Cancer remains a formidable problem affecting the lives of millions each year. An estimated 13 million people are currently living with cancer in the United States.\textsuperscript{1} An estimated 600,000 people lost their lives in 2013 due to cancer.\textsuperscript{1} The most common killers in the United States are lung cancer, breast cancer, and prostate cancer.\textsuperscript{1} Approximately 40.8\% of men and women in the United States will be diagnosed with some type of cancer during their lifetime.\textsuperscript{1} Currently, only 65.8\% of cancer patients are expected to survive more than 5 years following diagnosis.\textsuperscript{1} Cancer is the second most common cause of death in the United States and accounts for nearly 1 in every 4 deaths.\textsuperscript{2} Although cancer continues to affect the lives of many, new solutions are bringing promising results.

One new promising cancer treatment involves attacking cancer on the nanoscale. Nanomedicine is a relatively new field and is defined as the application of nanotechnology to the research and practice of medicine.\textsuperscript{3} New nanodrugs are being used to treat cancer. Nanodrugs are comprised of an anticancer agent and a nanosized carrier that selectively delivers the drug to a localized cancerous area by protecting the drug from the body’s immune system response during transport via active or passive targeting.\textsuperscript{3} Nanodrugs entered the market in 1995 with approval of the first nanodrug, doxorubicin, commercially known as Doxil.\textsuperscript{4} During the period after the approval of Doxil, 28 nanodrugs have been approved that utilize a variety of drug delivery platforms.\textsuperscript{5}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{PEG.png}
\caption{Structure of Polyethylene Glycol. \textit{Source:} http://web.mit.edu/3.082/www/team2_s02/PEG.jpg}
\end{figure}

The use of biocompatible nanomaterials has revolutionized drug delivery platforms.\textsuperscript{6} Drug delivery platforms frequently utilize polymers and those that largely involve polymers are now used by tens of millions of people annually.\textsuperscript{5} One of the most important polymers for the creation of nanosized carriers is polyethylene glycol (PEG). The general structure of PEG is depicted in Figure 1. PEG refers to any polymer of the general formula H(OCH\textsubscript{2}CH\textsubscript{2})\textsubscript{n} where n \geq 4.\textsuperscript{7} A suffix is sometimes applied to indicate the mean molecular mass (eg. Polyethylene glycol 4000).\textsuperscript{7} Polyethylene glycols with a molecular weight of up to 35,000 AMU are available commercially.\textsuperscript{8} The form polyethylene glycols take depends on temperature and mean molecular weight. Polyethylene glycols are clear viscous liquids or white solids.\textsuperscript{7} PEG is synthesized by a polymerization of ethylene oxide (EO) with water, mono ethylene glycol, or diethylene glycol as
a starting material under alkaline catalysis. The reaction is allowed to proceed until the desired molecular weight is achieved and then the reaction is terminated by neutralizing the catalyst with an acid such as lactic or acetic acid. PEG is biocompatible and biodegradable. PEG’s most interesting property is that PEG is soluble in water and therefore suitable for various unique applications.

One such application is the grafting of PEG onto the surface of nanocarriers in order to confer hydrophilicity. Grafting of PEG onto the surface of a nanoparticle or drug carrier is called PEGylation. By creating a hydrophilic surface, interactions of the nanodrugs with the intestinal mucosa are increased leading to better absorption from the GI tract when drugs are administered orally. Additionally, the half life of the nanoparticle can be significantly improved. PEG is the most frequently used “stealth” coating. PEG’s chemical structure consisting of repeating ethylene glycol monomers enables the formulation of hydrogen bonds between the polymer and the nearby water molecules in the body in such a way that closely resembles the normal tetrahedral coordination between water molecules. Therefore, many nanoparticles coated in PEG are able to pass through the circulatory system undetected for much greater periods of time.

In addition to acting as a stealth agent, PEG increases the Enhance Permeability and Retention (EPR) effect. The EPR effect is a unique phenomenon of solid tumors and is related to their anatomical and pathophysiological differences from normal tissues. Solid tumors have a high vascular density because of angiogenesis at the tumor site. Defective architecture leads to leaking in the tumors and increased absorption of macromolecules. The inclusion of PEG on a molecule’s surface leads to enhanced circulation in the blood stream and thereby increases the amount of time that a nanodrug spends interacting with tumor vasculature. By fine-tuning the size of the particles, the leaky vasculature of the tumor may be take advantage of and the nanocarriers will remain trapped within the tumor vasculature until degradation and release of the anticancer agent. PEG therefore enables enhanced delivery of nanodrugs by increasing the likelihood the nanodrugs arrive at the active site of interest.

Beyond acting as a surface coating, PEG can be utilized in the construction of polymeric nanoparticles or micellar liposomes and micelles. Nanoparticles include the subdivision nanocapsules and nanospheres. Nanocapsules are vesicular systems where a drug is confined within a cavity surrounded by a polymer membrane. Nanospheres are matrix systems where the drug is physically and uniformly dispersed. Polymeric nanoparticles are engineered from biocompatible and biodegradable polymers like PEG. Typically, polymeric nanoparticles are formulated through a self-assembly process using block-copolymers consisting of two or more polymer chains with different hydrophilicity. The copolymers will spontaneously assemble into a core-shells structure in an aqueous environment. The hydrophilic parts of the structure will face outwards and the hydrophobic parts inward. Liposomes are spherical vesicles with an aqueous interior and a vesicle shell. Liposomes contain single or multiple bilayered membrane structures composed of synthetic lipids. PEG proves as a useful agent for serving as a building block to certain platforms and as a stealth agent to others.

