

# POTENTIAL THERAPIES

**NEW DRUGS.** Most medicines used today were developed using trial-and-error techniques, which often do not reveal why a drug produces a particular effect. But the expanding knowledge gained from the new methods of molecular biology — the ability to determine the structure of receptors or other proteins — makes it possible to design safer and more effective drugs.

In a test tube, the potency of an agent can be determined by how well it attaches to a receptor or other protein target. A scientist then can vary the drug's structure to enhance its action on the desired target. Thus, subsequent generations of drugs can be designed to interact more selectively with the target or, in many cases, specific subtypes of the target, producing better therapeutic effects and fewer side effects.

While this *rational drug design* holds promise for developing drugs for conditions ranging from stroke and migraine headaches to depression and anxiety, it will take considerable effort to clarify the role of the different potential drug targets in these disorders.

Other promising candidates for drug therapies include trophic factors, antibodies engineered to modify the interactions and toxicity of misfolded proteins, small molecules that take advantage of specific biochemical pathways, interfering RNAs (RNAi) that reduce toxic levels of individual proteins, and stem cells that could replace dead or dying neurons.

## Trophic factors

One result of basic neuroscience research is the discovery of numerous growth factors or *trophic factors*, which control the development and survival of specific groups of neurons. Once the specific actions of these molecules and their receptors are identified and their genes cloned, procedures can be developed to modify trophic factor-regulated functions in ways that might be useful in the treatment of neurological disorders.

Once a trophic factor for a particular cell is found, copies of the factor might be genetically targeted to the area of the brain where this type of cell has died. The treatment may not cure a disease but could improve symptoms or delay the disease's progression.

Already, researchers have demonstrated the possible value of at least one of these factors, *nerve growth factor* (NGF). Infused into the brains of rats, NGF prevented cell death and stimulated the regeneration and sprouting of damaged neurons that are known to die in Alzheimer's disease. When aged animals with learning and memory impairments were treated with NGF, scientists found that these animals were able to remember a maze task as well as healthy

aged rats. NGF, which slows the destruction of neurons that use acetylcholine, also holds promise for slowing the memory deficits associated with normal aging.

Recently, several new factors have been identified. They are potentially useful for therapy, but scientists must first understand how they may influence neurons. Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) may be treated in the future with trophic factors or their genes.

In an interesting twist on growth factor therapy, researchers demonstrated that neutralization of inhibitory molecules can help repair damaged nerve fiber tracts in the spinal cord. Using

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antibodies to Nogo-A, a protein that inhibits nerve regeneration, Swiss researchers succeeded in getting some nerves of damaged spinal cords to regrow in rats and monkeys. Treated animals of both species showed large improvements in their ability to walk and use their forepaw digits after spinal cord damage.

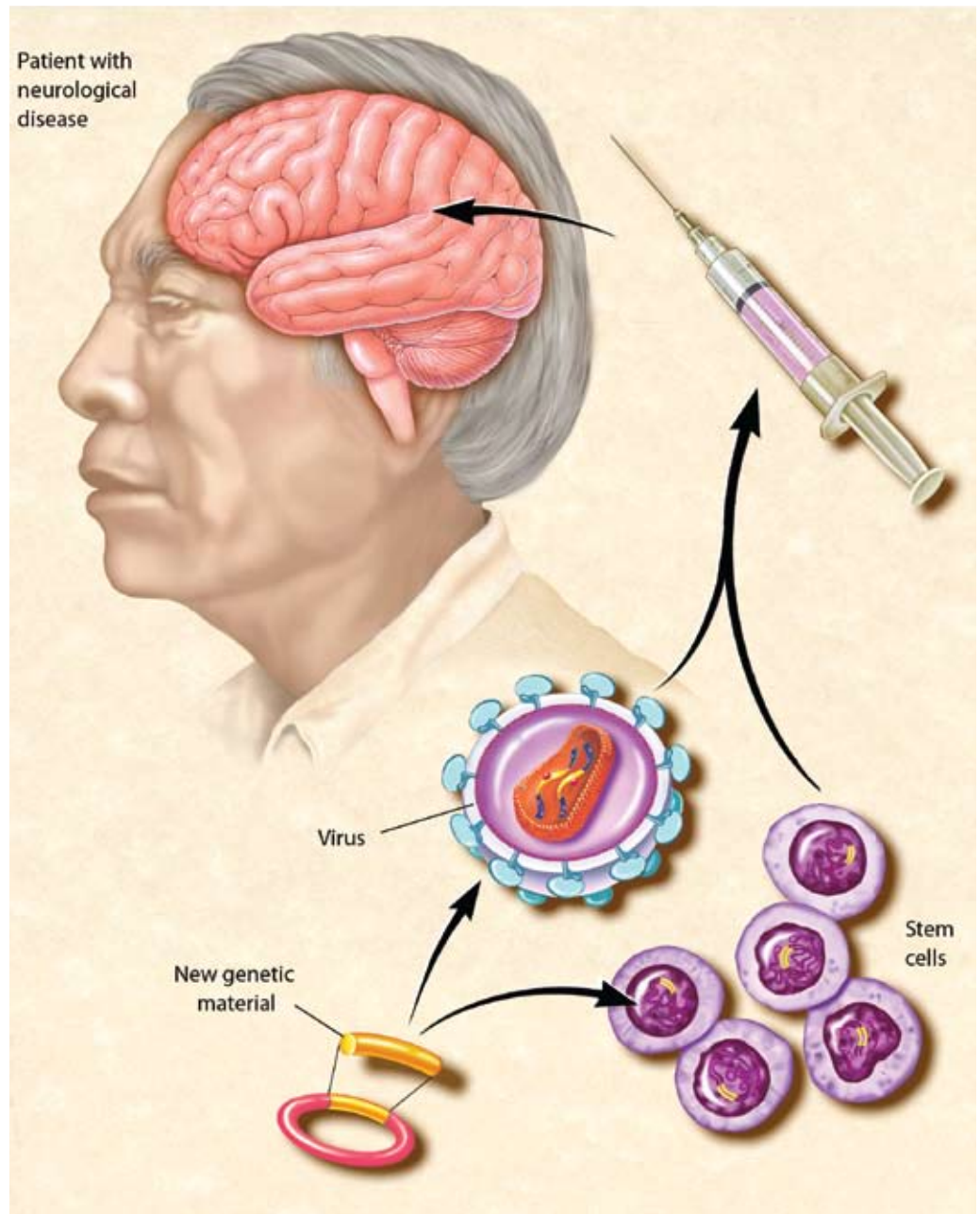
This research has been translated to a clinical setting where recently injured spinal cord injury patients are being treated with anti-Nogo-A antibodies in a clinical trial.

