheng, M.D.

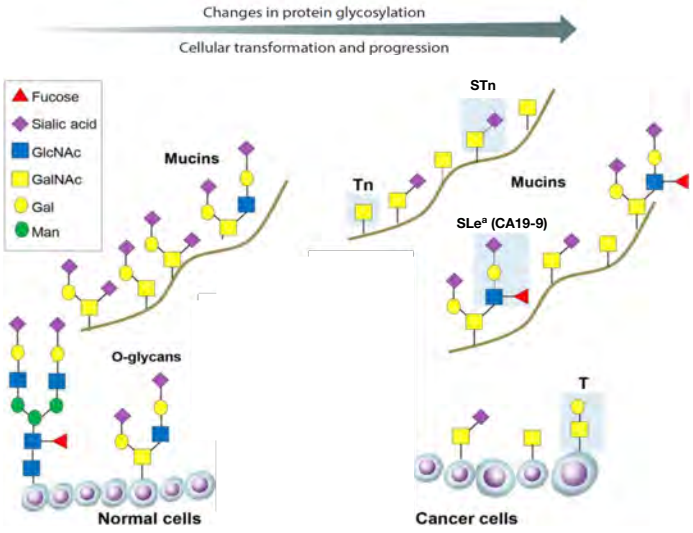
Post-doctoral Research Fellow
General Surgery Resident

jcheng3@bidmc.harvard.edu

HARVARD MEDICAL SCHOOL

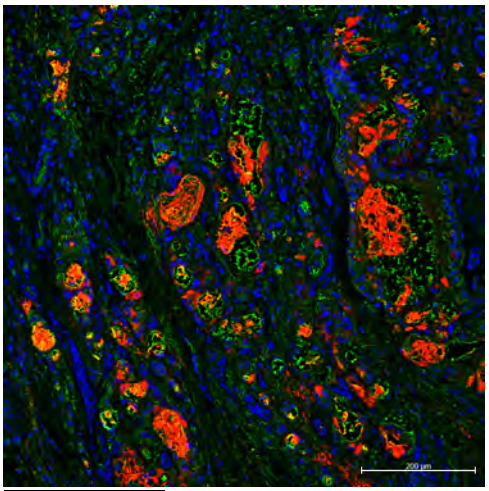
Beth Israel Lahey Health

The Expression of Tn antigen (CD175) and CA19-9/SLe^a in Pancreatic Disease with Differing Localization



Hypothesis: With expression of Tn antigen, CA19-9/SLe^a in different cells/tumor, there may be different glycoproteins carrying these antigens. Secretion of these antigens into blood may be diagnostically useful

Co-immunofluorescent staining with little overlap of Tn and CA19-9/SLe^a expression in tissue regions on PDAC and precursor lesions



ReBaGs6 (Tn)

CA19-9/SLe^a

DAPI

Dorothy Contiguglia-Akcan MD, MPH, FAAFP

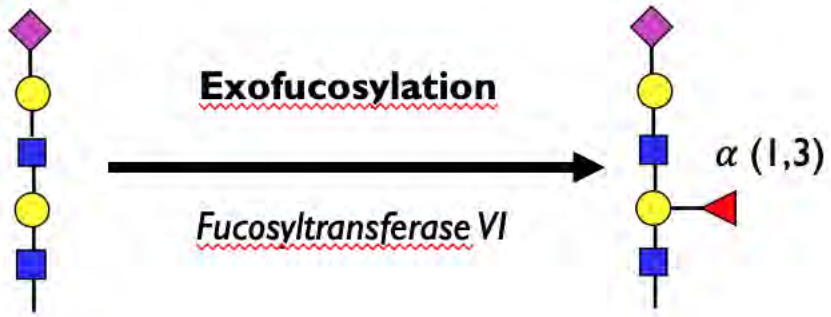
Assistant Professor

Florida International University

dcontigu@fiu.edu

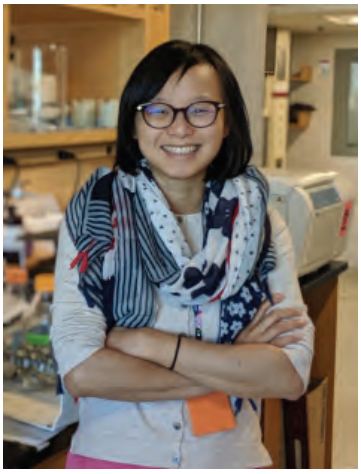
Directing the homing of Mesenchymal Stem Cell exosomes to sites of endothelial inflammation by exofucosylation.

Graphical Abstract:



Summary/Highlights:

Mesenchymal stem cells express unfucosylated sialyl-lactosamines which, once exofucosylated via glycosyltransferase-programmed stereosubstitution (GPS), enable these cells to bind to E-selectin (Sackstein et. al., 2017). Exosomes will be isolated from mesenchymal stem cells and studied in order to determine if they present similar glycans, and then exofucosylated with the goal of bestowing upon these vesicles the ability to bind to E-selectin, and therefore, to inflamed endothelium.

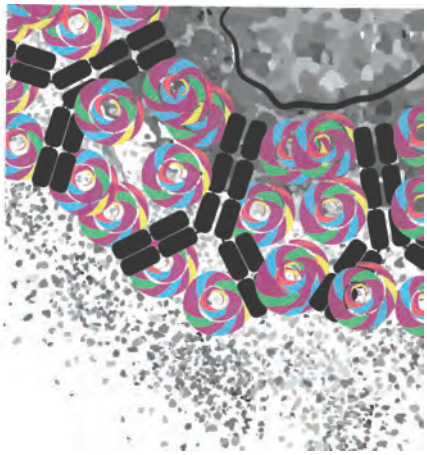


Kai-Ting Shade Ph.D.

