Journal of Genomic Medicine and Pharmacogenomics
JGMP, 1(1): 95-150
wwww.scitcentral.com

Original Research: Open Access

Interrogating the Epigenome to Unveil the Secrets of Neurodegeneration: Promising Epigenetic Therapies

Oscar Teijido[1*] and Ramón Cacabelos[2]

[1]*EuroEspes Biomedical Research Center, Institute of Medical Science and Genomic Medicine, Corunna, Spain;*

[2]*Chair of Genomic Medicine, Camilo José Cela University, Madrid, Spain.*

Received June 29, 2016; Accepted July 2, 2016; Published July 25, 2016

ABSTRACT

According to the WHO, cerebrovascular and neurodegenerative disorders affect one billion people around the world. Pathological phenotypes of neurodegeneration result from a combination of genomic, epigenomic, metabolic, and environmental factors, which hinder their treatment. Indeed, current FDA-approved conventional drugs used for treatment of neurodegenerative disorders provide very little beneficial effects, or, at best, reduce the pathological symptoms but do not detain disease progression. Furthermore, the unacceptable side effects of most of these treatments make them unsuitable for chronic treatments. One of the main reasons for this historical setback correlates with the poor knowledge about the molecular mechanisms of these pathologies, which results in the inappropriate drug target selection. Genetic components did not fully explain the mechanisms of those diseases. Furthermore, most treatments target symptomatic features of disease but they are not antipathogenic. During the last 15 years, the study of the role of the epigenetic machinery on gene regulation opens new and promising perspectives for a more accurate and effective treatment. Aberrant alterations in the epigenetic machinery result in dysregulation of gene expression at different levels in pathological conditions compared to healthy controls. The epigenetic approach allows the identification of key pathological targets in complex disorders that cannot be detected using genetic-based methods. Many of these epigenetic targets may be detected in early asymptomatic stages of the disease, which facilitates its treatment. Furthermore, the reversibility and potential restoring of epigenetic aberrations, unlike genetic mutations, sited epigenetic-based therapy as a promising tool to treat those complex disorders. This manuscript reviews the main epigenetic mechanisms involved in the most relevant neurodegenerative disorders nowadays, as well as the potential epigenetic-based drugs currently used in clinical trials for treatment of those disorders and future perspectives.

Keywords: Epigenomics, Epigenetic-based treatment, Neurodegeneration, Pharmacogenomics, Pharmacoepigenomics

INTRODUCTION

Neurodegenerative disorders are among the most serious health problems nowadays, especially in light of the increasing life expectancy, as the burden of most of these disorders significantly increases with advanced age. Indeed, according to the World Health Organization (WHO), the World Bank and the Harvard School of Public Health (the Global Burden of Disease Study) dementia and other neurodegenerative diseases will be the eighth cause of disease burden for developed regions in 2020 and the second leading cause ofdeath by 2050 [1,2], which constitutes a tremendous social and economical problem.

Neurodegeneration includes a number of earlier events, such as impaired metabolism, neuronal/glial dysfunction, impaired cell development, axonal transport defects, which finally lead to cell death. Normally, brain has plenty of resources to overcome and compensate these previous abnormal events, which remain asymptomatic. As a result, the first clinical manifestations of symptoms appear often when the rate of cell loss is sufficiently high to affect brain function and potential treatment is no longer feasible.

Corresponding author: Oscar Teijido Hermida, EuroEspes Biomedical Research Center, Institute of Medical Science and Genomic Medicine, 15165- Bergondo, Corunna, Spain, Tel: +34-981-780505; Fax: +34-981-780512; E-mail: epigenetica@euroespes. com

Citation: Teijido O & Cacabelos R. (2016) Interrogating the Epigenome to Unveil the Secrets of Neurodegeneration: Promising Epigenetic. Genomic Med Pharmacogenomics, 1(1): 95-150.

There is not yet a successful treatment for neurodegenerative disorders due to several reasons, including the following: (i) different types of neurodegenerative cognitive and motor impairment share the same pathological features [3]; (ii) pathological and clinical findings do not necessarily correlate [4,5]; (iii) a number of asymptomatic events, not recognized as neuropathological and normally not identified, may be essential for disease initiation and progression; (iv) mechanisms underlying the majority of neurodegenerative diseases are poorly understood and thus, drug targets are inappropriate since they do not fit into the real etiology of the disease; (v) most treatments are symptomatic, but not antipathogenic; (vi) the understanding of genome-drug interactions is very limited [6-8]. It is therefore important to find diagnostic strategies for detection of neurodegenerative diseases during early, preferably asymptomatic stages, when a pharmacological intervention is still possible.

Neurodegenerative diseases are complex multi-factorial disorders partially defined by genetic factors, but normally arouse due to a complex interplay of genetic and environmental factors, i.e., there is an epigenetic influence. Epigenomic regulation is a universal phenomenon of gene expression control during development, maturation, and aging in physiological conditions and is sited among the major regulatory elements that control metabolic pathways at the molecular level. At this regard, mechanisms such as memory and learning, age-related cognitive impairment, or behavior disorder, are mainly epigenetically regulated. Epigenetic mechanisms, influenced by internal (hormonal changes or response to medication, among others) or external (diet habits, physical exercise, stress, environment modifications, etc.) environmental changes in the organism, lead to changes in DNA methylation, chromatin structure, or non-coding RNA expression, that regulate gene expression at transcriptional or post-transcriptional levels without altering DNA sequence. Alterations in this meticulously controlled mechanism lead to an aberrant gene expression that becomes pathogenic [9-11].

Epigenetics is a relatively novel area of research that is currently attracting a high level of interest due to three main reasons: (i) the identification of epigenetic targets as key initiating events in complex disorders that could not be explained only by genetic factors; (ii) those epigenetic targets may be potential markers for an early diagnosis or prognosis of the disease; (iii) the reversibility and potential restoring of epigenetic aberrations, unlike genetic mutations, sited epigenetic-based therapy as a promising tool to treat those complex disorders. These important research findings led to an exponential increase on research publications related to epigenetic regulation and treatment of complex disorders, especially on cancer **(Figure 1),** achieving over 1500 research manuscripts and 350 review articles in 2015, and over 6500 publications (over 2000 review articles) during the last 15 years. Epigenetic research is also offering novel insights into the pathogenesis of those disorders [10], although research in this field is more recent than that for cancer and the number of released publications is still significantly lower (8-fold lower number of articles in 2015, approximately) (**Figure 1).**

This article reviews the main differential epigenetic modifications associated with aging, as comparison with those affecting the major pathogenic genes involved in neurodegenerative disorders, including Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, and Amyotrophic Lateral Sclerosis, as well as the potential epigenetic-based therapy strategies to treat those disorders and their potential success. The manuscript also includes aberrant epigenetic modifications in other gene targetsas potential early markers of neurodegenerative processes. Additionally, the implication of epigenetic modifications on pharmacogenomics-related genes associated with neurodegenerative disorders will be also discussed.

EPIGENETIC MECHANISMS

Epigenetic machinery results of great interest in science as it is sited among the major regulatory elements controlling metabolic pathways at the molecular level. In this regard, mechanisms such as memory and learning, elderly-associated cognitive impairment, or behavior disorder, are to some extent, epigenetically regulated [12-14]. Alterations on this epigenetic control, by endogenous (hormonal changes, synaptic alterations, response to medication) or exogenous factors (diet habits, physical exercise, stress, environment modifications) lead to abnormal gene expression that results to be pathogenic, although the genetic code remains intact.

Epigenetic mechanisms regulate gene expression at both, transcriptionally and post-transcriptionally levels. DNA methylation status, histone modifications, and chromatinstructure, control gene expression, whereas interference RNAs suppress gene expression post-transcriptionally [15] (**Figure 2, Table 1**).

DNA methylation

The level of methylation of a given gene promoter determines the level of expression of such gene. DNA methylation is a process by which methyl groups are incorporated into cytosine molecules by DNA methyltransferases (DNMTs). Methylation normally occurs at the CpG islands defined as regions where CG content is greater than 60%. Gene promoters with a rich content of CpG islands are most likely to be hypermethylated, since approximately 70% of CpG dinucleotides within the human genome are methylated. Methylation of gene promoter by DNMTs leads to a reduced gene expression (**Figure 2, Table 1**) by two different mechanisms: (i) by promoting the binding of transcription repressors; or (ii) by inhibiting the binding of transcription factors (**Figure 2)** [16-18].

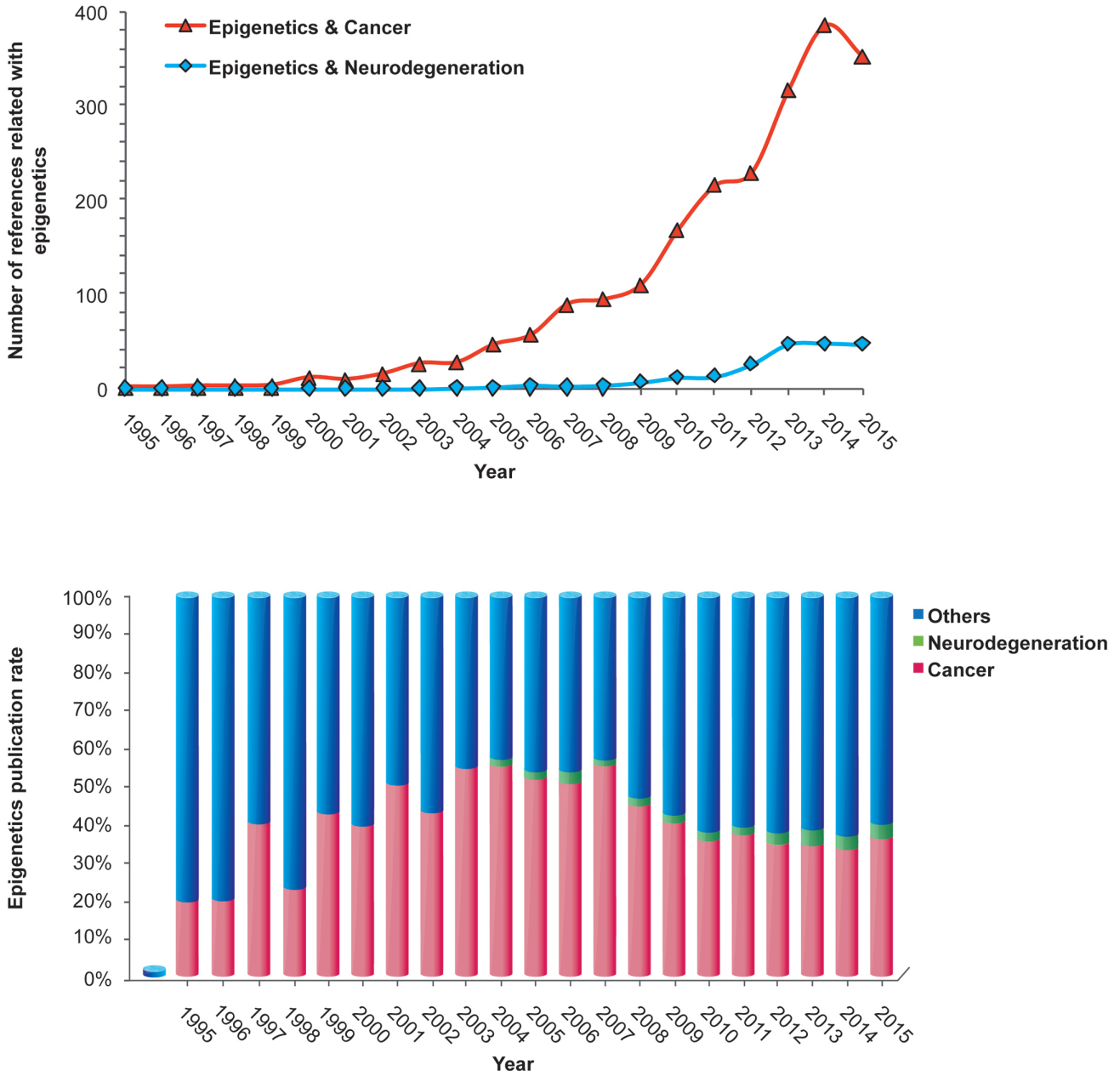

Figure 1. Position of epigenetics in current research.

However, DNA methylation at the gene sequence, but not at the promoter level, may activate transcription [19]. DNA methylation in mammalians is mediated by two DNMTs (DNMT3a and DNMT3b), which methylates new unmethylated cytosines, and by a DNMT1, which maintains the methylated status [20,21].

Gene promoter may also be hypomethylated by DNA demethylases (DNDMs) with the subsequent activation of transcription (**Table 1**). DNA demethylation can be produced by at least 3 enzyme families: (i) the ten-eleven translocation (TET) family, mediating the conversion of 5-methyl-cytosine (5mC) into 5-hydroxymethyl-cytosine (5hmC); (ii) the AID/APOBEC family, acting as mediators of 5mC or 5hmC deamination; and (iii) the BER (base excision repair) glycosylase family involved in DNA repair [22].

Histone modifications/chromatin remodeling

Chromatin stability and conformation is essential for regulation of gene expression, silencing transposable elements, and maintaining genome integrity. Chromatin conformation is controlled by ATP-dependent chromatin regulator complexes (ATP-CRCs) and post-translational histone modifications (HMs) (**Table 1).**

ATP-CRCs use ATP hydrolysis to move, destabilize, eject, or restructure nucleosomes, allowing the accessibility of transcription factors to DNA. The effects of ATP-CRCs on gene expression depend on the recruitment of coactivators or corepressors in the accessible promoters (**Figure 2, Table 1)** [22-24]. The main CRCs correspond to (i) the SWI/SNF (switching defective/sucrose nonfermenting) family; (ii) the ISWI (imitation SWI) family; (iii) the CHD (chromodomain, helicase, DNA binding) family; and (iv) the INO (inositol requiring 80 family) [24].

Post-translational modifications on histones modify the level of DNA package into a tight (close chromatin) or loose (open chromatin), altering the accessibility of genes to the transcription machinery (**Figure 2**). Histone modifications may also unravel the chromatin structure for the execution of a given function, such as transcription of a given gene, DNA duplication, DNA repair, or chromosome condensation (**Table 1)** [EM 22,25]. Out of the eight different histone modifications described, the most relevant include acetylation/deacetylation, methylation, phosphorylation, ubiquitylation, and sumoylation (**Table 1**).

Histone acetylation is associated with activation of transcription. The addition of acetyl groups by histone lysine-acetyltransferases (HATs or KATs) decreases the electrostatic DNA-histone interaction, leading to an open chromatin conformation [25,26]. The main HATs involve Gcn5-related *N*-acetyltransferases (GNATs), which includes GCN5, p300/cAmp-response element binding protein (CBP)-associated factor (PCAF), KAT6-8, CREB-binding protein/CBP (CREBBP/CBP), and EP300 [25-31]. As a counterpart, *histone deacetylation*, mediated by histone deacetylases (HDAC), increases the affinity of histones to DNA, leading to a more condensed chromatin structure and repressed transcription [12,18,23-30]. 18 HDACs, present in mammals, are organized into 4 classes (class I, II, III, IV): (i) Class I HDACs (HDAC1, 2, 3, and 8), nuclear proteins; HDAC1 and HDAC2 are often found in transcriptional corepressor complexes (*SIN3A, NuRD, CoREST)*, and HDAC3 is found in other complexes (SMRT/N-CoR); (ii) class II HDACs are subdivided into class IIa (HDAC4, 5, 7, and 9), and IIb (HDAC6 and 10), which are located in the nucleus-cytoplasm interface and in the cytoplasm, respectively; (iii) class III HDCAs belong to the sirtuin (SIRT) family, with nuclear (SIRT1, 2, 6, 7), mitocondrial (SIRT3, 4, 5), or cytoplasmic (SIRT1, 2) localization; and (iv) class IV HDAC (HDAC11), a nuclear protein [25-30]. In addition to regulation of transcription, histone acetylation has also been found to associate with (i) DNA repair, by upregulation of histone acetylatransferases and downregulation of histone deacetylases for H3K56 during DNA damage in budding yeast [25,32,33]; (ii) DNA replication, where histone acetyltransferase HBO1 is required [25,34,35]; and (iii) chromosome condensation [25,36,37].

Histone methylation and *demethylation* processes are mediated by histone methylases (HMTs) and demethylases (HDMTs), respectively. Those enzymes have a high specificity as they usually modify one single lysine per histonewhich may be translated into activation or repression of transcription [22,25,26,31,38,39]. Histone methylations H3K4, H3K36, and H3K79 are associated to activation of gene expression, whereas methylations at H3K9, H3K27, and H4K20, correspond to gene silencing. Histone methylation has also been associated with DNA repair [25,31,40,41].

The effects of *histone phosphorylation* on gene expression are poorly understood, although some studies agree on the transcription activation by H3 (S10) phosphorylation [25,26,31,42,43]. Phosphorylation of gamma-H2AX participates on DNA repair in mammalian cells [25,44], while phosphorylation at H3S10 and H3T3 plays a role on chromosome condensation [25,45,46].

Histone ubiquitylation is a large modification which mechanism remains unclear. It is though that keeps chromatin open by a “wedging” process, given its large size [25]. Ubiquitylation of human H2AK119, mediated by Bmi/Ring 1A protein is associated with transcriptional repression [25,47], whereas Ubiquitylation of H2BK20 by RNF20/RNF40 and UbcH6 promotes gene expression [25,48]. Histone ubiquitylation is also the most recently modification linked to DNA repair [25,47,49].

Histone sumoylation take place on all four core histones and leads to a repression of transcription in yeast [25,50].

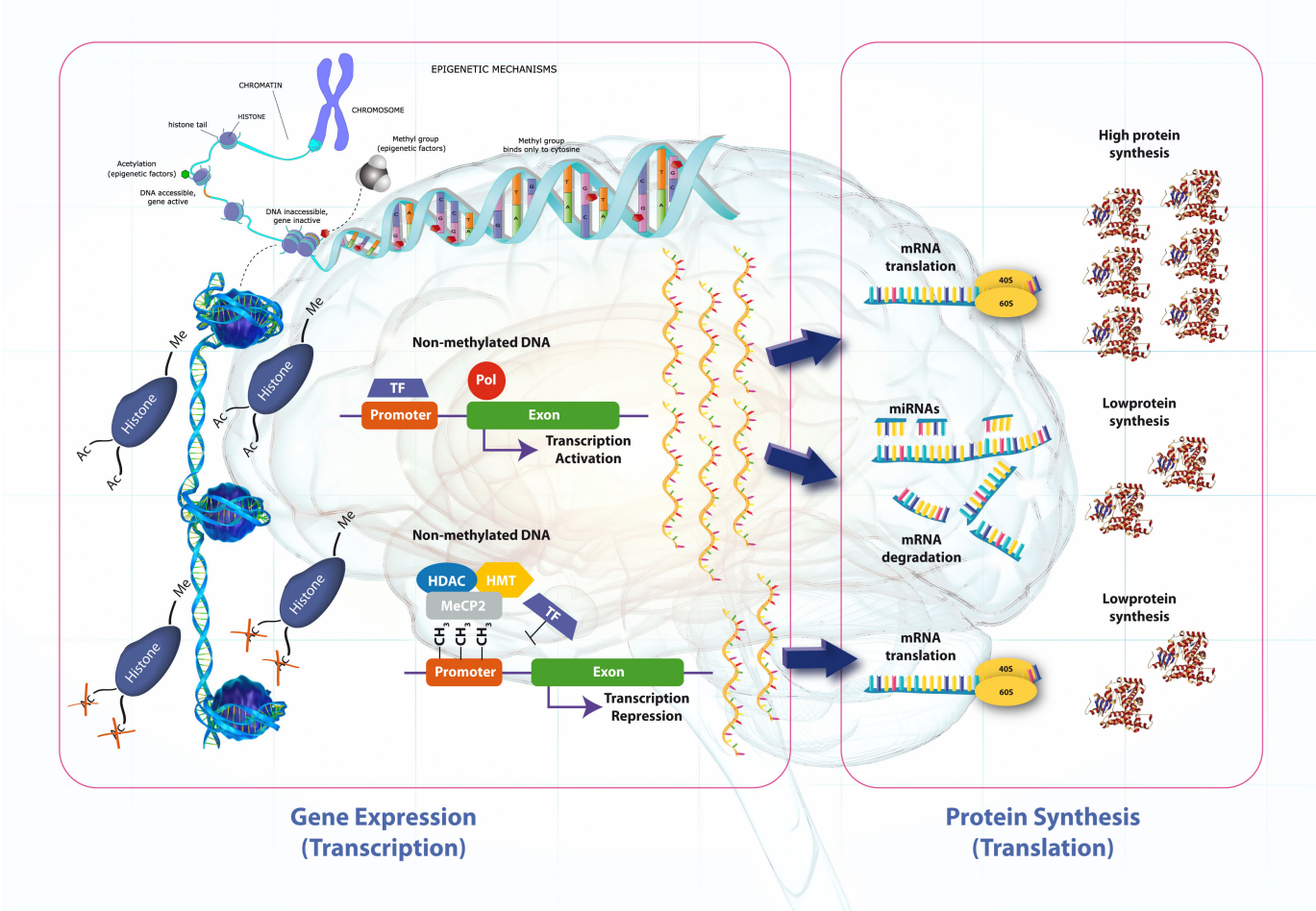

Figure 2. Epigenetic mechanisms controlling nervous system physiology. Gene expression is controlled by a variety of epigenetic mechanisms at transcriptional and post-transcriptional levels. Enzymatic-promoted histone post-translational modifications and other modulators regulate chromatin structure into a condensed ('closed chromatin') or loose conformation ('open chromatin'). 'Closed chromatin' conformation inhibits the interaction of gene promoters with the transcription machinery, which results in down-regulation of mRNA transcription. As counterpart 'open chromatin' allows the accessicility of transcription factors and promotes gene expression. Gene promoters containing hypomethylated CpG islands, promote binding of treanscription factors and gene expression, whereas hypermethylated gene promoters rather induce binding of transcription repressors, such as MeCP2, or activate enzymes such as HDACs or HMTs which promote chromating condensation and repressed mRNA transcription. Non-coding RNAs, such as lncRNAs or miRNAs, regulate gene expression post-tranlationally. Those ncRNAs bind target mRNAs resulting in enhanced or repressed gene expression. Ac: Acetyl group; Me: Methyl group; HDAC: histone deacetylase; HMT: histone methyltransferase; MeCP2: Methyl-CpG-binding protein 2; Pol: DNA polymerase; TF, Transcription factors; miRNAs: MicroRNAs.

Non-coding RNAs

Although transcription into mRNA is crucial for protein synthesis and cell function, only 5% of the eukaryotic genome is translated into protein, whereas 95% is transcribed into non-coding RNAs (ncRNAs) [51,52]. These ncRNAs can be classified into three groups: (i) Long non-coding RNAs (lncRNAs); (ii) housekeeping/structural RNAs, such asribosomal (rRNA), transfer (tRNA), and small nuclear RNAs (snRNA); and (iii) regulatory RNAs, including small interference RNAs (siRNAs), micro RNAs(miRNAs), and piwi RNAs(piRNAs) [53] (**Figure 2, Table 1**).

Lnc RNAs are long RNAs (>200 nucleotides), present in >8000 loci in the human genome and include large intergenic non-coding RNAs (lincRNA), natural antisense transcripts (NATs), non-coding RNA expansion repeats, promoter-associated RNAs (PARs), enhancer RNAs (eRNAs) [22,54,55]. LncRNAs regulate gene expression by interaction with proteins or RNA secondary structures, through genomic imprinting [56], by silencing genes in

somatic cells involved in brain development[57], or through interaction with membraneless subnuclear bodies that participate in nuclear organization (paraspeckles). Indeed, the lncRNA NEAT1, which localizes exclusively in paraspeckles, is upregulated in Huntington's disease [58] and in amyotrophic lateral sclerosis (ALS) [59]. NATs are lncRNAs arising from the opposite strand of genes regulating mRNA expression by competition for regulatory factors, or through physically hindering the progress of transcription. NATs have been associated with neurodegenerative, neurodevelopmental and psychiatric disorders (schizophrenia, bipolar disorder, autism, and fragile X mental retardation gene (*FMR1*) [60].

Regulatory RNAs are small RNAs (<200 nucleotides) which show mature forms of 20-30 nucleotides (nt) that associate with members of the Argonaute (AGO) superfamily of proteins, the central effectors of RNA interference (RNAi) pathways. miRNAs and siRNAs are post-transcriptional gene silencers, guiding AGO complexes to complementary mRNAs in the cytoplasm, inducing transcript degradation and blocking translation [54]. miRNAs repress translation with RISC (RNA-induced silencing complex) and induce mRNA degradation by binding to the 3' untranslated region (3'UTR). Other miRNAs may enhance mRNA translation and induce gene expression by binding to the promoter of the target gene. Specific small RNAs, piRNAs, associated with the PIWI clade of Argonautes, are essential for fertility, by silencing transposons in the germline [54].

Table 1. Epigenetic mechanisms and their implications in biological processes

Epigenetic Targets	Efectors	Activity	Biological implications
DNA methylation	DNMTs	DNA methylation	- Repressed transcription
	DNDMs	DNA demethylation	- Activated transcription
Chromatin structure	ATP-CRCs	Chromating remodeling to allow accesibility of TFs	- Activated / Repressed transcription
	Co-activators	Acumulation of transcription activators	- Activated transcription
	Co-repressors	Acumulation of transcription repressors	- Repressed transcription
Histone modifications	HATs	Histone acetylation	- Activated transcription - DNA repair - DNA replication - Chromosome condensation
	HDACs / SIRTs	Histone deacetylation	- Repressed transcription
	HMTs	Histone methylation	- Activated / Repressed transcription - DNA repair
	HDMTs	Histone demethylation	- Activated / Repressed transcription
	Protein kinases	Histone phosphorylation	- Activated transcription - DNA repair - Chromosome condensation
	Others	Histone ubiquitylation	- Activated transcription - DNA repair
		Histone sumoylation	- Repressed transcription
		ADP ribosylation	- Transcription regulation under DNA repair
Non-coding RNAs	Lnc RNAs	Protein and genomic DNA binding	- Translational regulation - Post-translational regulation
	miRNAs	Post-translational gene silencers	- Repressed translation

	siRNAs	Post-translational gene silencers	- Repressed translation
	piRNAs	Transposon silencers in the germ line	- Repressed translation

ATP-CRCs: ATP-dependent chromatin remodeling complexes; DNDMs: DNA demethylases; DNMTs: DNA methyltransferases; HATs: Histone lysine acetyltransferases; HDACs / SIRTs: Histone deacetylases / sirtuins; HDMTs: Histone lysine demethylases; HMTs: Histone lysine methyltransferases; Lnc RNAs: Long non-coding RNAs; miRNAs: Micro-RNAs; piRNAs: Piwi-interacting RNAs; siRNAs: Small interference RNAs; TFs: Transcription factors.

AGE-RELATED EPIGENETICS

Epigenomics sites in the interface between the individual and the internal and external environment, and therefore, the quality of genetic activity will depend on life habits and surrounding environment. Aberrant epigenetic processes are usually linked to unhealthy life style or during pathological conditions. However, normal physiological conditions, such as oxidative stress, also turn significantly modified during normal aging and related hallmarks [61]. These age-related physiological changes also relate to modifications in the epigenetic regulation patterns [62-64], increasing the risk for development of age-related neurodegenerative disorders.

DNA methylation

Methylation plays a crucial role during development. Many genes associated with cell death and survival, cell growth, organismal and tissue development, and cancer have been found hyper- and hypomethylated during age progression [18,65].

Several studies report a global loss of DNA methylation in age cells, although this occurs in a cell- and tissue-specific manner [66-73]. Some studies report a significant decrease of DNMT with age. Oliveira and colleagues [66] observed an age-related decrease of DNMT3a and DNMT3a2 in mice hippocampus which correlated with age-related cognitive decline in those mice. Indeed, experimental restoration of DNMTs decreased the severity of cognitive impairment [66]. Hernandez and colleges [67] found a DNMT1 decrease with aging in human fetal lung fibroblasts, which support other studies of global hypomethylation associated with cell senescence in blood [67-70]. Tohgi and colleages [71] found age-related hypomethylation of the amyloid β precursor protein, *APP*, gene, which is also an epigenetic trademark of Alzheimer's disease. In addition, 5-hydroxymethylcytosine (hmC) levels, corresponding to DNA demethylation, were found increased in mice hippocampus which correlates with risk for age-related neurodegenerative diseases [72-74].

In contrast, some loci have been found hypermethylated with age, including estrogen receptor, interferon γ, insulin-like growth factor II, promoters of tumor-suppressor genes such as lysyl oxidase (*LOX*), *p16INK4a*, runt-related transcription factor 3 (*RUNX3*), and TPA-inducible gene 1 (*TIG1*) [18].

A genome-wide methylation study analyzed 1,006 blood DNA samples of women aged 35 to 76 from the Sister Study, and found that 7,694 (28%) of the 27,578 CpGs assayed were associated with age, confirming the existence of at least 749 "high-confidence" age-related CpG (arCpGs) sites in normal blood [75]. These age-related changes were largely concordant in a broad variety of normal tissues. Interestingly, they found that the proportion of hypermethylated arCpGs (IM-arCpGs) was significantly higher (71-91%) than expected in a wide variety of tumor types. IM-arCpGs sites occurred almost exclusively at CpG islands and were disproportionately marked with the repressive H3K27me3 histone modification. These findings suggest that methylation at age-related sites increase the sensitivity of cells to become malignant, which may partially explain the increase in cancer incidence with age.

Another methylome-wide association study analyzed differential age-related methylation patterns in whole blood DNA from 718 individuals, within the range of 25-92 years old[76]. They sequenced the methyl-CpG-enriched genomic DNA fraction, averaging 67. 3 million reads per subject, to obtain methylation measurements for the ~27 million autosomal CpGs in the human genome, and adaptively combined methylation measures for neighboring, highly-correlated CpGs into 4,344,016 CpG blocks for association testing. Eleven age-associated differentially methylated regions (DMRs) passed Bonferroni correction. A total of 42 out of 70 selected DMRs showed hypomethylation and 28 showed hypermethylation with age. Hypermethylated DMRs were more likely to overlap with CpG islands and shores. Hypomethylated DMRs were more likely to be in regions associated with polycomb/regulatory proteins (EZH2) or histone modifications, such as acetylation (H3K9ac, H3K27ac) and methylation (H3K4m1, H3K4m2, H3K4m3). Among genes implicated by the top DMRs were protocadherins, homeobox genes, mitogen-activated protein kinases (MAPKs), ryanodine receptors, and genes with potential relevance for age-related disease.

Histone modifications

Post-translational histone modifications and chromatin structure also undergoes significant alterations with age. Histone H3 and H4 methylation declined progressively with age in rat brain [77-79], whereas histone phosphorylation increases with age [80-82].

Different reports show age-related histone acetylation decline *in vitro* [81,83], as well as decrease of H3K9ac and H4K12acin rat liverand brain, respectively [80,84], and monoacetylated H4 levels in rat cerebral cortex [85]. Indeed,

the histone acetylase CREBBP plays an important role on long-term memory formation in mice [86,87]. Acetylation of α-tubulin and histone H3K9 may activate cell function and gene expression to foster tissue repair. The direct activation of *P300/CBP*-associated factor (PCAF) by the histone acetylase activator pentadecylidenemalonate 1b (SPV-106) induces lysine acetylation in the woundedtissuearea. An impairment of PCAF and/or other GCN5 family acetylases may delay skin repair in physiopathological conditions [88]. Decrease in histone acetylation with age is in line with finding of increased expression of histone deacetylase HDAC2 [89]. Age-related decrease of histone acetylation leads to a close chromatin conformation and subsequent lack of accessibility for DNA repairing enzymes and other regulatory factors [85-90], which turns into an impaired synaptic plasticity and memory formation due to the transcriptional repression of crucial genes [91,92]. Contrary to HDAC2, class III histone acetylases, sirtuins (SIRT 1-7), are downregulated in aging, especially, SIRT1 [93-95]. Activation of sirtuins may extend lifespan, modulating calorie restriction mechanisms [96,97] and promoting a healthy aging, which delays the onset of neurodegenerative processes [98,99].

Non-coding RNAs

There is a correlation between changes in miRNA expression and aging: (i) miRNA lin-4 regulates lifespan in *C. elegans*; (ii) several miRNAs (miRNAs-34, -669c, -709, -93, -214) were found to be upregulated with age, while others (miRNAs-103, -107,-128, -130a, -155, -24, -221, -496, -1538, -17, -19b, -20a, -106a) appeared downregulated in peripheral tissues [100,101]; (iii) 70 miRNAs were found to be upregulated in the aging brain; 27 of these miRNAs may target genes of mitocondrial complexes III, IV, and F_0F_1-ATPase involved in oxidative phosphotylation and reduced expression in aging [102].

