Therapeutic Approaches

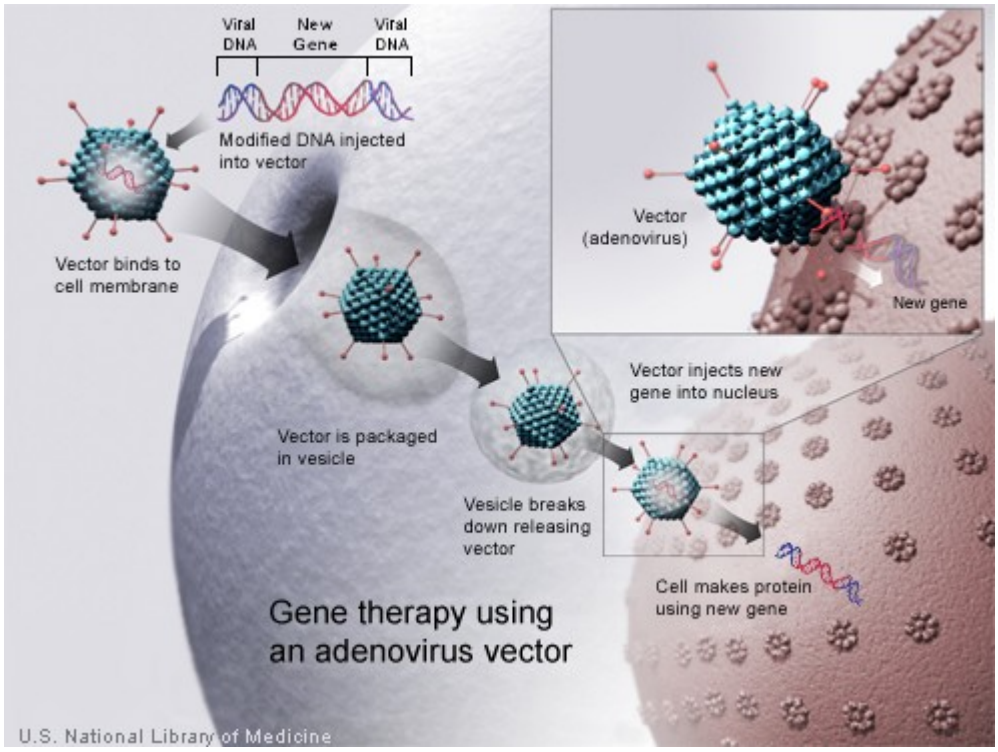
There are several major therapeutic approaches that may ultimately be useful in the treatment of the lysosomal storage and allied diseases. The majority - enzyme replacement therapy; gene therapy; bone marrow transplantation; neural stem cell therapy; and molecular or pharmacological chaperone therapy - are aimed at restoring enzyme activity. Other interventions - substrate deprivation and metabolic bypass therapy - are not aimed at restoring enzyme activity but are aimed at the reduction in the levels of the compounds that accumulate in the lysosomes. These are currently more theoretical approaches to therapy. Researchers still have much to learn. The most difficult diseases to treat are those which affect the central nervous system, and many believe that no single approach will be the solution for any one of these devastating diseases. Instead, the hope is that some combination of these approaches - mixed together in just the right recipe - will be able to halt, or even reverse, the ravaging effects of diseases like Tay-Sachs, Canavan, Sandhoff and others that ravage the brain.

Bone marrow or stem cell transplantation makes use of the fact that certain brain cells, as well as blood cells, arise from bone marrow or stem cells isolated from umbilical cord blood. Researchers theorize that such transplantation from a healthy donor would introduce healthy stem cells into the brain and multiply. However, it is not known if the number of healthy cells would be large enough to provide enough of the missing enzyme to make a clinical difference. If not, healthy stem cells could be genetically manipulated prior to transplantation to increase the production of the missing enzyme. Other factors which could limit the potential of bone marrow transplantation for the treatment of the lysosomal storage and allied diseases are: (1) the need to find an immunologically matched healthy bone marrow donor and (2) the risks associated with the bone marrow transplantation procedure. However finding a match with cryopreserved fetal cord blood is much easier and the risks associated with the transplant procedure are somewhat less than with conventional bone marrow transplantation.