Instructor in Medicine

Massachusetts General Hospital and
Harvard Medival School

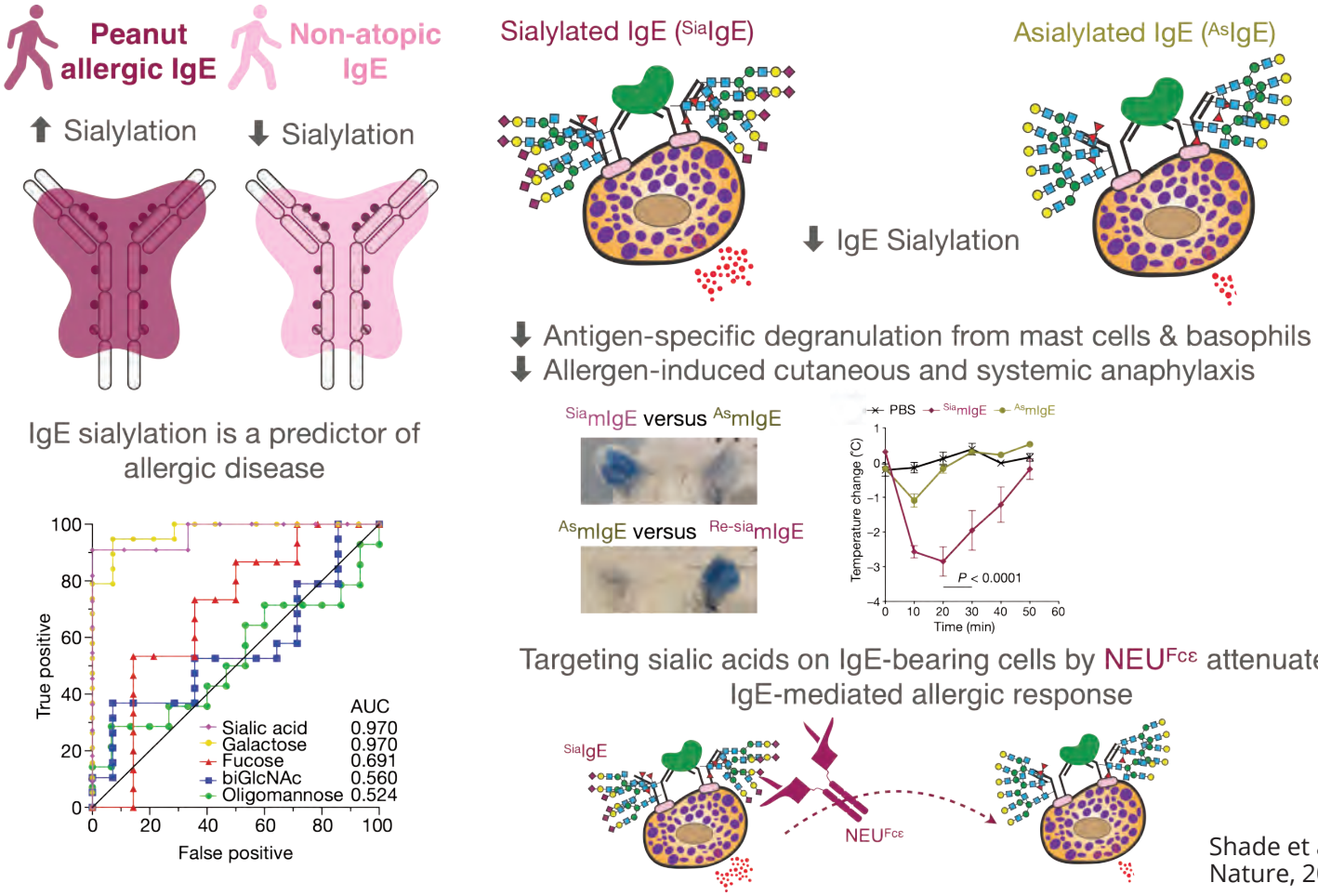
✉ kchuang1@mgh.harvard.edu



Research title

IgE Sialylation is a Determinant of Allergic Pathogenicity

Graphical Abstract



Shade et al., Nature, 2020

Highlights

- Allergic individuals have a higher IgE sialylation content compared to non-atopic individuals.
- Sialic acids regulate IgE-mediated inflammation.
- Proof of principle new therapeutic strategy to attenuate allergic response by targeting sialylation on IgE-sensitized cells.

JOHNS HOPKINS CLEVELAND CLINIC SCHOLARS

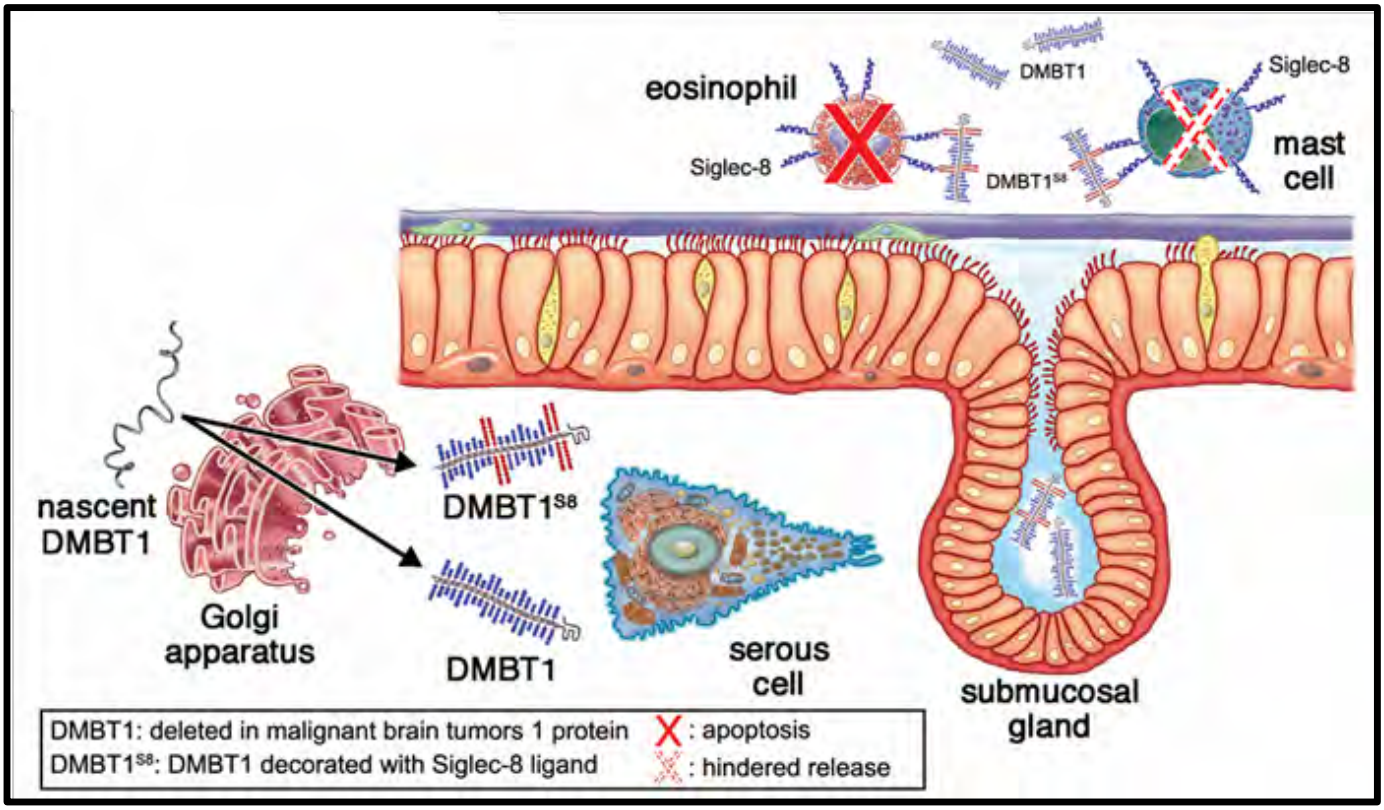
Anabel (Gonzalez-Gil) Alvarenga, Ph.D.

Postdoctoral Fellow
Johns Hopkins University

alvarenga@jhmi.edu

Controlling eosinophilic inflammation through its immuno-inhibitory receptor Siglec-8

Graphical Abstract:



Summary/Highlights:

DMBT1 is armed with Siglec-8 ligands to inhibit inflammation.

Kyriakos N. Papanicolaou, Ph.D.

Research Associate
Division of Cardiology,
Department of Medicine,
Johns Hopkins University School of Medicine

Mentoring team:

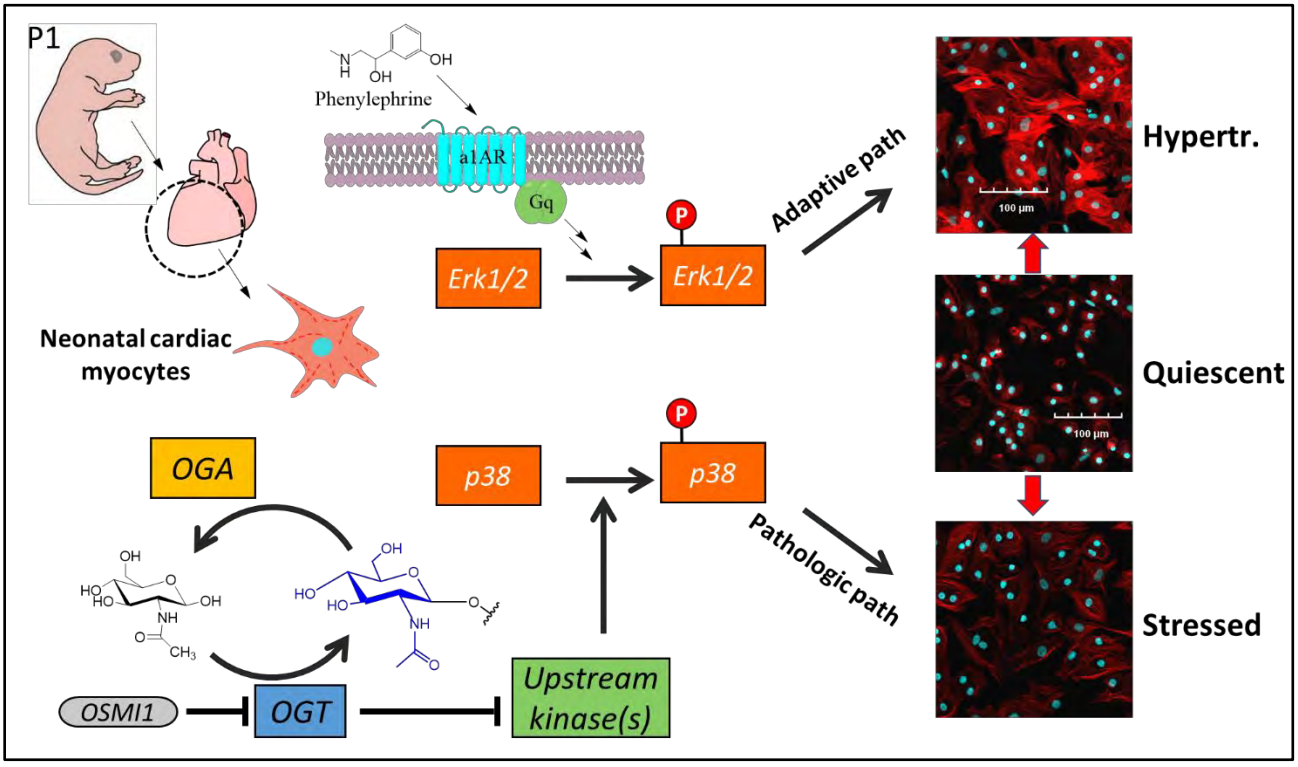
- Natasha Zachara Ph.D., Department of Biological Chemistry, JHU SOM
- D.Brian Foster Ph.D., Division of Cardiology, JHU SOM
- Brian O'Rourke Ph.D., Division of Cardiology, JHU SOM

Email: kyriakos@jhu.edu

Google scholar: https://scholar.google.com/citations?user=kSn_P3UAAAAJ&hl=en&oi=ao

Inhibiting OGT (*O*-GlcNAc transferase) activates a p38-stress response pathway in cardiac myocytes

Graphical Abstract:



Summary/Highlights: The signaling pathways that can tip the balance between physiologic and pathologic cardiac hypertrophy are high priority targets in the prevention of heart failure. Our data implicate OGT and O-GlcNAc signaling in the suppression of pathologic p38 activation in cardiomyocytes. Further work is required to define the signaling pathway under the control of OGT that leads to p38 activation

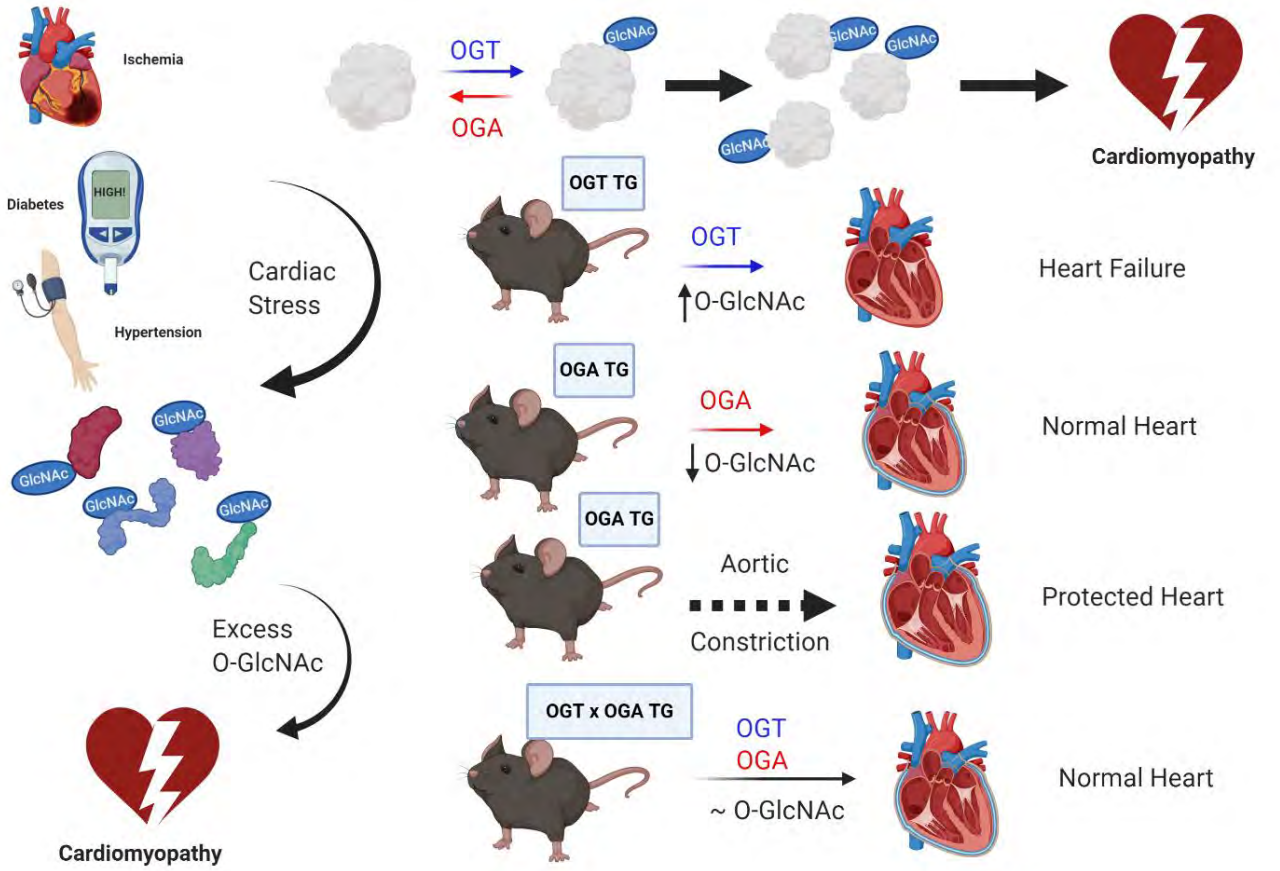
JOHNS HOPKINS MEDICINE

Priya Umapathi, M.D.

Assistant Professor, Division of Cardiology
Advanced Heart Failure, Cardiac Transplant & Mechanical Circulatory Support
Johns Hopkins
Mumapat1@jhmi.edu

Mentors: Mark Anderson MD,PhD, Natasha Zachara PhD, Gerald Hart PhD

"Excessive O-GlcNAcylation is a fundamental driver of heart failure"



Summary/Highlights:

1. OGT causes increased O-GlcNAcylation, dilated cardiomyopathy, premature death and impairment in mitochondrial energetics

2. Myocardial OGA overexpression decreases basal O-GlcNAc levels and is well tolerated

3. Myocardial OGA overexpression protects against cardiomyopathy after trans-aortic constriction and transgenic OGT overexpression

Yan Wang, M.D., Ph.D.