Table 2. Epigenetic modifications involved in neurodegenerative diseases

Disease	Pathogenic gene	Locus	Promoter length (bp)	3'UTR length (bp)	Defective protein	Methylation / Gene expression	Chromatin remodeling / Histone modifications	Non-coding RNAs
Alzheimer's disease (AD)	*APOE*	19q13. 2	996	…	APOE	Hypomethylated / Upregulated mRNA	-Reduced histone acetylation -Decreased SIRT1 in parietal cortex -Increased HDAC2 -Increased HDAC6 in cortex,hippocampus -H3K9 trimethylation in cortex,hippocampus H3S10 phosphorylation in hippocampus -Chromatin condensation in hippocampus H2AX phosphorylation in hippocampus	Dysregulated lncRNAs in AD Sox2OT, 1810014B01Rik, BC200, BACE1-AS, NAT-Rad18, 17A, GDNFOS Binding to *BACE, PSEN1,* and *APP* miR-9, miR-16, miR-29a/b/c, miR-17, miR-20a, miR-101, miR-106a/b, miR-107, miR-124, miR-125, miR-137, miR-147, miR-153, miR-195, miR-323-3p, miR-520c, miR-644, miR-655, let-7 family Associated to tau phosphorylation miR-9, miR-15 family, miR-16 family, miR-26a, miR-34, miR-146a, miR-181c Epigenetically regulated in AD miR-132/212, miR146a, miR-148a, miR-155, miR-184, miR-200, miR-200c/141
	APP	21q21. 3	1086	1176	APP	Upregulated mRNA		
	BACE1	11q23. 2-q23. 3	987	3994	beta secretase 1	Upregulated mRNA		
	BIN1	2q14	1076	642	BIN1	Upregulated mRNA		
	CD33	19q13. 3	1190	387	CD33	Upregulated mRNA		
	CLU	8p21-p12	1094	1399	CLU	Hypomethylated / Upregulated mRNA		
	CR1	1q32	966	2579	CR1	Hypomethylated / Upregulated mRNA		
	MAPT	17q21. 1	1094	…	TAU	Hypermethylated / Downregulated mRNA		
	PSEN1	14q24. 3	929	1198	PSEN1	Hypomethylated / Upregulated mRNA		
	SORL1	11q23. 2-q24. 2	996	…	SORL1	Downregulated mRNA		

								Specific circulating miRNAs miR-7 & miR-12 signatures (Blood) miR-9,miR-125b,miR-149a,miR-155 (CSF)
Parkinson's disease (PD)	*ATP8A2*	13q12. 13	1087	1380	AT8A2	Hypomethylated / Upregulated mRNA	-Reduced H3 acetylation mediated by α-synuclein -Up-regulation of Sirt2 mediated by α-synuclein -Reduced H3 methylation (H3K4me3,H3K27me3) -Toxin-mediated increase H4 acetylation by p300/CBP overexpression	Dysregulated lncRNAs in PD NaPINK,SoxOT,1810014B01Rik,BC200 Impaired in SCNA transgenic mice miR-7, miR-153 (down-regulated) miR-433 (up-regulated) miR-10a/b,miR-132,miR-212,miR-495 (dysregulated by α-synuclein) Stage or tissue specific miR-34b/c (early stages) miR133b (midbrain specific) Impaired through LRRK2 miR-184*, let-7
	APBA1	9q21. 12	994	1188	APBA1	Hypomethylated / Upregulated mRNA		
	CNTNAP2	7q35-q36	1038	…	CNTP2	Hypomethylated / Upregulated mRNA		
	CPLX2	5q35. 2	1050	4180	CPLX2	Hypomethylated / Upregulated mRNA		
	FAT1	4q35. 2	991	992	FAT1	Hypomethylated / Upregulated mRNA		
	FHIT	3p14. 2	951	382	FHIT	Hypomethylated / Upregulated mRNA		
	KCNH1	1q32. 2	920	…	KCNH1	Hypomethylated / Upregulated mRNA		
	MAGI2	7q21. 11	1041	2375	MAGI2	Hypomethylated / Upregulated mRNA		
	SMOC2	6q27	1089	1791	SMOC2	Hypomethylated / Upregulated mRNA		
	SNCA	4q22. 1	1097	1185	α-SYN	Hypomethylated / Upregulated mRNA		
	TNFA	6p21. 3	1028	907	TNFA	Hypomethylated / Upregulated mRNA		
	TUBA3E	2q21. 1	700	…	TBA3E	Hypomethylated / Upregulated mRNA		
Huntington's disease (HD)	*BDNF*	11p14. 1	1022	3213	BDNF	Hypermethylated / Downregulated mRNA	-Decreased histone acetylation -Increased histone methylation -Heterochromatin condensation	Dysregulated lncRNAs in PD HAR1F, HTTAS, DGCR5, NEAT1, TUG1 REST-associated dysregulation miR-9, miR-9*, miR-29b, miR-124a, miR-132 Targetting HTT miR-34b, miR-125b, miR-146a, miR-150, miR-214 (altered by mutant HTT)
	HTT	4p16. 3	1286	937	HD	Extensive methylation alteration		
	$A_{2A}R$	22q11. 23	904	993	adenosine receptor A2a	Hypermethylated / Downregulated mRNA		

								miR-196a (represses mutant HTT)
Amyotrophic Lateral Sclerosis (ALS)	*ALS2*	2q33. 1	1069	1394	ALS2	Hypermethylated / Downregulated mRNA	-Histone hypoacetylation -Histone methylation reduces *C9orf72* gene expression -Forced HDAC3 expression induces neurodegeneration -FUS binding to CBP induces hypoacetylation -Impaired ELP3 results in HAT impairment	Targeting TARDP miR-9,miR-132,miR-143,miR-558 Targeting FUS miR-9,miR-132,miR-134 Dysregulated in muscle cells miR-23a,miR-29b,miR-206,miR-455 Dysregulated in spinal cord miR-146*, miR-524-5p,miR-582-3p (binding 3'UTR of *NEFL*) miR24-2*, miR142-3p,miR-142-5p,miR-146b,miR-155,miR-1461 Blood-circulating miRNAs miR-149,miR-328,miR-338-3p,miR-451,miR-583,miR-638,miR-665,miR-1275 (leukocytes) miR-27^a,miR-32-3p,miR-146^a,miR-155 ($CD14^+CD16^-$ monocytes)
	ATXN2	12q24. 12	926	699	ATX2	Hypermethylated / Downregulated mRNA		
	C9orf72	9p21. 2	…	1746	CI072	Hypermethylated / Downregulated mRNA		
	DNMT1	19p13. 2	1061	381	DNMT1	Upregulated mRNA		
	DNMT3a	2p23	1020	1359	DNMT3a	Upregulated mRNA		
	OPTN	10p13	1020	1577	OPTN	Hypomethylated / Unaltered mRNA		
	SOD1	21q22. 11	988	497	SODC	Increase of DNMT1, DNMT3a, 5-mc		
	VEGF	6p12	996	…	VEGF	Hypomethylated / Upregulated mRNA		

2B1F: HLA class I histocompatibility antigen, DRB1-15 beta chain; *5-mc*: 5. methylcytosine; *A2AR*: adenosine A2a receptor; ALS2: Alsin; *ALS2*: Amyotrophic lateral sclerosis 2 (juvenile); *APBA1*:Amyloid beta (A4) precursor protein-binding, family A, member; *APOE*: apolipoprotein E; *APP*: amyloid beta (A4) precursor protein; *ATP8A2*: ATPase, aminophospholipid transporter, class I, type 8A, member 2; *ATXN2*: Ataxin 2; *BACE1*: beta secretase 1; *BDNF*: brain-derived neurotrophic factor; *BIN1*: bridging integrator 1; *C9orf72*: Chromosome 9 open reading frame 72; *CD33*: CD33 molecule; CI072: Protein C9orf72; *CLU*: clusterin; *CNTNAP2*: Contactin associated protein-like 2; *CPLX2*: *Complexin 2; CR1*: complement component 3b/4b receptor 1; *DNMT1a*: DNA (cytosine-5-)-methyltransferase 1 alpha; *DNMT3a*: DNA (cytosine-5-)-methyltransferase 3 alpha; FAT1: Protocadherin Fat 1; *FAT1*:FAT atypical cadherin 1; FHIT: Bis(5-adenosyl)-triphosphatase; *FHIT*: Fragile histidine triad; *HLA-DRB1*: Major histocompatibility complex, class II, DR beta 1; *HTT*: huntingtin; *KCNH1*:Potassium channel, voltage gated eag related subfamily H, member 1; *MAGI2*: Membrane associated guanylate kinase, WW and PDZ domain containing 2; *MAPT*: microtubule-associated protein tau; *OPTN*: Optineurin; *PSEN1*: presenilin 1; *SMOC2*:SPARC related modular calcium binding 2; *SNCA*: Synuclein, alpha (non A4 component of amyloid precursor); *SOD1*: Superoxide dismutase 1, soluble; SODC: Superoxide dismutase (Cu-Zn); *SORL1*: sortilin-related receptor; SPARC related modular calcium binding 2; *TNFA*: Tumor Necrosis Factor A; *TNFRSF1A*: Tumor necrosis factor receptor superfamily, member 1A; *TUBA3E*: Tubulin, alpha 3e; *VEGF:* vascular endothelial growth factor; α-SYN: Alpha-synuclein.

EPIGENOMICS IN NEURODEGENERATIVE DISORDERS: TARGETS AND POTENTIAL TREATMENTS

The knowledge of the human genome allows the detection of modifications in the sequence of certain genes responsible for a number of diseases, which provides a diagnosis, or even a prognosis of those diseases, and also the possibility of

developing more accurate and less expensive treatments. However, gene function is only partially defined by mutations or polymorphisms in complex multifactorial disorders. Epigenetic regulation involves all changes in gene function without altering DNA sequence, which may provide coverage for unknown mechanisms involving complex disorders that cannot be easily explained otherwise.

Aberrant epigenetic modifications in pathogenic genes involved in synaptic plasticity, cell development, immune response, and cell death, among others, lead to development of neurodegenerative and many other neurological diseases. **Table 2** displays the main pathogenic target genes with abnormal expression levels associated to the most common neurodegenerative diseases, including Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, and Amyotrophic Lateral Sclerosis. **Table 2** also includes the epigenetic mechanisms leading to these abnormal gene expressions.

Available treatments for neurodegenerative diseases provide limited beneficial effects and, in most cases, a payback of unacceptable side effects. Epigenetic mechanisms unveil many hidden aspects on the pathological processes related with memory and learning impairment, synaptic loss, and cell death, leading to neurodegeneration. Furthermore, epigenetic modifications involved in these complex disorders are reversible. Therefore, epigenetic-based treatments, targeting DNA methylation, chromatin remodeling, and non-coding RNAs, are a promising step for a successful treatment of neurodegenerative disorders (**Figure 3).** Some of those epigenetic-related treatments for neurodegenerative disorders (DNMT inhibitors, HDAC inhibitors, SIRT activators, HAT inhibitors, HMT inhibitors) are currently submitted to clinical trials (**Table 3).**

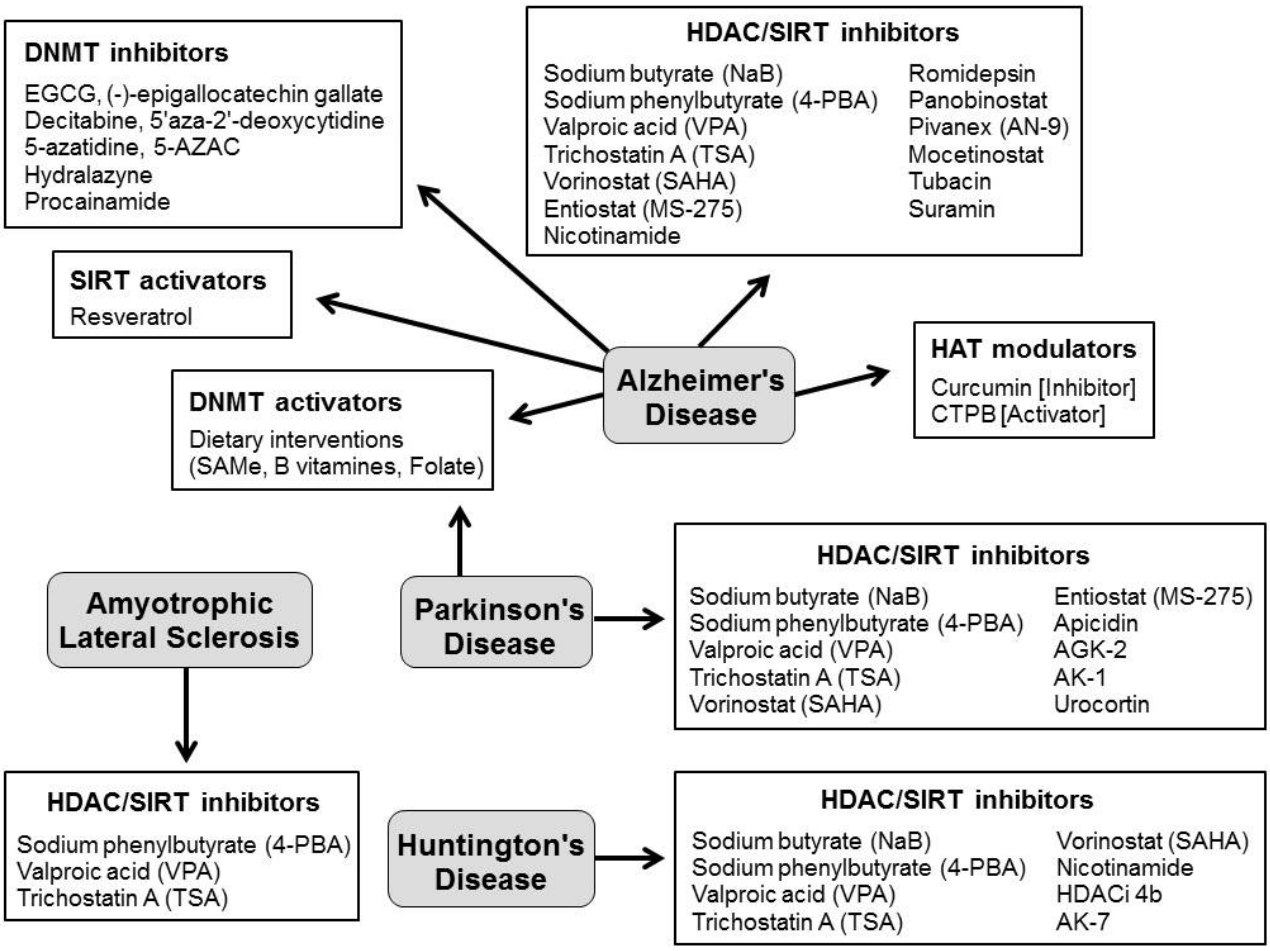

Figure 3. Epigenetic-based compounds under development for treatment of neurodegenerative diseases.

Table 3. Epigenetic-based treatments for neurodegenerative disorders submitted to clinical trials

Compound	Epigenetic Mechanism	Condition	Clinical Trials	Recruitment / Last Update
Name: **EGCG, (-)-epigallocatechin gallate, epigallocatechin 3-gallate, tea catechin, teavigo, catechin deriv. , 989-51-5** IUPAC name: **[(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate** Molecular formula: **$C_{22}H_{18}O_{11}$**Molecular Weight: **458. 37172 g/mol**	**Category:** DNMT inhibitors **Targets:** DNMT1	AD HD	NCT00951834 Phase II,III NCT01357681 Phase II	Completed / January 2016 Completed / June 2015
Name: **folate and other B vitamins** IUPAC name: **(2S)-2-[[4-[(2-amino-4-oxo-1H-pteridin-6-yl)methylamino]benzoyl]amino]pentanedioic acid** Molecular formula: **$C_{19}H_{19}N_7O_6$**Molecular Weight: **441. 39746 g/mol**	**Category:** DNA methylation activators **Targets:** THF, MTHF, SAMe	AD AD AD	NCT00056225 Phase III NCT01320527 Phase II NCT02457507 Phase IV	Completed / June 2009 Completed / March 2016 Completed/January 2016
Name: **sodium phenylbutyrate, buphenyl, 4-phenylbutiric acid, 4-phenylbutonoic acid, benzenebutanoic acid, benzenebutyric acid, butyric acid** IUPAC name: **sodium;4-phenylbutanoate** Molecular formula: **$C_{10}H_{11}NaO_2$**Molecular Weight: **186. 182909 g/mol**	**Category:** HDAC inhibitors **Targets:** class I HDAC (HDAC1,2,3,8); class IIa HDAC (HDAC4,5,7,9); class IIb HDAC (HDAC6,10)	PD HD ALS	NCT02046434 Phase I NCT00212316 Phase II NCT00107770 Phase I,II	Active, Nr / November 2015 Completed / August 2012 Completed / January 2010
Name: **valproic acid, 2-propylpentanoic acid, depakene, depakine, ergenyl, dipropylacetic acid, mylproin, convulex, myproic acid** IUPAC name: **2-propylpentanoic acid** Molecular formula: **$C_8H_{16}O_2$**Molecular Weight: **144. 21144 g/mol**	**Category:** HDAC inhibitors **Targets:** class I HDAC (HDAC1,2,3,8)	AD AD ALS	NCT01729598 Phase 0 NCT00071721 Phase III NCT00136110 Phase III	Completed / February 2015 Completed / September 2014 Completed / April 2007

Name: **nicotinamide, niacinamide, vitamin PP, aminicotin, nicotinic acid amide, amixicotyn, 3-pyridinecarboxamide, papulex, nicotylamide** IUPAC name: **pyridine-3-carboxamide** Molecular formula: **$C_6H_6N_2O$** Molecular Weight: **122. 12464 g/mol**	**Category:** HDAC inhibitors **Targets:** class III HDAC (SIRT1-7)	AD	NCT00580931 Phase I,II	Unknown / December 2013
Name: **resveratrol, *trans*-resveratrol, 501-36-0, 3,4',5-trihydroxystilbene, (E)-resveratrol, resvida** IUPAC name: **5-[(E)-2-(4-hydroxyphenyl)ethenyl]benzene-1,3-diol** Molecular formula: **$C_{14}H_{12}O_3$**Molecular Weight: **228. 24328 g/mol**	**Category:** HDAC activators **Targets:** class III HDAC (SIRT1)	AD AD AD AD AD HD	NCT01504854 Phase II NCT00678431 Phase III NCT01716637 Phase I NCT02502253 Phase I NCT01219244 Phase IV NCT02336633 Phase III	Completed / September 2014 Completed / November 2012 Completed / May 2016 Recruiting / March 2016 Recruiting / March 2016 Recruiting / June 2015
Name: **curcumin, diferuloylmethane, turmeric yellow, turmeric, gelbwurz, kacha haldi, curcuma, haldar, souchet** IUPAC name:**(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione** Molecular formula: **$C_{21}H_{20}O_6$**Molecular Weight: **368. 379 g/mol**	**Category:** HAT inhibitors **Targets:** HATs	AD AD AD AD AD AD	NCT01001637 Phase II NCT01811381 Phase II NCT00164749 Phase I,II NCT00099710 Phase II NCT01716637 Phase I NCT01383161 Phase II	Unknown / October 2009 Recruiting / February 2016 Completed / April 2008 Completed / December 2009Completed / May 2016 Active, Nr / December 2015
Name: **S-adenosylmethionine, ademetionine, AdoMet, donamet, methioninyladenylate, S-adenosyl-L-methionine, SAM-e** IUPAC name: **[(3S)-3-amino-3-carboxypropyl]-[[(2S,3S,4R,5R)-5-(6-aminopurin-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl]-methylsulfanium** Molecular formula: **$C_{15}H_{23}N_6O_5S^+$**Molecular Weight: **399. 445 g/mol**	**Category:** HMT inhibitors **Targets:** HMTs	AD PD	NCT01320527 Phase II NCT00070941 Phase II,III	Completed / March 2016 Completed / January 2013

AD: Alzheimer's disease; ALS: Amyotrophic Lateral Sclerosis; HAT: Histone Acetyl Transferases; HD: Huntington's Disease; HDACs: Histone Deacetylases; HMTs: Histone Methyl Transferases; MS: Multiple Sclerosis; MTHF: 5,10 methylenetetrahydrofolate; PD: Parkinson's Disease; SIRTs: Sirtuins; SAMe: S-adenosylmethionine; SMA: Spinal Muscular Atrophy; THF: Tetrahydrofolate.

Nr: not-recruiting.

Source: https://clinicaltrials. gov/

Despite the potential beneficial role of these epigenetic drugs, these compounds, as many other drugs, are subjected to pharmacogenetic regulation [8,22,23,103-110]. Pharmacogenomics accounts for 30-90% variability in pharmacokinetics and pharmacodynamics. The individual epigenomic profile provides information about the efficiency of drug transport and metabolism for this individual, which allows the development of a personalized medicine with a guarantee of success.

Genomic factors potentially involved in AD pharmacogenomics include at least 5 categories of gene clusters: (i) genes associated with disease pathogenesis; (ii) genes associated with the mechanism of action of drugs (enzymes, receptors, transmitters, messengers); (iii) genes associated with drug metabolism: (a) phase I reaction enzymes: alcohol dehydrogenases, aldehyde dehydrogenases, aldo-keto reductases, amine oxidases, carbonyl reductases, cytidine deaminase, cytochrome P450 enzyme family, cytochrome b5 reductase, dihydroprimidine dehydrogenase, esterases, epoxidases, flavin-containing monooxygenases, glutathione reductase/peroxidases, short-chain dehydrogenases/reductases, superoxide dismutases, and xanthine dehydrogenase; and (b): phase II reaction enzymes: amino acid transferases, dehydrogenases, esterases, glucuronosyl transferases, glutathione transferases, methyl transferases, N-acetyl transferases, thioltransferase, and sulfotransferases; (iv) genes associated with drug transporters (*ABCs, SLCs, SLCOs*); and (v) pleiotropic genes involved in multifaceted cascades and metabolic reactions. All these genes are under the influence of the epigenetic machinery conditioning their expression and the efficiency of their drug-metabolizing products (enzymes, transporters) [8,22,23,103-110].

ALZHEIMER'S DISEASE

According to the WHO, cerebrovascular and neurodegenerative disorders affect one billion people around the world. A number of these disorders are characterized by the onset of dementia. Disability caused by dementia increases dramatically with aging, by affecting 9 per 1000 of the population aged 65-74 years to 83 per 1000 in the population over 85 years old [41]. Alzheimer's disease (AD) is the major cause of dementia in Western countries, affecting 45-60% of the population, followed by vascular dementia and mixed dementia with prevalences of 30-40% and 10-20%, respectively [23,103]. AD is a polygenic and complex disorder characterized by the accumulation of β-amyloid (Aβ) in senile plaques, neurofibrillary tangles, dendritic desarborization, and neuronal loss, which leads to memory deterioration, dementia, and functional decline [23,103,104].

Over 600 different genes distributed across the human genome are potentially involved in AD pathogenesis, where environmental factors and epigenomic aberrations also participate [104-108]. The most relevant pathogenic genes involved in AD are displayed in **table 2**. The genetic defects identified in AD include, single-nucleotide polymorphisms (SNPs), mitochondrial DNA mutations, and Mendelian mutations. These last mutations affect genes directly involved in AD, including presenilins (*PSEN1, PSEN2*), Aβ-precursor protein (*APP*), apolipoprotein E (*APOE*), and the alpha-2-macroglobulin (*A2M*).

PSEN1 and *PSEN2* genes, encoding presenilins 1 and 2, are important determinants of the β-secretase activity responsible for proteolytic cleavage of the Aβ-precursor protein (APP). Polymorphisms/mutations in these genes are present in some cases of AD, leading to an impaired β-secretase activity and accumulation of Aβ [23,103,107,109]. The gene encoding apolipoprotein E (*APOE*), which is primarily associated with vascular risk and hypercholesterolemia, is the most prevalent risk factor for AD. The *APOE-ε4* allele, and especially the *APOE-ε4/ε4* genotype, are neurological signatures for AD [104,109-111]. It has been reported that *APOE-ε4* may influence AD by interacting with APP metabolism and Aβ accumulation, enhancing the hyperphosphorylation of the microtubule-associated tau protein, and starting a chain reaction involving oxidative processes, modification of the neuroimmunotrophic activity, altering lipid metabolism and transport, and membrane biosynthesis in sprouting and synaptic remodeling, and inducing apoptosis [104,109,110,112-114]. Interestingly, the allele *APOE-ε2*, which is associated with vascular risk, seems to be protective against dementia [104,109,110]. The *A2M* gene, encoding for the alpha-2-macroglobulin (a protease inhibitor), is also localized in amyloid plaques and interacts with Aβ and APOE. The polymorphism 2998G>A (rs669) in homozygosis increases the risk for the onset of AD by 4-fold compared with the general population [107,109,110].

Among all the attempts to treat AD, only five drugs, *tacrine, donepezil, rivastigmine, galantamine*, and *memantine*, have been approved by the FDA in the last three decades. It is well established that symptoms of AD, such as control of attention, memory and learning abilities, are related to a deficit of acetylcholine resulting in loss of cholinergic neurons [115,116]. The first strategy for AD treatment was to increase the acetylcholine levels at cholinergic synapses by using cholinesterase inhibitors. Unfortunately, the effects of these drugs are controversial and not clear benefits are reported [23,105,117]. The lack of success obtained by using cholinergic-promoting drugs, moved research into new pathological targets. At this regard, *memantine* was released as a high affinity antagonist of glutamatergic N-methyl-D-aspartate (NMDA) receptors, which would inhibit the prolonged influx of Ca^{2+} ions from extrasynaptic receptors and therefore would reduce neuronal excitotoxicity [118-122]. However, efficacy of memantine is also under debate [23,105,123,124]. New strategies were based on preventing Aβ deposition in senile plaques by β-secretase inhibitors or

immunotherapy, although the limited beneficial effects do not compensate the unacceptable side effects of these new drugs [105].

The poor cost-effectiveness of current treatment for AD requires the implementation of new strategies. At this regard, epigenetic-based drugs are potential candidates for the treatment of AD [18,22,23,105,125] (**Figure 3, Table 3).**

Epigenomic hallmarks of AD

Table 2 summarizes the prototypical epigenetic modifications found in AD. These modifications include aberrant patterns of DNA methylation, histone modifications, and non-coding RNAs, which alter the normal gene expression levels. Memory decline, which is a seminal symptom of AD, is regulated by gene expression, through DNA methylation patterns [13,23], and chromatin structure mediated by histone modifications. Thus, histone acetylation, which have consistently been shown to improve memory and learning, is dramatically reduced in most neurodegenerative and cognitive disorders [12,23,126]. Indeed, therapeutic approaches by using histone deacetylase inhibitors seem to be promising [12,23,126] (**Figure 3, Table 3).**

Aberrant DNA methylationand disruption of the miRNA regulatory circuits are also associated with accumulation of Aβ, which promotes the production of reactive oxygen species (ROS) and neuronal death in AD [14,23,127]. High metabolism and longevity of neurons result in the accumulation of DNA lesions. DNA repair machinery is usually inhibited by oxidative-induced post-translational modifications or degradation in AD, leading to cell death [23,128].

- DNA methylation of pathogenic genes. In agreement with the age-related risk for neurodegenation, there is a genome-wide decrease in DNA methylation reported in AD [18,23,31,129-133]. Accordingly, levels of 5mC and DNMT3a, associated with methylation, have been found significantly decreased in *APP/PS1* AD-transgenic mice and AD patients [133, 134]. Indeed, most of the relevant pathogenic genes associated with AD are hypomethylated (**Table 2).**

Promoter methylation status of *APP, PSEN1*, and *BACE1* has been widely studied due to the crucial role these genes play on Aβ generation. Abnormal processing of cell membrane APP is accompanied by high levels of 24-hydroxycholesterol, an endogenous ligand of Liver X receptor (LXR-α), in serum and CSF. LXR-α activation promote the overexpression of *PAR-4* gene which leads to an aberrant Aβ production, ROS generation, and cell death [135]. Although *APP* promoter was found to be hypomethylated in brain autopsy from individuals over 70 years as compared with younger cases [136,137], in SH-SY5Y cell lines [138], or in one single patient with AD [139], most of the studies suggest no correlation between *APP* methylation and AD progression [31,129-133,140]. Other relevant gene, the microtubule-associated protein tau (*MAPT*) has been found hypermethylated, which provides a link with sporadic neuropathology [18,23,141-143].

The β-secretase gene (*BACE1*) expression can be upregulated via demethylation in BV microglial cells [B Byun 2012] and has been also up-regulated in 3xTg-AD transgenic mice [144], which suggests the hypomethylation status of this gene in AD. The gene encoding presenilin (*PSEN1*) has been found to be hypomethylated resulting in mRNA overexpression in mostAD-related studies, including post-mortem [145], neuroblastoma cell lines [146], and mouse model [147,148]. All these studies suggest that this high *PSEN1* expression promotes Aβ production [149]. Interestingly, *PSEN1* and *BACE1* promoter methylation and expression are also linked to the folate/methionine metabolism. AD is associated with low levels of folate and S-adenosylmethionine (SAM)[150-153]. *In vitro* folate deprivation and *APP* transgenic mice models deprived of folate and vitamins B6 and B12 induced DNA hypomethylation promoting *PSEN1* and *BACE1* expression, which was restored when deficiency of folate and vitaminswassupplemented with SAM [146,147]. Folate deficiency also enhances hypomethylation-mediated expression of death receptors (*DR4*) and DNMTs in peripheral blood lymphocytes of AD patients and cultured neuroblast cells, which may promote DNA damage and cell death [154]. Vitamin B deficiency associated with AD also induces hypomethylation-mediated enhanced expression of the glycogen synthase kinase 3β gene (*GSK3β*), which is a major kinase that phosphorylates tau protein in brain, promoting the formation of neurofibrillary tangles (NFT) [155]. AD is also associated with increased plasma levels of homocystein (Hcy) [153], which inhibits methylation of protein phosphatase 2A (PP2A), which reduces its activity resulting in enhanced tau hyperphosphorylation and subsequent NFT formation [156].

The *APOE* gene is one of the hallmarks of AD. Epigenetic regulation of this gene is complex and not completely explored. Although *APOE* promoter is hypomethylated, *APOE-ε4* exhibits a fully methylated 3'-CpG island that is not extant in the *APOE-ε2* and *APOE-ε3* alelles [18,145]. The C>T transition in the 3'-CpG island, only associated with *APOE-ε4*, might prevent this site from being methylated, and therefore, this allele may change the epigenetic regulation of the *APOE* gene [18,145]. This modification may increase *APOE-ε4* expression which correlates with AD [157]. Indeed, differential methylation patterns associated with this C>T transition of *APOE-ε4*, might explain that most, but not all, *APOE-ε4* carriers develop AD [129].

Clusterin, or apolipoprotein J, gene (*CLU*), together with *APOE*, influence Aβ aggregation and clearance. *CLU* promoter is rich in CpG sites, but is hypomethylated, and

highly expressed in AD, which may be associated with brain atrophy, disease severity, and clinical progression [23,129,158]. Sortilin-related receptor (*SORL1*), neuronal *APOE* receptor that prevents accumulation of Aβ, is downregulated in AD [23,129,143,159]. *SORL1* gene is a good epigenetic marker in blood due to its differencial expression status among peripheral blood leukocytes, which may be a marker of aging in blood. Different promoter methylation patterns in *SORL1* gene between blood and brain comparing healthy elders and AD individuals is a marker of the disease [160].

Other relevant genes with anti-tumoral effects, but also apoptotic enhancers when overexpressed in AD, are the bridging factor 1, complement receptor 1 and the CD33 molecule (*BIN1, CR1*, and *CD33* genes, respectively) [161-165]. Other classical pro-apoptotic genes, such as caspases (*CASP1, 3, 7, 8, 9*), and genes involved in neuroinflamation, such as *TNF-α*, appear also up-regulated in AD neurons, contributing to Aβ production [166-169].

In despite of the global DNA hypomethylation linked to AD, several relevant genes involved in the disease are aberrantly hypermethylated. Neprilysin (NEP), one of the enzymes involved in Aβ degradation [170], is hypermethylated in AD. *NEP* gene expressionis therefore, down-regulated with aging and in AD, reducing Aβ clearance and promoting its accumulation [171]. The repetitive elements long interspersed element-1 (*LINE-1*) has been shown to be hypermethylated in AD patients. Interestingly, within the AD groups analyzed in this study, the group with enhanced *LINE-1* methylation showed the best cognitive performance [172]. *SORBS3* (*vinexin, SCAM-1* or *SH3D4*), encoding a cell adhesion molecule expressed in neurons and glia, is progressively hypermethylated with age. *S100A2*, a member of the S100 family of calcium binding proteins, which exhibits an age-dependent decrease in DNA methylation later in life, is also hypermethylated in AD [18,173].

