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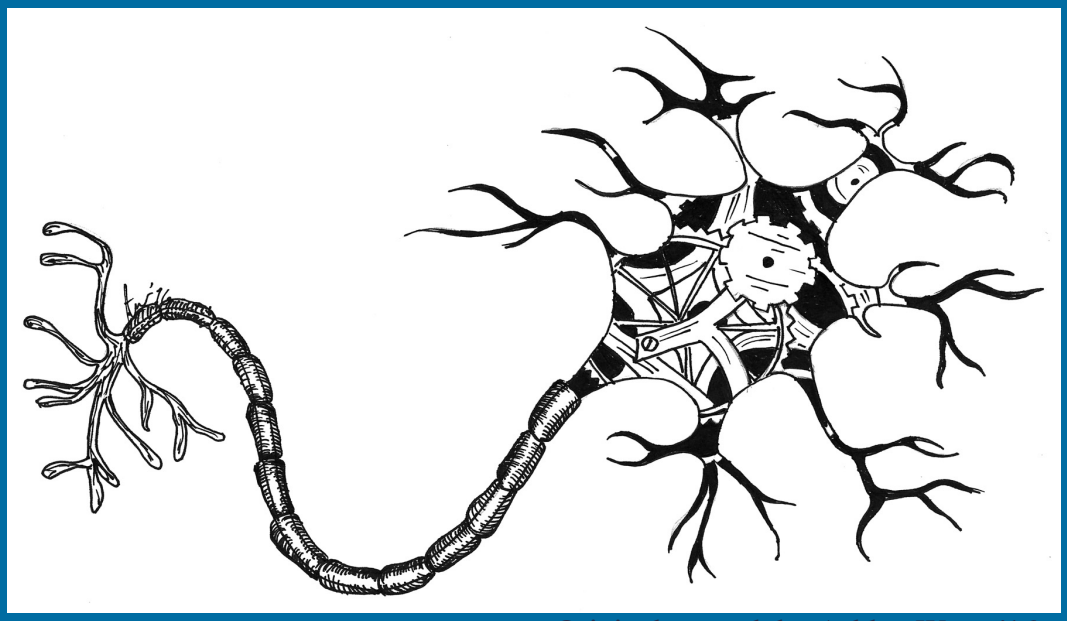

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Nanoparticles: A Medical Revolution in Development.

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The fruits of scientific and technological innovation largely supplement the typical lifestyle in modern, industrialized societies. The knowledge upon which modern neuroscience is based is the product of sustained dedication to empirical methods and analyses of biochemical phenomena. As a result, ailments of varying severity and type can be treated or cured with similarly various levels of success and safety. As time progresses, the rate of technological development will continue to accelerate exponentially. (Kurzweil, 2005) Such innovation will not be limited to technology; researchers will continue to discover underlying precursors to debilitating diseases and develop more effective treatments for these ailments.

Western medicine typically utilizes pharmacological agents in order to treat or cure conditions of the central nervous system (CNS). There are several routes by which a drug may be introduced to the body, including oral consumption, inhalation, and injection. Although research has supported the efficacy of many drugs in treating or curing scores of conditions, there remain several fundamental flaws that effectively decelerate Kurzweil's exponential development theory within the scope of neuropharmacology. First, the majority of administration methods require pharmacological knowledge and medical training to implement. Thus, the majority of medications developed for routine self-administration by the average consumer are restricted to oral administration. However, orally-administered drugs are subject to stomach acid and first

pass metabolism by the liver, making them the least medically effective treatment by mass. To compensate for this inefficiency, orally-administered dosages are significantly higher than that of other methods of administration, sometimes resulting in liver and/or kidney disease. (Meyer & Quenzer, 2013) Furthermore, drug absorption is heavily influenced by several factors including corresponding meal size, one's body mass, sex, and age. Consequently, the drug concentration in the blood and its pharmacological effect can vary significantly between individuals and administrations. Additionally, mistargeting a drug can result in a variety of adverse effects depending on the nature of the drug. For example, while selective serotonin reuptake inhibitors are effective treatments for depression, they are associated with gastrointestinal issues, sexual dysfunction, insomnia, and weight gain. (Ferguson, 2001) This may restrict the permissible dosage or require the administration of another drug to alleviate adverse effects. Lastly, drugs developed to treat diseases of the CNS by targeting neuronal soma or synaptic components are subject to the same characteristic flaws of any drug but also must cross the blood-brain-barrier (BBB). (Pridgen, Alexis, & Farokhzad, 2014) In order to facilitate the exponential development of more effective treatments, researchers have begun to circumvent these pharmacological flaws using nanoparticles.

