Supplementary Table I

Published Clinical Trials in HD.

Molecule/Target	Sponsor	Status
ACR16	Neurosearch	Phase III
AFQ056 - mGluR5	Novartis	Phase II
Atomoxetine	U. of Iowa	Phase II
Citalopram	NINDS	Phase II
CoQ10	NINDS	Phase III
Creatine	NCCAM/U. Rochester	Phase III
Dimebon	Medivation Inc.	Phase III
GDNF	Ceregene	Preclinical
HDAC4 inhibition	CHDI Foundation	Preclinical
Huntingtin ASO	ISIS Pharmaceuticals	Preclinical
Huntingtin siRNA	Alnylam	Preclinical
Improved CoQ10	Edison Pharmaceuticals	Preclinical
JNK3 inhibition	CHDI Foundation	Preclinical
KMO inhibition	CHDI Foundation	Preclinical
Lithium and Divalproex	NINDS	Phase II
LNK-XXX	Link Medicine	Preclinical
Memantine	UCSD	Phase IV
PDE inhibition	CHDI Foundation	Preclinical
PDHK inhibition	CHDI Foundation	Preclinical
Sirtuin-1 activation	CHDI Foundation	Preclinical
Sirtuin-1 inhibition	Siena Biotech	Phase I
TG2 inhibition	CHDI Foundation	Preclinical
TrkB modulation	CHDI Foundation	Preclinical

Supplementary Table II.

Published Pharmacological Studies in HD rodent models

Drug name	Summary	pmid
Amantadine	Possible efficacy for dyskinesia.	15178736
Amantadine	A letter on a small trial showed modest behavioral benefits but not dyskinesia. Previous study's authors responded.	15304616
Amantadine	Amantadine 300 mg/day had no effect on chorea or other symptoms	12873857
Amantadine	Double-blind placebo-controlled crossover study of amantadine shows imporvement in extremity chorea	12221159
Apomorphine	5 d continous infusion of apomorphine in 4 patients who responded acutely to treatment showed improved UHDRS motor section; and AIMS (abnormal involuntary movement scale).	17894335
Aripiprazole	Improved UHDRS score after two weeks of 10mg per day treatment.	18765501
Aripiprazole	Aripiprazole in the treatment of Huntington's disease: a case series.	19557093
Aripiprazole	Treatment of the symptoms of Huntington's disease: preliminary results comparing aripiprazole and tetrabenazine.	19170197
Atomoxetine	Randomized controlled trial of atomoxetine for cognitive dysfunction in early Huntington disease	19745649
Botulinum toxin-A	Effective treatment of bruxism in a single female patient with botulinum toxin-A.	15377749
Cabergoline	Cabergoline improved UHDRS after 1 wk of 2mg/day.	16629775
Cannabidiol	Study shows no efficacy of cannabidiol at 700 mg/day for 6 weeks in 15 HD patients	1839644
CNTF	Tolerability study in HD patients with encapsulated cells secreting CNTF	15585112
Creatine	Creatine reduced the elevated 8OH2'dG in serum.	16434666
Cyproterone acetate	50 mg per day eliminated hypersexuality in an elderly patient.	18691628
Cysteamine	Dose finding study of cysteamine in HD patients.	16258942
Donepezil	Donepezil was not effective in a 30 patient study.	17030764
Ethyl-eicosapentaenoic acid	Randomized controlled trial of ethyl-eicosapentaenoic acid in Huntington disease: the TREND-HD study.	19064745
Ethyl-eicosapentaenoic acid	MRI study monitoring effects of ethyl-EPA in cerebral atrophy. Shows benefits in thalamus and caudate	18831882
Ethyl-eicosapentaenoic acid	Imaging of 34 stage I or II HD patients in an ethyl-EPA trial showed that with a two time-point brain volume changes there is a significant group-level reductions in brain atrophy in the head of the caudate nucleus and the posterior thalamus.	18831882
Fluoxetine	Randomized, double-blind, placebo-controlled trial of this medication in nondepressed HD patients. Fluoxetine did not have an effect on non-depressed HD patients although it might be exert antidepressant effects in depressed HD patients.	9159735
Galantamine	A patient whose motor and psychiatric symptoms improved after administration of galantamine, an acetylcholinesterase inhibitor.	15101572
Gamma-Acetylenic GABA	A 14 HD patient study with gamma-Acetylenic GABA, an irreversible inhibitor of gamma-aminobutyric acid transaminase showed no benefit. CSF evaluation showed elevation of GABA in 10 subjects.	6258106

Gamma-vinyl GABA	A 6 HD patient study with gamma-vinyl GABA (2 g/day) revealed no effects in HD symptoms	6228746
Idebenone	A one-year, double-blind, parallel-group study in 100 HD patients demonstrated no effects of idebenone.	8866496
Ketamine	Ketamine was well tolerated at low and intermediate subanesthetic doses in 10 HD patients. Intermediate ketamine doses produced specific decline in memory and verbal fluency. Higher subanesthetic doses caused a significant increase in psychiatric symptoms and impairment of eye movements.	9222184
Lamotrigine	Lamotrigine improved motor and mood swing in single patient.	17853293
Levetiracetam	Levetiracetam reduced involuntary movements.	16340384
Lithium	No effects of lithium in a 6 HD patient study.	143188
Memantine	20 mg daily dose of memantine in 12 patients significantly improved motor symptoms, powered by improved chorea, but failed to improve patient's cognitive, behavioral, functional, or independence ratings. Most patients tolerated memantine without side effects.	17046312
Memantine	Possible slower progression in 27 patients.	15354397
Methylphenidate	Methylphenidate worsened symptoms of juvenile HD.	18658080
Minocycline	Minocycline produced benefits in motor and psychiatric endpoints.	15486519
Minocycline	Safety trial showed tolerability and safety over 8 wks.	15304592
Minocycline	Safety trial showed tolerability and safety over 6 months.	15197710
Modafinil	Modafinil increased alertness in a 20 patient trial but had no effect on cognitive functions or mood, and had deleterious effects on visual recognition and working memory.	18516718
Muscimol	Muscimol, a GABA receptor agonist, treatment did not result in improvement in 10 HD patients' motor or cognitive function.	152602
Nabilone	Nabilone improved mood and behavior, and reduced chorea, of patient.	17135385
Nabilone	44 patients in cross-over design to inform design of future studies; no major adverse events were found; no significant change in primary outcome measures of UHDRS found.	19845035
Nabilone	Nabilone increased chorea symptoms.	10584686
Olanzapine	Low dose in a single patient improved in motor, psychiatric and activity of daily living symptoms after four months of treatment.	15608976
Olanzapine	Open label study to assess effects on motor symptoms. Study shows efficacy in most motor subscores.	12410058
OPC-14117	The free-radical scavenger OPC-14117 showed no effects in symptoms severity but increased liver transaminase levels.	9595988
Perospirone	Improved motor and cognitive symptoms.	16887250
Proglumide	Proglumide, a cholecystokinin receptor antagonist, had no effects in 8 HD patients	8591802
Quetiapine	Case reporrt of patient subjectively feeling better with quetiapine than olanzapine.	15283541
Quetiapine	Quetiapine improved behavioral symptoms.	16384811

Ramecide hydrochloride	No effects of this NMDA receptor antagonist in 31 HD patients (200 or 600 mg/day)	8723144
Resveratrol	Resveratrol improved peripheral glucose levels in N171-Q82 but had no effect on survival, motor or cognitive endpoints.	20561979
Riluzole	Riluzole not effective in treating HD.	17702031
Riluzole	Riluzole protects Huntington disease patients from brain glucose hypometabolism and grey matter volume loss and increases production of neurotrophins.	19280185
Riluzole	Riluzole improves chorea intensity without effects in other endpoints	14663041
Riluzole	Riluzole showed effects at 3 months on motor scores, but not at 12 months in an open label study (50 mg twice a day)	11697523
Risperidone	Patients taking risperidone demonstrated significantly improved psychiatric functioning and motor stabilization, whereas patients not taking risperidone were stable psychiatrically and worsened motorically.	18297579
Rivastigmine	Treatment with 6mg rivastigmine for 2 years improved motor score and trend in reduction of functional disability and cognitive impairment.	17272969
Rivastigmine	Slight effect on cognitive and motor symptoms found.	15390067
Sodium phenylbutyrate	Doses of 12-15 g per day of phenylbutyrate well-tolerated in patients.	17702032
Sulpiride	Sulpiride, a dopamine receptor antagonist, did not affect symptoms in 11 HD patients even though it lowered total dyskenia scores	6236286
Terguride	No effects of terguride, a partial dopamine receptor agonis, in 8 HD patients	2575450
Tetrabenazine	Tetrabenazine reduced chorea for 5hrs in short term study of 10 patients.	17078062
Tetrabenazine	TBZ effectively suppresses HD-related chorea for up to 80 weeks. Patients treated chronically with TBZ should be monitored for parkinsonism, dysphagia and other side effects including sleep disturbance, depression, anxiety, and akathisia.	20021666
Tetrabenazine	84 patients studied, TBZ reduced chorea severityon UHDRS; improved CGI-I scale, compared to placebo.	16858878
Tetrabenazine	TBZ is a moderately effective treatment of a large variety of hyperkinetic movement disorders, with excellent effects in a subgroup with chorea and facial dystonia/dyskinesias.	15602104
Tetrabenazine	Treatment of the symptoms of Huntington's disease: preliminary results comparing aripiprazole and tetrabenazine.	19170197
Tiapride	Tiapride, a dopamine receptor antagonist, treatment significantly improved choreatic movements and motor skills in a 29 HD patient study.	6241563
Valproate	Valproic acid has benefit for HD patients with myoclonic hyperkinesia.	16507108
Venlafaxine XR	After 4 weeks of venlafaxine XR treatment (75, 150 or 225 mg), the symptoms of depression in HD patients decreased significantly relative to baseline. However, approximately one in five patients developed significant venlafaxine-related side effects (nausea and irritability).	19996754

Supplementary Table III.

Genetic approaches for disease modification in rodent models of HD.

Gene Symbol	Human Gene_ID	Summary Comments	Pmid
ACCN2	41	siRNA KD reduced mhtt aggregation and induced UPS in culture and in vivo.	18658163
CBP	1387	Heterozygote CBP knockout crossed to the N171-82Q model decreased their lifespan with no effect on motor function, neurodegenration or aggregation.	20448484
CNR2	1269	KO of CB2 enhanced microglial activation, worsened disease symptomatology and reduced mice lifespan in R6.2 mice.	19805493
BAG1	573	BAG1 overexpression in N171-82Q improved rotarod but only in male mice. OE in PC12 augmented the effects of Hsp70 by reducing aggregation and improving neurite outgrowth.	18400759
BDNF	627	Reduction in BDNF in R6/1 had no effect on mhtt aggregates, but worsened motor and neuropathology. Loss reversed by intrastriatal BDNF.	15342740
BDNF	627	BDNF +/- crossed to R6/1 showed worsened locomotor activity induced by amphetamine but no t by apomorphine; also worsened the nigral-striatal transport, and increased aggregation in nigra.	15934928
BDNF	627	R6/1:BDNF+/- mice showed earlier and worsened cognitive impairment than R6/1.	19121372
BDNF	627	Overexpression in forebrain improved motor, brain atrophy and inclusion outcomes. Increased ENK, DARPP32.	18086127
BDNF	627	BDNF and Noggin together induced striatal neuronal regeneration, delayed motor impairment, and extended survival in R6/2 mice.	17885687
CALM1	801	AAV CaM-fragment into R6/2 striatum improved motor and body wt.	19759302
CASP1	834	Two experiments done in R6/2 mouse model. Both dominant negative of CASP1 and CASP small molecule inhibitor decreased aggregation, improved motor/behavior, and increased lifespan.	10353249
CASP3	836	YAC128 mice expressing mutant htt, resistant to cleavage by caspase-3, showed no effects on the HD phenotypes.	16777606
CASP6	839	YAC128 mice resistant to caspase-6 but not caspase-3, maintain normal phenotypes and protected from toxicity of multiple stressors (NMDA, QA, and staurosporine).	16777606
CLPB	81570	Transgenic of yeast Hsp104 crossed to N171-82Q HD decreased aggregation and increased survival but had no effect on motor or body wt.	16204350
CNR2	1269	CB2 KO in R6/2 enhanced microglial activation, worsened motor, neuropath and lifespan.	19805493
CNTF	1270	CNTF gene therapy in YAC72 model showed reduction of hyperactivity, but no effect in clasping and rotarod. Ambiguous neurodegeneration changes (reduced striatal "dark cells").	14697316
CPLX2	10814	R6/2 phenotypes not affected by complexin II KO.	17352934
CREB1	1385	Transgenic A-CREB (loss of function CREB), when crossed to YAC128, significantly accelerated motor impairment.	19632326
DYNC1H1	1778	Dynein inhibitor EHNA increased mhtt aggregation toxicity. Partial LOF worsened fly eye phenotype. DYNC1H1 +/- crossed to N171-82Q worsened motor, survival; aggregation.	15980862
GDNF	2668	GDNF gene therapy in mouse R6/2 model shows no benefits.	15817265
GDNF	2668	GDNF gene therapy shows decreased degeneration, decreased aggregations, and improved motor function. This contradicts other gene therapy study.	16751280
GRIN2B	2904	GRIN2B OE and CAG-150 KI double mutant showed increased striatal degeneration and volume loss; no change in rotarod but reduced body weight and less exploratory and locomotor behavior.	19279257
HDAC1	3065	Mouse knockout HDAC heterozygote showed no effect in mouse R6/2 model.	Unpublished
HDAC4	9759	Heterozygotes of HDAC4 knockouts crossed to R6/2 mice led to improved motor/behavior and reduced aggregation.	Unpublished
HDAC5	10014	R6/2 crossed to HDAC5 KO showed no effect on HD outcomes.	Unpublished
HDAC7	51564	There is no improvement in a number of physiological or behavioral phenotypes in HDAC7 +/- crossed to R6/2.	19484127
HDAC9	9734	Knockout crossed to R6/2 showed no effect in the mouse.	Unpublished
HSF1	3297	Active HSF-1 expressed in skeletal muscle of tg mouse, when crossed to R6/2 reversed muscle phenotypes including aggregation, and improved lifespan despite lack of CNS effects.	16051598
HSPA1A	3303	Deletion of both Hsp70.1 and Hsp70.3 in R6/2 worsened survival, body weight, motor functions, and increased the size but not number of inclusions.	19605647

HSPA1A	3303	Overexpression only decreases mhtt inclusions in R6/2.	15115766
HSPA2	3306	Deletion of both Hsp70.1 and Hsp70.3 in R6/2 worsened survival, body weight, motor functions, and increased the size but not number of inclusions.	19605647
HSPA4	3308	Hsp70 overexpressing transgenic crossed to R6/2 showed a slight delay in body weight loss but no effect in all other outcomes.	12706247
HSPB1	3315	OE of Hsp27 has no effect on R6/2 phenotypes, oxidative stress or inclusions. Hsp27 can be activated by heat shock but remains inactive in the HD state in the double transgenic.	17360721
HTT	3064	HdhQ140 increased median and maximum lifespan of p53 KO with gender differences.	18242663
HTT	3064	In both mouse and cell culture HD models mHTT knockdown led to decreased aggregation; and in N171-82Q mice, improved stride length and rotarod performance.	15811941
HTT	3064	siRNA against mhtt improved HD phenotypes in R6/2.	16095740
HTT	3064	N571-htt-72Q-KR (non-Ac) in neuronal culture, in vivo, and in worms increased mhtt levels and increased toxicity compared to Ac-mhtt.	19345187
ITPR1	3708	AAV1-GFP-IC10 improved motor and MSN deficits in YAC128. Lenti-GFP-IC10 virus in YAC128 cultured MSNs stabilized Ca(2+) and reduced glutamate-induced apoptosis.	19193873
NOG	9241	BDNF and Noggin together induced striatal neuronal regeneration, delayed motor impairment, and extended survival in R6/2 mice.	17885687
NOS1	4842	-/- nNOS crossed to R6/1 worsened phenotypes (body weight, rotarod, clasping, survival) compared to control or to -/+ nNOS crosses.	12020853
NRTN	4902	CERE-120 (AAV2-NTN) reduced motor deficits, and neuronal loss in striatum and cortex in N171-82Q.	19150499
OGG1	4968	Oxidative lesions is age dependent and increases somatic expansion in R6/1 cells and neurons; age-dependent expansion is suppressed in OGG1 KO cross.	17450122
PARK2	5071	Parkin +/− crossed to R6/1 were more akinetic; had fewer inclusions and a more TUNEL+ cells in striatum but not in hippocampus.	19464273
PPARGC1A	10891	PGC-1alpha knockout crossed to CAG140 KI HD model worsened HD phenotypes. Lentiviral expression of PGC-1alpha in striatum of R6/2 reduced neurodegeneration.	17018277
PRNP	5621	Deletion of PrP had no effect on a variety of outcome measures in R6/2 except for a small improvement in rotarod from 6-12 wks; no effect in the N171-82Q model. Overexpressing PrP did not worsen the HD phenotypes.	19901559
PSME3	10197	REG-gamma +/- crossed to R6/2 did not improve the HD phenotype.	16311253
SLC6A3	6531	DAT KO crossed to Hdh92Q KI worsened locomotor and aggregation at 8 mo.	17065224
SOD1	6647	Overexpression had no effect on motor skills or lifespan.	15081595
SP1	6667	RNAi KD of Sp1 reduces toxicity of 3-NP on mhtt PC12 cells. Sp1 +/- crossed to HD mice increased lifespan.	16595660
STUB1	10273	CHIP+/- crossed to N171-82Q worsened degeneration, aggregation, and motor/behavior. OE in cell culture and zebra fish decreased toxicity and aggregation.	16207874
TGM2	7052	Cystamine imrpoves motor behavior and lifespan in R6/2 model even when the transglutaminase gene is knocked out. This indicates that TGT is NOT the target of cystamine.	15896882
TGM2	7052	TGM2 KO crossed to R6/1 improved body weight loss, striatal degeneration,motor behavior, and lifespan; increased intranuclear inclusions.	12181738
TGM2	7052	TGM2 knockout crossed to R6/2 shows decreased degeneration, increased aggregation, improved rotarod performance and increased lifespan.	15606898
TP53	7157	In N171-htt 82, fly, and cell culture, reducing p53 reduced toxicity. P53 KO reduced degeneration and improved motor/behavior in HD mouse, including clasping, clockwise rotational behavior in open field, decrease in prepulse inhibition in the startle response, and rotarod.	15996546
TP53	7157	p53 deficiency reduced mhtt expression in brain and testis, and increased mhtt aggregation in striatum.	16978870
UBB	7314	Expression of mhtt in UBB+1 mice showed more aggregates than in wildtype.	20005957
PPID	5481	KO of cyclophilin-D showed no alterations in body weight, survival, motor performances, grip strength, and no significant effect on the neuropathological features of R6/2 mice	20558522
UBC	7316	R6/2 crossed with Ubc+/- showed no effect on rotarod, grip strength, weight loss; but improved rearing and center-rearing activities.	19602042