Sánchez-Mut and colleages [174] studied 12 distinct mouse brain regions according to their CpG 5'-end gene methylation patterns, and the DNA methylomes obtained from the cerebral cortex were used to identify aberrant DNA methylation changes that occurred in two mouse models of AD. They translated these findings to patients with AD and identified DNA methylation-associated silencing of three target genes: thromboxane A2 receptor (*TBXA2R*), sorbin and SH3 domain containing 3 (*SORBS3*), and spectrin beta 4 (*SPTBN4*). These hypermethylation targets suggest that the cyclic AMP response element-binding protein (CREB) activation pathway and the axon initial segment might contribute to AD pathology.

- *Histone modifications/chromatin remodeling:* As occurring with aging, the global level of histone acetylation drastically declines, especially in temporal lobe of AD patients [175,176] and in animal models [12,177] (**Table 2).** This is associated with a low accessibility of genes for transcription factors and DNA repair machinery, and is translated into a decreased number of synapses memory impairment and poor learning abilities, among other symptoms. In despite of the global loss of histone acetylation, some targeted genes, such as *BACE1* in AD patients were found with an increased H3 acetylation at the promoter level, enhancing promoter accessibility and gene expression [144]. Decreased histone acetylation is in line with the finding of the elevated nuclear EP300 interacting inhibitor of differenciation 1 (EID1) in cortical neurons of AD patients. Overexpression of this HAT inhibitor (EP300 and CREBBP inhibitor) was suggested to be the cause of learning and memory impairments in those subjects [178]. CREBBP expression was also down-regulated in the transgenic mouse model 3xTg-AD [179]. Curiously, using transgenic mice overexpressing APPswe (Tg2576 mice), which promotes Aβ accumulation, the levels of acetylated H3 and H4 increased in prefrontal cortex and hippocampus, respectively [180].

Consistently with the histone acetylation decline, histone deacetylases play an important role in AD. Gräff and colleges [12] found that only HDAC2, but neither HDAC1 nor HDAC3, was up-regulated in prefrontal cortex and hippocampus of mice models of AD [12,92]. Along with the high HDAC2 expression, they found several hypoacetylation spots in targets associated with neuroplasticity, as well as down-regulated genes involved in learning, memory, and synaptic plasticity in the AD mice. The implication of HDAC2 in these AD hallmarks was confirmed when HDAC2 knock-down mice ameliorated the cognitive problems and aberrant synaptic plasticity. HDAC2, along with HDAC6 were markedly increased in post-mortem human brain samples from AD individuals, compared to controls [181]. Indeed, reduction of HDAC6 in a AD mouse model, mitigated learning and memory impairments [182]. HDAC6 is thought to interact with tau, affecting its phosphorylation and aggreagation [183,184]. HDAC6 also affects tau clearance through deacetylation of the heat-shock protein HSP90, which controls its refolding [184]. The role of HDACs in neurodegeneration does not solely affect to histone deacetylation, but they may target other proteins. For instance, HDAC6 targeting of α-tubulin [182,183,185] may be associated, at least in part, with mitochondrial impairment in AD.

A number of studies demonstrated that restoration of histone acetylation in AD animal models, induced sprouting of dendrites, increased number of synapses, and reinstated learning and memory impairments, even in the presence of brain atrophy and neuronal loss [12,91,92,177,179,186,187]. For this reason, the use of HDAC inhibitors may be potentialtherapeutic strategy to treat AD and other neurodegenerative disorders.

Nevertheless, not all HDACs have detrimental effects on learning and memory. Indeed, inhibition of class II HDACs

(HDAC4 and HDAC5) leads to those impairments as well [188,189]. A good example is represented by the negative effects of down-regulated SIRT1 in parietal cortex of AD patients [190]. SIRT1 has been linked to neurogenesis, DNA repair, apoptosis, cell response to stress, and other vital signaling pathways [191]. SIRT1 prevents from Aβ accumulation as it induces *ADAM10* expression, an α-secretase that cleaves APP without producing Aβ [192]. SIRT1 deacetylates tau protein, and thus its deficiency in AD, would enhance tau expression and NFT formation, which indicates that SIRT1 is beneficial for AD, [190,193,194]. Interestingly, SIRT1 is up-regulated in AD mice models, probably as a defense mechanism [191,193], although its expression is decreased in AD patients [190].

Increased histone phosphorylation is also associated to AD. H3 phosphorylation was found in frontal cortex of AD patients [195] and also H2A member X (H2AX) at S139 was also phosphorylated, as a sign of DNA damage in AD patients [196]. Ogawa and colleges [197] studied H3S10 phosphorylation, which is critical for chromosome compaction during cell division, due to the wrong cell cycle activation exhibited by AD neurons. They found that H3S10 phosphorylation was increased, although only in the cytoplasm of AD neurons, along with increased expression of MAPK kinase protein [198-200].

Other histone modifications have been associated to AD, although they are not yet extensively identified. Young pre-plaque AD transgenic mice exhibited significantly increased levels of methylated histones (H3K14, HeK9me2, and others) compared with wild-types [177,201,202]. There are also suspects about histone 1 ADP-ribosylation in AD, as poly[ADP]-ribose polymerase 1 (PARP-1) induces memory problems in mice [203]; and PARP-1 dysregulation is associated with amyloid pathology [204-206].

- *Non-coding RNAs.* A number of studies describe dysregulated non-coding RNAs affecting gene transcription and metabolic pathways in AD [18,23,55,129-133,207,208]. **Table 2** displays the most common lncRNAs and miRNAs affecting pathogenic genes, tau-phosphorylation pathways, or epigenetically regulated in AD.

The most common lncRNAs affecting pathogenic gene transcription in AD include Sox2OT, 1810014B01Rik (being those two also dysregulated in PD), BACE1-AS, NAT-Rad18, 17A, and GDNFOS [55,209-211]. BACE1-antisense (BACE1-AS) enhances stability and expression of*BACE1* mRNA, which leads to an increased protein production [55,209,210]. BACE1-AS is overexpressed in both, AD patients and AD mice models (Tg19959), in response of Aβ exposure, initiating a positive feedback in which Aβ activation of BACE1-AS enhances *BACE1* mRNA expression and Aβ production [55,209,210]. The lncRNA 17A is up-regulated in cerebral cortex of AD patients, which suggests its implication in promoting Aβ secretion as a result of inflammatory factors [211].

Among the miRNAs linked to AD-related pathogenic genes, the most common ones affect mRNA expression of *APP, BACE1,* and *PSEN* [14]. Several miRNAs have been identified in vitro to directly regulate the *APP* mRNA, including miRNA let-7, the miR-20a family (miRs-20a, -17 and -106b), miRs-106a and 520c, miR-101, miR-16, and miRs-147, -153, -323-3p, -644 and-655 [18,209,212,213,214,215,216]. Inhibition of miR-101 overexpression reduces *APP* and Aβ load in hippocampal neurons [213]. MiR-16 targets *APP* to potentially modulate AD pathogenesis, and miR-16 overexpression may lead to reduced *APP* expression [215]. Both miR-124 and polypyrimidine tract binding protein 1 (PTBP1) may alter splicing of *APP* exons 7 and 8 in neuronal cells [216]. Transcription of *BACE1* is affected by miRs-9, -29a/b-1, -29c, -107, -124, -298, -328 and -485-5p in AD. In transgenic HEK293-APP cells, transient miR-29a/b-1 overexpression decreases BACE1 levels and Aβ production [217]. miR-29c overexpression lowers BACE1 protein levels [218]. miRNAs repress *BACE1* through direct binding to sequences in its 3' untranslated region (3'UTR), whereas miR-485-5p represses *BACE1* via binding to its open reading frame in exon 6. miR-107 is downregulated at intermediate stages (Braak stage 3) of AD pathogenesis and might accelerate AD progression through control of *BACE1* [219]. miR-298, miR-328 and miR-195 inversely correlate with BACE1 protein, and downregulate Aβ levels by inhibiting the translation of *BACE1* [220,221]. miR-125 decreases whereas *BACE1* increases in animal models [221]. Overexpression of miR-485-5p reduces BACE1 protein levels by 30% while knockdown of miR-485-5p increases BACE1 protein levels [210]. The catalytic site of the gamma-secretases, presenilin (PSEN) regulates miR-146, which is a potent negative regulator of innate immune signaling. PSEN2 modulates cytokine responses by inhibiting miR-146a [222-225]. Therefore, defective preseniline may lead to up-regulation of miR-146a, which binds the interleukin-1 receptor-associated kinase-1 (IRAK) or the complement factor-H (CFH), decreasing their expression, contributing to neuroinflamation [226,227]. Other miRNA involved in AD-related inflammatory processes is miR-101, which binds cyclooxygenase-2 (COX-2). Down-regulation of miR-101 might enhance *COX-2* expression in AD, which promotes the inflammatory response [213].

Besides miRNAs interacting with AD-pathogenic genes, there are also other miRNAs involved in Aβ metabolism and accumulation. The RNA polymerase III-dependent ncRNA, NDM29, promotes APP amyloidogenesis and Aβ secretion [228]. miR-107 levels are reduced in AD temporal cortex [229,230]. Loss of miRs-9, 29a/b-1, -137 and -181c (currently down-regulated in AD frontal cortex) increases Aβ production and serine palmitoyltransferase (SPT), the first rate-limiting enzyme in ceramide biosynthesis [231]. miRNA-106b (down-regulated in anterior temporal cortex) can influence Aβ metabolism either through direct regulation

of APP itself, or via modulating APP trafficking, Aβ clearance and β- and γ-secretase activity through regulation of the ATP-binding cassette transporter A1 (*ABCA1*), which is elevated in the hippocampus, correlating with cognitive decline [232].

Several miRNAs also regulate tau metabolism. The miR-132/PTBP2 pathway influences *MAPT* exon 10 splicing in brain and may contribute to AD pathogenesis. It has been suggested that miR-124, -9, -132 and -137 might be involved in regulation of 4R/3R ratio in neuronal cells [233]. Down-regulation of miR-9 and miR-124 in AD might alter tau phosphorylation and therefore, NFT formation [233]. Tau phosphorylation is also regulated by miR-15a, which modulates the expression of the extracellular signal-regulated kinase 1 (ERK1). Down-regulated miR-15a in AD brains might play an important role in neuronal tau hyperphosphorylation [234]. Expression of miR-26a, a tau kinase GSK-3β repressor, is also aberrant in AD, and promotes Aβ production and NFT formation[235,236]. As mentioned above, tau deacetylation mediated by SIRT1, prevents its hyperphosphorylation, suggesting a protective role of SIRT1 in AD [190,193,194]. Therefore, SIRT1 down-regulation by miR-9, -34c and -181c, leads to an increasedtau acetylation and the accumulation of hyperphosphorylated tau in AD [237,238]. Other miRNAs, such as miR-128 and miR-212 are also involved in down-regulation of protective proteins and subsequent NFT formation [229,230,239].

Other miRNAs associated with neurophysiological roles are also dysregulated in AD. Synaptic plasticity is affected by miR-124, -125b, -132, -134, -138 and -219 in AD. Down-regulated miR-132 and up-regulated miR-125b have been found in different AD brain regions, probably affecting miniature excitatory postsynaptic currents (mEPSCs) [240].

Specific circulating miRNAs can be used as biomarkers to discriminate certain disease from healthy controls or among different disease forms. Those specific biomarkers may alsobe informative for the stage and progression of the disease, and they maybe used for early diagnosis [241]. A unique circulating 7-miRNA signature in plasma (hsa-let-7d-5p, hsa-let-7g-5p, hsa-miR-15b-5p, hsa-miR-142-3p, hsa-miR-191-5p, hsa-miR-301a-3p and hsa-miR-545-3p) can distinguish AD patients from normal controls with >95% accuracy [241]. Furthermore, 12-miRNA signature provided differentiated expression patterns in AD compared to controls with an accuracy of 93%, a specificity of 95% and a sensitivity of 92%. Furthermore, this miRNA signature was able to detect AD from other neurological disorders, such as MCI, multiple sclerosis, Parkinson disease, major depression, bipolar disorder and schizophrenia, with 74-78% accuracies [242]. Increased levels of miRNA-9, miRNA-125b, miRNA-146a, and miRNA-155 were also found in the CSF and brain tissue-derived extracellular fluid from patients with AD, suggesting that these miRNAs might be involved in the modulation or proliferation of miRNA-triggered pathogenic signaling in AD brains [243].

Epigenomic-based potential treatments for AD

Several potential treatments targeting epigenetic mechanisms in AD are currently submitted to clinical trials, according to data of the US Institutes of Health [244] (**Table 3**). These treatments include DNMT activators and inhibitors, HDAC inhibitors, SIRT activators, HAT inhibitors, and HMT inhibitors.

- DNA methylation activators. The global DNA hypomethylation associated with AD, indicates that strategies directed to increase DNA methylationmay be a promising target for AD therapy [22,23,31,110,133,146-149,245]. DNA methylation occurs within folate/methionine/homocystein metabolism, using folate, methionine, choline, and betaine enzyme's cofactors as micronutrients [18,143]. Vitamin B_6-dependent serine-hydroxymethyltransferase catalizes the conversion of tetrahydrofolate (THF) into 5,10-methylenetetrahydrofolate (MTHF), followed by the production of 5-MTHF catalized by vitamin B_2-dependent MTHF reductase (MTHFR). 5-MTHF is the methyl donor for remethylation of Hcy by cobalamin-dependent methionine synthase, yielding methionine, which is converted to SAMe by methionine adenosyltransferase. SAMe is the methyl donor for DNA, proteins, neurotransmitters, hormones, and phospholipids. Donation of methyl group promotes the synthesis of S-adenosylhomocysteine (SAH) which is hydrolyzed to homocysteine (Hcy) and adenosine by SAH hydrolase.

It is widely reported that AD is associated with high levels of Hcy and SAH and low levels of B vitamin, folate, and SAMe [18,150-153,156], which induces demethylation and overexpression of *PSEN1* and *BACE1*. Restored gene expression was found after folate and B vitamins supplementation in AD mice models [146,147,149,246], as well as enhanced cognitive functioning and slower progression of dementia [247-249]. All these results suggest vitamine B, folic acid, and SAMe may be diet supplements with brain protective properties for AD treatment [250,251]. However, some studies show no positive effect of folate and vitamine B_{12} supplementation, or they might even exacerbate neuropathology in patients with low vitamin B_{12} levels [252-254]. Nevertheless, some clinical trials using folate for treatment of mental decline-related disorders are in phase III and phase IV, which suggests that this treatment may accomplish with the safety, efficacy, and optimal use requirements [244] (**Table 3).**

- DNMT inhibitors. Some crucial pathogenic genes, such as *NEP, LINE-1, SORB3*, and genes associated with the *CREB* activations pathway are hypermethylated leading to development of AD. In this case, therapies based on reducing DNA methylation, may be the most appropriate [20-23,110,255-258]. DNMT inhibitors include:nucleoside

analogs, small molecules, natural products, antisense oligonucleotide inhibitors (MG98), and miRNAs.

Among nucleoside analogs, 5-aza-2'-deoxycytidine (Decitabine) and 5-azacytidine (Azacitidine) are FDA approved drugs for treatment of myelodisplastic syndrome and several types of cancer and multiple clinical trials have been performed with this two compounds for treatment of myelodisplastic syndrome, thalasemia, and diverse types of cancer (bladder, prostate, colon, lung, melanoma, leukemias) [20]. The small molecules hydralazine and procainamide are also FDA approved for hypertension and cardiac arrhythmia, respectively. These two compounds are partial competitive inhibitors of DNMT1, by interfering with the DNMT1 CpG-rich binding site. Natural products, such as curcumin derivatives RG-108 and SGI-1027, are non-nucleoside selective DNMT1 inhibitors [21]. Other natural products may be used as DNMT inhibitors, including psammaplins (inhibit both DNMT1 and HDACs [20]), tea polyphenols (epigallocatechin-3-gallate), catechins (catechin, epicatechin), and bioflavonoids (quercetin, genistein, fisetin).

Among all these DNMT inhibitors, only the bioactive compound from green tea, epigallocatechin-3-gallate (EGCG) is currently submitted to clinical trials for treatment of neurodegenerative disorders (Alzheimer's disease, Huntington disease, and Multiple Sclerosis) (**Table 3**). Several reasons site EGCG as a promising treatment for neurodegenerative diseases: (i) EGCG binds to many misfolded proteins, inhibiting their fibrillization [259]; (ii) EGCG restores mitochondrial respiratory rates and mitochondrial membrane potential by increasing ATP production and reducing ROS production in isolated mitochondria from hippocampus, cortex, and striatum [260]; (iii) ECGC activates α7 nicotinic acetylcholine receptor (α7 nAChR) signaling cascade along with its downstream pathway signaling molecules which restores *Bcl2* expression in Aβ-treated neurons [261].

- *HDAC inhibitors*. There is a wide variety of HDAC inhibitors (HDACi) under development to restore the global deacetylation linked to AD. Most of the HDACi have been shown beneficial effects on cognition and memory processes in animal models of AD [20,23,29,31,91,133,245]. The most effective HDACi tested in those models are (i) the short-chain fatty acids, class I HDACi[valproic acid (VPA)] and class I and II HDACis[sodium butyrate (NaB) and sodium phenylbutyrate (NaPBA, 4-PBA)]; (ii) the hydroxamic acids, class I and II HDACis [suberoylanilide hydroxamic acid (SAHA, vorinostat) and trichostatin (TSA)], (iii) the class III HDACi or SIRT(1-7) inhibitor nicotinamide/niacinamide. However, available data from the US Institutes of Health [244] shows that, among the wide variety of HDAC inhibitors used in research studies for AD treatment, only 4-PBA, VPA, and nicotinamide are submitted to clinical trials (**Table 3**). One of the first HDACi specifically tested for AD treatment was the Forum Pharmaceutical compound (FRM-0334), which addresses the issue of crossing the blood-brain barrier [262].

NaB, the sodium salt of 4-hydroxybutyric acid, increases the peripheral levels of hypothalamic-pituitary-adrenal axis hormones and glucose. NaB-mediated histone acetylation promotes LTP at Schaffer-collateral synapses in the CA1 area of hippocampus. NaB administration during four weeks reinstated learning and memory processes in transgenic AD mice, even at a very advanced stage of pathology [91]. Furthermore, animals treated with NaB prior to contextual fear conditioning, enhances formation of long-term memory [263,264]. Prolonged NaB treatment in APP/PS1-21 mice, increases histone acetylation in hippocampus, which promotes the expression of genes associated with associative learning and memory [265,266]. However, high doses of NaB induce stress-like response in the epigenetic machinery associated with learning and emotional behavior [267].

The HDACi NaPBA (4-PBA) increases histone acetylation promoting the expression of genes related to synaptic plasticity, such as the ionotropic glutamate receptor 1(*GluR1*), postsynaptic density protein 95 (*PSD95*), microtubule-associated protein 2 (*MAP2*), N-methyl-D-aspartate receptor subunit NR2B (*NMDA-NR2B*), and the synaptic associated protein scaffold (*SAP102*). In addition, 4-PBA reduces tau phosphorylation by promoting the active form of the GSK-3β, reduces Aβ accumulation, and restores memory function in transgenic AD mice [29,268]. Other studies showed the restored memory and learning functions in Tg2576 AD transgenic mice by decreasing tau phosphorylation, but without altering Aβ levels [269].

VPA is a fatty acid with anticonvulsant properties, originally used as treatment for epilepsy and as a mood-stabilizing agent and it has been tested in several clinical trials, for diverse clinical conditions [20]. VPA may alter the properties of the voltage-gated sodium channels or increase the γ-aminobutyric acid levels in the brain. VPA, along with NaB and SAHA, have been shown to alleviate memory deficits by increasing histone H4 acetylation [266]. Studies conducted by Su and colleges [270] demonstrated that VPA was able to reduce Aβ production in HEK cells transfected with a plasmid carrying the APP751 mutation and also in the APPV717F transgenic AD mice. Qing and colleges [271] found that APP23 transgenic mice treated with VPA, showed alleviated behavioral deficits by inhibiting GSK-3β-mediated γ-secretase cleavage of *APP*, resulting in a decreased Aβ production. Despite the beneficial effects of VPA in animal models, some clinical trialsperformed in humans revealed unsuccessful results by worsening the agitation and aggression of the disease in AD patients [272]. In other cases, the recommended doses did not show any beneficial effects and higher doses lead to unacceptable adverse effects [273,274]. In those cases, information about the pharmacogenetic profile of those patients would be

essential to anticipate the tolerance levels of this treatment for each individual.

TSA is an antifungal, antibacterial, protein synthesis inhibitor and a class I HDACi. TSA increases expression of selective genes, such as the brain-derived neurotrophic factor (*BDNF*), possibly through histone H4 acetylation, involving memory consolidation [275-277], and also restores memory function in APP/PS1-AD transgenic mice [12,177]. TSA enhances induction of LTP in hippocampus [263].

Vorinostat (SAHA) is the most developed HDACi, which binds to the catalytic domain of HDACs. SAHA was approved by FDA in 2006 for treatment of advanced cutaneous T-cell lymphoma. Although several tests have been shown beneficial effects of SAHA in animal models of neurodegeneration, there are not clinical trials available for this compound for this type of diseases. SAHA treatment enhances basal post-synaptic excitatory but not inhibitory synaptic function. Selective HDAC6 inhibitor vorinostat has been found to restore memory function in APPswe/PS1dE9-ADtransgenic mice [266], and also in non-AD models of learning deficits [92]. AD mice treated with SAHA achieved increased H4K12 acetylation and restored the expression of genes associated with learning [278]. SAHA, as well as VPA, has been shown to increase clusterin (*CLU*) expression *in vitro* [279].

Nicotinamide is a competitive inhibitor of class III NAD^+-dependent HDACs (SIRT inhibitor) which selectively reduces phosphorylated tau (at Thr231 level), associated with tubulin depolymerization, resulting in the increase of tubulin stability [280]. Furthermore, nicotinamide has been found to restore cognitive deficits in 3xTg-AD mice [280]. Similarly, the HDAC6 inhibitor and tubulin acetylator inducer, tubacin, also attenuates tau phosphorylation *in vitro* [181,281].

Other HDACis have been successfully tested for AD treatment in animal models, although no so many studies have been yet performed. The selective HDAC1 inhibitor entiostat (MS-275) reduced neuroinflammation and amyloid plaque deposition with the subsequent improvement of behavioral function in APPPS1-21 mice [282]. Other studies with the mercaptoacetamide-based class II HDACi (W2) showed improved memory and decreased Aβ and phosphorylated tau levels in 3xTg-AD mice [283].

- *SIRT activators.* It has been demonstrated that SIRTs, especially SIRT1, results beneficial for AD patients[190-194]. At this regard, SIRT activators (SIRTa) may also be a ingenious strategy to treat AD. Resveratrol is the most widely SIRTa in AD animal models and it is currently submitted to several clinical trials for treatment of AD, some of them reaching phase III and IV [244] (**Table 3).** Resveratrol, a natural compound found in red grapes, is a neuroprotector which inhibits Aβ aggregation, by scavenging oxidants and exerting anti-inflammatory activities [284]. Reveratrol improves long-term memory formation by promoting SIRT1 activity and inhibiting Aβ-induced apoptosis [285]. Interestingly, these effects are blocked in SIRT-1 mutant mice. Resveratrol might reduce miR-124 and miR-134 expressions, which may result in the up-regulation of cAMP response element-binding protein (CBP) levels and promote BDNF synthesis [64]. All these effects result in increased cell viability through the stabilization of Ca^{2+} homeostasis, reduction of $A\beta_{25-35}$ neurotoxicity, and Rho-associated kinase 1 down-regulation [64].

- *HAT modulators.* The strategy of increasing histone acetylation by using HDACi as treatment for AD may be also accomplished with HAT activators (HATas) targeting CBP, p300, and p300/PCAF [286]. However, the poor solubility and membrane permeability of these compounds make them unsuitable for this purpose [22,23,110]. The only known p300-especific activator which is able to cross the blood brain barrier after intraperitoneal injection is the N-(4-chloro-3-trifluoromethyl-phenyl)-2-ethoxy-6-pentadecyl benzamide (CTPB) [21], although it is not in clinical trials [20].

Another strategy consists in the usage of HAT inhibitors (HATis) [287], which include curcumin and curcumin derivatives. Curcumin is a phytochemical compound extracted from the rhizome of *Curcuma longa*, L. , used for dyspepsia, stress, and mood disorders [288]. Curcumin was the first p300/CBP-specific cell permeable HATi with no effect on PCAF, HDAC, and DNMT [20]. This compound induces heme oxygenase 1 and Phase II detoxification enzymes in neurons, protecting them from oxidation. Curcumin also normalized NADH dehydrogenase, succinic dehydrogenase, and cytochrome oxidase activaties in brains of rats treated with aluminum [289]. Curcumin has been found to prevent behavioral impairments, neuroinflammation, tau hyperphosphorylation, and Aβ-mediated cell signaling disturbances [290]. Combination of curcumin with other derivatives, such as demethoxycurcumin and bisedethoxycurcumin, constitute the turmeric [291], which has been reported to improve the behavioral symptoms of AD [292]. Curcumin is currently submitted to several clinical trials for AD treatment [244] (**Table 3).**

- *Histone methyltransferase inhibitors.* Histone methyltransferase inhibitors (HMTis) induce histone acetylation in order to regulate gene expression or for DNA repair. SAMe was the first HMTi used for treatment of cancer and it is currently in clinical trials for treatment of AD [244] (**Table 3).** This compound can also be used as strategy to restore DNA methylation, as it is the main methyl donor (along with L-methylfolate) in the body. SAMe improves memory and decreases *PSEN1* expression (by promoting promoter methylation), meliorating AD symptoms [250,251,293].

- *Non-coding RNAs.* Non-coding RNAs regulate expression of genes involved in brain development and function. Dysregulation of those ncRNAs are associated with a variety of diseases, but controlling the expression of those ncRNAs may also serve as potential treatments. Indeed, RNAi-based treatments represent a novel and promising therapeutic strategy for AD and other complex disorders [18,23]. Currently exploring strategies to manipulate miRNA levels for AD treatment include analogs of miRNA precursors and anti-miRNAs.

Overexpression of miR-124 and miR-195 may reduce Aβ levels by targeting *BACE1* [221,294]. Alternatively, targeting of miR-323-3p, might ameliorate inflammatory responses associated with AD [295]. Phosphatase and tensin homolog (PTEN) suppression by mmiR-26a may enhance synaptic plasticity and regulate neuronal morphogenesis [296]. P2X7 receptor (P2X7R), and ATP-gated cation channel, promotes secretion of inflammatory factors from activated microglia. Therefore, RNAi therapy targeting *P2X7R*, reduces microglia activation and increases microglial phagocytosis of $A\beta_{1\text{-}42}$ [297]. Other ncRNA-based therapies involving regulation of expression or AD-related pathogenic genes, as well as genes encoding epigenetic regulation, might be a promising and specific therapeutic approach for AD treatment [298].

- ***Other epigenetic treatments.*** Small molecules inhibitors to chromatin-associated proteins and bromodomain/chromodomain inhibitors, which regulate chromatin structure and inhibit targeting gene transcription, respectively, or dietary regimens based on B vitamins and folate, in order to increase SAMe levels in the organism, are promising therapeutic approaches submitted to preclinical studies [23,244,250,251,299,300].

PARKINSON'S DISEASE

Parkinson's disease (PD) is the second in the ranking of the most common neurodegenerative disorders, after AD, affecting 2% of the population over 60 years of age in the world [301], and involves genetic, environmental, cerebrovasular, and epigenetic factors [302-306]. PD is a complex neurodegenerative disease characterized by progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta and the formation of intracytoplasmatic inclusions made of accumulations of α-synuclein known as Lewy bodies [307,308].

Recent studies provide explanations about the implications of α-synuclein in PD at the molecular level. It has been recently established the interaction of α-synuclein with mitochondrial membranes [309-313] and its implication in mitochondrial impairment leading to cell death [314,315]. α-synuclein affects Complex I [311] and Complex IV [316] of the mitochondrial respiratory chain, leading to a bioenergetic dysregulation, resulting in ROS production and cell death. Experiments *in vitro* and in yeast mitochondria corroborate these results finding that α-synuclein was able to translocate from cytosol to the mitochondrial inner membrane through the voltage-dependent anion channel (VDAC) and target the mitochondrial respiratory chain [317].

Besides *SCNA* gene, encoding α-synuclein, over 100 other pathogeneic genes may be involved in PD, from which 15 PD loci (*PARK1-15*) and other loci, might be a direct cause of the disease [318]. Mutations in synuclein-alpha (*SNCA*), parkin 2 (*PARK2*), PTEN-induced putative kinase 1 (*PINK1*), parkin 7 (*PARK7, DJ1*), and leucine-rich repeat kinase 2 (*LRRK2*) genes are associated with the genetic etiology of PD, whereas other loci, such as, microtubule-associated protein tau (*MAPT*), *spatacsin*, polymerase (DNA) gamma, catalytic subunit (*POLG1*), glucosylceramidase beta (*GBA*), and ataxin (*SCA1, SCA2*), might be susceptibility genes associated with sporadic PD, normally associated with toxic or environmental exposure [133,304].

The loss of dopaminergic neurons during development of PD results in concomitant loss of dopamine in the affected areas (especially the nigrostriatal system) which is manifested with classic motor symptoms (resting tremor, rigidity, bradykinesia, postural instability, and slowness of movements which ends up in muscle atrophy), and other non-motor symptoms (depression, obsessive compulsive behavior, sleep disturbance, and cognitive impairment, among others). Current pharmacological treatments for PD are based on restoring the dopamine levels using different strategies: (i) increase dopamine availability by treatments with dopamine precursors, such as L-DOPA (levodopa), or dopaminergic agonists (cabergoline, pergolide, pramipexole, ropinirole, rotigotine); (ii) inhibition of dopamine catabolism or degradation, by using monoamine-oxidase B (MOB) inhibitors, such as rasagiline, or catecol-o-methylatransferase (COMPT) inhibitors, such as entacapone and tolcapone. Unfortunately, all these pharmacological treatments only provide relief for those symptoms but they do not stop or delay the progression of the disease. Furthermore, the exaggerate levels of dopamine generated through these treatments make it unease to wear off resulting in unacceptable side effects [303]. Interestingly, the hyperkinesia related to chronic L-DOPA therapy in animal models was found to be linked to histone H4 deacetylation in the striatum [319], thus suggesting the importance of regulation of epigenetic machinery and potential epigenetic therapies to treat PD.

Epigenomic hallmarks of PD

As for AD, and most degenerative disorders, global DNA hypomethylation and reduced histone acetylation seem to be the epigenetic hallmark of PD. However, some important differences in histone modifications are unique of PD. Aberrant miRNAs and lncRNAs expression linked to *SCNA, parkin, DJ-1*, and *PINK1* are the most important non-coding RNAs associated with PD (**Table 2).**

- *DNA methylation of pathogenic genes.* **Table 2** summarizes the main pathological PD-related genes with aberrant methylation/expression patterns. Global hypomethylation patterns in all these genes are linked to PD. This global hypomethylation may be associated with sequestration of DNMT1 by α-synuclein, which reduces DNA methylationin PD and dementia with Lewy bodies [320]. Overexpression of DNMT1 in vitro and in transgenic mice was able to restore the nuclear localization of DNMT1 [321,322]. Another reason for global reduced methylation may be, as for AD, that hcy levels have been also found elevated in PD patients, in detriment of SAMe levels [323,324]. This low SAM/SAH ratio added to a folate deficient diet was harmful to dopaminergic neurons in PD mouse models [325]. Importantly, a recent study found that epigenetic hallmarks of AD or PD, such as *APP* or *SCNA*, respectively, were linked to methylation markers like SAM and SAH [326]. Increased SAM/SAH ratio, which indicates a higher methylation potential, was linked to a better cognitive function [327].

Genome wide association studies found a direct implication of methylation status of α-synuclein and development of PD. The putative gene promoter, located in the intron 1 of *SCNA* gene (encoding α-synuclein), was significantly hypomethylated in blood and brain samples from PD patients as compared to controls [328]. This hypomethylation was associated with the overexpression of α-synuclein and protein aggregation leading to PD [321]. This hypomethylation/overexpression is observed in substantia nigra, putamen, and cortex of sporadic PD cases [322,329].

Masliah et al [306] identified 10 genes among the top 1000 members of the aging-related methylation module which were associated with PD (*SLC12A5*, *ABCA3*, *FHIT, FAT1*, *CPLX2*, *APBA1, MAGI2*, *CNTNAP2*, *ATP8A2*, *SMOC2*). *MRI1* and *TMEM9* were candidate genes with increased methylation, and the *GSST1*, *TUBA3E* and *KCNH1* genes showed decreased methylation. Methylation of the *HLA-DRB1, LRKK1, MMEL1, HLA-DQB1, OR12D3* and *VAV2* genes exhibited confusing results. A methylation-based EWAS in PD patients identified 20 unique genes with a sizable difference in methylation between PD and controls, while 17 were identified between PD with anxiety and PD without anxiety. *FANCC cg14115740* and *TNKS2 cg11963436* showed significant differential methylation between PD cases and controls [305].

Other genes were also found epigenetically regulated in PD. Increased levels of the tumor necrosis factor alpha (*TNF-α*) are associated with neuroinflammation and dopaminergic cell death in PD. Therefore, the higher vulnerability to TNF-α regulation found in dopaminergic neurons suggests the gene promoter is hypomethylated [330]. Importantly, *TNF-α* overexpression is usually detected in the cerebrospinal fluid of PD patients, as TNF-α induces apoptosis in neuronal cells [331]. It was recently reported the aberrant expression of clock genes in animal models of PD [332,333]. Methylation level of seven clock gene promoters was analyzed finding a reduced methylation in PD compared to controls [334]. In addition, DNA methylation, among other epigenetic mechanisms, plays an important role in mesodiencephalic dopaminergic neurons, which are severely affected in PD [335].

Some genes which mutations are associated with emergence and development of PD are epigenetically altered in other pathologies, such as cancer, but not in PD. For instance, analysis of methylation patters of *parkin* gene promoters from heterozygous PD patients for *parkin* gene mutations, PD patients without *parkin* mutations, and controls revealed no significant differences. However, deviant methylation patters in this gene have been observed in acute lymphoblastic leukemia [336,337]. The same occurred with the ubiquitin c-terminal hydrolase L1 gene (*UCHL1*), a subfamily member of deubiquitinating enzymes, implicated in the pathogenesis of PD. Differential methylation patters in UCHL1 were linked to diverse types of cancer [140,304,338-340], but not to PD [140].

- *Histone modifications/chromatin remodeling.* As for most of neurodegenerative disorders and age-related epigenetics, histone histone hypoacetylation is evidenced in PD [341] (**Table 2).** α-Synuclein-mediated histone modifications are crucial epigenetic mechanisms during development of PD. Increase of nuclear α-synuclein is neurotoxic and contributes to PD-related neurodegeneration probably by direct binding to histones, preventing H3 acetylation via interaction with SIRT2 [342,343]. Treatment with HDACi was able to reduce α-synuclein toxicity in neuroblastoma SH-SY5Y cells and in transgenic *Drosophila* [342-344]. Oxidative stress is a potential pathogenic mechanism in sporadic PD. Oxidative stress mediates binding of α-synuclein to the peroxisome proliferator receptor gamma coactivator-1-alpha (PGC1- α) promoter element. This binding causes histone deacetylation leading to down-regulation of PGC1-αexpression, which results in a reduction of mitochondrial biogenesis and consequently loss of mitochondrial function [345]. In agreement with that finding, PGC1-α levels were significantly reduced in neurons from post-mortem substantia nigra of PD patients [346]. The nonreceptor tyrosine kinase C-Abl also plays an important role in oxidative stress-induced neuronal cell death. C-Abl is activated in an 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP)-induced acute PD model. Conditional knockout of c-Abl in neurons or treatment of mice with STI571, a c-Abl family kinase inhibitor, reduced the loss of dopaminergic neurons and ameliorated the locomotive defects induced by short-term MPTP treatment. C-Abl-mediated phosphorylation of p38α (major substrate of c-Abl) is critical for its dimerization. Inhibition of p38α mitigates the MPTP-induced loss of dopaminergic neurons [347]. The oxidative stress-sensitive protein PKCδ also plays

a role on dopaminergic cell death through regulation by histone acetylation. Same as α-synuclein aggregates in Lewy bodies, the histone acetyltransferase EP300 contains prion-like domains serving as potential interaction sites for misfolded proteins, and enhance their aggregation [348]. Curiously, α-synuclein plays a protective role in this case, by interacting with EP300 and suppressing PKCδ expression, mediated by interaction with NF-kβ. Decrease of NF-kβ-mediated p65 acetylation and reduced EP300 activity, inhibits PKCδ, which protects dopaminergic neurons from apoptosis [349].

Polarization of microglial activation pathways also plays a role in dopaminergic cell loss leading to PD. This ratio is regulated by histone modifications, particularly by histone methylation. Frequency of classical (M1 phenotype) and alternative (M2 phenotype) activation pathways determines the detrimental or beneficial effects for CNS. Histone demethylase H3K27me3 Jumonji domain containing 3 (Jmjd3) is essential for M2-type activation. Suppression of Jmjd3 magnifies M1-mediated microglial overactivation leading to extensive cell death in substantia nigra in MPTP-intoxicated PD transgenic mice [350]. MPTP-mediated toxicity also reduces H3K4me3 levels in the striatum of mice and non-human primates, which can be reverted through chronic treatment with L-DOPA [319].

- *Non-coding RNAs.* Several lnc RNAs were found dysregulated in PD, including naPINK, SoxOT, 1810014B01Rik, BC200, which affect the expression of pathogenic genes involved in the disease [55] (**Table 2**). As DNA methylation and histone modifications regulate *SNCA* gene expression, some miRNAs regulate α-synuclein expression post-translationally. Two miRNAs (miR-7 and miR-153) regulate α-synuclein expression by direct binding. Binding of miR-7 to the 3'UTR of α-synuclein mRNA has a neuroprotective role in PD as represses α-synuclein expression [351]. Similarly, miR-153 represses *SNCA* at both, mRNA and protein levels [352]. However, those two miRNAs are downregulated *in vitro* and in animal models after exposure to MPTP, 1-methyl-4-phenyl-pyridinium ion (MPP^+) [351,352]. miR-433 is indirectly involved in *SNCA* expression through regulation of fibroblast growth factor 20 (FGF20). The 3'UTR SNP rs1270208 of FGF20 interferes with miR-433 binding, increasing FGF20 expression, which correlates with α-synuclein up-regulation and higher risk to develop PD [353]. In addition, α-synuclein alters the expression of other miRNAs. In transgenic mice overexpressing human A30P α-synuclein, the levels of miR-10a, -10b, -132, -212, and -495 are altered compared to those of non-transgenic littermates [354].

The expression of *LRRK2*, a gene involved in both sporadic and familial PD, is also altered by miRNAs. For instance, miR-205, which binds to the 3'UTR of *LRRK2*, is down-regulated, which correlates with increased LRRK2 protein expression levels in sporadic PD. However, miR-205 mitigated the aberrant neurite growth induced by *LRRK2* mutation R1411G in vitro [355]. E2F transcription factor 1 (E2F1) and differenciation regulated transcription factor protein (DP), associated with cell cycle regulation and cell survival, are regulated by let-7 and miR-184*. Up-regulated *LRRK2* or *LRRK2* mutants (I1915T or G2019S) inhibit the expression of those miRNAs, by promoting phosphorylation of eukaryotic translation initiation factor 4E binding protein (4E-BP), which inhibits the Aronaute 2, a pivotal constituent of the RISC, required for proper let-7 and miR-184* activity [356]. Disruption of those miRNAs results in reduced dopaminergic neuron numbers and locomotor activity in *Drosophila* [357]. let-7 and miR-184* overexpression corrects these deleterious effects of mutant *LRRK2* expression. The negative regulation of those miRNAs depends on the type of *LRRK2* mutations [356,358]. Thus, mutant *LRRK2* without enzymatic activity does not affect miRNA expression [357].

Other miRNAs alterations are specific for certain stages of the disease [359] or tissue-specific [360]. Down-regulation of 34b/c, which regulates mitochondrial function via modulation of DJ-1 and parkin, is particularly present in patients with early PD stage whom have not yet been treated with dopaminergic drugs [359]. Another miRNA molecule, miR-133b, found specifically in the midbrain dopaminergic neurons, was down-regulated in PD patients [360].

Identification of circulating miRNAs involved in PD provides one of the best diagnostic and prognostic markersof the disease by using non-invasive procedures, since it only requires blood or CSF extraction, and allows the following of disease progression *in vivo*. Studies performed in peripheral blood mononuclear cells of 19 PD patients and 13 controls, identified 18 differentially underexpressed miRNAs in PD patients [361]. Another study identified miR-1, miR-22-5p, and miR-29 as differentially expressed between PD and healthy patients, and miR-16-2-3p, miR-26a-2-3p, miR-30awere differential between treated and not-treated PD patients [362]. In blood leukocytes, 16 miRNAs were found differentially expressed between PD and healthy patients, including miR-16, miR-20a, and miR-320 [363]. Plasma from 31 PD patients versus 25 healthy controls differed in only one significantly up-regulated miRNA, miR-331-5p [364]. A second study, involving 32 PD patients and 32 healthy controls identified miR-1826, miR-450b-3p, miR-626, and miR-505 in plasma [365].

Epigenomic-based potential treatments for PD

As for AD, one of the epigenetic hallmarks of PD is general DNA hypomethylation, which promotes overexpression of pathogenic genes, such as *SNCA*, encoding α-synuclein. As mentioned above, this global decreased methylation is promoted by sequestering of DNMTs by α-synuclein [320-322] and decreased SAM/SAH ratio [323-326]. Thus, as for AD, one of the therapeutic approaches for PD treatment is to increase the levels of SAMe (one of the main donors of

methyl groups) by administration of B vitamins and folate in diet or as complementary treatment [250,251,327,366]. As expected, cultured cells exposed to PD-promoting neurotoxicity and treated with the DNMT inhibitor 5-aza-2'-deoxycytidine decreased cell viavility and increased apoptosis in dopaminergic neurons, exacerbating the neurotoxic damage [367].

The pathogenic cascade of neurodegenerative diseases normally involves oxidative stress and mitochondrial dysfunction. Therefore, antioxidant-rich diets might protect against cell death and delay or halt disease progression [368,369].

- *HDAC inhibitors.* Most of epigenomic-targeting treatments for PD are based on HDAC inhibition (**Figure 3),** due to the global reduced acetylation observed in cell cultures, PD-transgenic animal models, and patients with familial or sporadic PD. This HDACi therapy for PD also includes SIRTs, which, contrary to their beneficial effects on Aβ clearance in AD, they promote α-synuclein expression and aggregation leading to PD. Thus, SIRT inhibitors may constitute a potential therapeutic approach to reduce α-synuclein aggregation. However, only 4-PBA and VPA, but none of the SIRTis, are currently submitted to clinical trials, according to the NIH database [244] (**Table 3).**

Valproic acid (VPA) is one of the most extensively studied HDACis for PD treatment. Diverse studies show that VPA enhanced H3 acetylation and consequently reduced α-synuclein-mediated toxicity and decreased pro-inflammatory mediators, in cells and animal models exposed to PD-promoting toxic agents, such as MPTP, rotenone, or lipopolysaccaride [370-373]. Furthermore, VPA treatment promotes the expression of brain-derived neurotrophic factor (*BDNF*) and from glial cells (*GDNF*), which play critical roles in the growth, survival, and synaptic plasticity of neurons. VPA promotes histone H3 acetylation at the promoter level of *GDNF*, which enhances mRNA expression. In addition, VPA induces the expression of the heat-shock protein Hsp70, accompanied by promoter hyperacetylation and increased levels of H3 lysine di- and tri-methylation (H3K4Me2 and H3K4Me3), which is linked to recruitment of HAT p300[374]. VPA, as well as NaB and TSA, were able to rescue dopaminergic neurons death induced by MPP^+. Rescue was evidenced by the increase in dopamine uptake and by the number of neurons with positive tyrosine hydroxylase staining [375,376].

Low toxicity of sodium butyrate (NaB) makes this drug tolerable for treatment in animals and humans [377-379]. NaB may also be effective in reducing α-synuclein aggregation and toxicityand rescuing cognitive deficits associated with PD in animal models [380,381]. Accordingly, in α-synuclein overexpressing *Drosophila* models, PBA, as well as vorinostat (SAHA), reduced α-synuclein-mediated neurotoxicity [342], improved locomotor impairment, and reduced early mortality rates [344]. Similarly to VPA, NaB, TSA, and SAHA also promote H3 acetylation-mediated *GDNF* up-regulation in astrocytes [376,382,383]. NaB, as well as MS-275 and apicidin, also activate Hsp70, in a similar manner as VPA [374,384,385].

Other HDACis, such as 4-PBA or urocortin may execute their own neuroprotective effects, besides their influence on HDACs [380,386,387]. 4-PBA has been demonstrated to protect dopaminergic neurons, possibly through increased DJ-1 expression and activation of tyrosine hydroxylase promoter in the substantia nigra of mice treated with MPTP [380,388]. 4-PBA was also found to alter the expression of a variety of genes associated with antioxidant enzyme chaperones, including those ones critical for cell survival [387].

Sirtuins (particularly SIRT2), contrary to observations in AD, favor the pathological progression of PD by promoting α-synuclein expression and aggregation. In this regard, SIRT2 inhibition rescued α-synuclein-mediated toxicity in several animal models of PD [343]. The SIRT2 specific inhibitor AGK2 was found to increase tubulin acetylation and formation of large α-synuclein inclusions, resulting in the rescue of dopaminergic neurons *in vitro* and in a *Drosophila* PD model [343]. Other strategy to inhibit SIRT2 would be treatment with SIRT2 inhibiting siRNA, which would lead to a decreased SIRT2 expression with the subsequent reduced α-synuclein-mediated neurotoxicity.

HUNTINGTON'S DISEASE

Huntington's disease (HD) is an inherited disorder characterized by progressive degeneration of neurons within the striatum and cerebral cortex, which results in loss of motor functions, involuntary muscle contractions (chorea), cognitive decline (eventually resulting in dementia), and several behavioral changes. HD is a death-causing disease and no treatment is currently available [389,390]. HD is caused by a dominant mutation consisting in a CAG-repeat expansion (36-39 repeats), coding for glutamine, in the coding region of the huntingtin gene (*HTT*), resulting in a polyQ repeat sequence in the HTT protein [391]. HD is mainly a familial disorder with very rare cases of sporadic onset. Therefore, the main risk factors for developing HD are previous familial HD cases or high CAG repeat number. This expansion results in a dysfunctional HTT protein which disrupts gene expression in multiple pathways [392,393]. Wild-type HTT is located in the cytoplasm of neurons throughout the whole brain, and is suggested to be involved in intracellular transport, autophagy, transcription, mitochondrial bioenergetics, and signal transduction [394-397]. Despite the ubiquitous localization of Wild-type HTT in the brain, the mutant is specifically located at the medium-sized spiny neurons of brain areas related to motor functions, such as the neostriatal nuclei, caudate nucleus, and putamen [398-402]. Mutant HTT has been found to damage neurons at a large variety of pathways, including,

impairment of fast axonal transport, microtubule destabilization, mitochondrial dysfunction leading to oxidative damage, inflammatory reactions, excitotoxicity, and induction of apoptosis [403-405].

Epigenomic hallmarks of HD

Epigenomic profile of HD is mostly altered through the detrimental effects of *HTT* mutant which has a widespread impact on gene expression, through interactions with specific transcription factors [406] and also interferes with the core post-translational modifications of histones, turning chromatin into a more compact structure [407]. The main epigenetic modifications (DNA methylation, histone modifications, and ncRNAs) involved in HD are summarized in **Table 2.**

- DNA methylation of pathogenic genes. A first study performed by Farrer and colleges in 1764 patients carrying HD, concluded that DNA methylation might be involved in a genetic imprinting mechanism responsible for the expression of HD [408]. Other studies revealed the risk of triggering intergenerational extension or instability of CAG repeat expansions by changes in DNA methylation during epigenetic reprogramming [409,410].

Mutant *HTT* promotes hypermethylation-mediated down-regulation of important genes involved in neurogenesis [411]. Cognitive impairments observed in HD animal models might be linked to the reduced hippocampal neurogenesis, although this finding must be replicated in HD patients [402]. Down-regulation of *BDNF* expression, probably via hypermethylation, is crucial for the pathological progression of HD. Studies performed in HD-transgenic mice showed a differential expression of *BDNF* in HD compared to controls, but also sex-specific differences at individual CpG sites, which suggests a differential regulation of *BDNF* expression in the male and female brains [412]. Reduced expression levels of the adenosine A_{2A} receptor ($A_{2A}R$), a G-protein-coupled receptor, are also associated with HD. Down-regulated expression of $A_{2A}R$ was found associated with high levels of 5'UTR DNA methylation in $A_{2A}R$ from HD patients and with a decreased 5'UTR DNA hydroxymethylation in $A_{2A}R$ (*ADORA2A*) from HD-transgenic mice models [413,414]. Aberrant methylation was more evident when, apart from methylated cytosines, levels of 7-methyl guanine were also found in both animal models and HD patients [415].

- Histone modifications/chromatin remodeling. HD is characterized for a global histone deacetylation, and increased histone methylation, which repress gene transcription [416-420]. Histone hypoacetylation causes chromatin condensation and down-regulation of affected genes. Decreased histone acetylation during HD progression is mediated by mutant HTT sequestering CREBBP and inhibiting CREBBP's activity as histone acetylase. This CREBBP sequestering disrupts gene transcription at multiple pathways [86,87,416,417,419,421,422]. Transgenic mice expressing a form of CREBBP without HAT activity, or inactive p300/CBP (a CREBBP homolog), presented impaired long-term memory consolidation and contextual fear memory, but short-term memory was unaffected [87,423]. Studies performed in transgenic HD mice and mouse striatal cell lines, showed that early-onset HD was associated with a decreased H3 acetylation with subsequent down-regulation of targeted genes within the striatum, including brain-derived neurotrophic factor (*bdnf*), cannabinoid receptor 1 (*cnr1*), dopamine 2 receptor (*drd2*) and preproenkephalin (*penk1*). For both early- and late-onset HD, core histones H3 and H4 associated to those genes were also hypoacetylated in transgenic-HD compared to wild-type mice [416,420].

Formation of heterochromatin domains in HD is also caused by a global histone hypermethylation, which is suggested to be mediated by disruption of CREBBP functioning by mutant HTT [419,424]. CREBBP normally represses the expression of *Drosophila* Su(var)3-9 and enhancer of zeste proteins (SET) domain, bifurcated 1 (*SETDB1*), which encodes the HKMT SETDB1 that methylates H3K9. Therefore, as normal CREBBP prevents SETDB1-mediated histone methylation, shutdown of CREBBP by mutant HTT, activates SETDB1 and thus, enhances H3K9 methylation in striatal neurons of both transgenic HD mice and HD patients [419,424]. H3K9me is associated with decreased gene expression profiles in striatum, such as cholinergic receptor, muscarinic 1 (*CHRM1*), which has been proposed to induce synaptic dysfunction linked to HD [402,425,426]. Dysregulation of cholinergic signaling, specially affecting the medium spiny neurons of striatum, has been identified as a pivotal factor in the physiopathology of HD [427].

- Non-coding RNAs. Various dysregulated lncRNAs alter gene expression in HD, includingHAR1F, HTTAS, DGCR5, NEAT1, and TUG1 [55] (**Table 2).** The expression of miRNAs was found to be globally decreased in HD animal models and HD patients, and most of them are altered by mutant *HTT* expression. Reduced miRNA expression promotes the expression of their targeted mRNAs. Among the 24 miRNAs found down-regulated in brains from HD patients [428-430], the most relevant ones were miR-9, miR-9*, miR-29b, miR-124a, miR-132, which are regulated by the repressor element 1 silencing transcription factor (REST)in neurons [431,432]. Wild-type HTT sequesters REST in the cytoplasm of neurons and prevents binding of the repressor to DNA, whereas mutant HTT allows binding of REST and subsequent repression of many gene targets. Therefore, decrease levels of those miRNAs, would increase the transcription of REST, amplifying the accumulation of this protein in the presence of mutant HTT.

Other miRNAs,such as miR-34b, miR-125b, miR-146a, miR-150, and miR-214, are directly targeted by mutant HTT, [433,434], and normally down-regulated by mutant

HTT in a HD context. However, miR-196a has been found to decrease expression of mutant HTT through inhibition of protein synthesis or through enhancing protein degradation [435]. These results were obtained *in vitro* and confirmed in transgenic HD mice and pluripotent stem cells derived from HD patients. Therefore miR-196a mightplay a promising role on a potential therapeutic approach for HD treatment.

Epigenomic-based potential treatments for HD

The major processes leading to repression of gene expression associated with HD are HTT-mediated activation of transcription repressors by decreasing histone acetylation, increasing histone methylation, and, sometimes, through direct DNA hypermethylation. Therefore, most epigenetic-based pharmacological compounds for HD treatment are based on increasing histone acetylation and reduce histone methylation, or repressing mutant *HTT* gene.

Table 3 summarizes the few current epigenetic drugs under clinical trials for HD treatment, being the HDACis the most representative ones.

- ***HDAC inhibitors.*** Treatment with HDACis constitutes a potential therapeutic approach to restore histone acetylation and expression of crucial genes which are otherwise repressed during HD development. Most of these HDACis are displaying promising results in terms of neuropathology and motor symptoms [407,416,417,421,422]. Furthermore, HDACis improved memory function and behavior in CREBBP or KAT deficient mice models [86,87,414].

HDAC inhibition with SAHA or NaB improved memory deficits in mice [436-438]. SAHA treatment slowed photoreceptor degeneration and improved longevity of adult *Drosophila* in the presence of mutant *HTT* [439]. Additionally, SAHA reduces HDAC2 and HDAC4 levels and improves motor deficits in the R6/2 mouse model of HD [436,437]. Vorinostat (SAHA), as well as Trichostatin (TSA), increased alpha-tubulin lysine 40 acetylation in mouse striatal cells, and consequently, increased intracellular transport of *BDNF* [440]. TSA, as well as Valproic acid (VPA), promote H3 and H4 acetylation in a *Drosophila* model containing mutant *HTT*, as compared to controls [439].

Sodium butyrate (NaB) was found to slow neuronal degeneration in a *Drosophila* HD model [439] and to improve motor performance and decreased neuropathology in the R6/2-HD mouse model, overexpressing mutant HTT [438]. Furthermore, NaB treatment promoted H3 acetylation and restored the mRNA expression levels of genes affected by mutant HTT [416]. However, NaB may occasionally repress gene expression, since histone acetylation, promoted by NaB, may also increase the expression of transcription repressors [407].

Sodium phenylbutyrate (4-PBA) significantly improved HD symptoms in transgenic mice, and has been shown to increase H3 and H4 acetylation, decreased histone methylation, and increased life expectancy by reduction of neuronal degradation rate [421]. 4-PBA constitutes one of the most promising HDACi-based therapeutic agents, as it is already FDA-approved and thus, data from farmacokinetics, toxicity, and dosing are available. However, despite of the successful results obtained from animal models, the efficacy of this drug in HD patients is very low and requires the administration of very high doses which would result toxic for patients [441,442].

The pimelic diphenylamide 4b is a relatively novel HDACi which was effective on R6/2 mice, by improving HD-related behavioral and motor symptoms and restoring histone acetylation-mediated gene transcriptional abnormalities [407]. HDACi 4b also improved body weight, motor function and cognitive performance in a different mouse model expressing the first 171 amino acids of HTT with 82 CAG repeats (N171-82Q) [443]. It is suggested that HDACi 4b plays a role on post-translational mechanisms, by activating the kappaB kinase inhibitor (IKK), which enhances HTT phosphorylation and acetylation, followed by HTT degradation through ubiquitin-proteosomal and autophagy systems. HDACi 4b inhibits class I and II HDACs and also is thought to restore proper gene transcription in cells and HD animal models [443].

- ***Histone methyltransferase inhibitors.*** Histone hypermethylation is also included into the epigenetic hallmarks of HD. DNA intercalating anthracyclines, such as mithramycin A and chromomycin A3, specifically inhibit the binding of transcription factors to the GC-rich regions of gene promoters, thereby affecting gene expression [417,419,444], which occasionally may have neuroprotective effects. For instance, inhibition of transcription factors SP1 and SP3, related to detrimental responses after oxidative stress and DNA damage, may lead to neuroprotection. Mithramycin A was found to meliorate HD-related symptoms in R6/2-HD mice, probably by reducing the pericentromeric heterochromatin condensation [417,419,444]. Furthermore, mithramycin was found to inhibit the HKMT SETDB1 and thereby reduce H3K9 methylation and restore the cholinergic pathway in striatum of R6/2-HD mice [419]. Chromomycin A3 tips the H3K9 methylation/acetylation balance in favor of acetylation, improving the HD phenotype [444]. Therefore, mithramycin A and chromomycin A3 may be potential candidates for HD treatment. Unfortunately these drugs turn into toxic at high does, which is not suitable for the chronic use required for HD treatment. Nevertheless, they can provide a mechanistic hint for novel drugs with lower toxicity rates.

SIRT selective inhibitors, specifically SIRT2is, were also tested in animal models of HD. Genetic or pharmacological inhibition of NAD^+-dependent SIRT2 by nicotinamide, was neuroprotective in a Drosophila model [445]. Another selective HDACi, the SIRT2 inhibitor AK-7, was found to

improve motor functions, extend survival, and reduce polyQ-HTT aggreagation [446].

- Other epigenetic potential treatments. Interestingly, other epigenetic treatments target DNMT activators (EGCG) or SIRT activators (Resveratrol). Although the molecular mechanisms underlying neuroprotection in HD are still not well understood, these drugs are currently under clinical trials [244] (**Table 3**) and seem to be a promising therapy for HD treatment.

Dot-blot combined with atomic force microscopy studies revealed that ECGC modulated miss-folding and oligomerization of mutant HTT, reducing the polyQ-HTT toxicity *in vitro* and in HD animal models [447].

Resveratrol is a SIRT activation, which might exacerbate the histone hypoacetylation-mediated global gene underexpression and HD symptoms. However, activation of SIRT1 by resveratrol involves also beneficial effects at metabolic and mitochondrial level that may exert a neuroprotective function. An important substrate of SIRT1 is the peroxisome proliferator-activated receptor gamma co-activator-1α (PGC-1α), which is a main regulator of energy metabolism, and that is significantly impaired in HD. A variety of studies revealed a significant neuroprotection after treatment with resveratrol in cell cultures and HD animal models [448-450]. Conversely, other studies demonstrate beneficial effects of resveratrol on diabetes progression, but no effects in neuroprotection [451,452]. Despite of these controversial findings, resveratrol is currently under clinical trials [244] (**Table 3).**

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic Lateral Sclerosis (ALS) is an idiopathic, fatal neurodegenerative disease affecting primarily the motor system. ALS is one of the most common motor neuron degenerative disorders and usually starts after age 50, although earlier onset is also possible. The clinical symptoms include muscle atrophy, fasciculation, weakness, spasticity, and cognitive dysfunction, due to the loss of motor neuronal activity in the brainstem, spinal cord, and motor cortex [453,454]. The pathogenic mechanisms involved in this complex disorder are not very well explored, although some proposed pathways are related to oxidative stress, glutamate excitotoxicity, impaired axonal transport, neurothrophic deprivation, neuroinflammation, apoptosis, altered protein turnover, and influence from astrocytes and oligodendrocytes that might alter motor neuron microenvironment [455].

Familial ALS is predominantly hereditary in an autosomal dominant manner, whereas recesive or X-linked heritances are very rare. Several gene mutations have been associated with ALS, although the cellular and pathological mechanisms involving those gene mutations are still under investigation. Mutations in the superoxide dismutase 1 gene (*SOD1*) constitute the major genetic cause of ALS. SOD1 protein is responsible for destroying harmful superoxide radical produced by mitochondria. Mutations in SOD1 are gain-of-function, and thus protein retains its enzymatic function but aggregates in motor neurons causing toxicity [456,457].

The knowledge of the genome sequence allowed the identification of other gene mutations involved in ALS, including TAR DNA-binding protein (*TARDBP*), the RNA-binding protein fused in sarcoma (*FUS*), the catalytic subunit of HAT complex elongator protein (*ELP3*), the Amyotrophic Lateral Sclerosis 2, or alsin 2 (*ALS2*), ataxin 2 (*ATXN2*), and the neurofilament heavy peptide (*NEFH*). The chromosome 9 open reading frame 72 (*c9orf72*) was found to contain an hexanucleotide repeat in the non-coding region associated with ALS [458-460]. This repeat causes cellular toxicity after splicing out of the *c9orf72* mRNA transcripts and accumulates in the nuclei of affected cells. Mutations in the *UBQLN2* gene encoding ubiquilin 2 protein interfere with protein activity involved in degradation of ubiquitinated proteins, resulting in abnormal protein aggregation and causing cellular toxicity [461].

Epigenomic hallmarks of ALS

According to Al-Chalabi and colleges [458], around 10% of ALS forms are familial and caused by gene mutations whereas 90% are sporadic, i. e. , influenced by surrounding environment [458]. The epigenetic pattern of ALS involves a general hypermethylation [462], enforced by increased DNMT expression [463,471] and impaired demethylation machinery [472], and a significantly decreased histone acetylation. Several miRNAs are also dysregulated in ALS (**Table 2**).

- DNA methylation of pathogenic genes. DNA methylation patterns in ALS are still under debate and current results are sometimes confusing. DNA methylation analyses among pathogenic genes directly involved in ALS showed that only *SOD1*, *VEGF* (encoding the vascular endothelial growth factor), and *OPTN* (optineurin),were widely hypo- or unmethylated [131,462,463,464]. Lack of *SOD1* methylation could be involved in overexpression of SOD1 protein promoting its aggregation, which would mimic the effect caused by mutations in this gene. Interestingly, the hypomethylation status found in *OPTN* did not correspond with changes in gene expression [462].

In contrast, hypermethylated CpG islands in *c9orf72* and *ATXN2*, are associated with the pathogenic hexanucleotide and CAG repeats, respectively, which contributes to progression of ALS [463,465-467]. The *c9orf72* gene down-regulation is also promoted by histone methylation [468]. The ALS2 gene encodes for Alsin, which is a guanine nucleotide-exchange factor for the small GTPase Rab5. A recent genome-wide study of promoter methylation of individuals who experienced severe psychosocial trauma showed that, among the 248 differentially methylated gene

promoters in brain, the *ALS2* gene promoter showed the most significant hypermethylation [469]. The member 2 of the solute carrier family 1 (*SLC1A2* or *EAAT2*) was also found hypermethylated associated with down-regulated mRNA [463,470]. *SLC1A2* gene encodes SLC1A2 enzyme involved in phase III drug transport. Down-regulation of this enzyme is associated with a repressed activity, which would result in a poor assimilation of drugs following that pathway.

Hypermethylation may be also promoted by the up-regulation of DNMT1 and DNMT3a. Apoptosis of motor neurons was characterized by alterations in DNMT1, DNMT3a, and 5-methylcytosine in mouse ALS models of ALS, and similar to those in human ALS [463,471]. *ELP3* gene, encoding the core HAT elongator protein, is also involved in paternal DNA demethylation, probably via SAM domain [472]. Knock-down of ELP3 impairs paternal demethylation and might be another cause for the global gene promoter hypermethylation associated with ALS.

- *Histone modifications/chromatin remodeling.* ALS is characterized by a global histone hypoacetylation, in both ALS mouse models and ALS patients, which contribute, along with DNA hypermethylation, to downregulation of crucial genes for neuronal development, which finally triggers the apoptosis of neuronal cells. Decreased histone acetylation in ALS is mediated through different pathways:(i) Hypoacetylation mediated by forced expression of HDAC3, which was found to induce neurodegeneration in HT22 cultured hippocampal cells and in rat neurons [473]; (ii) Mutation in *SS18L1* inhibits interaction with the HAT machinery and alters the HAT catalytic subunit ELP3 which leads to a motor neuron axonal impairment in ALS [474]. ELP3-mediated HeK8 and H3K14 acetylation may promote expression of the heat shock protein Hsp70 [475], which is involved in clearance of aggregates aroused in the SOD1 mouse model and in protection against mutant-SOD1-induced neuronal death [476,477]. *FUS* overexpression induces hypoacetylation of histones H3K9 and H3K14 in the cyclin D1 (*CCND1*) gene promoter, altering cell cycle in ALS [478].

- *Non-coding RNAs.* Dysregulated miRNA expression contributes to ALS pathology and may be used as a tool for diagnosis. Main dysregulated miRNAs are associated to muscle cells, targeting ALS pathogenic genes, and circulating blood miRNAs. A variety of miRNAs are associated with pathogenic ALS-related genes. TARDP is a component of the Dicer and Drosha complexes that binds to primary transcripts of specific miRNAs. TARDP is involved in neurite outgrowth and neuronal differentiation through regulation of miRNA biogenesis and expression. Mutations in the *TARDP* gene cause differential expression of ALS-contributing mature and functional miRNAs, such as miR132, miR-143, and miR-558. Elevated expression of miR-132 and miR-9 rescue neurite outgrowth and neuronal differentiation impairment,respectively, in cells derived from *TARD*mutationsfrom ALS patients [479,480]. Similar to TARDP, the protein FUS binds to pre-mRNA molecules and determines their fate by regulating splicing, transport, stability, and translocation. FUS regulates miRNAs involved in synaptic plasticity and neuronal development, including miR-9, miR-132, and miR-134 [481]. Axon growth is regulated by miR-9, via modulation of microtubule-associated protein 1b (*MAP1B*) mRNA expression; miR-132 controls the expression of several genes involved in neuronal morphology and growth; miR-134 regulates neuronal development and dendritogenesis in response to neuronal activity [233,482,483-486].

Other miRNAs involved in ALS pathogenesis are located in peripheral tissues. The skeletal muscle specific miRNA, miR-206, is down-regulated in ALS mice harboring *SOD1* mutations. Overexpression of this miRNA promoted reinnervation process at the NMJ through regulation of HDAC4 and fibroblast growth factor (FGF) pathways [487]. High expression of miR23a, miR-29b, and miR-455, found in skeletal muscle of ALS patients, may cause dysregulation in mitochondrial gene expression [488]. Different studies found differential miRNA expression in spinal cord from ALS patients, such as miR-146*, miR-524-5p, and miR-582-3p, which were predicted to bind the 3'UTR of *NEFL* gene [489], and miR-24-2*, miR-142-3p, miR-142-5p, miR-1461, miR-146b, and miR-155, associated with sporadic ALS patients [490].

Potential role of miRNAs as biomarkers of ALS *in vivo* are those differentially expressed in peripheral blood. Leukocytes isolated from blood of 8 ALS patients and 12 healthy controls showed that miR-149, miR-328, miR-338-3p, miR-451, miR-583, miR-638, miR-665, and miR-1275, were dysregulated in ALS patients [491]. Human $CD14^{+}CD16^{-}$ monocytes isolated from ALS patients have a unique inflammatory miRNA profile, showing higher expression levels of miR-27a, miR-32-3p, miR-146a, and miR-155 [492].

Epigenomic-based potential treatments for ALS

General histone hypoacetylation repress gene expression and triggers apoptosis in motor neurons of ALS animal models and patients. Therefore, treatment with HDACis is currently the most studied strategy and has been found to restore the aberrantly down-regulated genes, and counteract apoptosis inhibition. Sodium phenylabutyrate (4-PBA) [493] and valproic acid (VPA) are currently submitted to clinical trials for ALS [244] (**Table 3**). Treatment of SOD1/G93A-ALS transgenic mice (characterized by presenting hypoacetylation in H4 and other histones in spinal cord sections) with 4-PBA resulted in survival and improved pathological phenotypes. Treatment with 4-PBA ameliorated histone acetylation and inhibited apoptosis through up-regulation of Bcl2, NF-kB, p50 and phospho-IkB, and through inhibition of caspases in the spinal tissues of transgenic mice [494]. Combination of drugs provided better

results than using them individually. In this regard, combination of 4-PBA with riluzole, the only currently FDA-approved drug for ALS treatment, or with AEOL 10150, a catalytic antioxidant, was significantly more effective than using either drug alone [495,496].

Effects of VPA treatment were more variable and inconsistent. Post-symptomatic treatment of SOD1/G93A-ALS transgenic mice increased lifespan, whereas pre-symptomatic treatment did not show any effect on the onset of motor symptoms [497]. Other studies in the same mice models, had small but significant beneficial effects on motor dysfunction and survival time [498]. However, trials in the SOD1/G86R-ALS showed that VPA improved histone acetylation, restored CBP activity, and reduced motor neuron death, but did not prolong survival [499]. Those inconsistencies might arise from differences in the mice strain used, VPA dosages, copies of the mutant gene, and other factors. Drug tolerance and effectiveness in patients will be given by their individual pharmacogenetic profile. Same as for 4-PBA, combination of VPA with other treatments exacerbate the beneficial effects compared to either drug alone [498]. Combination of VPA with lithium enhances Ser9 phosphorylation of GSK-3β in the lumbar spinal cord and brain. Trichiostatin a (TSA) was also found to restore histone acetylation in spinal neurons of ALS animal models, which led to a decreased axon demyelination and increase survival rate in those mice [500].

EPIGENETIC TARGETS INDIRECTLY INVOLVED IN NEURODEGENERATION

Besides the epigenetic mechanisms affecting pathogenic genes directly involved in neurodegenerative diseases, other genes with an indirect influence on the disease phenotype may also be epigenetically altered. Several conditions, such as diabetes or those related to impaired lipid metabolism and cholesterol, (metabolic syndrome spectrum, stroke, vascular disorders) are considered as risk factors for a future onset of neurodegenerative disorders [103,501-507]. For instance, alterations in cholesterol metabolism are involved in AD pathogenesis and over 40% of AD patients are hypercholesterolemic. Genes associated with inflammation, vascular risk factors, and lipid metabolism, contain methylated CpG sites in their promoters which exhibit aberrant DNA methylation patterns leading to alter mRNA expression of those genes in symptomatic or pre-symptomatic stages of neurodegeneration [18,129,132,330,508,509] (**Table 4).**

Certain polymorphisms in genes encoding apolipoproteins (*APOB, APOC3, APOE*) are associated with defective enzyme activity which result in aberrant increase of LDL-family lipoproteins, cholesterol, and triglyceride levels. In a similar manner, aberrant epigenetic regulation of those genes would lead to an altered expression and defective enzyme function. Impaired lipid metabolismis associated with vascular impairmentand subsequentdecreased brain oxygen and glucose supply. Depending on the anatomical site of the ischemic insult, this hypoxia might end up in stroke or dementia-related disorders. Furthermore, it is suggested that apolipoproteins also possess the ability to enhance clearance of Aβ and thus they can serve as early AD biomarkers. Therefore, aberrant expression of those genes can result in dysregulated Aβ-related metabolism and could enhance the formation of Aβ plaques. High levels of *APOB* mRNA and decreased *APOC3* mRNAare associated with risk for AD (**Table 4**). Identification of circulating Aβ-binding proteins in AD patients compared with individuals with AD family history (AD-FH) or without AD family history (NFH) indicate that *APOC3* was significantly reduced in AD-FH and AD compared with healthy controls, suggesting that APOC3 expression might be an early marker of AD [508]. The gene encoding apolipoprotein E (*APOE*), is primarily associated with vascular risk and hypercholesterolemia and the *APOE-ε4/ε4* haplotype is a hallmark of AD [104,109-111]. Although the *APOE* promoter is generally found hypomethylated, which would correspond to up-regulated gene expression, regulation of *APOE-ε4* allele is not fully understood. As not all *APOE-ε4* allele carriers develop AD or dementia-related disorders, it would be of real interest to know the difference on the methylation/mRNA status of this allele between individuals who develop or not AD. *APOE* expression is epigenetically down-regulated by miRNAs (miR-199a-3p, miR-199a-3p, and miR-1908-5p), which may also be used as diagnostic markers for AD [510].

Physiological symptoms of neurodegeneration involve impaired cell signaling and neuroinflamation. Up regulation of pro-inflammatory interleukins, such as *IL-1* and *IL-6*, as well as *TNF-α*, are signs of necrotic cell death. These three inflammatory markers were found up-regulated in AD [129,132,511], and *TNF-α*also in PD [330] (**Table 4**). *IL-1*, *TNF-α*, and *iNOS*, overexpression correspond to hypomethylated gene promoters [129,132,511]. Although methylation studies of *IL-6* in AD are still under debate, this IL has been highly-regulated in AD. Furthermore, *IL-6* up-regulation has been found linked to gene promoter hypomethylation in other pathologies, which suggests that this interleukin may also be hypomethylated in AD [129]. *TNF-α* was found hypomethylated in the dopaminergic neurons of the susbstantia nigra compared to other brain areas in PD patients and this is the cause of high *TNF-α* expression in these neurons [330]. Methylation of a single CpG in the*TNF-α* promoter inhibited the binding of SP1 and AP2 transcription factors and decreased *TNF-α* expression. Therefore, hypomethylation of this gene may explain the vulnerability of dopaminergic neurons to TNF-α inflammatory reactions [330].

One of the factors inducing global hypomethylation in neurodegenerative disorders, such as AD and PD, is the high hcy content in detriment of SAMe. The *MTHFR* gene encodes for the methylentetrahydrofolate reductase which remethylates the homocysteine into methionine. The

polymorphisms 1298A>C (rs1801131) and 677C>T (rs1801133) in *MTHFR*, result in a defective enzyme activity and the accumulation of homocysteine in plasma [512,513]. Hypermethylation of *MTHFR* gene promoter is the cause of down-regulated expression and subsequent low enzyme activity, resulting in the increase of hcy levels in AD patients [18,23,143] **(Table 4).** Epigenomic characterization of these genes might provide an early diagnosis in presymtomatic stages of neurodegenerative disorders, which would allow and early treatment that retain or delay the onset of the disease.

Table 4. Epigenetic modifications in genes associated with lipid metabolism, vascular risk factors, and inflammation, involved in neurodegeneration

Pathogenic gene	Locus	Promoter lenght (bp)	3' UTR length (bp)	Defective protein	Epigenetic modifications	Pathology
APOB	2p24. 1	--	394	APOB	Upregulated mRNA	**Risk for Alzheimer's disease**
APOC3	11q23. 3	960	278	APOC3	Down-regulated mRNA	**Risk for Alzheimer's disease**
APOE	19q13. 2	996	--	APOE	Hypomethylated Up-regulated mRNA	**Alzheimer's disease** **Dementia**
IL1B	2q14	964	668	IL1B	Hypomethylated Up-regulated mRNA	**Alzheimer's disease**
IL6	7p21	1214	500	IL6	Hypomethylated Up-regulated mRNA	**Alzheimer's disease**
MTHFR	1p26. 32	959	--	MTHFR	Hypermethylated Down-regulated mRNA	**Alzheimer's disease**
TNFA	6p21. 33	1028	907	TNFA	Hypomethylated Up-regulated mRNA	**Alzheimer's disease** **Parkinson's disease**

APOB: apolipoprotein B; *APOC3*: apolipoprotein CIII; *APOE*: apolipoprotein E; *IL1B*: interleukin 1 beta; *IL6*. interleukin 6; *MTHFR*: methylenetetrahydrofolate; *TNFA*: tumor necrosis factor.

Drug effectiveness, required dosage, and toxicity depend on drug pharmacodynamics and pharmacokinetics. However, it is necessary to know the individual pharmacogenetic profile for an adequate personalized treatment. Individual differences in drug response are associated with genetic and epigenetic variability and disease determinants. Pharmacogenetic response to drugs can be classified into five different gene categories: (i) pathogenic genes involved in disease development or potential risk. Not all individuals carrying the same disease present the same affected pathogenic genes; (ii) genes associated with the mechanism of action of drugs (enzymes, receptors, messengers, etc); (iii) genes associated with drug metabolism. This category includes genes related to Phase I enzymes: alcohol dehydrogenases (*ADHs*), monoamine oxidases (*MAOs*), cytochrome p450 family genes (*CYPs*), among others, and Phase II enzymes: UDP glucuronosyltransferases (*UGTs*), gluthatione S-transferase family genes (*GSTs*), N-acetyltransferase (*NATs*), sulfonotransferases (*SULTs*), etc. ; (iv) genes associated with drug transporters (Phase III): ATP-binding cassette family members (*ABCs*), solute carrier superfamily (*SLCs*), solute carrier organic transporter family (*SLCOs*); (v) pleiotropic genes involved in multiple pathways and metabolic reactions [7,8,22,23,103,105,107,108]. The efficiency of drug metabolizing products is influenced by genetic and epigenetic modifications on these genes [29,30,103,105]. Aberrant epigenetic modifications of pathogenic genes involved in the main neurodegenerative disorders (AD, PD, HD, ALS) and their effects are described in the above sections of this manuscript. In addition, epigenetic alterations in genes involved in drug metabolism and transport play a key role in the development of drug resistance. Information about epigenetic modifications of drug metabolism- and transport-related genes associated with neurodegenerative disorders is very low [22,23,129,131-133,306,514,515]. **Table 5** summarizes the main aberrant DNA methylation profiles in genes involved in drug metabolism and transport, found during neurodegenerative processes.

Table 5. Epigenetic modifications in drug metabolism-related and in transporter genes associated with neurodegenerative disorders.

Category	Gene	Locus	Promoter length (bp)	Pathology	Epigenetic changes
Phase I Drug Metabolism Genes	*CYP2E1*	10q26.3	918	Parkinson's Disease	Hypomethylated Up-regulated mRNA
Phase II Drug Metabolism Genes	*GSST1*	22q11.2	917	Parkinson's Disease	Hypomethylated Upregulated mRNA
	GSTTP1	11q13	958	Parkinson's Disease	Hypermethylated Downregulated mRNA
Phase III Transporter Genes	*ABCA3*	16p13.3	2201	Parkinson's Disease	Hypomethylated Upregulated mRNA
	ABCA7	19p13.3	967	Alzheimer's Disease	Hypomethylated Upregulated mRNA
	SLC1A2	11p13	996	Amyotrophic Lateral Sclerosis	Hypermethylated Downregulated mRNA
	SLC12A5	20q13.12	958	Parkinson's Disease	Hypomethylated Upregulated mRNA
	SLC24A4	14q32.12	1029	Alzheimer's Disease	Hypomethylated Upregulated mRNA
	SLC25A24	1p13.3	1059	Parkinson's Disease	Hypomethylated Upregulated mRNA

ABCA3: ATP-binding cassette, sub-family A (ABC1), member 3; *ABCA7*: ATP binding cassette subfamily A member 7; *CYP2E1*: cytochrome P450 family 2 subfamily E member 1; *GSST1:* Glutathione S-transferase theta 1; *GSTTP1*: Glutathione S-transferase pi 1; *SLC12A5*: Solute carrier family 12 (potassium/chloride transporter), member 5; *SLC1A2*: solute carrier family 1 member 2; *SLC24A4*: solute carrier family 24 member 4; *SLC25A24*: solute carrier family 25 member 24.

A number of polymorphisms associated with the pharmacogenomic profiles are well characterized and allow the prediction of many phenotypic variations in drug response. However, there is not clear information about the effects of epigenetic variations of these genes on drug response. For instance, we could predict that hypermethylation leading to down-regulation of genes involved in drug metabolism might lead to defective enzymes and generation of drug resistance, which would require and increased dosage and risk of toxicity. At counterpart, gene promoter hypomethylation-mediated overexpression, might involve an ultra rapid metabolic response which would result in lower drug effectiveness. Several transporter genes are also involved in the control of cholesterol homeostasis and influence AD and PD pathogenesis. *ABCA1, ABCBC1*, and *ABCG2* influence AD and Aβ deposition in extracellular senile plaques [516-522]. Brain ABCA1 mediates cholesterol and phospholipid efflux and lipidates APOE to allow its interaction with Aβ and inhibit formation of Aβ deposits [523]. ABCA2, the most abundant ABC transporter in human and rodents, may regulate esterification of plasma membrane-derived cholesterol by modulation of sphingolipid metabolism. Dysregulation of *ABCA2* gene may be involved in AD

pathogenesis [524]. Expression of these *ABC* transporter genes is epigenetically regulated through interaction with miRNAs, such as miR-33a/b-5p, miR-106b, and miR-758-5p, regulating *ABCA1*gene expression [510].

CONCLUSIONS AND FUTURE PERSPECTIVES

During the last decades, the attempts to develop accurate treatments for neurodegenerative diseases were unsuccessful. The complexity of these multigenic disorders hindered the understanding of the molecular mechanisms underlying their pathological progression which led to development of erratic therapeutic interventions for those diseases. FDA-approved drugs are symptomatic but do not inhibit or decrease disease progression in addition of the unbearable side effects in most cases. Therefore, there is an urgent need to develop new treatments that delay the onset of neurodegenerative disorders, improve the quality of life, and reduce the disease management costs. For instance, it has been estimated that a new drug, approved by 2025, capable to delay AD onset by 3-5 years, would decrease prevalence of the disease by 30%, and thus reduce the cost of AD management by $300-400 billion/yearin the USA by 2050 [525].

Epigenomics opens new avenues for treatment allowing: (i)a better understanding of molecular, metabolic, and cellular mechanisms of the disease; (ii) identification of new diagnostic targets, not only during symptomatic, but also at early and asymptomatic stages of the disease; (iii) identification of new modifications associated with drug resistance; (iv) design of potential and promising treatments targeting pathological rather than symptomatic hallmarks of disease; (v) Given the reversibility of epigenetic modifications, epigenetic drugs, or even dietary interventions, capable of reverse epigenetic alterations are promising perspectives for a new era of treatment for neurodegenerative disorders.

Most of those epigenetic-based drugs are submitted to clinical trials and FDA-approved for treatment of complex heterogenic diseases, such as cancer. However, none of these drugs are yet FDA-approved for treatment of neurodegeneration-related disorders, and just a few of them are under clinical trials for this purpose. A variety of those potential treatments, especially HDAC inhibitors, are successful in animal models although some of them are not very effective at physiological doses in human patients. Treatments targeting DNA methylation or miRNAs seem to display more promising results nowadays. Further research finding new epigenetic targets linked to neurodegenerative diseases would provide new epigenetic strategies for those disorders.

In order to examine drug efficiency and tolerability in human patients, it is necessary to administrate them according to the pharmacogenetic profile of each individual. Pharmacogenomics provides multiple benefits for clinical trials and even for chronic treatment, including: (i) identification of candidate patients with ideal genomic profile for a particular drug; (ii) regulation of drug dosage according to the pharmacogenomic profile; (iii) enhance drug efficiency; (iv) reduction of drug interactions and adverse reactions; (iv) reduction of costs derived from inappropriate drug selection. Pharmacogenomics thus allows personalized treatments according to requirements of each individual. Pharmacogenomics provides information about polymorphisms affecting pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes affecting drug pharmacokinetics and pharmacodynamics, whereas pharmacoepigenomics deals with the influence that epigenetic alterations may exert on those genes. Interestingly, pharmacogenomics, which is associated with drug resistance, is reversible, and thus may change in response to endogenous and exogenous stimulus, such as pathological conditions, drug administration, dietary regimens, etc.

Different strategies may be implemented to improve drug efficiency. Appropriate combination of drugs, in accordance with pharmaco(epi)genomic profile, current prescriptions, anamnesis, and clinical history of the patient, may exacerbate their beneficial effects better than either separate drug [495,496]. For instance, it has been recently published that administration of statins are neuroprotective in stroke, cerebral ischemia, AD, PD, multiple sclerosis, epilepsy, and traumatic brain injury [526], due to their cholesterol lowering ability [527]. Furthermore, co-administration of Atorvastatin with the nutraceutical LipoEsar® (E-SAR-94010; LipoEsar®) enhances the hypolipemic effects of Atorvastatin and allows reduction of statin doses in order to minimize adverse reactions [509].

The use of nutraceuticals, not only as dietary complements, but also as for therapeutic treatments is becoming more extensive nowadays. Nutraceuticals are vegetable or marine bioderivatives obtained by means of non-denaturing biotechnological processes, which enable the preservation of the bioactive properties. The natural precedence of these products added to the absence of synthetic additives rules out the risk for adverse side effects. LipoEsar® has been demonstrated to reduce total cholesterol, LDL-cholesterol, and triglycerides, and to increase the levels of HDL-cholesterol levels in blood. LipoEsar® is also a powerful anti-atheromatous compound [105,110,528]. As hypercholesterolemia is one of the hallmarks of dementia-related neurodegenerative disorders, hypolipemic effect of LipoEsar® in combination with Atorvastatin, may constitute a potential treatment for neurodegenerative disorders involving dementia with barely non side-effects [105,509]. Another promising nutraceutical compound, Atremorine® (E-PodoFavaLin-15999®), is obtained from the vegetable species *Vicia faba, L*, a natural source of L-Dopa. Atremorine® displays spectacular effects on Parkinson's disease animal models and patients. Combination of

Atremorine with other dopaminergic compounds increase dopamine levels at physiological range and reduces the required dosage of those compounds, minimizing the possibility of adverse reactions [529]. It will be of great interest to examine the effects of these nutraceutical compounds on the epigenetic machinery in order to establish a new and promising direction in the treatment of neurodegenerative and other complex disorders.

REFERENCES

1. Murray CJL, Lopez AD (1996) The Global Burden of Disease. World Health Organisation, The Harvard School of Public Health,Geneva.
2. Menken M, Munsat TL, Toole JF (2000) The global burden of disease study: implications for neurology. Arch Neurol 57: 418-420.
3. Schneider JA, Arvanitakis Z, Bang W, Bennet DA (2007) Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 69: 2197-2204.
4. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) (2001) Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Lancet 357: 169-175.
5. Prohovnik I, Perl DP, Davis KL, Libow L, Lesser G, Haroutunian V (2006)Dissociation of neuropathology from severity of dementia in late-onset Alzheimer disease. Neurology 66: 49-55.
6. Cacabelos R (2011) The path to personalized medicine in mental disorders: The handbook of neuropsychiatric biomarkers, endophenotypes and genes. (4th edn), Springer, Netherlands.
7. Cacabelos R (2007) Pharmacogenetic basis for therapeutic optimization in Alzheimer's disease. Mol Diagn Ther 11: 385-405.
8. Cacabelos R (2008) Pharmacogenomics and therapeutic prospects in dementia Eur Arch Psychiatry Clin Neurosci 258: 1-553.
9. Tammen SA, Friso S, Choi SW (2013) Epigenetics: the link between nature and nurture. Mol Aspects Med 34: 753-764.
10. Sweatt JD (2013) The emerging field of neuroepigenetics. Neuron 80: 624-632.
11. Harris RA, Nagy-Szakal D, Kellermayer R (2013) Human metastable epiallele candidates link to common disorders. Epigenetics 8: 157-163.
12. Gräff J, Tsai LH (2013) The potential of HDAC inhibitors as cognitive enhancers. Annu Rev Pharmacol Toxicol 53: 311-330.
13. Mikaelsson MA, Miller CA (2011)The path to epigenetic treatment of memory disorders. Neurobiol Learn Mem 96: 13-18.
14. Van den Hove DL, Kompotis K, Lardenoije R, Kenis G, Mill J, et al. (2014) Epigenetically regulated microRNAs in Alzheimer's disease. Neurobiol Aging 35: 731-745.
15. Szulwach KE, Jin P (2014) Integrating DNA methylation dynamics into a framework for understanding epigenetic codes. Bioessays 36: 107-117.
16. Bestor TH, Edwards JR, Boulard M (2015) Notes on the role of dynamic DNA methylation in mammalian development. PNAS 112: 6796-6809.
17. Gavery MR, Roberts SB (2013) Predominant intragenic methylation is associated with gene expression characteristics in a bivalve mollusc. Peer J 1: e215.
18. Wang J, Yu JT, Tan MS, Jiang T, Tan L (2013) Epigenetic mechanisms in Alzheimer's disease: Implications for pathogenesis and therapy. Ageing Res Rev 12: 1024-1041.
19. Laurent L, Wong E, Li G, Huynh T, Tsirigos A, et al. (2010) Dynamic changes in the human methylome during differentiation. Genome Res 2: 320-231.
20. Nebbioso A, Carafa V, Benedetti R, Altucci L (2012) Trials with epigenetic drugs: An update. Mol Oncol 6: 657-682.
21. Cuadrado-Tejedor M, Oyarzabal J, Lucas MP, Franco R, García-Osta A (2013) Epigenetic drugs in Alzheimer's disease. BioMol Concepts 4: 433-445.
22. Cacabelos R (2014) Epigenomic networking in drug development: from pathogenic mechanisms to pharmacogenomics. Drug Dev Res 75: 348-365.
23. Cacabelos R, Torrellas C (2014) Epigenetic drug discovery for Alzheimer's disease. Expert Opin Drug Discov 9: 1059-1086.
24. Clapier CR, Cairns BR (2009) The biology of chromatin remodeling complexes. Ann Rev Biochem 78: 273-304.
25. Kouzarides T (2007) Chromatin modifications and their function. Cell 128: 693-705.
26. Strahl BD, Allis CD (2000) The language of covalent histone modification. Nature 403: 41-45.

27. Huynh JL, Casaccia P (2013) Epigenetic mechanisms in multiple sclerosis: Implications for pathogenesis and treatment. Lancet Neurol 12: 195-206.

28. Sterner DE, Berger SL (2000) Acetylation of histones and transcription-related factors. Microbiol Mol Biol Rev 64: 435-459.

29. Konsoula Z, Barile FA (2012) Epigenetic histone acetylation and deacetylation mechanisms in experimental models of neurodegenerative disorders. J Pharmacol Toxicol Methods 66: 215-220.

30. Xu K, Dai XL, Huang HC, Jiang ZF (2011) Targeting HDACs: a promising therapy for Alzheimer's disease. Oxid Med Cell Longev 2011: 143269.

31. Landgrave-Gómez J, Mercado-Gómez O, Guevara-Guzmán R (2015) Epigenetic mechanisms in neurological and neurodegenerative diseases. Frontiers Cell Neurosci 9: 58.

32. Celic I, Masumoto H, Griffith WP, Meluh P, Cotter RJ, et al. (2006) The sirtuins hst3 and Hst4p preserve genome integrity by controlling histone h3 lysine 56 deacetylation. Curr Biol 16: 1280–1289.

33. Maas NL, Miller KM, DeFazio LG, Toczyski DP (2006) Cell cycle and checkpoint regulation of histone H3 K56 acetylation by Hst3 and Hst4. Mol Cell 23: 109-119.

34. Doyon Y, CayrouC, Ullah M, Landry AJ, Cote V, et al. (2006) ING tumor suppressor proteins are critical regulators of chromatin acetylation required for genome expression and perpetuation. Mol Cell 21: 51-64.

35. Iizuka M, Matsui T, Takisawa H, Smith MM (2006) Regulation of replication licensing by acetyltransferase Hbo1. Mol Cell Biol 26: 1098-1108.

36. Shogren-Knaak M, Ishii H, Sun JM, Pazin MJ, Davie JR, et al. (2006) Histone H4-K16 acetylation controls chromatin structure and protein interactions. Science 311: 844–847.

37. Vaquero A, Scher MB, Lee DH, Sutton A, Cheng HL, et al. (2006) SirT2 is a histone deacetylase with preference for histone H4 Lys 16 during mitosis. Genes Dev 20: 1256-1261.

38. Balazs R (2014) Epigenetic mechanisms in Alzheimer's disease. Degener. Neurol Neuromuscul Dis 4: 85-102.

39. Bannister AJ, Kouzarides T (2005) Reversing histone methylation. Nature 436: 1103-1106

40. Huyen Y, Zgheib O, Ditullio RA Jr, Gorgoulis VG, Zacharatos P, et al. (2004) Methylated lysine 79 of histone H3 targets 53BP1 to DNA double-strand breaks. Nature 432: 406-411.

41. Botuyan MV, Lee J, Ward IM, Jim JE, Thompson JR, et al. (2006) Structural basis for the methylation statespecific recognition of histone H4-K20 by 53BP1 and Crb2 in DNA repair. Cell 127: 1361-1373.

42. MacDonald N, Welburn JP, Noble ME, Nguyen A, Yaffe MB, et al. (2005) Molecular basis for the recognition of phosphorylated and phosphoacetylated histone h3 by 14-3-3. Mol. Cell 20: 199-211.

43. Pokholok DK, Zeitlinger J, Hannett NM, Reynolds DB, Young RA (2006) Activated signal transduction kinases frequently occupe target genes. Science 313: 533-536.

44. Fillingham J, Keogh MC, Krogan NJ (2006) gH2AX and its role in DNA double-strand break repair. Biochem Cell Biol 84: 568-577.

45. Fischle W, Tseng BS, Dormann HL, Ueberheide BM, Garcia BA, et al. (2005) Regulation of HP1-chromatin binding by histone H3 methylation and phosphorylation. Nature 438: 1116-1122.

46. Dai J, Sultan S, Taylor SS, Higgins JM (2005) The kinase haspin is required for mitotic histone H3 Thr 3 phosphorylation and normal metaphase chromosome alignment. Genes Dev 19: 472-488.

47. Wang H, Zhai L, Xu J, Joo HY, Jackson S, et al. (2006) Histone H3 and H4 ubiquitylation by the CUL4-DDB-ROC1 ubiquitin ligase facilitates cellular response to DNA damage. Mol Cell 22: 383-394.

48. Zhu B, Zheng Y, Pham AD, Mandal SS, Erdjument-Bromage H, et al. (2005) Monoubiquitination of human histone H2B: the factors involved and their roles in HOX gene regulation. Mol Cell 20: 601-611.

49. Bergink S, Salomons FA, Hoogstraten D, Groothuis TA, de Waard H, et al. (2006) DNA damage triggers nucleotide excision repairdependent monoubiquitylation of histone H2A. Genes Dev 20: 1343-1352.

50. Nathan D, Ingvarsdottir K, Sterner DE, Bylebyl GR, Dokmanovic M, et al. (2006) Histone sumoylation is a negative regulator in Saccharomyces cerevisiae and shows dynamic interplay with positiveacting histone modifications. Genes Dev 20: 966-976.

51. ENCODE Project Consortium (2012) An integrated encyclopedia of DNA elements in the human genome. Nature 489: 57-74.

52. Pennisi E (2012) Genomics. ENCODE project writes eulogy for junk DNA. Science 337: 1159-1161.

53. Ernst C, Morton CC (2013) Identification and function of long non-coding RNA. Front Cell Neurosci 7: 168.

54. Jiao AL, Slack FJ (2014) RNA-mediated gene activation. Epigenetics 9: 27-36.

55. Wu P, Zuo X, Deng H, Liu X, Liu L, Ji A (2013) Roles of long noncoding RNAs in brain development, functional diversification and neurodegenerative diseases. Brain Res Bull 97: 69-80.

56. Merelo V, Durand D, Lescallette AR, Vrana KE, Hong LE, et al. (2015) Associating schizophrenia, long non-coding RNAs and neurostructural dynamics. Front Mol Neurosci 8: 57.

57. Qureshi IA, Mehler MF (2010) Genetic and epigenetic underpinnings of sex differences in the brain and in neurological and psychiatric disease susceptibility. Prog Brain Res 18: 77-95.

58. Johnson R (2012) Long non-coding RNAs in Huntington's disease neurodegeneration. Neurobiol Dis 46: 245-254.

59. Nishimoto Y, Nakagawa S, Hirose T, Okano HJ, Takao M, et al. (2013) The long non-coding RNA nuclear-enriched abundant transcript 1_2 induces paraspeckle formation in the motor neuron during the early phase of amyotrophic lateral sclerosis. Mol Brain 6: 31.

60. Velmeshev D, Magistri M, Faghihi MA (2013) Expression of non-protein-coding antisense RNAs in genomic regions related to autism spectrum disorders. Mol Autism 4: 32.

61. Beckman KB, Ames BN (1998) The free radical theory of aging matures. Physiological reviews78: 547-581.

62. Cencioni C, Spallotta F, Martelli F, Valente S, Mai A. et al. (2013) Oxidative stress and epigenetic regulation in ageing and age-related diseases. Int J Mol Sci 14: 17643-17663.

63. Rodrigues HF, Souza TA, Ghiraldini FG, Mello ML, Moraes AS (2014) Increased Age is Associated with Epigenetic and Structural Changes in Chromatin from Neuronal Nuclei. J Cell Biochem 115: 659-665.

64. Zhao YQ, Jordan IK, Lunyak VV (2013) Epigenetics components of aging in the central nervous system. Neurotherapeutics 10: 647-663.

65. Horvath S (2013) DNA methylation age of human tissues and cell types. Genome Biol 14: R115.

66. Oliveira AM, Hemstedt TJ, Bading H (2012) Rescue of aging-associated decline in Dnmt3a2 expression restores cognitive abilities. Nat Neurosci 15: 1111-1113.

67. Hernandez DG, Nalls MA, Gibbs JR, Arepalli S, van der Brug M, et al. (2011) Distinct DNA methylation changes highly correlated with chronological age in the human brain. Hum Mol Genet 20: 1164-1172.

68. Bollati V, Schwartz J, Wright R, Litonjua A, Tarantini L, Suh H, et al. (2009) Decline in genomic DNA methylation through aging in a cohort of elderly subjects. Mech Ageing Dev 130: 234-239.

69. Lopatina N, Haskell JF, Andrews LG, Poole JC, Saldanha S, Tollefsbol T (2002) Differential maintenance and de novo methylating activity by three DNA methyltransferases in aging and immortalized fibroblasts. J Cell Biochem 84: 324-334.

70. Pan K, Chen Y, Roth M, Wang W, Wang S, et al. (2013) HBP1-mediated transcriptional regulation of DNMT1 and its impact on cell senescence. Mol Cell Biol 33: 887-903.

71. Tohgi H, Utsugisawa K, Nagane Y, Yoshimura M, Ukitsu M, et al. (1999) The methylation status of cytosines in a tau gene promoter region alters with age to downregulate transcriptional activity in human cerebral cortex. Neurosci Lett 275: 89-92.

72. Munzel M, Globisch D, Bruckl T, Wagner M, Welzmiller V, Michalakis S, et al. (2010) Quantification of the sixth DNA base hydroxymethylcytosine in the brain. Angew Chem Int Ed Engl 49: 5375-5377.

73. Song CX, Szulwach KE, Fu Y, Dai Q, Yi C, Li X, et al. (2011) Selective chemical labeling reveals the genome-wide distribution of 5-hydroxymethylcytosine. Nat Biotechnol 29: 68-72.

