

Histone Deacetylase Inhibitors – A Possible Treatment for HD

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Abstract:

At a workshop held in August 2001 at the Memorial Sloan Kettering Cancer Center, more than 20 scientists from cancer and HD research fields met to discuss the potential for conducting clinical trials of histone deacetylase (HDAC) inhibitors in patients with HD. Paul Marks' group at MSKCC presented data regarding the evolution of a class of these agents called hybrid polar compounds, their mechanistic and structural properties, and results from both preclinical and clinical trials. These studies indicate that the agents inhibit tumor growth and have low toxicity. HD researchers presented data from studies investigating the role of HDACs in perturbations of gene expression, seen in models of polyglutamine disease. In two *Drosophila* models and a yeast model, HDAC inhibitors appear to interfere with the neurodegenerative process. Workshop participants urged additional studies in other HD animal models in preparation for human clinical trials. In order to begin human trials of HDAC inhibitors in HD patients, researchers will need to define the optimal study population and identify appropriate clinical and biological endpoints.

On August 9, 2001, a workshop at the Memorial Sloan Kettering Cancer Center brought together two groups of scientists pursuing different goals while utilizing the same strategy. Histone deacetylase (HDAC) inhibitors are a class of agents that have recently gained attention for their anti-tumor activity. Meanwhile, scientists searching for a cure or treatment for Huntington's disease (HD) have been working to determine whether HDAC inhibitors might be effective in halting the neurodegeneration that characterizes the disease. At the recent Gordon Conference on triplet repeat diseases, several scientists discussed work they had been doing in this area, and the idea arose that it might be beneficial to meet with HDAC researchers in the oncology community and compare notes. Paul Marks, whose lab at Memorial Sloan Kettering has been leading the way in developing HDAC inhibitors as a cancer treatment, offered to host such a meeting.

The goal of the workshop was to identify a practical approach that could lead to clinical trials of HDAC inhibitors for the treatment of HD. Marks' group brought to the

table experience working with these agents in both preclinical and clinical studies. HD researchers working with HDAC inhibitors are at an earlier stage of development, but eager to move quickly ahead.

Huntington's disease

The workshop started with a brief summary by Jang-Ho Cha of the history, clinical characteristics, genetics, pathological features, and mechanistic theories of HD. Originally described in 1876, HD is a familial neurodegenerative disease characterized by a triad of clinical features: a progressive movement disorder, cognitive decline, and psychiatric symptoms. Currently, there is no treatment available that delays the onset of symptoms or slows progression. Symptomatic treatment, presymptomatic testing, and genetic counseling are all that clinicians have to offer HD patients and their families. “We’re fixing leaks on a sinking boat,” said Cha. “We know we’re not altering the course of the disease.”

Cha went on to describe the neuropathologic features of the disease. In the post mortem brain, a distinctive pattern of cell loss concentrated in the striatum is evident. The pattern of nerve cell death seen in the post mortem brain has revealed important clues about the mechanism of the disease. Flint Beal’s laboratory has been investigating the role of excitotoxins in nerve cell death. Injections of excitotoxins showed that these glutamate-like substance kill cells along a pattern that almost exactly recreates the pattern of cell death that is seen in the post mortem HD brain, said Cha. “This gave rise to a really prevalent line of thinking, which is that maybe what happens in HD is some dysregulation of the glutamate system.” However, there are several other candidate mechanisms, all of which are supported by some evidence and many of which may be

related. These include: apoptosis, caspase activation, aggregation of abnormal proteins, calcium dysregulation, mitochondrial dysfunction, sequestration of transcription factors, phosphorylation abnormalities, and cytoskeletal transport abnormalities.

As cells are lost, the shape of the basal ganglia tends to change. Using serial volumetric magnetic resonance imaging (MRI), changes in the volume of those nuclei can be detected as early as three years prior to the onset of symptoms, said Cha. Yet, shrinkage of the nucleus is not the most sensitive marker of disease that can be detected using imaging methods. More sensitive neurochemical changes measurable by positron emission tomography (PET) and nuclear magnetic resonance spectroscopy (NMRS) may in the future point to pathological changes in the brain that occur long before symptoms appear.

The relevance of these clinical and neuropathologic findings in the development of new therapies is two-fold. First, understanding the mechanism will help guide the rational development of new therapeutics. Second and more important to the issue at hand, imaging and clinical markers may be useful to monitor the efficacy of therapeutic agents. According to Cha, there are many abnormalities that can be monitored in the HD patient, including motor function, lactate levels (measurable by NMRS), and dopamine receptor levels (measurable by PET). Some of these technologies are just now being explored and need to be fully validated. What isn't clear is which abnormalities correlate with the clinical phenotype, so what to follow becomes an important question to be answered. In the CARE-HD (Coenzyme Q₁₀ and remacemide in Huntington's disease) study just completed, clinical features monitored included functional capacity, motor and behavioral features, and cognitive performance, as assessed the Unified Huntington's

Disease Rating Scale (UHDRS)ⁱ. In the NINDS-funded PREDICT-HD (Neurobiologic Predictors of Huntington's Disease Onset) study, assessments will include volumetric MRI and sophisticated neurocognitive testing. PET and fMRI may also be added.

HD in Venezuela

Nancy Wexler briefly summarized the work she has led over the past 22 years with a large pedigree of people with HD in Venezuela. It was this population that facilitated the identification of the genetic marker for HD in 1983 and later the actual gene in 1993. Now we know that in people with HD, there is a repeat expansion of the CAG trinucleotide in a gene that has been named *huntingtin*. The gene is inherited in an autosomal dominant fashion, and above a certain threshold of CAG repeats, individuals develop the disease. The huntingtin protein (htt) in these individuals includes long chains of glutamine residues, thus the moniker “polyglutamine disease.” In addition to HD, there are at least 8 other polyglutamine diseases, with the repeat expansion in different genes.

The Venezuela pedigree now includes 17,000 people; about 14,000 who are alive today. The Venezuela research team has collected extensive data with good clinical measures and thus has learned a great deal about the progression of the disease over time. About 1,000 individuals in this pedigree have been genotyped, allowing for prospective, longitudinal study of the natural history of the disease presymptomatically. The phenoconversion rate, i.e., the rate of going from being presymptomatic to symptomatic, is about 30% for every year a person lives over the age of 30. In contrast, the phenoconversion rate in the United States is about 17%; although there is less extensive

longitudinal data available in the U.S, where only 3% of the 150,000 people at risk for HD have been genotyped.

HDAC inhibitors for cancer therapy

Following the introduction to HD, attention shifted to HDAC inhibitors. HDACs are enzymes that catalyze the removal of acetate groups from the amino terminal lysine residues of nucleosomal histones. The opposing enzymes, histone acetyl transferases (HATs), put acetate groups onto histones. The extent of histone acetylation is thought to regulate transcription. Deacetylation dampens gene expression and inhibition of deacetylation promotes gene expression. HDAC inhibitors have been shown to induce growth arrest, differentiation, and/or apoptosis in transformed cells.

Victoria Richon presented work aimed at understanding the mechanism and activity of these agents. The work began with an observation that murine erythroleukemia (MEL) cells could be induced to differentiate into erythroid cells in response to dimethylsulfoxide. Following this observation, a search began for other small molecules that similarly are able to induce differentiation in transformed cells as a potential new therapy. Ronald Breslow, in collaboration with the Marks group synthesized over 700 small molecules that have been tested. This led to the evolution of a group of agents called hybrid polar compounds (HPC,) including hexamethylene bisacetamide (HMBA,) M-carboxycinnamic acid bishydroxyamide (CBHA,) suberoylanilide hydroxamic acid (SAHA,) and suberoyl-3-aminopyridineamide hydroxamic acid (pyroxamide), which induce differentiation to different degrees and at different concentrations. HMBA was tested in clinical trials in patients with acute myelogenous leukemia (AML). While it induced remission or partial remission in some patients, the relatively high optimal

inducing concentration meant that patients needed to take as many as 50 pills per day, and the treatment was associated with adverse side effects including thrombocytopenia.

The team went back to the drawing board.

In studies of the mechanism of action, the Marks group observed that the structure of these agents resembled that of other natural products such as trichostatin A (TSA), a potent histone deacetylase inhibitor. Working with Nikola Pavletich, they have crystallized TSA and co-crystallized TSA with histone deacetylase protein, showing how these compounds bind and inhibit histone deacetylase activity.