Doxil was the first clinically implemented and FDA approved nanoparticle drug carrier. Doxil consists of a PEGylated liposomal carrier of crystalline doxorubicin. Doxil is used primarily to treat solid tumors. The liposomal carrier used is functionalized with PEG to improve particle stability and protect against aggregation, protein adsorption, and cell uptake. With the inclusion of PEG, the drug saw a dramatic reduction in bodily clearance of over 250-fold for liposome-encapsulated doxorubicin compared to that of the free drug. Additionally, the
PEGylated particles resulted in a 60-fold reduction in the volume distribution which resulted in a decreased cardiovascular toxicity by 3-fold.\(^9\) Another study found the decrease in volume distribution to be $\sim 1000 \text{ L/m}^2$ to $\sim 2.8 \text{ L/m}^2$ because of its restriction to distribution within the plasma.\(^11\) By adding a PEGylated nanocarrier, the effectiveness of Doxil increased dramatically and adverse side effects were greatly diminished leading to increased patient compliance and quality of life.\(^9\)

The inclusion of PEG functional groups on a nanocarrier led to similar results in the drug Paclitaxel. Paclitaxel is one the most widely used chemotherapy agents and is the first line of treatment for ovarian, breast, lung, and colon cancer.\(^12\) Additionally, Paclitaxel is the second line of treatment for AIDS-related Kaposi’s sarcoma.\(^12\) Paclitaxel is also known as Taxol and Onxol.\(^12\) It belongs to a class of chemotherapy drugs that are known as antimicrotubule agents and inhibits the growth of the tumor by blocking cell division.\(^12\) Paclitaxel has poor aqueous solubility and in clinical trials displayed some drawbacks such as neurotoxicity and neutropenia.\(^13\) Higaki et al demonstrated that by PEGylating a liposomal carrier of Paclitaxel, there was a decrease in rapid distribution to the liver just after dosing. Additionally, PEGylation of the liposome markedly reduced the affinity of the liposome for the liver and spleen which resulted in prolonged blood residence time of the liposomes. The clearances for the liver and spleen were approximately one tenth of those for naked liposomes. Thus, PEG is demonstrating remarkable results for improving the drug delivery of anticancer agents.

Beyond acting as an effective building block for polymeric nanoparticles and as a stealth agent for liposomes, PEG has other noteworthy utilizations for other medical challenges. One application is in hydrogels such as FocalSeal and SprayGel. FocalSeal uses a PEG liquid that is applied and then transformed into a waterproof hydrogel seal by irradiation.\(^14\) The sealant works to protect wound sites from leaking while the tissue heals and eventually naturally degrades and dissolves.\(^14\) Clinical trials have demonstrated that 93-100\% of surgery patients treated with FocalSeal remain free of air leaks, compared to 20-30\% of patients who did not receive the same treatment.\(^14\) SprayGel prevents post-operative adhesion formation.\(^14\) Adhesions are a type of scar tissue that often develop on internal wounds after surgery that can cause severe pain, small-bowel obstructions, and infertility in women.\(^14\) SprayGel is prevents post-operative adhesion formation.\(^14\) PEG hydrogels are those another application demonstrating the versatility and importance of PEG to the medical field.

PEG gels are also now giving hope to those who have lost their voice.\(^15\) Close to 6\% of the US population has some kind of voice disorder, with the majority of cases involving scarring of the vocal cords.\(^15\) Professors Steven Zeitels of Laryngeal Surgery at Harvard Medical School and Robert Langer of MIT have teamed up to develop a new polymer gel that mimics key traits of human vocal cords.\(^15\) Polyethylene glycol was used as a starting material and by slightly altering the structure and linkage of PEG molecules, the researchers were able to control the material’s viscoelasticity.\(^15\) Viscoelasticity was an important property for the gel because it is critical to voice production as it allows the vocal cords to vibrate when air is expelled through the lungs.\(^15\) Tests showed that the gel, termed PEG30, can restore vibration to stiff, non-vibrating vocal folds present in patients suffering from vocal-fold scarring.\(^15\) The team is looking to soon start clinical trials and if they reach FDA approval, the gel would likely be approved as an injectible medical device, injected at least once every six months due to its degradability.\(^15\)

PEG 3350, or the active ingredient in Miralax, is used to treat occasional constipation.\(^16\) PEG 3350 can be used to hold water in the stool in order to soften and increase the number of
bowel movements. Additionally, it is used as bowel preparation for colonoscopies. PEG is an extremely versatile compound in the medical field and has uses even as a laxative.

Biomaterials can be used to positively affect the safety, pharmacokinetics and duration of release of new and important drugs and are therefore having a large impact in the treatment of cancer and other diseases. PEG has revolutionized many areas of medicine and drug delivery. As PEG is continually investigated and applied to new challenges, the medical field is seeing new breakthroughs. PEG is a molecule with a promising future.
Works Cited


References: