

NasMEC: Nanosphere-Mediated Epilepsy Control

Abstract

Nanosphere-Mediated Epilepsy Control (NasMEC) uniquely integrates multiple technologies to prevent seizures in patients with epilepsy, a neurological disorder affecting over 50 million people worldwide. Currently, there is no cure for epilepsy. Within twenty years, NasMEC will permanently cure epilepsy. NasMEC's adeno-associated viruses safely eliminate epileptic neurons, while surgically injected nanospheres transport healthy neurons to the correct area of the brain, thus retaining normal brain function. pH-sensitive nanospheres detect pH changes around epileptic neurons during a seizure, releasing viruses which will transduce surrounding neurons. NasMEC will relieve the financial and emotional burden of epilepsy, significantly improving the quality of life of afflicted individuals.

NasMEC: Nanosphere-Mediated Epilepsy Control

Present Technology

Epilepsy is a neurological disorder affecting over 50 million people worldwide. In the United States, it is estimated that more than 2.5 million people have epilepsy. This disorder is characterized by recurrent abnormal and uncontrolled electrical activity in the brain, called seizures that can last from a few seconds to a few minutes. Epileptic seizures are usually caused when either excitatory neurons “fire” too much, or when there is a lack of inhibitory neurons to stop the other neurons from firing. Having a seizure can be frightening to both affected individuals and their families (Leppik, 2007).

Currently there is no cure for epilepsy. Prescription antiepileptic drugs (AEDs) are the most common treatment, but a significant percentage of people are resistant to AEDs. Furthermore, only 5% of epileptic individuals are suited for epilepsy neurosurgery (Bialer, 2002). AEDs have many adverse side effects, ranging from drowsiness and nausea to depression (Leppik, 2007). Recent studies show that AEDs also affect cognitive abilities including attention, reaction time and speed of information processing (Hessen et al., 2006). The direct and indirect cost of epilepsy in the US is estimated to be \$12.5 billion each year (Singh, 2006).

Our proposed technology, Nanosphere-Mediated Epilepsy Control (NasMEC), integrates neuron culture, nanospheres, pH-sensitive polymers, and adeno-associated viral vectors to permanently stop seizures.

The first integrated technology is neuron culture. Neurons have traditionally been assumed to be in a terminally differentiated state. However, recent technologies have shown that progenitor and differentiated cells can be grown in culture (*in vitro*). This allows for the creation of transplantable neurons to replace malfunctioning or damaged nerve tissue. The growth of

neurospheres is a technique for generating large numbers of neural stem cells (NSCs), proliferating cells that can give rise to any type of neuron (Campos, 2004).

Neurospheres are organized floating clusters of NSCs that have been exposed to growth factors and other molecules. Each neurosphere contains NSC progenitors, differentiated cells, undifferentiated cells, and glia cells, embedded in an organized framework, called an extracellular matrix, allowing for the versatile production of many types of nerve cells. Neurospheres are self-renewing, having the potential to create millions of cells for many years (Campos, 2004).

The second integrated technology is nanosphere technology. Nanospheres are hollow nanoparticles currently being studied and used as biodegradable controlled release drug agents. Nanospheres usually have a polymer coating and vary in size from a few nanometers to several hundred nanometers (Lynn et. al., 2001).

The third integrated technology, pH-sensitive polymer, is a particular type of polymer coating that is sensitive to pH changes. These polymers swell when they detect changes in pH levels, creating holes that allow the release of the materials inside. Once the pH level returns to normal, the polymer will return to regular size, thus closing the holes in the nanospheres (Brannon-Peppas, 1997).

The final integrated technology is gene therapy using adeno-associated viruses (AAVs). AAVs are some of the smallest viruses possessing a non-enveloped isosahedral capsid. Only around 22 nanometers in size, they have the ability to transduce a wide variety of cells. AAVs are non-pathogenic viruses, causing only minimal immune responses. Because of their wide host range, safety profiles, and the ability to transduce differentiated cells, AAVs have been widely used as viral vectors in gene therapy (Monahan & Samulski, 2000).

