# Review Criteria for GlycoMIP In-House Research Project Proposals

(last updated: October 11, 2022)

In-House Research Project Proposals will be evaluated against GlycoMIP's In-House research goals and objectives. Overarching Research Objectives (OROs) will not change during the award period, but Specific Research Objectives (SROs) will be created each year, beginning May 1, 2021. Below are the OROs for each of the four research Loops, followed by the SROs (by year). Project proposals should reference the appropriate OROs and SROs and will be evaluated by an internal review panel against a project's ability to meet stated goals.

**The main goals of GlycoMIP's In-House Research program include:**

1. Develop new chemical and enzymatic methods and protocols for the automated synthesis of glycopolymers with the guidance of advanced machine-learning techniques
2. Develop advanced automated modeling protocols that better account for the effects of molecular environment on the conformations and physical properties of glycopolymers.
3. Implement autonomous and automated computational methods for predicting and assigning the spectra (ROA, VCD, MS) of glycopolymers.
4. Develop high-throughput methods for accurately predicting and measuring the strengths of carbohydrate-protein interactions.

**Overarching Research Objectives (OROs)** (Established in 2020, final revisions May 2022):

Description of Overarching Research Objectives (OROs) for Each In-House Research Loop, associated PIs and Loop "Leads"

**Loop 1:** Novel Glycomaterials
**Leads: Matson / Deshmukh**

**ORO 1.1** Prepare interfacially-active polysaccharide-containing copolymers. **Deshmukh, Edgar, Johnson, Matson, Moore**

**ORO 1.2** Develop new methods to synthesize, characterize, and model proteoglycan-mimetic polymers. **Deshmukh, Edgar, Johnson, Matson, Moore**

**Loop 2:** Biocatalysis in Glycomaterial Creation
**Lead: Roman**

**ORO 2.1** Develop new enzyme-based methods to synthesize glycomaterials that are suited for automation. **Linhardt, Liu, Roman**

**ORO 2.2** Advance methods to characterize solution-, gel-, and solid-state glycomaterials at the molecular and nanostructural level. **Roman**

**ORO 2.3** Develop software for the prediction of ROA and VCD spectra for a given carbohydrate. **Crawford**

| Loop 3: Rational Glycomaterial Design<br>**Lead: Woods** |
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**ORO 3.1** Launch Interface Enabling Automated MD Simulation and Analysis of Engineered Glycomaterials. **Woods**

**ORO 3.2** Improve the accuracy of predicted carbohydrate interaction energies. **Woods**

**ORO 3.3** Advance the development of atomistic glycomaterial modeling. **Welborn, Woods**

**ORO 3.4** Develop high throughput methods for quantifying carbohydrate interactions. **Esker, Schulz**

| **Loop 4:** Machine Learning in Glycoscience<br>**Lead: Hong** |
|---|

**ORO 4.1** Automated synthesis of glycans and glycomaterials. **Helm**

**ORO 4.2** Automation of glycan structure determination by NMR, LC-MS and $MS^n$. **Azadi, Helm, Hong**

**ORO 4.3** Machine learning applied to structural analysis of glycans and glycomaterials. **Hong**

**ORO 4.4** Machine learning of automated glycan synthesis. **Kong**

**ORO 4.5** Predicting biophysical properties from molecular characterization/modeling data. **Azadi, Helm, Hong, Kong**

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**Specific Research Objectives (SROs)** (Established for each year of the project, beginning May 1, 2021):

<u>**Year 1**</u> (May 1, 2021 thru April 30, 2022) Specific Research Objectives (SROs) for each In-House Research Loop, associated PIs and related OROs.

| **Loop 1:** Novel Glycomaterials (formerly Accelerating the discovery of novel glycomaterials)<br>**Leads: Matson / Deshmukh** | **Relevant ORO** |
|---|---|
| **SRO 1.1.1** Evaluation of phase behavior in base un-compatibilized blends by phase contrast optical microscopy and small-angle laser light scattering. **Moore** | **1.1** |
| **SRO 1.1.2** Evaluation of interfacial tension in base un-compatibilized blends; breaking thread method. **Moore** | **1.1** |
| **SRO 1.1.3** Develop synthetic methods for chain-extension polypeptide synthesis using *N*-thiocarboxyanhydrides. **Matson** | **1.1** |
| **SRO 1.1.4** Develop transferable coarse-grained models of mono/polysaccharides and other polymers of interest. **Deshmukh** | **1.1** |
| **SRO 1.1.5** Develop method for synthesis of poly(hydroxyalkanoic acid)-polysaccharide block copolymers by displacement chemistry. **Edgar** | **1.1** |