There are three classes of HDACs in humans with limited tissue specificity, i.e., HDAC4 has some neuronal localization but is not exclusively found in the neural system. Further studies by Marks' group have demonstrated that several of the small molecules are active against Class I and Class II HDACs. In microarray experiments, they have shown that in different cell lines, the expression of less than 2% of genes is regulated following culture with the inhibitor.

SAHA has a low optimal inducing concentration with relatively strong induction of differentiation. Studies revealed that in MEL cells treated with SAHA at the optimal concentration, all four histones become acetylated. According to Richon, hyperacetylation of histones is associated with activation of transcription. One of the genes they have been studying is p21, a gene that regulates cell cycle progression. Using T24 bladder carcinoma cells, they showed that a single dose of SAHA resulted in arrest in the G1 phase, associated with acetylation of histones in the p21 promoter and induction of p21. This induction of transcription was shut off at 24 hours, suggesting that there may be different factors coming on and off during induction of transcription and

pointing to the need to develop finely-tuned dosing regimens. Richon noted that, in animal studies, the half-life of SAHA in serum is very short, with 50% excreted unchanged and the remainder metabolized to innocuous compounds. Marks suggested that the short half-life may explain the low toxicity of this agent.

In animal studies of mice with a CWR22 human prostate cancer xenograft, SAHA was shown to be effective in inhibiting tumor growth with no toxicity other than mild peritonitis that was also seen in the control mice. Inhibition of tumor growth was associated with acetylation of histones and induction of p21 expression. A similar observation was made in neuroblastoma xenografts treated with CBHA.

The agents were also tested in a chemopreventive model, in which SAHA was incorporated into the diet prior to the induction of mammary tumors in rats. The incidence of tumors in these rats was decreased from 95% to 60%, and the tumors that did develop were smaller, said Richon. Again, no toxicity was observed at doses that inhibited the development of tumors.

As a result of these promising preclinical trials, the group began a Phase I clinical trial of SAHA in end-stage cancer patients, as described by Kevin Kelly. Using 2-hour infusions, 5 days per week for 3 weeks, they did a dose escalation study and saw very little toxicity. In addition they looked at mononuclear cells and saw evidence of histone acetylation and an accumulation of acetylated histones in tumors. They also saw some antitumor effects and relief of tumor-related symptoms, especially at the higher dose levels. They are about to begin studies using an oral formulation of SAHA and have other compounds in various stages of preclinical evaluation, said Kelly. No studies have yet been done to assess whether compounds cross the blood brain barrier.

HDAC inhibitors for treatment of HD

The rationale for pursuing SAHA or other HDAC inhibitors as a potential treatment for HD arose from evidence suggesting that enzymes which affect gene expression at the level of chromatin structure seem to be perturbed in models of polyglutamine disease.

Joan Steffan described work carried out in Leslie Thompson's lab. In a paper published in 2000ⁱⁱ, Steffan and Thompson hypothesized that the mutant huntingtin protein (htt) might cause apoptosis through transcriptional repression mechanisms similar to those of the tumor suppressor gene, p53. They demonstrated that, like p53, mutant htt interacts with the coactivator CREB binding protein (CBP) and the corepressor mSin3a; and that the expression of mutant htt repressed transcription of genes regulated by p53, the *p21* and *MDR-1* luciferase reporters. These data suggest that mutant htt may behave similarly to the viral protein E1A, which interacts with CBP/p300, repressing transcription and leading to cell death. (for more on this, see the HDF workshop report "P53 & Huntington's disease - a relationship?", held June 26-27, 2000, ,” available at <http://www.hdfoundation.org/workshop.htm>).

Steffan mapped the interaction of htt to the acetyltransferase/CH3 domain of CBP, and found that htt inhibits acetyltransferase activity *in vitro* and decreased levels of acetylated histones in cell culture. She also showed that the HDAC inhibitors butyric acid, SAHA and TSA reverse this phenomenon.

Thompson then went on to feed butyrate and SAHA to *Drosophila* with expanded polyglutamines and those expressing htt exon1 protein. Both types of flies have a

neurodegenerative phenotype. Thompson showed that butyrate and SAHA both blocked neurodegeneration and rescued lethality.

Paul Taylor next described work done in Kurt Fischbeck's lab at NINDS. The Fischbeck lab studies a different polyglutamine disease, Kennedy's disease, in which motor neurons of the spinal cord and brainstem gradually degenerate. Patients with Kennedy's disease experience progressive weakness and a moderate amount of sensory involvement but no dementia or cognitive impairment. The gene responsible for the disease was identified in 1991 and found to be the androgen receptor with an expanded polyglutamine tract. Inherited as an x-linked disorder, the disease has an incidence of about 1:40,000 (substantially less than HD) and affects males more severely than females.

Alex McCampbell, a graduate student working in Fischbeck's lab began to investigate the hypothesis that one possible target of the expanded polyglutamine could be some limiting factor that is critical for neuron survival. He took a candidate approach to search for this factor. McCampbell showed that expanded polyglutamine androgen receptor constructs formed nuclear inclusions, which sequestered CBP while at the same time reducing soluble CBP. He transfected cells with truncated forms of androgen receptor with expanded polyglutamine of varying lengths and demonstrated polyglutamine-length-dependent toxicity. He then showed that CBP, co-transfected into these cells, rescued that toxicity. Finally, he showed that toxicity could also be rescued by treating these cells with certain HDAC inhibitors.

In order to learn more about the mechanism of polyglutamine-induced toxicity, Taylor has employed a drosophila model developed by Parsa Kazemi-Esfarjani. In this

model, 127Q (shorthand for 127 polyglutamines) is expressed under control of the yeast promoter UAS. This promoter is silent in the absence of the transcription factor Gal4. Flies carrying 127Q can be crossed to various driver lines, expressing Gal4 under a tissue-specific promoter, to drive expression in whatever cell type one wishes to study. If driven in the eye, the fly will have a largely degenerated eye. These flies are then crossed with other lines in which an enhancer has been inserted to drive increased expression of CBP. These crosses produce offspring with 100% functional rescue of the eye degeneration. “We think this suggests that CBP function may be integral to mediating the toxicity of mutant polyglutamine,” said Taylor.

Next the group plans to investigate the effect of knocking out different HDACs. And, they would like to do array analysis comparing the gene effects in flies treated with SAHA to flies engineered to overexpress CBP.

Robert Hughes described work in yeast that also implicates HDACs as possible mediators of huntingtin toxicity. Hughes, working in collaboration with Stan Fields and Jim Olson, is developing yeast-based tools for high throughput drug discovery and to help answer questions of biological function and dysfunction. Expression of htt exon 1 with expanded polyglutamine results in nuclear aggregates. Aggregates are also formed when cells are induced to express non-expanded htt plus a nuclear localization signal, suggesting that there is something about sending the material into the nucleus that facilitates aggregate formation. In yeast, nuclear aggregation does not result in cell death or gross toxicity. However, cells expressing nuclear expanded polyglutamine do grow a little bit slower.

In order to better understand this phenomenon, the group decided to do a transcript profile on these cells using DNA microarrays containing all 6,000 yeast genes. When expanded polyglutamine is in the nucleus, they saw about 26 genes significantly repressed. Some other genes, particularly those related to protein folding and chaperone function, are induced. The genes that were repressed to the greatest degree were what Hughes called “a curious collection of transporters and things involved in phosphate metabolism.” By comparing this repression pattern to other databases looking at yeast mutants, Hughes deduced that the most reasonable match was to genes involved in histone acetylase function. Further study has demonstrated that of the 26 genes that are down-regulated, 10 of these overlap with 15 core genes regulated by the Gcn5 histone acetylase complex called SAGA. “So that was a fairly tantalizing coincidence perhaps, or an indication that what these cells were experiencing was a defect in histone acetylase function,” said Hughes.

At the suggestion of Alex McCampbell, they next looked at responsiveness of their cells to TSA. They took the most severely down-regulated promoter, PHO84, fused to a lacZ reporter gene and showed significant down regulation of the promoter in the presence of expanded polyglutamine and a partial rescue of this down regulation in the presence of TSA. Work done in Stuart Schrieber’s lab at Harvard indicates that PHO84 is repressed by HDA1, which, according to Michael Grunstein at UCLA, may counterbalance the activity of Gcn5. These observations, coupled Hughes’ observations, suggest that nuclear expanded polyglutamine interferes with the Gcn5 complex in yeast.

As tantalizing as these results are, Paul Marks pointed out that in all tissues studied, no clear pattern has emerged about the tissue specificity of different HDAC

complexes. Moreover, a literature review found no evidence that any of the HDAC inhibitors have specificity, with the possible exception of HDAC6. Flint Beal's lab is now working with the Marks' group to investigate the specific response of various tissues of the brain to a single IP injection of SAHA.

Emma Hockly, working in Gillian Bates' laboratory has been looking at behavioral changes that occur in HD mice following treatment with SAHA and phenylbutyrate. SAHA was given by daily subcutaneous injection for 5 weeks at doses of 25 mg/kg. At that dose, they have not seen any effect, nor have they seen toxicity. Marks suggested the dose may be too low. He also suggested oral dosing by putting the drug in the feed as soon as the animals are weaned. Since some studies suggest prevention of symptoms might be possible by giving animals the drug as early as possible, Robert Pollack suggested giving the drug to lactating females.

Prospects for a clinical trial of SAHA for the treatment of HD

With the common goal of getting HDAC inhibitors such as SAHA to the clinic as soon as possible and in the most effective way as possible, the group turned their attention to discussion of a number of issues: What animal studies are needed prior to human trials? Which animal models should be included in these studies? How translatable or transferable is the experience Marks' group has attained with cancer patients? Who will be the clinical trial populations? One of the first challenges that will need to be addressed is finding agents that have the ability to cross the blood brain barrier. According to Marks, a medicinal chemist has looked at the various compounds and suggested which ones are most likely to cross the blood brain barrier. SAHA is not one of these, he said.

Animal studies. The many HDAC inhibitors that have been identified appear to differ primarily in terms of water solubility and optimal dose. They appear to have the same target and biological effects, at least in terms of their effect on tumors. Studies in the various HD models may identify other differences between these compounds, as well as further clarifying optimal dose, solubility, etc. Animal studies will definitely be needed to assess the ability of these agents to cross the blood brain barriers, but such studies will not require the use of HD mice.

Several mouse models were discussed that could be potentially useful in studying HDAC inhibitors. The R6/2 mouse (Bates) is probably the most extensively studied. Other models suggested included the conditional transgenic mouse (Yamamoto/Hen); full-length YAC transgenic models (Hayden); Borchelt mice, which have two exons but neuropathologic features more similar to the human disease; and the Aronin mice. If time course is a problem, Bates' R6/1 mouse, which has the same construct as the R6/2 but with different repeat numbers and a more protracted course, might be considered. Paul Taylor suggested looking at a non-HD model, such as Al LaSpada's SCA-7 mouse. (For more on the various animal models, see the March 28, 1999 workshop report "New Therapies: Screening in Animal Models. New York, New York," available at <http://www.hdfoundation.org/workshop.htm>).

How to get compounds for animal studies. Marks said the compounds are coming from a company called Aton Pharma, Inc. Some sort of practical material transfer agreement will need to be worked out with them so that HD researchers can get access to the compounds. "This is something they weren't prepared for," said Marks. "But there's no question we'll work it out."

Human trials. There was some discussion of moving immediately to human trials despite the limited data available in animal models and the limited information available about histone acetylation in HD patients. Said David Housman, “The most critical thing is, if this is a mode that is going to be effective we need to find compounds that have a greater effect in animal model systems, and that should be the first focus.”

Jim Olson suggested running animal studies and human Phase I trials in parallel. If the compound gets into the brain and is not toxic, and if animal studies show that the compound reverses pathology, more extensive human trials might be warranted. A compromise, noted by Carl Johnson, might be to continue with animal studies but wait to do human trials until the oral compound is available, which Marks suggested will be in 6 to 10 months.

Two important issues remain to be clarified before human trials begin. First, who will be included in the study population; and second, which markers of efficacy will be assessed?

Study population. The first question is whether study participants should be symptomatic or presymptomatic. In the cancer population, one of the hopes, supported by some animal data, is that HDAC inhibitors might prevent the onset of clinical symptoms. Jang-Ho Cha noted that there are few reliable measures that can be assessed in presymptomatic patients. Even if it has been determined that a patient has the gene, it is hard to predict age of onset. Therefore, “the power analysis starts to explode,” he said.