History

Written records of seizures date back more than 5,000 years. Many people in the past believed epileptic individuals were possessed by evil. For example, the ancient Romans assumed that touching an epileptic individual would result in being possessed by demons and devils. Epilepsy was first regarded as a brain disorder by Hippocrates in 400 BC. In spite of knowledge of the true origin of epilepsy, discrimination against epileptic individuals still exists throughout the world (Leppik, 2007).

The first effective drug for epilepsy treatment, bromide, was developed in 1857. Bromide remained the only AED for over 60 years in spite of its unfavorable side effects, including sedation and gastro-intestinal distress. In 1953, phenytoin became the first AED to be extensively tested in animals before commercial release. Many other AEDs have been developed, though each has an array of side effects. Many AEDs use sedation and inhibition of neurons in order to control seizures. As a result, many people taking AEDs show signs of depression (Leppik, 2007).

The first *in vitro* cell culture involving neurons, conducted in 1907 by Ross Harrison, set the pace for modern cell biology. In 1890, Ramon y Cajal theorized that axons of neurons are created before the neurons are completely developed, and then shorten or elongate as needed. In the 1950s, organotypic culture (culture of whole slices of tissues) allowed neuronal maturation and myelination *in vitro*. Scientists involved in this field include Rita Levi-Montalcini, Victor Hamburger and Stanley Cohen. Levi-Montalcini and Cohen later received the 1986 Nobel Prize in Physiology or Medicine for the discovery of nerve growth factors (Tiffany-Castiglioni, 2006).

Nanospheres have existed for a quarter of a century. Incorporating natural and synthetic polymers, they were first intended to deliver drugs to targeted areas of the body. Recent efforts

have focused on the use of pH-sensitive nanospheres and nanoparticles to deliver necessary drugs to destroy characteristically high pH cancer cells (Biggs, 2007; Nano News, 2005).

In 1950, an article in *Nature* described phase transition of pH-sensitive polymers. Since then, many pH-sensitive polymers have been developed, including those containing pH-sensitive functional groups. These react to pH levels by changing physical properties, such as swelling and solubility, allowing the polymers to perform a variety of tasks (Bae et al., 1998).

Adeno-associated viruses were serendipitously discovered in 1965 as a contaminant in laboratory stocks of adenovirus. Realizing their potential, scientists worked with AAVs to create effective viral vectors for gene therapy. Since the 1990s, they have been used to deliver essential genes to patients with cystic fibrosis, cancer, and hemophilia. Recent studies show that they can also be used to deliver suicide genes to host cells (Gonçalves, 2005). Furthermore, the viruses can be engineered to not reproduce, and to be safely excreted from the human body (Monahan & Samulski, 2000).

Future Technology

NasMEC requires four components: neuron culture, engineered adeno-associated viruses, delivery of viruses and neurons using nanospheres, and safe viral transduction of epileptic neurons.

There is a theory that a non-stem cell can be converted into an adult stem cell by producing a similar environment to that of neurospheres. This means that scientists will find it no longer necessary to use fetal tissue in the production of stem cells (Campos, 2004). After creation, stem cells will be induced to differentiate into NSCs, using the methods developed by Zhang et al. (2006). Zhang's team used a neural stem cell-conditioned medium to convert embryonic stem cells into NSCs. Thus, it is likely that the same methods will also convert non-

fetal stem cells into NSCs. The resulting neural stem cells will be exposed to appropriate cell culture processing, fibroblastic growth factor and/or the epidermal growth factor to cause them to form neurospheres (Reynolds & Rietz, 2005). Using a newly developed method of cutting the neurospheres into quarters rather than dissociating the cells, a 1.5 million-fold increase in the cell numbers can occur in less than 200 days (Svendsen et al., 1998). After creating a sufficient number of neurons for transplantation, neurospheres will be exposed to conditions that cause the neurons to become GABAergic (inhibitory). Some neurons will remain undifferentiated so that, depending on whether or not the area of transplant needs more GABAergic neurons, they can become either GABAergic or excitatory. Once some of the neurons are differentiated, the neurons will be dissociated from their previous neurosphere configuration, thus ready for transplantation (Bruce Wheeler, personal communication, December 21, 2007).

