Final Report

"EMF Wearable"

An Innovative Approach To Treat Neuroblastoma

Need Statement: *A treatment tool for neuroblastoma to reduce average hospitalization stay time and cost.*

I. Need Identification & Validation

A. Disease Fundamentals

Neuroblastomas are one of the most prevalent cancers that plague pediatric patients in hospitals. These neuroblastoma tumors have been known to come from the adrenal medulla or paraspinal sites (Tsubota & Kadomatsu, 2018). Currently, it is believed that the sympathoadrenal lineage of the neural crest is the most feasible place where neuroblastomas originate (Cheung & Dyer, 2013). The neural crest is one of the main sites for cell growth and development during the fetal stage, this is mainly due to the fact that it has such a high degree of multipotency and its cells have the ability to migrate across the embryo and differentiate into specific regions of the human body as parts of the central nervous system (Le Douarin & Dupin, 2018). Much of the reason for this can be attributed to oncogenes and their activation to create tumors as the neural crest continues to differentiate into more cells with that gene. This would eventually form the neuroblastoma inside the adrenal gland. In a recent study, it was found that in 240 high-risk neuroblastoma patients there is a correlation with somatic mutations in their DNA. These mutations can be found at the ALK, PTPN11, ATRX. There is also a correlation with chromosomal DNA mutations at 17q gain, 11q loss, and MCYN amplification (Schulte, 2013). It has been found that if diagnosed prior to 18 months along with a neuroblastoma that is not MYCN amplified, there is a better chance of remission (Shao et al., 2015)(Schmidt et al., 2005). Depending on the location of the neuroblastoma in the sympathetic nervous system there are different characteristics that are prevalent from the primary tumor location. These locations can range from the adrenal gland (most common), the abdomen, neck, thoracic cavity, or the pelvis. Neuroblastomas are categorized as stages 1, 2A, 2B, 3, 4, and 4S according to the International Neuroblastoma Staging System (INSS). If the patient's status progresses to a stage 4 or 4S it means that the tumor has metastasized and spread away from the primary tumor (DuBois et al., 1999). However, when this happens it has been seen in some cases that the tumor undergoes spontaneous regression without treatment (Brodeur & Bagatell, 2014). Along with the INSS, there is an International Neuroblastoma Risk Group (INRG) which was created to help create risk assessment of neuroblastoma tumors and pretreatment measures. The risk of the tumors are classified with the stages L1, L2, M, and MS. Neuroblastoma is the most prevalent cancer outside of the cranium in children younger than 15 years old. It has a prevalence rate of 6- 10% of all cancers in children in high income countries while only having a prevalence rate of 1- 3% in low and middle income countries (Stiller, 2004). This difference in prevalence rates can

most likely be attributed to poor diagnosis, improper pathologic evaluation with immunohistochemistry, and poor medical imaging technology.

B. Current Options

According to Cohn et al. (2009), "if pathologic examination is unequivocal for neuroblastoma, or tumor cells are detected in bone marrow, and there are elevated urinary vanillylmandelic acid and homovanillic acid levels, then a diagnosis can be made." Imaging techniques such as CT and MRI are used in the early detection of abdominal masses, while histogram confirmation of the disease can be obtained by biopsy incision in conjunction with immunochemical staining (Papaioannou, 2005). Neuroblastoma is classified into multiple risk categories: low-risk or localized, intermediate-risk, and high-risk or life-threatening, which can also be identified using CT and MR imaging (Monclair et al., 2009). Diagnosis and treatment of neuroblastomas involve close monitoring and cooperation amongst the patients' families, pediatricians, and pediatric oncologists. Depending on the stages of neuroblastomas, treatment plans may vary. According to Monclair et al. (2009), surgery can easily remove the tumor in low-risk (localized) and intermediate-risk cases. In more severe cases, chemotherapy may help shrink the tumor before surgical removal. Radiation therapy is used as an alternative for high-risk neuroblastoma or those suffering from life-threatening side effects of chemotherapy. There is a considerably high possibility of recurrent neuroblastomas, which lays a need for follow-up care post-surgery or post-cancer-treatment (Swift et al., 2018).

Having your child diagnosed with a neuroblastoma is extremely scary but due to the recent advancements in treatment options it is becoming much more curable. These options have included high-dose myeloablative chemotherapy with autologous hematopoietic stem cell transplantation and immunotherapy with the anti-GD2 antibody and cytokines (Matthay, 2016). One massive drawback from current treatment options after therapy sessions is treatment induced toxicities. Right now the best opportunity for the highest quality of life post treatment relies on early detection with the use of low-toxic therapy options to reduce side effects. Nanotechnology can also be a strong contender for improving patient quality of life, reducing hospital times and as well as reducing the need for hospitalization. This comes in the form of nano-drug delivery systems and drugs with specific targets which will result in lower side effects, more therapeutic effects, and advancements in the drugs pharmacokinetic properties (Mobasheri et al., 2020). Some of the most useful of these are metal nanoparticles, the most prevalent being gold nanoparticles. These metal coated particles have the ability to enter endothelial cells and then get trapped inside of them. This allows for nanoparticles filled with drugs to enter directly into the target cells with less side effects than typical immunotherapy (Greish, 2010; Iyer et al., 2006).

C. Stakeholder & Market Analysis

Cancer treatment creates a huge burden for the patients, the patients' families, and societies. In the US, annual cancer care is expected to cost up to $157.8 billion in 2020, a mere 27% increase from $124.6 billion in 2010 (Mariotto et al., 2011). As the incidence of neuroblastoma is increasing drastically, the reimbursement schemes, development of new drugs and their approvals and funds for research will make up the growth of the neuroblastoma drug market.