The term "nanoparticles" refers to devices that are smaller than 100 nanometers and typically constructed via atomic or molecular manipulation. The growing field of nanomedicine is the use of nanoparticles that are structurally designed to augment current treatments for a variety of diseases, including those of the CNS. Liposomes are phospholipid nanovesicles, a type of nanoparticle, that are engineered to increase pharmacological efficiency by facilitating payload passage across the BBB and targeting specific tissues within the brain. (Bamrungsap et al., 2012) The liposome's hydrophilic surface permits active passage through the BBB via

selective, active-transport proteins. Similarly, the addition of surface coatings can function to extend nanoparticle half-life (i.e. polyethylene glycol) or increase cellular uptake of the liposome (i.e. bovine serum albumin). (Pehlivan, 2013) (Jokerst et al., 2011) Furthermore, the integration of endogenous membrane proteins and ligands allows researchers to chemically tailor nanoparticles to reach targets of interest. Lastly, the addition of fluorescent probes and chemical markers provide methods of nanoparticle detection and imaging. (Pehlivan, 2013)

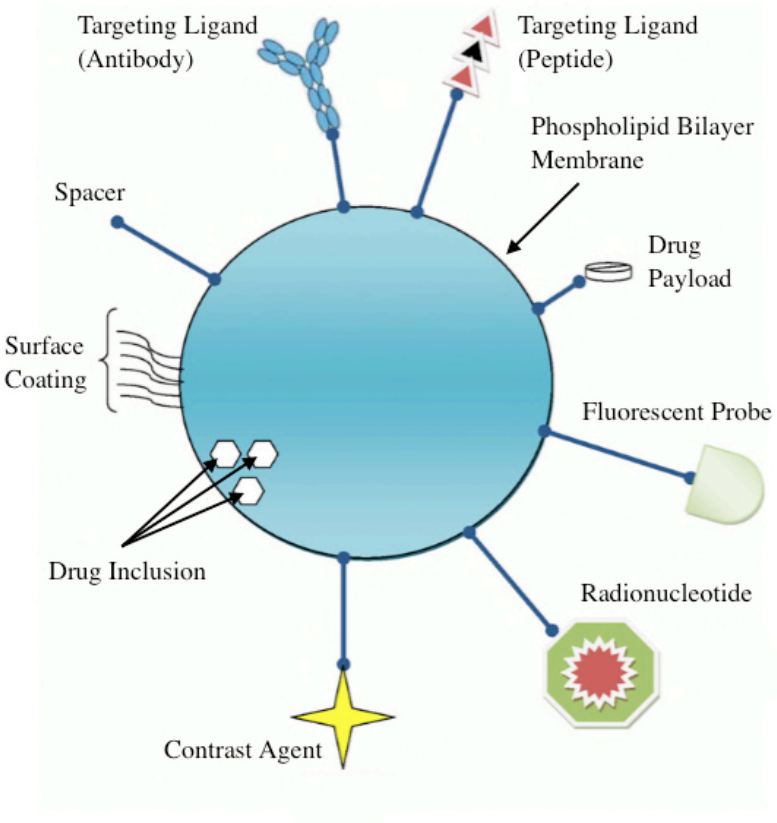

Figure 1: The Structure and Membrane Components of a Liposome. The outer surface of liposomes can be customized to fulfill specific functions, deliver drug payloads with variable release rates, and include membrane components dedicated to detection and imaging. Figure from (Pehlivan, 2013). Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23959851

Liposome administration is a versatile approach that has successfully increased drug arrival at target sites and dose consistency in experimental settings. A study published in

Experimental Neurology tested the efficacy of dopamine-containing liposomes both *in vitro* and in an animal model of Parkinson's disease. (During et al., 1992) In the *in vitro* condition, dopamine release was somewhat slower than first-order kinetics, which the researchers attributed to intermolecular forces between the slightly positive dopamine the negative charge of the liposome membrane, thus decreasing the release rate. Furthermore, they reported that the liposomes continued to release dopamine consistently for more than 40 days. For the *in vivo* condition, rats underwent unilateral lesioning via an apomorphine injection to the right striatum, resulting in rotational locomotion. Subjects treated with dopamine-carrying liposomes exhibited a significantly reduced rate of rotations per minute compared to control subjects for two weeks post-injection, as shown in Figure 2.