Through scans such as electroencephalograms, it is possible to locate the particular area of the brain where a seizure is focalized. For example, over 20 million people in the world have temporal lobe epilepsy, a common form of epilepsy where seizures are focalized in a specific region of the brain (Shetty, 2007). Neurosurgeons will surgically inject the solution containing pH-sensitive nanospheres and the neuron-containing nanospheres into the focal point of the seizure. After transplantation, no other surgical procedures are necessary; the next seizure will begin the process of therapeutic lesion and neuron replacement.

The normal pH of the fluid surrounding all the brain's cells, the extracellular fluid (ECF), is around 7.4 (Biggs, 2007). During an epileptic seizure, the pH of the ECF becomes more alkaline for a brief period, and then becomes very acidic. We will apply the pH-sensitive polymer (PHSP) as a coating outside of the nanospheres. These coated nanospheres will play a key role in the delivery of AAVs to the brain. The PHSP will react with an acidic pH lower than

the normal ECF pH. Therefore, it will only react with the ECF surrounding epileptic neurons. Once exposed to the lower pH, the nanospheres will swell, creating openings in the polymer that allow AAVs to flow out and integrate into surrounding cells. When the pH levels of the ECF returns to normal, the nanospheres will shrink back to their original size (Brannon-Peppas, 1997). Only nanospheres carrying AAVs will have a PHSa coating.

The method we will use to create these nanospheres is called sonochemistry. Sonochemistry uses high-intensity ultrasound to create hollow nanospheres. In the process, silica nanospheres of the desired diameter are first created. Then the pH-sensitive polymer that forms the outer coating will be subjected to high-intensity ultrasound to create microparticles of the pH-sensitive polymer, which will bind to the surface of the silica spheres. After the particles of the pH-sensitive polymer are created, the spheres are heated, producing an even coating of the polymer. Once coated, the silica spheres are etched away from inside the spheres using hydrofluoric acid, leaving a hollow interior, and the pH-sensitive polymer as the coating on the sphere (Kloeppe, 2005).

Once released into the ECF, the adeno-associated viruses will integrate into epileptic neurons and the surrounding nerve cells. Because epileptic neurons are usually focalized, it is likely that the targeted neurons will be abnormal. The AAVs will cause transduced neurons to produce an enzyme X and a suicide enzyme. Enzyme X is an undeveloped enzyme that does not naturally occur in the human body. Its purpose is to mark the transduced neurons so that the neuron-containing nanospheres will be able to detect its presence and release its neurons.

There are multiple methods of causing apoptosis (programmed cell death) in cells targeted viral vectors. Our main method is to use the suicide enzyme called caspase-3. AAVs would carry the RNA to produce the activated form of the protein caspase-3. Once this activated

form is produced, the neuron will initiate apoptosis and die. In an interview with Dr. David Clayton (Professor of Molecular and Cell Biology at the University of Illinois), he informed us that carrying caspase-3 in AAVs would be an effective method of causing cell death in a short period of time, usually between 12-24 hours (David Clayton, personal communication, January 22, 2008). Eventually, the viruses can be programmed to be safely excreted from the body without reproducing or harming other cells (Paul Gold, personal communication, January 10, 2008). An alternative method of causing apoptosis in neurons is to use suicide genes called herpes simplex thymidine kinase and ganciclovir (Fukui et al., 2001).

The non-viral nanospheres will contain neurons, mostly GABAergic, but also some undifferentiated. These nanospheres will not be coated with pH-sensitive polymer, but will possess a polymer coating that release its contents only when it encounters enzyme X. These neurons will replace the epileptic neurons, thus retaining normal brain function in that area. An immune response is unlikely because the transplanted neurons are originally non-stem cells taken from the affected individual. Once in the brain, the neurons will adapt to the environment in which they are placed, developing specific characteristics that are needed or expressed in the site of transplantation (Kim et al., 2006).

