Title
Investigating developmental and functional deficits in neurodegenerative disease using transcriptomic analyses

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Investigating developmental and functional deficits in neurodegenerative disease using transcriptomic analyses

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Biomedical Sciences

by

Ryan Gar-Lok Lim

Dissertation Committee:
Professor Leslie M. Thompson, Chair
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2016
DEDICATION

This dissertation is dedicated to my parents, sister, and my wife. I love you all very much and could not have accomplished any of this without your love and support. Please take the time to reflect back on all of the moments we've shared, and know, that it is because of those moments I have been able to succeed. This accomplishment is as much yours as it is mine.
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ABSTRACT OF THE DISSERTATION

Investigating developmental and functional deficits in neurodegenerative disease using transcriptomic analyses

By

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Doctor of Philosophy in Biomedical Sciences

University of California, Irvine, 2016

Professor Leslie M. Thompson, Chair

Loss of neurons is a key macroscopic feature that unites all neurodegenerative diseases including Huntington’s disease (HD) and Amyotrophic lateral sclerosis (ALS). These diseases affect distinct neuronal subtypes, e.g. striatum and cortex in HD and motor neurons in ALS. However, it is clear that common molecular mechanisms may underlie pathogenic features of each disease. Currently, there is no disease modifying treatment for HD or ALS. It is critical to elucidate the specific mechanisms leading to pathogenesis.

A single gene mutation, a CAG repeat expansion within the HD gene, causes HD. In contrast, 90% of all cases of ALS are sporadic and of the known gene mutations that cause familial versions of the disease, there are several contributing genes with the C9orf72 mutation accounting for the majority. Ultimately, in both diseases, numerous cellular functions are impacted including protein homeostasis, transcriptional regulation, cellular signaling, and bioenergetics; causing dysfunction and cell death.

A shared pathogenic feature which seems, at least in part, to be causative is the dysregulation of gene expression. In order to study this and other pathogenic mechanisms,
we utilized patient-derived induced pluripotent stem cells (iPSCs) from both HD and ALS subjects and differentiated them into relevant cell types. For HD, mixed neural cells directed towards a striatal fate and brain endothelial cells (BECs) were generated, and motor neurons generated from ALS subjects. These cells were compared to lines generated from unaffected, healthy subjects for unbiased “omics” analysis to identify potential mechanisms underlying neurodegeneration.

My data suggest that mutant Huntingtin impairs neurodevelopmental pathways that could disrupt synaptic homeostasis and increase vulnerability to the expanded polyglutamine repeats over time. Additionally, I provide the first iPSC-derived barrier-forming EC model for a neurodegenerative disease to date, demonstrating specific barrier defects that may underlie crucial aspects of HD pathology.

RNA-seq analysis was also performed for iPSC-derived ALS motor neurons as a component of a large consortium effort to identify cell-based signatures. Alternative splicing and mislocalization of RNA binding proteins (RBPs) appears to also contribute to ALS pathogenesis, and here we identify RBPs that could contribute to this aberrant alternative splicing and dysregulated RNA biology.
INTRODUCTION

Huntington’s disease, the neurovascular unit and the blood-brain barrier
1.1 Huntington’s Disease

Huntington’s disease (HD) is an inherited autosomal dominant neurodegenerative disorder. It is a devastating disease that typically affects individuals during the prime of their lives. HD was first described by George Huntington in a publication entitled “On Chorea” in 1872. His original description of the disease includes many of the same descriptive clinical traits that are still used today, including: motor abnormalities, psychiatric symptoms, and the hereditary and progressive nature of the disease\(^1,2\). In 1993, The Huntington’s Disease Collaborative Research Group discovered that the disease is caused by a CAG repeat expansion within the Huntingtin gene (HTT); this repeat in turn encodes a polyglutamine tract expansion within the Huntingtin protein\(^3\). While unaffected individuals have typically around ~20 CAG repeats, 40 or more CAG repeats cause HD symptoms within a typical lifespan, and CAG repeats above ~60 cause juvenile onset HD\(^4\). There are cases of affected individuals with an intermediate range between 36 and 39 repeats with decreased clinical manifestation of the disease. Even below this range, (between ~29-34 repeats), there are cases of DNA instability and expansions of the CAG repeats to pathogenic numbers during meiosis, thus offspring can inherit a disease allele. During spermatogenesis the CAG domain is particularly susceptible to expansion into juvenile repeat ranges\(^5\). Although CAG repeat length primarily determines the age of onset, the actual disease onset varies quite broadly. For instance, individuals with an adult onset repeat of the same length, can vary by 50 years in the range of disease onset, a variability dictated by other genetic and environmental effects\(^6,7\). Recent genome wide association studies have linked changes in disease onset to genes involved in DNA repair and mitochondrial function\(^8\). Interestingly, independent
studies have shown these processes are impacted by expression of mutant HTT (mHTT). Chronic mHTT protein expression produces a spectrum of cumulative cellular aberrations, including those affecting cell signaling, transcription, autophagy, calcium homeostasis, and bioenergetics\textsuperscript{9,10}. Neuropathology classically includes cortical atrophy and extensive loss of striatal medium spiny neurons in the basal ganglia\textsuperscript{11}. However, emerging data also shows abnormal phenotypes in other cells of the CNS and even of cells in peripheral tissues such as skeletal muscle\textsuperscript{12-17}.

Based on clinical and neuropathological evaluation, a series of defining stages are used to describe the course of disease in HD and identify the earliest stages of disease through progression into more severe symptoms\textsuperscript{18,19}. These stages include the premanifest, prodromal, and fully manifest stages, the latter being broken further into early, moderate, and advanced sub-stages. During the prodromal stage, cognitive and psychiatric changes occur. These progress until the motor symptoms start to increase in severity, which typically is the stage at which the disease is clinically diagnosed. In the manifest stage of the disease, motor, cognitive, and psychiatric abilities drastically decline and the disease invariably ends in death. Patients usually survive an average of 18 years from the onset of motor symptoms\textsuperscript{20}.

Currently, there are no disease modifying treatments for HD, although there are approved treatments that are utilized to help manage symptoms of the disease. Further, potential treatments are in various stages of clinical trials, many of which are focused on managing symptoms and improving overall quality of life for the patients. The only FDA approved treatment for is tetrabenazine (TBZ), which targets chorea by reducing dopamine signaling. Unfortunately, the drug is not without side-effects. In some patients, TBZ in known
to cause severe aggravation of psychiatric symptoms, thus worsening anger and depression. However, as our understanding of disease mechanisms improves, and new technologies are developed, new treatments that may modify disease progression are emerging. Most prominently are clinical trials in progress to reduce levels of HTT through antisense oligonucleotide-based gene silencing.

1.2 HTT structure and function

The \textit{HTT} gene is located on chromosome 4p16.3. Although, the identification of the HD gene was over 20 years ago, the normal function of HTT is still not fully understood\textsuperscript{3}. The entire HTT protein itself is very large at \~350kDa and contains unique domains, some much better studied than others due to the significance they play in the mutant context and in pathogenesis of HD\textsuperscript{22}. Exon 1 has been extensively studied and contains the CAG repeat domain which encodes the polyQ stretch\textsuperscript{21}. The polyQ stretch is preceded by a highly conserved N-terminal domain of 17 amino acids, which functions as a cytosolic retention signal and possibly a nuclear export signal\textsuperscript{21}, and followed by a proline-rich domain\textsuperscript{21}. The majority of the protein has not been as well studied and is mainly composed of repeating Huntingtin, elongation factor 3 (EF3), protein phosphatase 2A (PP2A), and the yeast kinase TOR1 (HEAT) domains\textsuperscript{22}. Less characterized HEAT domains are found in other proteins and are predicted to function as a scaffold for protein-protein interactions\textsuperscript{22,23}.

Extensive post-translational modification has been well characterized within the N-terminal domains and to some degree within the HEAT domains. Sites for phosphorylation, sumoylation, palmitoylation, and acetylation exist and are vital for normal HTT function. The polyP tract influences the PTM of the first 17 amino acids\textsuperscript{24}. For instance, S13 and S16 are
both phosphorylated and important for the clearance of HTT\textsuperscript{25} and regulate the nuclear and cytoplasmic localization of HTT. HTT can shuttle in and out of the nucleus but is mainly found in the cytoplasm where the majority of its function has been characterized. At the organismal level HTT is ubiquitously expressed but does have varying expression levels across tissue types and even within cell types of the same tissues\textsuperscript{26}. The highest level of expression of HTT is in the CNS, which may contribute to the unique susceptibility of the CNS to mHTT\textsuperscript{20}. In addition to the PTM of HTT, HTT is also proteolytically cleaved at numerous sites across the protein forming various truncated versions of the protein. These forms are less understood but it is hypothesized that various forms of HTT can have different localization and function\textsuperscript{20}.

**Normal HTT function and possible loss-of-function contributions to HD**

The complexity of HTT’s normal function is highlighted by the many forms of HTT due to PTMs and proteolytic cleavage of the protein. Using techniques including yeast two hybrid, co-immunoprecipitations and large-scale proteomic analyses to characterize the interactome of HTT, over ~350 proteins have been identified that interact with HTT\textsuperscript{27}. These proteins function in a variety cellular processes including: RNA processing and transcription, vesicle trafficking, metabolism, protein clearance, and other functions, providing credence to the hypothesis that HTT acts as a scaffolding protein.

Although not fully understood, there is experimental evidence that normal HTT acts as a scaffold and is directly involved in vesicle trafficking, regulation of ciliogenesis, cell division, endocytosis, autophagy, and neuronal transcription\textsuperscript{21,28-34}. These biological processes span tissue types and developmental stages. Depending on the tissue and timing,
HTT will control different physiological functions. For example, early studies showed that homozygous gene knockout is embryonic lethal and leads to an impairment in gastrulation\textsuperscript{35}. Other studies in which the gene was knocked down during embryonic stages showed deficits to cortical and striatal development, leading to death just after birth\textsuperscript{30}. The polyQ track seems to be especially important to the CNS as deleting the polyQ tract in mice leads to neurological impairments. These results highlighted a potential role for HTT in autophagy\textsuperscript{36,37}. Normal HTT function in the CNS does not end at this stage, as studies indicate that HTT directly regulates the transcriptional control of neuronal differentiation, maturation, function, and homeostasis. HTT also contributes to the proper division of mammary stem cells and their differentiation into proper cellular compositions which highlights its importance outside the CNS\textsuperscript{32}.

HTT has important functions in the CNS, regulating proper formation and maintenance of the brain during development and in the adult CNS. Several genes that directly or indirectly interact with HTT are involved in regulation of neuronal gene expression, including: CREB, REST, and BDNF/TrkB signaling. HTT controls the transport of BDNF in cortical cells delivering this neurotrophic factor to striatal cells and activating TrkB signaling, which in turn activates ERK and leads to the expression of neuronal homeostatic genes\textsuperscript{28}. Moreover, BDNF expression is regulated by REST which silences the expression of neuronal genes through changes in histone acetylation, and is normally sequestered in the cytoplasm in a complex with HTT and huntingtin associated protein 1 (HAP1) \textsuperscript{29}. The expansion of the polyQ track into the disease range disrupts these sequentially ordered processes. This example of HTT dysregulation highlights one of the earliest and most reproducible disease phenotypes, namely transcriptional dysregulation.
Classically, the pathogenic attributes of mHTT have been described as gain-of-function (GOF) as opposed to a loss-of-function (LOF), but this terminology might be too black and white to accurately describe the effects of the mutation. Rather, the mutation of HTT leads to a dominant effect that causes impairment of various cellular processes, some of which are a function of normal HTT, but possibly in more subtle ways than a classic loss of function mutation. Transcriptional dysregulation of BDNF can occur due to HTT not properly sequestering REST in the cytoplasm, but also could be due to the mHTT fragments being mislocalized and accumulating in the nucleus, where they may disrupt the transcription of many genes. Moreover, despite the growing knowledge of HTT’s function in many important cellular and molecular processes, the loss of normal HTT function doesn’t mimic HD. For instance, loss of HTT function has been naturally replicated in patients that have only one functional copy of HTT due to a silencing mutation in the gene or due to chromosomal deletion\textsuperscript{38}. These individuals do not manifest with HD. Furthermore, knockdown of total HTT in animal studies and cellular models of HD rescues some of the pathological phenotypes\textsuperscript{39-41} suggesting that full expression of normal HTT is not required. Therefore, it is possible that the expanded repeat subtly impairs normal HTT function thereby reducing the overall health and homeostasis of the cell and creating an environment of greater susceptibility for the dominant mutant effects.

1.3 mHTT pathogenesis

mHTT pathogenesis involves many of the same cellular functions described above, as well as aberrant activities that result in the context of the mutation (Figure 1.1). In this
section I will focus mainly on transcriptional dysregulation but will also introduce new pathogenic mechanisms that occur specifically due to mHTT expression.

**The dominant pathological features of mHTT - a gain-of-toxic function?**

The polyQ expansion causes the HTT protein and fragments to form numerous multimeric, aggregated species that are thought to contribute to pathology in unique ways. HD is a true dominant disease in that homozygous carriers of the HD mutation do not show increased severity compared to heterozygous individuals in HD\textsuperscript{20}. Fragmented forms of HTT occur normally via proteolytic cleavage, by caspases, calpains and aspartyl proteases, however here is an accumulation of fragmented HTT in HD. Cleavage of the protein or alternative splicing\textsuperscript{42} of the transcript can create an N-terminal fragment which contains the N17 domain and the expanded polyQ track. The N-terminal fragment of mHTT is extremely toxic in cellular and animal models of HD, often leading to rapidly progressing phenotypes\textsuperscript{20}. N-terminal fragments can cause transcriptional dysregulation, accumulating in the nucleus and directly binding chromatin and DNA\textsuperscript{31}. Oligomerization and aggregation of mHTT occurs in the nucleus and cytoplasm and consequences of chronic mHTT expression are transcriptional dysregulation, impairment of proteostasis, and metabolic dysfunction\textsuperscript{20}. It was hypothesized that these aggregates were the main drivers of pathology by impairing proteostasis and sequestering binding partners, preventing their normal function \textsuperscript{43}. However, larger mHTT inclusions do not correlate with cell death or transcriptional dysregulation and are hypothesized to be protective, whereas soluble oligomeric forms of mHTT correlate with toxicity\textsuperscript{44}. 
Post translational modifications (PTMs) control the accumulation of HTT in its normal form and the aberrant regulation of these processes, including phosphorylation and sumoylation of mHTT contribute to pathogenesis\textsuperscript{24,25}. An increase in sumoylation of the HTT is implicated in the accumulation of toxic forms of the protein. A reduction in the enzyme, PIAS1, that controls this modification of HTT, can decrease this accumulation, increase survival, and improve behavioral assessments in mouse models of the disease\textsuperscript{24,45,46}.

In addition to dysregulation at the protein level, the mHTT gene also can gain new properties at the RNA level. mHTT mRNA forms abnormal secondary structures and can bind to RNA-binding proteins much like toxic C9ORF72 RNA foci in ALS\textsuperscript{47,48}. Repeat-associated non-ATG (RAN) translation has recently been identified as a potential contributor to pathogenesis in several repeat disorders, including ALS and Spinocerebellar ataxia 8 (SCA8), specifically due to the mutant expansion found in the mRNA derived from the causative genes. For example, in C9ORF72-mediated ALS (C9-ALS) the expanded hexanucleotide repeat is RAN translated, resulting in the formation of toxic dipeptides\textsuperscript{49}. Interestingly, this same type of RAN translation occurs in HD due to the expanded CAG repeats in the mRNA\textsuperscript{50}. The short peptides formed by the CAG repeat expansion are toxic to neural cells.

In later chapters I will discuss pathologies in C9orf72-associated-ALS and will briefly discuss some of the similarities seen between HD and ALS, and the significance to our understanding of each disease and treatment strategies.

**Cellular pathologies and non-neuronal contributions to HD**

The disruption in molecular processes described above lead to cellular impairments that have primarily been attributed to neurons (Figure 1.1). In this section I will briefly
describe the cellular processes that become disrupted in HD, and present evidence that autonomous deficits in other non-neuronal cell types that may also directly contribute to HD pathogenesis.

The medium spiny neurons of the striatum display the most overt degeneration in HD. These cells show an impairment in the proteostasis network, mitochondrial deficits, an increase in reactive oxygen species and inflammation, and transcriptional dysregulation (Figure 1.1)\textsuperscript{18}. In addition to these neuronal subtypes, cortical neurons display early transcriptional changes and impaired axonal transport\textsuperscript{18}. While it is clear that neurons are affected by mHTT pathogenesis, growing evidence indicates that cell autonomous deficits in other non-neuronal cells also contribute to the pathology. Recent studies support a role for microglia and astrocytes in HD pathogenesis\textsuperscript{14-16}. Selective expression of mHTT in microglia and astrocytes in animal and cell models disrupts their normal function and contributes indirectly to the death and dysfunction of neurons. mHTT expression in astrocytes alters expression of glutamate transporters and potassium ion channels which promotes accumulation of these molecules in the CNS and neuronal excitotoxicity\textsuperscript{14}. Microglia activation and increased inflammatory and ROS activity also contribute to HD; however, it was not known whether the increase in cytokines and ROS were cell-autonomous effects. Recent studies showed that mHTT expression in microglia increased expression of pro-inflammatory genes through activation of myeloid lineage-determining transcription factors\textsuperscript{16}. Therefore, there is increasing evidence that multiple cell types in the CNS have independent influences towards HD.

Most recently, vascular changes have also been described in HD. These changes include increased cerebral blood volume and small vessel density\textsuperscript{51,52}. The latter is caused
by an increase in vascular endothelial growth factor (VEGF) secretion by HD astrocytes\textsuperscript{13}. These data indicate that altered signaling between neurons, astrocytes, and brain endothelial cells (BECs) and pericytes, that make up the vasculature, could be accelerating impairments to cellular functions in HD, which eventually leads to neuronal damage in a coordinated effort. Signs that there were changes to the HD CNS vasculature prompted me to investigate BEC function. BECs line blood vessels that supply the CNS with oxygen and nutrients in a controlled manner through formation of a barrier, termed the blood-brain barrier (BBB), that protects the CNS from toxic molecules and immune cells\textsuperscript{53,54}. While impairment in BBB function have been described in both HD patients and animal models\textsuperscript{55}, it is currently unknown how these impairments arise in HD and whether they are due to cell-extrinsic (altered signaling between BECs and other cells of the CNS) or intrinsic deficits from mHTT expression in BECs.

These questions are explored in Chapter 2 of this dissertation, but in order to better understand the significance of the BBB to HD, and other neurodegenerative diseases, one must first understand how the BBB function and its normal role in maintaining CNS homeostasis. In the next few sections I will describe the development, maintenance, and function of the BBB and how specific BBB functions are disrupted in HD.

