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# Synergistic Cancer Treatment: A Hypothetical Combination of Several Unique Cancer Treatments

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Virotherapy, the use of viruses to lyse cancer cells, was first thought of in the early nineteenth century (Elizabeth and Russell). However the lack of technology, such as genetic manipulation and cloning, made it nearly impossible to force a virus to specifically attack cancer cells. Advances in both genetics and general knowledge about viral and cell structure now allows for nearly complete control over the virus's structure and processes that occur during infection. Such technology is described within the "Materials and Method" section of "Rapid Pathogenesis Induced by a Vesicular Stomatitis Virus Matrix Protein Mutant: Viral Pathogenesis Is Linked to Induction of Tumor Necrosis Factor Alpha" by Jean Publicover et al.

Oncolytic viruses are viruses that will have increased propagation in cancer cells via conditional replicating circumstances. The conditional replicating circumstances will generally be unique to each type of virus. Also, these viruses' probability of infecting cancer cells depends upon the types of targeting being used to trigger the viruses to infect just cancer cells and how many of these different targeting methods are being used. Methods of targeting range from altering the virus's DNA to altering its domain. The domain is a protein located on the end of protein which extends from the main section of the virus; the proteins which extend from the main section of the virus are commonly referred to as viral spikes. These spikes allow for recognition of host cells. That is, the protein spike of the virus connects to a specific protein

receptor on the cell membrane of the host cell (Black 272). The connection between the two proteins is extremely specific and accounts for the virus's ability to differentiate between cells. Also, cancer cells have some structural differences from that of healthy cells (Ozoren and El-Deiry; Raffo et al.). Thus, viruses are capable of differentiating between healthy cells and cancer cells based on their structural differences. These differences are mainly observed on the cell membrane, which expresses abnormal ratios of protein receptors. These differences can be used as an advantage to specifically target the cancer cells.

There are several different methods to increase the oncolytic ability of viruses. The two more common methods are transductional targeting and transcriptional targeting. In transductional targeting the receptor sites on the cell membrane of the cancer cell are altered, the domains of the virus are altered, or both are altered. Complementary DNA can be used to increase the number of receptor sites on the cell membrane of the cancer cells. Complementary DNA, cDNA, is generally described as “a doublestranded DNA version of an mRNA molecule” (“cDNA”). More specifically, in eukaryotic cells the mRNA that is transcribed from the desired gene is removed. Then enzyme called reverse transcriptase will change the mRNA molecule from to double stranded DNA molecule, or cDNA. Once removed, multiple copies of the DNA fragment are made, which are further transfected into the desired host cells. Promega Corporation describes transfection as “the process of introducing nucleic acids into eukaryotic cells by nonviral methods” (“Transfection”). If cDNA is transfected into a cell, it will cause the cell to express the proteins that are encoded by the cDNA. This process can occur by physical or chemical means. The chemical method involves cationic lipids and molecules (e.g. calcium phosphate and DAEA-dextran (“Transfection”). The molecules and lipids are positively charged to better associate with the negatively charged cell membrane. However, they work differently.

The molecules, which have a positive charge, are attracted to the negative charge of the nucleic acids. Since the molecules have an excess charge, the molecules will also be attracted to the negative charge of a cell membrane. Thus, the genetic material is forced into the cell by means of endocytosis (“Transfection”). However, some of the chemicals can be extremely toxic in vivo and small pH changes will deactivate others, thus making the positively charged molecules not the preferred choice in long-term studies.

When long-term transfection studies are being done, lipids are generally chosen as the form of transfection (“Transfection”). Before injected into the tissue, the negatively charged genetic material is surrounded by positively charged artificial liposomes. After injection, the positively charged liposomes will then fuse with the cell’s membrane and the genetic material is released into the cell. The physical method takes a different approach. The physical method involves direct microinjections of the genetic material (“Transfection”). Although very precise, this method is extremely expensive and laborious. In virotherapy transfection is used to force cancer cells to produce more cell surface markers for the virus to attach and recognize the cell as a suitable host cell. Thus, transfection can be used to increase the chance that the virus will identify the cancer cell as a host cell and infect the cancer cell. Also, transfection of certain cell surface markers can allow the virus quicker entry into the cell. Adaptor molecules, which are antibodies, rose against domains of the virus can increase the infection rate of cancer cells and reduce the infection rate of normal cells (Morrison et al.). Not only would this technology allow the virus to be more specific to cancer cells, but can also allow the virus to infect cell types it may not have been able to infect before the addition of adaptor molecules. Adaptor molecules perform this by attaching the base to the virus and one end of the antigen-binding site to the domain of the virus and the second antigen-binding site attaching to a receptor only found in, or