74. Chouliaras L, van den Hove DL, Kenis G, Keitel S, R Hof P, van Os J, et al. (2012) Age-Related Increase in Levels of 5-Hydroxymethylcytosine in Mouse Hippocampus is Prevented by Caloric Restriction. Curr Alzheimer Res 9: 536-544.

75. Xu Z, Taylor JA (2014) Genome-wide age-related DNA methylation changes in blood and other

tissues relate to histone modification, expression, and cancer. Carcinogenesis 35: 356-364.

76. McClay JL, Aberg KA, Clark SL, Nerella S, Kumar G, Xie LY, et al. (2014) A methylome-wide study of aging using massively parallel sequencing of the methyl-CpG-enriched genomic fraction from blood in over 700 subjects. Hum Mol Genet 23: 1175-1185.
77. Thakur MK, Kanungo MS (1981) Methylation of chromosomal proteins and DNA of rat brain and its modulation by estradiol and calcium during aging. Exp Gerontol 16: 331-336.
78. Gupta S, Kim SY, Artis S, Molfese DL, Schumacher A, Sweatt JD, et al. (2010) Histone methylation regulates memory formation. J Neurosci 30: 3589-3599.
79. Wang CM, Tsai SN, Yew TW, Kwan YW, Ngai SM (2010) Identification of histone methylation multiplicities patterns in the brain of senescence-accelerated prone mouse 8. Biogerontology 11: 87-102.
80. Kawakami K, Nakamura A, Ishigami A, Goto S, Takahashi R (2009) Age-related difference of sitespecific histone modifications in rat liver. Biogerontology 10: 415-421.
81. Nakamura A, Kawakami K, Kametani F, Nakamoto H, Goto S (2010) Biological significance of protein modifications in aging and calorie restriction. Ann NY Acad Sci 1197: 33-39.
82. Chwang WB, O'Riordan KJ, Levenson JM, Sweatt JD (2006) ERK/MAPK regulates hippocampal histone phosphorylation following contextual fear conditioning. Learn Mem 13: 322-328.
83. Ryan JM, Cristofalo VJ (1972) Histone acetylation during aging of human cells in culture. Biochem. Biophys. Res Commun 48: 735-742.
84. Peleg S, Sananbenesi F, Zovoilis A, Burkhardt S, Bahari-Javan S, et al. (2010) Altered histone acetylation is associated with age-dependent memory impairment in mice. Science 328: 753-756.
85. Pina B, Martinez P, Suau P (1988) Differential acetylation of core histones in rat cerebral cortex neurons during development and aging. Eur J Biochem 174: 311-315.
86. Alarcón JM, Malleret G, Touzani K, Vronskaya S, Ishii S, et al. (2004) Chromatin Acetylation, Memory, and LTP Are Impaired in CBP< sup>+/−</sup> Mice: A Model for the Cognitive Deficit in Rubinstein-Taybi Syndrome and Its Amelioration. Neuron 42: 947-959.
87. Korzus E, Rosenfeld MG, Mayford M (2004) CBP histone acetyltransferase activity is a critical component of memory consolidation. Neuron 42: 961-972.
88. Spallotta F, Cencioni C, Straino S, Sbardella G, Castellano S, et al. (2013) Enhancement of lysine acetylation accelerates wound repair. Commun Integr Biol 6: e25466.
89. Chouliaras L, van den Hove DL, Kenis G, Draanen M, Hof PR, et al. (2013) Histone deacetylase 2 in the mouse hippocampus: attenuation of age-related increase by caloric restriction. Curr Alzheimer Res 10: 868-876.
90. Perry M, Chalkley R (1982) Histone acetylation increases the solubility of chromatin and occurs sequentially over most of the chromatin. A novel model for the biological role of histone acetylation. J Biol Chem 257: 7336-7347.
91. Fischer A, Sananbenesi F. Wang X, Dobbin M, Tsai LH (2007) Recovery of learning and memory is associated with chromatin remodelling. Nature 447: 178-182.
92. Guan JS, Haggarty SJ, Giacometti E, Dannenberg JH, Joseph N, et al. (2009) HDAC2 negatively regulates memory formation and synaptic plasticity. Nature 459: 55-60.
93. Quintas A, de Solis AJ, Diez-Guerra FJ, Carrascosa JM, Bogonez E (2012) Age-associated decrease of SIRT1 expression in rat hippocampus: prevention by late onset caloric restriction. Exp Gerontol 47: 198-201.
94. Sommer M, Poliak N, Upadhyay S, Ratovitski E, Nelkin BD, et al. (2006) DeltaNp63alpha overexpression induces downregulation of Sirt1 and an accelerated aging phenotype in the mouse. Cell Cycle 5: 2005-2011.
95. Sasaki T, Maier B, Bartke A, Scrable H (2006) Progressive loss of SIRT1 with cell cycle withdrawal. Aging cell 5: 413-422.
96. Guarente L, Picard F (2005) Calorie restriction--the SIR2 connection. Cell 120: 473-482.
97. Rutten BP, Brasnjevic I, Steinbusch HW, Schmitz C (2010) Caloric restriction and aging but not overexpression of SOD1 affect hippocampal volumes in mice. Mech Ageing Dev 131: 574-579.
98. Haigis MC, Sinclair DA (2010) Mammalian sirtuins: biological insights and disease relevance. Annu Rev Pathol 5: 253-295.

99. Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, et al. (2006) Resveratrol improves health and survival of mice on a high-calorie diet. Nature 444: 337-342.

100. Hooten NN, Abdelmohsen K, Gorospe M, Ejiogu N, Zonderman AB, et al. (2010) microRNA expression patterns reveal differential expression of target genes with age. PLoS One 5: e10724.

101. Hackl M, Brunner S, Fortschegger K, Schreiner C, Micutkova L, et al. (2010) miR-17, miR-19b, miR-20a, and miR-106a are down-regulated in human aging. Aging Cell 9: 291-296.

102. Li N, Bates DJ, An J, Terri DA, Wang E (2011) Up-regulation of key microRNAs, and inverse down-regulation of their predicted oxidative phosphorylationtarget genes, during aging in mouse brain. Neurobiol Aging 32: 944-955.

103. Cacabelos, R (2008) Pharmacogenomics in Alzheimer's disease. Methods Mol Biol 448: 213-357.

104. Cacabelos R, Fernández-Novoa L, Lombardi V, Kubota Y, Takeda M (2005) Molecular genetics of Alzheimer's disease and aging. Methods Find Exp Clin Pharmacol 27: 1-573.

105. Cacabelos R, Cacabelos P, Torrellas C, Tellado I, Carril JC (2014) Pharmacogenomics of Alzheimer's disease: novel therapeutic strategies for drug development. Methods Mol Biol 1175: 323-556.

106. Takeda M, Martínez R, Kudo T, Tanaka T, Okochi M, et al. (2010) Apolipoprotein E and central nervous system disorders: Reviews of clinical findings. Psychiatry Clin Neurosci 64: 592-607.

107. Cacabelos R, Fernández-Novoa L, Martínez-Bouza R, McKay A, Carril JC, et al. (2010) Future trends in the pharmacogenomics of brain disorders and dementia: Influence of APOE and CYP2D6 variants. Pharmaceuticals 3: 3040-3100.

108. Cacabelos R, Takeda M (2006) Pharmacogenomics, nutrigenomics and future therapeutics in Alzheimer's disease. Drugs Future 31: 5-146.

109. Cacabelos R, Martínez R, Fernández-Novoa L, Carril JC, Lombardi V, et al. (2012) Genomics of Dementia: APOE-and CYP2D6 Related Pharmacogenetics. Int J Alzheimers Dis 518901.

110. Cacabelos R (2012) World Guide for Drug Use and Pharmacogenomics. (1st edn), EuroEspes Publishing, Corunna, Spain.

111. Strittmatter WJ, Weisgraber KH, Huang DY, Dang LM, Salvesen GS, et al. (1993) Binding of human apolipoprotein E to synthetic amyloid beta peptide: isoform-specific effects and implications for late-onset Alzheimer disease. Proc Natl Acad Sci USA 90: 8098-80102.

112. Strittmatter WJ, Saunders AM, Schmechel D,Pericak-Vance M, Enghild J, et al. (1993) Apolipoprotein E: high-avidity binding to β-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci USA 90: 1977–1981.

113. Corder EH, Saunders AM, Strittmatter WJ,Schmechel DE, Gaskell PC,et al. (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261: 921-923.

114. Roses AD (2004) Pharmacogenetics and drug development: the path to safer and more effective drugs. Nat Rev Genet 5: 645-656.

115. Davies P, Maloney AJ (1976) Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet 2: 1403.

116. Kása P, Rakonczay Z, Gulya K (1997) The cholinergic system in Alzheimer's disease. Prog Neurobiol 52: 511-535.

117. Qizilbash N, Birks J, López-Arrieta J, Lewington S, Szeto S (2000) Tacrine for Alzheimer's disease. Cochrane Database Syst Rev. 2: CD000202.

118. Kornhuber J, Bormann J, Retz W, Hübers M, Riederer P (1989) Memantine displaces [3H] MK-801 at therapeutic concentrations in postmortem human frontal cortex. Eur. J Pharmacol 166: 589-590.

119. Chen HS, Pellegrini JW, Aggarwal SK, Lei SZ, Warach S, et al. (1992) Open-channel block of N-methyl-D-aspartate (NMDA) responses by memantine: therapeutic advantage against NMDA receptor-mediated neurotoxicity. J Neurosci 12: 4427-4436.

120. Chen HS, Lipton SA (1997) Mechanism of memantine block of NMDA-activated channels in rat retinal ganglion cells: uncompetitive antagonism. J Physiol (Lond.) 499: 27-46.

121. Rogawski MA, Wenk GL (2003) The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease. CNS Drug Rev 9: 275-308.

122. Robinson DM, Keating GM (2006) Memantine: a review of its use in Alzheimer's disease. Drugs 66: 1515-1534.

123. Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, et al. (2003) Memantine in moderater-to-severe Alzheimer's disease. New Engl J Med 348: 1333-1341.

124. Schneider LS, Dagerman KS, Higgins JP, McShane R (2011) Lack of evidence for the efficacy of memantine in mild Alzheimer disease. Arch Neurol 68: 991-998.

125. Kubota T, Takae H, Miyake K (2012) Epigenetic mechanisms and therapeutic perspectives for neurodevelopmental disorders. Pharmaceuticals (Basel) 5: 369-383.

126. White AO, Wood MA (2014) Does stress remove the HDAC brakes for the formation and persistence of long-term memory? Neurobiol Learn Mem 112: 61-67.

127. Zawia NH, Lahiri DK, Cardozo-Pelaez F (2009) Epigenetics, oxidative stress, and Alzheimer disease. Free Radic Biol Med 46:1241-1249.

128. Brochier C, Langley B (2013) Chromatin modifications associated with DNA double-strand breaks repair as potential targets for neurological diseases. Neurotherapeutics 10: 817-830.

129. Mastroeni D, Grover A, Delvaux E, Whiteside C, Coleman PD, et al. (2011) Epigenetic mechanisms in Alzheimer's disease. Neurobiol Aging 32: 1161-1180.

130. Faltraco F, Lista S, Garaci FG, Hampel H (2012) Epigenetic mechanisms in Alzheimer's disease: state-of-the-art. Eur J Neurodener Dis 1: 1-19.

131. Lu H, Liu X, Deng Y, Qing H (2013) DNA methylation, a hand behind neurodegenerative diseases. Front Aging Neurosci 5: 85.

132. Luca Lovrečić, Aleš Maver, Maja Zadel, Borut Peterlin (2013) The role of epigenetics in neurodegenerative diseases.

133. Lardenoije R, Latrou A, Kenis G, Kompotis K, Steinbusch HW, et al. (2015) The epigenetics of aging and neurodegeneration. Prog Neurobiol 131: 21-64.

134. Chouliaras L, Mastroeni D, Delvaux E, Grover A, Kenis G, et al. (2013) Consistent decrease in global DNA methylation and hydroxymethylation in the hippocampus of Alzheimer's disease patients. Neurobiol Aging 34: 2091-2099.

135. Raina A, Kaul D (2010) LXR-α genomics programmes neuronal death observed in Alzheimer's disease. Apoptosis 15: 1461-1469.

136. Tohgi H, Utsugisawa K, Nagane Y, Yoshimura M, Genda Y, et al. (1999) Reduction with age in methylcytosine in the promoter region -224 approximately-101 of the amyloid precursorprotein gene in autopsy human cortex. Brain Res Mol Brain Res 70: 288-292.

137. Brohede J, Rinde M, Winblad B, Graff C (2010) A DNA methylation study of the amyloid precursor protein gene in several brain regions from patients with familial Alzheimer disease. J Neurogenet 24: 179-181.

138. Guo X, Wu X, Ren L, Liu G, Li L (2011) Epigenetic mechanisms of amyloid-betaproduction in anisomycin-treated SH-SY5Y cells. Neuroscience 194: 272-281.

139. West RL, Lee JM, Maroun LE (1995) Hypomethylation of the amyloid precursor protein gene in the brain of an Alzheimer's disease patient. J Mol Neurosci 6: 141-146.

140. Barrachina M, Ferrer I (2009) DNA methylation of Alzheimer disease and tautopathy-related genes in postmortem brain. J Neuropathol Exp Neurol 68: 880-891.

141. Piaceri I, Raspanti B, Tedde A, Bagnoli S, Sorbi S, et al. (2015) Epigenetic modifications in Alzheimer's disease: cause or effect?. J Alzheimers Dis 43: 1169-1173.

142. Iwata A, Nagata K, Hatsuta H, Takuma H, Bundo M, et al. (2014). Altered CpG methylation in sporadic Alzheimer's disease is associated with APP and MAPT dysregulation. Hum Mol Genet 23: 648-656.

143. Chouliaras L, Rutten BP, Kenis G, Peerbooms O, Visser PJ, et al. (2010) Epigenetic regulation in the pathophysiology of Alzheimer's disease. Prog Neurobiol 90: 498-510.

144. Marques SC, Lemos R, Martins M, de Mendoça A, et al. (2012) Epigenetic regulation of BACE1 in Alzheimer's disease patients and in transgenic mice. Neuroscience 220: 256-266.

145. Wang SC, Oelze B, Schumacher A (2008) Age-specific epigenetic drift in late-onset Alzheimer's disease. PLoS One 3: e2698.

146. Fuso A, Seminara L, Cavallaro RA, D'Anselmi F, Scarpa S (2005) S-adenosylmethionine/homocysteine cycle alterations modify DNA methylation status with consequent dysregulation of PS1 and BACE and beta-amyloid production. Mol Cell Neurosci 28: 195-204.

147. Fuso A, Nicolia V, Cavallaro RA, Ricceri L, D'Anselmi F, et al. (2008) B-vitamin deprivation induces hyperhomocystinemia and brain S-adenosylhomocysteine, depletes brain S-adenosylmethionine, and enhances PS1 and BACE expression in amyloid-beta deposition in mice. Mol Cell Neurosci 37: 731-746.

148. Fuso A, Nicolia V, Pasqualato A, Fiorenza MT, Cavallaro RA, et al. (2011) Changes in Presenilin 1 gene methylation pattern in diet-induced B vitamin deficiency. Neurobiol Aging 32: 187-199.

149. Fuso A, Cavallara RA, Nicolia V, Scarpa S (2012) PSEN1 promoter demethylation in hyperhomocystinemic TgCRND8 mice is the culprit, not the consequence. Curr Alzheimer Res 9: 527-535.

150. Bottiglieri T, Godfrey P, Flynn T, Carney MW, Toone BK, et al. (1990) Cerebrospinal fluid S-adenosyl-methionine in depression and dementia: effects of treatment with parenteral and oral S-adenosyl-methionine. J Neurol Neurosurg Psychiatry 53: 1096-1098.

151. Morrison LD, Smith DD, Kish SJ (1996) Brain S-adenosylmethionine levels are severely decreased in Alzheimer's disease. J Neurochem 67: 1328-1331.

152. Serot JM, Christmann D, Dubost T, Bene MC, Faure GC (2001) CSF-folate levels are decreased in late-onset AD patients. J Neural Transm 108: 93-99.

153. Coppedè F, Tannorella P, Pezzini I, Migheli F, Ricci G, et al. (2012) Folate, homocysteine, vitamin B12, and polymorphisms of genes participating in one-carbon metabolism in lateonset Alzheimer's disease patients and healthy controls. Antioxid Redox Signal 17: 195-204.

154. Wang Y, Xu S, Cao Y, Xie Z, Lai C, et al. (2014) Folate deficiency exacerbates apoptosis by inducing hypomethylation and resultant overexpression of DR4 together with altering DNMTs in Alzheimer's disease. Int J Clin Exp Med 7: 1945-1957.

155. Nicolia V, Fuso A, Cavallaro RA, Di Luzio A, Scarpa S (2010) B vitamin deficiency promotes tau phosphorylation through regulation of GSK3beta and PP2A. J Alzheimers Dis 19: 895-907.

156. Sontag E, Nunbhakdi-Craig V, Sontag JM, Diaz-Arrastia R, Ogris E, et al. (2007) Protein phosphatase 2A methyltransferase links homocysteine metabolism with tau and amyloid precursor protein regulation. J Neurosci 27: 2751-2759.

157. Caesar I, Gandy S (2012) Evidence that an APOE 4 'double whammy' increases risk for Alzheimer's disease. BMC Med 10: 36.

158. Suuronen T, Nuutinen T, Ryhänen T, Kaaniranta K, Salminen A (2007). Epigenetic regulation of clusterin/apolipoprotein J expression in retinal pigment epithelial cells. Biochem Biophys Res Commun 357: 397-401.

159. Offe K, Dodson SE, Shoemaker JT, Fritz JJ, Gearing M, et al. (2006) The lipoprotein receptor LR11 regulates amyloid beta productionand amyloid precursor protein traffic in endosomal compartments. J Neurosci 26: 1596-1603.

160. Furuya TK, da Silva PN, Payao SL, Rasmussen LT, de Labio RW, et al. (2012) SORL1 and SIRT1 mRNA expression and promoter methylation levels in agingand Alzheimer's disease. Neurochem Int 61: 973-975.

161. PL De Jager,G Srivastava,K Lunnon,Burgess J, Schalkwyc LC, et al. (2014) Alzheimery's disease pathology is associated with early alterations in brain DNA methylation at ANK1, BIN1, RHBDF2 and other loci. Nat Neurosci 17: 1156-1163.

162. Karch CM, Jeng AT, Nowotny P, Cady J, Cruchaga C, et al. (2012) Expression of novel Alzheimer's disease risk genes in control and Alzheimer's disease brains. PLoS One 7: e50976.

163. Chapuis J, Hansmannel F, Gistelinck M, Mounier A, Van Cauwenberghe C, et al. (2013) GERAD consortium. Increased expression of BIN1 mediates Alzheimer genetic risk by modulating tau pathology. Mol Psychiatry 18: 1225-1234.

164. Karch CM, Cruchaga C, Goate A (2014) Alzheimer's disease genetics: from the bench to the clinic. Neuron 83: 11-26.

165. Griciuc A, Serrano-Pozo A, Parrado AR, Lesinski AN, Asselin CN, et al. (2013) Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta. Neuron 78: 631-643.

166. Xie Z, Culley DJ, Dong Y, Zhang G, Zhang B, et al. (2008) The common inhalation anesthesic isofluorane induces caspase activation and increases amyloid beta-protein level in vivo. Ann Neurol 64: 618-627.

167. Xiong M, Zhang T, Zhang LM, Lu SD, Huang YL, et al. (2008) Caspase inhibition attenuates accumulation of beta-amyloid by reducing beta-secretase production and activity in rat brains after stroke. Neurobiol Dis 32: 433-441.

168. Müerköster SS, Werbing V, Koch D, Sipos B, Ammerpohl O, et al. (2008). Role of myofibroblasts in innate chemoresistance of pancreatic carcinoma--epigenetic regulation of caspases. Int J Cancer 123: 1751-1760.

169. Wilson AG (2008) Epigenetic regulation of gene expression in the inflammatory response and relevance to common diseases. J Periodontol 79: 1514-1519.

170. Iwata N, Tsubuki S, Takaki Y, Watanabe K, Sekiguchi M, et al. (2000) Identification of the major Abeta1-42-degrading catabolic pathway in brain parenchyma: suppression leads to biochemical and pathological deposition. Nat Med 6: 143-150.

171. Chen KL, Wang SS, Yang YY, Yuang RY, Chen RM, et al. (2009) The epigenetic effects of amyloid-beta(1-40) on global DNA and neprilysin genes in murine cerebral endothelial cells. Biochem Biophys Res Commun 378: 57-61.

172. Bollati V, Galimberti D, Pergoli L, Dalla Valle E, Barretta F, et al. (2011) DNA methylation in repetitive elements and Alzheimer disease. Brain Behav Immun 25: 1078-1083.

173. Siegmund KD, Connor CM, Campan M, Long T, Weisenberg DJ, et al. (2007) DNA methylation in the human cerebral cortex is dynamically regulated throughout the life span and involves differentiated neurons. PLOS ONE 2: e895.

174. Sanchez-Mut JV, Aso E, Panayotis N, Lott I, Dierssen M, et al. (2013) DNA methylation map of mouse and human brain identifies target genes in Alzheimer's disease. Brain 136: 3018-3027.

175. Stilling RM, Fischer A (2011) The role of histone acetylation in age-associated memory impairment and Alzheimer's disease. Neurobiol Learn Mem 96: 19-26.

176. Zhang K, Schrag M, Crofton A, Trivedi R, Vinters H, et al. (2012) Targeted proteomics for quantification of histone acetylation in Alzheimer's disease. Proteomics 12: 1261-1268.

177. Francis YI, Fà M, Ashraf H, Zhang H, Staniszewski A, et al. (2009) Dysregulation of histone acetylation in the APP/PS1 mouse model of Alzheimer's disease. J Alzheimers Dis 18: 131-139.

178. Liu R, Lei JX, Luo C, Lan X, Chi L, et al. (2012) Increased EID1 nuclear translocation impairs synaptic plasticity and memory function associated with pathogenesis of Alzheimer's disease. Neurobiol Dis 45: 902-912.

179. Caccamo A, Maldonado MA, Bokov AF, Majumder S, Oddo S (2010) CBP gene transfer increases BDNF levels and ameliorates learning and memory deficits in a mouse model of Alzheimer's disease. Proc Natl Acad Sci USA 107: 22687-22692.

180. Lithner CU, Hernandez CM, Nordberg A, Sweatt JD (2009) Epigenetic changes related to beta amyloid-implications for Alzheimer's disease. Alzheimer's Dementia 5: P304.

181. Ding H, Dolan PJ, Johnson GV (2008) Histone deacetylase 6 interacts with the microtubule associated protein tau. J Neurochem 106: 2119-2130.

182. Govindarajan N, Rao P, Burkhardt S, Sananbenesi F, Schluter OM, et al. (2013) Reducing HDAC6 ameliorates cognitive deficits in a mouse model for Alzheimer's disease. EMBO Mol Med 5: 52-63.

183. Simões-Pires C, Zwick V, Nurisso A, Schenker E, Carrupt PA, et al. (2013) HDAC6 as a target for neurodegenerative diseases: what makes it different from the other HDACs? Mol Neurodegener 8: 7.

184. Cook C, Carlomagno Y, Gendron TF, Dunmore J, Scheffel K, et al. (2014) Acetylation of the KXGS motifs in tau is a critical determinant in modulation of tau aggregation and clearance. Hum Mol Genet 23: 104-116.

185. XiongY, Zhao K, Wu J, Xu Z, Jin S, et al. (2013) HDAC6 mutations rescue human tau induced microtubule defects in Drosophila. Proc Natl Acad Sci USA 110: 4604-4609.

186. Kilgore M, Miller CA, Fass DM, Hennig KM, Haggarty SJ, et al. (2009) Inhibitors of class 1 histone deacetylases reverse contextual memory deficits in a mouse model of Alzheimer's disease. Neuropsychopharmacology 35: 870-880.

187. Peleg S, Sananbenesi F, Zovoilis A, Burkhardt S, Bahari-Javan S, et al. (2010) Altered histone acetylation is associated with age-dependent memory impairment in mice. Science 328: 753-756.

188. Agis-Balboa RC, Pavelka Z, Kerimoglu C, Fischer A (2013) Loss of HDAC5 impairs memory function: implications for Alzheimer's disease. J Alzheimers Dis 33: 35-44.

189. Kim MS, Akhtar MW, Adachi M, Mahgoub M, Bassel-Duby R, et al. (2012) An essential role for histone deacetylase 4 in synaptic plasticity and memory formation. J Neurosci 32: 10879-10886.

190. Julien C, Tremblay C, Émond V, Lebbadi M, Salem Jr N, et al. (2009) SIRT1 Decrease Parallels the Accumulation of tau in Alzheimer Disease. J Neuropathol Exp Neurol 68: 48.

191. Morris BJ (2013) Seven sirtuins for seven deadly diseases of aging. Free Radic Biol Med 56: 133-171.

192. Donmez G, Wang D, Cohen DE, Guarente L (2010) SIRT1 suppresses beta-amyloid production by activating the alpha-secretase gene ADAM10. Cell 142: 320-332.

193. Kim D, Nguyen MD, Dobbin MM, Fischer A, Sananbenesi F, et al. (2007) SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis. Embo J 26: 3169-3179.

194. Min SW, Cho SH, Zhou Y, Schroeder S, Haroutunian V, et al. (2010) Acetylation of tau inhibits its degradation and contributes to tauopathy. Neuron 67: 953-966.

195. Rao JS, Keleshian VL, Klein S, Rapoport SI (2012) Epigenetic modifications in frontal cortex from Alzheimer's disease and bipolar disorder patients. Translational Psychiatry 2: e132.

196. Myung NH, Zhu X, Kruman II, Castellani RJ, Petersen RB, et al. (2008) Evidence of DNA damage in Alzheimer disease: phosphorylation of histone H2AX in astrocytes. Age 30: 209-215.

197. Ogawa O, Zhu X, Lee HG, Raina A, Obrenovich ME, et al. (2003) Ectopic localization of phosphorylated histone H3 in Alzheimer's disease: a mitotic catastrophe? Acta Neuropathol 105: 524-528.

198. Hyman BT, Elvhage TE, Reiter J (1994) Extracellular signal regulated kinases. Localization of protein and mRNA in the human hippocampal formation in Alzheimer's disease. Am J Pathol 144: 565-572.

199. Perry G, Roder H, Nunomura A, Takeda A, Friedlich AL, et al. (1999) Activation of neuronal extracellular receptor kinase (ERK) in Alzheimer disease links oxidative stress to abnormal phosphorylation. Neuroreport 10: 2411-2415.

200. Zhu X, Castellani RJ, Takeda A, Nunomura A, Atwood CS, et al. (2001) Differential activation of neuronal ERK, JNK/SAPK and p38 in Alzheimer disease: the 'two hit' hypothesis. Mech Ageing Dev 123: 39-46.

201. Lithner CU, Lacor PN, Zhao WQ, Mustafiz T, Klein WL, et al. (2013) Disruption of neocortical histone H3 homeostasis by soluble Aβ: implications for Alzheimer's disease. Neurobiol Aging 34: 2081-2090.

202. Fischer A (2014) Targeting histone-modifications in Alzheimer's disease. What is the evidence that this is a promising therapeutic avenue? Neuropharmacology 80: 95-102.

203. Fontan-Lozano A, Suarez-Pereira I, Horrillo A, del-Pozo-Martin Y, Hmadcha A, et al. (2010) Histone H1 poly[ADP]-ribosylation regulates the chromatin alterations required for learning consolidation. J Neurosci 30: 13305-13313.

204. Abeti R, Abramov AY, Duchen MR (2011) Beta-amyloid activates PARP causing astrocytic metabolic failure and neuronal death. Brain 134: 1658-1672.

205. Liu HP, Lin WY, Wu BT, Liu SH, Wang WF, et al. (2010) Evaluation of the poly(ADP-ribose) polymerase-1 gene variants in Alzheimer's disease. J Clin Lab Anal 24: 182-186.

206. Strosznajder JB, Czapski GA, Adamczyk A, Strosznajder RP(2012) Poly(ADP-ribose) polymerase- 1 in amyloid beta toxicity and Alzheimer's disease. Molecular neurobiology 46:78-84.

207. Grasso M, Piscopo P, Confaloni A, Denti MA (2014) Circulating miRNAs as biomarkers for neurodegenerative disorders. Molecules 19: 6891-6910.

208. Maciotta S, Meregalli M, Torrente Y (2013). The involvement of microRNAs in neurodegenerative diseases. Front Cell Neurosci 7: 265.

209. Hebert SS, De Strooper B (2009) Alterations of the microRNA network cause neurodegenerative disease. Trends Neurosci 32: 199-206.

210. Faghihi MA, Modarresi F, Khalil AM, Wood DE, Sahagan BG, et al. (2008) Expression of a noncoding RNA is elevated in Alzheimer's disease and drives rapid feed-forward regulation of β-secretase. Nature Med 14: 723-730.

211. Massone S, Vassallo I, Fiorino G, Castelnuovo M, Barbieri F, et al. (2011) 17A, a novel noncoding RNA, regulates GABA B alternative splicing and signaling in response to inflammatory stimuli and in Alzheimer disease. Neurobiol Dis 41: 308-317.

212. Vilardo E, Barbato C, Ciotti M, Cogoni C, Ruberti F (2010) MicroRNA-101 regulates amyloid precursor protein expression in hippoccampal neurons. J Biol Chem. 285: 18344-18351.

213. Long, JM, Lahiri DK (2011) MicroRNA-101 downregulates Alzheimer's amyloid- precursor protein levels in human cell cultures and is differentially expressed. Biochem Biophys Res Commun 404: 889-895.

214. Delay C, Calon F, Mathews P, Herbert SS (2011) Alzheimer-specific variants in the 3'UTR of Amyloid precursor protein affect microRNA function. Mol Neurodegener 6: 70.

215. Liu W, Liu C, Zhu J, Shu P, Yin B, et al. (2012) MicroRNA-16 targets amyloid precursor protein to potentially modulate Alzheimer's-associated pathogenesis in SAMP8 mice. Neurobiol Aging 33: 522-534.

216. Smith P, Al Hashimi A, Girard J, Delay C, Hérbert SS (2011) In vivo regulation of amyloid precursor protein neuronal splicing by microRNAs. J Neurochem 116: 240-247.

217. Hébert SS, Horré K, Nicolaï L, Papadopoulou AS, Mandemakers W, et al. (2008) Loss of microRNA cluster miR-29a/b-1 in sporadic Alzheimer's disease correlates with increased BACE1/-secretase expression. Proc Natl Acad Sci USA 105: 6415-6420.

218. Zong Y, Wang H, Dong W, Quan X, Zhu H, et al. (2011) miR-29c regulates BACE1 protein expression. Brain Res 1395: 108-115.

219. Wang WX, Rajeev BW, Stromberg AJ, Ren N, Tang G, et al. (2008) The expression of microRNA miR-107 decreases early in Alzheimer's disease and may accelerate disease progression through regulation of -site amyloid precursor protein-cleaving enzyme 1. J Neurosci 28: 1213-1223.

220. Boissonneault V, Plante I, Rivest S, Provost P (2009) MicroRNA-298 and microRNA-328 regulate expression of mouse -amyloid precursor protein-converting enzyme 1. J Biol Chem 284: 1971-1981.

221. Zhu HC, Wang LM, Wang M, Song B, Tan S, et al. (2012) MicroRNA-195 downregulates Alzheimer's disease amyloid- production by targeting BACE1. Brain Res Bull 88: 596-601.

222. Cao Z, Henzel WJ, Gao X (1996) IRAK: a kinase associated the interleukin-1 receptor. Science 271: 1128-1131.

223. Swantek JL, Tsen MF, Cobb MH, Thomas JA (2000) IL-1 receptor-associated kinase modulates host responsiviness to endotoxin. J Immunol 164: 430-436.

224. Flannery S, Bowie AG (2010)The interleukin-1 receptor-associated kinases: critical regulators of innate immune signalling. Biochem Pharmacol 80: 1981-1991.

225. Jayadev S, Case A, Alajajian B, Eastman AJ, Moller T, et al. (2013). Presenilin 2 influences miR146 level and activity in microglia. J Neurochem 127: 592-599.

226. Cui JG, Li YY, Zhao Y, Bhattacharjee S, Lukiw WJ (2010) Differential regulation of interleukin-1 receptor-associated kinase-1 (IRAK-1) and IRAK-2 by microRNA-146a and NF-(B in stressed human astroglial cells and in Alzheimer disease. J Biol Chem 285: 38951-38960.

227. Taganov KD, Boldin MP, Chang KJ, Baltimore D (2006) NF-B-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc Natl Acad Sci USA 103: 12481-12486.

228. Massone S, Ciarlo E, Vella S, Nizzari M, Florio T, et al. (2012) NDM29, A RNA polymerase III-dependent non coding RNA, promotes amyloidogenic processing of amyloid precursor protein (APP) and amyloid secretion. Biochim Biophys Acta 1823: 1170-1177.

229. Wang WX, Huang Q, Hu Y, Stromberg AJ, Nelson PT (2011) Patterns of microRNA expression in normal and early Alzheimer's disease human temporal cortex: white matter versus gray matter. Acta Neuropathol 121: 193-205.

230. Wang WX, Wilfred BR, Madathil SK, Tang G, Hu Y, et al. (2010) miR-107 regulates granulin/progranulin with implications for traumatic brain injury and neurodegenerative disease. Am J Pathol 177: 334-345.

231. Geekiyanage H, Chan C (2011) MicroRNA-137/181c regulates serine palmitoyltransferase and in turn amyloid, novel targets in sporadic Alzheimer's Disease. J Neurosci 31: 14820-14830.

232. Akram A, Schmeidler J, Katsel P, Hof PR, Haroutunian V (2010) Increased expression of cholesterol transporter ABCA1 is highly correlated with severity of dementia in AD hippocampus. Brain Res 1318: 167-177.

233. Smith PY, Delay C, Girard J, et al. (2011) MicroRNA-132 loss is associated with tau exon 10 inclusion in progressive supranuclear palsy. Hum Mol Genet 20: 4016-4024.

234. Hébert SS, Papadopoulou AS, Smith P, Papon MA, Planel E, et al. (2010) Genetic ablation of Dicer in adult forebrain neurons results in abnormal tau

hyperphosphorylation and neurodegeneration. Hum Mol Genet 19: 3959-3969.

235. Caputo V, Sinibaldi L, Fiorentino A, Parisi C, Catalanotto C, et al. (2011) Brain derived neurotrophic factor (BDNF) expression is regulated by microRNAs miR-26a and miR-26b allele-specific binding. PLoS One 6: e28656.

236. Mohamed JS, Lopez MA, Boriek AM (2010) Mechanical stretch up-regulates microRNA-26a and induces human airway smooth muscle hypertrophy by suppressing glycogen synthase kinase 3. J Biol Chem 285: 29336-29347.

237. Schonrock N, Humphreys DT, Preiss T, Götz J (2012) Target gene repression mediated by miRNAs miR-181c and miR-9 both of which are down-regulatedby amyloid. J Mol Neurosci 46: 324-335.

238. Zovoilis A, Agbemenyah HY, Agis-Balboa RC, Stilling RM, Edbauer D, et al. (2011) microRNA-34c is a novel target to treat dementias. EMBO J 30: 4299-4308.

239. Carrettiero DC, Hernandez I, Neveu P, Papagiannakopoulos T, Kosik KS (2009) The cochaperone BAG2 sweeps paired helical filament-insoluble tau from the microtubule. J Neurosci 29: 2151-2161.

240. Sethi P, Lukiw WJ (2009) Micro-RNA abundance and stability in human brain: specific alterations in Alzheimer's disease temporal lobe neocortex. Neurosci Lett 459: 100-104.

241. Kumar P, Dezso Z, Mackenzie C. Oestreicher J, Agoulnik S, et al. (2013) Circulating miRNA biomarkers for Alzheimer's disease. PLoS One8: e69807.

242. Leidinger P, Backes C, Deutscher S, Schmitt K, Mueller SC, et al. (2013) A blood based 12-miRNA signature of Alzheimer disease patients. Genome Biol 14: R78.

243. Alexandrov PN, Dua P, Hill JM, Bhattacharjee S, Zhao Y, et al. (2012) microRNA (miRNA) speciation in Alzheimer's disease (AD) cerebrospinal fluid (CSF) and extracellular fluid (ECF). Int J Biochem Mol Biol 3: 365-373.

244. National Institute of Mental Health (2016) ClinicalTrials. gov [Internet]. Bethesda (MD): National Library of Medicine (US).

245. Coppedè F (2014) The potential of epigenetic therapies in neurodegenerative diseases. Front Genet 5: 220.

246. Lee S, Lemere CA, Frost JL, Shea TB (2012) Dietary supplementation with S-adenosyl methionine delayed amyloid-β and tau pathology in 3xTg-AD mice. J Alzheimers Dis 28: 423-431.

247. Tchantchou F, Graves M, Falcone D, Shea TB (2008) S-adenosylmethionine mediates glutathione efficacy by increasing glutathione S-transferase activity: implications for S-adenosyl methionine as a neuroprotective dietary supplement. J Alzheimers Dis 14: 323-328.

248. Durga J, van Boxtel MP, Schouten EG, Kok FJ, Jolles J, et al. (2007) Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet 369: 208-216.

249. Haan MN, Miller JW, Aiello AE, Whitmer RA, Jagust WJ, et al. (2007) Homocysteine, B vitamins, and the incidence of dementia and cognitive impairment: results from the Sacramento Area Latino Study on Aging. Am J Clin Nutr 85: 511-517.

250. Martin SL, Hardy TM, Tollefsbol TO (2013) Medical chemistry of the epigenetic diet and calory restriction. Curr Med Chem 20: 4050-4059.

251. Dauncey MJ (2013) Genomic and epigenomic insights into nutrition and brain disorders. Nutrients 5: 887-914.

252. Malouf R, Grimley Evans J, Areosa Sastre A (2003) Folic acid with or without vitamin B12 for cognition and dementia. Cochrane Database Syst Rev 4: CD004514

253. McMahon JA, Green TJ, Skeaff CM, Knight RG, Mann JI, et al. (2006) A controlled trial of homocysteine lowering and cognitive performance. N Engl J Med 354: 2764-2772.

254. Campbell NRC (1996) How safe are folic acid supplements? Arch Intern Med 156: 1638-1644.

255. Lötsch J, Schneider G, Reker D, Parnham MJ, Schneider P et al. (2013) Common non-epigenetic drugs as epigenetic modulators. Trends Mol Med 19: 742-753.

256. Kelly TK, De Carvalho DD, Jones PA (2010) Epigenetic modifications as therapeutic targets. Nat Biotechnol 28: 1069-1078.

257. Issa JP, Garcia-Manero G, Giles FJ, Mannari R, Thomas D, et al. (2004) Phase I study of low-dose prolonged exposure schedules of the hypomethylating agent 5-aza-2'-deoxycytidine (decitabine) in hematopoietic malignances. Blood 103: 1635-1640.

258. Momparler RL, Bouffard DY, Momparler LF, Dionne J, Belanger K, et al. (1997) Pilot phase I-II study on 5-aza-2'-deoxycytidine (Decitabine) in patients with metastatic lung cancer. Anticancer Drugs 8: 358-368.

259. Bieschke J (2013) Natural compounds may open new routes to treatment of amyloid diseases. Neurotherapeutics 10: 429-439.

260. Dragicevic N, Smith A, Lin X, Yuan F, Copes N, et al. (2011) Green tea epigallocatechin-3-gallate (EGCG) and other flavonoids reduce Alzheimer's amyloid-induced mitochondrial dysfunction. J Alzheimers Dis 26: 507-521.

261. Zhang X, Wu M, Lu F, Luo N, He ZP, et al. (2014) Involvement of alpha7 nAChR signaling cascade in epigallocatechin gallate suppression of beta-amyloid-induced apoptotic cortical neuronal insults. Mol Neurobiol 49: 66-77.

262. Arrowsmith CH, Bountra C, Fish PV, Lee K, Schapira M (2012) Epigenetic protein families: a new frontier for drug discovery. Nat Rev Drug Discov 11: 384-400.

263. Levenson JM, O'Riordan KJ, Brown KD, Trinh MA, Molfese DL, et al. (2004) Regulation of histone acetylation during memory formation in the hippocampus. J Biol Chem 279: 40545-40559.

264. Levenson JM, Sweatt JD (2005) Epigenetic mechanisms in memory formation. Nat Rev Neurosci 6: 108-118.

265. Govindarajan N, Agis-Balboa RC, Walter J, Sananbenesi F, Fischer A (2011) Sodium butyrate improves memory function in an Alzheimer's disease mouse model when administered at an advanced stage of disease progression. J Alzheimers Dis 26: 187-197.

266. Kilgore M, Miller CA, Fass DM, Hennig KM, Haggarty SJ, et al. (2010) Inhibitors of class I histone deacetylases reverse contextual memory deficits in a mouse model of Alzheimer's disease. Neuropsychopharmacol 35: 870-880.

267. Gagliano H, Delgado-Morales R, Sanz-Garcia A, Armario A (2013) High doses of the histon deacetylase inhibitor sodium butyrate trigger a stress-like response. Neuropharmacol 79C: 75-82.

268. Ricobaraza A, Cuadrado-Tejedor M, Marco S, Pérez-Otaño I, García-Osta A (2012) Phenylbutyrate rescues dendritic spine loss associated with memory deficits in a mouse model of Alzheimer's disease. Hippocampus 22: 1040-1050.

269. Ricobaraza A, Cuadrado-Tejedor M, Perez-Mediavilla A, Frechilla D, Del Rio J, et al. (2009) Phenylbutyrate ameliorates cognitive deficit and reduces tau pathology in an Alzheimer's disease mouse model. Neuropsychopharmacol 34: 1721-1732.

270. Su Y, Ryder J, Li B, Wu X, Fox N, et al. (2004) Lithium, a common drug for bipolar disorder treatment, regulates amyloid-precursor protein processing. Biochem 43: 6899-6908.

271. Qing H, He G, Ly PT, Fox CJ, Staufenbiel M, et al. (2008) Valproic acid inhibits Abeta production, neuritic plaque formation, and behavioral deficits in Alzheimer's disease mouse models. J Exp Med 205: 2781-2789.

272. Herrmann N, Lanctôt KL, Rothenburg LS, Eryavec G (2007) A placebo-controlled trial of valproate for agitation and aggression in Alzheimer's disease. Dement Geriatr Cogn Disord 23:116-119.

273. Tariot PN, Raman R, Jakimovich L, Schneider L, Porsteinsson A, et al. (2005) Divalproex sodium in nursing home residents with possible or probable Alzheimer Disease complicated by agitation: a randomized, controlled trial. Am J Geriatr Psychiatry 13: 942-949.

274. Forester B, Vanelli M, Hyde J, Perez R, Ahokpossi C, et al. (2007) Report on an open-label prospective study of divalproex sodium for the behavioral and psychological symptoms of dementia as monotherapy and in combination with second-generation antipsychotic medication. Am J Geriatr Pharmacother 5: 209-217.

275. Ishimaru N, Fukuchi M, Hirai A, Chiba Y, Tamura T, et al. (2010) Differential epigenetic regulation of BDNF and NT-3 genes by trichostatin A and 5-Aza-2'-deoxycytidine in Neuro-2a cells. Biochem Biophys Res Commun 394: 173-177.

276. Tian F, Marini AM, Lipsky RH (2010) Effects of histone deacetylase inhibitor trichostatin A on epigenetic changes and transcriptional activation of Bdnf promoter I by rat hippocampal neurons. Ann NY Acad Sci 1199: 186-193.

277. Vecsey CG, Hawk JD, Lattal KM, Stein JM, Fabian SA, et al. (2007) Histone deacetylase inhibitors enhance memory and synaptic plasticity via CREB: CBP-dependent transcriptional activation. J Neurosci 27: 6128-6140.

278. Peleg S, Sananbenesi F, Zovoilis A, Burkhardt S, Bahari-Javan S, et al. (2010) Altered histone acetylation is associated with age-dependent

memory impairment in mice. Science 328: 753-756.

279. Nuutinen T, Suuronen T, Kauppinen A, Salminen A (2010) Valproic acid stimulates clusterin expression in human astrocytes: implications for Alzheimer's disease. Neurosci Lett 475: 64-68.

280. Green KN, Steffan JS, Martinez-Coria H, Sun X, Schreiber SS, et al. (2008) Nicotinamide restores cognition in Alzheimer's disease transgenic mice via a mechanism involving sirtuin inhibition and selective reduction of Thr231-phosphotau. J Neurosci 28: 11500-11510.

281. Haggarty SJ, Koeller KM, Wong JC, Grozinger CM, Schreiber SL (2003) Domain-selective small-molecule inhibitor of histone deacetylase 6 (HDAC6)-mediated tubulin deacetylation. Proc Natl Acad Sci USA 100: 4389-4394.

282. Zhang Z, Schluesener YHJ (2013) Oral administration of histone deacetylase inhibitor MS-275 ameliorates neuroinflammation and cerebral amyloidosis and improves behavior in a mouse model. J Neuropathol Exp Neurol 72: 178-185.

283. Sung YM, Lee T, Yoon H, DiBattista AM, Song J, et al. (2013) Mercaptoacetamide-based class II HDAC inhibitor lowers Aβ levels and improves learning and memory in a mouse model of Alzheimer's disease. Exp Neurol 239: 192-201.

284. Granzotto A, Zatta P (2011) Resveratrol acts not through anti-aggregative pathways but mainly via its scavenging properties against Abeta and Abeta-metal complexes toxicity. PLoS ONE 6: e21565.

285. Feng X, Liang N, Zhu D, Gao Q, Peng L, et al. (2013) Resveratrol inhibits beta-amyloid-induced neuronal apoptosis through regulation of SIRT1-ROCK1 signaling pathway. PLoS ONE 8: e59888.

286. Chatterjee S, Mizar P, Cassel R, Neidl R, Selvi BR, et al. (2013) A novel activator of CBP/p300 acetyltransferases promotes neurogenesis and extends memory duration in adult mice. J Neurosci 33: 10698-10712.

287. Narayan PJ, Dragunow M (2010) High content analysis of histone acetylation in human cells and tissues. J Neurosci Methods 193: 54-61.

288. Witkin JM, Li X (2013) Curcumin, an active constituent of the ancient medicinal herb Curcuma longa L. : some uses and the establishment and biological basis of medical efficacy. CNS Neurol. Disord. Drug Targets 12: 487-497.

289. Sood PK, Nahar U, Nehru B (2011) Curcumin attenuates aluminum-induced oxidative stress and mitocondrial dysfunction in rat brain. Neurotox Res 20: 351-361.

290. Hoppe JB, Coradini K, Frozza RL, Oliveira CM, Meneghetti AB, et al. (2013) Free and nanoencapsulated curcumin suppress beta-amyloid –induced cognitive impairments in rats: Involvement of BDNF and Akt/GSK-3beta signaling pathway. Neurobiol Learn Mem 106: 134-1344.

291. Ahmed T, Gilani AH (2013) Therapeutic potential of turmeric in Alzheimer's disease: curcumin or curcuminoids?. Phytother Res 28: 517-525.

292. Hishikawa N, Takahashi Y, Amakusa Y, Tanno Y, Tuji Y, et al. (2012) Effects of turmeric on Alzheimer's disease with behavioral and psychological symptoms of dementia. Ayu 33: 499-504.

293. Peedicayil J (2014) Epigenetic drugs in cognitive disorders. Curr Pharm Des 20: 1840-1846.

294. Fang MR, Wang J, Zhang XB, Geng Y, Hu ZY, et al. (2012) The miR-124 regulates the expression of BACE1/beta-secretase correlated with cell death in Alzheimer's disease. Toxicol Lett 209: 94-105.

295. Xu T, Li L, Huang C, Li X, Peng Y, et al. (2014) MicroRNA-323-3p with clinical potential in rheumatoid arthritis, Alzheimer's disease and ectopic pregnancy. Expert Opin Ther Targets 18: 153-158.

296. Li B, Sun H (2013) Mir-26a promotes neurite outgrowth by repressing PTEN expression. Mol Med Rep 8: 676-680.

297. Ni J, Wang P, Zhang J, Chen W, Gu L (2013) Silencing of the P2X(7) receptor enhances amyloid-beta phagocytosis by microglia. Biochem Biophys Res Commun 434: 363-369.

298. Varela MA, Roberts TC, Wood MJ (2013) Epigenetics and ncRNAs in brain function and disease: mechanisms and prospects for therapy. Neurotherapeutics 10: 621-631.

299. Helin K, Dhanak D (2013) Chromatin proteins and modifications as drug targets. Nature 502: 480-488.

300. Picaud S, Wells C, Felletar I, Brotherton D, Martin S, et al. (2013) RVX-208, an inhibitor of BET transcriptional regulators with selectivity for the second bromodomain. Proc Natl Acad Sci USA 110: 19754-19759.

301. Dauer W, Przedborski S (2003) Parkinson's disease: mechanisms and models. Neuron 39: 889-909.

302. Feng Y, Jankovic J, Wu YC (2015) Epigenetic mechanisms in Parkinson's disease. J Neurol Sci 349: 3-9.

303. Kaidery NA, Tarannum S, Thomas B (2013) Epigenetic landscape of Parkinson's disease: emerging role in disease mechanisms and therapeutic modalities. Neurotherapeutics 10: 698-708.

304. Coppedè F (2012) Genetics and epigenetics of Parkinson's disease. Sci World J 489830.

305. Moore K, McKnight AJ, Craig D, O'Neill F (2014) Epigenome-wide association study for Parkinson's disease. Neuromolecular Med 16: 845-855.

306. Masliah E, Dumaop W, Galasko D, Desplats P (2013) Distinctive patterns of DNA methylation associated with Parkinson disease: identification of concordant epigenetic changes in brain and peripheral blood leukocytes. Epigenetics 8: 1030-1038.

307. Spillantini MG, Schmidt ML, Lee, VM, Trojanowski JQ, Jakes R, et al. (1997) Alpha-synuclein in Lewi bodies. Nature 388: 839-840.

308. Takeda A, Mallory M, Sundsmo M, Honer W, Hansen L, et al. (1998) Abnormal accumulation of NACP/alpha-synuclein in neurodegenerative disorders. Am J Pathol 152: 367-372.

309. Li WW, Yang R, Guo JC, Ren HM, Zha XL, et al. (2007) Localization of alpha-synuclein to mitochondria within midbrain of mice. Neuroreport 18: 1543-1546.

310. Cole NB, Dieuliis D, Leo P, Mitchell DC, Nussbaum RL (2008) Mitochondrial translocation of alpha-synuclein is promoted by intracellular acidification. Exp Cell Res 314: 2076-2089.

311. Devi L, Raghavendran V, Prabhu BM, Avadhani NG, Anandatheerthavarada HK (2008) Mitochondrial import and accumulation of alpha-synuclein impair complex I in human dopaminergic neuronal cultures and Parkinson disease brain. J Biol Chem 283: 9089-9100.

312. Parihar MS, Parihar A, Fujita M, Hashimoto M, Ghafourifar P (2008) Mitochondrial association of alpha-synuclein causes oxidative stress. Cell Mol Life Sci 65: 1272-1284.

313. Zhang L, Zhang C, Zhu Y, Cai Q, Chan P, et al. (2008) Semi-quantitative analysis of alpha-synuclein in subcellular pools of rat brain neurons: an immunogold electron microscopic study using a C-terminal specific monoclonal antibody. Brain Res 1244: 40-52.

314. Hsu LJ, Sagara Y, Arroyo A, Rockenstein E, Sisk A, et al. (2000) α-synuclein promotes mitochondrial deficit and oxidative stress. Am J Pathol 157: 401-410.

315. Schon EA, Przedborski S (2011) Mitochondria: the next (neurode) generation. Neuron 70: 1033-1053.

316. Elkon H, Don J, Melamed E, Ziv I, Shirvan A, et al. (2002) Mutant and wild-type alpha-synuclein interact with mitochondrial cytochrome C oxidase. J Mol Neurosci 18: 229-238.

317. Rostovtseva TK, Gurnev PA, Protchenko O, Hoogerheide DP, Yap TL, et al. (2015) α-Synuclein Shows High Affinity Interaction with Voltage dependent Anion Channel, Suggesting Mechanisms of Mitochondrial Regulation and Toxicity in Parkinson Disease. J Biol Chem 290: 18467-18477.

318. Nuytemans K, Theuns J, Cruts M, Van Broeckhoven C (2010) Genetic etiology of Parkinson disease associated with mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2 genes: a mutation update. Hum Mutat 31: 763-780.

319. Nicholas AP, Lubin FD, Hallett PJ, Vattem P, Ravenscroft P, et al. (2008) Striatal histone modifications in models of levodopa-induced dyskinesia. J Neurochem 106: 486-494.

320. Desplats P, Spencer B, Coffee E, Patel P, Michael S, et al. (2011) Alpha-synuclein sequesters Dnmt1 from the nucleus: a novel mechanism for epigenetic alterations in Lewy body diseases. J Biol Chem 286: 9031-9037.

321. Ammal Kaidery N, Tarannum S, Thomas B (2013) Epigenetic landscape of Parkinson's disease: emerging role in disease mechanisms and therapeutic modalities. Neurotherapeutics 10: 698-708.

322. Jowaed A, Schmitt I, Kaut O, Wüllner U (2010) Methylation regulates alpha-synuclein expression and is decreased in Parkinson's disease patients' brains. J Neurosci 30: 6355-6359.

323. O'Suilleabhain PE, Sung V, Hernandez C, Lacritz L, Dewey BR, et al. (2004) Elevated plasma homocysteine level in patients with Parkinson disease. Arch Neurol 61: 865-868.

324. Brattstrom L (2001) Plasma homocysteine and MTHFR C677T genotype in levodopa-treated patients with PD. Neurology 56: 281.

325. Duan W, Ladenheim B, Cutler RG, Kruman II, Cadet JL, et al. (2002) Dietary folate deficiency and elevated homocysteine levels endanger

dopaminergic neurons in models of Parkinson's disease. J Neurochem 80: 101-110.

326. Obeid R, Schadt A, Dillmann U, Kostopoulos P, Fassbender K, et al. (2009) Methylation status and neurodegenerative markers in Parkinson disease. Clin Chem 55: 1852-1860.

327. Kalbe E, Kessler J, Calabrese P, Smith R, Passmore AP, et al. (2004) DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. Int J Geriatr Psychiatry 19: 136-143.

328. Pihlstrøm L, Berge V, Rengmark A, Toft M (2015) Parkinson's disease correlates with promoter methylation in the α-synuclein gene. Mov Disord 30: 577-580.

329. Matsumoto L, Takuma H, Tamaoka A, Kurisaki H, Date H, et al. (2010) CpG demethylation enhances alpha-synuclein expression and affects the pathogenesis of Parkinson's disease. PLoS ONE 5: e15522.

330. Pieper HC, Evert BO, Kaut O, Riederer PF, Waha A, et al. (2008) Different methylation of the TNF-alpha promoter in cortex and substantia nigra: Implications for selective neuronal vulnerability. Neurobiol Dis 32: 521-527.

331. Mogi M, Harada M, Narabayashi H, Inagaki H, Minami M, et al. (1996) Interleukin (IL)-1 beta, IL-2, IL-4, IL-6 and transforming growth factor-alpha levels are elevated in ventricular cerebrospinal fluid in juvenile parkinsonism and Parkinson's disease. Neurosci Lett 211:13-16.

332. Cai Y, Liu S, Sothern RB, Xu S, Chan P (2010) Expression of clock genes Per1 and Bmal1 in total leukocytes in health and Parkinson's disease. Eur J Neurol 17: 550-554.

333. Hood S, Cassidy P, Cossette MP, Weigl Y, Verwey M, et al. (2010) Endogenous dopamine regulates the rhythm of expression of the clock protein PER2 in the rat dorsal striatum via daily activation of D2 dopamine receptors. J Neurosci 30: 14046-14058.

334. Lin Q, Ding H, Zheng Z, Gu Z, Ma J, et al. (2012) Promoter methylation analysis of seven clock genes in Parkinson's disease. Neurosci Lett 507: 147-150.

335. van Heesbeen HJ, Mesman S, Veenvliet JV, Smidt MP (2013) Epigenetic mechanisms in the development and maintenance of dopaminergic neurons. Development 140: 1159-1169.

336. Agirre X, Roman-Gomez J, Vazquez I, Jimenez-Velasco A, Garate L, et al. (2006) Abnormal methylation of the common PARK2 and PACRG promoter is associated with downregulation of gene expression in acute lymphoblastic leukemia and chronic myeloid leukemia. Int J Cancer 118: 1945-1953.

337. Cai M, Tian J, Zhao GH, Luo W, Zhang BR (2011) Study of methylation levels of parkin gene promoter in Parkinson's disease patients. Int J Neurosci 121: 497-502.

338. Thomas B, Beal MF (2011) Molecular insights into Parkinson's disease. F1000 Med Rep 3: 7.

339. Kagara I, Enokida H, Kawakami K, Matsuda R, Toki K, et al. (2008) CpG hypermethylation of the UCHL1 gene promoter is associated with pathogenesis and poor prognosis in renal cell carcinoma. J Urology 180: 343-351.

340. Yu J, Tao Q, Cheung KF, Jin H, Poon FF, et al. (2008) Epigenetic identification of ubiquitin carboxyl-terminal hydrolase L1 as a functional tumor suppressor and biomarker for hepatocellular carcinoma and other digestive tumors. Hepatology 48: 508-518.

341. Chuang DM, Leng Y, Marinova Z, Kim HJ, Chiu CT (2009) Multiple roles of HDAC inhibition in neurodegenerative conditions. Trends Neurosci 32: 591-601.

342. Kontopoulos E, Parvin JD, Feany MB (2006) Alpha-synuclein acts in the nucleus to inhibit histone acetylation and promote neurotoxicity. Hum Molec Genet 15: 3012-3023.

343. Outeiro TF, Kontopoulos E, Altmann SM, Kufareva I, Strathearn KE, et al. (2007) Sirtuin 2 inhibitors rescue alpha-synuclein-mediated toxicity in models of Parkinson's disease. Science 317: 516-519.

344. St Laurent R O'Brien LM Ahmad ST (2013) Sodium butyrate improves locomotor impairment and early mortality in a rotenone-induced Drosophila model of Parkinson's disease. Neurosci 246: 382-390.

345. Siddiqui A, Chinta SJ, Mallajosyula JK, Rajagopolan S, Hanson I, et al. (2012) Selective binding of nuclear alpha-synuclein to the PGC1alpha promoter under conditions of oxidative stress may contribute to losses in mitochondrial function: Implications for Parkinson's disease. Free Radic Biol Med 53: 993-1003.

346. Zheng B, Liao Z, Locascio JJ, Lesniak KA, Roderick SS, et al. (2010) PGC-1alpha, a potential therapeutic target for early intervention in Parkinson's disease. Sci Transl Med 2: 52ra73.

347. Wu R, Chen H, Ma J, He Q, Huang Q, et al. (2015) c-Abl-p38α signaling plays an important role in MPTP-induced neuronal death. Cell Death Differ 23: 542-552.

348. Kirilyuk A, Shimoji M, Catania J, Sahu G, Pattabiraman N (2012) An intrinsically disordered region of the acetyltransferase p300 with similarity to prion-like domains plays a role in aggregation. PloS One 7: e48243.

349. Jin H, Kanthasamy A, Ghosh A, Yang Y, Anantharam V, et al. (2011) Alpha-Synuclein negatively regulates protein kinase Cdelta expression to suppress apoptosis in dopaminergic neurons by reducing p300 histone acetyltransferase activity. J Neurosci 31: 2035-2051.

350. Tang Y, Li T, Li J, Yang J, Liu H, et al. (2014) Jmjd3 is essential for the epigenetic modulation of microglia phenotypes in the immune pathogenesis of Parkinson's disease. Cell Death Differ 21: 369-380.

351. Junn E, Lee KW, Jeong BS, Chan TW, Im J, et al. (2009) Repression of alpha synuclein expression and toxicity by microRNA-7. Proc Natl Acad Sci USA 106: 13052-13057.

352. Doxakis E (2010) Post-transcriptional regulation of alpha-synuclein expression by mir-7 and mir-153. J Biol Chem 285: 12726-12734.

353. Wang G, van der Walt JM, Mayhew G, Li YJ, Zuchner S, et al. (2008) Variation in the miRNA-433 binding site of FGF20 confers risk for Parkinson disease by overexpression of alpha-synuclein. Am J Hum Genet 82: 283-289.

354. Gillardon F, Mack M, Rist W, Schnack C, Lenter M, et al. (2008) MicroRNA and proteome expression profiling in early-symptomatic alpha-synuclein(A30P)-transgenic mice. Proteomics Clin Appl 2: 697-705.

355. Cho HJ, Liu G, Jin SM, Parisiadou L, Xie C, et al. (2013) MicroRNA-205 regulates the expression of Parkinson's disease-related leucine-rich repeat kinase 2 protein. Hum Mol Genet 22: 608-620.

356. Imai Y, Gehrke S, Wang HQ, Takahashi R, Hasegawa K (2008) Phosphorylation of 4E-BP by LRRK2 affects the maintenance of dopaminergic neurons in Drosophila. Embo J 27: 2432-2443.

357. Gehrke S, Imai Y, Sokol N, Lu B (2010) Pathogenic LRRK2 negatively regulates microRNA-mediated translational repression. Nature 466: 637-641.

358. Smith WW, Pei Z, Jiang H, Dawson VL, Dawson TM, et al. (2006) Kinase activity of mutant LRRK2 mediates neuronal toxicity. Nat Neurosci 9: 1231-1233.

359. Minones-Moyano E, Porta S, Escaramis G, Rabionet R, Iraola S, et al. (2011) MicroRNA profiling of Parkinson's disease brains identifies early downregulation of miR-34b/c which modulate mitochondrial function. Hum Mol Genet 20: 3067-3078.

360. Kim J, Inoue K, Ishii J, Vanti WB, Voronov SV,et al. (2007) A MicroRNA feedback circuit in midbrain dopamine neurons. Science 317: 1220-1224.

361. Martins M, Rosa A, Guedes LC, Fonseca BV, Gotavac K, et al. (2011) Convergence of miRNA expression profiling, α-synuclein interaction and GWAS in Parkinson's disease. PLoS One 6: e25443.

362. Margis R, Rieder CR (2011) Identification of blood microRNAs associated to Parkinson's disease. J Biotechnol 152: 96-101.

363. Soreq L, Salomonis N, Bronstein M, Greenberg DS, Israel Z, et al. (2013). Small RNA sequencing-microarray analyses in Parkinson leukocytes reveal deep brain stimulation-induced splicing changes that classify brain region transcriptomes. Front Mol Neurosci 6: 10.

364. Cardo LF, Coto E, de Mena L, Ribacoba R, Moris G, et al. (2013) Profile of microRNAs in the plasma of Parkinson's disease patientes and healthy controls. J Neurol 260: 1420-1422.

365. Khoo SK, Petillo D, Kang UJ, Resau JH, Berryhill B, et al. (2012) Plasma-based circulating microRNA biomarkers for Parkinson's disease. J Parkinsons Dis 2: 321-331.

366. Xu Z, Li H, Jin P (2012) Epigenetics-Based Therapeutics for Neurodegenerative Disorders. Curr Transl Geriatr Exp Gerontol Rep 1: 229-236.

367. Wang Y, Wang X, Li R, Yanf ZF, Wang YZ, et al. (2013) A DNA methyltransferase inhibitor, 5-aza-2'-deoxycytidine, exacerbates neurotoxicity and upregulates Parkinson's disease-related genes in dopaminergic neurons. CNS Neurosci Ther 19: 183-190.

368. Kolosova NG, Shcheglova TV, Sergeeva SV, Loskutova LV (2006) Long-term antioxidant supplementations attenuates osxidative stress markers and cognitive deficits in senescent-accelerated OXYs rats. Neurobiol Aging 27: 1289-1297.

369. Bega D, Gonzalez-Latapi P, Zadikoff C, Simuni T (2014) A review of the clinical evidence for complementary and alternative therapies in Parkinson's disease. Curr Trat Opinions Neurol 16: 314.

370. Kidd SK, Schneider JS (2011) Protective effects of valproic acid on the nigrostriatal dopamine system in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. Neuroscience 194: 189-194.

371. Chen PS, Wang CC, Bortner CD, Peng GS, Wu X, et al. (2007) Valproic acid and other histone deacetylase inhibitors induce microglial apoptosis and attenuate lipopolysaccharide-induced dopaminergic neurotoxicity. Neuroscience 149: 162-169.

372. Peng GS, Li G, Tzeng NS, Chen PS, Chuang DM, et al. (2005) Valproate pretreatment protects dopaminergic neurons from LPS-induced neurotoxicity in rat primary midbrain cultures: role of microglia. Brain Res Mol Brain Res 134: 162-169.

373. Monti B, Gatta V, Piretti F, Raffaelli SS, Virgili M, et al. (2010) Valproic acid is neuroprotective in the rotenone rat model of Parkinson's disease: involvement of alpha-synuclein. Neurotox Res 17: 130-141.

374. Marinova Z, Ren M, Wendland JR, Leng Y, Liang MH, et al. (2009) Valproic acid induces functional heat-shock protein 70 via class I histone deacetylase inhibition in cortical neurons: a potential role of Sp1 acetylation. J Neurochem 111: 976-987.

375. Chen PS, Peng GS, Li G, Yang S, Wu X, et al. (2006) Valproate protects dopaminergic neurons in midbrain neuron/glia cultures by stimulating the release of neurothrophic factors from astrocytes. Mol Psychiatry 11: 1116-1125.

376. Wu X, Chen PS, Dallas S, Wilson B, Block ML, et al. (2008) Histone deacetylase inhibitors up-regulate astrocyte GDNF and BDNF gene transcription and protect dopaminergic neurons. Int J Neuropsychopharmacol 11: 1123-1134.

377. Daniel P, Brazier M, Cerutti I, Pieri F, Tardivel I, et al. (1989) Pharmacokinetic study of butyric acid administered in vivo as sodium and arginine butyrate salts. Clin Chim Acta 181: 255-263.

378. Egorin MJ, Yuan ZM, Sentz DL, Plaisance K, Eiseman JL (1999) Plasma pharmacokinetics of butyrate after intravenous administration of sodium butyrate or oral administration of tributyrin or sodium butyrate to mice and rats. Cancer Chemother Pharmacol 43: 445-453.

379. Miller AA, Kurschel E, Osieka R, Schmidt CG (1987) Clinical pharmacology of sodium butyrate in patients with acute leukemia. Eur J Cancer Clin Oncol 23: 1283-1287.

380. Zhou W, Bercury K, Cummiskey J, Luong N, Lebin J, et al. (2011) Phenylbutyrate-up-regulates the DJ-1 protein and protects neurons in cell culture and in animal models of Parkinson disease. J Biol Chem 286: 14941-14951.

381. Rane P, Shields J, Heffernan M, Guo Y, Akbarian S, et al. (2012) The histone deacetylase inhibitor, sodium butyrate, alleviates cognitive deficits in pre-motor stage PD. Neuropharmacol 62: 2409-2412.

382. Kidd SK, Schneider JS (2010) Protection of dopaminergic cells from MPP+-mediated toxicity by histone deacetylase inhibition. Brain Res 1354: 172-178.

383. Chen H, Dzitoyeva S, Manev H (2012) Effect of valproic acid on mitochondrial epigenetics. Eur J Pharmacol 690: 51-59.

384. Marinova Z, Leng Y, Leeds P, Chuang DM (2011) Histone deacetylase inhibition alters histone methylation associated with heat shockprotein 70 promoter modifications in astrocytes and neurons. Neuropharmacol 60: 1109-1115.

385. Leng Y, Marinova Z, Reis-Fernandes MA, Nau H, Chuang DM (2010) Potent neuroprotective effects of novel structural derivatives of valproic acid: potential roles of HDAC inhibition and HSP70 induction. Neurosci Lett 476: 127-132.

386. Huang HY, Lin SZ, Chen WF, Li KW, Kuo JS, et al. (2011) Urocortin modulates dopaminergic neuronal survival via inhibition of glycogen synthase kinase-3beta and histone deacetylase. Neurobiol Aging 32: 1662-1677.

387. Roy A, Ghosh A, Jana A, Liu X, Brahmachari S, et al. (2012) Sodium phenylbutyrate controls neuroinflammatory and antioxidant activities and protects dopaminergic neurons in mouse models of Parkinson's disease. PloS One 7: e38113.

388. Gardian G, Yang L, Cleren C, Calingasan NY, Klivenyi P, et al. (2004) Neuroprotective effects of phenylbutyrate against MPTP neurotoxicity. Neuromolecular Med 5: 235-241.

389. Urdinguio RG, Sanchez-Mut JV, Esteller M (2009) Epigenetic mechanisms in neurological diseases: genes, syndromes, and therapies. Lancet Neurol. 8: 1056-1072.

390. Ryu H, Rosas HD, Hersch SM, Ferrante RJ (2005)The therapeutic role of creatine in Huntington's disease. Pharmacol Ther 108: 193-207.

391. MacDonald ME, Ambrose CM, Duyao MP, Myers RH, Lin C, et al. (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72: 971-983.

392. Okazawa H(2003) Polyglutamine diseases: a transcription disorder? Cell Mol Life Sci 60: 1427-1439.

393. Sugars KL, Rubinsztein DC (2003) Transcriptional abnormalities in Huntington disease. Trends Genet 19: 233-238.

394. Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, et al. (1996) Exon 1 of the< i> HD</i> Gene with an Expanded CAG Repeat Is Sufficient to Cause a Progressive Neurological Phenotype in Transgenic Mice. Cell 87: 493-506.

395. Nucifora FC Jr, Sasaki M, Peters MF, Huang H, Cooper JK, et al. (2001) Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. Science 291: 2423-2428.

396. Cattaneo E (2003) Dysfunction of wild-type huntingtin in Huntington disease. News Phyisol Sci 18: 34-37.

397. Ross CA, Poirier MA (2004) Protein aggregation and neurodegenerative disease. Nat Med 10: S10-17.

398. Graveland GA, Williams RS, DiFiglia M (1985) Evidence for degenerative and regenerative changes in neostriatal spiny neurons in Huntington's disease. Science 227: 770-773.

399. Ferrante RJ, Kowall NW, Richardson EP Jr (1991) Proliferative and degenerative changes in striatal spiny neurons in Huntington's disease: a combined study using the section-Golgi method and calbindin D28k immunocytochemistry. J Neurosci 11: 3877-3887.

400. Kowall NW, Ferrante RJ, Martin JB (1987) Patterns of cell loss in Huntington's disease. Trends Neurosci 10: 24-29.

401. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, et al. (1985) Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol 44: 559- 577.

402. Lee J, Hwang YJ, Kim KY, Kowall NW, Ryu H (2013) Epigenetic mechanisms of neurodegeneration in Huntington's disease. Neurotherapeutics 10: 664-676.

403. Beal MF, Ferrante RJ (2004) Experimental therapeutics in transgenic mouse models of Huntington's disease. Nat Rev Neurosci 5: 373-384.

404. Szebenyi G, Morfini GA, Babcock A, Gould M, Selkoe K, et al. (2003) Neuropathogenic forms of huntingtin and androgen receptor inhibit fast axonal transport. Neuron 40: 41-52.

405. Trushina E, Dyer RB, Badger JD, Ure D, Eide L, et al. (2004) Mutant huntingtin impairs axonal trafficking in mammalian neurons in vivo and in vitro. Mol Cell Biol 24: 8195-8209.

406. Li SH, Cheng AL, Zhou H, Lam S, Rao M, et al. (2002) Interaction of Huntington disease protein with transcriptional activator Sp1. Mol Cell Biol 22: 1277-1287.

407. Thomas EA, Coppola G, Desplats PA, Tang B, Soragni E, et al. (2008) The HDAC inhibitor 4b ameliorates the disease phenotype and transcriptional abnormalities in Huntington's disease transgenic mice. Proc Natl Acad Sci USA 105: 15564-15569.

408. Farrer IA, Cupples LA, Kiely DK, Conneally PM, Myers RH (1992) Inverse relationship between age at onset of Huntington disease and paternal age suggests involvement of genetic imprinting. Am J Hum Genet 50:528-535.

409. Behnkrappa A, Doerfler W (1994) Enzymatic amplification of synthetic oligodeoxyribonucleotides: implication for triplet repeat expansions in the human genome. Human Mutat 3: 19-24.

410. Gorbunova V, Seluanov A, Mittelman D, Wilson JH (2004) Genome-wide demethylation destabilizes CTG. CAG trinucleotide repeats in mammalian cells. Hum Mol Genet 13: 2979-2989.

411. Ng CW, Yildirim F, Yap YS, Dalin S, Matthews BJ, et al. (2013) Extensive changes in DNA methylation are associated with expression of mutant huntingtin. Proc Natl Acad Sci USA 110: 2354-2359.

412. Zajac MS, Pang TY, Wong N, Weinrich B, Leang LS, et al. (2010) Wheel running and environmental enrichment differentially modify exon-specific BDNF expression in the hippocampus of wild-type and pre-motor symptomatic male and female Huntington's disease mice. Hippocampus 20: 621-636.

413. Villar-Menendez I Blanch M, Tyebji S, Pereira-Veiga T, Albasanz JL, Martin M, et al. (2013) Increased 5-methylcytosine and decreased 5-hydroxymethylcytosine levels are associated withreduced striatal A(2A)R levels in Huntington's disease. Neuromol Med 15: 595-309.

414. Wood H(2013) Neurodegenerative disease: Altered DNA methylation and RNA splicing could be key mechanisms in Huntington disease. Nat Rev Neurol 9: 119-119.

415. Thomas B, Matson S, Chopra V, Sun L, Sharma S, et al. (2013) A novel method for detecting 7-methyl guanine reveals aberrant methylation levels in Huntington disease. Anal Biochem 436: 112-120.

416. Sadri-Vakili G, Bouzou B, Benn CL, Kim MO, Chawla P, et al. (2007) Histones associated with downregulated genes are hypo-acetylated in Huntington's disease models. Hum Mol Genet 16: 1293-1306.

417. Ferrante RJ, Ryu H, Kubilus JK, D'Mello S, Sugars KL, et al. (2004) Chemotherapy for the brain: the antitumor antibiotic mithramycin prolongs survival in a mouse model of Huntington's disease. J Neurosci. 24:10335-10342.

418. Jenuwein T, Allis CD (2001) Translating the histone code. Science 293: 1074-1080.

419. Ryu H, Lee J, Hagerty SW, Soh BY, McAlpin SE, et al. (2006) ESET/SETDB1 gene expression and histone H3 (K9) trimethylation in Huntington's disease. Proc Natl Acad Sci USA 103: 19176-19181.

420. Hazeki N, Tsukamoto T, Yazawa I, Koyama M, Hattori S, et al. (2012) Ultrastructure of nuclear aggregates formed by expressing and expanded polyglutamine. Biochem Biophys Res Commun 294: 429-440.

421. Gardian G, Browne SE, Choi DK, Klivenyi P, Gregorio J, et al. (2005) Neuroprotective effects of phenylbutyrate in the N171- 82Q transgenic mouse model of Huntington's disease. J Biol Chem 280: 556-563.

422. McFarland KN, Das S, Sun TT, Leyfer D, Xia E, et al. (2012) Genome-wide histone acetylation is altered in a transgenic mouse model of Huntington's disease. PloS One 7 :e41423.

423. Oliveira AM, Wood MA, McDonough CB, Abel T (2007) Transgenic mice expressing an inhibitory truncated form of p300 exhibit long-term memory deficits. Learn Mem 14: 564-572.

424. Lee J, Hagerty S, Cormier KA, Kim J, Kung AL, et al. (2008) Monoallele deletion of CBP leads to pericentromeric heterochromatin condensation through ESET expression and histone H3 (K9) methylation. Hum. Mol. Genet. 17:1774-1782.

425. Calabresi P, Centonze D, Gubellini P, Pisani A, Bernardi G (2000) Acetylcholine-mediated modulation of striatal function. Trends Neurosci 23: 120-126.

426. Cha JH, Kosinski CM, Kerner JA, Alsdorf SA, Mangiarini L, et al. (1998) Altered brain neurotransmitter receptors in transgenic mice expressing a portion of an abnormal human huntington disease gene. Proc Natl Acad Sci USA 95: 6480-6485.

427. Wang Z, Kai L, Day M, Ronesi J, Yin HH, et al. (2006) Dopaminergic control of corticostriatal long-term synaptic depression in medium spiny neurons is mediated by cholinergic interneurons. Neuron 50: 443-452.

428. Johnson R, Zuccato C, Belyaev ND, Guest DJ, Cattaneo E, et al. (2008) A microRNA-based gene dysregulation pathway in Huntington's disease. Neurobiol Dis 29: 438-445.

429. Packer AN, Xing Y, Harper SQ, Jones L, Davidson BL (2008) The bifunctional microRNA miR-9/miR-9* regulates REST and CoREST and is downregulated in Huntington's disease. J Neurosci 28: 14341-14346.

430. Marti E, Pantano L, Banez-Coronel M, Llorens F, Minones-Moyano E, et al. (2010) A myriad of miRNA variants in control and Huntington's disease brain regions detected by massively parallel sequencing. Nucleic Acids Res 38: 7219-7235.

431. Zuccato C, Tartari M, Crotti A, Goffredo D, Valenza M, et al. (2003) Huntingtin interacts with REST/NRSF to modúlate the transcription of NRSE-controlled neuronal genes. Nat Genet 35:76-83.

432. Ooi L, Wood IC (2007) Chromatin crosstalk in development and disease: lessons from REST. Nat Rev Genet 8: 544-554.

433. Ghose J, Sinha M, Das E, Jana NR, Bhattacharyya NP(2011) Regulation of miR-146a by RelA/NFkB and p53 in STHdhQ111/HdhQ111 Cells, a Cell Model of Huntington's Disease. PloSOne 6: e23837.

434. Sinha M, Ghose J, Bhattacharyya NP (2011) Micro RNA -214,-150,-146a and-125b target Huntingtin gene. RNA Biol 8: 1005-1021.

435. Cheng PH, Li CL, Chang YF, Tsai SJ, Lay YY, et al. (2013) miR-196a ameliorates phenotypes of Huntington disease in cell, transgenic mouse, and induced pluripotent stem cell models. Am J Hum Genet 93: 306-312.

436. Hockly E, Richon VM, Woodman B, Smith DL, Zhou X, et al. (2003) Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. Proc Natl Acad Sci USA 100: 2041-2046.

437. Mielcarek M, Benn CL, Franklin SA, Smith DL, Woodman B, et al. (2011) SAHA decreases HDAC 2 and 4 levels in vivo and improves molecular phenotypes in the R6/2 mouse model of Huntington's disease. PloS One 6: e27746.

438. Ferrante RJ, Kubilus JK, Lee J, Ryu H, Beesen A, et al. (2003) Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington's disease mice. J Neurosci 23: 9418-9427.

439. Steffan JS, Bodai L, Pallos J, Poelman M, McCampbell A, et al. (2001) Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in Drosophila. Nature 413: 739-743.

440. Dompierre JP, Godin JD, Charrin BC, Cordelières FP, King SJ, et al. (2007) Histone deacetylase 6 inhibition compensates for the transport deficit in Huntington's disease by increasing tubulin acetylation. J Neurosci 27: 3571-3583.

441. Ebbel EN, Leymarie N, Schiavo S, Sharma S, Gevorkian S, et al. (2010) Identification of phenylbutyrate-generated metabolites in Huntington disease patients using parallel liquid chromatography/electrochemical array/mass spectrometry and off-line tandem mass spectrometry. Anal Biochem 399: 152-161.

442. Hogarth P, Lovrecic L, Krainc D (2007) Sodium phenylbutyrate in Huntington's disease: a dosefinding study. Mov Disord 22: 1962-1964.

443. Jia H, Kast RJ, Steffan JS, Thomas EA (2012) Selective histone deacetylase (HDAC) inhibition imparts beneficial effects in Huntington's disease mice: implications for the ubiquitin-proteasomal and autophagy systems. Hum Molec Genet 21: 5280-5293.

444. Stack EC, Del Signore SJ, Luthi-Carter R, Soh BY, Goldstein DR, et al. (2007) Modulation of nucleosome dynamics in Huntington's disease. Hum Mol Genet 16: 1164-1175.

445. Pallos J, Bodai L, Lukacsovich T, Purcell JM, Steffan JS, et al. (2008) Inhibition of specific HDACs and sirtuins suppresses pathogenesis in a Drosophila model of Huntington's disease. Hum Molec Genet 17: 3767-3775.

446. Chopra V, Quinti L, Kim J, Vollor L, Narayanan KL, et al. (2012) The sirtuin 2 inhibitor AK-7 is neuroprotective in Huntington's disease mouse models. Cell Rep 2: 1492-1497.

447. Ehrnhoefer DE, Duennwald M, Markovic P, Wacker JL, Engemann S, et al. (2006) Green tea (-)-epigallocatechin-gallate modulates early events in huntingtin misfolding and reduces toxicity in Huntington's disease models. Hum Mol Genet 15: 2743-2751.

448. Duan W, Guo Z, Jiang H, Ware M, Li XJ, et al. (2003) Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. Proc Natl Acad Sci USA 100: 2911-2916.

449. Parker JA, Arango M, Abderrahmane S, Lambert E, Tourette C, et al. (2005) Resveratrol rescues mutant polyglutamine cytotoxicity in nematode and mammalian neurons. Nat Genet 37: 349-350.

450. Kumar P, Padi SS, Naidu PS, Kumar A (2006) Effect of resveratrol on 3-nitropropionic acid-induced biochemical and behavioural changes: possible neuroprotective mechanisms. Behav Pharmacol 17: 485-492.

451. Pasinetti GM, Wang J, Marambaud P, Ferruzzi M, Gregor P, et al. (2011) Neuroprotective and metabolic effects of resveratrol: therapeutic implications for Huntington's disease and other neurodegenerative disorders. Exp Neurol 232: 1-6.

452. Ho DJ, Calingasan NY, Wille E, Dumont M, Beal MF (2010) Resveratrol protects against peripheral deficits in a mouse model of Huntington's disease. Exp Neurol 225: 74-84.

453. Kiernan M, Vucic S, Cheah B, Turner M, Eisen A, et al. (2011) Amiotrophic lateral sclerosis. Lancet 377: 942-955.

454. Pratt AJ, Getzoff ED, Perry JJ (2012) Amyotrophic lateral sclerosis: update and new developments. Degener Neurol Neuromuscul Dis 1–14.

455. De Carvalho M, Swash M (2011) Amiotrophic lateral sclerosis: an update. Curr Opin Neurol 24: 497-503.

456. Bruijn LI, Houseweart MK, Kato S, Anderson KL, Anderson SD, et al. (1998) Aggregation and motor

neuron toxicity of an ALS-linked SOD1 mutant independent from wild-type SOD1. Science 281: 1851-1854.

457. Furukawa Y, Fu R, Deng HX, Siddique T, O'Halloran TV (2006) Disulfide cross-linked protein represents a significant fraction of ALS-associated Cu, Zn-superoxide dismutase aggregates in spinal cords of model mice. Proc Natl Acad Sci USA 103: 7148-7153.

458. Al-Chalabi A, Jones A, Troakes C, King A, Al-Sarraj S, et al. (2012) The genetics and neuropathology of amyotrophic lateral sclerosis. Acta Neuropathol 124: 339-352.

459. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, et al. (2011) Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron 72: 245-256.

460. Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, et al. (2011) A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron 72: 257-268.

461. Deng HX, Cheng W, Hong ST, Boycott KM, Gorrie GH,et al. (2011) Mutations in UBQLN2 cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia. Nature 477: 211-215.

462. Figueroa-Romero C, Hur J, Bender DE, Delaney CE, Cataldo MD, et al. (2012) Identification of Epigenetically Altered Genes in Sporadic Amyotrophic Lateral Sclerosis. PLoS One 7: e52672.

463. Paez-Colasante X, Figueroa-Romero CA, Sakowski SG, SA Feldman EL (2015) Amyotrophic lateral sclerosis: mechanisms and therapeutics in the epigenomic era. Nat Rev Neurol 11: 266-279.

464. Oates N, Pamphlett R (2007) An epigenetic analysis of SOD1 and VEGF on ALS. Amyotroph Lateral Scler 8: 83-86.

465. Laffita-Mesa J, Bauer P, Kouri V, Serrano L, Roskams J, et al. (2012) Epigenetics DNA methylation in the core ataxin-2 gene promoter: novel physiological and pathological implications. Hum. Genet. 131:625-638.

466. Xi Z, Zinman L, Moreno D, Schymick J, Liang Y,et al. (2013) Hypermethylation of the CpG island near the G_4C_2 repeat in ALS with a C9orf72expansion. Am J Hum Genet 92: 981–989.

467. Xi Z, Zhang M, Bruni AC, Maletta RG, Colao R,et al. (2014) Hypermethylation of the CpG-island near the C9orf72 G_4C_2-repeat expansion in FTLD patients. Hum Mol Genet 23: 5630–5637.

468. Belzil VV, Bauer PO, Gendron TF, Murray ME, Dickson D,et al. (2014) Characterization of DNA hypermethylation in the cerebellum of c9FTD/ALS patients. Brain Res 1584: 15-21.

469. Labonte B, Suderman M, Maussion G, Navaro L, Yerko V, et al. (2012) Genome-wide epigenetic regulation by early-life trauma. Arch Gen Psychiatry 69: 722-731.

470. Rothstein JD, Vankammen M, Levey AI, Martin LJ, Kuncl RW (1995) Selective loss of glial glutamate transporter GLT-1 in amyotrophic lateral sclerosis. Ann Neurol 38: 73-84.

471. Chestnut BA, Chang Q, Price A, Lesuisse C, Wong M, et al. (2010) Epigenetic regulation of motor neuron cell death through DNA methylation. J Neurosci 31: 16619-16636.

472. Okada Y, Yamagata K, Hong K, Wakayama T, Zhang Y (2010) A role for the elongator complex in zygotic paternal genome demethylation. Nature 463: 554-558.

473. Bardai FH, D'Mello SR (2011) Selective toxicity by HDAC3 in neurons: regulation by Akt and GSK3beta. J Neurosci 31: 1746-1751.

474. Simpson CL, et al. (2009) Variants of the elongator protein 3 (ELP3) gene are associated with motor neuron degeneration. Hum Mol Genet 18: 472-481.

475. Han Q, Lu J, Duan J, Su D, Hou X, et al. (2008) Gcn5- and Elp3-induced histone H3 acetylation regulates hsp70 gene transcription in yeast. Biochem J 409: 779-788.

476. Koyama S, Arawaka S, Chang-Hong R, Wada M, Kawanami T, et al. (2006) Alteration of familial ALS-linked mutant SOD1 solubility with disease progression: its modulation by the proteasome and Hsp70. Biochem Biophys Res Commun 343: 719-730.

477. Patel YJ, Payne Smith MD, de Belleroche J, Latchman DS (2005) Hsp27 and Hsp70 administered in combination have a potent protective effect against FALS-associated SOD1-mutant-induced cell death in mammalian neuronal cells. Brain Res Mol Brain Res 134: 256-274.

478. Wang X (2008) Induced ncRNAs allosterically modify RNA-binding proteins in cis to inhibit transcription. Nature 454(7200):126-130.

479. Kawahara Y, Mieda-Sato A (2012) TDP-43 promotes mcroRNA biogénesis as a component of the Drosa and Dicer complexes. Proc. Natl. Acad. Sci. USA. 109:3347-3352.

480. Zhang Z, Almeida S, Lu Y, Nishimura AL, Peng L, et al. (2013) Downregulation of MicroRNA-9 in iPSC-derived neurons of FTD/ALS patients with TDP-43 mutations. PLoS One 8: e76055.

481. Morlando M, Dini Modigliani S, Torrelli G, Rosa A, Di Carlo V, et al. (2012) FUS stimulates microRNA biogénesis by facilitating co-transcriptional Drosha recruitment. EMBO J 31: 4502-4510.

482. Edbauer D, Neilson JR, Foster KA, Wang CF, Seeburg DP, et al. (2010) Regulation of synaptic structure and function by FMRP-associated microRNAs miR-125b and miR-132. Neuron 65: 373-384.

483. Dajas-Bailador F, Bonev B, Garcez P, Stanley P, Guillemot F (2012) microRNA-9 regulates axon extension and branching by targeting Map1b in mouse cortical neurons. Nat Neurosci 15: 697-699.

484. Herbert SS, Sergeant N, Buee L (2012) MicroRNAs and the regulation of Tau metabolism. Int J Alzheimers Dis 406561.

485. Shaltiel G, Hanan M, Wolf Y, Barbash S, Kovalev E, et al. (2013) Hippoccampal microRNA-132 mediates stress-inducible cognitive deficits through its acetylcholinesterase target. Brain Struct Funct 218: 59-72.

486. Fiore R, Khudayberdiev S, Christensen M, Siegel G, Flavell SW, et al. (2009) Mef2-mediated transcription of the miR379-410 cluster regulates activity-dependent dendritogenesis by fine-tuning Pumilio2 protein levels. EMBO J 28: 697-710.

487. Williams AH, Valdez G, Moresi V, Qi X, McAnally J, et al. (2009) MicroRNA-206 delays ALS progression and promotes regeneration of neuromuscular synapses in mice. Science 326: 1549-1554.

488. Russel AP, Wada S, Vergani L, Hock MB, Lamon S, et al. (2012) Disruption of skeletal muscle mitochondrial network genes and miRNAs in amyotrophic lateral sclerosis. Neurobiol Dis 49C: 107-117.

489. Campos-Melo D, Droppelmann CA, He Z, Volkening K, Strong MJ (2013) Altered microRNA expression profile in amyotrophic lateral sclerosis: a role in the regulation of NFL mRNA levels. Mol Brain 6: 26.

490. Koval ED, Shaner C, Zhang P, Du Maire X, Fischer K, et al. (2013) Method for widespread microRNA-155 inhibition prolongs survival in ALS-model mice. Hum Mol Genet 22: 4127-4135.

491. De Felice B, Guida M, Guida M, Coppola C, De Mieri G, et al. (2012) A miRNA signature in leukocytes from sporadic amyotrophic lateral sclerosis. Gene 508: 35-40.

492. Butovsky O, Siddiqui S, Gabriely G, Lanser AJ, Dake B, et al. (2012) Modulating inflammatory monocytes with a unique microRNA gene signature ameliorates murine ALS. J Clin Invest 122: 3063-3087.

493. Cudkowicz ME, Andres PL, Macdonald SA, Bedlack RS, Choudry R, et al. (2009) Phase 2 study of sodium phenylbutyrate in ALS. Amyotroph Lateral Scler 10: 99-106.

494. Ryu H, Smith K, Camelo SI, Carreras I, Lee J, et al. (2005) Sodium phenylbutyrate prolongs survival and regulates expression of antiapoptotic genes in transgenic amyotrophic lateral sclerosis mice. J Neurochem 93: 1087-1098.

495. Del Signore SJ, Amante DJ, Kim J, Stack EC, Goodrich S, et al. (2009) Combined riluzole and sodium phenylbutyrate therapy in transgenic amyotrophic lateral sclerosis mice. Amyotroph Lateral Scler 10: 85-94.

496. Petri S, Kiaei M, Kipiani K, Chen J, Calingasan NY, et al. (2006) Additive neuroprotective effects of a histone deacetylase inhibitor and a catalytic antioxidant in a transgenic mouse model of amyotrophic lateral sclerosis. Neurobiol Dis 22: 40-49.

497. Sugai F, Yamamoto Y, Miyaguchi K, Zhou Z, Sumi H, et al. (2004) Benefit of valproic acid in suppressing disease progression of ALS model mice. Eur J Neurosci 20: 3179-3183.

498. Feng HL, Leng Y, Ma CH, Zhang J, Ren M, et al. (2008) Combined lithium and valproate treatment delays disease onset, reduces neurological deficits and prolongs survival in an amyotrophic lateral sclerosis mouse model. Neurosci 155: 567-572.

499. Rouaux C, Panteleeva I, René F, Gonzalez de Aguilar JL, Echaniz-Laguna A, et al. (2007) Sodium valproate exerts neuroprotective effects in vivo through CREB-binding protein-dependent mechanisms but does not improve survival in an amyotrophic lateral sclerosis mouse model. J Neurosci 27: 5535–5545.

500. Yoo YE, Ko CP (2011) Treatment with trichostatin A initiated after disease onset delays disease

progression and increases survival in a mouse model of amyotrophic lateral sclerosis. Exp Neurol 231: 147-159.

501. Marquer C, Laine J, Dauphinot L, Hanbouch L, Lemercier-Neuillet C, et al. (2010) Increasing membrane cholesterol of neurons in culture recapitulates Alzheimer's disease early phenotypes. Mol Neurodegener 9: 60.

502. Akram A, Schmeidler J, Katsel P, Hof PR, Haroutunian V (2010) Increased expression of RXRα in dementia: an early harbinger for the cholesterol dyshomeostasis?. Mol Neurodegener 5: 36.

503. Bourdel-Marchasson I, Mouries A, Hemer C (2010) Hyperglycaemia, microangiopathy, diabetes, and dementia risk. Diabetes Metab 36: S112-S118.

504. Cacabelos R (2004) Genomic characterization of Alzheimer's disease and genotype-related phenotypic analysis of biological markers in dementia. Pharmacogenomics 5: 1049-1105.

505. Liu JP, Tang Y, Zhou S, Toh BH, McLean C, et al. (2010) Cholesterol involvement in the pathogenesis of neurodegenerative diseases. Mol Cell Neurosci 43: 33-42.

506. Maulik M, Westaway D, Jhamandas JH, Kar S (2013) Role of cholesterol in APP metabolism and its significance in Alzheimer's disease pathogenesis. Mol Neurobiol 47: 37-63.

507. Vance JE (2012) Dysregulation of cholesterol balance in the brain: contribution to neurodegenerative diseases. Dis Model Mech 5: 746-755.

508. Shih YH, Tsai KJ, Lee CW, Shiesh SC, Chen WT, et al. (2014) Apolipoprotein C-III is an amyloid-β-binding protein and an early marker for Alzheimer's disease. J Alzheimers Dis 41: 855-865.

509. Cacabelos R, Torrellas C, Teijido O, Carril JC (2016) Pharmacogenetic considerations in the treatment of Alzheimer's disease. Pharmacogenomics.

510. Goedeke L, Fernández-Hernando C (2014) MicroRNAs: a connection between cholesterol metabolism and neurodegeneration. Neurobiol Dis 72: 48-53.

511. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, et al. (2000) Inflammation and Alzheimer's disease. Neurobiol Aging 21: 383-421.

512. Bethke L, Webb E, Murray A, Schoemaker M, Feychting M, et al. (2008) Functional polymorphisms in folate metabolism genes influence the risk of meningioma and glioma. Cancer Epidemiol. Biomarkers Prev 17: 1195-1202.

513. Wald DS, Law M, Morris JK (2002) Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. Brit Med J 325: 1202-1207.

514. Kim IW, Han N, Burckart GJ, Oh JM (2014) Epigenetic changes in gene expression for drug-metabolizing enzymes and transporters. Pharmacotherapy 34: 140-150.

515. Peng L, Xhong X (2015) Epigenetic regulation of drug metabolism and transport. Acta Pharm Sin B 5: 106-112.

516. Cacabelos R, López-Muñoz F (2014) The ABCB1 transporter in Alzheimer's disease. Clin Exp Pharmacol 4: e128.

517. Abuznait AH, Kaddoumi A (2012) Role of ABC transporters in the pathogenesis of Alzheimer's disease. ACS Chem Neurosci 3: 820-831.

518. Wolf A, Bauer B, Hartz AM (2012) ABC transporters and the alzheimer´s disease enigma. Front Psychiatry 3: 54.

519. Qosa H, Abuznait AH, Hill RA, Kaddoumi A (2012) Enhanced brain amyloid-β clearance by rifampicin and caffeine as a possible protective mechanism against Alzheimer's disease. J Alzheimers Dis 31: 151-165.

520. Karch CM, Cruchaga C, Goate AM (2014) Alzheimer's disease genetics: from the bench to the clinic. Neuron 83: 11-26.

521. van Assema DM, Lubberink M, Bauer M, van der Flier WM, Schuit RC, et al. (2012) Blood-brain barrier P-glycoprotein function in Alzheimer's disease. Brain 135: 181-189.

522. Silverberg GD, Messier AA, Miller MC, Machan JT, Majmudar SS, et al. (2010) Amyloid efflux transporter expression at the blood-brain barrier declines in normal aging. J Neuropathol Exp Neurol 69: 1034-1043.

523. Koldamova R, Fitz NF, Lefterov I (2010) The role of ATP-binding cassette transporter A1 in Alzheimer's disease and neurodegeneration. Biochim Biophys Acta 1801: 824-830.

524. Davis W Jr (2014) The ATP-binding cassette transporter-2 (ABCA2) regulates esterification of plasma membrane cholesterol by modulation of sphingolipid metabolism. Biochim Biophys Acta 1841: 168-179.

525. Cacabelos R, Teijido O, Carril JC (2016) Can cloud-based tolos accelerate Alzheimer's disease

drug discovery? Expert Opin Drug Discov 11: 215-223.

526. Scicchitano F, Constanti A, Citraro R, Sarro G, Russo E (2015) Statins and epilepsy: preclinical studies, clinical trials and statin-anticonvulsant drug interactions. Curr Drug Targets 16: 747-756.

527. Pac-Soo C, Lloyd DG, Vizcaychipi MP, Ma D (2011) Statins: the role in the treatment and prevention of Alzheimer's neurodegeneration. J Alzheimers Dis 27: 1-10.

528. Cacabelos R, Vallejo AI, Lombardi V, Fernández-Novoa L, Pichel V (2004) E-SAR-94010 (LipoEsar®): a pleiotropic lipoprotein compound with powerful anti-atheromatous and lipid lowering effects. CNS Drug Rev 10: 200-201.

529. Carrera I, Fernandez-Novoa L, Sampedro C, Aliev G, Cacabelos R (2016) Dopaminergic neuroprotection with Atremorine in Parkinson´s disease. Current Medicinal Chemistry.