
The Research Pipeline - taking drugs from the lab to the clinic

Here's an overview of some of the more promising potential treatments moving through the research pipeline.

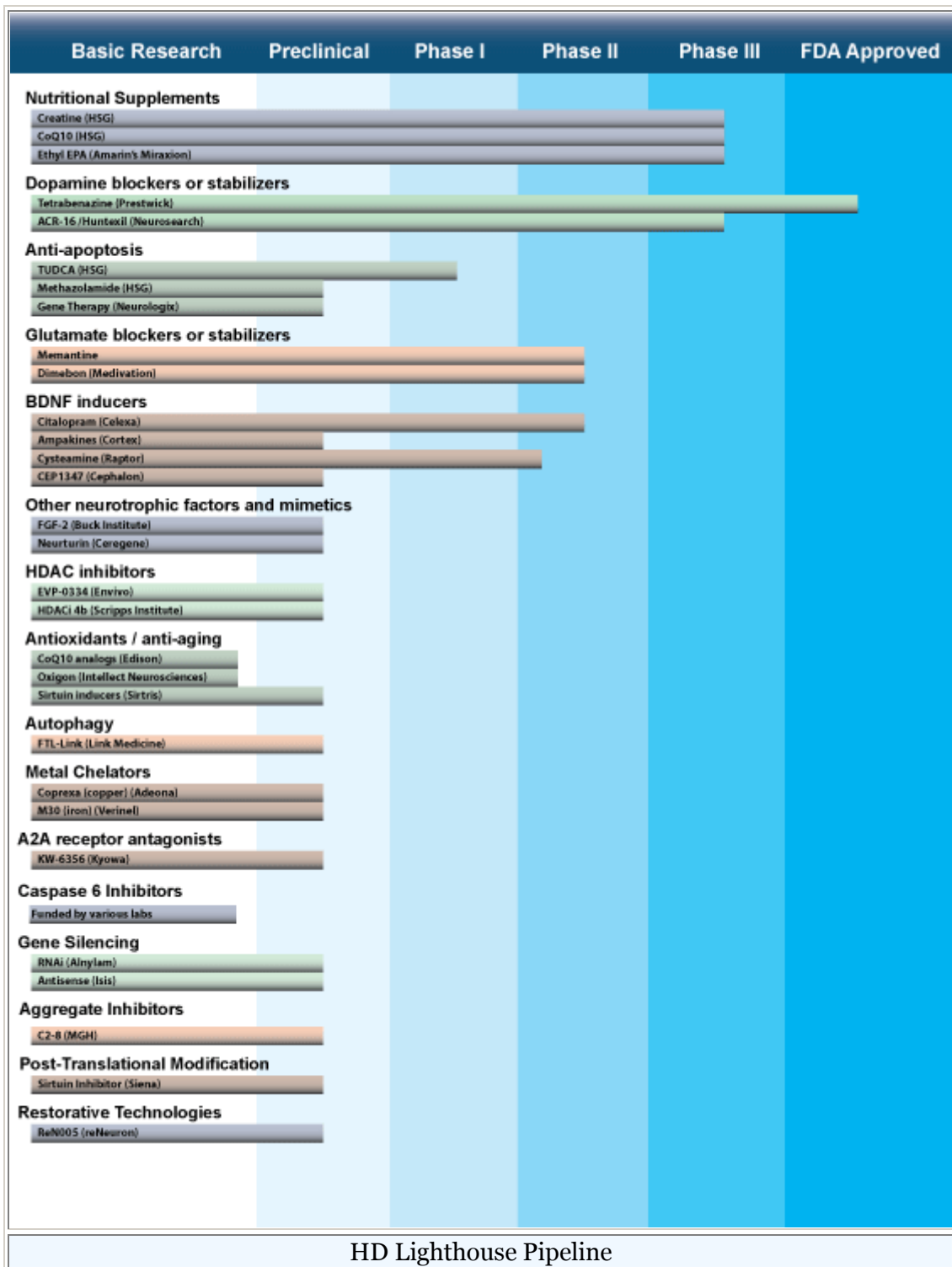
Editor's Comment:

Basic research into what goes wrong in the brain in Huntington's continues to provide insights into how the disease might be treated. As targets are identified, existing drugs known to address that target are reviewed and drug development efforts are instituted. Promising drugs are tested in animal models such as drosophila (fruitflies) and mice engineered to get Huntington's Disease. If the drug is effective and side effects are minimal, toxicology studies are done and the drug can proceed to clinical trials. If the drug shows efficacy but the side effects are serious, the drug may be redesigned. Once a drug is ready for clinical trials, it must proceed through three stages before being approved as a treatment.