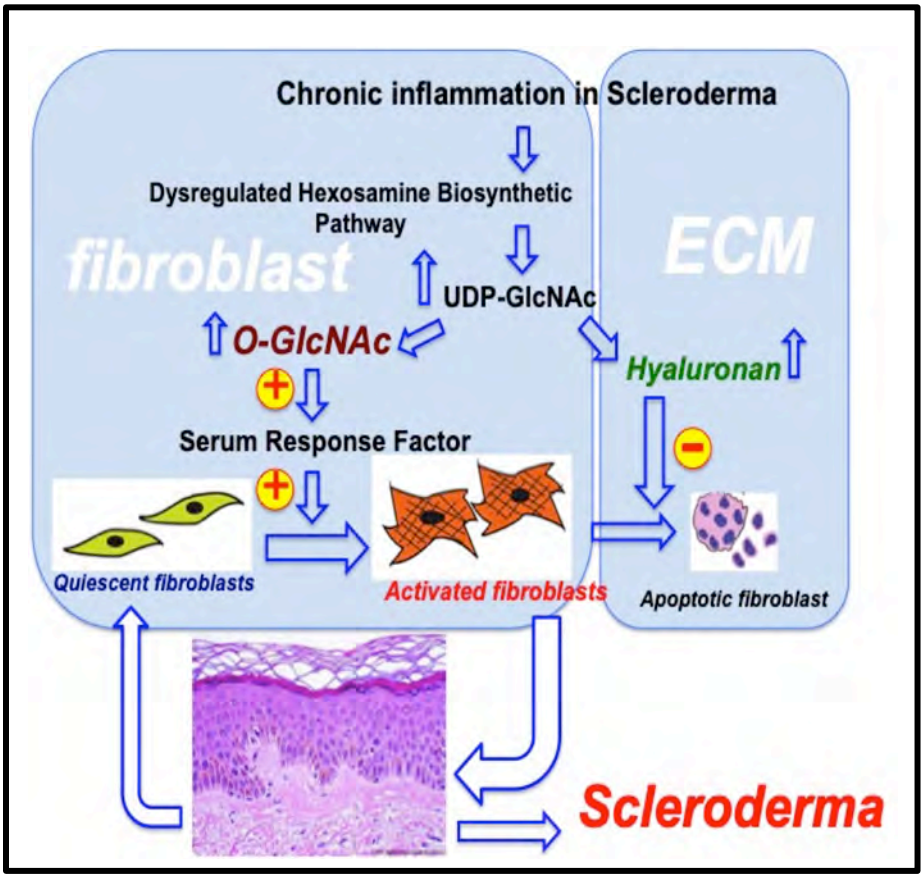
Research Associate
Department of Biomedical Engineering
Cleveland Clinic Lerner Research Institute

Glyco Mentor: Vincent C. Hascall, Ph.D.
Clinical Mentor: Edward V. Maytin, M.D.,Ph.D.

wangy5@ccf.org

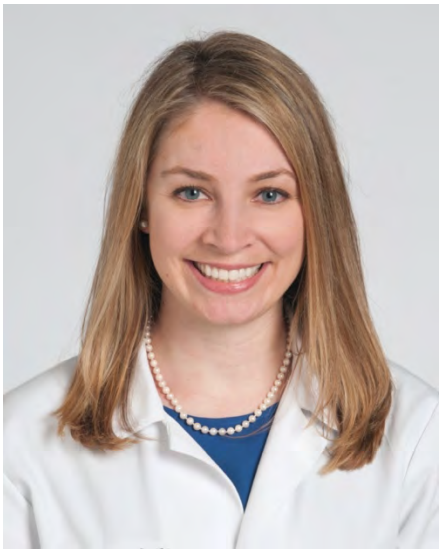
The role of Hyaluronan and protein O-GlcNAcylation in regulating fibroblast turnover and function in Scleroderma

Graphical Abstract:



Summary/Highlights:

- Dysregulated Hexosamine Biosynthetic Pathway (HBP) in scleroderma results in upregulated protein O-GlcNAcylation & increased hyaluronan (HA) synthesis in skin fibroblasts.
- Protein O-GlcNAcylation governs fibroblast activation and myofibroblast differen-tiation by regulating the expression and function of serum respone factor.
- HA regulates fibroblast turnover by rendering the cells more resistent to apoptosis.



Nicole Welch, M.D.

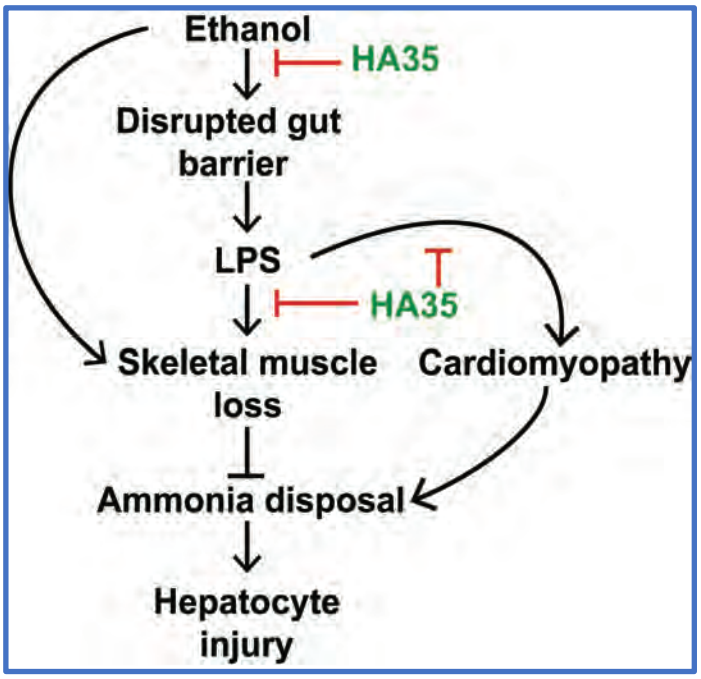
Associate Staff
Cleveland Clinic

Mentors: Dr. Srinivasan Dasarathy
Dr. Vince Hascall

welchn@ccf.org

Hyaluronan 35 prevents endotoxin mediated dysregulated skeletal muscle proteostasis during ethanol exposure

Graphical Abstract:



Project Summary/Highlights: Ethanol sensitizes skeletal muscle to the adverse effects of endotoxins (lipopolysaccharides, LPS) and HA35, a specific-sized hyaluronan, can modulate these responses

WISCONSIN BLOODCENTER SCHOLARS

Daniel K. Afosah, Ph.D.

Postdoctoral Fellow

K12 Scholar: 2019-present

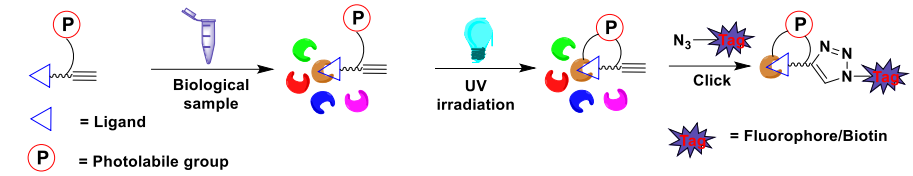
Virginia Commonwealth University

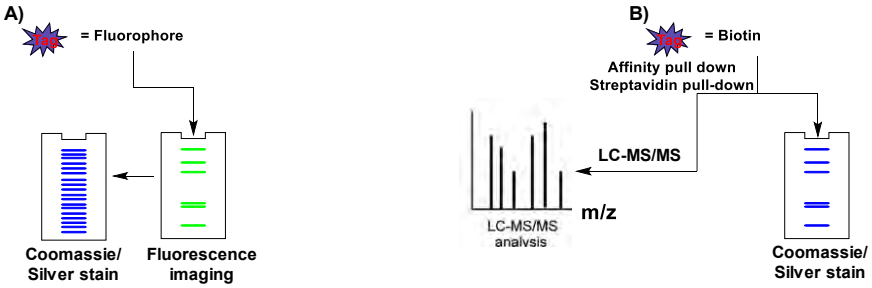
afosahd@vcu.edu

Translational Glycomics Center

Mentor:
Umesh R. Desai, Ph.D.

