BMES 124

Promoting Proper Remyelination in Multiple Sclerosis Patients

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Abstract
The objective of this paper was to create a design that would treat the symptoms of Multiple Sclerosis, and more specifically treat the underlying condition of demyelination of the myelin sheath. The design to alleviate this condition was to create a drug named "drug 124." This drug would be modeled off of the drug Copaxone, that is currently on the global market. The rationale behind this is that drugs are relatively easy to manufacture and the technology is already out, making this the most inexpensive method of solving MS. The design was set out to minimize side effects as much as possible and to eliminate any malformations on the myelin sheath. Ultimately, if successful, this design could have a much broader impact on the medical community by being able to treat diseases similar to Multiple Sclerosis, without much adjustment.

Introduction/Background
Multiple sclerosis is a chronic disease that attacks the central nervous system. The key components of the central nervous system are the brain, the spinal cord and optic nerves. Patients with multiple sclerosis often lose muscle control, vision, balance and sensation. In MS, the brain and spinal cord are damaged by a body's own immune system. Thus, Multiple Sclerosis is an autoimmune disease. In autoimmune diseases, the body's immune system mistakes normal tissue as foreign and attacks them. The nerves of the central nervous system act as the body's messenger system. Each nerve is covered by myelin, a fatty substance which insulates them. Myelin helps transmit impulses between the brain and other parts of the body. The deterioration of the Myelin sheath is referred to as demyelination. While nerves can regain myelin, improper remyelination is equally destructive to the body. Remyelination occurs in two main phases: "colonization of lesions by oligodendrocyte progenitor cells and the differentiation of OPC's into myelination oligodendrocytes that contact demyelination axons to generate functional myelin sheaths" (Chari). Theoretically, enhancing this repair process (by providing more remyelination-enhancing factors) will provide the body with the necessary means to properly and completely remyelinate.
Approximately 400,000 people in the United States suffer from multiple sclerosis. While it is incurable, there are treatments that keep patients from frequently relapsing. Researching and developing the myelin process will not only aid patients with multiple sclerosis but those with other demyelinating diseases as well. In addition, enhancing the remyelination process, which is a part of the immune response, will lead to a major advancement in curing autoimmune diseases.

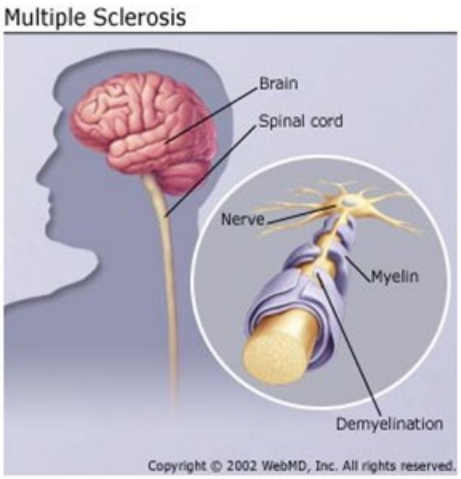


Figure 1: Deterioration of Myelin Sheath in Multiple Sclerosis

Problem Statement (text body ~ 1 page)

The deterioration of the myelin sheath is the principle cause of multiple sclerosis. Improper remyelination leads to even more scar tissue and impairment of neural transmissions. While demyelination is caused by the body's immune system attacking itself, remyelination is promoted by the same immune system. Thus, it has been hypothesized that enhancing the myelin-forming factors of the immune system will overshadow the demyelination process and promote complete remyelination of nerves, alleviating the pains of multiple sclerosis.

Remyelination is primarily a chemical process, thus the fix will be drug (chemical) therapy. The aim of this design is to regenerate myelin sheaths completely in order to eliminate malformations and the symptoms of partial remyelination. One of the symptoms of incomplete remyelination is the disruption of nerve signals, the main communication method of the human body. In addition, the drug must not interfere with other naturally occurring processes or produce disrupting side effects. Successful development of drug therapy for complete remyelination of neurons will alleviate the symptoms of not only multiple sclerosis but other demyelinating diseases.