The global neuroblastoma drug market size will grow by $190.82 million between 2019 and 2023 (Global, 2019). The 37% increase came from North America alone, or $70.61 million. Each year, the market is predicted to grow at a rate of 4%. Furthermore, the annual growth rate for 2019 is predicted to be 0.07 %. North America is predicted to have the biggest market share from 2019 to 2023. Pfizer, Johnson & Johnson, United Therapeutics, Bristol-Myers Squibb, and Teva Pharmaceuticals are some of the prominent participants in the industry (Global 2019). According to a study conducted by Mordor Intelligence (2022), the market size for neuroblastoma therapy is expanding at a CAGR of 6.3 percent. North America has the largest market, while the Asia Pacific has the fastest-growing market. In the United States, neuroblastoma in children under the age of 15 is around 10.54 cases per 1 million. Almost 37% of patients' diagnoses are newborns, and 90% are children under five. Compared to other cancer therapies, the survival rate for neuroblastoma patients with current treatment choices is 6%. Similar products, such as EMF wearable devices, have a market size of $535 million in worldwide net revenues in 2021. In 2021, about 22000 patients will have been treated with this gadget globally. This device is predicted to improve patient survival in conjunction with traditional therapy. In 2020, the market had net revenue of $494 million and was treating over 18000 patients globally.

Since neuroblastoma is the most common infantile cancer (accounting for 30% of cancer cases) with a considerably high metastasis rate in children around 15-month-old (Sharp et al., 2011), parents usually have to carry both the emotional and financial burden of the disease treatment. According to Roser et al. (2019), parents of children with cancer may suffer substantial income loss. Specifically, half of the parents of children with cancer in the US may have to sort to individual fundraising to pay for healthcare-related costs (Bona et al., 2014). Consequently, the financial burden from cancer-related costs has pushed nearly 15% of the studied families to fall under the poverty line (Bona et al., 2014). More importantly, the effect of this financial strain can be felt as long as 2.6 years after diagnosis, even in recovered cases (Bilodeau et al., 2017). This undeniably proves the enormous financial burden that childhood cancer can have on the parents, especially in families of low socio-economic backgrounds.

Several factors drive the above financial burden. First, the cost of cancer treatment varies significantly depending on the severity of the disease and the types of insurance the patients possess (Mariotto et al., 2011). Additionally, the cycle of care for neuroblastoma mainly involves pediatricians, oncologists, and surgeons in clinics and hospitals. Therefore, insurance-related payments account for a large portion of cancer treatment costs. According to one Canadian study, the average cost for neuroblastoma treatment would be around $205,747. This cost includes 90 days pre-diagnosis and 1-year post-diagnosis (Huang et al., 2022)). One example is Endoscopic Endonasal Approach (EEA). This approach involves a combination of chemotherapy and surgery. As mentioned above, chemotherapy is used to shrink and isolate the tumor, which undergoes surgical removal. Surgery time varies depending on the complexities of each case, but it usually takes between two to six hours for endoscopic endonasal surgery. The patients are also required to undergo close monitoring and special care following the surgery (Jho et al., 2012)).
The total cost for this approach ranges from $11,438 to $12,513. Similar approaches such as MIPS (endoscopic endonasal minimal invasive approach) and SLTS (sublabial transseptal approach) cost around $18,095 to $21,005 per procedure (Oosmanally et al., 2011). The cost may vary due to several other factors such as possibilities of complication, hospitalization duration, and nursing care. Therefore, insurance and out-of-pocket payments vary based on the

disease conditions, caregiving requirements, and the safety and technological characteristics of the innovation. For this reason, it is also hard to use cancer treatment costs to justify an unmet need in the field. Secondly, financial losses can stem from opportunity costs due to frequent travel for treatment, prolonged hospitalization, and demanding caregiving, especially in severe cases involving a combination of modalities such as surgery, chemotherapy, and radiotherapy (Roser et al., 2019). These requirements not only physically, emotionally, and financially affect the patients but also create a toll on their families. According to a study conducted by Syse et al. (2011), extended hospital stay and frequent traveling mean work and income disruption for one or both parents. Often, one of the parents must quit their job or sacrifice employment opportunities to take care of their child. Several studies have suggested that parents are both vulnerable to working hours or job loss after the child's diagnosis, although it differs for mother and father across geographical regions (Lähteenmäki et al., 2007). In all, the associated cost from parents' income disruption contributes significantly to the financial burden in families with children suffering from cancer.

A need for a non-invasive neuroblastoma treatment to reduce hospital visits and the need for hospitalization is evident, considering how they affect the patients' families' financial situation. Non-invasive treatment can help improve the quality of life for the child and the need for constant caregiving. Less-frequent trips to hospitals also save time and avoid disrupting the parents' working flow. A non-invasive solution that deviates from the current equivalent but costly treatment such as chemotherapy and radiotherapy may help minimize unexpected side effects, reducing hospitalization needs and decreasing the duration of stay. This saves money from a prolonged hospital stay but also helps parents to maintain their job and professional career. In all, an innovation that can address the above need may make a massive change in the healthcare scene for neuroblastomas and other types of childhood cancer.

II. Device Idea

A. Working Mechanism

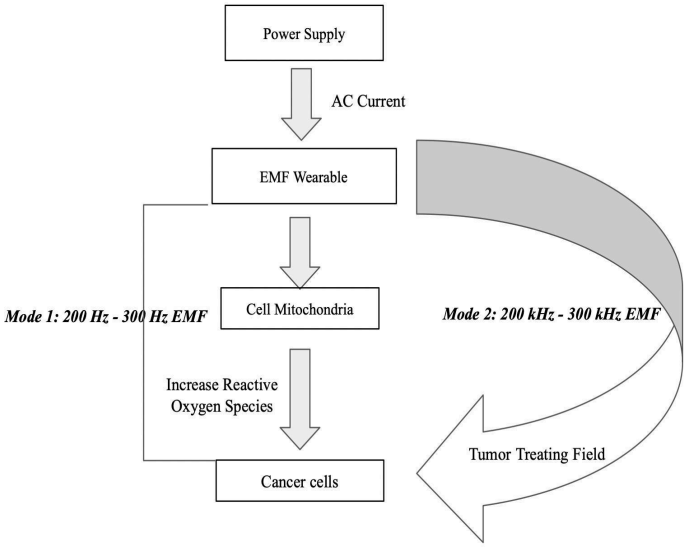

Figure 1. Block diagram demonstrating two modes of operations of EMF Wearable

The device (EMF Wearable) is a wearable device that can deploy electromagnetic field target therapy. The device should not cause obstruction during movement. It is designed for children under five years of age, per observation that neuroblastoma is more common in this age group. The device needs to be safe for use in minor patients, and easy to operate for at home usage. Since EMF Wearable is non-invasive, cost-effective, and can be used at home, it will be able to save the patients and their parents frequent trips from and to the hospital. It may also reduce or eliminate hospitalization needs in some cases of neuroblastoma.

EMF Wearable operates in two modes (figure 1) - the low-frequency mode or mode 1, and the high-frequency mode or mode 2. Mode 1 deploys EMF at frequencies in the range of 200Hz-300Hz. This is because EMF of this frequency range has been shown to increase the concentration of Reactive Oxygen Species (ROS), especially hydrogen peroxide, in the mitochondria, which induces oxidative stress and direct DNA damage to destroy cancer cells (Sengupta et al., 2018 & Sherrard et al., 2018). In contrast, EMF at high frequencies (200kHz-300kHz) is used in mode 2. According to Mun et al. (2017), EMF with the magnetic field strength around 0.7-3V/cm at frequencies around 200kHz-300kHz has been effective in active cell mitosis in tumors. For the treatment of Neuroblastoma, mode 1 and mode 2 can be deployed separately or in combination depending on the tumor's location and its tissue properties. Mode 1 uses EMF at low-frequencies thus having a deeper penetration into the body. This is useful to reach tumors located deep in the body. However, the main disadvantage of mode 1 is the possibility of undesired nerve stimulation or cell membrane properties changes, which are common with low-frequency EMF (Hardell & Sage, 2008). Therefore, mode 1 is not a good option for treating tumors in highly-sensitive tissues. For this case, mode 2 should be a good choice. High-frequency EMF, despite not being able to penetrate deep into bodily tissues, does not stimulate nerves and change the properties of the cell membrane. However, EMF at frequencies above 100kHz may elevate the temperature and cause damage to the surrounding tissues (Hardell & Sage, 2008). Due to the above reasons, mode 2 is a mode of choice for tumors near the skin or those in sensitive areas with a dense concentration of nerves. Furthermore, mode 1 & mode 2 can be deployed interchangeably (by frequency modulation) to take advantage of the benefits and avoid the disadvantages of each operating mode.

B. EMF treatment compared to other solutions

The application of EMF is one of the most advanced approaches to cancer treatment. Current solutions in neuroblastoma treatment are chemotherapy, radiotherapy, and surgery. All the above are invasive and may cause unbearable pain thus compromising patients' quality of life. Our device used dynamic alternation of electromagnetic fields at different frequencies to treat cancer. It is a non-invasive treatment and causes little to no pain. It has the ability to specifically target the tumor site, and prevent it from proliferating or destroying the cancer cells without damaging the surrounding area. The use of EMF in the form of a wearable device thus is not only effective but also convenient. It helps address the need for a cancer treatment that does not require frequent hospital visits and prolonged hospital stays.

C. Feasibility

This device is quite attainable considering similar designs of commercially available devices such as Optune or NovoTTF – 200T (mentioned later in section IV of this report). The device is portable with the use of batteries rather than using conventional methods of direct

powering from the plug. EMF Wearable uses different electromagnetic fields at varying frequencies for the dynamic application of different therapeutic properties. As for SMF, at 0Hz, it can induce angiogenesis and metastasis: PFM at (0 – 300Hz) enhances drug delivery system efficiency and improves patient conditions; PFM at (300Hz – 100KHz) - for tumor destruction and PFM at (100KHz – 300GHz) enhances the immune system in advanced cancer patients (Sengupta et al., 2018). Varying frequencies and intensity of electric field can also create TTF, induce thermal effect, or create ROS, which helps destroy or stop cancer cells from actively dividing. In all, a well-designed model of frequencies and intensity alternation can effectively induce cellular inhibition and enhanced apoptosis to reduce the size of the tumor and maximize the survivability of the patients.

D. Competing Technologies

The main competitor in this field is TTF wearable devices. The prime example is devices from Novocure. The tumor treating fields interfere with dividing cancer cells by either slowing down or stopping the GBM cancer cell division. In contrast, EMF Wearable uses varying electromagnetic fields for treatment. It can be used to treat other types of cancer, besides neuroblastomas. It can be used both as a standalone or in conjunction with other therapies such as chemotherapy and radiotherapy.

III. Device Design & Simulation

A. 3D Model Design (Zachary)

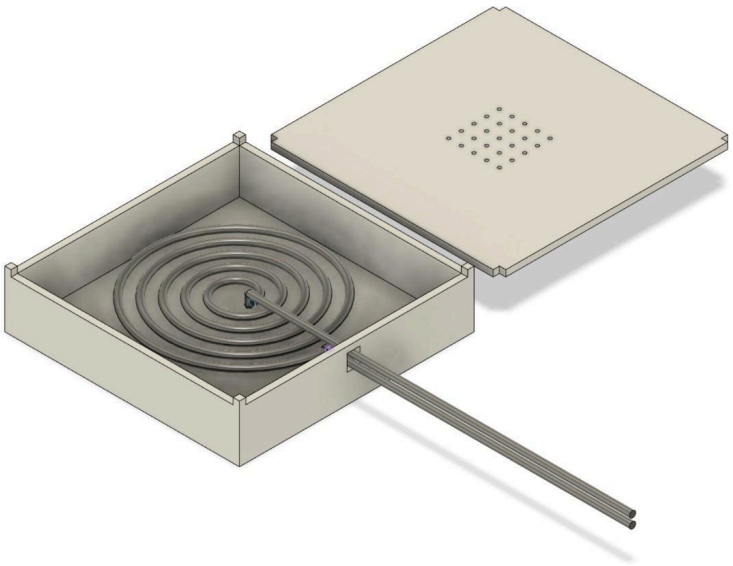

Figure 2. Visualization of an EMF Wearable electrode in Fusion 360

Using Fusion 360, we designed the main functioning components of our wearable device which are the panels that are placed onto the patients in order to generate the EMF targeting therapy. This design consists of a copper coil shown in the image to the right inside of a soft

