NDnano
Notre Dame Nanoscience and Technology

NDnano Summer Undergraduate Research
2022 Project Summary

1. Student name & home university:
Salmady Ramos Valentín, University of Puerto Rico Mayagüez

2. ND faculty name & department:
Prof. Matthew J. Webber, Chemical and Biomolecular Engineering

3. Summer project title:
Dendrimer Synthesis for Nanoscale Glucose-Responsive Assemblies

4. Briefly describe new skills you acquired during your summer research:

Synthesis, NMR, Spectrum analysis, Safety, Lab work

5. Briefly share a practical application/end use of your research:
Glucose-responsive materials are of interest for applications in smart insulin delivery for diabetes therapies. Dendrimers work as the building block for the crosslinked dynamic-covalent networks which form materials capable of storing insulin.

6. 50- to 75-word abstract of your project:

Dendrimers are structurally ordered, multifunctional, and highly branched polymeric molecules. Here, we seek to design dynamic-covalent crosslinked hydrogel materials using dendrimer building blocks containing PBA-diol conjugates to sense and respond to high glucose levels to release an accurate amount of encapsulated insulin. Dendrimers are a great candidate for these materials thanks to their high number of functional groups and their controlled, simple, defect-free, cost-effective synthesis.

7. References for papers, posters, or presentations of your research:

Xiang, Y.; Xian, S.; Ollier, R. C.; Yu, S.; Su, B.; Pramudya, I.; Webber, M. J. Diboronate Crosslinking: Introducing Glucose Specificity in Glucose-Responsive Dynamic-Covalent Networks. *Journal of Controlled Release* 2022, *348*, 601–611.
Webber MJ, Anderson DG. Smart approaches to glucose-responsive drug delivery. J Drug Target. 2015;23(7-8):651-5. doi: 10.3109/1061186X.2015.1055749. PMID: 26453161; PMCID: PMC5450160.
Gates, B. D.; Vyletel, J. B.; Zou, L.; Webber, M. J. Multivalent Cucurbituril Dendrons for Cell Membrane Engineering with Supramolecular Receptors. *Bioconjugate Chemistry* 2022.

Diabetes impacts millions of people worldwide. Current treatments involve self administration of insulin or mechanical pump. Unfortunately, both methods have their downsides. They require routine monitoring and estimation of insulin dose, which is sometimes inaccurate leading to imprecise control that causes problematic high and low blood glucose levels in patients. A convenient strategy would be having a material that automatically responds to instant high blood glucose levels and releases an appropriate amount of insulin. That is why in the search for improved therapies glucose-responsive materials are of interest for applications in smart insulin delivery. These materials would be capable of sensing glucose and undergoing nanoscale conformational changes for insulin release that is dictated by blood glucose level.

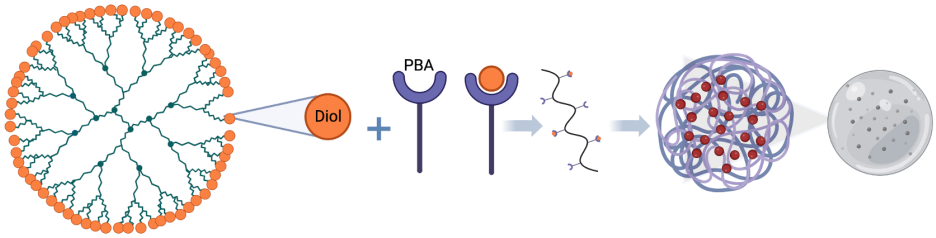


Figure 1. Dendrimer building block diol functionalized with PBA-diol crosslink interactions forming a network with insulin stored inside

My project seeks to design dynamic-covalent crosslinked hydrogel materials using dendrimer building blocks containing PBA-diol conjugates to sense and respond to high glucose levels by releasing an appropriate amount of insulin. The highly branched architecture of dendrimers presents a multivalent and multifunctional unit that can be used to create effective crosslinking interactions. The PBA-diol chemistry is susceptible to competition from glucose since it is a cis-1,2 diol. This in turn creates dynamic-covalent crosslinked hydrogels where their equilibrium-governed bond exchange would allow appropriate insulin release at high glucose concentrations.