Design Rationale

The purpose of this design was to alleviate the symptoms of MS and treat the underlying cause of symptoms, demyelination of the myelin sheath. The chief reason that the group chose to select a chemical therapy approach to repairing the remyelination process is because this method is the most cost effective, which would leave more resources open to improve our design, and allow for more money to be made if this design were to be put on the medical market. The ability to have a cost effective solution to MS and its related diseases would allow for a company to better compete with other medical companies with solutions to MS. Another reason the group chose to approach MS from a chemical therapy aspect was that technology in immunology already exists, and there are thousands of chemists already available to perform research on remyelination. This would allow a lower amount of time that is spent waiting for production to start and different machines to be manufactured to engineer our solution. With the existing technology all that would have to be done is for chemical resources to be obtained, then the existing technology configured to produce the design.

Design Criteria

The design of the proposed model had a few needs when it came to specifications. The first and most important piece of criteria that needed to be met was that the group's design needed to fully remyelinate the myelin sheaths, without this vital condition the entire point of the design would be useless because all the symptoms of Multiple Sclerosis and diseases similar to it would still occur. In addition to this, the symptoms would progressively get worse as the myelin sheaths become more and more damaged. The second specification that the group decided was that our design couldn't have any side effects; realizing that this ideal is impossible we strove to at least have only negligible side effects. In today's pharmaceutical market many drugs are out that attempt to solve diseases, but the drugs that are on the market have potentially fatal side effects, or side effects that make living life difficult for a patient. Because of this reason, it was obvious to the group that side effects deserved to be one of the main concerns of this design. The final constraint that the group focused on was that our drug needed to be relatively inexpensive, because without this constraint only a few people could afford to buy this drug, which inevitably decreases profit margins. There are many other constraints that must be considered before our drug were to be put into circulation, such as readily available information about this drug, and how to manufacture it.

The main criteria that the group focused on, remyelination, had sub criteria that also needed to be met in order for this design to be considered a success. These sub criteria were that any malformations on the myelin sheath needed do be eliminated to prevent any adverse reactions after the sheath is repaired, and the symptoms of incomplete myelination (HHHH) needed to be relieved. When all of the parts of this overall condition a patient will begin to observe their symptoms to subside as more cells are repaired, which is the overall goal of this design.

Design Constraints

Taking into consideration the criteria laid out to the design team. The team discussed the different constraints that would apply to the design. The first set of constraints that surface immediately were the physical and economic constraints. Something brought about in the first discussion were the subjects of the products marketing, manufacturing, supplying the teams needs and cost. The team decided that manufacturing in mass would not be needed until a later date when the product was ready, and that marketing in the same manner would not be an issue.

- First was the cost of the product. While the team decided that it wanted to work toward a complete resolution (MS) the team also decided that it would not be meaningful if it was not available to the public. Meaning that the drug would need be either easily manufactured, highly effective, both or do well enough at combating the malady that it could alleviate other costs involved in (MS) such as patient care, treatment, or therapy to a point that the cost of the product outweighs the cost of the alternative.
- Second the manufacturing of the product. In its initial stages the team requires its own way to manufacturing prototypes with chemical synthesizer and other equipment, purchased directly or by working with a lab, or company to gain access to these technological needs. Once the team develops a working product contracting manufacturing needs to other companies will be much more cost effective and necessary.
- The third and last direct economic constraint is the need of a supplier that is reliable, secure and certified. This could be most likely found with a company or lab if we had decided to join one of those to make our manufacturing costs simple. However if the team stuck to manufacturing by itself the need for a supplier would be a much more important issue as supply of chemicals is often regulated heavily and it is not often that chemicals would be sold in the smaller amounts that the team would require and thus most likely require a greater monetary investment by the team.

With consideration of the listed constraints, the team has a chemical product aiming to be cost effectiveness and manufactured by the team itself. Once these requirements are met the team can move on the next set of constraints how the drug is tested, administered, and its direct effect on the body.

- First is the lack of clinical opportunities. This is a serious consideration as the ability to test the drug's effectiveness on an actual system is vital to its success. So until a working prototype is developed the drug will need to be tested on either tissue samples, animals, or simply simulated in a computer program.
- Second is the time period that the drug is effective or the number of treatments that the drug needs to be effective. The team decided that the goal for the drug would be a one and done

process, or at least be a series of treatments that would then lead to a complete restoration of the nervous system and eradication of the malady. This we decided was a much better route than to develop a drug that patients would be reliant upon both because of cost, but also for the wellbeing of the individual treated.