### 1.4 The neurovascular unit and the blood-brain barrier

**Structure and function**

Neurons, astrocytes, BECs and pericytes form the neurovascular unit (NVU) (Figure 1.2)\textsuperscript{53,54,56,57}. Each of these cells signal to each other through secreted and cell-contact mediated interactions to maintain homeostasis of the CNS, and regulate its interactions with
BECs of the NVU form the BBB which prevents entry of toxic molecules and immune cells, and regulates the influx of metabolites needed by the brain. The BBB regulates the permeability of these solutes and cells through four mechanisms: 1) The formation of tight junctions that prevent paracellular permeability, 2) downregulation of genes which are required for transcytosis, 3) expression of specialized transporters and efflux genes, and 4) downregulation of leukocyte adhesion molecules (LAMs) to prevent the entry of immune cells.

BECs are highly polarized and express specific proteins on the luminal and abluminal faces of the cell, as well as unique proteins that connect them with each-other. The physical barrier of the BBB is generated through expression of a set of key genes that control paracellular and transcellular permeability. The barrier properties of BECs are particularly relevant to the study of CNS diseases, including HD, both in the context of disease pathogenesis and in the development of therapeutics. Disruption of the BBB has not only been shown in HD but also other CNS diseases, directly or indirectly contributing to their pathogenesis. Developing therapeutics that can cross the BBB and rescue some of the aberrant barrier properties, might be a very difficult task that will require a better understanding of the BBB in disease.

In the next sections I will explain the mechanisms of the genes which make up the BBB, and will describe how the BBB is formed from signaling between cells of the NVU. This information is important to understand before one can interpret how the BBB may be involved in HD.

**Genes that form the BBB**
Tight junctions (TJs) are formed between two neighboring ECs to create a paracelluar barrier that is impermeable to water, ions and solutes (Figure 1.2). TJ proteins fall into two groups: integral and anchoring proteins. Integral proteins include CLAUDINs and OCCLUDIN that form the "kissing points" between two neighboring tight junctions. Proper formation of tight junctions can prevent the movement of small molecules and even ions which results in high transendothelial electrical resistance (TEER) values, \( >2000 \Omega \text{cm}^2 \), when measuring resistance in isolated vessel and even in, \textit{in vitro} cultures. These proteins adhere to the cytoskeleton through connection with intracellular ZONA OCCLUDENs, ZO-1, -2 and -3 proteins. In addition to tight junctions and anchoring proteins, adherens junctions form the initial connection between neighboring endothelial cells. Junctional adhesion molecules (JAMs) and CADHERIN-5 form the initial cell-cell contact and recruit TJ proteins that form the barrier. CADHERIN-5 (also known as VE-CADHERIN) and CD31/PECAM-1 form the initial contact between cells and are bound to the cytoskeleton via \( \alpha-, \beta-, \) and \( \gamma-\)CATENIN. In addition to recruiting and properly localizing TJ proteins, AJ proteins are also involved in establishing the initial polarity of BECs. CLAUDINS are the most abundant and functionally relevant tight junction proteins, as mice deficient for OCCLUDIN can actually form normal tight junctions with normal barrier. CLDN-5 and CLDN-3 have been the best characterized at the BBB. CLDN-5 has been shown to be regulated by Wnt and Shh signaling and is critical for preventing paracellular permeability, while CLDN-3 is regulated mainly by WNT. However, the role of CLDN-3 at the BBB is less understood, albeit it is thought to be a TJ protein required for formation, but not maintenance of the BBB. CLDN-5 on the other hand has been shown to specifically blockade the influx of small molecules <800D. The functions of many other CLDNs have been studied in epithelial cells,
with some CLDNs allowing selective ion influx through much like and ion channel\textsuperscript{67}. Although, there is not a complete picture of exactly how many of the greater than 20 CLAUDIN (CLDN) genes in the human genome are expressed at the BBB \textsuperscript{67,79-80}.

In addition to paracellular permeability, BECs regulate transcellular permeability by down regulation of proteins involved in transcytosis (Figure 1.2)\textsuperscript{81,82}. The expression of CAVEOLIN-1 and Plasmalemmal vesicle associated protein-1 (PLVAP) is markedly reduced in the maturing BECs, in comparison to peripheral ECs, and can be visualized by the reduction in endocytotic vesicles\textsuperscript{83,84}. These vesicles regulate the transport of larger molecules and cells by endocytosis. Receptor-mediated transport of larger molecules, such as transferrin and albumin, can specifically activate transcytosis to transport these molecules across the BBB\textsuperscript{85}. The rate of transcytosis is very low in the healthy brain, and only increases during BBB breakdown in pathological setting such as ischemic stroke \textsuperscript{64,86}.

BECs also control the transport of specific molecules into and out of the CNS through the presence of solute carrier (SLC-) and ATP-binding cassette (ABC-) transporters (Figure 1.2)\textsuperscript{87}. These transporters help to deliver specific metabolic nutrients to the CNS and also efflux toxic compounds out of the brain. A classic example of an important SLC- gene that impacts how the BBB regulates the homeostasis of the CNS, is SLC2A1 (GLUT1). GLUT1 is a glucose transporter and is highly and specifically expressed on BECs to supply the CNS with glucose through the bloodstream. The CNS accounts for approximately 20\% of the entire bodies’ glucose-derived energy consumption, and its regulation and uptake is vital to the function of the CNS. BECs also use transporters to specifically block molecules from entering into the CNS. Lipophilic molecules that are able to passively diffuse through the lipid bilayer membrane are effluxed out of the ECs before they can pass into the CNS by multidrug
High expression of PGP, and other multidrug resistance proteins, on the luminal side of the ECs help to efflux toxic molecules out of the CNS and into the bloodstream. The CNS regulates these functions by controlling the expression of BBB genes through NVU signaling, which is disrupted in HD.

**Signaling at the NVU – development and maintenance of the BBB**

Angiogenesis, i.e. the formation of new blood vessels is tightly coupled to BBB formation. The BBB develops shortly after embryonic angiogenesis, utilizing some of the same signaling factors involved in angiogenesis, secreted by the surrounding neural cells. The CNS vasculature first forms as endothelial cells from the perineural vascular plexus (PNVP) invade the CNS by angiogenesis, in a highly regulated spatiotemporal fashion. The control of angiogenesis is regulated by several pathways including Notch, VEGF, ANG-1/2, TIE-1/2, and WNT signaling. These signals are secreted from neural progenitors and non-neuronal cells and contribute to the formation of the BBB. Neural progenitors secrete alternatively spliced forms of VEGF protein to generate soluble and membrane adherent versions, which creates a gradient that guides the sprouting vessels. These vessels are enclosed by a basement membrane deposited by pericytes which wrap around the BECs. Astrocyte end feet also attach to the BECs and pericytes through another basement membrane, the glia limitans. Each neural cell type contributes unique signals to the BECs regulating the expression of specific BBB genes. This signaling and the importance of neural cell signaling to the formation of the BBB has been shown in both *in vitro* and *in vivo* studies. *In vitro* cultures of primary BECs quickly lose their barrier properties, which can be recovered by co-culturing these cells with neural cells or feeding them media conditioned by...
secreted factors from neural cells. This was also shown in an in vivo study which transplanted non-vascularized CNS tissue into mesodermal tissue leading to the generation of BBB properties in the ECs which vascularized the CNS tissue from the mesodermal tissue. This was not replicated in mesodermal tissue transplanted into the CNS. The CNS derived vessels that vascularized the mesodermal tissue did not generate BBB properties. These studies illustrate the necessity of neural signals to form and maintain the BBB.

WNT signaling has been shown to be particularly important for the formation of the CNS vasculature, and BBB (Figure 1.2). Specifically, canonical WNT signaling is activated in CNS vessels during murine embryogenesis. Activation of beta-catenin correlates with the timing of canonical WNT ligands 7a and 7b expression in neural progenitors. Studies of gene expression and formation of BBB genes during activation or inhibition of the canonical WNT pathway shows an active role of this pathways in directly targeting and inducing the expression of BBB genes. Nuclear localization of beta-catenin allows it to activate expression of target genes. Beta-catenin works in concert with LEF/TCF transcription factors, directly targeting BBB genes and other downstream WNT targets, including Adenomatosis polyposis coli down-regulated 1 (Apcdd1), which can be used as a marker for canonical WNT activation. Apcdd1 is a downstream target of the canonical WNT pathway that also acts in a negative feedback loop to inhibit the pathway. The canonical WNT pathway can also be activated in a ligand-independent mechanism that depends on the localization and anchoring of beta-catenin to adherens junctions. The large flux of free beta-catenin allows for its translocation into the nucleus. Other signaling pathways also contribute to BBB formation, including SHH signaling from astrocytes and PDGF-beta signaling to recruit pericytes for deposition of the extracellular matrix (EMC).
which forms the first basement membrane\textsuperscript{54,56,108}. TGF-β signaling is not as well studied, but is hypothesized to have a unique role in the formation of the BBB. The knockout of GRP124 on BECs alters normal TGF-β signaling and reduces the expression of GLUT1, a glucose transporter uniquely expressed in BEC\textsuperscript{56}.

The changing spatiotemporal expression of each of these signaling genes regulates BBB development, indicating that many pathways overlap in their ability to contribute to the regulation of the BBB, and that BECs do not obtain their BBB properties from just one set of unique signals. This again highlights why understanding the individual and cumulative contributions of each of the cells of the NVU to HD pathogenesis is critical to fully understanding the disease.

**The BBB in HD and other neurodegenerative diseases**

Very little is known about the contributions of the BBB in the pathogenesis of neurodegenerative disease. Through the development of novel techniques and better understanding of the BBB, it is becoming more accepted that several CNS diseases are associated with altered function of the BBB. The best-known example is the infiltration of peripheral immune cells into the CNS in multiple sclerosis. The infiltration of these T cell directly contributes to the pathogenesis of the disease by an autoimmune response towards the myelin sheath that helps to insulate the axons of neurons. Destruction of these proteins leads towards loss of neuronal function and degeneration of the affected neurons. The overt breakdown of BBB function by the infiltration of the peripheral immune cell is not as overt in other neurodegenerative diseases, however more subtle effects are observed that show specific BBB mechanisms fail to protect the diseased CNS. There are examples in Alzheimer's disease, amyotrophic lateral sclerosis, and even in HD whereby alterations in BBB genes
cause functional differences in the BBB. In AD, several features of the BBB are disrupted, including decreased GLUT1, altered cleavage and transport of amyloid beta by LRP1, and increased BBB permeability in AD patients due to a mutation in apoE4, a gene linked to familial forms of AD. Mutations of SOD1, that can cause a genetic form of ALS, also disrupt the BBB with decreased expression of tight junctions leading to leakage of serum proteins through the BBB and into the CNS.

Most recently, evidence of vascular changes in HD have been observed that impact BBB function. One of the earliest studies to show BBB changes in HD was a study in 2012 in a mouse model of HD, where by an altered BBB response to lipopolysaccharide allowed for an increase in extravasation of Evan’s blue dye, a compound that is normally blocked from entering the CNS. Another early study of the BBB in HD showed increased BBB permeability due to an increase in MMP9 expression in a rat model of HD, following treatment with 3-nitropropionic acid to mimic the striatal loss seen in HD patients. As highlighted above, more recent studies of the CNS vasculature in HD patients show an increase in small vessel density, transcytotic vesicles, and PGP, as well as a decrease in CLDN5 and OCLN. These proteins directly contribute to the function of the BBB and their dysregulation suggests that the BBB could directly contribute to the pathogenesis of HD.

However, little is known about the mechanisms and sequence through which BBB impairment arises in HD. It is unclear if BBB deficits are secondary to neurodegeneration or if they actively contribute to neurodegeneration. For instance, we do not know if intrinsic deficits in the BECs themselves, due to the presence of a disease gene or feature, causes inherent dysregulation within the BECs and BBB, helping to drive neuronal dysfunction and
neurodegeneration. In chapter 3, I provide evidence for a direct role in HD, using patient-induced pluripotent stem cell (iPSC)-derived BECs. My data expands upon the previously published BBB impairments in HD by providing insight into the cell autonomous effects of mHTT expression in HD-BECs.

Since iPSCs were utilized in all of the studies presented in this dissertation the last section of this introduction will provide the reader with a basic overview understanding of iPSC biology and disease modeling, and highlight the benefits obtained by modeling HD using iPSCs.

1.5 Modeling HD with patient derived iPSCs

Due to the monogenic basis of HD, researchers have generated many cellular and animal models of the disease. There have been large animal models, including sheep and non-human primates, and smaller animals including murine models and songbirds. Much of what we know about HD pathological mechanisms has come from murine models of the disease. These mouse models include: fragment, full-length, and knock-in models, all of which recapitulate certain aspects of the human disease. For example, the fragment models largely focus on the N-terminal region of the mutant gene, with the R6/2 mouse being one example with a very short lifespan and rapid progression, representing aspects of symptomatic HD. Although much has been learned from studying these animal models we do not know how well they recapitulate the human disease. To date, no treatment has yet translated effectively from mouse studies to humans.

In order to overcome the limitations presented by animal models, I have utilized iPSC technology. iPSCs are pluripotent stem cells which have been reprogrammed from
somatic cells from patients. Adult somatic cells, like fibroblasts and blood cells, can be taken from any human and reprogrammed using a combination of reprogramming factors towards a state which mimics many aspects of embryonic stem cells (ESCs). Originally, a combination of factors which included: OCT4, SOX2, and either KLF4 and c-MYC, or NANOG and LIN28 were utilized for epigenetically reprogramming the state of these somatic cells by lentiviral induction. For our studies we have utilized cells reprogrammed using a non-integrating episomal method with: OCT4, SOX2, KLF4, NANOG, c-MYC, and LIN28, but many new methods including mRNA and miRNA can be used for reprogramming. These cells were generated from HD patient fibroblasts as part of a larger effort of the HD iPSC consortium. Our consortium was formed with the goal of modeling HD using iPSCs and the specializations of many labs across the globe, with a central site (Clive Svendsen, Cedars Sinai) generating the iPS lines.

Once iPSCs are generated, they can then be differentiated into any cell type of the adult human body by the addition of specific medium containing growth factors and molecules that mimic their in vivo development. The novelty of using iPSCs for disease modeling is more than just the fact that the system is now representative, at least in vitro, of the human system, but also that disease genes can be studied in their endogenous forms\textsuperscript{114-116}. Using iPSCs from HD patients allows us to correlate clinical characteristics such as: precise phenotyping, age of onset, and disease progression to cellular and molecular feature of the differentiated cells. We are also able to study specific cell types independently and together, cells which are normally only available as postmortem tissue. Furthermore, disease can be studied temporally as the cells differentiate and “age” through different stages of development. Our lab has published data on these HD patient-derived iPSCs showing CAG
length dependent phenotypes in neural stem cells, with some functional studies on mature neural cells\textsuperscript{117}. The work described in chapter 2 has taken these studies further by using multi-omic analyses and additional functional assays on the mature neural cells with striatal like characteristics.

1.6 Overview of dissertation

This dissertation summarizes the collective work I have conducted as a doctoral candidate, and focuses on providing a concise understanding of the novel mechanistic insights attained through the transcriptomic analysis of HD and ALS patient iPSCs. Multiple diseases and cell types were analyzed providing an enormous amount of complex data. In this dissertation, I describe how these data show a fundamental role for transcriptomic dysregulation in pathogenesis in both of these diseases, and provide novel evidence that fills in some of the gaps in the field where pathology is not yet fully understood mechanistically, including: altered neurodevelopment and neurogenesis of neurons and BBB impairments in HD, and abnormal RNA processing and cell adhesion in ALS.

As stated in the introduction, chapter 1 focuses on using transcriptomic and epigenomic analyses, RNAseq and ChIPseq, respectively, to gain further understanding of transcriptional dysregulation in HD neural cells, and defines key pathogenic pathways that could be targeted for therapeutic relief. Here we show how the HD iPSC-derived neural cells not only recapitulate known phenotypes of the disease but also show novel gene changes that implicate a role for neurodevelopment and neurogenesis in HD. It has widely been thought that the HD mutation did not exert its effect during development, however more recent studies suggest that early changes may occur that influence later disease\textsuperscript{118-126}. These
data provide a mechanistic insight and as a proof of concept show that gene changes can be therapeutically targeted and reversed with a small molecule.

In chapter 2, I utilize the same approach of differentiating HD patient-derived iPSC into a cell type of interest, but focus on BECs to study vascular abnormalities found in HD murine models and patients\textsuperscript{13,51,55,63,127}. I demonstrate that HD-BEC have intrinsic deficits that are independent of their interactions with astrocytes of the NVU. These deficits include an increase in angiogenic potential and impairments in BBB properties. Paracellular and transcellular pathways through the BBB are disrupted and could directly contribute to HD pathogenesis. These deficits appear to arise from transcriptional dysregulation that is caused by mHTT expression within the BECs, and gives clarity to the question of whether BEC and BBB impairments that could contribute to neurodegeneration are primary or secondary effects.

Chapter 3 shifts directions towards more recent work as a member of the NeuroLINCS consortium, which use iPSC technology to model ALS. Using similar multi-omic approaches as described in chapter 1 we identified molecular mechanisms which could explain the altered cellular adhesion and RNA processing in C9ORF72- associated ALS. We also identified similar pathologies in HD and ALS. These overlapping similarities will allow us to compare mechanisms of pathogenesis between each disease and gain insight on signatures common across neurodegenerative diseases, and those that selectively contribute to individual diseases. Better understanding of both diseases will help guide discoveries of selective treatments for each disease.

In the last chapter, 4, I will summarize the overall findings and highlight novel findings that have opened new paths of research where there were previously gaps or lack
of understanding. I will also contrast the information we have obtained from each model system and how neurons and BECs could be both independently and collectively contributing to HD, as well as how the insight gained from comparing what we've learned in HD to ALS and vice versa could lead to a better understanding of both diseases. Lastly, I will present the future experiments that will move these findings forward.
1.7 Figures

**Figure 1.1 Schematic diagram of Huntington disease cellular pathogenesis.** Yellow boxes highlight pathways with potential for biomarker development. In some cases, the molecule might be involved directly in pathogenesis, as with huntingtin itself, and might, therefore, also be a therapeutic target and serve as a pharmacodynamic marker, as well as a marker of disease status. Abbreviations: 3-HK, 3-hydroxykynurenine; Ac, acetyl group; BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; KMO, kyurenine monooxidase; NMDA, N-methyl-d-aspartate; P, phosphate group; QUIN, quinolinic acid; ROS, reactive oxygen species; Su, SUMO post-translational modifications; TNF, tumour necrosis factor. © 2014 Macmillan Publishers Limited. (Ross, C. A. et al. Nat. Rev. Neurol. 10, 204–216 (2014)).
Figure 1.2 The neurovascular unit and blood-brain-barrier. 