Technology for Studying Glycosaminoglycan–Protein Interactions





Keywords:

GAGs, GAG mimetics, cancer stem cells, thrombopoiesis

Summary/Highlights:

Glycosaminoglycans (GAGs) modulate a variety of biological processes in the body. Our focus is modulation of cancer stem cells and thrombopoiesis by GAGs, and mimetics thereof. The field is beset with major challenges because technologies to identify specific targets of GAGs are not available. Our work involves developing tools to elucidate proteins that are selectively targeted by GAGs/mimetics. We have developed a photoaffinity labeling probe for this purpose. This technology could be easily implemented for many GAG – protein systems in general.

Afosah D. K., et al. Identification of protein targets of a non-saccharide glycosaminoglycan mimetic selectively inhibiting colorectal cancer stem cells (In preparation).

Adam Kanack, Ph.D.

Postdoctoral Fellow

K12 Scholar: 2019-present

Medical College of Wisconsin

akanack@mcw.edu

Mentors:
Nancy Dahms, Ph.D.

Platelet and myeloid cell phenotypes in a rat model of Fabry disease

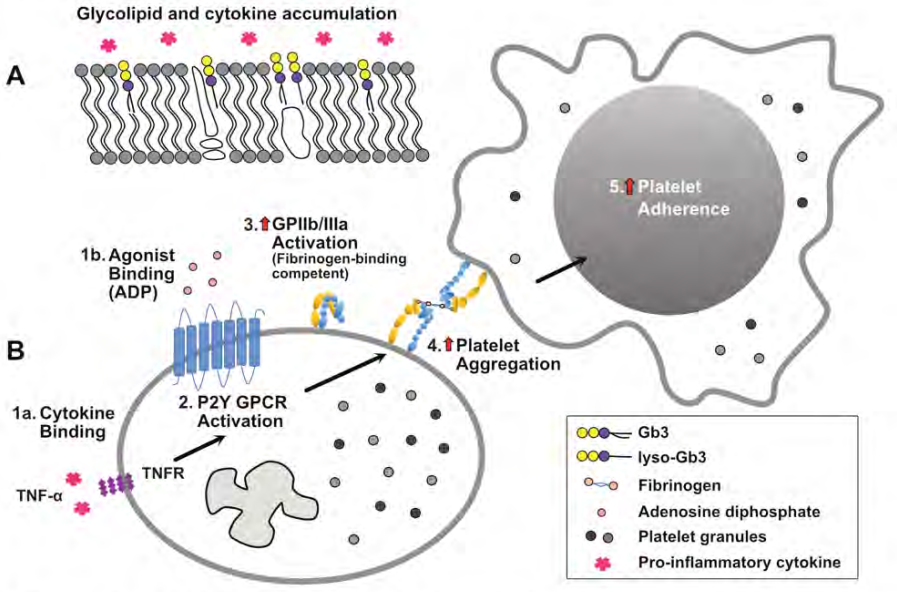
Keywords:

Fabry disease, lysosomal storage diseases, glycosphingolipids, Gb3, lyso-Gb3

Summary/Highlights:

Fabry disease is caused by a deficiency of the lysosomal enzyme α-Galactosidase A (α-Gal A) and results in the accumulation of terminal α-galactose-containing glycosphingolipids (GSLs). Notably, patients with Fabry disease experience ischemic strokes at a rate 5- to 8-times higher than the general public. However, the mechanisms by which an accumulation of α-Gal A substrates increases thrombotic risk remains incompletely understood. Using a rat model of Fabry disease developed by our lab, we are investigating the mechanisms by which GSL accumulation contributes to prothrombotic phenotypes. We have found that a combination of systemically elevated proinflammatory cytokines and GSL accumulation in platelets correlate with increased platelet activation, adhesion, and aggregation in response to the platelet agonist ADP. Overall, these studies provide new insight into the mechanisms contributing to the prothrombotic patient phenotypes associated with Fabry disease and provide therapeutic targets for future studies.

Suggested Model:



A) Platelets from α-Gal A deficient rats accumulate glycolipids and are exposed to elevated levels of pro-inflammatory cytokines. **B)** Platelets from α-Gal A deficient rats have increased platelet activation, aggregation and spreading in response to the agonist ADP.

Melissa Lee-Sundlov, Ph.D.

Research Scientist

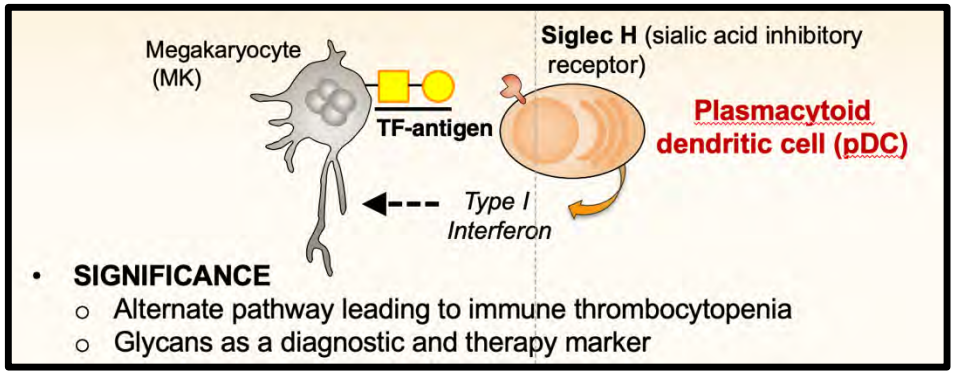
K12 Scholar: 2019-present

Johns Hopkins University

mleesundlov@versiti.org

Mentors:
Karin Hoffmeister, M.D.

The Role of Sialylation in Regulating Platelet Production in the Bone Marrow



Keywords:

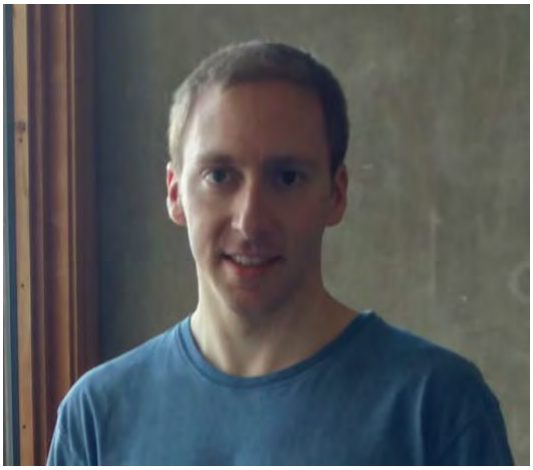
Sialic acid, platelets, megakaryocytes, plasmacytoid dendritic cells, Siglec H, immune thrombocytopenia

Summary/Highlights:

Immune thrombocytopenia (ITP), characterized by low platelet count, is a highly heterogenous disorder. Glycans, especially the lack of terminal sialic acid has been recently been linked to contribute to pathogenic mechanisms of ITP. Our investigations, currently in review in Blood, show that the plasmacytoid dendritic cell suppresses bone marrow platelet production by secretion of Type I interferon, likely mediated by Siglecs. My future aims are to investigate how we can use glycans as a prognostic tool and get a handle on the heterogeneity of ITP.