Stem cells are immature cells that have the capability to develop into all of the different types of cells. The two leading sources of cells include mesenchymal cells (from blood) and neural stem cells (from brain). In mice, stem cells have been shown to spread throughout the brain, a necessity when it comes to treating diseases that affect the entire brain. Stem cells can also be genetically modified to produce and secrete high levels of a missing enzyme, such as Hex-A. Human clinical trials may still be many years away but the results in mice are promising. For example, when neural stem cells genetically engineered to produce Hex-A were inserted into the brains of mice with Tay-Sachs they traveled throughout the brain and produced therapeutic levels of the needed enzyme. The enzyme then broke down the GM2 ganglioside, preventing its accumulation. For general information explaining stem cells, as well as current research,
see http://stemcells.nih.gov/index.asp.

Enzyme replacement therapy (ERT) is a therapeutic approach in which the specific enzyme that is inactive or absent in affected individuals is replaced with functional enzyme molecule isolated or produced in the lab. ERT has been successful for the treatment of Gaucher Type 1, Fabry, MPS I and, most recently, has received approval for Pompe disease. ERT is effective in the non-neurological symptoms of Mucopolysaccharidosis Types I, II IV and VI, Pompe and Niemann-Pick B, but has not yet proven to be beneficial

in storage diseases that primarily affect the central nervous system since the replacement enzymes do not efficiently cross the blood-brain barrier. To learn more on how enzyme replacement therapy works in Gaucher disease visit
http://www.cerezyme.com/patient/treatment/cz_pt_treatment.asp



Gene therapy is an intervention in which the gene that is mutated in affected individuals is augmented by the introduction of a functional version of the gene. The gene can be introduced as free DNA, in a lipid coat (liposome) or as part of a viral vector. The latter is the most common way of introducing genes and it involves modification of a specific virus so that it cannot cause disease and then having it carry the gene for the missing enzyme to the brain or any other organ of interest. Gene therapy is under investigation as a treatment for numerous disorders, including Canavan disease. Gene therapy's promise is presently limited by a number of factors including: (1) the difficulty of creating effective vectors, especially for gene delivery to non-dividing cells such as those in the brain; (2) the need to introduce the gene into a large number of cells in order to have a clinical effect; (3) the potential for an oncogenic (cancer) event to occur as a result of the random insertion of the gene into the host cell chromosomes; and (4) the extensive review processes now needed for all gene therapy trials. To learn more on the theory of gene therapy visit
http://ghr.nlm.nih.gov/handbook/therapy/procedures

Gene therapy is designed to introduce genetic material into cells to compensate for abnormal genes or to make a beneficial protein. If a mutated gene causes a necessary protein to be faulty or missing, gene therapy may be able to introduce a normal copy of the gene to restore the function of the protein.

A gene that is inserted directly into a cell usually does not function. Instead, a carrier called a vector is genetically engineered to deliver the gene. Certain viruses are often used as vectors because they can deliver the new gene by infecting the cell. The viruses are modified so they can't cause disease when used in people. Some types of virus, such as retroviruses, integrate

their genetic material (including the new gene) into a chromosome in the human cell. Other viruses, such as adenoviruses, introduce their DNA into the nucleus of the cell, but the DNA is not integrated into a chromosome.

The vector can be injected or given intravenously (by IV) directly into a specific tissue in the body, where it is taken up by individual cells. Alternately, a sample of the patient's cells can be removed and exposed to the vector in a laboratory setting. The cells containing the vector are then returned to the patient. If the treatment is successful, the new gene delivered by the vector will make a functioning protein.

Researchers must overcome many technical challenges before gene therapy will be a practical approach to treating disease. For example, scientists must find better ways to deliver genes and target them to particular cells. They must also ensure that new genes are precisely controlled by the body.