## Engineered antibodies

The immune system has evolved to very specifically identify and modify factors both inside and outside of cells. It is sometimes possible to trick the body into attacking proteins that cause neurological diseases by “vaccinating” patients against these proteins.

## CELL AND GENE THERAPY.

In potential therapy techniques, scientists plan to insert genetic material for a beneficial neurotransmitter or trophic factor into stem cells or a virus. The cells or virus are then put into a syringe and injected into the patient where they will produce the beneficial molecule and, it is hoped, improve symptoms.



This approach has shown some promise in Alzheimer's disease, although it also carries risks, such as increased inflammation when the brain reacts to the antibodies against its proteins. Another new approach combines genetic engineering with immunology to engineer antibodies or fragments of antibodies that can bind to and alter the disease characteristics of specific proteins. These therapies could be delivered either as proteins or as genes.

Promising preliminary results have been obtained for Huntington's (HD), Parkinson's (PD), and Alzheimer's (AD) diseases and neurodegenerative disorders such as variant Creutzfeldt-Jakob

disease (vCJD), known as prion diseases. vCJD has been linked to bovine spongiform encephalopathy, or "mad cow" disease. For example, fruit flies (*Drosophila*) that get HD because they have been modified to carry the mutant human gene are generally too weak and uncoordinated to break out of their pupal case the way normal insects do. However, when they also express the gene for an anti-HD antibody, all of them emerge as young adults. Furthermore, these treated flies live longer than the untreated ones that do manage to emerge, and the treated ones show less pathology in their brains.

## Small molecules and RNAs

Clarifying the processes that underlie brain damage will open up the potential to use small-molecule drugs to alter these processes. Some success has occurred in developing animal models using approaches based on known mechanisms of drugs. Examples include drugs such as antibiotics and anti-tumor drugs, which appear to reduce the neuronal damage in ALS, HD, and PD. Thousands of small molecule drug candidates can be tested using high-throughput screening to alter a cellular property that represents an important part of a disease process. Because many neurodegenerative diseases involve proteins that misfold and clump abnormally, lasers are used to measure whether proteins are clumped inside cells that have been robotically distributed into tiny wells, along with the small molecules to be tested. A machine then scans the wells and reports whether particular drugs have changed the protein clumping, so that these drugs can be tested further. New leads for drugs to treat AD and prion diseases have recently been described using these methods.

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Several neurodegenerative diseases are caused by the accumulation of abnormal proteins. If the cells made much less of such proteins to begin with, then presumably the disease would progress much more slowly. A new class of potential drugs is based on removing the RNAs that code for the proteins that are causing damage. Mouse models of HD and ALS appear to have responded positively to such treatments, which are delivered via gene therapies.

## Cell and gene therapy

Researchers throughout the world are pursuing a variety of new ways to repair or replace neurons and other cells in the brain. For the most part, these experimental approaches are still being

worked out in animals and cannot be considered therapies for humans at this time.

Scientists have identified *embryonic neuronal stem cells* — unspecialized cells that give rise to cells with specific functions — in the brain and spinal cord of embryonic and adult mice. Stem cells can continuously produce all three major cell types of the brain: neurons; *astrocytes*, the cells that nourish and protect neurons; and oligodendrocytes, the cells that surround axons and allow them to conduct their signals efficiently. The production abilities of stem cells may someday be useful for replacing brain cells lost to disease. A more limited type of stem cell also has been discovered in the adult nervous system in various kinds of tissue, raising the possibility that these adult stem cells might be pharmacologically directed to replace damaged neurons.

In other work, researchers are studying a variety of viruses that may ultimately be used as “Trojan horses,” carrying therapeutic genes to the brain to correct nervous system diseases. Adeno-associated virus (AAV) and human or equine lentivirus seem to be the safest and most efficient at this time. AAV and equine lentivirus are being used in clinical trials in patients with PD. Herpes simplex virus and adenovirus vectors also have been evaluated in early-stage human trials for treating brain tumors.