A) The neurovascular unit composed of endothelial cells, pericytes, and astrocyte endfeet. Neuronal cell also contributes through signaling to and from the other cells of the NVU. 

B) The blood-brain barrier. Genes that form the BBB including paracellular barrier genes (TJs: ZO-1, CLDN, OCLN) and transcellular genes (CAV1, PGP, and ion channels). Signaling from cells of the NVU including Wnt signaling contributes to the expression of BBB genes.
1.9 References


Piontek, J. et al. Formation of tight junction: determinants of homophilic interaction between classic claudins. FASEB journal : official publication of the Federation of


Chapter One

Altered neurodevelopment of Huntington's disease iPSC-derived neural cells and pharmacological rescue by Isx-9

The HD iPSC Consortium#
2.1 Summary of Chapter 1. This chapter is taken from a manuscript under re-review.

In this chapter, we investigate epigenomic changes in HD neural cells. Using neural cultures derived from Huntington’s disease (HD) patient-derived induced pluripotent stem cells (iPSCs), we attempted to identify key pathogenic changes to neuronal function and the underlying transcriptional changes that drive these pathologies. Unbiased “omics” analysis was used to identify these mechanisms. RNA-Seq analysis identified genes in glutamate/GABA signaling, axonal guidance and calcium influx whose expression was decreased in HD cultures. One-third of gene changes were in pathways regulating neuronal development and maturation. When mapped to stages of mouse striatal development, the profiles aligned with earlier embryonic stages of neuronal differentiation. A strong correlation between HD-related histone marks, gene expression and unique peak profiles associated with dysregulated genes was observed, suggesting a coordinated epigenetic program. Treatment with Isoxazole-9, which targets key dysregulated pathways, led to amelioration of expanded polyglutamine repeat-associated phenotypes in neural cells and cognition and synaptic pathology in R6/2 mice. These data suggest that mutant Huntingtin impairs neurodevelopmental pathways that could disrupt synaptic homeostasis and increase vulnerability to the pathologic consequence of expanded polyglutamine repeats over time. The idea that HD has developmental phenotypes is a newly emerging hypothesis, however the extent to which they occur and their exact contributions to the disease is unclear. The work discussed in this chapter helps to provide evidence that supports that e impairment may arise from reversible alterations in the epigenome and transcriptome. We also show how these changes seems to be involved in functional deficits and cell death, and provide an interpretation of the findings in the context of contributions towards disease
susceptibility and progression. My contribution to this work was in the context of performing transcriptomics, analysis of transcriptional dysregulation and in coordination of the consortium.

2.2 Introduction

Huntington’s disease (HD), a dominantly inherited neurodegenerative disorder, is characterized by motor abnormalities, psychiatric symptoms, and cognitive deficits\textsuperscript{2,18}. The disease is caused by a CAG repeat expansion within the Huntingtin gene (\textit{HTT}) that encodes a polyglutamine tract expansion within the Huntingtin protein\textsuperscript{3}. CAG repeats of 40 or more cause symptoms within a typical lifespan, and above \textasciitilde60 cause juvenile onset HD\textsuperscript{4}. Mutant HTT (mHTT) protein is implicated in a spectrum of cellular aberrations, including those affecting cell signaling, transcription, autophagy, calcium homeostasis, and bioenergetics\textsuperscript{9,10}. Neuropathology includes cortical atrophy and extensive loss of striatal medium spiny neurons\textsuperscript{11}. Clinical onset and neurodegeneration are primarily predicted by the CAG repeat expansion and largely considered to result from cumulative toxic insults, together with environmental and other genetic factors\textsuperscript{6}.

However, emerging data, particularly for juvenile onset HD, suggest there may be deficiencies of neurodevelopment and in the differentiation of neural stem/progenitor cells within the adult striatum\textsuperscript{128}, a process that now appears to occur throughout life\textsuperscript{129,130}. Indeed, adult neurogenesis appears to be impaired in the striatum of HD patients having increased cell proliferation\textsuperscript{118}, however, there is an absence of adult-born neurons in the striata of HD patients\textsuperscript{119}, suggesting that while neurogenesis can be initiated, maturation
may be impaired. Neuroimaging with MRI and PET scans of pre-manifest HD brains detect changes in striatal, cortical and whole brain volume well before the onset of symptoms\textsuperscript{131-133}. Measures of head circumference in premanifest HD subjects (with CAG repeat expansion but prior to motor diagnosis) indicate potentially reduced brain volumes compared to unaffected repeat subjects\textsuperscript{134}.

Patient-derived induced pluripotent stem cells (iPSCs), somatic cells reprogrammed to a pluripotent state by introducing specific transcription factors\textsuperscript{113,135}, provide an important resource to decipher mechanisms underlying neurological disease (e.g.\textsuperscript{114}), and have a growing impact on the design of novel therapeutic strategies\textsuperscript{136,137}. Using induction factors, iPSCs can be differentiated into multipotent neural stem progenitor cells that can subsequently produce mature neural subpopulations (e.g.\textsuperscript{116,138-141}). We previously reported that differentiated HD-derived iPSCs display expanded CAG-associated phenotypes\textsuperscript{117}.

The present study uses neural cells differentiated from HD patient-derived iPSC lines with juvenile onset CAG repeat expansions (60 and 109 repeats) to explore the effects of pathological $HTT$ alleles by using parallel cultures for unbiased "-omics" analyses, including RNA sequencing (RNA-Seq) and chromatin immunoprecipitation sequencing (ChIP-Seq). This discovery-based approach revealed consistent deficits related to neurodevelopment and adult neurogenesis, suggesting that specific gene networks represent potential therapeutic targets applicable for early disease intervention. Notably, a small molecule, Isoxazole-9 (Isx-9), that targets many of the key dysregulated gene networks identified, normalized CAG repeat-associated phenotypes in HD iPSC-derived neural cultures and synaptic pathology in R6/2 mice, demonstrating that these potential developmental, transcriptional, and functional deficits can be restored and synaptic homeostasis improved.
2.3 RESULTS

Differentiation of iPSCs with expanded HD and non-disease CAG repeats

iPSC lines from non-diseased and HD fibroblasts with CAG repeats from 21–33 (non-disease) and 60 and 109 (juvenile onset HD range), previously reprogrammed using integrating viral reprogramming methods\textsuperscript{117}, were generated with non-integrating episomal factors (Figure 2.1\textsuperscript{114}. Lines were named using established nomenclature\textsuperscript{143} (Figure 2.1: e.g., CS09iHD109 designated 109Q), and pluripotency and normal karyotypes confirmed. iPSC lines were differentiated for 56 days into mixed neural cultures containing neurons, glia and neural progenitors by a previously characterized method\textsuperscript{117,144}. Lines showed the expected expression of germ lineage markers (Figures 2.2 & 2.3). Immunocytochemistry and non-biased stereological counting of the differentiated iPSC lines revealed that glial, neural progenitor and neuronal marker were expressed and levels overall in HD versus non-disease lines were not significantly different (Figure 2.2a-e), with total counted cells expressing glial fibrillary acidic protein (GFAP, 16.1%), neuronal markers TUJ1 (26.5%) and MAP2\textsubscript{ab} (14.8%), and striatal marker DARPP-32 (14.3%) (Figure 2.2b-e). Oligodendrocyte (Figure 2.2f), endoderm (SOX17, FOXA2), mesoderm (MYO1), and microglia (IBA1) (Figure 2.3a, b) markers were absent. The iPSC lines have a similar overall composition from staining data, and nestin staining appears similar in these cultures (Figure 2.2a). At earlier time points, our data shows that nestin-expressing neural progenitor cells may persist longer in the highly expanded 109Q repeat line\textsuperscript{142} and that nestin-positive cells were more susceptible to cell stress after acute brain-derived neurotrophic factor (BDNF) withdrawal, suggesting early and subtle effects exerted by expanded CAG repeats.
**RNA-Seq analysis of differentiated iPSCs**

To investigate pathogenic molecular mechanisms that may reflect more subtle alterations, unbiased whole-genome and multi-platform approaches were used in parallel iPSC cultures differentiated as above. Whole-transcriptome analysis (RNA-Seq) was performed and principal component analysis (PCA) showed separation of HD 109Q and 60Q lines (two clones each) from non-disease 33Q, 28Q, and 21Q lines, indicating minimal variability within groups and that the maximal variance can be explained by disease and non-disease differences (Figure 2.1b). Subsequent statistical analysis using the Bioconductor package DESeq (RNA-Seq Differential Expression (DE))\(^{145}\) revealed 1869 differentially expressed genes (DEGs) between HD and non-disease lines (Appendix 2 Table 3.7). Hierarchical clustering (Figure 2.1c) of log2 transformed gene expression values derived from this analysis showed that samples clustered by repeat length, with distinct separation and expression patterning between HD (109Q, 60Q) and non-disease samples (21Q, 28Q, 33Q). Independent clonal lines derived from individual subjects clustered tightly together with low variability within groups (Figure 2.1c).

**RNA-Seq analysis suggests altered neurodevelopment in HD lines**

Ingenuity pathway analysis ((IPA) Figure 2.4) was used to investigate biological changes through analysis of genes identified by DEseq analysis. Top altered biological functions were assigned and ranked according to significance of the observed/expected differential expression of genes involved, and a z-score was calculated based on each gene’s fold-change value/direction and the accumulated contribution of those genes to a biological function/process. When we evaluated categories associated with gene expression changes, 543 of the 1869 DEGs (Appendix 2 Table 3.7) (29%) fell within functional categories.
centered on development, and the top three categories were *cellular development*, *nervous system development and function*, and *tissue development* (Figure 2.5a). Over half (59%) of these genes are associated with nervous system development and function\textsuperscript{146-148}, including several among the top 100 genes ranked by a FDR adjusted p-value.

A subset of these neural developmental genes and their physical and regulatory interactions with each other are depicted in Figure 2.5b, with *NEUROD1* as a highly enriched hub. HTT interacts physically with the products of two of the genes that are among the most significantly down regulated in the RNA-Seq dataset: NEUROD1 and GAD\textsuperscript{149,150}. Expression of the proneuronal bHLH gene NEUROD1 was markedly decreased across all HD lines (Appendix 2 Table 3.7), as was NEUROD1 protein (Figure 2.15d). *NEUROD1* is a key regulator of neurodevelopment, being expressed in embryonic neuroepithelial cells\textsuperscript{151}, and of adult neurogenesis, involved in terminal differentiation as well as maturation and survival of adult-born murine neurons\textsuperscript{152}. Of the genes in this interacting network (Figure 2.5b), several regulate expression of *NEUROD1* (*POU4F1\textsuperscript{153}, NEUROG2\textsuperscript{154}, ASCL\textsuperscript{155}, and REST\textsuperscript{156}) and are dysregulated or predicted to have aberrant activities. The RNA expression levels for several of these interacting genes, including *NEUROD1*, were validated by qPCR (Figure 2.6).

Based on the HD RNA expression profiles, the activation or inhibition of several upstream regulators was predicted by IPA (Figure 2.5c). These include several that are implicated in HD pathogenesis, such as increased REST and decreased BDNF signaling\textsuperscript{157}. Of interest, REST-mediated epigenetic remodeling regulates the developmental switch of synaptic NMDA (N-methyl-D-aspartate) receptors from GluN2B to GluN2A subunits, thus decreasing expression of Grn2B\textsuperscript{158}. In agreement with dysregulation of this activity, Grn2B was significantly downregulated (-2.4 fold) in the RNA-Seq data set. Several genes essential
for proper neurogenesis, including \textit{NEUROD1}, \textit{NEUROG2} and \textit{ASCL1}\textsuperscript{130,151,159} and the microRNA miR-124 (which antagonizes the REST pathway during embryonic central nervous system (CNS) development\textsuperscript{160}), are predicted to have inhibited activity. Interestingly, several genes involved in the TGFβ pathway (\textit{TGFB2}, \textit{TGFB3}, \textit{TGFB3R}) were up-regulated in the differentiated HD iPSCs with upstream regulators TGFβ1 and TGFβ1R having predicted activation. TGFβ signaling has been implicated as a “switching factor” whose levels and temporal activity require tight regulation during development to determine neuronal cell fate\textsuperscript{161} and this signaling network was also disrupted in neural stem cells (NSCs) derived from HD patient iPSCs\textsuperscript{125}. Highlighted within the center of this network were genes overlapping the IPA predicted regulators, and genes that are major hubs which have the most direct connections to other genes in the larger network, suggesting a significant association of this network to HD.

\textbf{Cellular pathways related to neuronal function are altered in HD iPSC-neural cells}

In addition to the key categories, dysregulated pathways were also identified by IPA from the list of dysregulated genes found by DESeq analysis, including axonal guidance, WNT signaling, Ca\textsuperscript{2+} signaling, neuronal CREB signaling, and glutamate and GABA receptor signaling (Figure 2.7a). Each is important for neuronal development and maturation and altered in HD models or human HD\textsuperscript{1,9,10}. Axonal guidance pathways regulate the precise patterns of connectivity, integrating actions of guidance cues and receptors. Four families of molecules and receptor genes provide axon guidance cues\textsuperscript{162}, including NETRINS, SLITS, EPHRINS and SEMAPHORINS, and genes within each family are dysregulated in the RNA-Seq data set (Appendix 2 Table 3.7) with the majority of genes being down-regulated.
Intracellular calcium signaling promotes axonal and dendritic outgrowth, providing a connection between alterations in axonal guidance and calcium-signaling pathways, and is critical for neuronal synaptic activity-regulated transcription and maturation\(^{163}\). Widespread dysregulation of Ca\(^{2+}\) signaling pathways in the HD samples (Figure 2.7b) included gene members of the glutamate-regulated NMDA and AMPA (\(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors (\(\text{GRIN1, GRIN2B, GRIN2C, GRIN2D and GRIA1, GRIA2, GRIA4, respectively}\))\(^{,}\) nicotinic acetylcholine receptor subunits (\(\text{CHRNA2, A3, A4, A5, A6, B2 and B4}\)), several subunits of the voltage-gated Ca\(^{2+}\) channel \(\text{CACNA1 (A,B,D,E and I)}\), and the plasma membrane Ca\(^{2+}\)-ATPase (\(\text{ATP2B2}\)), in addition to the calcium sensors and downstream effectors \(\text{CAMKII, CALM and CREB}\) (Figure 2.7b). Among the down-regulated DEGs in the glutamate/gamma-aminobutyric acid (GABA) signaling pathways are glutamate decarboxylases, \(\text{GAD1 and GAD2}\), which are GABAergic neuron markers. Several other DEGs in the HD iPSC-neural cultures are involved with GABA synthesis, release, reuptake or degradation (e.g., \(\text{ABAT, the solute carriers SLC1A3, SLC1A6, SLC32A1 and SLC6A1}\)). As glutamate is transported into neurons via \(\text{SLC1A3 and SLC1A6 (EAAT1 and EAAT4)}\), the down-regulation of these genes in differentiated HD iPSCs would be predicted to yield reduced glutamate substrate for GABA synthesis. This is significant, given that GABAergic neurons are the most vulnerable to mHTT toxicity\(^{164}\). The set of dysregulated genes also display integrated features and potential effects on nervous system development and function, including clustering of DEGs in CREB, WNT and axonal guidance signaling, synaptic function (Figure 2.8a, b), and integration with calcium signaling, as above.
Comparison of HD iPSC lines to mouse striatal gene expression indicates altered maturation

To further investigate the connection between gene expression dysregulation and neuronal development, the 1869 DEGs from the RNA-Seq analysis were compared to a comprehensive list of genes involved in mouse striatal development. In fact, 1647 mouse genes displayed over 70% homology to the 1869 human genes. Matching these 1647 orthologs with the microarray mouse developmental data using Xspecies identifiers yielded 679 overlapping genes. Statistical analysis (Cox-squared approximation with Yates’s correction) gave p<0.0001, demonstrating an unlikely overlap by chance. Because of the test’s non-exact nature, a Monte Carlo method was also used and yielded the same p < 0.0001. Hierarchical clustering analysis of these 679 genes for sample and gene clusters showed (Figure 2.9a) that the HD60Q and HD109Q RNA-Seq samples clustered with the proliferative germinal zone samples, while the non-disease samples clustered with the post-mitotic mantle zone samples (expanded dendrogram, Figure 2.9a), suggesting that the differentiated HD lines are maturing slower than the non-disease lines, or improperly shutting-off gene expression involved in earlier stages of neuronal development.

In concordance with the neurodevelopmental origin, enriched GO terms for the set of 679 genes (Figure 2.9b) included synaptic transmission (GO:0007268), nervous system development (GO:0007399), CNS development (GO:0007417), and a series of more specific processes, such as axonal guidance (GO:0007411), cell adhesion and locomotor behavior (GO:0007626), similar to the categories enriched in the RNA-Seq. Further investigation of the RNA-Seq data into the functional category nervous system development and function revealed similar subcategories that include: synaptic transmission, axon guidance, neuronal
development, coordination, and memory. The activation z-scores predict that most of these cellular processes have decreased or inhibited function in the HD lines (Figure 2.10a).

Using the hierarchical cluster algorithm with average linkage for gene expression values, we obtained thirteen different clusters from the 679 genes. Remarkably, gene Cluster I (Fig. 2.11 & 2.10b) contains NEUROD1 and related genes that are expressed significantly higher in non-disease repeat samples, supporting the idea that neurodevelopmental processes are altered in the HD lines. Of note, WNT signaling was significantly altered within this cluster as well, consistent with this class of ligands being critical for CNS development\textsuperscript{146} and the role of WNT signaling in NEUROD1 activation\textsuperscript{165}.

To visualize the connections between genes in the gene sets, we analyzed these data with the Thomson Reuters platform, Metacore®, a curated database for functional analysis. By using a direct interactions algorithm, the most enriched result within the 679 genes contained 296 nodes and included developmentally described transcription factors (DLX2, c-MYC, DACH1, MEF2A, hASH1) and relevant pathway regulators (TGFβ receptor), similar to RNA-Seq results. Figure 2.9c summarizes this network including transcription factors, protein kinases, kinase receptors and ligands.

Finally, HD DEGs were compared to genes that change in expression during human striatal maturation\textsuperscript{147}. Strikingly, genes implicated in the development of human striatum are also regulators of genes differentially expressed in our HD neural cells (Figure 2.10c). These data indicate a core network of genes that both contribute to the maturation of the human striatum and are altered in HD iPSC-derived neural cells.
**ChIP-Seq analysis reveals HD chromatin signatures and epigenetic changes to genes within functional pathways consistent with altered neuronal maturation**

Widespread transcriptional and epigenetic changes suggest that epigenetic dysregulation represents primary pathognomonic molecular features of HD\(^{166-170}\) and chromatin remodeling has been implicated in neural development and synaptic plasticity\(^{171}\). ChIP-Seq was performed for three histone marks: H3K4me3 (promoter-specific activation), H3K27ac (enhancer), and H3K36me3 (in actively transcribed gene bodies). In both HD and non-disease lines, most H3K4me3 peaks were in promoter and intronic regions, and most H3K27ac and H3K36me3 peaks were in intergenic regions. There did not seem to be a relationship between the number of peaks observed and \(mHTT\) repeat length.