- Third is that the drug cannot be rejected by the body, it has to as some point be recycled by the body and/or disposed of. The team decided that while rejection was not acceptable we did not want to introduce compounds to the body that would stick around forever.
- Fourth is the negation of malformations in the remyelination process as well as negative side effects of the drug. Through research by the team it was discerned that while remyelination is what is needed to cure (MS) it was found that malformations (plaques) in the myelin could disrupt nerve signals much like demyelination itself. Also the team decided that the drug should avoid causing negative side effects that are commonplace among pharmaceuticals.
- Lastly it was decided that the drug should target the nerve centers explicitly through localized delivery. Since half of the purpose of the drug is to prevent the immune system from destroying myelin faster than remyelination takes place it is necessary to slow down the immune response. However if the drug slows down the entire immune system the patient would be incredibly vulnerable to illness. So it was decided that if it would be feasible the drug should work locally with the nervous system specifically.

S.W.O.T Analysis

Strengths	**Weaknesses**
Experience with Clinical Trials Ambition	Lack of experience and knowledge Lack of connections
Opportunities	**Threats**
Research opportunities with professors and local hospitals University Resources	Ethical implications Lack of manpower Lack of funding Competition

Alternative Approaches to Solution

Three alternative approaches to the design available are drug therapy, gene therapy, and nerve regeneration. A decision matrix listing pros and cons below shows a scoring system for determining which approach would be appropriate for our design. The pros and cons for each alternative approach listed are general considerations covering immunology technology, resources, related research, and social impact, specifically applicable to multiple sclerosis.

	Drug Therapy	Gene Therapy	Nerve Regeneration
PROS			
Prolonged, site specific therapy	X	X	
New RNA-interfacing technique		X	
Targets progressive forms of MS	X	X	X
Existing developments to build upon	X		
Restore immune function	X		
Cost effective research and development	X		
CONS			
Therapeutic molecule delivery barriers	X	X	X
Controversial; Use of stem cells		X	X
Pathogenesis is partially understood	X	X	X
Gene linked to MS is unknown; Requires genetic alteration		X	X
Risk of relapse or negative response to therapy	X	X	X
Best therapy option:	2	-2	-4

Table 1: Decision Matrix: Alternative Approaches for Multiple Sclerosis

The Design: Drug 124

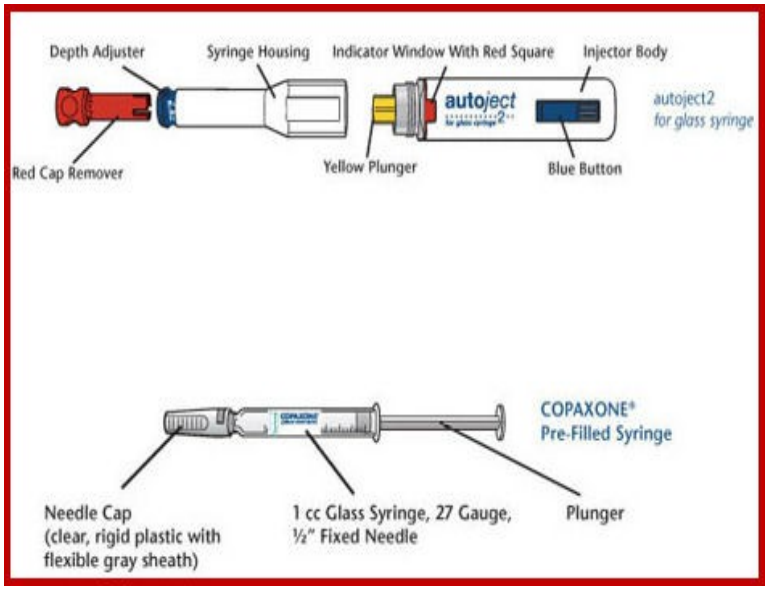
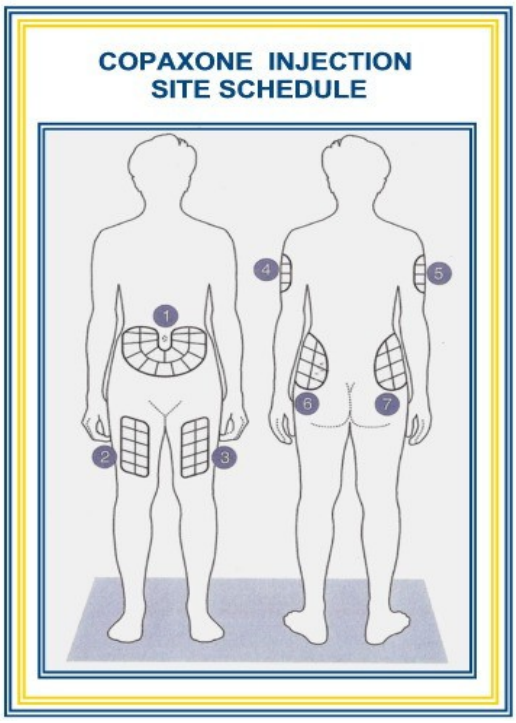


