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As the number of laboratories studying Huntington's disease (HD) expands, the complexity of the illness becomes more apparent. At a conference sponsored by the Hereditary Disease Foundation in August, 1999, over 150 scientists met in Boston to share their latest findings, brainstorm about possible collaborations, and hypothesize about how the pieces fit together. Presentations by some 60 of the participants highlighted recent progress, yet made clear that much remains to be done in the quest to find a cure for the devastating disease.

The search for better models

One of the most important advances in HD research since the gene was cloned in 1993 has been the development of mouse models, which allow scientists to define more precisely the pathophysiology of the illness; to study behavioral consequences of gene alterations and neuropathologies; and to evaluate the efficacy of proposed therapeutic strategies. Currently, the most widely used mouse models of HD are those developed in 1996 by Gillian Bates and colleagues, the R6/1 and R6/2 mice, which are transgenic for exon 1 of the HD gene with varying lengths of polyglutamine repeats.

The Bates mice are being used in numerous laboratories to study the developmental progression of motor and behavioral symptoms as a window into the underlying neuropathology and to explain the neuropathologic features of the disease at a molecular and biochemical level. Valerie Bolivar presented work done in R6/1 mice, which revealed subtle motor and behavioral deficits prior to the development of more obvious symptomatology. The assay she used, which assesses grooming behavior, has been linked to striatal lesions in rats. Similarly in R6/2 mice, Stephen Dunnett showed that although motoric deficits do not appear until 8 weeks of age, significant deterioration in learning was observed between 3.5 weeks and 8 weeks of age.

The Bates mice have also been used

extensively to probe at the mechanisms of cognitive and motor dysfunction. Kerry Murphy presented evidence of changes in synaptic plasticity preceding overt behavioral symptoms, suggesting a role in the development of cognitive dysfunction. Dopamine has been implicated in the development of motor symptoms of HD. Marjorie Ariano found that in symptomatic HD transgenic mice, D1 receptor is profoundly lost, although cAMP is still elevated, indicating an alteration in the dopamine pathway.

While the Bates mice have provided researchers with a model of undisputed value, there are inconsistencies in data that remain unexplained. For example, English R6/2 mice live longer than those raised in the Americas, and while the R6/2 mouse is diabetic in most labs, it does not appear diabetic in others. Daniel Goldowitz suggested that differences in genetic background may be important. "It's a general issue to be addressed but also very specific when we have issues like NMDA receptor toxicity or survival," he said. Other participants raised the issue of environment. Perhaps differences in feeding and nurturing can help explain the survival discrepancies.

Meanwhile, the search continues for additional models. In perhaps the most exciting presentation of the conference, Ai Yamamoto described a reversible mouse model of HD. This mouse expresses the human exon 1 transgene with an expanded polyglutamine repeat under the control of a Tet-Off system and CamKII promotor. The promotor allows for high expression in the forebrain; the Tet-Off system allows the investigator to turn off expression of the gene with doxycycline. In the absence of doxycycline, the animals express the transgene at high levels in the striatum, cortex, septum, and hippocampus and display the expected progressive phenotype with claspings and tremor. Severely affected animals were treated with doxycycline beginning at 18 weeks of age. Four months later, the treated animals demonstrated a dramatic reversal both in neuropathologic features and

motor behaviors.

The implications of Yamamoto's research are immediately apparent, said Anne Young. "People tend to think that we have to get to people before they have symptoms, because there's no way we're going to reverse any of this, we might be able to stabilize it. And what Ai's really showing is that if you catch it at the right time, you could reverse it."

Diane Merry and colleagues have created a transgenic mouse model for another neurodegenerative disease caused by expansion of polyglutamine tracts, spinal and bulbar muscular atrophy (SBMA). In SBMA, the repeats occur in the androgen receptor and the disease affects motor neurons.

Other mouse models described include both knock-in and knock-out mice and yeast artificial chromosome (YAC) transgenic mice expressing normal and mutant human huntingtin. The knock-in mice described by Vanessa Wheeler parallel many of the features of the early pathogenic stages of HD; however, Wheeler said the mice may not live long enough to observe neuropathologic and behavioral problems. Peggy Shelbourne also created knock-in mice, in her case with 70-80 repeats. In contrast to the R6/1 and R6/2 mice, Shelbourne's mice displayed no differences in lifespan or fertility and no evidence of neuronal cell loss, but did show some behavioral and motor characteristics resembling HD and signs of impaired synaptic plasticity. The YAC transgenic mice with 72 CAG repeats described by Blair Leavitt develop behavioral and neuropathologic characteristics similar to those observed in HD.