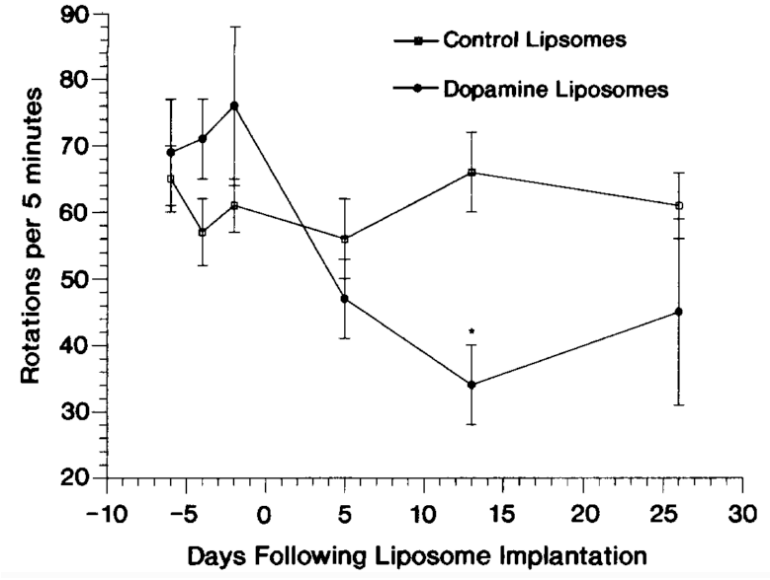

Figure 2: The Effect of Dopamine-Carrying Liposomes on Rotational Locomotion in *Rattus norvegicus*. Behavior was assessed via apomorphine-induced rotation, measured in the number of rotations per five-minute period. Notice that subjects assigned to the experimental condition initially exhibited more profound rotational locomotion prior to treatment compared to control subjects. Furthermore, note that experimental subjects exhibited significantly less rotational locomotion compared to control subjects, post treatment. Figure from (During et al., 1992). Retrieved from: http://www.sciencedirect.com/science/article/pii/001448869290053S

The capability to steadily release a drug over an extended period is advantageous because it provides a more constant and efficient supply of the chemical than could oral administration. Consistent administration is especially important for the optimal treatment of affective disorders and neurodegenerative diseases, such as schizophrenia and Parkinson's disease. (Meyer & Quenzer, 2013)

Another study (Wohlfart et al., 2012) tested the efficacy of nanoparticles in facilitating BBB passage of several chemicals, including doxorubicin (a common chemotherapy drug) and nerve growth factor. The outer surface of the nanoparticles studied contained Apolipoprotein E (ApoE), which binds to endogenous receptors and facilitates passage across the BBB. The researchers found that ApoE-enhanced nanoparticles successfully transported drug payloads (36-600 nm) across the BBB. They concluded that the ability to transport large chemicals across the BBB is a ground-breaking innovation that could augment a variety of treatments for neurological diseases and disorders. However, the researchers noted that such nanoparticles must be rapidly biodegradable, otherwise they would accumulate within the CNS.

Several studies have successfully enhanced neuropharmacological treatments using nanoparticles. (During et al., 1992)(Wohlfart et al., 2012) However, as technological development accelerates exponentially (Kurzweil, 2005), nanomedicine will become increasingly capable as well. Scientists have recently developed a molecular 3D printer that is able to synthesize molecules from atomic building blocks. (Russon, 2015) As nanoparticles and molecular 3D printing develop, their capabilities will fuse and produce nanoparticles capable of synthesizing molecules from a library of chemical blueprints. Rather than injecting drug-delivery nanoparticles, molecule-synthesizing nanoparticles may become implantable, providing the benefits of nanomedicine without requiring regular injections. This will initially be developed for

medical purposes and may eventually maximize drug efficiency and reduce medical costs. As a result, molecule-synthesizing nanoparticles will become a permanent neurobiology/technology hybrid system in its integral role in nanomedicine.

I have abided by the Wheaton College Honor Code in this work.

Brian Portelli

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