Since in the United States most people at risk of HD have chosen not to get tested, the question becomes one of whether the at risk population, only about half of whom would have the abnormal gene, would be willing to participate in a drug trial and whether

the drug is safe enough to give to unaffected people. Nancy Wexler said that in focus groups of people at risk, many have said they would be willing to participate in a drug trial if the drug was not too toxic. She said that if the gene status were available for patients, one could potentially design a clinical trial that would include gene-negative individuals from the standpoint of inclusion in the study, but have the randomization done so that only gene-positive individuals actually receive the active drug.

Symptomatic patients will be easier to come by. In other studies done in the United States with symptomatic patients, “there were lines of people waiting to sign up,” said Anne Young. One group of patients who might be candidates for a drug trial is a group of 50 advanced patients at Terence Cardinal Cooke Health Care Center, a long-term care facility. About 16 of these patients are ambulatory. Kevin Kelly noted that there is a lot of resistance to using such an advanced population because of consent issues. These patients are also likely to have multiple medical complications that could make interpretation of the results difficult. Steven Hersch added that clinical measures for advanced patients are not very good.

Jang-Ho Cha voiced another concern: that treatment with HDAC inhibitors might result in worsened symptoms in HD patients. “Even though the role of apoptosis is hotly debated in the HD field, one thing that is clear is that if you put mutant htt in any cell line whose cells are more susceptible to toxic insults, they die,” he said. “We’re talking about introducing compounds which may have as an effect promoting apoptosis. I think there’s a huge potential, at least a theoretical possibility, that we might be triggering off apoptosis. In normal humans, that may not be an issue, but in humans where every one of those cells is loaded with mutant htt, their apoptotic threshold might be very different.”

Endpoints. The issue of identifying clinical or biological endpoints is an important one that needs to be clarified. The best clinical measure, according to Anne Young, is the neurologic exam. Other measures such as MRI and PET studies have been more difficult to follow over time because the technology has changed. Robert Pollack noted the importance of including psychiatric assays in any efficacy study. Since mutant htt protein may affect cortical cells that provide critical neuropeptides to the striatum, psychiatric effects may precede motor effects in the appearance of the disease, he said.

The Huntington Study Group (HSG) is already set up to run multi-center clinical trials. There are about 50 centers around the country which all use the same rating scales, forms, etc., with good inter-rater reliability. Psychiatric symptoms are included as part of the clinical evaluation. The HSG also has a protocol office and data management office. Several trials have already been run through this group, including the previously mentioned CARE-HD trial and a trial of minocycline. Steve Hersch noted that one of the problems in looking at clinical markers is that most of the phase II trials have lasted for about 3 to 4 months, which may not be long enough to detect a difference in symptoms.

Identifying good biomarkers has proven to be a more vexing problem, due in part to the fact that the biological mechanism of neurodegeneration is still not clear. (For more on this, see the June, 2001 workshop report “Biomarkers for Huntington’s Disease,” available at <http://www.hdfoundation.org/workshop.htm>). Bernard Ravina said that some kind of biomarker will be needed that measures disease activity and is specific for this class of drugs. Jim Olson suggested looking at histone acetylation in mononuclear cells of treated and untreated HD patients, controls, and HD animal models.

Kurt Fischbeck, however, noted that the defect may appear only in the brain and not in peripheral blood.

Conclusion

Paul Marks summed up perhaps everyone's feelings when he said, after learning about the clinical, neuropathological, mechanistic, genetic, and epidemiologic aspects of HD, "My reaction is that it's much more complicated than I anticipated."

Notwithstanding the uncertainties associated with HD, the potential of HDAC inhibitors for treating the disease appear promising. Clinical trials for cancer patients are proceeding with positive results. Although HDAC inhibitors may intervene in tumorigenesis for reasons completely different from how they may intervene in HD, the cancer trials have shown that the agents have low toxicity. Future studies with oral formulations may make the agents even more acceptable to both cancer and HD patients. Early preclinical work in HD models has also been promising, indicating that in several animal models, HDAC inhibitors appear to interfere with the neurodegenerative process. The challenge for the future will be to learn more about the effect of these agents in various animal models of HD and then to move them quickly yet safely into human clinical trials. The spirit of cooperation evident at the workshop bodes well for this effort.

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ⁱ Neurology 2001;57:397-404

ⁱⁱ PNAS 97:6763-8, 2000