polymer box. This coil will have 5 revolutions and have an inner diameter of 8mm and an outer radius of 30mm at the largest part. The copper wire in the coil will have a diameter of 2mm. This box will be made out of silicone based rubber due to its high rate of biocompatibility. It is often used in implanted medical devices and it has high performance and strength (Mohanan, 1999). While also being impervious to flaws and cracks. Silicone rubber also has been shown to be safe in toxicity tests when used in safety tests (Mohanan, 1999). Along the underside of the box, we will run silicone pressure sensitive adhesive tape that is developed by 3M. This tape is designed to be placed directly onto the patient's skin and be removed without irritation. The specific tape that we would use would be 3M™ Medical Silicone Tape 2477P, Double Sided Silicone/Acrylate Thermoplastic Elastomer, Configurable. This is because it is repositionable on the patient and is used for delicate areas around wounds (3M, tape). The dimensions of the box will be 74mm x 74mm x 18mm with the walls having a thickness of 2mm. This means the inside of the box to be 70mm x 70mm x 14mm which allows there to be at least 5mm of separation on all sides of the coil away from the box. On the base of the box there are 2mm x 2mm prongs on all 4 corners with the 4 corners on the lid having matching slots so that the lid fits in place tightly without the ability to shift around. Then on the lid there is an array of 25 1mm diameter holes, which along with the 5mm of separation allow for the device to naturally cool itself and release heat which will help to prevent burns on the patient. Then for the parts of the wire sticking out of the silicone rubber box they will be plastic coated and insulated to prevent accidental burns and electrocution.

B. Circuit Board Design (Manish)

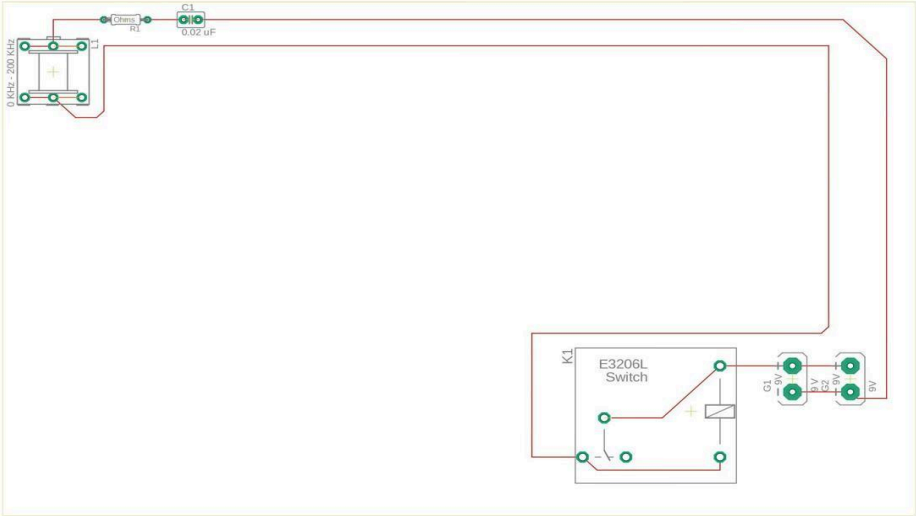

Figure 3. Simplified circuit board design of EMF Wearable using EAGLE

The EMF wearable device's circuit schematic is shown in figure 3. This gadget has a battery, a coil, a resistor, a capacitor, and a switch; moreover, all components are linked together by connecting wires (red). This circuit’s power supply is illustrated with a battery since EAGLE did not provide the AC supply in the board schematic. The resistor’s value is 40 Ohms, and the capacitor’s is 0.02uF. The power supply should be able to provide AC voltage up to 20V (peak-to-peak). This exact voltage used in the device varies depending on the desired strength and

distribution of the EMF emitted by the device (elaborated more in III.C). Overall, these circuit's components should keep the operating current as below 0.5A, aligning with most domestic appliances nowadays. The total power for this circuit is expected to reach a maximum around 10W.

C. Simulation Strategy

Simulation of the device is critical to the evaluation of its performance and safety to the user. For this purpose, COMSOL Multiphysics is usually used to analyze the EMF created surrounding the coil and in the human body. Important results for simulations are the magnetic field strength, the magnetic flux density, and the electric field strength. For EMF simulation, the Radio Frequency module in COMSOL Multiphysics is needed. However, the module was not included in version 5.2, which was the only version available for use in computer labs at the School of Engineering and Applied Sciences, GWU. Due to this limitation, Sim4Life - another finite element method software, was chosen as an alternative.

Sim4Life is a numerical modeling software with powerful physics solvers that resemble those of COMSOL Multiphysics. It has an extensive collection of human phantoms with advanced tissue models and is especially useful in assessing the interaction between physics models and the human body. Since the EMF propagates unevenly in air and in the human body with rapidly-decreasing strength away from the center of the conducting coil, the device's emitted EMF has to be modified to treat tumors at different locations in the body. The parameters to be adjusted for the modification of the EMF from the device include its operating voltage (and as a result, operating current) and frequency. The simulation of EMF Wearable in Sim4Life provides an estimate of the EMF created at different current and frequency values. It is also a good source of information when evaluating the performance of the device's design.

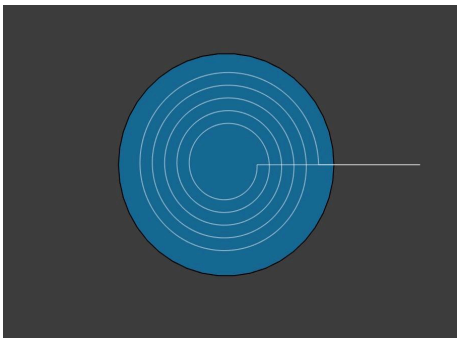

Figure 4. The device's model in Sim4Life

Figure 4 illustrates the model design with specific parameters in Sim4Life. The coil has 5 turns with an outer radius of 30mm and the inner radius of 8mm. Enclosing the coil is a protective layer of silicone rubber with the overall radius of 31m. For the simulation of the device, a current of 0.5A was run through the coil with the frequency of 200kHz (corresponding to mode 2 operation).The simulation deploys the Low-frequency solver in Sim4Life to derive the overall EMF. The resolution was set at 0.01mm to best capture the distribution and magnitude of the EMF.

