CHEMICAL APPROACHES TO STUDYING THE BIOLOGICAL FUNCTIONS OF HEPARAN SULFATE

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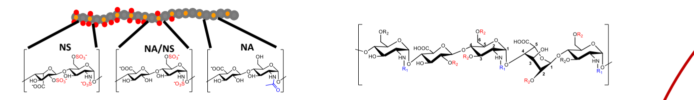
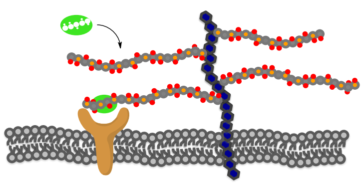
HEPARAN SULFATE GLYCOSAMINOGLYCANS

Challenges Arise from Diversity of HS Structures



- Long, linear polysaccharide found in all animal tissues
- One or more chains attach to cell-surface or ECM proteins to form HSPGs
- Mediate a variety of biological functions from angiogenesis to bacterial adhesion
- Four possible sites of sulfation: *N*, 6-*O*, 3-*O* and 2-*O*
- One possible site for acetylation: N-acetylation
- Presence of two uronic acid epimers: Iduronic Acid or Glucuronic Acid

HS Mediates A Wide Array of Biological Functions



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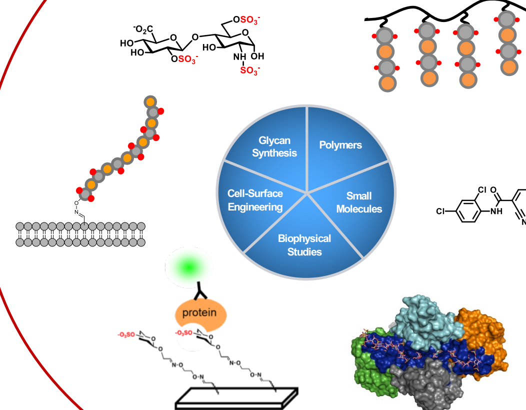
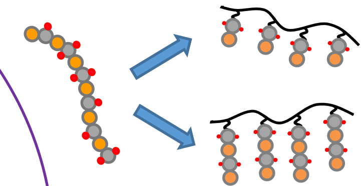
- Left: HSPG mediates docking of soluble ligand to a cell-surface receptor via ternary complex

TOOLBOX FOR STUDYING HS BIOLOGY



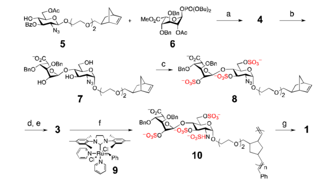
USING BIOMIMETICS TO PROBE HS BIOLOGY

Synthetic Polymers as Mimetics of HS Polysaccharides



- Synthetic polymers decorated with "pendant" oligosaccharides
- Can easily control the length and sulfation patterns
- Provide access structurally defined mimetics of natural heparin and heparan sulfate

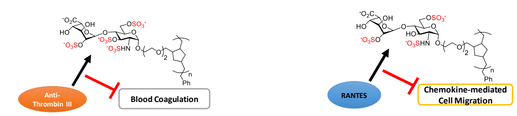
Synthesis of Hep/HS Glycopolymers



Conditions:
(a) TMSOTf, CH_2Cl_2, −30 ° C, 85%. (b) 0.7 M LiOH, H_2O_2, 25 ° C; MeOH, 4 M NaOH, 25 ° C, 82% over two steps. (c) SO_3•TMA, DMF, 60 ° C, 71%. (d) PMe_3, THF, 25 ° C, quant. (e) SO_3•pyr, pyr/Et_3N, 60 ° C, 54% over two steps. (f) MeOH:$(CH_2Cl)_2$, 55 ° C. (g) $Pd(OH)_2$/C, 1 atm H_2, MeOH, phosphate buffer (pH 7.4), 63–92%.

Gama *et al. Nature Chem. Biol.* **2006**, *2*, 467.
Rawat *et al. J. Am. Chem. Soc.* **2008**, *130*, 2959.