We previously identified an epigenetic pattern in wild-type mice that marked genes with altered expression in R6/2 mice\(^{172}\), that express an expanded repeat containing HTT fragment\(^{173}\), by comparing RNA-Seq and ChIP-Seq data sets. Here, we used k-means clustering to identify five predominant patterns of the distributions of these histone marks around the TSS in the non-disease differentiated iPSC lines. In agreement with mouse tissue, genes with altered expression in high-repeat-number HD lines were more likely to be members of a cluster that we labeled class 1 for the mark H3K4me3 (\(p=3.7e-6\) for genes with higher expression in HD, \(p=1.1e-36\) for lower expression). This cluster was characterized by a broad peak just downstream of the TSS in non-disease cell lines (Figure 2.12a). A similar pattern for H3K27ac (\(p=6.3e-25\) for higher expression, \(p=3.5e-45\) for lower expression) was observed (Figure 2.12b). In both cases, GO enrichment analysis showed that class 1 genes were enriched for neuronal terms, such as *neuron differentiation* (FDR=2.2e-24 H3K4me3, FDR=8.73e-31 H3K27ac) (Table 2.1a and b), supporting the idea that this class marks a
coherent group of genes relevant to the disease and dysregulated in the HD lines. For H3K36me3, genes that were up-regulated in high-repeat cell lines were likely to be members of a cluster that we labeled as class 5 in non-disease cell lines, which had a peak closest to the TSS of the gene (p=5.7e-7 for higher expression, p=1.1e-4 for lower expression) (Figure 2.12c). GO analysis of H3K36me3 class 5 genes showed enrichment for neurological terms, such as synapse (FDR=7.09e-8) (Table 2.1c). Significantly, these profiles were observed in histone mark data from non-disease repeat cell lines, marking genes that are affected in the HD lines. Therefore, these findings provide an important mechanistic clue by revealing the potential vulnerability of promoters with a specific “signature” of histone mark occupancy that leads to transcriptional dysregulation in HD. These classes of genes and the enzymes that regulate their histone marks could therefore be selective targets for therapies attempting to restore transcriptional regulation to the normal state.

Changes in histone marks associated with polyglutamine expansion revealed widespread epigenetic changes near relevant genes. Pooled data from all expanded repeat HD cell lines were compared to the pooled data from the non-disease samples. Genes within 10kb of H3K27ac peaks that were stronger in HD lines were associated with structural GO terms such as actin cytoskeleton (FDR=7.72e-5) (Figure 2.12d), and genes associated with higher levels of H3K27ac in the non-disease lines were significantly associated with neurological GO terms, such as synaptic transmission (FDR=1.39e-11) and neuron differentiation (FDR=4.69e-9) (Figure 2.12d). These results are similar to the RNA-Seq results and suggest that disease-dependent modification of epigenetic components subtly affects cell lineage determination and perturbs neuronal fate specification. Genes near H3K4me3 peaks with higher levels in HD cell lines were significantly associated with cell-
adhesion terms including cadherin (FDR=1.4e-21) and calcium-dependent cell-cell adhesion (FDR=6.68e-5) (Table 2.1d). Cell adhesion machineries mediate several neuronal functions, including neurite outgrowth and synaptogenesis\textsuperscript{174,175}. Subsequent IPA analysis of genes with differential peak heights identified pathways and functional categories in common with RNA-Seq results including calcium signaling, GABA receptor signaling, axonal guidance, and nervous system and skeletal muscle development and function.

We examined both RNA-seq data and ChIP-seq data together to combine these datasets. We observed a highly significant correlation between the ChIP-Seq signal and RNA-Seq (Pearson p<1e-10 in all cases), which suggested a tight link between these two processes (Figure 2.13 and 2.14a). When each epigenetic class is individually considered, the correlations between levels of ChIP-Seq signal and RNA-Seq are even more striking (Figure 2.13a-f). For example, H3K27Ac levels and transcription changes for class 1 genes in the 21Q cell line have a correlation coefficient of 0.7 (p<1e-10). In every cell line, class 1 genes in H3K27ac and class 5 genes in H3K36me3 showed the highest correlation between ChIP-Seq counts and mRNA expression (correlation plot, Figure 2.13). Tracks for the gene ELAV are provided as an example of this correlation between ChIP-Seq and RNA-Seq signals (Figure 2.14a).

**Transcription factor motifs from ChIP-Seq analysis are involved in neuronal development**

To complement the IPA analysis, we next used sequence motif analysis which is less biased by the literature. Given the association of the H3K27ac mark with genes involved in neuronal fate and signaling, we looked for motifs that were significantly enriched near those H3K27Ac
peaks that were stronger in the HD lines and, conversely, those that were stronger in the non-disease lines. THEME software\textsuperscript{176} was used and our analysis was restricted to areas of CpG-poor DNA sequence, as this often results in more tissue-specific motif discoveries\textsuperscript{177}. We disregarded transcription factors not expressed across all six cell lines. The top motifs are shown in figure 2.14b.

GO enrichment analysis of all transcription factors with a p value <0.05 highlighted several differences. The primary type of DNA-binding region utilized by these transcription factors appeared to differ, with motifs near non-disease-biased H3K27ac peaks enriched for zinc finger (FDR=7.57e-24) and helix-loop-helix DNA binding terms (FDR=2.62e-4), but those under HD-biased peaks were enriched for the GO terms homeobox (FDR=6.99e-59), fork-head (FDR=5.27e-17), and leucine zipper (FDR=3.15e-11) (Figure 2.14c). Within HD and non-HD-biased H3K27ac peaks, categories of transcription factors were enriched for the term embryonic morphogenesis (HD FDR=2.38e-12, non-disease FDR=2.24e-5) and similar embryonic development terms. Interestingly, transcription factors whose motifs were found near HD-biased peaks were also enriched for terms related to neuronal development, including \textit{forebrain} (FDR=3.98e-5), \textit{diencephalon} (FDR=0.043) and \textit{regulation of nervous system development} (FDR=0.026), supporting the concept of altered neurodevelopmental pathways in the HD lines. Enrichment of certain motifs also highlights additional pathways that may affect neuronal development. For instance, the transcription factor MEF2 is linked to peaks that are stronger in HD (p=3.62e-18), suggesting increased activity. MEF2 has been implicated in regulating a transcriptional program in neurons that regulate activity-dependent synapse development and synapse number in neurons\textsuperscript{163}. NEUROD is a member of a cluster of motifs enriched near peaks that are stronger in non-disease cell lines (p=3.06e-
22), consistent with the downregulation of the \textit{NEUROD1} transcript in HD. REST similarly shows enrichment in non-disease cell lines (p= 1.98e-7), indicating that REST-regulated genes have lower H3K27ac in HD cell lines, consistent with REST being a significant predicted upstream regulator of differentially expressed genes (Figure 2.5c). These motif results provide evidence that master regulators of nervous system development and function are altered in HD lines compared to controls.

\textbf{I5x-9 corrects CAG repeat-associated neurodevelopmental and neuronal phenotypes in differentiated HD iPSCs}

The data above suggest that HD iPSC-derived neural cells have epigenetic changes leading to altered expression of genes regulating pathways involved in neurogenesis and synaptic activity, which could then have functional consequences as described for differentiated HD iPSCs\textsuperscript{117,178}. Of particular interest is \textit{NEUROD1}, a gene that is markedly decreased in HD neural cultures (Appendix 2 Table 3.7) and belongs to a cluster of motifs with reduced presence at H3K27ac peaks (Figure 2.14c). Notably, \textit{NEUROD1} binds to and confers transcriptional competence on epigenetically silenced neuronal genes\textsuperscript{179}. To first determine whether \textit{NEUROD1} repression depends on the presence of HTT in HD neural cultures, we first evaluated whether a \textit{HTT}-directed antisense oligonucleotide (ASO)\textsuperscript{142} could normalize expression in a highly expanded repeat line (109Q) and observed that \textit{HTT} silencing in HD neural cultures increased \textit{NEUROD1} expression (Figure 2.15a). We next asked whether transcriptional alterations in the HD neural cells could be modulated by enhanced expression of \textit{NEUROD1} in the same line and found that lentiviral transduction of \textit{NEUROD1} cDNA into differentiated 109Q iPSCs was sufficient to acutely increase expression of the
majority of these genes (Figure 2.15b, Figure 2.16a). Genes upstream of NEUROD1, such as POU4F2, were not upregulated. In general, increases were not as significant in an unexpanded line for a subset of genes evaluated (Figure 2.15b). The extent to which an increase could be detected appeared to be limited by transduction efficiency, which ranged from 30-40% depending on the line. Therefore, we next evaluated whether pharmacologic modulation by a small molecule could de-repress a set of transcriptionally repressed genes identified by RNA-Seq.

The small molecule isoxazole 9 (Isx-9) up-regulates genes, including NEUROD1, via Ca$^{2+}$ influx, and induces neuronal differentiation of cortical and subventricular zone (SVZ) progenitors$^{57}$. Two sets of differentiated non-disease (21Q, 33Q) and HD (60Q, 109Q) repeats were evaluated to determine if a neurogenic profile was reestablished after culture treatment with 20 µM Isx-9, a dose that induces neurogenesis in a variety of cells, adult mouse whole brain, and SVZ progenitors$^{57}$. Expression of NEUROD1 (Figure 2.15c) and other selected genes within categories, including neurodevelopment and neuronal function (POU4F2), Ca$^{2+}$ signaling (CALB1, CAMK4, ATP2B2), GABA synthesis (GAD1) and potassium channels involved in neuronal excitability (KCNQ3, CACNA1A) were evaluated and qRT-PCR showed that Isx-9 treatment activated transcription of these genes (independent experiments and lines shown, S10b & c). Corroborating qPCR data, assessment of representative proteins showed that Isx-9 treatment of differentiated HD and non-disease cells maintained in BDNF-free media increased protein levels for NEUROD1 (Figure 2.15d), CALB1 and CAMK4 (Figure 2.16d). This was not due simply to differences in cell composition as early differentiation cell markers tested (doublecortin and nestin) did not show differences in treated versus untreated (Figure 2.17).
To establish whether Isx-9 could modulate mHTT-related phenotypes, a series of functional assays were used. BDNF withdrawal causes reduced cell viability of differentiated HD iPSC cultures in a CAG repeat–dependent manner\textsuperscript{[20]}, therefore differentiated iPSCs were transferred to BDNF-free media, with or without 20 µM Isx-9, and compared to cultures supplemented with 20 ng/ml BDNF. BDNF withdrawal produced significant cell death in the HD (109Q) line (Figure 2.18a), detected by a nuclear condensation assay, but not in a non-disease (21Q) line (Figures 2.18a, cell image Figure 2.19a). A nearly complete rescue of cell death was observed when the differentiated HD iPSC cultures were treated with 20 µM Isx-9 during BDNF withdrawal (Figure 2.18a). Importantly, this rescue depended on the presence of NEUROD1, as knock-down with a NEUROD1 shRNA prevented the ability of Isx-9 to rescue this phenotype (Figure 2.18b).

The lines evaluated above all represent juvenile-onset CAG repeat lengths. However, we were interested to know if we could observe phenotypes in HD neural cells with CAG repeats closer to the CAG sizes more commonly found in HD. Using a similar differentiation method that yielded numerous MAP-2 positive cells that contained ~5-15% DARPP-32, and low levels of proliferating cells (Figure 2.20), we examined the survival of control and HD neural cells by robotic microscopy (RM)\textsuperscript{[44,117,180]. RM is a custom-built automated platform to collect epifluorescence or confocal images from individual MAP2+ staining cells in a high-throughput fashion over their lifetime with high sensitivity to detect phenotypic differences in neurons from HD patients or other cell types in the absence of stress\textsuperscript{[28,70,71]. We subjected HD iPSC-derived neural cells with 46-48 CAG repeats (46Qn1 and 46Qn10) and 53-58 CAG repeats (53Qn3 and 53Qn5) to RM. Survival analysis showed a significantly higher cumulative risk of death in HD cells than that of the 18Qn2 and 18Qn6 lines. Due to a low n
(n=2), the 18Qn6 clone was not significantly different to the Q46 clones by itself (Figure 2.19 (b)); however, when combined with its sister clone there was enough statistical power to detect survival differences (Figure 2.18c). Remarkably, addition of 20 µM Isx-9, significantly increased the survival of all HD clonal lines (Figure 2.18B and Figure 2.19). Isx-9 also increased survival of the control line but appeared less effective and robust, as we only detected a significant increase in survival in the 18Qn2 in one set of experiments (Figure 2.19, a versus b, c and d).

We also determined if there were morphological differences in the HD neural cells compared to controls. In murine models and human HD, mHTT elicits a progressive degenerative morphology in dendrites and branches or axons. Therefore, we examined the neurite-like processes in control and HD neural cells. Processes were measured on ~day 39 of differentiation. To control for intra-experiment variability, we normalized within each experiment by the average length of the controls that were differentiated alongside the HD cells. Interestingly, we found that for all HD lines examined, the neurite-like processes of 46Q, 53Q and 109Q were significantly longer than for controls, 18Q and 28Q (Figure 2.18d and Figure 2.21). This result was surprising given previous observations of progressive degeneration of neuronal processes, however, upon closer investigation there is clear evidence for expansive developmental changes as a result of mHTT expression in human tissues. These results suggest that a component of mHTT pathology is an alteration in the developing circuits - possibly due to a loss in axonal guidance cues and signaling events that instruct proper connectivity, such as is observed in the RNA-Seq analysis - which lead to an over proliferative phenotype consistent with that observed in the neural cells. Remarkably, addition of Isx-9 restored the neurite-like processes length in the HD i-neurons closer to that
of controls, but did not affect any of the controls (Figure 2.18d), suggesting that Isx-9 can correct the aberrant signaling events and guidance cues that are specific to HD iPS-derived neural cells.

**Isx-9 improves cognition and synaptic pathology in R6/2 mice**

RNA-Seq analysis and functional annotation suggest impairment to genes involved in synaptic signaling and learning and memory (Appendix 2 Table 3.7 gene list and Fig. 2.10a) and previous work suggests that Isx-9 can improve memory in mice\(^\text{120}\). Thus, we determined whether Isx-9 treatment could provide neuroprotection in R6/2 transgenic mice\(^\text{173}\). We first determined if motor impairment in the mice could be improved with Isx-9 treatment, but we observed no statistically significant rescue of rotarod, pole test or grip strength deficits. However, when we evaluated for cognition (recognition memory), Isx-9 treated R6/2 mice had better cognitive performance (exploratory preference score) than their vehicle treated counterparts (69.3% vs 54.62%) (Figure 2.23a). Non-transgenic Isx-9 treated mice showed no significant improvement in this task, suggesting that the treatment is normalizing the effect of the mutant transgene.

To determine if this cognitive improvement corresponds to a reduction in synaptic pathology, mice were sacrificed 5 weeks after initiating treatment and the tissue was dissected for synaptic staining. Cortico-striatal synapses in the dorsal striatum were identified through colocalization of the presynaptic marker VGLUT1 and postsynaptic density protein HOMER1. As expected\(^\text{186}\), R6/2 mice treated with vehicle alone showed fewer cortico-striatal synapses than nontransgenic littermate controls (Figure 2.23b, c). Remarkably, R6/2 mice treated with Isx-9 had more synapses than those treated with
vehicle alone but numbers of synapses in non-transgenic mice were not affected, consistent
with cognitive outcomes (Figure 2.23b, c). These results demonstrate rescue of synaptic
pathology after treatment with Isx-9 and that could involve neuronal maturation. Further,
the in vivo data are consistent with the altered neurite length in the imaging data presented
above, and with the rescue of other in vitro deficits after treatment with this compound.
These results agree with the altered neurite length in the HD iPSCs in the imaging data
presented above, and are in line with the rescue of the other in vitro deficits after treatment
with this compound.

2.4 DISCUSSION

A concept that is recently emerging in our understanding of HD, particularly juvenile HD, is
that dysregulation of early developmental pathways may affect later pathophysiology,
potentially compounded by a relative lack of productive striatal neurogenesis that might
otherwise compensate. These processes can be difficult to systematically track in mouse
models and human brain. However, they can be effectively studied in iPSCs, which allow for
an assessment of neuronal pathways at early stages and during the differentiation process.

In the current study, we analyzed differentiated iPSCs derived from HD and
unaffected subjects using unbiased multi-“omics” and bioinformatics, and identified
alterations in genes and gene pathways critical to neuronal function and synaptic activity
that are associated with the expression of a pathological CAG repeat length. These
differentiated iPSCs represent relatively early stages of neuronal development (mixed
populations of glia, immature neurons and mature neurons), allowing for the elucidation of
pathogenic mechanisms that may affect later onset or progression of disease. Comparison of
the DEGs and epigenetic motifs in differentiated HD iPSCs with highly expanded, juvenile onset range CAG repeats, suggests that there are alterations in an integrated epigenetic network that affect neuronal development and maturation in early development and could impair adult neurogenesis. Importantly, the application of a small molecule, Isx-9, that can modulate these pathways, provides neuroprotection in both juvenile and adult-onset range repeat lines, restores the structure of neuronal processes in these cells and improves synaptic pathology in R6/2 mice, suggesting that the pathogenic pathways identified here may be targeted therapeutically.

**Altered gene expression of neurodevelopmental pathways and synaptic homeostasis in HD lines**

The changes in gene expression determined by RNA-Seq and the comparison to that of mouse developmental transcription implicate altered neurodevelopment and maturation in HD pathophysiology. Neuronal and neurodevelopmental pathways are altered in the differentiated HD neural cells, including those regulated by WNT and NEUROD1, and affect expression of related genes such as ASCL1 (Mash1), GAD1, and POU4F2. The WNT pathway is important in telencephalon development and in guiding fate decisions. Levels of PSD2 and GAD1, which are among the most significantly down-regulated genes in the differentiated HD lines, are essential for the development of the human striatum. HD mutation-associated changes in expression of genes encoding ion channels, GABA synthesis and transport, Ca\(^{2+}\) influx and bHLH pro-neural proteins are also observed. Over time, expanded polyglutamine toxicity may overwhelm the homeostatic capacity and compensatory mechanisms in the brain, causing neurodegeneration.
Of particular relevance is the prediction that REST is the most activated upstream regulator of the observed differential gene expression in the HD cells compared to controls. REST is implicated in neurotoxicity of mHTT\textsuperscript{157} and in the dysregulation of genes such as BDNF. It is also a master regulator of neurogenesis and neurodevelopment\textsuperscript{188-190}, potentially as a hub for recruitment of epigenetic chromatin modifying enzymes. Recent findings suggest that REST promotes neural stem/progenitor cell self-renewal but restricts generation and maturation of neurons\textsuperscript{191}, consistent with reduced maturation in the HD neural iPSCs. Additional targets of REST include GABA\textsubscript{A} receptors. Given that GABA receptors are among the earliest neurotransmitter systems to emerge during development, this epigenetic regulation by REST may contribute to unbalanced generation of GABAergic and glutamatergic neurons, thus impacting neurodevelopment. REST also regulates the transition from neuronal progenitors to mature neurons, in part through its regulation of miR-124\textsuperscript{192}, which is predicted to be inhibited in the differentiated HD lines.