Submitted Publication: **Lee-Sundlov, M. M.**, Burns, R.T., Kim, T.O., Grozovsky, R., Giannini, S., Zheng Y., Rivadeneyra, L., Glabere, S.,, Kahr, W.H.A., Abdi, R., Despotovic, J.M., Wang, D., Hoffmeister, K.M.: Immune cells surveil aberrantly sialylated O-glycans on megakaryocytes to regulate platelet count via Siglec H. *Under 2nd Revision in Blood.*

UC SAN DIEGO SCHOLARS

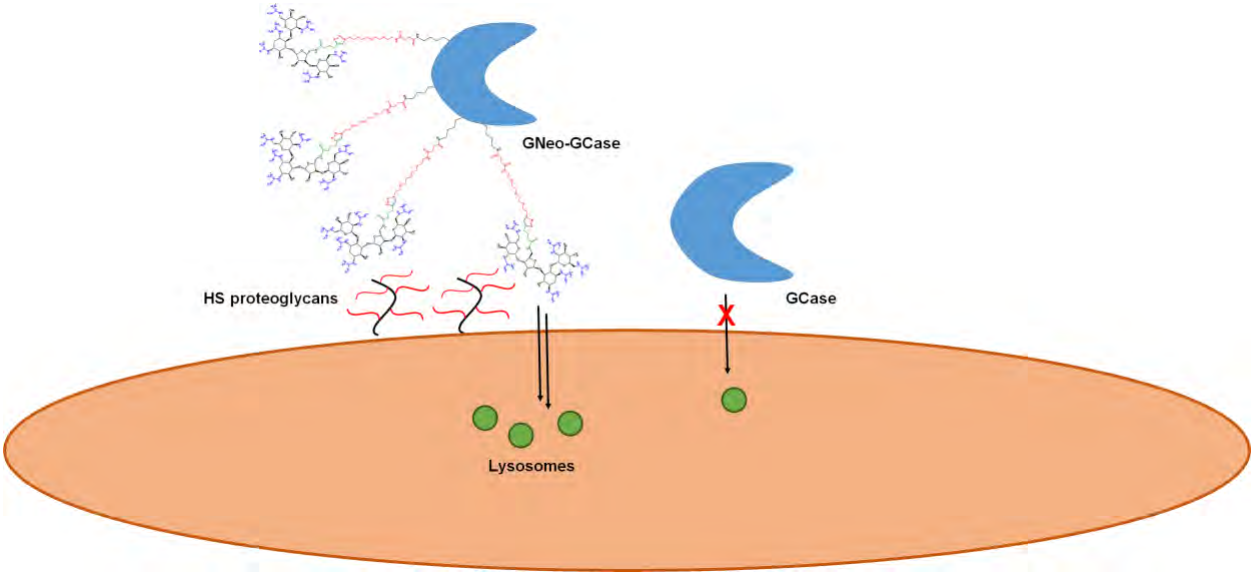


Phillip Bartels, PhD

University of California, San Diego

Mentor: Yitzhak Tor

Targeting Neurodegeneration in Gaucher's and Parkinson's Diseases with a GNeo-GCase Conjugate



Glucosylceramidase (GCase), encode by the GBA gene, is a lysosomal hydrolase that removes glucose from glucosylceramide as the final step in glycosphingolipid recycling. Homozygous mutation of GBA results in Gaucher's Disease (GD), some forms of which are neurodegenerative. Mutation of a single copy does not lead to GD, but it is considered the highest genetic risk factor for Parkinson's Disease.

The aim of my project is to modify GCase for enhanced uptake in neurons, which cannot be targeted by traditional enzyme replacement therapy. Specifically, I have covalently modified GCase with Guanidinylated Neomycin (GNeo), a small molecule that delivers cargoes to the lysosome via a heparan sulfate-dependent endocytic pathway. GNeo-GCase conjugates have been prepared and isolated on a heparin column, and retain full catalytic activity and partner protein binding. Treatment of WT and Gaucher fibroblasts has shown that a bulk concentration of 50 nM conjugate restores activity to WT levels within 2 hours, and uptake is significantly enhanced as compared to treatment with native GCase.

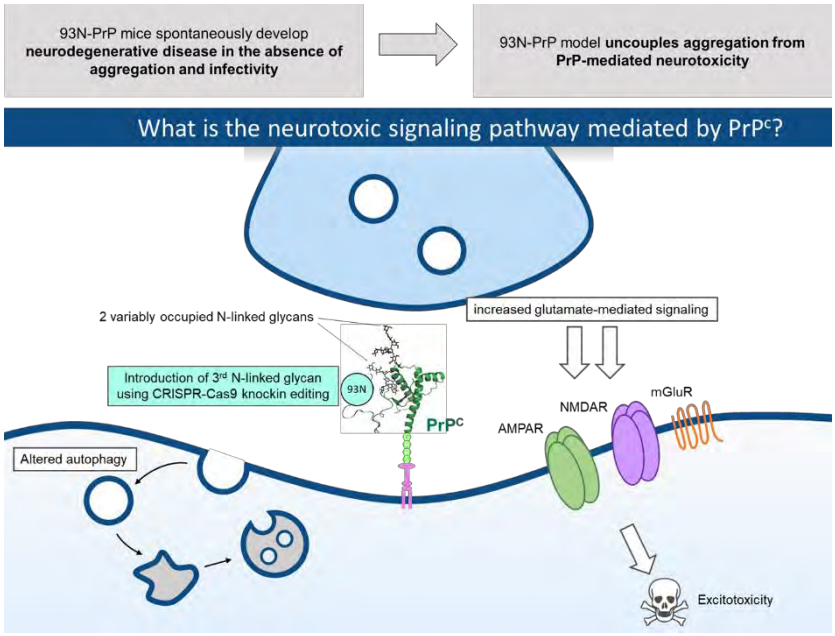
Julia Callender, Ph.D.

Postdoctoral Fellow
University of California San Diego

jcallend@health.ucsd.edu

Manipulating PrP glycan structure to understand toxic signaling pathways driving prion-induced neurodegeneration

Graphical Abstract:



Summary/Highlights:

- Prion proteins cause an infectious and rapidly progressive neurodegenerative disease characterized by an exponential increase in aggregation of prion protein (PrP).

- PrP exists on the outer leaflet of the cell membrane as a (GPI)-anchored glycoprotein containing two variably occupied N-linked glycosylation sites on its carboxy terminus. Previous work has shown that glycan modifications impact PrP aggregation and neuronal toxicity.

- We have engineered a knockin mouse model that express the prion protein PrP with an additional third glycan in the unstructured N-terminal region (*Prnp*^{93N}). This model **spontaneously develops neurodegenerative disease in the absence of PrP aggregation and infectivity**, thereby **uncoupling PrP aggregation from PrP-mediated neurotoxicity.**

Dillon Chen, MD. Ph.D.

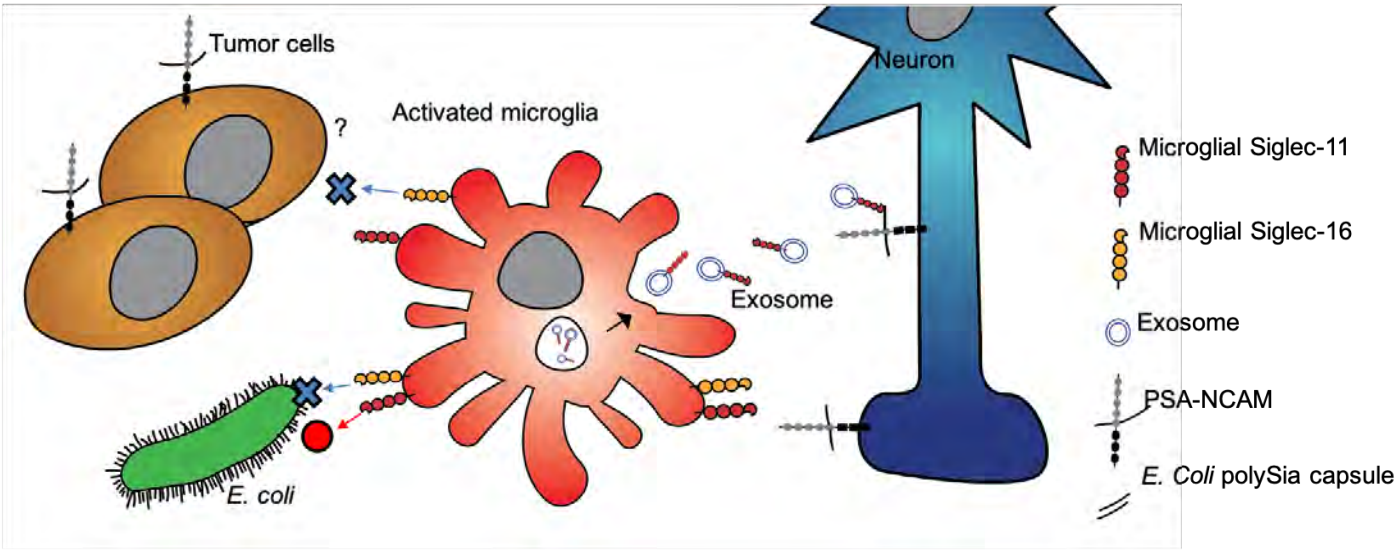
Assistant Professor
UC San Diego/Rady Children's Hospital San Diego