Figure 2: Subcutaneous Injection of Copaxone



The Design - Drug 124

Our design Drug 124 imitates Copaxone, an existing drug produced by Teva Corp. Copaxone is the most frequently marketed and prescribed drug used to treat multiple sclerosis. Multiple Sclerosis patients using Copaxone complain of permanent scarring of underlying tissue caused by subcutaneous, Copaxone injections. The current method of Copaxone administration destructs fat cells in localized areas where it has been injected. Drug124 differs from Copaxone in that the drug can be easily self-administered discreetly through a nanoscale polymer film designed for localized drug delivery.

Drug124 Analysis (Based on Copaxone - glatiramer acetate)	
Administration	Nanoscale Polymer films (4mm layer) Contains 20 mg of glatiramer acetate and 40 mg of mannitol
Amino Acids (Average Molecular fraction)	L-glutamic acid (0.141), L-alanine(0.427), L-tyrosine(0.095), and L-lysine (0.338)
Physical Attributes	Clear, white, to slightly yellow. Photosensitive.
FDA Approved	Yes
PH Range	5.5 – 7.0 pH
Biological Activity	Blocks the induction of experimental autoimmune encephalomyelitis (EAE) Simulates myelin basic protein
Known Side Effects (In 13% of users)	Nausea, chills, joint aches, neck pain, headache, anxiety, flushing, itching, tingling, irregular heartbeat, chest pains, tightness in throat shortness of breath
Clinical Trials	Significant reduction in annual relapse rate and a reduction in new lesions as shown on magnetic resonance imaging (MRI) compared to control subjects who were given a placebo.
Use During Pregnancy	Pregnancy Category B - No adverse effects have been found in animal studies, no adequate, well-controlled studies have been done in pregnant women to demonstrate its safety in humans.