The chart below provides an overview of significant drug targets, drugs, and compounds in the research pipeline. As potential treatments move through the pipeline, some will perform well and receive high priority for future research funding. Others will be found to be ineffective and drop out. A drug that has positive effects in a cell model of the disease may not help a mouse model, for example. However, because research is proceeding in parallel, progress continues unabated. Resources can quickly be redirected away from unsuccessful efforts toward research that continues to hold promise. Each day brings us closer to treatments.

Some of the drugs or supplements below will be tested to see if they safely and effectively treat symptoms while others will be tested to see if they delay expected onset or slow progression of the disease. However, some symptomatic treatments may later be shown to treat the disease itself.

There are other compounds which have shown promise as potential treatments. This chart covers the ones where there appear to be efforts to take them to the next stage of the pipeline. There may be additional compounds of which we are unaware since the chart is based on published information. There may be developments in pharmaceutical or biotech companies and in academic laboratories that haven't been publicized as yet.



The students at [Stanford University HOPES](#) developed several pages that provide additional insight into the drugs and supplements in these trials. Click on the links titled something like "xxx for HD by HOPES" for more information.

Nutritional supplements

Energy metabolism is known to be impaired in Huntington's Disease. Both creatine and CoQ10 boost energy in the cell. In addition both act as antioxidants. Both are in Phase III clinical trials but enrollment has

not been completed.

[Creatine for HD by HOPES](#) | [CoQ10 for HD by HOPES](#).

Ethyl EPA is a purified version of eicosapentaenoic acid, an Omega 3 fatty acid found in fish oil. A Phase III clinical trial managed by the Huntington Study Group and sponsored by Amarin Pharmaceuticals was suggestive of benefit after six months of use but not conclusive. There may be an additional trial to resolve the issue.

[Miraxion LAX-101 for HD by HOPES](#).

Dopamine blockers or stabilizers

Blocking or stabilizing the neurotransmitter dopamine has been shown to reduce chorea. In addition, there is evidence to suggest that normal amounts of dopamine may be toxic in the brain in Huntington's Disease.

Xenazine (tetrabenazine) works as a dopamine depletor and is available in the U.S. as an FDA-approved treatment for chorea associated with Huntington's disease. It has been available in Europe and Canada for many years.

[Tetrabenazine for HD by HOPES](#)

ACR-16, now called Huntexil, is a dopamine stabilizer. A Phase III trial of ACR-16 was completed early in 2010 in Europe and in the fall of 2010 in the U.S.. The results were promising but not conclusive and a new Phase III trial will probably be conducted soon.

Anti-apoptosis

Tauroursodeoxycholic acid or TUDCA is an endogenous bile acid which inhibits mitochondrial apoptosis. It is currently in Phase I trials sponsored by the HSG; results are expected soon.

[TUDCA for HD by HOPES](#)

Methazolamide is an inhibitor of cytochrome c, an enzyme involved in apoptosis.

Neurologix is investigating the potential of gene therapy using a mutated form of the XIAP gene. XIAP stands for x-linked inhibitor of apoptosis protein.

Glutamate blockers or stabilizers

The excitotoxicity theory holds that neurons are abnormally sensitive to glutamate; overstimulation by this important neurotransmitter can lead to cell death.

[Glutamate Blockers for HD by HOPES](#)

Memantine is a glutamate stabilizer that is FDA approved to treat Alzheimer's dementia. As a result of a preclinical study which showed that memantine blocks toxic extrasynaptic activity while allowing normal synaptic activity, a large Phase III trial is planned.

[Memantine for HD by HOPES](#)

Dimebon has several promising mechanisms. In addition to regulating glutamate, it also inhibits acetylcholinesterase and is thought to regulate calcium homeostasis, preventing the pathological opening of the mitochondrial permeability transition pores. Calcium handling is impaired in Huntington's Disease. Following promising results in a phase II trial, HSG is conducting a Phase III trial for Medivation.

[Dimebon for HD by HOPES](#)

BDNF inducers

Brain derived neurotrophic factor (BDNF) protects brain cells and promotes neurogenesis, the growth of new ones. Levels of BDNF are known to be reduced in the brains of HD patients. SSRI (selective serotonergic reuptake inhibitor) antidepressants are known to elevate BDNF and one such antidepressant, Celexa, is in Phase II clinical trials. In addition, Cortex Pharmaceuticals has an ampakine in preclinical testing and Raptor Pharmaceuticals is planning Phase II trials of cysteamine; both induce BDNF.

[BDNF Inducers for HD by HOPES](#) | [Cysteamine for HD by HOPES](#)

CEP-1347, an anti-apoptosis drug was found to improve the R6/2 mice by increasing BDNF levels.