The differences in behavior, neuropathology, lifespan, and other physiological attributes in the various mouse models under development raise important questions about their relevance to the human disease. For the time being, the Bates mice continue to dominate the field, in part because they are readily available from the Jackson Laboratory. Anne Young encouraged those who have developed other mouse strains to get them into Jackson so that other researchers can study them in greater detail.

Despite the recognition that animal models are essential to the quest for new treatments for HD and other illnesses, they have limitations and researchers continue to search for models that provide additional tools for studying the genetics and neuropathology of HD, or that better mimic the human disease.

James Gusella described a homolog of the HD gene isolated in drosophila. The gene, which is currently being sequenced, should allow scientists to apply the techniques of drosophila genetics to better understand the normal physiologic role of huntingtin. Leslie Thompson has also used drosophila, as well as an inducible cell model, to study the role of polyglutamine repeats in neurotoxicity. Anne Hart investigated the mechanism of polyglutamine toxicity using *C. elegans*, which allows her to express huntingtin fragments with varying numbers of glutamines in easily accessible sensory neurons. Robert Hughes expressed both wild type and CAG-expanded human huntingtin in yeast, looking for factors that influence the formation of nuclear inclusions. These models will be useful as screens for suppressors of polyglutamine repeat cytotoxicity.

Cell systems are also providing new information about the pathogenic mechanisms of HD and are being used to screen for possible therapeutic agents. Elena Cattaneo has expressed wild-type and mutant huntingtin as well as truncated proteins in striatal derived ST14A cells in order to study the biological effects of the different constructs. Quynh Chu-LaGriff has established continuous cultures of neural stem cells from R6/2 HD mice, which can be induced to differentiate into different classes of neurons and glia. Astrid Lunkes and colleagues have developed a cellular model that induces different forms of mutant and wild-type huntingtin in a neuroblastoma cell line. Abigail Hackham has been using NT2 cells to study huntingtin-mediated toxicity in neurons. Steven Suhr has established several inducible cell lines that overexpress polyglutamines in response to the addition of non-toxic ligands. Andreas Wytenbach also reported on an inducible cell line, using the Tet-On approach, that expresses HD exon 1 with varying

numbers of glutamines in response to doxycycline.

>From gene to disease – getting from here to there

The central question that the Bates mice and other models seek to answer is how the mutant gene causes disease. With this knowledge, researchers hope they will be able to find therapeutic strategies that will reverse the neurodegeneration. Since it was first discovered that the HD gene, as well as the genes responsible for several other neurodegenerative diseases, contains expanded polyglutamine repeats, numerous explanations have been floated about how these lead to neuronal death. Researchers are pursuing several tracks, all of which may contribute to understanding the disease.

Gain or loss of function?

Anton Reiner presented evidence in support of the hypothesis that HD involves a gain of function mutation. Using two different methods to create chimeras, he showed that no offspring survive that are homozygous for a deletion of the huntingtin gene (double knock-out chimeras), but that inner cell mass injection of cells homozygous for the huntingtin deletion yields chimeric mice with no sign of disease despite the presence of homozygous KO cells in the adult brain. These results suggest that huntingtin plays an important role in the functioning of extraembryonic membranes, but that it is not critical for neuronal development and survival.

Jang Ho Cha suggested, however, that the question of whether HD involves a gain or loss of function is too simplistic. “Clearly there is a gain of function that’s already been ascribed to mutant huntingtin as a protein moiety -- if aggregated it can move into the nucleus. But one of the things that we see that are presumably sequelae of the gain of function that mutant huntingtin has are some losses of organismal function, like neurotransmitter receptors and decreases in specific mRNA populations. So you can have, as a consequence of gain of function, loss of the ability of cells to carry out certain jobs that they need to

do as a result of one genetic modification.”

Kenneth Fischbeck added, “It’s a question of whether some relative loss of function of huntingtin could be contributing to the pathogenesis. I think that unless you know the normal function of huntingtin you can’t say whether that’s true or not.”