Copaxone vs Drug124 Pathway

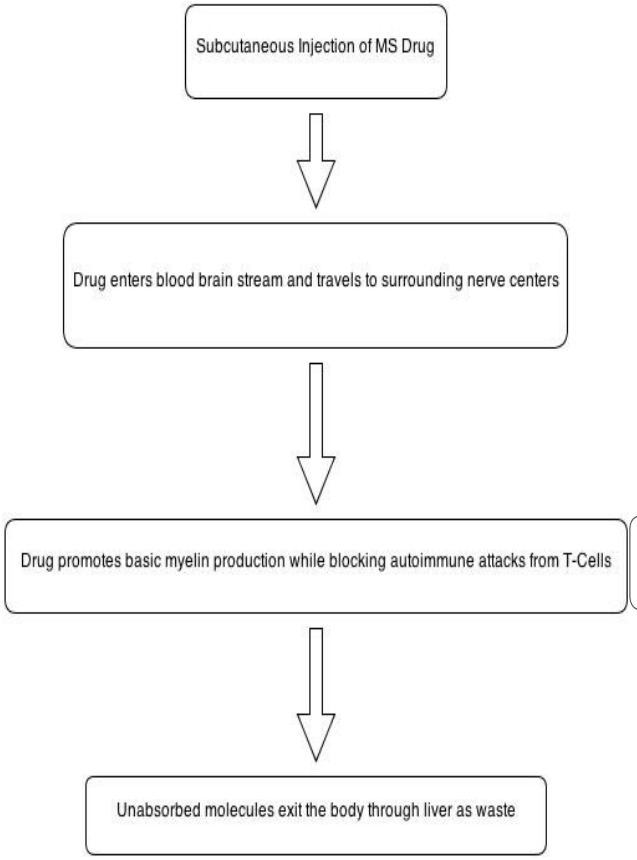


Chart 1: Copaxone Pathway

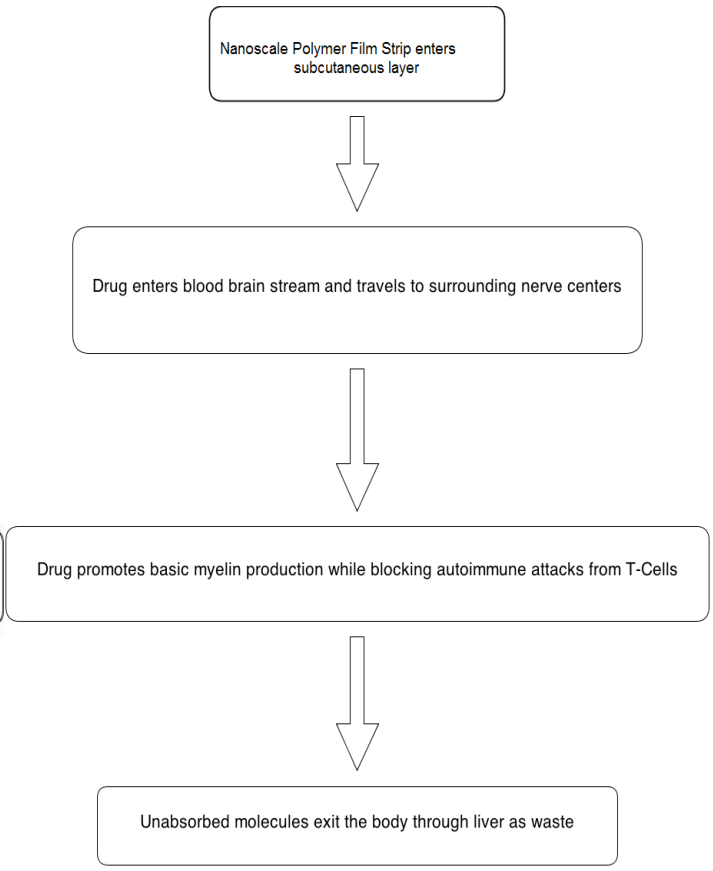


Chart 2: Drug124 Pathway

Impact

Currently there are approximately 250,000 to 350,000 citizens in the United States that are living with Multiple Sclerosis. With the life expectancy of these patients matching those of without the disease, the United States spends billions of dollars annually to treat these patients. The development of this drug would alleviate not only the patients but also a hefty portion of funds pouring into patient funds yearly. Moreover, an environmental cause has been discovered as a factor for this disease. Although it would not entail a major impact, this drug would not discourage any person of living in certain regions with temperate climates. Multiple Sclerosis worsens after an acute viral illness and therefore leave many patients living in fear of causes of even the simplest viral illnesses. This drug will provide alleviation to the patients who calculate daily risks of catching a viral illness.

There are numerous diseases similar to Multiple Sclerosis in which they are all classified as demyelinating diseases within the nervous system. With the success of Drug -124 this would solve the core issues that arise within creating a treatment for these diseases. For instance, this drug will aid the discovery of treatments for Vitamin B12 disease, Devic's disease, Optic Neuritis, and Tabes Dosalis. All these demyelinating diseases are prevalent through the nation and this drug will be the next step to the solution.

Fail-Safe

With the method of a localized drug delivery this drug would not be directly targeted of the affected cells, but applied locally and controlled over time. This allows for a more controlled treatment of the release of Drug-124 and a safer method of performing the therapy. The reason for this fail-safe is to monitor this drug over time and to allow the administrator more control over the drug. Moreover, this method limits the amount of side-effects since traditional methods of drug inducing dissipates in the body faster. For instance, an oral pill will quickly travel through one's bloodstream and therefore dissipate quicker than a controlled drug delivery.

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