Breakthroughs

In order for NasMEC to become a reality many breakthroughs must occur. Nanosphere technology researchers will need to expand the nanospheres to the micron level to accommodate neurons, viruses, and the nutrient serum inside the spheres. This stride will enable neurons to live for a period of time inside of the sphere.

Determining a way to insert neurons and a nutrient source into the nanospheres is the next necessary breakthrough. Currently there is no research dealing with the insertion of neurons

into nanospheres, though this may easily be achieved. Serum inside nanospheres will provide nutrients to nourish the neurons until release.

Being able to create a stem cell from a somatic cell must also take place. The stem cells will be used to produce neurons in neurospheres. Cells produced using this method should be able to function in exactly the same way as do normal neurons. Following recent developments, we believe that this can be achieved within a few years.

Another breakthrough involves the development of an enzyme that is not produced anywhere in the body, but can be produced by neurons without affecting normal body function. This would be the enzyme that the AAVs use to genetically program the neurons to produce. The neuron-containing nanospheres must also be able to react to this enzyme, acting as a green light for those nanospheres to expand and release the neurons.

Presently, viruses are not produced on a large scale. In order for our technology to work, large-scale production of AAVs must occur. It has been found possible to produce AAVs *in vitro* and use them as viral vectors to replace defective genes in individuals. There are clinical trials and development associated with the production of AAVs *in vitro* and its safe excretion from the body (Fukui et al., 2001). In recent years, scientists have been able to make great strides in this field, and it is very likely that AAVs can be produced on a large scale within twenty years.

Richard Smalley, often regarded as the “Father of Nanotechnology”, once said:

“Twenty years from now... nanotechnology will have given us specially engineered drugs, which are nanoscale cancer-seeking missiles, a molecular technology that specifically targets just the mutant cancer cells in the human body and leaves everything blissfully alone... (Mongillo, 2007, p.xix)”

Scientific progress is occurring rapidly. We have confidence that these breakthroughs can be achieved, allowing NasMEC to be developed and in use within twenty years.

Design Process

Our preliminary research centered on neural diseases and disorders such as Parkinson's, Huntington's, Alzheimer's, multiple sclerosis, and epilepsy. One of our group members mentioned that he had many seizures in childhood. Not knowing much about seizures, we further explored it. As this topic became more interesting, we dug deeper.

After doing considerable research on epilepsy and its treatments, we began brainstorming possible technologies that can work better than the current treatments. In the field of nanotechnology, we looked at designing nanobots capable of detecting epileptic neurons and destroying them. We also learned about a current technology called stretchable silicon. This technology enables silicon not only to bend, but to stretch. Realizing the great potentials of this technology, our group went to the office of the leading scientist in this field: Dr. John Rogers (Professor of Material Science and Engineering; Professor of Chemistry at the University of Illinois). After an hour-long interview, we thought about potential applications, including nanobots made of stretchable silicon that are able to go into the brain and detect blood pressure, glucose levels, temperature, and more. These nanobots could also detect the abnormality of epileptic neurons and kill them (John Rogers, personal communication, November 30, 2007).

Right about this time, Brad Dworak of the Neurotech group at the Beckman Institute of Advanced Science and Technology at the University of Illinois came to our class to discuss growing neurons on a chip. Motivated by this, we interviewed Dr. Bruce Wheeler (group leader of Neurotech; professor of the Department of Bioengineering at the University of Illinois). He provided us useful information about epilepsy, neurons, and viruses. We decided not to pursue the use of nanobots because of their high expenses and developmental issues.

Our next idea used viruses to kill epileptic neurons. But there was a problem – how can the virus detect whether a neuron is epileptic or not? That was when one of our group members visited the medical library at the Washington University at St. Louis, and found a book about pH levels in neurons during epilepsy. Further researching this topic, we discovered that nanospheres with pH polymer sensors can detect this change. Viruses can be inserted into nanospheres that can be used to detect the epileptic neurons, and release the viruses, which will kill those neurons.