more commonly expressed in, cancer cells. This will cause the virus to lose its ability to bind to its original receptor site, but the virus will now have the ability to bind to whatever receptor specified. However, adaptor molecules will only affect the initial input viruses and will not be inherited by future viruses (Morrison et al.). Furthermore, the side effects of adaptor molecules are not completely understood. Lastly, the receptor-binding domains can be altered. The domains are altered by genetically altering the virus. The genetic alteration can involve the deletion or addition of a single gene or several genes. Altering the receptor-binding domains of the virus has the ability to change the receptor sites that the virus would attach, thus changing the tropism of the virus (Davydova et al.).

Transcriptional targeting is the insertion of a tumor-specific promoter or promoters (Davydova et al.). A promoter is a region of DNA that must be transcribed into RNA before the following DNA is transcribed into RNA. The promoter will require one or more transcription factors to be active at a single point in time. A transcription factor is a protein that binds to sections of DNA and controls the transcription of DNA into RNA at the promoter. Because there can be several transcription factors that must be active at the same time, the promoter is normally only expressed in the desired type of cell. In other words, if the cell doesn't have all of the transcription factors active at the same time, the promoter is not expressed. If the promoter is not expressed, then the viral genes cannot be expressed. Also, there is a similar type of viral genetic alteration denominated attenuation. Attenuation is the removal of a section or sections of the viral genome that are not necessary to infect and lyse the cancerous cell, but are required to infect and lyse healthy cells (Elizabeth and Russell).

On a different topic, Interferons can have many different applications for tumor treatment. However, interferons alone are far too weak to effectively treat whole tumors. As

explained by Stojdl et al., the effectiveness of interferon treatment has limited results due to genetic mutations that produce interferon pathway proteins. Thus, the cancer cells are unable to transport interferon across their cell membranes and are relatively unaffected by the interferon treatment. There are two types of interferon, type I and type II. Type I interferon includes both alpha and beta interferon, while type II only includes gamma interferon. Alpha and beta are normally used in the body to defend against viral infection by triggering normal cells to produce enzymes. Altogether, these enzymes are called antiviral proteins, which will breakdown any of the virus's genetic material (Black 448). However, gamma interferon affects pathogens less directly. Gamma interferon is capable of triggering macrophages to attack pathogens (Trost et al.), such as viruses or cancer cells. Both types of interferon may be used for cancer treatment. If the cancer cell is able to take in the interferon, then the cell will either undergo apoptosis or be readily attacked by cytotoxic T cells—a type of white blood cell that naturally attack cancer cells—and macrophages. Also, gamma interferon up-regulates certain genes and proteins that influence cellular apoptosis (Schroder et al.). These genes and proteins include IRF – 1, Caspase 1, PKR, DAPs, Cathepsin D, Fas \ Fas ligand, and TNF –  $\alpha$  receptor. IRF – 1 is a tumor-suppressor gene and is initiated by signals such as damaged DNA. IRF – 1 is required for the induction of apoptosis, but its proapoptotic effects are attributed to IRF – 1 induced caspase 1. Caspase 1 is a cystein protease, which cleaves the precursor of IL – 1 $\beta$  and IL – 18. IL – 1 $\beta$  is abbreviated for interleukin – 1Beta and IL – 18 is abbreviated for interleukin 18. Both IL – 1 $\beta$  and IL – 18 are polypeptides and are involved with cellular apoptosis. Once activated, these cytokines bring about apoptosis through means of macrophage activation (Sansone et al.). Macrophages induce apoptosis in cancer cells through several mechanisms, such as the release of the molecule nitric oxide (Cui et al.). PKR is an antiviral enzyme that is known to be an