Gene expression

Using microarray technology, Ruth Luthi-Carter has been studying the expression of some genes in R6/2 mice. She presented data indicating that these mice show altered expression of a subset of striatal and cortical genes prior to the onset of disease symptoms, suggesting a possible role in pathogenesis. Marcela Karpuj has used microarrays to look at gene expression in human brain samples, comparing expression in patients with HD and multiple sclerosis (MS). She found increases in several genes related to ubiquitination, mitochondrial and ribosomal function, as well as in neuronal, glial, and transcriptional factor genes. MS patients, in contrast, showed increased expression of a different set of genes, primarily those related to immune regulation.

Christian Néri presented data suggesting that huntingtin protein may interact with nuclear proteins involved in transcription. His lab has identified a protein in *c. elegans* that is homologous with a transcription regulator in humans and which interacts with an N-terminal huntingtin fragment. This interaction is modulated by the length of the polyglutamine expansion. Lucius Passani and colleagues have identified a spliceosomal WW-domain protein, HYP A, that interacts with both normal and mutant huntingtin. The binding is region specific; in R6/2 mice, the protein colocalizes with most intranuclear inclusions in the striatum but with only a few inclusions in the cerebral cortex. According to Passani, these findings suggest that HYP A may play a role in HD pathogenesis by altering nuclear function, such as pre-mRNA splicing.

Polyglutamine expansion

Vanessa Wheeler described knock-in mouse models in which CAG stretches of various lengths

were inserted into the mouse homologue of the HD gene. Insertion of 92 or 111, but not 50, glutamines produced a progressive phenotype, with cellular localization of mutant huntingtin moving from the cytoplasm to the nucleus. In the nucleus, staining is initially diffuse but becomes more punctate and eventually forms aggregates. The nuclear inclusions were found in the medium-spiny projection neurons, which are the targets of pathogenesis in humans.

Francesca Persichetti studied the conformational properties of the full-length and truncated huntingtin protein with expanded glutamine tracts. She showed that truncated amino-terminal protein with either 23 or 150 repeats formed aggregates and did not react with the glutamine-specific monoclonal antibody 1F8. In contrast, both full-length proteins retained reactivity with 1F8 and did not form aggregates.

Several labs have been investigating the mechanism of polyglutamine pathogenesis. Anne Hart, working in *c. elegans*, showed that expression of the N-terminal huntingtin fragment with 150 glutamines, but not 95, 23, or 2 glutamines, caused neurodegeneration but not cell death. She conducted a genetic screen to find mutations that enhance the neurodegeneration, and identified one such mutation in a gene called *pqe-1* (polyQ enhancer-1). Cloning of this gene is underway, which may provide additional clues about the molecular mechanism of polyglutamine-induced neurotoxicity and may also identify therapeutic targets.

In *drosophila*, Parsa Kazemi-Esfarjani has also been screening for genetic factors that modify the polyglutamine-mediated neurodegeneration. He described one gene, which is homologous to the human heat shock protein 40 (Hsp40), that appears to suppress the neurodegenerative effects of a 127-CAG repeat insertion. Leslie Thompson, also working in *drosophila*, expressed a peptide containing 108 polyglutamines that results in complete lethality, suggesting that polyglutamine repeats alone, independent of disease protein context, cause neuronal degeneration.

Christopher Ross has been studying

polyglutamine-mediated cellular toxicity in both HD and another disease associated with polyglutamine expansion, DRPLA (dentatorubral-pallidoluysian atrophy). While he has shown that under stress, HD cells depolarize their mitochondrial membranes, indicating direct toxicity of huntingtin fragments, other lines of evidence indicate that the site of cell death is nuclear rather than cytoplasmic. His data suggest that nuclear transcription machinery, especially co-repressor complexes, may play a role in polyglutamine pathogenesis.

Steven Suhr and colleagues have been studying the mechanism of polyglutamine-induced cell death in two models: one an inducible cell model and another *in vivo* system using adeno-associated virus (AAV) vectors to deliver polyglutamine constructs into rat and primate brains. In the inducible model, at the time of maximum cell death (day 5 in the rat), about half of the cells that are TUNEL positive also have spherical inclusions called SMPs, leading Suhr to conclude that most of the cells dying from polyglutamine-induced cell death are taking on SMPs. In the rat model, they have found that a “substantial population” of infected cells have large intracellular aggregates and die soon after infection, while other cells survive up to 8 months following infection and have small intranuclear aggregates.

In the Tet-On inducible cell model presented by Andreas Wytenbach, aggregate formation and cell death were both time and polyglutamine-length dependent. He has been studying the fibrillar structure of the aggregates for more clues about their formation.