Using information from Dr. Wheeler, we decided to grow replacement neurons using neurospheres to compensate for the lost neurons. Our third idea differs from our final idea in that the former required two separate injections, and three different sets of nanospheres. The first set of nanospheres contained viruses that programmed the epileptic neurons to produce green fluorescent marker protein (GFP), and enzyme X. This enabled the second set of nanospheres, containing a different group of viruses, to detect neurons with GFP and kill them. At the same time, a third set of nanospheres containing neurons would be released. Because this approach required two separate injections, the use of GFP, and an extra set of viruses, we decided to combine them all into one injection, and not use GFP because of its potential expense.

Consequences

As a result of our technology, there will be many positive changes in the lives of epileptic individuals. They will no longer need to worry about having an uncontrolled seizure. This will relieve a heavy emotional burden, allowing individuals to live life more freely. Additionally, epileptic individuals will no longer experience the side effects of AEDs nor be required to remember to take their daily medication, thus saving both money and time. The cost of the AED lamotrigine approaches \$41,000 per year, higher than chemotherapy for breast cancer (Bialer et al., 2002).

NasMEC can also lead to new treatments for other diseases. Because NasMEC integrates so many technologies, many new potential technologies hidden within each present technology are just waiting to be unveiled. In neurosphere technology, neurons could be grown *in vitro* for other purposes, such as brain injuries or Huntington's disease. Nanospheres could be used to deliver not only neurons, but also drugs to specific areas of the body. pH-sensitive polymers can also be used to detect cancer cells. Furthermore, adeno-associated viruses can be used to target cancer cells instead of nerve cells using the same mechanisms and technologies. NasMEC is a very flexible technology, and can spur many scientific developments.

Many AEDs are in the process of being developed, each one costing around half a million dollars (Bialer et al., 2002). NasMEC can solve this problem with a one-time expense in developing the technology, saving money for curing other diseases.

Like most new technologies, initial expense of developing NasMEC, producing it, and clinical trials will be reflected in its cost. As time goes on, the technology's prices will gradually go down. Many developing countries will have limited access to AEDs. Even when there is access, most people cannot afford the medications. After the development of NasMEC, more people will be able to afford to pay NasMEC's one-time fee, and never have to worry about having another seizure.

Soon, NasMEC will become accessible worldwide, and many people who had sudden seizures in the past will no longer have to worry about them. Our goal in developing NasMEC is to relieve the epilepsy-associated burden of millions of people, and give them a significantly improved quality of life.

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**Uniquely
Engineered**

**NasMEC: Aiming to
give epileptic patients a
better quality of life**

► **Learn how NasMEC cures
epilepsy**



Epilepsy affects over 50 million people worldwide. In the U.S., the number is over 2.5 million. Epilepsy is characterized by recurrent uncontrollable seizures. For a patient's family, a seizure can be very frightening. Unfortunately, there is no cure for epilepsy (Leppik, 2007). NasMEC will change all that, giving epileptic individuals a significantly improved quality of life.

External Links About Epilepsy

- >> [Epilepsy Foundation](#)
- >> [Epilepsy.com](#)
- >> [Center for Disease Control & Prevention](#)
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The homepage will play a flash movie about epilepsy. Clicking it will direct it to the Future Technology page. The navigation menu, header, and footer will accompany each webpage. All non-public domain graphics are cited.