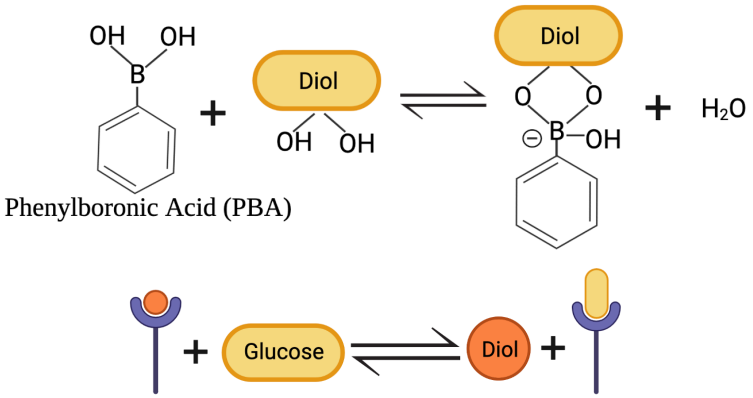


Figure 2. Phenylboronic acid(PBA)-diol interaction and equilibrium bond exchange with glucose

Several studies have demonstrated dendrimer-based building blocks for the formation of self-assembled nanoscale networks. Dendrimer synthesis offers the opportunity of generating structurally precise nanoscale architectures reminiscent of those found in biology.

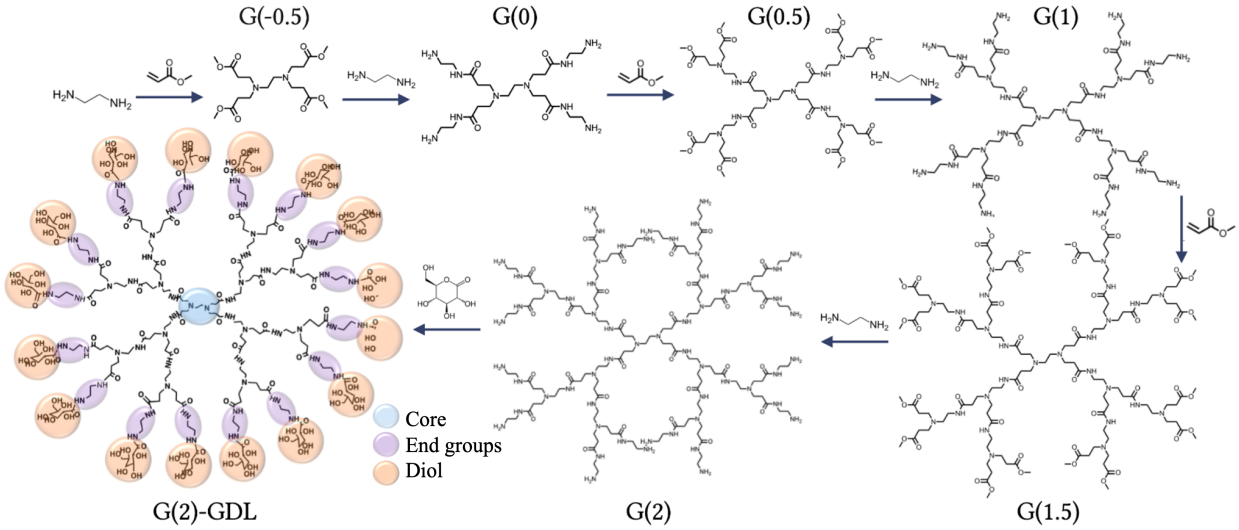
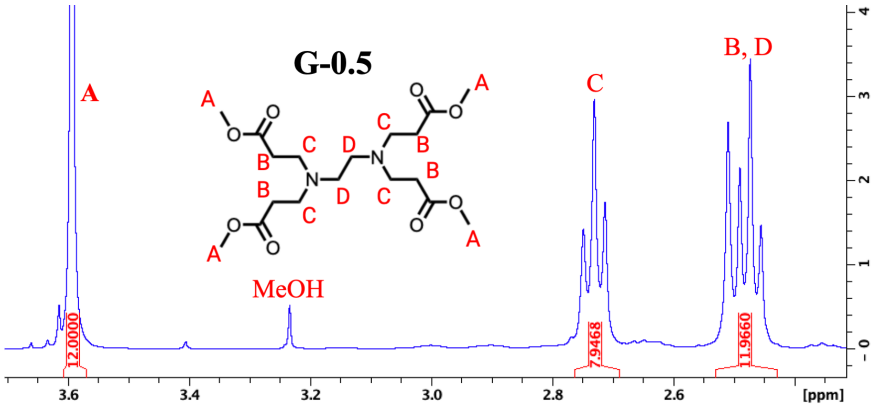