**Epigenetic signatures may provide insights into differential transcriptional programs that impact neurodevelopment and maturation**

Our data support the concept of epigenetic “signatures” that contribute to the differential regulation of transcription in HD. Most importantly, genes with a particular “shape” or profile of H3K4me3 and H3K27ac peaks in the differentiated non-disease lines were enriched for DEGs in the RNA-Seq analysis of HD lines. This tight association was also reported in an HD mouse model and for selected genes in human autopsy samples\textsuperscript{166,172}. We suggest an emerging theme that groups of genes marked by distinct epigenetic patterns associate with or drive specific properties, such as tissue-specific activities and
developmental processes, including cortical development. Initial analysis of sequences near differentially acetylated regions revealed an enrichment in motifs associated with developmental regulation, specifically of genes implicated in HD such as SP1. Interestingly, dysregulated SP1-mediated transcription has been previously demonstrated in HD model systems. Our data reflects potentially altered binding of SP1 and of other transcription factors such as MEF2, NEUROD1, NKX2, p53 and FOXO, showing selectively enriched motifs at Class I promoters. Similar to our findings here, a genome-wide analysis of H3K4me3 of neuronal nuclei from HD prefrontal versus non-disease human tissue resulted in an enrichment for genes implicated in neuronal development and neurodegeneration, notably HES4, which targets ASCL1 (Mash1). Given the concordance of results from mouse brain tissue and the human cells, epigenetic patterns may represent critical mechanisms underlying pathogenesis, and may provide identification of potential enzymes and pathways for the development of therapeutic approaches.

Neurodevelopment and neurogenesis: A therapeutic target for Huntington's disease?

We observed significantly decreased NEUROD1 expression in all differentiated HD lines, which was alleviated by total HTT knockdown (HTT ASO), as well as deficits in other regulatory pathways (e.g., TGFβ, ASCL1) whose central roles would be expected to impact embryonic and/or adult neurogenesis in HD. Impaired neurogenesis in HD and a role for NEUROD1 is supported by previous work describing aberrant hippocampal neurogenesis in R6/2 mice associated with a reduction of NeuroD1. In the human HD SVZ overlying the caudate nucleus, a variety of proliferating progenitor stem cells display a heterogeneity of GABA(A) receptor subunits, supporting the presence of immature neural cells. A series
of published studies have highlighted an increase in SVZ progenitor cell populations in HD ES cells, mouse models and human tissue, suggesting an upregulation of cues that simulate progenitor cell proliferation and neurogenesis (e.g. 118,197). In the early stages of HD, postmortem brain sections showed evidence for proliferative changes such as increased numbers and sizes of dendritic spines184 and within the SVZ of the HD brain, there are significant increases in both proliferation and the size of the SVZ and number of newly born neurons118,197,198. Further in developing murine ESCs, ESCs with expanded repeats have more elaborate and longer processes than ESCs with normal CAG repeat lengths199. This is consistent with our observation that neurites are longer in adult onset HD neural cells. However, while adult neurogenesis appears to initiate within the striatum, these newborn neurons and interneurons are absent in the striatum of advanced stage HD patients200, suggesting that maturation of neuronal precursors may not proceed appropriately.

Developmental-related abnormalities have been observed in several HD model systems that could be relevant for later disease pathogenesis. In the differentiated juvenile onset HD iPSCs, we previously showed a selective early persistence of nestin-positive immature neural progenitor cells that were particularly vulnerable to BDNF withdrawal-induced toxicity142. Rodent studies, including using HTT constructs that express adult onset range repeats, support the notion of deficits in striatal development in HD124,201. Even for adult onset repeat ranges, autopsied brain tissue display impairments that are likely to have occurred during development and may arise as a consequence of epigenetic factors121,195 eliciting subsequent dysregulation of developmental genes in human HD brain, such as homeobox genes. Recent work in a conditional transgenic HD mouse model suggests that impairments arising from an expanded polyglutamine expressed only during
development\textsuperscript{123} may have consequences later in life, leading to phenotypes comparable to those seen in models with continuous mHTT expression. Finally, in an extensive integrated genomics and proteomics study of tissue from HD knock-in mice, co-expression network analysis (WGCNA) revealed that the module with the strongest association with CAG length and most extensive gene expression dysregulation contained striatal gene identity genes\textsuperscript{122}, consistent with the concept that there could be altered cell fate and maturation during development or impaired striatal neurogenesis.

Clinical signs and symptoms take years to develop in adult onset HD, possibly reflecting the powerful cognitive reserves and synaptic plasticity that exist in the human brain. However, it is possible that early neurodevelopmental effects may disrupt homeostasis of the system, establishing an enhanced vulnerability to later neurodegenerative effects of mutant HTT over time. While effects on development may not show up until adulthood, subclinical transcriptional alterations could create a different “starting” point in HD relative to non-HD brain. These pathways may also contribute to aberrations in structural connectivity that likely influence clinical phenotypes\textsuperscript{202}. Strikingly, a new study\textsuperscript{203} reveals that children carrying the \textit{APOE} e4 risk allele for Alzheimer’s disease display altered brain development that may establish a neuroanatomical vulnerability to AD, suggesting potential commonality across neurodegenerative disease.

To investigate the potential therapeutic implications of the combined “-omics” and functional studies, we evaluated whether a small molecule intervention that mitigates transcriptional dysregulation could improve neuronal function. Isx-9 restored expression of selected dysregulated gene and protein expression patterns, and provided neuroprotection after BDNF withdrawal. This neuroprotection depended on \textit{NEUROD1} gene expression,
suggesting that NEUROD1 is necessary for Isx-9 action, although it remains to be determined whether this is sufficient. Isx-9 promotes Ca\(^{2+}\) influx in neural stem/progenitor cells through NMDA receptor signaling and pathways activated by G-protein-coupled receptors\(^{204}\), systems which are transcriptionally dysregulated in the HD lines. In the developing brain and during adult neurogenesis, electrical activity is essential for the differentiation, maturation and integration of neuronal circuitry\(^{205,206}\). This activity-dependent neurogenesis (termed excitation-neurogenesis coupling) is mediated by GABA-induced depolarization, Ca\(^{2+}\) influx and subsequent induction of neurogenic gene expression\(^{204,207}\). In this study, HD mutation-associated changes in expression of genes encoding ion channels, GABA synthesis and transport, Ca\(^{2+}\) influx and bHLH pro-neural genes were observed. Despite the complexity of the pathways identified using the omics-based methods of the current study, we were able to identify a small molecule which could target the pathways affected. The promising rescue of phenotypic deficits in cells for both juvenile onset and adult onset repeat lengths, the normalization of neurite length in adult CAG repeat neural cells, and improved cognition and rescue of synaptic pathology with Isx-9 in R6/2 mice suggests the potential for therapeutic strategies to overcome the aberrations in developmental networks and thus abrogate increased neuronal vulnerability and later neurodegeneration in HD. It is intriguing to consider that the beneficial effects of Isx-9 in an adult mouse could indicate an ongoing role for developmental pathways in adulthood that may be linked to overall plasticity or response to injury. Future iPSC-based \textit{in vitro} and \textit{in vivo} studies will need to clarify the extent to which the epigenetic alterations are observed in HD and define the mechanisms for rescue.
2.5 Figures

**Figure 2.1. Patient iPSC lines and statistical analysis of RNA-Seq.** (a) Table of iPSC Lines. Clinical information on subjects with HD and non-disease controls for generation of non-integrating iPSC lines. Abbreviations: CS–Cedars-Sinai; n(clones)–non-integrating; UK–unknown; N/A–not applicable.; HD–Huntington's disease. All are of Caucasian ethnicity, with the exception of the 21Q non-disease line derived from individual of African American descent. (b) Principal component analysis (PCA) of log2 normalized global gene expression values (RPKM, reads per kilobase per million mapped reads) from differentiated HD and non-disease iPSCs with distinct grouping of HD (red) and non-disease (blue) lines. Clear separation can be seen between HD and non-disease groups with minimal variability between samples within non-disease samples and 60Q and 109Q HD samples. (c) Heat map depicting Euclidian distance hierarchical clustering of log2 transformed gene expression values (RPKMs) of the significantly differentially expressed genes (1869) between HD and non-disease (colors displayed by row min and max values, red = higher and green = lower expression). Clustering shows level of transcriptional dysregulation between each group, and similar expression patterning between non-disease lines and within expanded CAG repeat lines. In each expanded repeat line, there are downregulated genes within the key pathways.
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Figure 2.2. Staining and quantification of neuronal, and oligodendrocyte, differentiation markers. (a) Immunocytochemistry at day 56 of differentiation demonstrates that both HD and non-disease iPSC lines can generate glial (GFAP) and neuronal (TUJ1, MAP2ab, DARPP32) cells. Scale bar represents 100 mm. (b) Non-biased stereological counts of TUJ1 at day 56 of differentiation indicate that there is no difference in the percent of cells TUJ1-positive between HD and non-disease (CTR). The HD109Q line did have significantly lower TUJ1-positive cells than the CTR21Q and the HD60Q lines (one-way ANOVA, * p<0.05, ** p<0.01); however, this reflects line-to-line variability versus a CAG repeat effect. (c) Non-biased stereological counts of MAP2ab at day 56 of differentiation indicate that there is no difference in the percent of cells MAP2ab-positive between HD and non-disease. (d) Non-biased stereological counts of DARPP32 at day 56 of differentiation indicate that while there is no difference in the percent of DARPP32-positive cells between HD and non-disease. (e) Non-biased stereological counts of GFAP indicate there is no difference in the percent of cells GFAP-positive between HD and non-disease. (f) Glial markers PDGFRα and O4 were found to be absent in the iPSC-neural cultures at day 60 of differentiation, whereas at day 112 of oligodendrocyte differentiation from iPSCs, these glial markers were found. Approximately 1000 cells were counted per slide for three independent differentiations.
Figure 2.3. Staining of endoderm, mesoderm and microglial differentiation markers.  
(a) The endodermal markers SOX17 and FOXA2 were absent in the iPSC-neural cultures at day 60 of differentiation, but they were present in differentiated cultures of iPSC-endoderm.  
(b) The microglial marker Iba1 was absent in day 60 iPSC-neural cultures, but present in wild-type mouse brain sections. Likewise, the mesodermal marker myosin was absent in day 60 iPSC-neural cultures, but present in sections of rat gastrocnemius muscle.
Figure 2.4. IPA gene symbols and relationships. IPA legend for gene networks and relationships/edges. www.qiagen.com/ingenuity
Figure 2.5. RNA-Seq identifies altered neurodevelopmental genes and functions.  
(a) IPA analysis of DEGs showing top five functional categories showing differential expression of genes related to development (based on –log(p-value) calculated by Fisher’s exact test.  
(b) Gene network showing interactions of DEGs, colored in red (up) and green (down), involved in neuronal development and relevant to HD pathogenesis. Several key regulatory pathways have been added to show interactions and possible contribution to novel findings, including REST and miR-124 which are predicted upstream regulators with z-scores of 4.038 and -3.638, respectively.  
HTT is highlighted in orange and connects several critical gene pathways.  
NEUROD1 presents as a major node.  
(c) Upstream analysis of RNA-Seq DEGs. Genes with a |z-score| > or < 2.0 are assigned a predicted activation state, allowing inferred protein activity based on observed differential gene expression. Analysis of HD DEGs predicts activation or inhibition of several genes known to be involved in HD pathogenesis, as well as possible novel regulators.
a

Cellular Development
Nervous System Development and Function
Tissue Development
Behavior
Cellular Assembly and Organization

b

c

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Figure 2.6. Quantitative PCR supports altered gene expression identified by RNA seq. (a-f) New differentiations of representative non-disease (21Q) and HD (109Q) lines were performed and select genes evaluated by RT-qPCR. All exhibited altered expression consistent with that identified by RNA-seq.
Figure 2.7. RNA-Seq reveals altered pathways involved in neuronal function. (a) Top IPA canonical pathways showing differential expression of genes related to axonal guidance, CREB, Ca²⁺ and Wnt signaling, glutamate and GABA receptor signaling. Pathways ranked by –log(p-value) calculated by Fisher’s exact test with threshold set to 0.05 (corresponding to the yellow threshold label and vertical line on the graph). Line graph shows ratio of DEGs in each canonical pathway. (b) Calcium signaling pathway showing genes differentially expressed in HD iPSC-derived neural cells (red = up in HD and green = down in HD). Calcium networks are greatly affected in HD cells compared to non-diseases with a p-value of 2.19x10⁻⁴ calculated by Fisher’s exact test. Genes involved in extracellular and intracellular signaling are altered and may negatively contribute to neuronal survival and maturation.
Figure 2.8. Hierarchical clustering of genes differentially expressed in several top canonical pathways. (a) Heat map showing hierarchical clustering of log2 transformed gene expression values (RPKMs) of the significantly differentially expressed genes (1869) found in several of the top affected canonical pathways (colors displayed by row min and max values, yellow = higher and blue = lower expression). Genes/rows are sorted by involvement in specific pathways that have been marked by color and shows pathway convergence on key regulator genes founds in both axonal guidance and either CREB or WNT signaling. Fold change is shown to the right of the gene symbol and represents the average change of HD/non-disease. A clear pattern of differential gene expression in each pathway provides an indication of activation or inhibition of the pathway. (b) Table showing normalized log2 gene expression values of the top up and down regulated genes in Fig. S5a. Each gene is categorized by pathway involved and HD vs non-disease fold change is displayed.
Figure 2.9. Gene expression changes reflect altered striatal development. (a) Heatmap of genes common to mouse microarray analysis and human RNA-seq data. Values are in SD normalized by gene separately by set (human and mouse) (values: red = +3, green = -3). Hierarchical clustering analyses with average linkage for sample, and genes are displayed with dendrograms, and clusters are obtained automatically Cluster A (red) includes germinal zone (GZ) samples and HD human samples, whereas Cluster B (green) contains human non-disease samples and mantle zone (MZ) mouse samples. (b) Gene Ontology (GO) Biological Process (BP) terms enrichment of all 679 common genes depicted in the heatmap. (c) Summary of the most enriched “analyzed network” result from Metacore® using genes from Cluster I that contains NeuroD1. Metacore’s (r) Direct Interactions network was obtained from the 679 common human-mouse genes. The network depicted is filtered to include only: transcription factors, protein kinases, receptors with kinase action and ligands.
Figure 2.10. RNA-Seq functional subcategories, interaction map of common striatal genes, and table of genes that regulate human striatal maturation and HD differential gene expression. (a) RNA-Seq functional subcategories under the super-category nervous system development and function. Select categories listed are predicted to be decreased by calculation of activation z-score. P-value calculated by Fisher’s exact test of expected/observed genes found within specific subcategories. Predicted state of subcategories shows a decrease in neuronal development and function, including: synaptic transmission, long-term potentiation, guidance of axons, and organismal effects to learning and memory. (b) Interaction map: Largest connected Network by Direct Interaction sets in Metacore® platform, green lines represent activation red lines inhibition. (c) 1869 DEGs from RNAseq analysis between HD and non-diseased differentiated iPSCs were compared to genes involved in human striatal maturation147. Genes relevant to human striatal maturation, identified by changes in expression between 8w human striatal brain samples and 30DIV striatal hPNs, were also genes predicted to be upstream regulators of the DEGs found in the HD versus non-diseased iPSC-derived samples.
Figure 2.11. GO enrichment of common striatal genes. GO enrichment p-value graphs, values are in $-\log_{10}$. 
Figure 2.12. ChIP-Seq for H3K4me3, H3K27ac, and H3K36me3 in HD iPSC-derived neurons. (a-c) Genes were clustered according the shape, or profile, of ChIP-Seq reads near their TSS for H3K4me3 (column 1, a), H3K27ac (column 2, b), and H3K36me3 (column 3, c). Top panel shows the average profile for each cluster. Bottom panels show the number of genes with lowered (middle) or raised (bottom) expression in HD cell lines in each cluster expected at random (lighter bars) and in the data (darker bars). P-values were calculated using the hypergeometric test. (d) Gene Ontology categories assigned to genes with differential H3K27Ac peaks and false discovery rate adjusted p-value. Enriched (increased acetylation/peak height) genes in HD show categories related to muscle development, function, and cytoskeleton; while non-disease-enriched genes show categories related to neuronal development and function.
### Table: HD-enriched and Control-enriched Genes GO Term Analysis

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<th>Control-enriched genes GO term</th>
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Figure 2.13. RNA-Seq and ChIP-Seq correlation plots. (a-c) The number of ChIP-Seq read counts mapped to the area around gene transcription start sites (-2kb to +3 kb) was correlated with the expression level of that gene according to RNA-Seq. Data are for the 21Qn1 cell line, for all genes in HD-associated epigenetic classes. Pearson r and two-tailed p values are shown. Read counts were calculated after normalizing data with FIXSEQ (82). (d-f) The number of ChIP-Seq read counts mapped to the area around gene transcription start sites was correlated with the expression level of that gene, according to RNA-Seq for genes in all epigenetic classes.
Figure 2.14. RNA-Seq and ChIP-Seq differential peak height and motif analysis. (a) The number of H3K27Ac ChIP-Seq reads and RNA reads mapped to the area of the human genome around ELAVL3, a neuron-specific ribosome binding protein that is down regulated in HD. Reads from the 21Qn1 non-disease cell line (top) and 60Qn8 HD line (bottom) are shown. Using k-means clustering of the peak profile of ELAVL3 was assigned to class 1, with its broad peak extending into the gene body from the TSS. Reads were visualized using Integrated Genome Browser. (b) The top 10 motifs found under H3K27ac peaks enriched in HD versus non-disease samples are shown. Motifs were clustered according to similar binding site sequences. The left column shows all members of a cluster, the middle column shows an example binding site for that cluster, and the third column shows the p-value of enrichment of the best member of that motif cluster over the peaks enriched in the opposite treatment group. (c) Gene Ontology categories assigned to enriched transcription factor motifs in HD or non-disease samples and false discovery rate adjusted p-value.
## ELAVL3