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|---|---|
| **SRO 1.1.6** Combinatorial base blend formulation and evaluation of base blend phase behavior *via* directed rheological sensing. **Johnson** | **1.1** |
| **SRO 1.1.7** Develop transferable models for building blocks of glycosaminoglycan analogs. **Deshmukh** | **1.2** |
| **SRO 1.1.8** Plan synthetic routes to sulfated glycosaminoglycan analogs. **Edgar** | **1.2** |
| **SRO 1.1.9** Plan sensor surface functionalization approaches for GAG-mimetic polymer immobilization. **Johnson** | **1.2** |
| **SRO 1.1.10** Plan synthetic routes to mono/di-saccharide-containing graft polymers. **Matson** | **1.2** |
| **SRO 1.1.11** SAXS and SANS characterization of GAG-mimetic polymers; state of dispersion, conformation. **Moore** | **1.2** |

| **Loop 2:** Biocatalysis in Glycomaterial Creation (formerly Accelerating the development of designer glycomaterials) **Lead: Roman** | **Relevant ORO** |
|---|---|
| **SRO 2.1.1** Train new postdoctoral fellows and graduate students in the methods required to execute the project. **Linhardt, Liu** | **2.1** |
| **SRO 2.1.2** Identify model compounds/carbohydrates and generate a library of ROA and VCD spectra. **Roman** | **2.2, 2.3, 2.4** |
| **SRO 2.1.3** Explore the use of polarizable force fields in carbohydrate modeling. **Welborn** | **2.3** |
| **SRO 2.1.4** Identify methods to engage solvation phenomena in the prediction of carbohydrate ROA and VCD spectra. **Crawford** | **2.3, 2.4** |

| **Loop 3:** Rational Glycomaterial Design (formerly Accelerating knowledge in glycan recognition and Advancing glycan modeling) **Lead: Woods** | **Relevant ORO** |
|---|---|
| **SRO 3.1.1** Install computer servers and user facility instruments, validate, and create working environment. **Esker, Woods** | **3.1, 3.4** |
| **SRO 3.1.2** Hire and train students/staff **Esker, Woods** | **3.1, 3.2, 3.4** |
| **SRO 3.1.3** Create Web-suite with User Login Environment for Modeling Services. **Woods** | **3.1** |
| **SRO 3.1.4** Create a workflow in C++/python that enables MD simulations of oligosaccharides to be prepared and submitted automatically. **Woods** | **3.1** |
| **SRO 3.1.5** Evaluate AMOEBA polarizable force field issues for oligosaccharides. **Welborn** | **3.3** |
| **(New) SRO 3.1.6** Create and characterize the binding of hyperbranched oligosaccharides in terms of affinity and avidity for protein receptors. **Schulz** | **3.4** |

| **Loop 4:** Machine Learning in Glycoscience (formerly Accelerating automation of glycan synthesis and analysis)<br>**Lead: Hong** (formerly Helm) | **Relevant ORO** |
|---|---|
| **SRO 4.1.1** Prioritize oligosaccharide standards needed for synthesis and characterization based upon deficits in molecular modeling, NMR and MS needs. **Helm** | **4.1, 4.2, 4.3, 4.4** |
| **SRO 4.1.2** Develop a framework for downloadable data repositories of glycomaterial NMR spectra. **Azadi, Hong** | **4.2, 4.3** |
| **SRO 4.1.3** Develop a framework for downloadable data repositories of glycomaterial LC-MS data. **Azadi, Hong** | **4.2, 4.3** |
| **SRO 4.1.4** Focusing on descriptive models of glycan synthesis, research and understand the impact of the possible inputs, such as molecular properties, anomeric selectivity, reaction conditions, etc., and review existing modeling methods (data driven, simulations, experimental) to understand their pros and cons. **Kong** | **4.3, 4.4** |

**Year 2** (May 1, 2022 thru April 30, 2023) Specific Research Objectives (SROs) for each In-House Research Loop, associated PIs and related OROs.

| **Loop 1:** Novel Glycomaterials<br>**Leads: Matson / Deshmukh** | **Relevant ORO** |
|---|---|
| **SROs related to interfacially active materials** | |
| **SRO 1.2.1** Develop synthetic method for synthesizing a range of polysaccharide-containing copolymers on the ~1 g scale. **Matson** | **1.1** |
| **SRO 1.2.2** Synthesize polysaccharide/poly(hydroxyalkanoic acid) block copolymers to compatibilize polysaccharide/PLA blends on a larger scale. **Edgar** | **1.1** |
| **SRO 1.2.3** Evaluate phase behavior in a matrix of formulations of solvent cast compatibilized blends by phase contrast optical microscopy and small-angle laser light scattering. **Moore, Johnson, Deshmukh** | **1.1** |
| **SRO 1.2.4** Demonstrate continuous reaction monitoring *via* high throughput characterization. **Johnson, Matson, Edgar** | **1.1** |
| **SRO 1.2.5** Develop a molecular-level understanding of the structural and chemical features controlling the conformations of polysaccharide-containing block copolymers in solvents. **Deshmukh, Edgar** | **1.1** |
| **SRO 1.2.6** Investigate diffusion/transport of solute molecules in polymer blends and their rheological properties. **Johnson** | **1.1** |
| **SRO 1.2.7** Evaluate novel polysaccharide hydrogel rheology for printing of responsive materials. **Johnson, Edgar** | **1.1** |