Figure 3. Example of polyamidoamine dendrimer synthesis alternating michael addition (methyl acrylate) followed by amidation (EDA), up to generation 2 end group functionalized with glucono-delta-lactone(GDL)

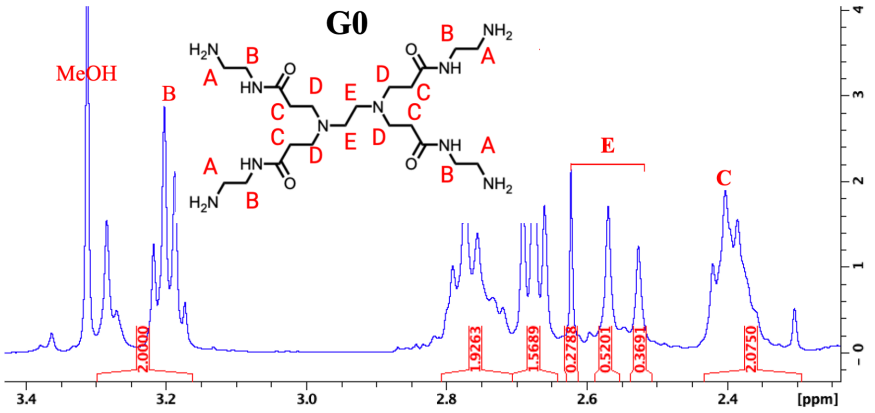
In order to prepare dendrimers, we use multi-step controlled divergent synthesis that involves building the dendrimer from a multifunctional core and extending it outward through a series of repetitive reactions. The synthesis starts with an ethylenediamine(EDA) core, then alternating michael addition (methyl acrylate) followed by amidation with EDA until a generation 2 (G2) dendrimer is achieved. The addition reaction took 2 days, whereas the amidation took 7 days. After achieving G2 dendrimer with 16 arms, the end groups were functionalized with Glucono-delta-lactone (GDL).

After each reaction, ^{1}H NMR was employed to analyze the molecular structure and verify formation of the desired product. With this characterization we assured no reactant remained following each step to avoid the creation of first generation dendrimers in the next reaction. Having reagent left would lead to the formation of new dendrimers with fewer end groups and lower functionalization of the material.



Proton	Expected	Obtained
A	12	12
C	8	7.9468
B,D	12	11.966

Figure 4: Labeled ^{1}H NMR spectrum for G-0.5 PAMAM dendrimer in D_2O



Proton	Expected	Obtained
B	2	2
C	2	2.075
D	2	1.9263
E	1	1.168
A	2	1.5689

Figure 5: Labeled ^{1}H NMR spectrum for G0 PAMAM dendrimer in D_2O

High yield and completion of each synthetic step is important to ensure purity and consistency. In order to successfully implement dendrimers in these applications, structural defects in higher generations must be avoided. Dendrimers are a great candidate for these assemblies thanks to their high number of functional groups and their controlled, simple, cost-effective synthesis. Also, it is possible to achieve defect-free nanostructures leading to higher diol functionalization. For future work, in vitro and in vivo experiments need to be conducted to study glucose responsiveness and therapeutic function of these materials.