Biological Activity of Heparin and HS Glycopolymers

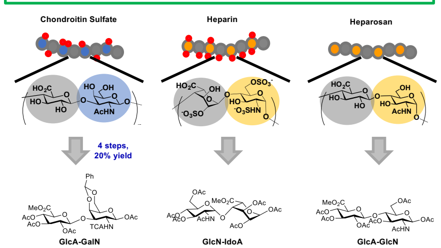


- By changing the sulfation pattern and length, we can target different proteins
- Polymers bearing a specific tetra-sulfated motif, inhibited anti-thrombin III blood coagulation cascades
- Polymers bearing a specific tri-sulfated motif, inhibited RANTES-induced cell migration

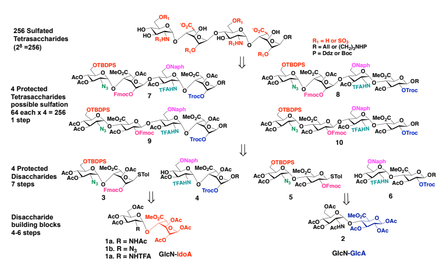
Sheng *et al. J. Am. Chem. Soc.* **2013**, *135*, 10898; Oh *et al. Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 11796.

USING CHEMICAL SYNTHESIS TO UNDERSTAND STRUCTURE-FUNCTION RELATIONSHIPS

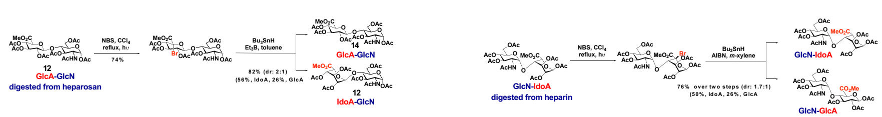
Ready Access to Synthetic Building Blocks from Natural Polysaccharides



Proposed Synthesis of HS Tetrasaccharide Libraries



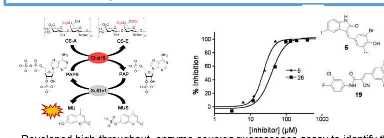
Epimerization Enables Access to Greater Diversity of Disaccharides



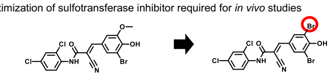
N. Pawar *et al. Angew. Chem. Int. Ed. Engl.* **2019**, *58*, 18577.

MANIPULATING SULFATION PATTERNS TO STUDY HS BIOLOGY

Development of Sulfotransferase Inhibitors

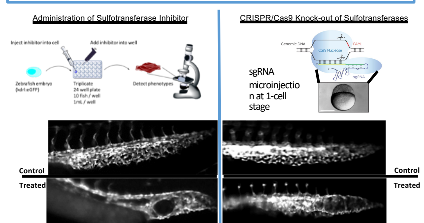


- Developed high-throughput, enzyme-coupled fluorescence assay to identify the first cell-permeable, small-molecule inhibitors of sulfotransferases
- Inhibitors exhibit dose-dependent inhibition of Chst15 using a [35S]-labeling assay
- Optimization of sulfotransferase inhibitor required for *in vivo* studies

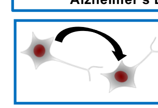


Cheung *et al. ACS Chem. Biol.* **2017**, *12*, 3126.

HS Sulfation Regulates Vascular Development

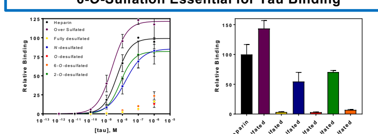


Alzheimer's Disease: A Prion-like Disease?

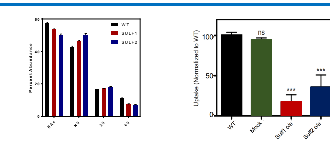


- Tau protein implicated in progression of Alzheimer's Disease
- Recent studies suggest trans-neuronal spreading of pathogenic tau species
- Recent studies highlight HSPGS as putative receptors

6-*O*-Sulfation Essential for Tau Binding



Sulf1/2 Overexpression Modulate HSPGs and Tau Uptake



- Over-expression of Sulf1 and Sulf2 both decrease the abundance of 6-*O*-sulfation
- Over-expression of Sulf1 and Sulf2 both decrease the uptake of tau

Rauch *et al. Sci. Rep.* **2018**, *8*, 6382.