| SROs related to proteoglycan-mimetic polymers | |
|---|---|
| **SRO 1.2.8** Computationally design architectures of polysaccharide-containing block copolymers and perform CG MD simulations to develop a molecular-level understanding of the relationship between their structure and properties. **Deshmukh** | **1.2** |
| **SRO 1.2.9** Plan synthesis of GAG analogs with sequence control. **Edgar** | **1.2** |
| **SRO 1.2.10** Characterize thermodynamic binding parameters from sensor data associated with GAG-functionalized surface binding reactions. **Johnson** | **1.2** |
| **SRO 1.2.11** Synthesize graft polymers with oligosaccharide side chains on a small scale. **Matson** | **1.2** |
| **SRO 1.2.12** Refine scattering models for conformational analysis and electrostatic structure for GAG and proteoglycan-mimetic polymers. **Moore** | **1.2** |

| **Loop 2:** Biocatalysis in Glycomaterials Creation<br>**Lead: Roman** | **Relevant ORO** |
|---|---|
| **SRO 2.2.1** Identify a suitable solid support for the automatable, enzyme-based synthesis. **Linhardt, Liu** | **2.1** |
| **SRO 2.2.2** Develop a new method for the biocatalytic modification of glycomaterials in a continuous flow system. **Roman** | **2.1, 2.2** |
| **SRO 2.2.2** Establish procedures that yield high-quality vibrational optical activity and rheometry data for validation of computational predictions. **Roman** | **2.2, 2.3** |
| **SRO 2.2.4** Develop a new or refine the existing protocol [Palivec et al., *Phys. Chem. Chem. Phys.*, 2020, 22, 1983.] for the prediction of ROA and VCD spectra of carbohydrates. **Crawford** | **2.2, 2.3** |

| **Loop 3:** Rational Glycomaterials Design (formerly Advancing glycan modeling)<br>**Lead: Woods** | **Relevant ORO** |
|---|---|
| **SRO 3.2.1** Establish a web-accessible interface that guides a user through the steps of submitting an MD simulation online. **Woods** | **3.1** |
| **SRO 3.2.2** Develop a theoretical approach to computing carbohydrate-binding energies that includes explicit (atomic) water molecules. **Woods** | **3.1** |
| **SRO 3.2.3** Evaluate the accuracy and performance of explicit-solvent binding energy predictions compared to free energy methods. **Woods** | **3.2** |
| **SRO 3.2.4** Compute electric fields from polarizable NPT simulations (AMOEBA) from glycan-glycan and glycan-protein ensembles generated with AMBER/GLYCAM. **Welborn** | **3.3** |
| **SRO 3.2.5** Synthesize a library of biotinylated and non-biotinylated oligosaccharide binding partners. **Esker, Schulz** | **3.4** |
| **SRO 3.2.6** Evaluate a direct-binding assay for glycan-bead conjugates from automated synthesis using flow cytometry. **Esker** | **3.4** |

| | |
|---|---|
| **SRO 3.2.7** Create and characterize the binding of hyperbranched oligosaccharides in terms of affinity and avidity for protein receptors. **Schulz** | **3.4** |
| **SRO 3.2.8** Identify polysaccharides that form double helices and evaluate for applicability in synthesis, modeling and characterization. **Schulz, Woods** | **3.4** |
| **SRO 3.2.9** Identify proteins that form well-defined interactions with polysaccharides and evaluate for applicability in synthesis, modeling and characterization. **Welborn** | **3.4** |
| **SRO 3.2.10** Perform a comparison of measured binding affinities for ITC, BLI and SPR to develop benchmark data for theoretical modeling validation. **Esker** | **3.4** |

| **Loop 4:** Machine Learning in Glycoscience<br>**Lead: Hong** | **Relevant ORO** |
|---|---|
| **SRO 4.2.1** Training of undergraduate students, graduate students, post docs and visiting scientists. **All** | **All** |
| **SRO 4.2.2** Prioritize 2,3 and 2,6 linked sialic acids. All glycans will be analyzed by $MS^n$ at both the UGA and VT facilities. The data will be provided for ML. **Azadi, Helm, Hong** | **4.2, 4.3** |
| **SRO 4.2.3** Collect $MS^n$ data on the set of NIST standard glycans for characterization based upon deficits and MS needs both by UGA and VT. The data will be provided for ML. **Azadi, Helm, Hong** | **4.2, 4.3** |
| **SRO 4.2.4** Optimize the synthesis of a branched oligosaccharide with varying Glyconeer reaction conditions. Record all conditions during the optimization process, which will be provided for ML. **Helm, Kong** | **4.1, 4.3, 4.4** |
| **SRO 4.2.5** Continue literature review and developing descriptive models of Glycan synthesis (research and understand the impact of the possible inputs, such as molecular properties, anomeric selectivity, reaction condition, etc.) **Helm, Kong** | **4.1, 4.4** |