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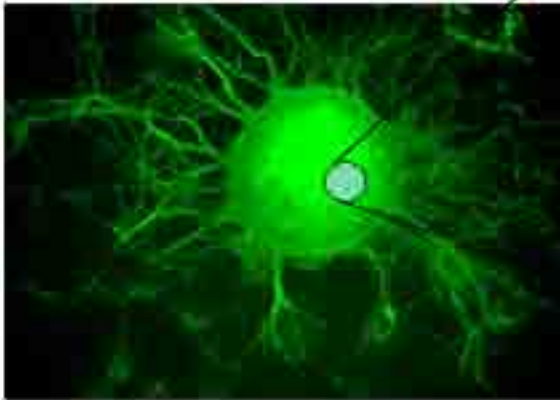
Nanosphere-Mediated
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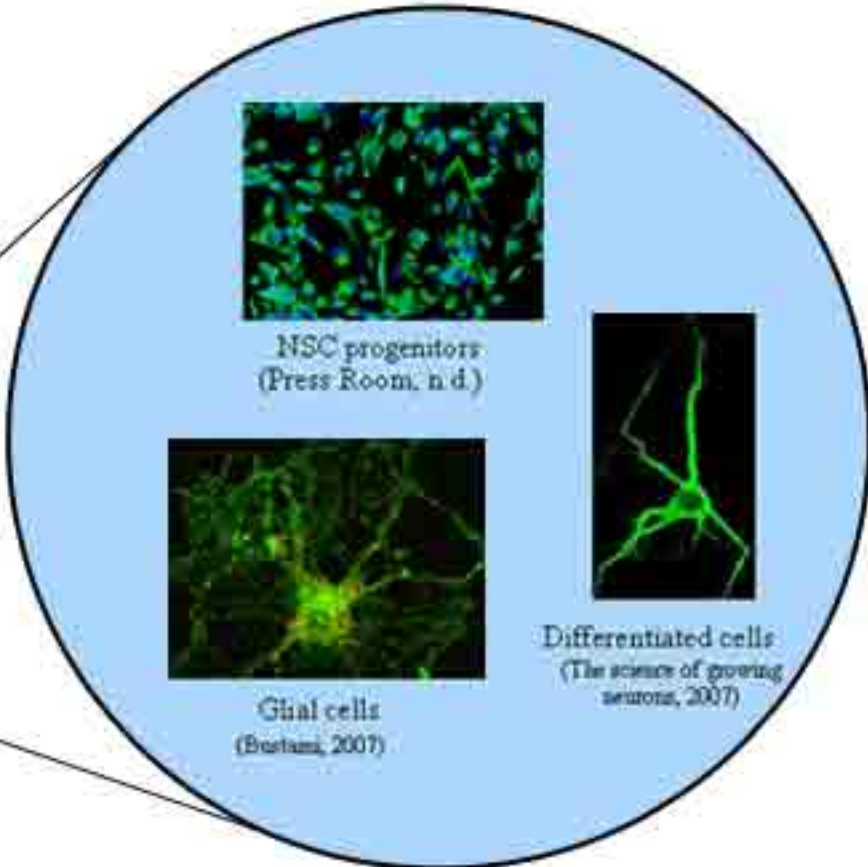
Neurospheres

Neurospheres are clusters of neural stem cells that have been exposed to growth factors and other important molecules. Neurospheres contain many different neurons, allowing for the production of many different cells. They are self-renewing, meaning that they can regenerate damaged parts (Campos, 2004).

NasMEC uses neurospheres to grow neurons that can replace epileptic neurons in the brain.



Przyborski, n.d.



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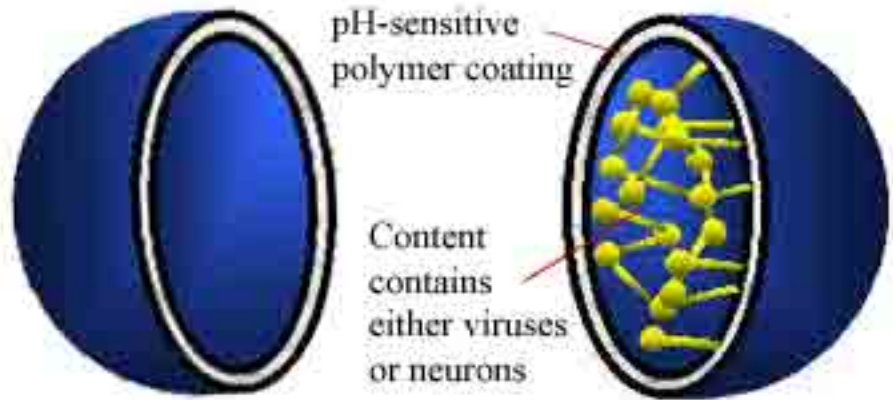
NasMEC