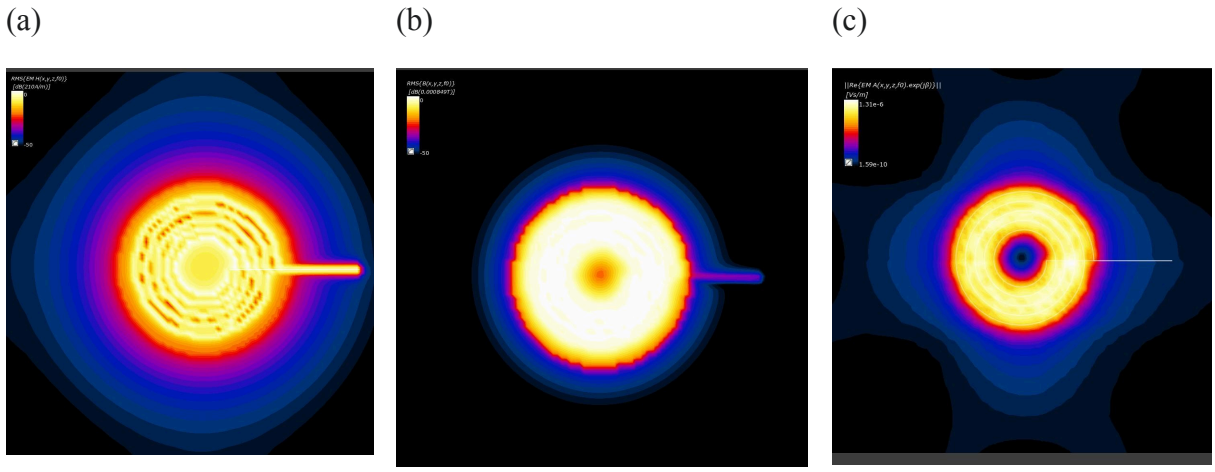

Figure 5 . EMF simulation results obtained in Sim4Life. Magnetic field strength distribution **(a)** magnetic flux density (**b**), and electric field strength (**c**) on the surface of the device.

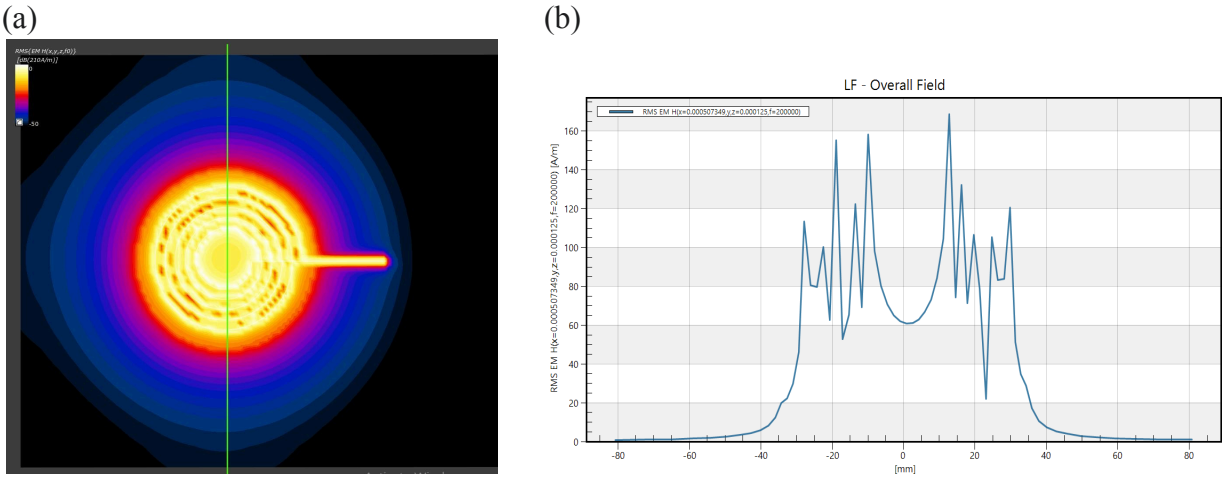

Figure 6. Data extraction using the slice view in Sim4Life. **a** Magnetic field strength distribution on the surface of the device. **b** The 2D plot line of data (magnitude vs distance) extracted along a line on the slice view (green line in **a**).

Figure 5 shows the results of the EMF simulation in Sim4Life. Results were shown in a slice view at the surface of the device in the transverse plane. One can also extract slice views from other planes (frontal & sagittal plane) if needed. The extracted data provided information regarding the strength of each EMF component at specific locations surrounding the device. Data on the slice views could also be extracted along a specified line (the green line in figure 6.a) in a comma separated values (.csv) file for 2D line plotting (figure 6.b) or for further analysis.

To demonstrate the role of device simulation in the design process, assuming that a small-sized neuroblastoma tumor of diameter 2mm is located at 2.2cm below the skin surface, how would the device's emitted EMF interact with this tumor? In this situation, since the electrode should be attached to the skin surface, the distance between the device and the tumor is

also 2.2cm. Therefore, the EMF strength at 2.2cm from the device's surface is the expected exposure at the tumor side. To extract the EMF strength at 2.2cm from the device's surface, it is necessary to first extract the slice view of each EMF component - magnetic field strength, magnetic flux density, and electric field strength - at the center of the device (figure 7. a,c, &e). A straight line crossing the center of the coil was then drawn on the slice vie, and data was extracted along its length to derive the exact values for EMF components at a distance 2.2cm from the center.

For the simulation of the device at 200kHz and 0.5A operating current, the magnetic field strength at 2.2cm above or below the center of the coil was found to be 15.07A/m, while the magnetic field flux density and electric field strength stood at $1.89 * 10^{-5}$T and $1.89 * 10^{-8}$V/m (or $1.89 * 10^{-10}$/cm), respectively. Considering the desired magnetic field strength for mode 2 is 0.7-3V/cm, the simulation result suggests an increase in the operating current (by increasing operating voltage) to achieve the desired therapeutic effect. In order to derive the best parameters of mode 1 & mode 2 for the treatment of Neuroblastoma tumors with different shapes, sizes, and locations, more simulations need to be performed with other combinations of current and frequency values.