Individuals with two mutant HD alleles have been reported to have a similar age of onset as their heterozygous siblings. David Rubinsztein has been studying the molecular basis for this phenomenon, called true dominance. In a cell culture model, he showed that a 21-repeat construct (wild-type) can be sequestered in inclusions seeded by the mutant construct and that the 21-repeat construct neither enhances nor interferes with inclusion formation. In contrast, an

increase in the number of repeats in the mutant allele does affect age at onset.

Neuronal inclusions

In R6/2 mice, Ann Morton showed that in the hippocampus, the appearance of neuronal inclusions, both intranuclear (NII) and extranuclear (ENI) parallels the mental and motoric decline.

Astrid Lunkes, using a cell line expressing mutant full-length huntingtin showed that processing of the protein results in truncated forms of huntingtin corresponding to a caspase-3 cleavage product at late time points and an even more truncated N-terminal product at earlier time points. The latter one is most likely responsible for the initial formation of cytoplasmic and nuclear inclusions. Mark Becher used antipeptide antibodies directed to different epitopes of huntingtin to further characterize the intranuclear inclusions in neocortical sections and cytological nuclear preps from HD cases. His work indicates that the caspase I cleavage site (at aa247) is intact in many nuclear aggregates. Other sites at aa513, 530, 552, and 589 remain possible candidates to produce the N-terminal fragments found in nuclear inclusions. Vivian Hook has also studied proteolytic processing of the huntingtin protein. Her work in brain tissue from HD patients shows that the cortex, striatum, and cerebellum (the control) process the protein differently, resulting in fragments of different sizes in the cortex and striatum. This may have implications in terms of pathogenesis, she suggested.

The mechanisms of intranuclear inclusion formation have been studied by Crislyn D'Souza-Schorey. She has identified a protein called arfaptin 2 that induces the formation of huntingtin inclusions by interacting with two small G proteins. Arfaptin 2 plays a role in membrane trafficking and cytoskeletal remodeling, she said, which may be important in inclusion formation.

The cell culture work of Frédéric Saudou, however, indicates that nuclear inclusion formation does not correlate with apoptosis. His lab has found a dominant interfering mutant form of a ubiquitin-conjugating enzyme that inhibits the

formation of inclusions while accelerating mutant huntingtin-induced cell death. Saudou suggested that the formation of inclusions may be a part of a cellular strategy for degrading or inactivating toxic forms of the mutant. The therapeutic implications of this are discussed below (see "Therapeutic approaches").

Excitotoxicity

Patrik Brundin examined the role of glutamate receptor-mediated excitotoxicity in R6/1 mice. Unexpectedly, in comparison to wild-type mice in which intrastriatal infusions of quinolinic acid (an NMDA-receptor agonist) cause massive neuronal death, the HD mice were resistant to NMDA-induced damage. Åsa Petersén, meanwhile, studied the effect of dopamine on neurodegeneration by directly injecting dopamine, which is normally neurotoxic, into the striatum of R6/1 mice. The R6/1 mice showed reduced susceptibility to dopamine, suggesting that striatal neurons have a reduced sensitivity to toxic damage by dopamine as well as by excitotoxins.

Lynn Raymond has been pursuing the hypothesis that neurodegeneration in HD is caused, at least in part, by overactivation of NMDA-type glutamate receptors. She co-transfected cells with either htt-15 or htt-138 and NMDA receptor subunits and then assayed for cell death after incubation with NMDA and glycine. Her data indicates that cells expressing htt-138 show enhanced excitotoxicity and apoptosis in response to NMDA.

Nansheng Chen has been pursuing the hypothesis that enhanced NMDA receptor activation triggers intracellular calcium accumulation, caspase activation, huntingtin cleavage, and eventually, apoptotic cell death in the affected neurons in HD. He showed evidence that mice NMDA receptors were selectively enhanced in mice transgenic for mutant but not normal huntingtin. One possible explanation for the enhanced sensitivity of NMDA receptors in the HD mouse was suggested by Michael Levine. In electrophysiological studies using the R6/2 mouse, he found more depolarized resting

membrane potentials and elevated input resistances.