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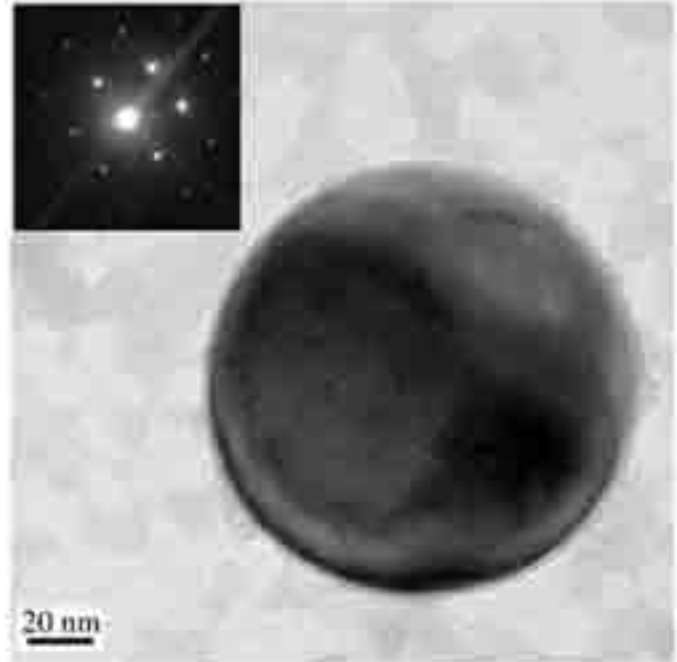
[Present Technology](#) >> [pH-sensitive Nanospheres](#)

pH-sensitive Nanospheres

Nanospheres are hollow spheres on the nanoscale that are composed of polymers. Nanospheres are currently used for the transportation of drugs to areas of the body (Lynn et al., 2001). By applying a pH-sensitive polymer coating, nanospheres will be able to detect changes in pH levels. NasMEC uses these nanospheres to transport adeno-associated viruses and neurons to targeted areas of the brain.



A cutaway of a nanosphere (Lambert, 2002).



A nanosphere as seen through a Transmission Electron Microscope (TEM). The sphere has a diameter of ~70 nm ("NSF", 2005).

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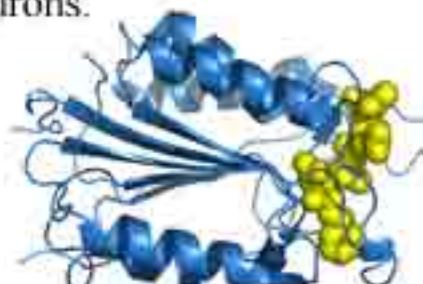
Present Technology >> Adeno-associated Viruses