### Control Enriched

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Figure 2.15. Isx-9 induces expression of *NEUROD1*. (a) Total *HTT* silencing increases *NEUROD1* gene expression in HD iPSC-derived neural cultures. High CAG repeat (109Q) cultures were treated with HTT ASOs and show enhanced *NEUROD1* transcript levels. (b) *NEUROD1* over-expression enhances neuronal gene expression in high CAG repeat lines. HD iPSC-neural cultures were transduced with either human *NEUROD1* overexpression lentivirus or pFUGW-eGFP. NEUROD1 overexpression lentivirus (ABM) and was used at 1X10^6 IU/ml for transduction. Subsequent qPCR demonstrates increased expression of *NEUROD1*, CALB1 and CAMK4. (c) Isx-9 enhances NEUROD1 expression. qPCR was performed on iPSC-neural cultures after treatment with 20µM Isx-9. Increased *NEUROD1* mRNA was detected in one non-disease (21Q) and both HD (60Q and 109Q) lines. (d) Isx-9 western analysis. NEUROD1 protein levels increase after treatment with 20µM Isx-9 in the absence of BDNF. Conversely, BDNF did not increase NEUROD1 protein expression in the absence of Isx-9. For qPCR analysis, a statistical difference in gene expression between vehicle and Isx-9 treatment was determined using an unpaired two-tailed t-test. WB results quantification (densitometry) were normalized to actin. Statistical significance between Isx-9 and untreated cells (NIM) was determined by one-way ANOVA.
Figure 2.16. NEUROD1 overexpression and Isx-9 increases expression of down-regulated transcripts. (a) NEUROD1 over-expression enhances neuronal gene expression in high CAG repeat lines. Several genes were evaluated in the high CAG repeat HD line 109Q after either human NEUROD1 overexpression lentivirus or pFUGW-eGFP. qPCR demonstrates increased expression of GAD1, ATP2B2 and KCNQ3. (b) Isx-9 enhances expression of NEUROD1 and other neuronal genes POU4F2, CAMK4 and CALB1 in non-disease (21Q, 33Q) and HD cultures (60Q, 109Q). (c) Additional genes were tested in 21Q and 109Q lines with increased expression of GAD1, CALB1, CAMK4, POU4F2, KCNQ3 and CACNA1A in all cultures, as well as increased expression of ATP2B2 in the HD 109Q line. (d) Isx-9 western analysis. 21Q and 109Q cell lines demonstrate increased protein expression of CALB1 and CAMKIV after Isx-9 treatment. For qPCR analysis, a statistical difference in gene expression between vehicle and Isx-9 treatment was determined using an unpaired two-tailed t-test. WB results (densitometry) were normalized to actin. Statistical significance between Isx-9 and untreated cells (NIM) was determined by one-way ANOVA.
Figure 2.17. HD and control neural cells show no difference in cell composition after ISX-9 treatment. Immunocytochemistry at day 56 of differentiation demonstrates that both HD and non-disease iPSC lines can generate neural progenitors (Nestin, Doublecortin). Scale bar represents 100 um.
Figure 2.18. Isx-9 treatment improves CAG repeat-associated phenotypes. (a) **Nuclear condensation assay.** Differentiated neural cultures were treated with Isx-9 or BDNF as described above for the ATP assay. Cell death, by nuclear condensation, is reduced in the HD 109Q line treated with Isx-9. (b) **NEUROD1 Knockdown.** The HD iPSC derived neural cells were transduced with lentiviral particles carrying vectors encoding either Scramble or NEUROD1 shRNA (KD) (shRNA and pFUGW-eGFP lentiviruses at 100ng/ml for transduction) for 24 h, and then transferred to neural induction medium (NIM) without additives or supplied with 20 µM Isx-9 for 48 h. The nuclear condensation assay performed as described earlier (HD iPSC Consortium, Cell Stem Cell, 2012). NT–Non-transduced control. **: p<0.005 vs Scramble control shRNA. (c) Isx-9 increases survival of HD i-neurons. HD and control i-neurons were differentiated for ~28 days and transfected with mApple driven off of the MAP-2 promoter (Bhat et al., 2014) and plated into 96 well plates. 20 µM Isx-9 was added to the medium on differentiation day 32 and subjected to RM imaging for 9 days as described117. Images were used to follow individual cells over time and cell death was recorded to assess the effect of Isx-9 on HD and control cells. Left: Using Cox proportional hazards analysis reveals that the cumulative risk of death of the 46Qn1/n10 lines is greater than the controls 18Qn2/n6 (Hazard Ratio (HR) = 1.3, p= 0.0281). Addition of 20 µM Isx-9 decreases the cumulative risk of death of all 46Q n1/n10 (HR=0.74, p=7.92e-07) but also the controls (HR=0.75, p=0.08). Control 18Qn2/n6 +DMSO, n=124 cells, Control 18Qn2/n6 +ISX-9, n=143 cells, (4 experiments); 46Qn1/n10 + DMSO, n= 702 cells, 46Qn1/n10+ISX-9, n= 783 cells, (6 experiments). Right: The cumulative risk of death of 53Qn3/n5 is significantly greater than that of the control neural lines 18Qn2/6 (HR= 1.3, p= 0.00209) Addition of 20 µM Isx-9 rescues the survival deficit of 53Qn3 (HR= 0.78, p=0.0078) but also the controls (HR 0.75, p=0.08). Control 18Qn2/n6 +DMSO, n= 452 cells, Control 18Qn2/6 + ISX-9, n =452 cells, (7 experiments); 53Qn3/5+DMSO, 1047 cells, 53Qn3/5+ISX-9, n= 1107 cells, (7 experiments). Data shown are all experiments combined in to one curve. The individual survival curves are shown in Fig. S11. (d) HD cells have longer neurite-like process length than controls and are restored by ISX-9. HD and control iPSCs were differentiated as above. 20 µM ISX-9 was added to the medium on differentiation day 32 and subjected to robotic microscopy (RM) for 7 days. On day 39, processes from neurons were measured in micron length using Neuron J208. To control for intra-experiment variability, each individual process length was normalized by dividing the average length of the corresponding control within each experiment. In the cases where two controls were used within an experiment, the average of the two was used to normalize. Actual process lengths average between ~100- 400 µm per cell and averaged 1-3 processes per cell. The HD lines, Q46n1 (p < 0.0001, *), Q46n10 (p< 0.0001,**), Q53n3 (p= 0.0001,**), Q53n5 (p< 0.0001,**), Q109n4 (p< 0.0001,**) and Q109n5 (p< 0.0001, 0.0010, *) have significantly longer process length compared to control cell lines, Q18n2, Q18n6 and Q28n6 (asterisks denote p values respectively). The addition of ISX-9 rescues the abnormal increased process length in HD lines, Q46n1 (p < 0.0001), Q46n10 (p=0.0390), Q53n3 (p< 0.0001), Q53n5 (p= 0.0024), Q109n4 (p= 0.0038) and Q109n5 (p < 0.0001) but does not alter process length in control cell lines, Q18n2 (p= 0.9997), Q18n6 (p= 0.9347) and Q28n6 (p > 0.9999). One-way
Anova was performed and p values reported by a Šidák multiple comparisons. Q18n2 (254 cells, 7 experiments), Q18n2 +ISX-9 (187 cells, 6 experiments), Q18n6 (208 cells, 4 experiments), Q18n6 + ISX-9 (290 cells, 4 experiments) Q28n6 (152 cells, 4 experiments), Q28n6 + ISX-9 (149 cells, 4 experiments), Q46n1 (540 cells, 7 experiments), Q46n1 +ISX-9 (708 cells, 7 experiments), Q46n10 80 cells, 1 experiment), Q46n10 + ISX-9 (168 cells, 1 experiment), Q53n3 (574 cells, 7 experiments), Q53n3 +ISX-9 (640 cells, 7 experiments), Q53n5 (285 cells, 5 experiments), Q53n5 +ISX-9 (387 cells, 5 experiments), Q109n4 (125 cells, 2 experiments), Q109n4 +ISX-9 (119 cells, 2 experiments) and Q109n5 (244 cells, 8 experiments), Q109n5-9 (201 cells, 7 experiments).
Figure 2.19. Representative pictures used for nuclear condensation assay and Cumulative risk of death for adult onset range differentiated iPSCs. (a) Differentiated iPSC cultures were treated with Isx-9 or BDNF for 48 h. Nuclei were stained with Hoechst 3343. The images were obtained on an Axiovert 200 inverted microscope and quantified using Volocity. Representative images are show for each condition. Inserts illustrate healthy nuclei (left panel) and condensed nuclei (right panel). (b) The cumulative risk of death of both the 46Q n1 (HR= 2.1, p= 4.16e-06) and 46Qn10 (HR= 2.9, p= 0.000243) is greater than the control 18Qn2 line. Addition of 20 µM ISX-9 decreases the cumulative risk of death of 46Qn1 (HR= 0.79, p= 0.004961) and in the 46Qn10 (HR=0.65, p= 5.42e-06). (c) Although we saw a trend in the survival curve of the 46Qn10, we did not see significant differences in the CRD between the 18Q n6 risk of death to the 46Q n1 (HR= 0.87, p= 0.4) and the 46Qn10 (HR= 1.2106, p= 0.367148) likely due to a low n as when we combine clones the difference becomes significant. Control 18Qn2 +DMSO, n=69 cells, Control 18Qn +ISX-9, n= 78 cells, Control 18Qn6+DMSO, n=55 cells, Control 18Qn6 +ISX-9, n= 66 cells, (n=2 experiments). 46Qn1 + DMSO, n= 414 cells, 46Qn1+ISX-9, n= 474 cells, (n=5 experiments); 46Qn10+DMSO, n= 289 cells, 46Qn10+ISX-9 n= 310cells, (n=5 experiments). (d, e) We evaluated the cumulative risk of death of the 53Qn3 lines compared to the controls. We found evidence of non-proportionality for a subset of the lines so we used log rank tests to assess the differences of survival between the HD and controls lines and the effects of ISX-9 on the HD and control lines. All p values are reported from the logrank test209, however we report the hazard ratios as an estimate of the hazard from the Cox proportional hazards model. (d, e) The cumulative risk of death of the 18Qn2 is lower risk of death than the 53Qn3 (HR= 1.4, p= 0.06 approaching significance) and 53Qn5 (HR=1.3 p= 0.00572). Addition of 20 µM ISX-9 increases survival of 53Qn3 (HR= 0.74, p= 2.4e-06) and 53Qn5 (HR=0.8, p= 0.0198) i-neurons. ISX-9 does not significantly change cumulative risk of death for the control Q18n2 (p= 0.931). The cumulative risk of death of 18Qn6 is lower than the 53Qn3 (HR= 1.2, p= 0.0535 approaching significance) and 53Qn5 (HR=1.3, p= 0.00622). ISX-9 does not significantly change cumulative risk of death for the control Q18n6 (p= 0.197). Control 18Qn2 +DMSO, n=345 cells, 18Qn +ISX-9, n= 324 cells, (n=4 experiments) Control 18Qn6+DMSO, n=145cells, 18Qn6 + DMSO, n= 128 cells, (n=3 experiments); 53Qn3+DMSO, 695 cells, 53Qn3+ISX-9, n= 726 cells, (n=6 experiments); 53Qn5+DMSO, 352 cells, 53Qn5+ISX-9, 381cells (n=3 experiments).
Figure 2.20. Representative images of immunohistochemistry staining of differentiated cells that were used in robotic microscopy for survival and neurite-like process length analysis. Cells stain for ~5-15% DARPP-32 positive cells and ~1% Ki67 cells. To determine percent of cells staining for DARPP-32 or Ki67, we subjected the DAPI nuclear stained images our custom plugin in ImageJ to create an ROI for each cell. The images were processed, thresholded, and masked. These masks subjected to particle analysis that constraints size and shape to reduce the measuring of artifacts. The masked ROIs were overlayed on to the green channel images and pixels were measured for fluorescent intensity and size. The average intensity values were normalized to the size of the nuclei, and only the nuclei with a value or 0.2 or greater were counted as significant. The number of positive staining nuclei was divided by total number of nuclei to determine the percentage of Ki-67 and DARPP-32 positive cells. MAP-2 (red) and DARPP-32 (green) staining (a-d) and staining for MAP-2 (red) and Ki67 (green) (e-h), of the (a,e) control 28Q, (b,f) 46Q (c,g) 53Q and (d,h) 109Q. Scale bar is 100 µm.
Figure 2.21. Representative images of neurons that were subjected to neurite-like length analysis. To be completed. Example images of cells analyzed for process length, (a) 18Qn2, (b) 28Qn6 (c) 46Qn1 (d) 46Qn10 (e) 53Qn3 (f) 53Qn5 (g) 109n4 (h) 109Qn5. Scale bar is 100 um.
Figure 2.22. **Motor behaviors are not rescued by Isx-9 treatment in R6/2 mice.** Mice were initially tested for specific HD related behavior deficits using tasks that examine motor impairment. Genotype effects were observed by 8 weeks; however, Isx9 did not provide statistically significant differences in treated versus control mice in rotarod (a) or pole test (b) assays. (a) Rotarod indicates no motor improvements in Isx-9 treated mice. Non-transgenic (NT) and R6/2 mice treated with vehicle (veh) or Isx-9 were subjected to the rotarod task to evaluate motor ability. Impairment was observed in R6/2 mice. Bars represent mean ± SEM (n = 10/group at 8 weeks age), one-way ANOVA with Student’s t-test post hoc *p=0.000000002. (b) Pole test indicates no motor improvements in Isx-9 treated R6/2 mice, impairment in NT mice. Non-transgenic (NT) and R6/2 mice treated with vehicle (veh) or Isx-9 were subjected to the pole test task to evaluate motor ability. Impairment was observed in R6/2 mice and NT mice treated with Isx-9. Bars represent mean ± SEM (n = 10/group at 9 weeks age), one-way ANOVA with Student’s t-test post hoc *p=0.005 **p=0.0007. (c) Grip strength test indicates no improvements in Isx-9 treated mice. Non-transgenic (NT) and R6/2 mice treated with vehicle (veh) or Isx-9 were subjected to the grip strength task to evaluate forelimb grip. Impairment was observed in R6/2 mice. Bars represent mean ± SEM (n = 10/group at 9 weeks age), one-way ANOVA with Student’s t-test post hoc *p=0.0001.
Figure 2.23. Treatment with Isx-9 improves cognition and rescues loss of cortico-striatal synapses in R6/2 mice. (a) Cognition is improved in NOR treated mice. Non-transgenic (NT) and R6/2 mice treated with vehicle (veh) or Isx-9 were subjected to the novel object recognition (NOR) task to evaluate long-term recognition memory. Bars represent mean + SEM (n = 6-10/group at 10 weeks age), one-way ANOVA with Student’s t-test post hoc. (b) Bar-chart shows quantification of cortico-striatal synapses in these mice. R6/2 mice treated with Veh show a significantly reduced number of synapses relative to that seen in the Ntg Veh control (n=3 p<0.01). Treatment with Isx-9 had no effect on synapse numbers in Ntg mice but significantly increased numbers in R6/2 mice relative to those seen in mice treated with Veh alone (n=3 p<0.05). (c) Fluorescence micrographs of sections of the dorsal striatum from Ntg and R6/2 mice treated with Veh or Isx-9. Sections were stained with post-synaptic marker Homer and pre-synaptic marker VGLUT1, cortico-striatal synapses are denoted by overlap between the two markers (yellow). Note the reduced number of synapses in the R6/2 Veh treated mice relative to those seen in the Ntg which is rescued by treatment with Isx-9.
Table 2.1. GO term enrichment of Class 1 genes, H3K36me3 enriched genes, and H3K4me3 enriched genes. (a) & (b) GO terms assigned to genes falling under the Class 1 epigenetic profile for H3K27Ac and H3K4me3, respectively. (c) GO terms assigned to genes falling under the Class 5 epigenetic profile for H3K36me3. (d) GO terms assigned to genes with higher H3K4me3 peaks in HD or non-disease cells, respectively. GO terms and false discovery rate adjusted p values were found using DAVID Functional Annotation Clustering tool. The top GO term from each annotation cluster is reported.

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Table 2.2. **Primer Information.** Accession numbers and oligo sequences used for qRT-PCR.

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| CAMK4       | NM_001744        | Forward: TATTCTTCTCGCTTCATCC  
Reverse: CTGTGACGAGTTCTAGGACCAG |
| POU4F2      | NM_004575        | Forward: TATGCGGAGAGCCTGTCTCCA  
Reverse: TCTTGCCTGGAGACGATGTC |
| ATP2B2      | NM_001683        | Forward: CATCCTCAACGAACCTCACCCTG  
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| CACNA1A     | NM_001127222     | Forward: CTGTGACGCCCTTCCACCTG  
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2.6 References


153 Qiu, F., Jiang, H. & Xiang, M. A comprehensive negative regulatory program controlled by Brn3b to ensure ganglion cell specification from multipotential retinal


182 Laforet, G. A. *et al.* Changes in cortical and striatal neurons predict behavioral and electrophysiological abnormalities in a transgenic murine model of Huntington’s


### 2.7 Materials and Methods

**Generation and characterization of human non-integrating iPSCs using episomal plasmids**

HD and non-disease repeat iPSCs were generated and characterized as described

Unaffected and apparently healthy non-disease (GM05400, 03814 and 02183) and HD (GM09197) human fibroblast cell lines were obtained from the Coriell Institute for Medical Research, under their consent and privacy guidelines as described. The parental fibroblast for the 109CAG (Coriell, ND39258) repeat HD line was obtained from John’s Hopkins
University under Dr. Russell Margolis's IRB protocol #NA00018358. All procedures were performed in accordance with the institutional review board’s guidelines at the Cedars-Sinai Medical Center under the auspices of IRB-SCRO Protocols Pro00028429 (Transplantation of iPSC-derived human neural progenitors), Pro00021505, and Pro00032834. Upon iPSC generation at Cedars Sinai, they were renamed CS00iCTR-21nXX, CS14iCTR-nXX, CS25iCTR-18nXX, CS83iCTR-33nXX, CS13iHD-43nXX, CS03iHD53nXX, and CS109iHD-109nXX to reflect, 1) last two digits of parental lines identifier, 2) non-disease or HD line, 3) CAG repeat number, and 4) XX is the clone number\textsuperscript{143,210}. Fibroblasts were reprogrammed into non-integrating and virus-free iPSC lines using the Amaxa Human Dermal Fibroblast Nucleofector Kit to express episomal plasmids with six factors: OCT4, SOX2, KLF4, L-MYC, LIN28, and p53 shRNA (Addgene)\textsuperscript{211}. This method has a significant advantage over viral transduction, because exogenously introduced genes do not integrate and are instead expressed episomally in a transient fashion. Specifically, fibroblasts (0.8 x 10\textsuperscript{6} cells per nucleofection) were harvested, centrifuged at 200g for 5 min, re-suspended carefully in Nucleofector® Solution (VPD-1001, Lonza), and the U-023 program was applied. All cultures were maintained under norm-oxygen conditions (5%O\textsubscript{2}) during reprogramming, which further enhance the efficiency of iPSC generation. The medium was kept on for 48 h and gradually changed to chemically defined mTeSR®1 medium containing small molecules to enhance reprogramming efficiency. The small molecules used were 1) sodium butyrate (0.5 mM), 2) glycogen synthase kinase 3β inhibitor of the Wnt/β-catenin signaling pathway (CHIR99021, 3 μM), 3) MEK pathway inhibitor (PD 0325901, 0.5 μM), and 4) selective inhibitor of TGF-β type I receptor ALK5 kinase, type I activin/nodal receptor ALK4 and type I nodal receptor ALK7 (A 83-01, 0.5 μM). Individual iPSC colonies with ES/iPSC-like
morphology appeared at days 25-32 and those with best morphology were mechanically isolated, transferred onto 12-well plates with fresh Matrigel™ Matrix, and maintained in mTeSR1® medium. The iPSC clones were further expanded and scaled up for further analysis, expanded and cryopreserved.

