An Atomic Force Microscopy Study of Riboflavin Receptor Targeting Nanoparticles

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Most common anticancer drugs kill healthy cells in addition to cancerous cells, producing many side effects that have become the signature of cancer treatment. A targeted approach to drug delivery could prove to be less toxic to the entire system by directing treatment to certain cells. Nanoparticles, coupled with ligands, provide a platform for targeted delivery of chemotherapeutics and imaging agents to cancer cells. Our research considers the use of a nanoparticle subgroup called dendrimers. These highly branched complexes allow conjugation with other molecules, such as agents for targeting, detection, and therapy. We study dendrimers that are conjugated with riboflavin molecules that serve as targeting agents.

Riboflavin, more commonly known as vitamin B\textsubscript{2}, has shown to be promising in the area of targeted drug delivery. There is an over-expression of riboflavin receptors on the cell membrane of breast and prostate cancer cells. These receptors allow riboflavin to enter the cell and assist in the formation of the redox cofactors that are necessary for growth and division of the cell. We can use riboflavin receptors as a biomarker to direct the drug only to cancerous cells. One way of achieving this is by attaching riboflavin and a common anticancer drug, such as methotrexate, to a dendrimer platform. This system would concentrate the cancer drug to the source of the problem, decreasing toxicity to other cells and enabling delivery at an overall lower concentration.

Through this summer’s work, we sought to understand the binding interaction of a riboflavin-conjugated dendrimer with a single riboflavin receptor. To study these most basic interactions, our lab implements a force-pulling method using Atomic Force Microscopy (AFM). We covalently attach a riboflavin-conjugated dendrimer to a gold tip of approximately 10µm, and attach the riboflavin receptor to a gold surface (Figure 1). By moving toward the tip toward the surface we can induce binding and consequently break the bond on withdrawal of the tip, measuring the force of the process. Repeating this bond making and breaking process over a thousand times allows us to determine the force which produces the most frequent bond failure. Furthermore, varying the speed at which the tip approaches the surface allows for further analysis and modeling of data to yield useful kinetic parameters.

These kinetic findings help define the bond strength between the riboflavin-conjugated dendrimer and the riboflavin receptor. The parameters we attain through our kinetic modeling specifically help us understand the energy barriers preventing bond breakage ($k^†$, $\Delta G^‡$) and how quickly the binding interaction is broken ($k_{off}$). This information can help our collaborators better understand this system in application to drug dosing and other practical aspects.

Our work this summer has introduced me the technical challenge of obtaining information about molecules on the nano-level. Learning this force-pulling technique has been extremely rewarding and has taught me much about the experimental and analytical process of determining kinetic parameters from single molecule interactions. Additionally, participating in this research project has helped me further develop a wide range of skills for a career in medical research.

Figure 1. Riboflavin-conjugated dendrimer attached to AFM tip approaching riboflavin receptors immobilized on the surface.