dyc017@ucsd.edu

UC San Diego
SCHOOL OF MEDICINE

Molecular Properties of Siglec-11 and Siglec-16 in Neuroinflammation

Graphical Abstract:



Summary/Highlights:

The paired immune-receptors Siglec-11 and Siglec-16 have uniquely human molecular properties.

SUN-MI CHOI, MD PHD

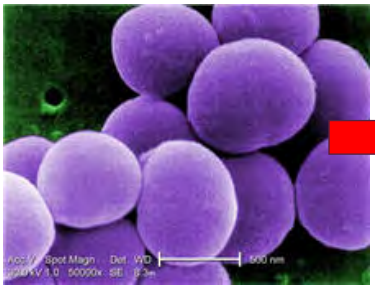
Postdoctoral Fellow

University of California, San Diego

Mentor: Victor Nizet

DYSFUNTIONAL AIRWAY MUCOSAL IMMUNITY IN CHRONIC SINUSITIS INCREASE SUSCEPTIBILITY TO MRSA

Graphical Abstract:



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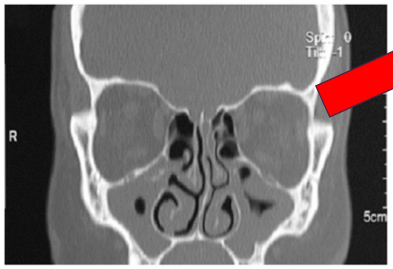
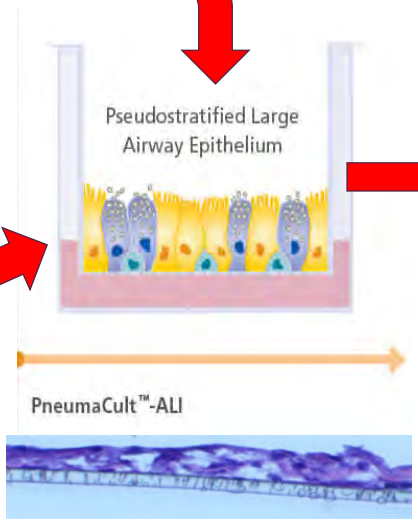
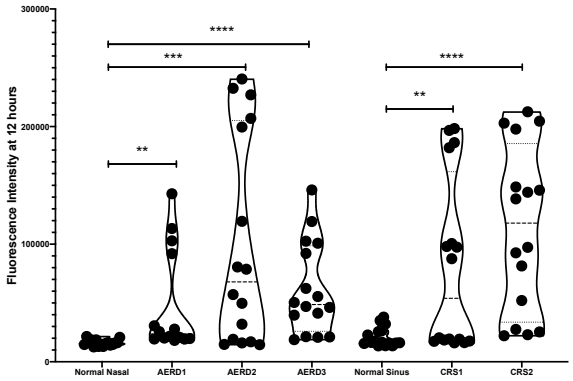


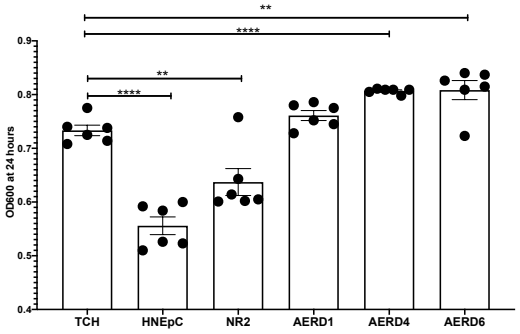
https://www.cdc.gov/hai/organisms/staph.html

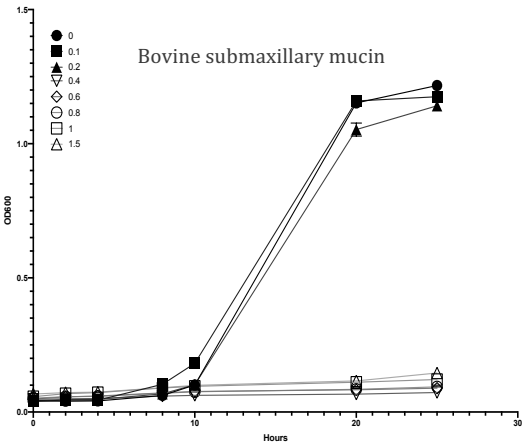
Middleton's Allergy Principles and Practice, 2014



UCSD Glycobiology Histopathology core







Summary:

Chronic sinusitis epithelium is more susceptible to MRSA. BSM inhibits growth of MRSA. Differences in mucin might predispose chronic sinusitis patients to MRSA.

Graham Heberlig, Ph.D.

Postdoctoral Fellow
K12 Scholar: Jan. 2021 – Present
University of California, San Diego

gwheberlig@ucsd.edu

Mentor:
Michael Burkart, Ph.D.

Structural Examination of Lipid A Biosynthesis Complexes

Summary

Lipid A, also known as endotoxin, is a glucosamine based saccharolipid essential for the growth of most gram-negative bacteria. It serves as a hydrophobic anchor for lipopolysaccharide (LPS) which is required for virulence. Lipid A is biosynthesized via the Raetz pathway which intersects with fatty acid biosynthesis (FAB) through the incorporation of 3-hydroxy-acyl chains donated by acyl carrier proteins (ACPs). Chemical synthesis of ACP-linked probe molecules will facilitate structural (re)characterization of the four ACP-acyltransferase complexes required to generate mature Lipid A. These structural studies may provide new strategies toward antibiotic and vaccine development.