Caspases and Apoptosis

Caspases are a family of proteases that play a role in apoptosis. In order to learn more about the role of caspases in the pathogenesis of HD, Robert Friedlander and colleagues crossed R6/2 mice with transgenic mice expressing a dominant negative form of caspase-1 (NSEM17Z). Both R6/2 and R6/2-NSE M17Z mice develop normally up to about 7 weeks of age, when the R6/2 mice begin to show progressive symptoms of HD. In contrast, the disease progresses much more slowly in the R6/2-NSE M17Z mice. They perform better on tests of motor function and have a significant delay in both disease onset and mortality. In addition, Jang-Ho Cha, working with Friedlander, showed that while R6/2 mice have decreased levels of the neurotransmitter receptors D1, D2 and A2a at both the mRNA and protein levels, the NSEM17Z mice had normal levels at 9 weeks of age and lacked ubiquitin- and huntingtin-positive neuronal intranuclear inclusions (NII) that are seen in R6/2 mice. Western blots showed that endogenous huntingtin is abnormally cleaved in R6/2 mice but not in the double mutants, suggesting that caspase-1 activation may play a role in the pathogenesis of HD.

Friedlander also showed that continuous intracerebroventricular infusion of a caspase inhibitor improved the motor function and lifespan of R6/2 mice. Cheryl Wellington also presented data suggesting that caspase inhibitors may protect cells from huntingtin-mediated apoptosis. But, she added, "We have never seen so far any evidence of caspase-1 specific cleavage fragments produced from huntingtin in any cellular model, so we're not convinced that caspase-1 is the most relevant caspase in the cleavage of huntingtin itself."

Research presented by Blair Leavitt indicates that endogenous huntingtin may itself have anti-apoptotic properties. Elena Cattaneo's research indicates that wild-type huntingtin prevents caspase 3 activation, which could explain its anti-apoptotic properties. Other research suggests that

caspases cleave mutant huntingtin into fragments that lead to apoptotic cell death.

Another protein involved in apoptosis is the cytoskeletal associated protein, HIP-1 (Huntingtin interacting protein-1). Abigail Hackam investigated the mechanism of HIP-1 mediated toxicity. She hypothesized that altered binding of mutant huntingtin with HIP-1 promotes cell death through activations of caspases and JNK and suggested that inhibitors of these two pathways may have therapeutic properties.

Mitochondrial energy impairment

Paolo Guidetti presented evidence showing that reductions in mitochondrial energy metabolism, which can be seen in the brains of advanced cases of HD, are not present in the early stages of the illness or in HD transgenic mice, suggesting that the impairment is a consequence, rather than a cause of neurodegeneration. However, using magnetic resonance spectroscopy, Anthony Schapira showed that ATP production is reduced in both symptomatic and pre-symptomatic HD patients, indicating that mitochondrial metabolism may be abnormal. He suggested that this might be a useful marker of disease in pre-symptomatic HD. He also said that the pattern of enzyme loss in HD is different from that seen in other neurodegenerative diseases.

While the conclusions of these two researchers appear at odds, Schapira said that they are not necessarily contradictory. "One of the things that's come across very strongly in this meeting is that different mice do different things. The question is, where does mitochondrial dysfunction appear in the cascade and is it a direct component of the cascade from CAG to cell death?" Schapira said that the pattern of mitochondrial dysfunction seen in HD differs from that seen in other neurodegenerative diseases, indicating that it is not a common problem of degeneration. In addition, the MRS data indicates that there is a mitochondrial defect in muscle tissue of these patients, suggesting that the CAG repeats may directly affect mitochondrial function. But does it cause cell death? The answer to that question, said Schapira, will come from cell

models.

Transglutaminase

Tissue transglutaminase, an enzyme that crosslinks proteins into filamentous aggregates has been suggested as a contributing factor in the formation of nuclear and cytoplasmic inclusions in HD. Mathieu Lesort showed that this enzyme is indeed elevated in HD brains in a grade-dependent manner. "We think that it is a contributing factor to facilitate the formation of inclusions," he said. It was suggested that antibodies might be used to probe for transglutaminase within aggregates or that transglutaminase inhibitors might further elucidate the role of this enzyme.

Therapeutic approaches

Inhibition of apoptosis

As discussed earlier, the research presented by Friedlander and Wellington support the idea that aggregate formation and toxicity are mediated by caspase cleavage of huntingtin and that caspase inhibition may have therapeutic potential for HD. Several caspase inhibitors have been suggested as possible therapeutic agents for HD. Ivelisse Sanchez showed that the protective effects of the caspase 9 inhibitors are downstream of the polyglutamine-induced recruitment and activation of caspase 8. Further characterization of the polyglutamine-protein interactions and interactions with signalling pathways that lead to neurotoxicity may suggest other biological targets for inhibition.