important effector of apoptosis (Vorburger et al.). However, the manner in which PKR induces apoptosis is under research and is not fully understood. DAPs are death-associated proteins related to gamma interferon induced apoptosis (Yamamoto et al.). However, the relation is poorly defined. Cathepsin D is a lysosomal protease that activates apoptosis by means of Bax activation. Bax is a pro-apoptotic member of the Bcl-2 gene family and induces apoptosis through the selective release of mitochondrial apoptosis inducing factor (Bidere et al.). Fas is a cell membrane receptor that is known as a factor for apoptosis activation. Fas is expressed in many cells types, but is down regulated in cancer cells. Fas ligand (FasL) activates Fas and is generally expressed in activated T cells and a few other types of cells, which includes some types of cancer. Also, research has shown that gamma interferon produces Fas in tumor cells at sufficient quantities to initiate apoptosis (Dai et al.). TNF -  $\alpha$  (tumor necrosis factor - alpha) receptor is another type of receptor that is known to initiate apoptosis in cancer cells. Gamma interferon is known to increase the number of TNF -  $\alpha$  receptors in cancer cells (Tsujiimoto et al.).

This hypothesis is based on injections of a mutated vesicular stomatitis virus in combination with alpha and gamma interferon, which may be used to effectively treat and possibly cure multiple types of cancer. The vesicular stomatitis virus is commonly referred to as VSV and is a (-) sense RNA virus that consists of six main structures: glycoprotein, matrix protein, large protein, phosphoprotein, nucleoprotein, and RNA. Each structure has a purpose. The glycoprotein is located on the most outer surface of the virus. The glycoprotein's purpose is to bind to a receptor site on the cell membrane and induce endocytosis (Jeetendra et al.). However, the actual receptor site that the glycoprotein binds with is currently unclear. The matrix proteins are located just underneath the virus's capsid. Once released into the host cell's

cytoplasm, the matrix proteins will travel to the nucleus and block the nuclear pores (Publicover et al.). Once the nuclear pores are blocked, none of the host cell's RNA can leave the nucleus. Because the host cell's RNA cannot leave the cell, antiviral proteins cannot be produced. This effectively stops the cell from fragmenting the virus's RNA and stops the cell's normal functions. The large protein and phosphoprotein are both located within the center of the virion. The large protein and phosphoprotein serve the same purpose, which is to transcribe and replicate the viral genome (Gaudier et al.). This will effectively create more strands of viral RNA and other viral partials. The nucleoprotein is located on the RNA in the center of the virus. The nucleoprotein "is involved in multiple functions including transcription, replication, and assembly" (Green et al.). Since the VSV belongs to the Rhabdoviridae family, it will have (-) sense RNA (Black 262 and 276). Since the VSV has (-) sense RNA, the RNA would normally need to be integrated into the host's DNA. However due to the large protein, phosphoproteins, and nucleoproteins, there is no need for this process and the RNA is copied in the cytoplasm of the cell. As the viral parts are being recreated several thousand times, the parts will naturally form new VSV virions. Then, the VSVs will bud from the host cell and be released into the surrounding tissue and will be able to infect more cells. Although budding will not necessarily kill the host cell immediately, the host cell will die after a ranging period of infection.

In nature, the VSV has some oncolytic ability. This is caused by the VSV's unusual weakness to human alpha and beta interferon (Shinozaki et al.). Also, the VSV is pantropic. In other words, the VSV is able to infect "all cell types tested to date" (Coil and Miller). When the VSV infects a normal cell, that cell will produce interferon. The interferon produced by the infected cell will then pass into surrounding cells, but will not affect the cell that produces the interferon. The cells that received the interferon will then produce enzymes that will fragment

any of the virus's genetic material that is released into the cell. However, cancer cells may have ineffective interferon pathways (Stojdl et al.). The damaged pathways are a result of certain mutations within the cancer cell's DNA. This mutation has two very important effects on the cancer cell. First, the cancer cell has become immune to the effects of interferon, one of which is the production of a specific cell surface protein. The protein is tumor necrosis factor (TNF)-related apoptosis-induced ligand (TRAIL). This protein bolsters the induction of apoptosis and is also a component of T cell cytotoxicity (Kayagaki et al.). Secondly, the lack of interferon also means the lack of a strong antiviral defense. The lack of interferon defenses will thus promote the VSV's tropism in such cancer cells.