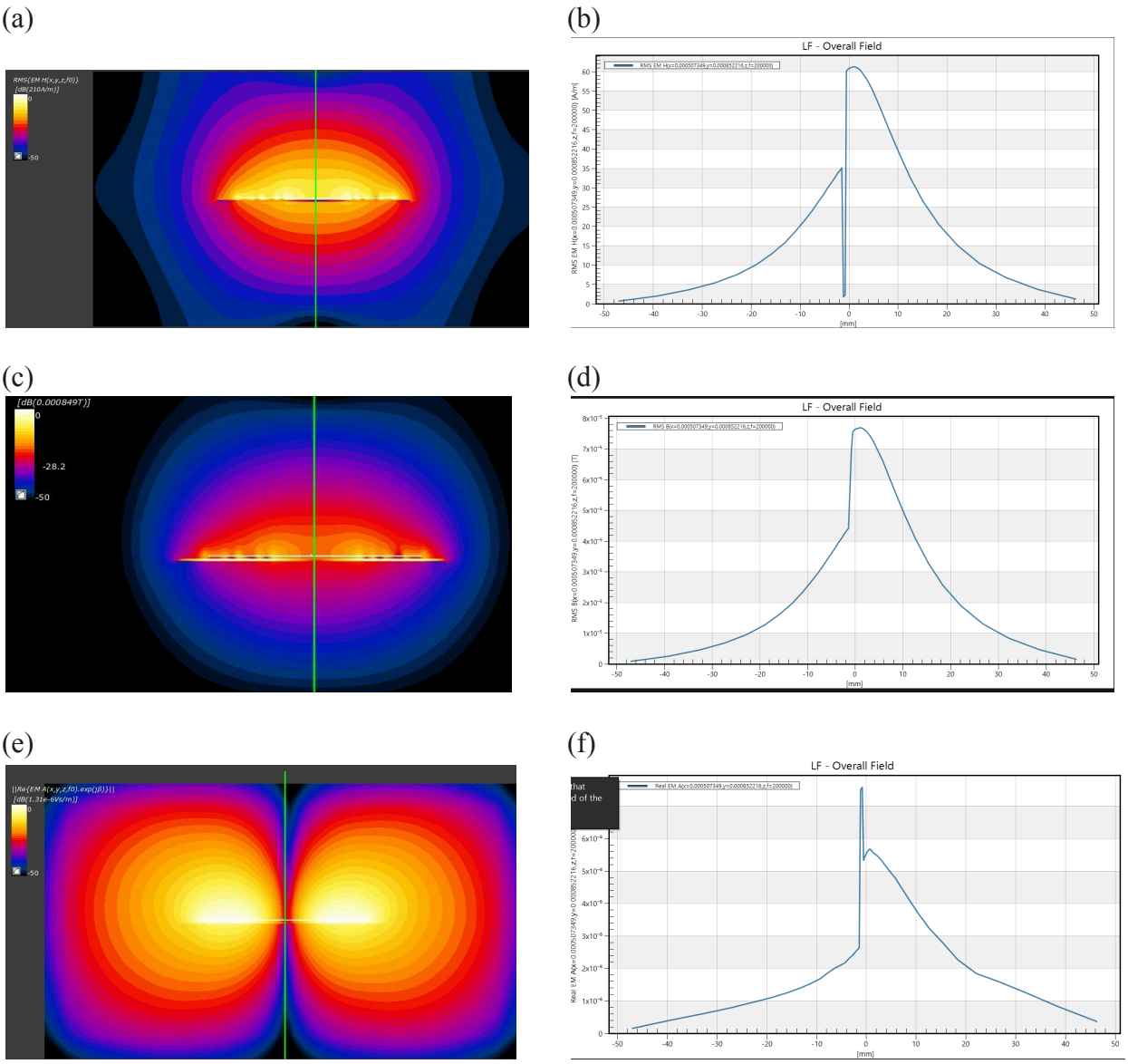

Figure 7. Slice views of the magnetic field strength (**a**), magnetic flux density (**b**), and electric field strength (**c**) in the frontal plane. The values of these EMF components were also extracted along a vertical line crossing the center of the coil (**b**, **d**, & **f,** respectively) for analysis of the EMF exposure at 2.2cm away from the center.

D. Device's Safety Issues

1. Electrical Safety

Since EMF Wearable is an electronic device, one needs to pay attention to its electrical safety. For this purpose, a thermal switch is included in the circuit (figure 3). This switch has a thermal sensor that automatically turns off the circuit should its temperature rise above a certain limit. This guarantees the current does go out of control, which is dangerous to the user.

2. *Thermal Dissipation*

Since the EMF is created by running a current through a conducting coil, exacerbated heating may take place on the surface of the coil. Considering the direct contact between the device and the skin surface, if this thermal effect is not dissipated effectively, it may cause terrible burn at the attach side. To address this problem, the soft polymer cover of the coil is designed to have 25 holes on the upper surface. The hole accommodates the inward flow of air and offers a natural cooling method. Other methods of heat dissipation are also considered. One of them is vapor cooling, which is very common in small electronic devices such as cell phones or laptops. Vapor cooling is usually employed to address the thermal issue of small devices with high power and as a result high heat fluxes. In vapor cooling, a layer of highly-volatile liquid suspended in an evaporator wick is placed on top or near a heating area. The heat absorbed by the vapor cooling layer is transferred to the evaporator wick. The liquid inside (mostly *distilled water*) then vaporizes and moves in a circular motion, forming an isothermal heat spreader. The vapor condenses at the condenser surface, and then the heat can be removed by natural cooling (Wei & Sikka, 2006).