**Human iPSC characterization**

Human iPSCs were rigorously characterized at the Cedars-Sinai iPSC core using several assays. G-Band karyotyping ensured a normal karyotype, and genomic DNA PCR confirmed the absence of episomal plasmid genes, as described\textsuperscript{210,212}. Pluripotency was assessed by immunostaining with surface and nuclear pluripotency markers for subsequent flow cytometry quantification (> 80% SSEA4 and Oct3/4 double positivity), by quantitative RT-PCR of endogenous pluripotency genes, and by gene-chip and bioinformatics-based PluriTest assays. Spontaneous embryoid body differentiation confirmed the capacity to form all germ layers.

*Karyotype.* Spheres were incubated in Colcemid (100 ng/mL; Life Technologies) for 30 min at 37°C and then dissociated using TrypLE for 10 min. They were then washed in phosphate buffered saline (PBS) and incubated at 37°C in 5mL of hypotonic solution (1g KCl, 1g Na citrate in 400mL of water) for 30 min. The cells were centrifuged for 2.5 min at 1500 RPM and resuspended in fixative (methanol: acetic acid, 3:1) at room temperature for 5 min. This was repeated twice, and finally cells were resuspended in 500 µl of fixative solution and submitted to the Cedars-Sinai Clinical Cytogenetics Core for G-band karyotyping.
**iPSC Neural Differentiation**

iPSC colonies grown on Matrigel in TeSR media (feeder-free) were scraped into EGF/FGF2 (100 ng/ml each) containing medium (70:30 DMEM:F12 plus 2%B27) and grown as floating neural progenitor spheres for at least nine passages\(^2\). Cells for immunocytochemistry or BDNF withdrawal were then be plated on PLO/laminin coated coverslips and cells for “omics” studies and western blotting were plated on Matrigel-coated six-well plates. The cells were then differentiated in DMEM:F12 with 1% N2 for 7 days. For the next 21 days, cells were differentiated in 20 ng/ml BDNF (20 ng/ml; Peprotech 450-02), rhShh (200 ng/ml; R&D 1845-SH), and Dkk1 (100 ng/ml; R&D 1096-DK-010) to promote a rostral forebrain fate. Cells were then matured in 20 ng/ml BDNF, dibutyryl cyclic AMP (dbcAMP, 0.5 mM; Sigma D0260) and valproic acid (VPA, 0.5 mM; Sigma P4546) for the rest of the differentiation. Medium was half-changed three times per week or as needed.

**Immunocytochemistry.** Cells were fixed in 4% paraformaldehyde (PFA) at RT, rinsed with PBS, and permeabilized with 5% normal goat and/or donkey serum containing 0.2% Triton X-100 for 30 min at room temperature. Cells were then labeled with primary antibodies Tuj 1:1000 (Sigma T8660), DARPP32 1:400 (Cell Signaling 19A3), GFAP 1:1,000 (AB1572), Map2ab (Sigma, 1:50), Myosin (Developmental Studies Hybridoma Bank MF 20-C, 1:20), Iba1 (Wako 019-19741, 1:500), Sox17 (R&D AF1924, 1:500), FoxA2 (Abnova H00003170-M01, 1:500), O4 (StemCell 01416, 1:50), PDGFR (Santa Cruz SC-338, 1:500), Ki-67 (EMD MAB4190MI, 1:400) for 60 min at room temperature or overnight at 4°C, and then the appropriate fluorescently tagged secondary antibodies for 60 min at room temperature. Hoechst nuclear dye was used to label nuclei. Cells were counted using stereological software (stereoinvestigator). Counting criteria included estimating the population of all
cells on the coverslip by co-localization of a given mark with the nuclear marker DAPI.
Sampling was performed using a 20X magnification. To estimate the total number of cells on
each coverslip of a given population, the fractionator was used to project a given number of
cells for the entire population. To ensure that the sampling size was correct it was ensured
that each count had a 2nd estimated CE (Schmitz-Hof) of less than 0.1.

**iPSC Neural Differentiation for Robotic Microscopy**

HD and control i-neurons were differentiated using a similar protocol as described above.
iPSCs were made into EZ spheres\textsuperscript{213} and switched in to DMEM+ ½ X N2 and ½ X B-27 for 5
days. On day 5, the medium was changed to DMEM+ ½ X N2 and ½ X B-27 plus 25 ng/mL
BDNF. On day 7, medium was changed to DMEM+ ½ X N2 and ½ X B-27 plus 25 ng/mL
BDNF, 10 nM Pumorphamine and 100 ng/ml Dickkopf 1 for 3 weeks. On day ~28, cells were
transfected with mApple driven off of the MAP-2 promoter(Bhat et al., 2014) using Amaxa
Nucleofection and placed in to DMEM+ ½ X N2 and ½ X B-27 supplemented with 25 ng/mL
BDNF, 0.5mM dbcAMP and 0.5mM valproic acid on growth factor reduced matrigel. On day
~32 cells were subjected to robotic microscopy and imaged daily for 9 days. Medium was
changed every 2-3 days as needed. Neuronal cells were staining using MAP-2 (Chicken Map-
2, Abcam, against all three isoforms).

**Western Blot Analysis**

For western blots, cells were differentiated for 42 days as above, washed in PBS,
resuspended in JLB buffer (50 mM Tris-HCl pH 9, 150 mM NaCl, 10% glycerol, 0.1% Roche
PIC, 20 mM NaH2(PO)4, 25 mM NaF, 2 mM EDTA, 1% Triton X-100) and sonicated. Protein
concentrations were determined using Bradford assay (Promega), according to manufacturer’s directions. Approximately 50 µg of protein was loaded into Mini-PROTEAN® TGX Precast gels (Bio-Rad Laboratories, Hercules, CA), separated with 90 V for approximately 1.5 h, electro-transferred onto PVDF membrane (BioRad Turbo transfer) in a semi-dry transfer system for 7 min at 1.3 A. The membrane was blocked in 6% dry non-fat milk in Tris-buffered saline plus 0.1% Tween 20 (Sigma-Aldrich) for 1h at RT and then exposed to primary antibody against Map2 (1:1000, mouse, Sigma-Aldrich) and β-actin (1:500, rabbit, Sigma-Aldrich) to ensure equal protein loading in block for 1.5 h at RT. Anti-mouse and anti-rabbit secondary antibodies conjugated to peroxidase (1:10,000, Jackson Labs) was applied in block for 1 h at RT, followed by exposure to chemiluminescence kit (Super Signal West Femto Maximum Sensitivity Substrate, Thermo Scientific).

**RNA-Seq**

RNA was isolated from cell pellets with a Qiagen RNeasy Kit with QIAshredder homogenization. RNA-Seq libraries were made with 1µg of RNA using the Illumina Tru-Seq v2 protocol. Final PCR products were run on 2% agarose E-Gels (Invitrogen) and libraries were size selected at 300 bases. Libraries were sequenced on one lane of the Hi-Seq 2000 at 50 bases. Reads were trimmed to 40 bases and mapped to the hg18 genome with bowtie (0.12.7) with setting --best --m 1 --v 2. Counts per gene were calculated by counting reads mapping to constitutive exons; counts for each gene were then analyzed with the R package DESeq (1.0.6) to identify differentially expressed genes with a single comparison of HD versus non-disease. A 10% false discovery rate cutoff and log2 difference of 0.5 between wild-type and HD conditions was used for significance. Outliers were further excluded by
restricting the residual variance quotients to less than 10. Counts were also used to calculate ‘reads per kilobase of exon per million mapped reads’ (RPKM) values for each gene. Data are shown in RPKMs. Data were analyzed through the use of QIAGEN’s Ingenuity® Pathway Analysis (IPA®, QIAGEN Redwood City, www.qiagen.com/ingenuity).

Openarray

RNA isolation and retrotranscription: Total RNA was isolated using TRI Reagent (Sigma-Aldrich T9424) following the manufacturers’ protocol. Ten µl of total RNA at a concentration of 200 ng/µL (2 µg in total) for each sample was reverse-transcribed with random primers using the High-Capacity RNA-to-cDNA Kit (Life Technologies 4387406). Ten µl of retrotranscription cocktail (2 µL of 10x RT buffer, 2 µL of random primers, 1 µL of dNTP mix; 1 µL of MultiScribe reverse transcriptase) were added to each sample (20 µL total volume). After gentle mixing, the samples were incubated for 10 min at room temperature followed by 2 h at 37º, 10 min on ice and 10 min at 75º. Openarray: Customized Openarrays (Life Technologies) containing 112 TaqMan probes, that specifically detect all isoforms of each of the 106 genes, selected from the literature, and six housekeeping genes (18S, B2M, HPRT1, HSP90AB1, RPL13A, UBC) as reference genes, were produced and validated. cDNAs were loaded onto the custom OpenArrays and run as recommended by the manufacturer on the QuantStudio 12K Flex Real-Time PCR system by Servei Veterinari de Genètica Molecular at Faculty of Veterinary in Universitat Autònoma de Barcelona (Spain). Data analysis: Relative gene expression values were calculated with -2ΔCt (Livak and Schmittgen, 2001) using Expression Suite Software 1.0.3 (Life Technologies). RQ minimum and maximum values (error bars) were calculated with a confidence level of 95%, using Benjamini-Hochberg false
discovery rate to adjust p-values. Maximum allowed Ct included in calculations is 34 and Cq confidence > 0.8. Multivariate Student’s t-test was applied and values of p < 0.05 were considered statistically significant. Error bars are presented in all graphs as standard deviation (SD). Gene expression profile data are represented in graphics as relative quantity of \(2^{\Delta\Delta Ct}\) of 21Q normalized to others.

**Quantitative PCR**

Total RNA was passed through RNeasy spin columns (Qiagen) for further clean up. Oligo(dT)-primed cDNA synthesis was performed on 200-300 ng of total RNA using the Superscript III RT Kit (Life Technologies). Primers for qPCR were designed by Origene and ordered through Eurofins MWG Operon. qPCR was performed using SYBR Green (Bio Rad) in a 384-well format on a ViiA 7 real-time PCR system (Applied Biosystems 4309155). Gene expression for each sample was normalized to RPLPO, and expression under treatment conditions further normalized to untreated samples. Statistical analysis of differences in gene expression between vehicle and Isx-9 treatment was performed using an unpaired two-tailed t-test.

**Microarray Analysis of Mouse Striatal Development**

Mouse development samples spanning from embryonic day 12.5 to 18.5 and covering the lateral ganglionic eminence (LGE), germinal zone (GZ) and mantle zone (MZ) were obtained by laser microdissection and hybridized to Affymetrix chip Mouse_ST1 with ~27,800 geneprobe sets. Using R software with Bioconductor, affy, and limma packages, microarray data were subjected to quality metrics assessment (arrayQualitymetrics) and robust multi-
array normalization. A linear fit algorithm with Bayesian correction was applied grouping biological replicates of samples and designing a contrast matrix that compared zones and regions giving as a result 3,633 differentially expressed genes (DEG’s) which complied with criteria fold change>2, adjusted p<0.01 (Benjamini-Hochberg procedure).

**Human-Mouse Gene Expression Comparison**

A list of 1869 human genes was compared with our microarray data once the Gene symbol and Uniprot identifiers for mouse genes were added via the XSpecies identifier obtained from original human Refseq on BRM software from Pacific Northwest National Laboratory\textsuperscript{214}, yielding 1674 matching human-mouse IDs. Matches were further cross-checked with our list of 3633 DEG’s that resulted in a list consisting of 679 genes. We separately normalized the values given for human samples, and the log2 of intensity of probe for mice data using the Genesis Software\textsuperscript{215}. Further heatmap representation ranging for -3 to 3 SD was thus possible and hierarchical clustering with average linkage for samples and genes was performed using Euclidian distance.

**Gene Ontology (GO) Enrichment and External Database Networks**

GeneCodis web-based software was used to obtain GO enrichment of gene lists by modules, the Thomson Reuters platform Metacore® was used to obtain curated literature-described relationships between gene products and perform external network analysis with is direct relationship algorithm to build networks in our dataset.

**ChIP-Seq Preparation and Analysis**
ChIP libraries were prepared from the cell lines and the resulting sequences were analyzed as described. Antibodies that specifically recognize H3K4me3 (Millipore, Billerica, MA), H3K27ac (Abcam, Cambridge, UK), and H3K36me3 (Abcam) were used. Sequences were aligned to the hg19 genome from UCSC using Bowtie with an m parameter of 1. To call peaks, MACS was run on each cell line sample individually, with an mfold parameter of 10, 30, and p value threshold of 1e-5. As MACS results for individual lines were very similar, sequences for all HD cell lines were combined as were all non-disease cell line for each histone mark. MACS was run on these samples against a uniform background, with the same parameters. Differential peaks between the non-disease sample and the high-repeat sample were called using these MACS peaks as the input to MAnorm with the –overlap-independent parameter, m value of 1, and p value threshold of 0.01. Peaks were mapped to all gene TSS’s within 10 kb, according to the RefSeq database, and then lists of those nearby genes were run through DAVID Functional Annotation Clustering tool. Identifying profiles: Transcription start sites were taken from the RefSeq database, and filtered so that only those sites with no other sites within 7 kb were considered. If more than one TSS was reported for one gene, the TSS that had the most H3K4me3 reads in its immediate vicinity in our cell lines was chosen as the “primary” TSS. Raw data from each non-disease cell line was first normalized using Fixseq, and then reads in the region around each TSS were counted and stored as a vector. These vectors were binned, normalized, and then clustered by the k-means algorithm using Euclidean distance and complete linkage. Genes were assigned to the cluster to which the vector of reads around its TSS was assigned. Genes in each cluster were analyzed with DAVID Functional Annotation Clustering tool. The average vector of those assigned to each cluster was calculated and shown in Fig. 3A. The lists of genes in each cluster...
was compared to list of genes which change expression in HD cell lines, and the
hypergeometric test was used to assess the significance of the overlap. Motif Analysis: Reads
from H3K27ac ChIP-Seq in the non-disease lines and the four HD lines were combined and
MACS and MAnorm were run using the same parameters as above. Resulting differential
regions were split into CpG-high and CpG-poor regions, and THEME\textsuperscript{176} was used to find
enriched motifs in the CpG-poor regions of HD-biased peaks and non-disease-biased peaks.
The set of motif hypotheses is derived from all vertebrate-specific scoring matrices (PSSMs)
from TRANSFAC\textsuperscript{219}, filtered for sufficient information content (>9 total bits). P-values were
calculated using THEME by using the other set of peaks as background sequences, (i.e. HD-
enriched peaks as foreground and non-disease-enriched peaks as background, and vice
versa). THEME calculated the overrepresentation of the motif in the foreground compared
to the background sequences. Motif hypotheses were then clustered according to similar
binding site motifs, and the top p-value for all motifs in a cluster is reported.

**HTT Knockdown**

Neural cultures were generated from iPSC monolayer grown on Matrigel-coated 6-well
plates, using a 37-day protocol\textsuperscript{220}. HTT knockdown was achieved by supplementation of the
culture medium with HTT-specific (TCTCTATTGCACATTCCA) or control
(CCTTCCCTGAAGTTCCTCC) ASO\textsuperscript{142} such that neurons received 4 doses of 1µM ASO over 7
days immediately before harvest at day 37. Total RNA was isolated from untreated, control-
and HTT-ASO treated neural differentiations with TRIzol and 400 ng of RNA used for RT-
PCR. For qPCR analysis, a statistical difference in gene expression between control- and HTT-
ASO treatment was determined using an unpaired two-tailed t-test.
**NEUROD1 Overexpression**

Differentiated cultures were transduced at day 39 of culture with $1 \times 10^6$ IU human NEUROD1 overexpression virus (pLenti-GIII-EF1α vector) (Applied Biological Materials) or 100 ng GFP control (pFUGW-eGFP) (Addgene; Cambridge, MA). All cultures received a complete medium change daily and were harvested at day 53. Gene expression was determined by RT-qPCR as described, beginning with 500 ng total RNA.

**Isx-9 Treatment - iPSCs**

*Quantitative RT-PCR.* Cell cultures received daily media changes containing 20 µM Isx-9 (Tocris, Minneapolis, MN), beginning at day 37, until harvested at 56 days in vitro (DIV). DMSO was used as the vehicle control. Total RNA was isolated from untreated, vehicle- and Isx-9-treated neural differentiations with TRIzol (Life Technologies). 300ng of RNA were used for RT-PCR. For qPCR analysis, a statistical difference in gene expression between vehicle and Isx-9 treatment was determined using an unpaired two-tailed t-test. *Western blot analysis.* Cells were lysed with RIPA buffer supplied with 1% Triton X-100 (both from Sigma) and 0.5% Protease Inhibitor Cocktail (Set III, Calbiochem). Antibodies for detection of NEUROD1, CALB1, and CAMKIV were purchased from Cell Signaling. Equal loading was verified by western blotting of actin (mouse primary antibodies from Sigma). Densitometry was done using ImageJ software and statistical analysis was performed using one-way ANOVA for four independent experiments. *

*Nuclear condensation assay.* Nuclear condensation assay of iPSC-neurons was performed as described\textsuperscript{117}. Cultures were supplemented with 20 µM Isx-9 or 20 ng/ml BDNF. Briefly, cells were automatically analyzed
under an inverted fluorescence microscope (Axiovert 200, Zeiss) and images were digitized from 49 independent fields per well. Quantification of cell survival was done using the Volocity software (Perkin Elmer) by automated measurement of the average intensity of Hoechst 33342 stained nuclei of transfected cells visualized by eGFP expression. Cells were considered as viable when their intensity was lower than 200% of the control intensity. Statistical analysis was performed using One-way ANOVA for at least three independent experiments.

