DENDRON AVIDITY PLATFORMS WITH ORTHOGONAL FOCAL POINT COUPLING SITE
Thesis Defense by Daniel McNerny
Chair: James R. Baker, Jr., M.D.
Tuesday, August 31st at 9:30 am

Abstract of Thesis
This thesis explores the design and synthesis of bifunctional or modular platforms from poly(amidoamine) (PAMAM) dendrons. PAMAM dendrons with an orthogonal focal point are evaluated, testing several click chemistry reactions for high conversion and mild conditions. The orthogonal reaction chemistry used at the dendron focal point gives a precise 1:1 ratio of the attachment of multiple functionalities to a small molecular weight, chemically stable high avidity molecule.

In the first component of the thesis, dendrons were synthesized with c(RGDyK) peptide on the surface to create a scaffold for cellular targeting and multivalent binding. Binary dendron-RGD conjugates were synthesized with a single imaging agent, therapeutic drug, or additional functionalized dendron at the focal point after an copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) click reaction. The targeted-dendron platform was shown to specifically target αVβ3 integrin expressing human umbilical vein endothelial cells (HUVEC) and human glioblastoma cells (U87MG) in vitro via flow cytometry. Specific targeting of the dendron-RGD platform was further confirmed by confocal microscopy. Biological activity of the targeted drug conjugate was confirmed via XTT assay.

The remainder of the thesis explores click chemistry reactions that do not require a metal catalyst, which may cause undersired toxicity for some biological applications. Thiol-based click chemistry, specifically the thiol-ene and thiol-yne reactions, is explored on dendron platforms. The thiol click reactions provide an improved efficiency, compared to CuAAC, by reaching quantitative conversion of the focal point in most cases. The thiol click reactions suffer from some setbacks: the need for a thermal or photoinitiator may prevent the conjugation of some functional ligands and the thiol chemistry is more prone to side reactions.

Finally, strain-promoted alkyne-azide cycloadditions are examined. The ring-strain click chemistry displayed a high degree of orthogonality and quantitative conversion when applied to dendrons. Unfortunately, attempts to build dendrons from a cyclooctyne core were unsuccessful, as traditional growth reactions led to the partial cleavage of the strained ring. However, an alternative convergent synthesis approach is suggested. In general, these studies of orthogonal coupling pathways serve as a framework to selectively combine relevant functions to well-defined modular platforms for many diagnostic and therapeutic applications.