Nonetheless, the VSV doesn't have enough oncolytic ability to treat cancer. However, the technology previously described permits changes in both the VSV and the cancer cells. These changes will greatly increase the oncolytic ability of the VSV. There are two specific changes to the VSV that will occur in this hypothesis. The first change involves the VSV, while the second change involves the cancer cells. The first change will be the deletion of methionine 51, M51 from the VSV's genome. Deleting this gene will leave the VSV unable to create its matrix proteins (Publicover et al.). Without these proteins, the VSV has little protection against the effects of interferon. More precisely, the VSV's RNA has no protection against the antiviral enzymes that interferon triggers to be produced inside of the cell. However, since cancerous cells cannot take in interferon, the virus will still function as normal. This, in theory, will keep the healthy cells unaffected by the VSV. The second change, the alterations to the cancer cells' membranes, will be done by means of transfecting phosphatidylserine cDNA into the cells through lipid vectors described previously. Phosphatidylserine cDNA, or PS cDNA, will force the cancerous cells into producing more PS molecules in their cell membranes. Even though PS

isn't the receptor site for VSV, an increase of PS in the cell membrane will increase the rate at which the VSV will enter the cell (Coil and Miller; Carneiro et al.). The actual mechanisms that occur to cause this are somewhat unknown. Nonetheless, the bond that the PS and the viral glycoprotein form would most likely cause a pulling motion. Since PS is generally found on the inner leaflet of the cell membrane, this pulling motion could be the cause of the decreased viral entry time. A decreased treatment time is important for two reasons. The first reason is that the tumor won't have as much time to spread or enlarge. Secondly, there will not be as much of a concern that the patient's immune system will eradicate the virus. Also according to mathematical data and equations from "Towards Predictive Computational Models of Oncolytic Virus Therapy: Basis for Experimental Validation and Model Selection," a reduced infection rate should increase the overall success rate of the treatment (Wodarz and Komarova).

Alone neither interferons nor a modified VSV would be able to effectively treat cancers. However, their synergistic effects will theoretically have a devastating affect on tumors. At the start of the treatment, the modified VSVs will quickly and effectively start infecting and lysing cancer cells. While the VSVs are serving their purpose, the alpha and gamma interferons will serve their purpose. Alpha interferon will assist in the initiation of apoptosis in any cancer cells that are still able to transfer it into the cell and assist healthy cells against the modified VSVs, which have their own defense mechanisms disengaged. The gamma interferon will have two very important effects. The gamma interferon will up regulate several pro-apoptotic genes and proteins within the cancer cells and trigger more macrophages to start attacking the tumor. Also, one can only assume that these macrophages will also attack the viruses. However, it is unclear as to the degree that the additional macrophages will affect the VSVs.

This treatment is intended to treat multiple types of cancer simply via the alteration of administration and dosages. Although there are many different types of cancer, there is a general procedure that will apply for most cancer treatments. The general treatment will include the amount of tumors, where the tumors are located, and how large are the tumors. The amount and size of tumors will be required to properly administer correct doses of alpha interferon, gamma interferon, mutated VSVs, and PS cDNA. The location of the tumor(s) will identify the way in which treatment must be administered. In other words, lung cancers and skin cancers may require different means of administration. The general first step will be the transfection of PS cDNA into cancer cells via means of a lipid vector. Since the cancer cells will not instantly produce the PS in their membranes, a time delay of around twenty-four hours is to be expected. However, the delay may be more or less after further testing. After the time delay, the interferons will be administered into the tumor(s). As soon as the interferons are injected, the viral injections should be administered. The reason that these steps must be close together is because alpha interferon breaks down quickly in the body (Bukowski et al.). Also, having these steps together should lower any negative the macrophages will have on the VSVs. Interferon alpha doses will be set at 6.0micrograms/kg/week (Bukowski et al.). Gamma interferon doses will be set at 1mg/m<sup>2</sup> daily (Mani and Poo). The exact maximum tolerated doses of the mutated VSVs and PS cDNA are still unclear. It is important to acknowledge that these doses are not absolute; they are to be used as possible starting doses. Doses may be altered for several reasons. Particularly, doses of the M51 mutant VSV may need to be increased or decreased based upon the patient's immune system. Also depending on the length of treatment, doses may be subjected to change and alteration.