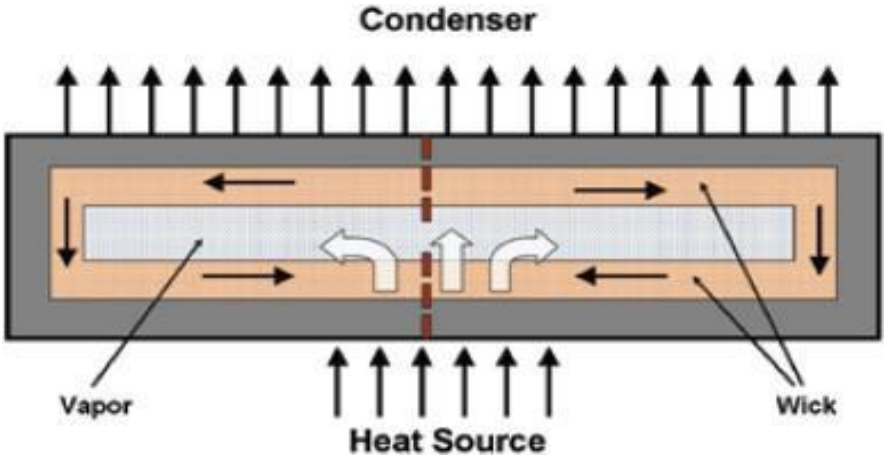

Figure 8. Structure & working mechanism of a vapor cooling layer

Some of the advantages of adopting vapor cooling include the fact that it is isothermal to 1 - 2 degrees Celsius. The system is also smaller than traditional cooling systems such as fans. The cooling layers can be as thin as 3mm and have minimal thermal resistance, allowing them to be utilized to cool many systems at the same time. With wick modifications, their effectiveness may be increased to considerably greater strength.

3. *Electromagnetic field exposure*

The device relies on an electromagnetic field for its therapeutic function, raising concerns regarding its safety for the human body. As mentioned above, prolonged exposure to EMF at high frequencies (above 100kHz) may damage biological tissues due to overheating (Hardell & Sage, 2008). On the other hand, low-frequency fields may cause unexpected nerve stimulation or change cell membrane properties that affect the normal function of the body. Several studies have also looked into the carcinogenicity of EMF. Although experiments have shown that

prolonged exposure to a strong EMF can cause cancer in small animal models such as mice, there is not enough evidence to prove a similar case in humans (Miah & Kamat, 2017). To best protect the general public from any harmful effects of EMF exposure, several international and governmental agencies have composed guidelines regarding safety limits for EMF exposure. Two of the most prominent guidelines are the ICNIRP 2010 by the International Commission on Non-Ionizing Radiation Protection and the IEEE C95.1 by the International Committee on Electromagnetic Safety. However, ICNIRP 2010 is more commonly referenced due to its stricter requirements regarding EMF exposure.

General Public Exposure Limits[a]			
Frequency range	E-field strength *E (V / m)*	Magnetic field strength *H (A / m)*	Magnetic flux density *B (μT)*
3 kHz – 10 MHz	83	21	27
Occupational Exposure Limits[b]			
Frequency range	E-field strength *E (V / m)*	Magnetic field strength *H (A / m)*	Magnetic flux density *B (μT)*
3 kHz – 10 MHz	170	80	100

Table 1. EMF safety limits specified in ICNIRP 2010 (Ahmad et al., 2018)

Simulations should be conducted in COMSOL Multiphysics or Sim4Life on the device to evaluate its safety for use at home and on children. The device's emitted magnetic and electric field strength, as well as the specific absorption rate (SAR), should stay below the above limits to guarantee the safety of the device for the user and the general public use. For EMF Wearable, simulations at 0.5A and 200kHz in Sim4Life yielded an EMF with all values staying well below the safety limits proposed by ICNIRP 2010.

IV. Future Development

At this stage of device development, EMF Wearable has a relatively simple design of a single coil with essential circuit components. To meet the expectation of being able to treat different stages of neuroblastoma and tumors of different sizes and locations, the EMF emitted by the device needs to be modified in terms of its strength and distribution. To be specific, the shape and magnitude of the EMF can be adjusted using the array design for the electrode. This means multiple coils with different arrangements can create a variety of shapes, sizes, and distributions of the EMF due to the interference of each coil's EMF with one another. Furthermore, improvements can also be made regarding the circuit design to achieve higher power usage efficiency. This will help minimize energy loss due to thermal effects. The main safety concern for any electronic device is the overheating of the circuit components. This is especially true for a device with such a large surface area and direct contact with the skin surface as EMF Wearable. Due to this reason, future designs of the device should aim for a highly

effective cooling system. Finally, simulations in COMSOL Multiphysics Sim4Life will be used as the main testing method for each device design until the design is finalized and ready for real-life evaluation. Rigorous clinical studies will be designed and conducted to assess the performance of the device.

V. IP Considerations

For our wearable medical device we would be applying for a utility patent. This patent type lasts 20 years before having to be renewed. Utility patents costs start at $3000 dollars but can reach upwards of $20,000 dollars. Our claims for our patent would be the usage of an electromagnetic field for targeted therapy of cancer cells by reactive oxygen species activation using frequencies 200-300Hz in combination with tumor treating field of 200-300kHz. A similar device to ours is the Optune wearable (NovoFFT-100A)and it has the patent classifications A61N1/32, A61K31/196, A61N1/36002, A61N1/40, and A61P43/00 (Moshe, 2016). The classifications with A61N apply to electrotherapy. The classification A61K covers devices that are specially adapted for bringing pharmaceutical products into particular physical or administering forms. And the classification A61P covers therapeutic activity of chemical compounds or medicinal preparations already classified as such in subclasses A61K or C12N with the term drugs including chemical compounds or compositions with therapeutic activity. In terms of our freedom to operate as a company we will need to have usage of different technologies than that of Optune wearable and if so we will be able to get a patent for our product. To overcome this, our idea has novelty as compared to Optunes design because of the fact that we have a different design and technical detail from them. This would allow for our company to have freedom to operate without paying royalties to Optune.

VI. Regulatory Strategy

Any medical device that wants to be legally sold and distributed in the US has to be cleared or approved by the Federal Drug Administration (FDA). The regulations that devices have to comply with in this process entirely depends on their classification. Medical devices are categorized into three classes depending on their potential harm and risk to the human body: Class I (low-risk), class II (moderate-risk), and class III (high-risk) (FDA, 2022). In addition, there are three main regulatory pathways that devices may go through Premarket Approval (PMA), 510k, and De Novo (FDA, 2022). Most class I devices do not need to go through any of these three pathways, with a few exceptions that need a 510k application. However, they have to comply with some general controls set forth by the FDA. Class II is the most common designation of medical devices in the US and generally requires 510k clearance of substantially equivalent to a predicate (a previously cleared device (class II or De Novo) with similar safety and technological characteristics). They also have to adhere to some special controls to guarantee their safety and effectiveness. Due to their technical novelty, some class II devices undergo the De Novo process to establish a new device category. Other exceptions (but not common) in this class require PMA approval. All class III devices have to go through PMA and need to be supported by a large amount of clinical data to prove their safety and effectiveness. Devices in this class also need to have well-defined risk mitigation strategies to be approved by the FDA.