Other neurotrophic factors and mimetics

In addition to BDNF, researchers are also looking at other neurotrophic factors and synthetic compounds that mimic their effects with the hope that they will be neuroprotective in HD patients. One candidate is fibroblast growth factor 2 which promoted neurogenesis and extended survival time in the R6/2 mice. It is still in preclinical testing.

Ceregene has developed a viral vector for delivering a gene for the neurotrophic factor neurturin into the brain. This potential treatment is in Phase II clinical trials for Parkinson's Disease and preclinical testing for Huntington's Disease.

HDAC inhibitors

The dysregulation of gene transcription has been shown to be a significant problem in Huntington's Disease. The HD protein interferes with the normal expression of genes. Histone deacetylase inhibitors may be able to reverse or partially reverse this dysfunction. Envivo has a candidate drug which performed well in preformed well in preclinical testing. Repligen has licensed an HDAC inhibitor from Scripps Research Institute which reduced pathology and at least partially restored gene transcription; Repligen and Scripps recently received a \$6.04 million grant from NIH for optimization and preclinical testing.

[HDAC Inhibitors for HD by HOPES](#)

Antioxidants/anti-aging

Huntington's disease is a disease of aging in that cells in the areas of the brain that are affected by HD are for some time able to cope with the challenges presented by the mutant protein. As we age, our cellular defense mechanisms become less efficient. There is a group of genes called sirtuins which appear to regulate aging. In the spring of 2008 Sirtris Pharmaceuticals announced that there is new data showing that in a preclinical model of Huntington's disease, mice live longer and have less disease pathology in the brain with increased SIRT1 expression. Sirtris has several compounds with induce SIRT1 expression.

One problem that increases with aging which is thought to be particularly damaging in HD is oxidative stress. During energy metabolism, free radicals of oxygen are produced which can damage proteins, lipids, and DNA if there aren't enough antioxidants available with which to bond. As mentioned above, creatine and CoQ10 are antioxidants. Intellect Neurosciences is doing preclinical studies with their synthetic version of Indole-3-propionic acid.

[Antioxidants for HD by HOPES](#)

Autophagy

The normal huntingtin's protein is cleared away from the cell through the ubiquitin proteasome system. This housekeeping process is not effective with the HD version of the protein. There is an alternate way to clear away the HD protein called autophagy. Link Medicine has a candidate drug to do this. In addition, researchers have been exploring the possibility of using existing drugs approved for other purposes to induce autophagy.

Metal chelators

Both excess copper and excess iron have been shown to contribute to HD pathology. Pipex Pharmaceuticals, in collaboration with researchers at the VA Medical Center at Ann Arbor, is doing preclinical testing of their copper chelator. Varinel, an Israel Pharmaceutical company is testing their copper chelator in HD mouse models with funding from CHDI.

[Metal Chelators for HD by HOPES](#)

A2A receptor antagonists

Research shows that there is an aberrant amplification of the adenosine 2A receptor signaling in striatal cells in people with Huntington's Disease. Kyowa Pharmaceuticals has licensed its A2A receptor antagonists to Lundbeck for development as a potential HD treatment.

Caspase 6 inhibitor

When an HD mouse model was engineered to be resistant to caspase 6, the HD protein was not cleaved, the protein did not accumulate in the nucleus of the cell, and the mice did not develop Huntington's Disease. Various labs are working to develop a safe and effective caspase six inhibitor.

[Caspase 6 for HD by HOPES](#)

Genetic Approaches

If the HD gene could be stopped from expressing itself, the result could be a virtual cure. Anylam is working on ways to interference with messenger RNA so that instructions to make the HD protein are not sent out.

[RNAi for HD by HOPES](#)

The antisense approach being taken by Isis is somewhat different in that it is possible for a drug to do this. Delivery will be a big challenge in both approaches.

Aggregate Inhibitors

MGH has a drug development lab and has a new candidate drug, C2-8, which increases survival time in the HD mice and reduces cell loss in the striatum.

Post Translational Modifications

Siena Biotech has a Sirt1 inhibitor. The Sirt1 protein is also a deacetylase. Inhibiting it appears to modify the acetylation of the HD protein causing the enhancement of the clearance of the HD protein.

Restorative Technologies

Research with the HD mice suggests that stopping the HD gene from expressing itself would result in improvement even well into the progression of the disease. However, restorative treatments will likely be necessary for full recovery of later stage patients. ReNeuron has a line of stem cells which has shown efficacy in a cell model of HD. Preclinical work is being done.

Changes

- Minocycline was removed from the pipeline following disappointing results in the phase II trials.
- ACR-16 and Dimebon moved further through the pipeline into phase III trials.
- Cogane was removed following its failure to be effective in HD mice.
- Links to the Stanford University HOPE site, for more information, were added.

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