The cost of this treatment should be less expensive than radiotherapy and chemotherapy treatments. There are several reasons that this treatment will be less expensive. First, the modified viruses are very easy to create and reproduce in a laboratory with modern technology. Second, all the interferon used will be easily attainable through recombinant DNA methods. Lastly, the cDNA that will be needed to force the cancer cells to produce more PS in their cell membrane is also attainable through inexpensive recombinant DNA methods.

Like most other cancer treatments, there will be side effects. However unlike other cancer treatments, such as chemotherapy or radiotherapy, the expected side effects are far less hazardous. The side effects of this treatment can be assumed to resemble a compilation of gamma and alpha interferon side effects in conjunction with the symptoms caused by wild type VSV. The research data for the side effects of gamma interferon were gathered from data from "Single institution experience with recombinant gamma-interferon in the treatment of patients with metastatic renal cell carcinoma" (Mani and Poo). The common side effects of gamma interferon injections (greater than forty percent of total patients) at doses of  $1\text{mg}/\text{m}^2$  are as follows: fever/chills, anorexia, fatigue, nausea, and vomiting. The rare side effects of gamma interferon injections (less than forty percent of total patients) at doses of  $1\text{mg}/\text{m}^2$  were leukopenia and abnormal liver functions and no severe side effects were observed. The data for the side effects of alpha interferon were gathered from "Pegylated Interferon Alfa-2b Treatment for Patients With Solid Tumors: A Phase I/II Study" (Bukowski et al.). The common side effect of alpha interferon injections (more than forty percent of all patients) after a twelve week period at  $6.0\text{micrograms}/\text{kg}/\text{week}$  were as follows: fever/chills, nausea, anorexia, fatigue, headache, vomiting, diarrhea, dyspnea, and injection site pain. The rare side effect of alpha interferon injections (less than forty percent of all patients) after a twelve week period at

6.0micrograms/kg/week where myalgia, dizziness, pain, and dry mouth. After a one year period of treatment, most initial side effects were observed in less than forty percent of all patients. However, thrombocytopenia, leukopenia, and neutropenia became startling common in patients. Thrombocytopenia was observed in seventy-six percent of all patients, leukopenia was observed sixty-nine percent of all patients, and neutropenia was observed in fifty-two percent of all patients. Lastly, it's commonly known that unlike other members in its family, a wild type VSV infection has only mild to moderate flu symptoms. Altogether, the common side effects of this treatment would most likely consist as follows: fever/chills, nausea, anorexia, fatigue, headache, vomiting, diarrhea, and injection site pain. The more rare side effects of this treatment could include abnormal liver functions, dyspnea, myalgia, leukopenia, thrombocytopenia, and neutropenia. It is important to note that these are certainly likely side effect, but unforeseen side effects may still exist. Also as shown by alpha interferon research, the side effects of this treatment may vary over long periods of time.

The advantages of the modified VSV in combination with alpha and gamma interferon over other cancer treatments are numerous. This treatment is expected to be relatively quick, simple, inexpensive, and only mild side effects are expected. These are advantages that no other cancer treatment in current medical practice can offer. Although this is only a hypothesis and has not been tested in any laboratory, there is still an abundance of research that provides evidence that this hypothesis be met with success. Evidence can be seen in similar clinical tests with similar viruses and interferons, such as "Prophylactic Alpha Interferon Treatment Increases the Therapeutic Index of Oncolytic Vesicular Stomatitis Virus Virotherapy for Advanced Hepatocellular Carcinoma in Immune-Competent Rats" by Shinozaki et al. However, only very

professional and carefully executed laboratory experiments can supply the data to determine the effectiveness of this treatment.

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