EMF Wearable should be classified as a Class III device. The classification process of the device is based on information about previously approved devices with similar technological

characteristics. Most of these devices come from Novocure Inc., a company specializing in wearable devices that use Tumor Treating Field (TTF) to treat different types of cancer. As of the time this report is written, Novocure devices have been used on more than 22,000 patients, with yearly revenue reaching $535 million in 2021. Contributing to this impressive record is Optune - the company's first FDA-approved wearable device used in patients with glioblastoma (a type of brain cancer) (FDA, 2022). Optune consists of a portable power supply with electrodes placed on the scalp to emit electromagnetic fields. The device uses alternating current to create a magnetic field of specific frequencies (around 200kHz) called Tumor Treating Field (TTF), which is able to prevent cancer cells from actively dividing. According to the FDA database, Optune is designated as a Class III device with product code NZK (Simulator, Low Electric Field, Tumor Treatment) and in direct supervision of the Neurology review panel. Optune went through the PMA process (P100034) and was approved by the FDA in 2015. Another similar device is NovoFFT-200T which also came from Novocure. NovoFFT-200T is used to treat mesothelioma - a type of cancer caused by asbestos and usually found in the lining of the lung or abdomen. The device has a similar design to Optune but with different electrode placement. NovoFFT-200T is a class III device (product code QGZ - Electrical Tumor Treatment Field) but went through Humanitarian Device Exemption (HDE - H180002) as an improved version of Optune (FDA, 2022). Optune and NovoFFT-200T are the most notable examples of devices that use electromagnetic fields to treat cancer. However, the two devices are different in how and when they are used in cancer treatment. While Optune is used as the last resource, only after other treatments fail to prove their effectiveness, NovoFFT-200T is used in conjunction with chemotherapy. Therefore, Optune is mostly utilized in the last stages and NovoFFT-200T in the early treatment of cancer.

The group's device (EMF Wearable) with the idea of using electromagnetic fields to treat neuroblastoma differs from Optune and NovoFFT-200T in two ways. First, the device used electromagnetic fields of varying frequencies to take advantage of three therapeutic effects of electromagnetic fields - tumor treating field, thermal effect, and ROS creation. Second, the device can be used as both a single treatment or in conjunction with other cancer treatments such as chemotherapy, radiotherapy, and surgery, considering the disease's progress and the doctor's recommendation. Due to those reasons, the device is most likely to be classified as a Class III device and must go through the PMA application. As a class III device, EMW Wearable needs to have well-defined clinical data to prove its safety and effectiveness. Therefore, the clinical study design is of the utmost importance in the PMA application process.

A clinical study design for EMF Wearable has its inspiration from those used for Optune and NovoFFT-200T. This is because the FDA has already approved the two devices for their distribution in the US. Specifically, EMF Wearable needs to prove its safety for the target population and its effectiveness in treating neuroblastoma. The clinical study should be conducted on at least 1000 minor patients under five years of age with pathological or histological evidence of neuroblastoma. Patients in the study are newly diagnosed with neuroblastoma or recurrent cases. At the beginning of the study, there should be an equal number of cases in all four stages of neuroblastoma with at least three months of life expectancy. All participants need to provide their guardian or parents' consent for the study and have access to EMF Wearable. The study will be conducted in an uncontrolled environment with a person being to operate EMF Wearable to simulate at-home usage. Data about the disease progress are collected every other week for 4 to 6 weeks. The final result will be analyzed and compared with

other treatments such as chemotherapy, radiotherapy, and surgery. In particular, the clinical study will also evaluate how the device may interfere with other treatments when being used simultaneously.

VII. Contributions

Team members: Khanh Nguyen, Manish Sharma, & Zachary Kunz

Disease research: The disease was chosen after discussion regarding assignment 1 of Khanh and Zachary. The team then chose to focus on Neuroblastoma. Since Zachary did an in-depth research on this disease for his assignment, he was the main contributor to the disease fundamentals and current solutions. Khanh then researched relevant information for stakeholder analysis, and Manish on market analysis.

Device Ideas: All team members participated in brainstorming the ideas for the device. Khanh came up with the suggestion of using an electromagnetic field for a wearable device that has therapeutic properties. Khanh found a highly similar device (Optune) and shared his ideas of using electromagnetic TTF and thermal effects to treat neuroblastoma. Other team members then dive deep into this kind of device and research relevant therapeutic effects of the electromagnetic field. Manish researched SFM, PFM, and the creation of ROS using electromagnetic fields. Zach was responsible for investigating related patents and potential. Khanh with experience in FDA device regulation handled the FDA regulations required for the device.

Device design: Joint efforts of all members. The overall design was first proposed by Khanh and elaborated by all team members.

Written Report:

The team met frequently to discuss how to properly divide sections of the report without compromising the overall quality. In general, each team member was responsible for a specific section of the report. Proofread, and final formatting and edits were done by Khanh.

I. Need identification & validation
   A. Disease fundamentals (Zachary)
   B. Current Options (Zachary)
   C. Stakeholder analysis (Khanh) & market analysis (Manish)

II. Device idea
   A. Working mechanism (Khanh)
   B. EMF Wearable compared to current options (Khanh)
   C. Feasibility (Manish)
   D. Competing Technology (Manish)

III. Device design & simulation
   A. 3D design (Zachary)
   B. Circuit board design (Manish)

C. Simulation Strategy (Khanh)
D. Device's safety issues
    a. Electrical safety (Manish)
    b. Thermal issue (Manish)
    c. EMF exposure (Khanh)

IV. Future Development (Khanh)

V. IP considerations (Zachary)

VI. Regulation Strategy (Khanh)

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