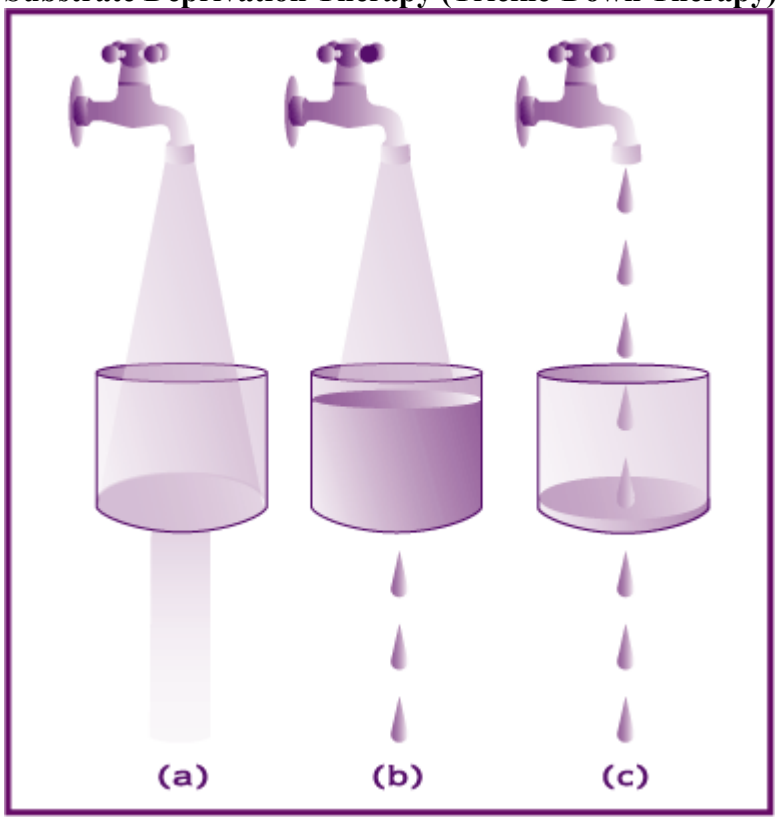
Metabolic bypass therapy is another biochemical approach that makes use of special chemicals called activators to increase the synthesis or activity of alternative lysosomal enzymes to make them capable of degrading larger amounts of a substrate like GM2 than normal. If one could increase the activity of an enzyme other than Hex-A to degrade GM2, then it could partially compensate for the absence of Hex-A and "by-pass" the cell's need for Hex-A. This approach is still theoretical, but researchers are currently looking for activators and appropriate "by-pass" enzymes.

Pharmacological or molecular chaperone therapy is among the newest therapeutic ideas for the allied diseases. Pharmacological chaperones are small molecules that specifically bind to and stabilize the functional form or three-dimensional shape of a misfolded protein in the endoplasmic reticulum (ER) of a cell. When misfolded because of a genetic mutation, the protein (or enzyme) is unable to adopt the correct functional shape. This misfolded protein is recognized by the quality control system in the cell, and destroyed, leading to decreased amounts of enzyme that gets transported from the cell's ER to the cell's lysosome: hence, reduced enzyme activity. The binding of the chaperone molecule helps the protein fold into its correct three-dimensional shape. This allows the protein to be properly trafficked from the ER and distributed to the lysosome in the cell, thereby increasing enzyme activity and cellular function, reducing substrate and stress on cells. As of summer 2006, pharmacological chaperone therapy is in early stage clinical trials for lysosomal storage diseases Fabry and Gaucher Type I. At the end of pharmacological chaperones please add. To learn more on this mechanism of action visit
http://www.amicustherapeutics.com/technology/moa.asp

Substrate deprivation (also called substrate synthesis inhibition, substrate reduction, substrate balancing) is a biochemical approach that makes use of novel chemicals called inhibitors that decrease the production of the molecule that typically accumulates to high levels in persons with lysosomal storage diseases. For example, children with Tay-Sachs disease accumulate high levels of G_{M2} in brain cells and it is this accumulation which causes the brain cells to die. If one could decrease the synthesis of GM2, the substrate for the missing enzyme, then one would presumably decrease cell death and moderate the course of the disease. The inhibitor Zavesca ® (miglustat), approved in Europe and the United States for the treatment of Gaucher Type 1, is in clinical trials in persons affected with Niemann-Pick

Type C, and in children with juvenile G_{M2}, Tay-Sachs and Sandhoff and in children under the age of 2 with Tay-Sachs and Sandhoff disease. A three-year clinical trial of miglustat in persons affected with Late Onset Tay-Sachs disease ended in spring 2006, with unsatisfactory conclusions. Participants did not reach certain clinical endpoints that were part of the trial, such as improved muscle strength status, and Actelion, the drug company, decided not to file for an additional FDA indication for use with LOTS. Studies with other substrate reduction compounds may occur in the future, and some affected individuals or parents of those affected do explore with their physicians the option of using this treatment on an "off-label" basis.

Substrate Deprivation Therapy (Trickle-Down Therapy)



a) In most individuals the substrate (water) can be degraded efficiently by adequate enzyme (hole).

b) In affected individuals the amount of enzyme is insufficient to degrade the substrate and it accumulates.

c) In affected individuals treated with substrate synthesis inhibitors the amount of substrate is decreased to match the amount of residual enzyme to prevent accumulation.