So-Young Kim, PhD

Postdoctoral Scholar

K12 Participation: 2019-present

University of California San Diego

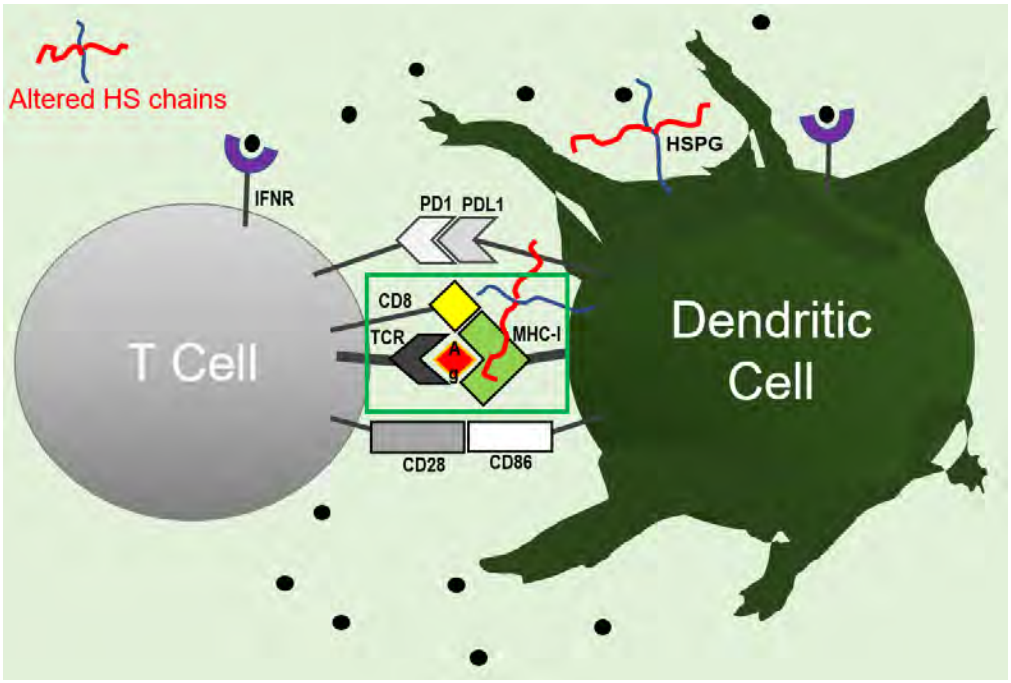
✉ **y0k001@health.ucsd.edu**

Mentor: Mark M. Fuster, MD

Heparan sulfate in dendritic cell mediated cancer & viral immunity

Keywords: heparan sulfate, antigen presenting cell, dendritic cell, cytotoxic T cell, cancer microenvironment, viral microenvironment, and immunological synapse.

Summary: While some roles for heparan sulfate (HS) in cancer and viral pathogenesis have been extensively studied, including mechanisms that facilitate proliferation and migration of cancer cells and viral attachment to epithelial cells, less is known about how HS on the antigen presenting cell surface may function in these settings. We have recently demonstrated anti-tumor and anti-viral phenotypes in mouse models with genetically altered HS chains on dendritic cells (DCs). The primary focus of my work is to uncover the mechanisms that mediate these phenotypes, including various aspects that targeting HS may modulate at the DC – T cell immunological synapse.



Gupta, P., Johns, S.C., **Kim, S.Y.**, El Ghazal, R., Zuniga, E.I. and Fuster, M.M., 2020. Functional Cellular Anti-Tumor Mechanisms are Augmented by Genetic Proteoglycan Targeting. *Neoplasia*, 22(2), pp.86-97.

Kim, S.Y., Jin, W., Sood, A., Montgomery, D.W., Grant, O.C., Fuster, M.M., Fu, L., Dordick, J.S., Woods, R.J., Zhang, F. and Linhardt, R.J., 2020. Characterization of heparin and severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) spike glycoprotein binding interactions. *Antiviral research*, 181, p.104873.

Ryan Porell, Ph.D.

Postdoctoral Fellow
K12 Scholar: Oct. 2018 – Present
University of California, San Diego

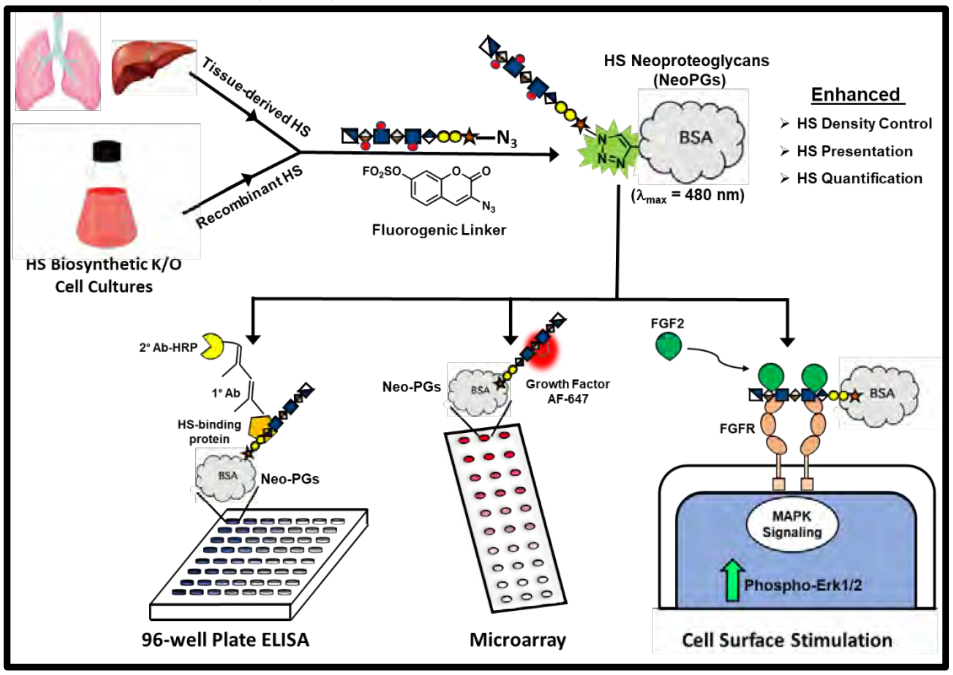
rporell@ucsd.edu

Mentor:
Kamil Godula, Ph.D.

Development of Neoproteoglycan Materials for Protein-GAG Profiling and Functional Analyses

Keywords: Microarray, glycosaminoglycan, growth factor, heparan sulfate, binding analyses, fluorescent linker, glycoconjugate, receptor signaling.

Summary/Highlights:



We demonstrate an effective strategy to generate GAG-BSA neoproteoglycan materials using tissue derived and recombinant GAG conjugated to BSA protein through a fluorescent linker. We use these materials in protein binding platforms and translate binding specificity into biological function in cellular assays.

Relevant Publication: Clausen TM, *et al.* SARS-CoV-2 Infection Depends on Cellular Heparan Sulfate and ACE2. *Cell.* 2020 Nov 12;183(4):1043-1057.e15. 2020 Sep 14. PMID: 32970989; PMCID: PMC7489987.

UC San Diego Health Sciences

Glycobiology Research and Training Center

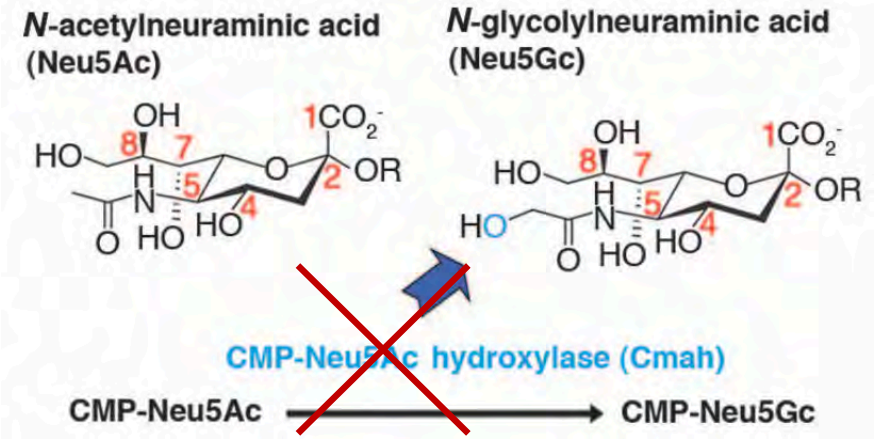
Ruth Siew, MD

Rady Children's Hospital San Diego

rsiew@health.ucsd.edu

Sialic Acid Interactions in Cystic Fibrosis (CF)

"Humanizing" mice with elimination of Neu5GC → **Led to exaggerated CFTR-dependent cholera phenotypes similar to humans**



Inactivated enzyme in humans

Create a more "human-like" mouse model by eliminating Neu5Gc that better mimics the severe CFTR-dependent CF lung phenotype of chronic lung damage and inflammatory pneumonia

Mentors: Victor Nizet & Ajit Varki