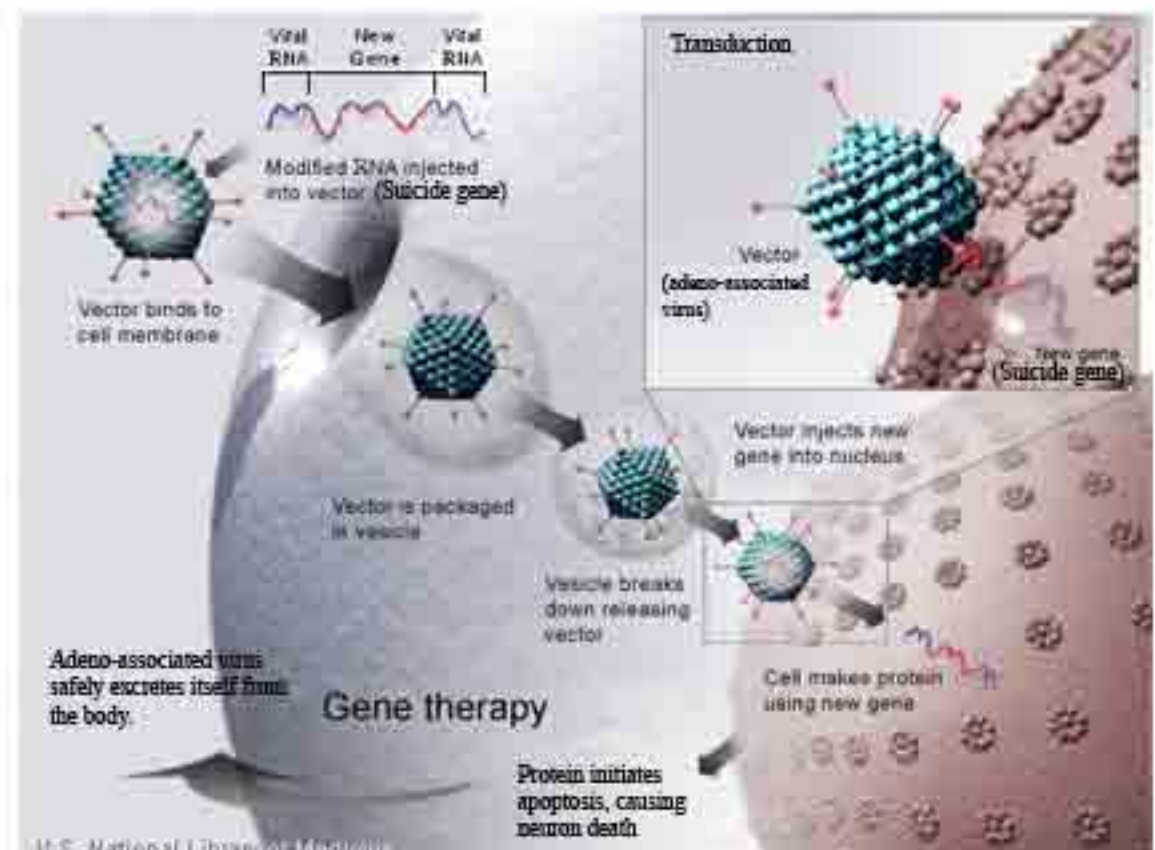
Adeno-associated Viruses

Adeno-associated viruses (AAVs) are non-pathogenic viruses that are often used in gene therapy to replace defective genes in the human body. At around 22nm, AAVs are often used because of their wide host range, safety profiles, and the ability to transduce differentiated cells (Monahan & Samulski, 2000).

NasMEC uses AAVs to deliver suicide enzymes (caspase-3) to cause apoptosis in neurons.

Caspase-3
(Based on the Protein Data Bank)





Gene therapy

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Summary of Procedure

START →



Adeno-associated
virus

Neurons are grown as neurospheres.

Epileptic neurons are replaced with new neurons, while the viruses are excreted from the body.

↓

Two types of nanospheres containing neurons and adeno-associated viruses are injected into affected areas of the brain.

Seizures no longer occur, while brain retains normal function.

↓


pH-sensitive nanospheres containing viruses swell when they detect changes in pH levels during a seizure.

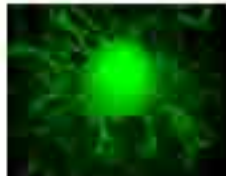
Neuron-containing nanospheres swell when detect enzyme X, releasing neurons into the affected areas.

↓

Viruses are released, infecting nearby neurons (mostly epileptic-causing). Viruses program neurons to produce enzyme X, and transduce them with suicide enzymes, causing apoptosis.

Nanosphere ("NSF", 2003)





Neurosphere
(Przyborski, n.d.)

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Graphics Page # ____ of 5 (must include 5 forms)