Frédéric Saudou and colleagues, for example, have been studying the signaling pathways elicited by BDNF and IGF-1, both of which promote cell survival. They found a protein called Akt, a downstream effector of IGF-1, that protects against huntingtin-induced cell death and the formation of inclusions.

Inhibition of aggregation

Another possible therapeutic strategy would be to prevent the formation of insoluble aggregates. As a first step towards identifying aggregation inhibitors, Peter Thumfort and

colleagues have been developing a high-throughput screening assay using a protein generated by fusing huntingtin exon 1 containing 67 glutamines with GST. Aggregate formation using this protein was temperature sensitive and also appears to involve metal ions.

Jean-Michel Lecerf and Anne Messer also presented a novel strategy for inhibiting intracellular aggregates. They used an anti-HD specific intrabody, a single-chain peptide representing the minimum binding fragment of the antibody. They fused this intrabody to cytoplasmic, nuclear, or lysosomal retargeting signals and showed that this construct reduced aggregate formation in COS-7 cells that had been cotransfected with the HD gene with varying numbers of polyglutamine repeats.

Gene therapy

According to Ron Mandel, an effective gene therapy strategy for HD must meet three conditions: long-term transgene expression, high transduction efficiency, and regulated transgene expression. Using recombinant adeno-associated virus as a vector, Mandel has achieved long-term expression of L-dopa and GDNF as well as high transduction efficiency. Further, he reported that new production methods are producing vector at higher titres and with better purity.

Eric Kmiec described a novel approach to repairing genetic mutations at the DNA level using chimeric oligonucleotides, or "chimeraplasts," composed of both DNA and RNA. The approach has been used successfully to correct mutations in bacteria, cell, and animal models, as well as in the development of a therapy for the rare liver disorder, Crigler-Najjar. Kmiec has recently begun experiments aimed at altering or interrupting the CAG repeat in the Huntington gene. In a normal copy of the Huntington gene with 20 CAG repeats, he has been able to achieve a single base change that resulted in the conversion of a CAG to a CTG.

Ruben Boado suggested antisense as a means of down-regulating the expression of the Huntington gene. He tested a series of oligodeoxynucleotide (ODN) molecules

complementary to the AUG initiation codon of the HD transcript and identified one directed to the methionine initiation codon of the HD gene that had maximum ability to prevent expression of the HD protein.

Putting it all together

The challenge for scientists studying HD is to make sense of the ever-growing morass of data and to shape it into a reasonable model of the developmental progression of the disease from numerous perspectives: clinical, genetic, pathophysiological, molecular, and biochemical.

Patrik Brundin suggested such a model in which he plotted the time course of huntingtin cleavage, aggregate formation, and cell death in relation to the appearance of symptoms. "I would suggest that the symptoms may not be related primarily just to cell death," he said. "Cell death may be very important in later stages of symptomatology, but it may not be what we're studying in the transgenic mice and it may not be the most important part of the pathogenic process."

Brundin suggested that in the early stages of the disease, protein aggregates may form first in the cytoplasm and then move to the nucleus. Work presented by Xiao-Jiang Li indicates that small aggregates form in axon terminals and dendrites, which if toxic, might explain the changes Kerry Murphy reported in LTP and LTD. The loss of dendrites and axons in the absence of cell death may also explain shrinkage in the striatum, and why in the transgenic mice there are behavioral abnormalities without any clear cell death. Aggregate induced pathology not associated

with cell death may also explain why Ai Yamamoto was able to reverse the symptoms in mice and may have important therapeutic implications.

The questions of where and when aggregates form and what they are composed of is still unclear, noted Marcy MacDonald. "I would remind you that there is some conflicting data out there that needs to be explained; data that doesn't fit with the straightforward idea that huntingtin gets cleaved and the fragments go to the nucleus and form an aggregate." While aggregates appear to be composed of amino terminal fragments, it is not yet clear whether the ability to aggregate resides only in the fragment or in the full-length protein as well. MacDonald also stressed the importance of looking at interacting proteins and the processes involved in producing the small fragments.

"This debate will never be answered," said Matthew During. "The ultimate answer is going to come from the clinic." With gene therapy, he said, scientists now have the ability to deliver various genes efficiently into the brain. This approach could be used to test the effect of over-expressing wild type huntingtin or to deliver other proteins that might modulate aggregate formation, for example. Dan Goldowitz, however, cautioned about relying too heavily on gene therapy and suggested that a rational approach targeting the proximal events in pathogenesis may be a more fruitful strategy.