**NEUROD1 Knockdown.** The HD iPSC derived EZ-spheres were differentiated in 24-well plates coated with Matrigel (BD), transduced with pGFP-sh lentiviral particles carrying vectors encoding either Scramble control or NEUROD1 shRNA (KD) (Origene) for 24 h and, then transferred to Neural Induction Medium (NIM) without additives or supplied with 20 µM Isx-9 for 48 h. Lentivirus was used at concentration 100 ng/ml. The nuclear condensation assay performed as described.\(^{117}\)

**Isx-9 Treatment of R6/2 Mice**

All animal procedures were performed in accordance with National Institutes of Health and University of California guidelines. R6/2 transgenic (~120 +/- 5 CAG repeat) mice and their non-transgenic littermates obtained from the Jackson Laboratory. Isx-9 was prepared as 2 mg/ml of 30% vehicle (2-hydroxypropyl)-β-cyclodextrin in sterile milliQ-purified H₂O). R6/2 and age-matched non-transgenic mice (n = 10) were obtained at 5 weeks of age and given a previously established dose of Isx-9 (20mg/kg) by daily intraperitoneal injection after a brief acclimation period. Mice were tested in behavior tasks each week thereafter and
then sacrificed at 10 weeks of age. All mice were housed on a 12 h light/dark schedule with ad libitum access to food and water. Behavioral Assessment: Mice were assigned to groups in a semi-randomized manner. Behavioral tests were performed at 6, 7, 8, 9 or 10 weeks of age depending on the task. Researchers were blind to which mice had been injected during experiment testing and data collection. To minimize experimenter variability a single investigator conducted each behavioral test. Rotarod, pole test and grip strength were performed as described\(^ {46} \). Novel object recognition: Each mouse was exposed to two objects and allowed to explore for a period of time, after which, one of the objects was replaced by another. If memory is functioning normally, the mouse will spend more time exploring this novel object than it does exploring the familiar object. If exploration of all objects is the same, this can be interpreted as a memory deficit. A white plastic tub was used for testing and a mounted digital camera recorded movement. Two different objects were tested to ensure that the animals do not have an innate bias towards one or another; 100 mL glass beaker turned upside down vs. two hump tall mega lego block. Lighting was adjusted to 25 Lux using black trash bags taped over the overhead lights. Mice were acclimated to the testing room then placed in the tubs without any objects to freely explore the area for 5 min, habituation to box. The next day after acclimation mice were presented the same object (either two beakers or two blocks) for 5 min. On the third day mice were presented with a new object replacing one old. Using the recorded data the amount of time that the animal interacts with each object is scored in seconds. An exploratory preference score (time spent exploring the novel object divided by the total time spent exploring box objects x 100) is calculated. An exploratory preference score of 50% indicated chance performance, and a higher preference score indicated intact memory performance. \( R6/2 \) Synaptic Immunohistochemistry: Mice
were trans-cardially perfused with 4% PFA and after dissection tissue was post-fixed for a further 2h before being placed in a 30% sucrose solution for 48hr. The tissue was subsequently embedded in a 2:1 mixture of 30%sucrose:OCT and frozen. 80μm sections were cut and incubated with blocking solution (10% normal goat serum and 0.4% triton) followed by incubation with antibodies to Homer-1 (Synaptic systems) and VGLUT1 (Millipore). Subsequently sections were incubated with appropriate secondary antibodies (Invitrogen), and coverslips mounted onto the slides with mounting medium (Vector Shield). To visualize synaptic staining sections were imaged on a Zeiss LSM 700 confocal microscope at 63x magnification. Digital pictographs were captured and Image J software used to quantify co-localized pre and post-synaptic puncta.

**Robotic Imaging Analysis**

Images were taken every 24 hours for 9 days as described\(^4\) on an inverted microscope (Nikon Ti Eclipse) that contains the PerfectFocus system, a 20× Plan Fluor S 0.45NA ELWD objective and a 16-bit electron multiplying charge-coupled device(EMCCD) which is cooled to -70C (Andor iXon 888). Illumination was delivered from a Sutter Lambda XL Xenon lamp. Semrock BrightLine full-multiband filter sets for DAPI, FITC, TRITC, were used for excitation and detection. The illumination, filter wheels, focusing, stage movements and image acquisitions were fully automated and coordinated with publicly available (ImageJ and μManager) software and a custom written image acquisition plugin. During longitudinal experiments, plates were kept in a robotically controlled incubator (Liconic STX44) and were delivered to the microscope stage that is housed in an OKO-Labs environmental chamber by an automated robotic arm (Peak Robotics). Scheduling and automation was
controlled with Green Button Go (Biosero). Survival Analysis: Images from differentiated i-neurons were montaged using custom based scripts written in Pipeline Pilot Pipeline Pilot (Accelrys, San Diego, CA). The images were then tracked in MATLAB using custom-based algorithms developed in our lab. These programs allowed us to keep track of the amount of time each cell lived and died during the course of 9 days. Cells were tracked only if they had neuronal morphology as reported\textsuperscript{117}. Cell death was prescribed to cells that showed morphological features of cell death such as cellular blebbing, cell rupture or loss of fluorescent signal\textsuperscript{44}. Survival time for each cell was denoted as the last time the cell was seen alive. Scripts written in R’s survival package were used to generate cumulative risk of death curves and to perform Cox proportional hazards analysis\textsuperscript{222} or log-rank test\textsuperscript{209} to assess the relative risk of death between the HD i-neurons and controls and the effect of ISX-9 on survival. The cumulative risk of death curves were assessed for violations of proportionality by evaluating both the cumulative risk of death curves and by using the using cox.zph function in the R survival package.

There were no violations of proportionality except when analyzing the Q18n2 +DMSO and Q18n2 +ISX-9 and 53Qn3 +DMSO survival probabilities in the Q53 datasets. We found strong evidence for non-proportional hazards between the two groups. In particular, we observed crossing Kaplan Meier survival curves and a cox.zph with p values of 2.97e-05 for Q18n2 +DMSO and a 1.38e-04 for Q18n2 +ISX-9 and 2.00e-02 53Qn3 +DMSO. Further inspection of the data revealed that the cause for this is that one of the repeated experiments for group did not match the typical trends for the other runs of the experiment. While for each individual run of the experiment, the proportional hazard assumption appeared appropriate, when combining all runs into a single experiment group, the outlier experiment
was the main cause of the non-proportional hazards. Rather than drop the outlier group, we used a log rank test that does not require the assumptions of the proportional hazards to evaluate the differences in survival between the Q53 and control dataset. To estimate the approximate HR between groups, we used the HR values from the Cox proportional hazards model for this dataset.

**Statistical analysis**

Multiple statistical models were used during these analyses and are detailed further in the specific materials and methods above, Figure legends. (*) p<0.05; (**) p<0.01; (***) p<0.001; (****) p<0.0001.
Chapter Two

Blood-brain barrier and angiogenic deficits in Huntington’s disease iPS cell-derived brain endothelial cells

Ryan G. Lim, Chris Quan, Andrea M. Reyes-Ortiz, Theresa A. Gipson, Amanda J. Kedaigle, Jennifer Stocksdale, Malcolm S. Casale, Clive N. Svendsen, Ernest Fraenkel, David E. Housman, Dritan Agalliu*, and Leslie M. Thompson*
3.1 Summary of Chapter 2: This chapter is taken from a manuscript currently under revision.

This chapter focuses on investigating whether mHTT has intrinsic effects in brain endothelial cells (BECs), a cell type that shows abnormal function in HD. The work presented here looks at transcriptional changes that occur due to mHTT expression, and identifies dysregulated genes that impair BEC and BBB function. While there is apparent dysfunction of the BBB in neurological disorders including Huntington’s disease (HD), the underlying mechanisms remain elusive given limitations with the use of rodent models and post-mortem tissue to identify primary deficits. Transcriptome analysis of human induced pluripotent stem cell (iPSC)-derived BECs from HD patients or unaffected controls demonstrates alterations in HD-BEC signaling pathways crucial for angiogenesis and BBB development, and structural components that control BBB permeability. These deficits translate to functional barrier deficiencies, increased angiogenesis and aberrant drug efflux. Co-culture of healthy astrocytes with HD-BECs does not rescue barrier deficits, suggesting intrinsic abnormalities contribute to BBB dysfunction. We provide the first iPSC-derived BBB model for a neurodegenerative disease, demonstrating specific barrier defects that may underlie crucial aspects of pathology with implications for drug delivery in HD. The results from this work helps to move the field forward by providing evidence for primary BBB deficits that arise during the progression of a neurodegenerative disease. I have fully contributed to all aspects of this work and writing of the manuscript.

3.2 Introduction
Huntington’s disease (HD) is a devastating neurodegenerative disorder caused by a CAG repeat expansion in the first exon of the huntingtin (HTT) gene encoding an expanded polyglutamine (polyQ) track in the Huntingtin (HTT) protein. A broad range of functions are impacted by chronic mutant HTT (mHTT) expression (mHTT). Progressive cognitive, psychiatric and motor impairment and a corresponding degeneration of striatal medium spiny neurons and atrophy of cortical neurons is characteristic of the disease. Emerging data suggests that impairment of the neurovascular unit (NVU) and blood-brain barrier (BBB) function may contribute to neurodegenerative diseases, including HD. The NVU is composed of both neuronal and non-neuronal cells (astrocytes, pericytes) that regulate CNS homeostasis and interactions with blood vessels. Brain endothelial cells (BECs) in NVU form the main component of BBB that restricts paracellular and transcellular entry of molecules and immune cells through the presence of tight junctions (TJs) and restricted transport via a limited number of caveolae and selective transporters. Induced pluripotent stem cell (iPSC)-derived astrocytes from HD subjects and astrocyte from HD mouse models show both increased VEGF levels and alterations in ion channel function. Chronic mHTT expression also triggers vascular abnormalities leading to BBB deficits such as increased cerebral blood volume, small vessel density, and BBB permeability in HD patients and rodent models of HD.

Alterations in signaling pathways and structural proteins that regulate EC barrier function, such as WNT signaling and reduced expression of BBB TJ proteins, have also been identified in both mouse and human HD brain. Nevertheless, it is unclear if cell-intrinsic deficits in BECs contribute to HD pathology or if BBB dysfunction is secondary to...
neurodegeneration and deficits of other NVU cells (e.g. astrocytes)\textsuperscript{13-15}. Moreover, little is known about downstream targets of BBB-specific pathways and how these are altered in CNS diseases such as HD. This is in part due to a lack of a robust \textit{in vitro} model of the human BBB carrying disease mutations. With the development of iPSCs\textsuperscript{113,229} and efficient protocols to generate cells of the NVU, including brain endothelial cells (BECs)\textsuperscript{230,231}, there is opportunity to investigate primary contributions of NVU cells in a neurodegenerative disease.

To address whether BECs have intrinsic deficits in HD, we generated human iPSC-derived BECs from either unaffected or HD subjects and performed transcriptome and functional analyses. RNA-sequencing of BECs represents a resource of the human BBB transcriptome which expands upon previous human BEC transcriptomic datasets\textsuperscript{87,232}. Transcriptome analysis and an \textit{in vitro} angiogenic assay suggests that HD-BECs have increased angiogenic potential. A set of novel BEC genes that could play roles in normal and diseased human barrier function are identified through transcriptomic analysis and will help to decipher how BECs regulate the transport of the complex milieu of metabolites in either healthy or diseased CNS. Functional assays show impairment in transendothelial electrical resistance (TEER), which is not rescued by co-culture with healthy astrocytes, impaired transcytosis, and transporter function. This HD-BEC model represents an important resource to evaluate therapeutics that can restore normal function to the HD BBB and to assist in assessing drug delivery to the HD CNS across the BBB.

\textbf{3.3 Results}

\textit{Generation and transcriptome analysis of unaffected control human iPSC-derived BECs.}
To establish iPSC-derived BECs, we differentiated control iPSCs from unaffected individuals into BECs as described\textsuperscript{230,231}. Two control iPSC lines from unaffected individuals having 33 or 28 CAG repeats in the \textit{Htt} gene (CS83iCTR33n1, designated 33Qn1 (33Q); CS14iCTR28n6, designated 28Qn6 (28Q)) were evaluated \textsuperscript{[142,233], see Experimental Procedures}. All differentiated cells expressed markers of human BECs including PECAM1 (CD31) and GLUT1 (SLC2A1), and formed linear TJs as assessed by uniform localization of the BBB-specific TJs: CLAUDIN-5 (CLDN5), OCCLUDIN (OCLN), and TIGHT JUNCTION PROTEIN 1 (TJP1), also known as ZO1, at cell-cell junctions (Figure 3.1B). The percentage of pure BECs after subculturing onto collagen and fibronectin was over 90% for both lines (Figure 3.2). Functionally, BECs exhibited a high TEER, characteristic of BECs over several days, peaking between 48 and 72 hours post-subculture, and sustaining values greater than 300\(\Omega\times\text{cm}^2\) (Figure 3.1C). iPSC-derived BECs were analyzed for expression of BBB-specific genes by comparing their transcriptome profile (RNA-Seq) to gene expression data from other BEC studies. iPSC samples were differentiated in two separate batches, using relative low and high passage number (15-30). We compared our data to previous datasets collected from primary human BEC samples using laser capture microdissection or purification, or from two immortalized BEC lines, hCMEC/D3 and HBEC-5i\textsuperscript{234-237} (datasets are listed in Table 3.1 and \textsuperscript{232}). Due to known difficulties in comparing RNA-Seq and microarray expression \textsuperscript{238}, we focused on a binary approach, comparing whether a gene was expressed or not expressed, qualitatively assessing expression of BBB genes.

The control iPSC-derived BEC data were mined for genes essential for BBB function, including adherens and tight junction, caveolar and transporter proteins. CLDNs are the
principal constituents of TJs that form a paracellular barrier. Although, CLDN-3 and -5 are the major TJs of the human BBB, we found several other CLDN genes (e.g. CLDN-1, -4, -7, -11, -12, -18, -19, -20, -23) were also expressed in our data and previous data. However, some CLDN genes (e.g. CLDN-2, -6, -8, -9, -10, -15 and -16) were uniquely expressed in iPSC-derived BECs (Figure 3.3A). OCLN and all three JAM proteins (F11R, JAM2 and -3) were expressed in each dataset whereas ZO-3 was uniquely detected in iPSC-BECs. A second important constituent of the BBB are transporter proteins, including solute carrier, receptor-mediated, and active efflux transporters, that play a vital role in maintenance of CNS homeostasis. Recent profiling of 359 human solute carrier transporters (SLC) and 49 ATP-binding cassette (ABC) genes revealed 286 uniquely identified in human BECs with 59 of these genes expressed 2 fold-higher than in human cortex. Our RNA-Seq data identified 297 genes that overlapped with the 330 genes of the combined SLC and ABC families identified by the publicly available datasets and identified an additional 93 novel SLC and ABC genes (Figure 3.3B & Table 3.2). In order to determine the significance of finding 297 of the 330 transporter genes, we used a Chi squared test with Yates’ correction, and calculated a one-tailed p-value of 0.009. The high statistical significance of overlap validates the use of an iPSC-derived BEC model to investigate the function of novel SLC and ABC transporters.

Finally, we analyzed potential signaling regulators in human iPSC-derived BECs. Previous work has highlighted the importance of several pathways for BBB development and maturation including canonical WNT, SHH, NOTCH, PDGF, TGF, ANGPT and retinoic acid signaling pathways. Using transcription factor motif analysis, we identified motifs that were enriched upstream of BBB-specific genes expressed in the control iPSC-derived BECs (Figure 3.3C & Table 3.3). Specifically, THEME software was used to look for motifs in the
upstream regions enriched over the background regions against every motif in the
TRANSFAC and SELEX databases. The HIF-1 motif, where the transcription factor HIF-
1 binds during hypoxic conditions to upregulate pro-angiogenic genes such as VEGF, was
highly enriched (Figure 3.3C). ELK-1 and STAT-3 motifs were also enriched suggesting that
these transcription factors may regulate expression of transporter and efflux proteins at the
BBB.

The transcriptome of HD iPSC-derived BECs reveals potential angiogenic and barrier
defects

To determine whether the presence of highly expanded polyQ repeats impacts BEC
gene expression and function, four human HD iPSC lines with expanded repeats of 60Q, 66Q,
71Q, and 109Q (CS21iHD60n8, CS04iHD66n4, CS81iHD71n3, and CS09iHD109n1),
representative of early onset HD, were differentiated into BECs. Much like the control
iPSCs, the HD iPSC-derived BECs all had greater than 90% pure populations (Figure 3.2).
RNA-Seq was carried out for all four HD lines as described above. Raw count data were
quantified, and log2 transformed for unsupervised statistical and exploratory analysis to
examine significant differences between HD and control cells (Figure 3.3D). Although the
highest global expression variance is seen across all patient samples in principle component
(PC) #1, there is clear separation between control and HD samples accounting for the second
major variance across PC #2. Differential expression between control and HD-BECs was
analyzed, and hierarchical clustering of log2 transformed gene expression values shows
separation of HD and control samples while clustering samples based on polyQ track length
(Figure 3.3E).
In order to identify specific pathways and regulators that might play a role in vascular alterations in HD, we conducted Ingenuity Pathway Analysis (IPA) and motif analysis on our differentially expressed genes (DEGs). These analyses provided a snapshot of altered pathways and predicted regulators between control and HD-BECs. WNT/β-catenin, pro-angiogenic, adherens and tight junction, and leukocyte extravasation signaling, as well as caveolar-mediated endo- or transcytosis, which all play essential roles in EC barrier function, were altered (Figure 3.3F). To identify transcription factor activity changes that might contribute to altered gene expression and pathway activation, upstream regulator analysis (IPA) and motif analysis were performed on HD-BECs as above. Several regulators of BBB genes were predicted to be activated in HD-BECs including: WNT3A, GLI2, ANGPT2, and TGFβ1 (Figure 3.3G). Further, motif analysis on genes expressed only in HD-BECs, or upregulated in HD-BECs, revealed many DEGs in our dataset could be regulated by HIF-1, TGFβ or ELK-1 (Table 3.4). These data indicate HIF-1-regulated signaling could play a role in barrier development and maintenance of healthy BECs, and in promoting pathogenesis in HD-BECs.

**HD-BECs have a higher angiogenic ability compared to control BECs**

To further identify functional categories of our DEGs, we conducted GO analysis, using Cytoscape for visualization. Biological process enrichment, revealed that terms related to angiogenesis and vessel morphogenesis were altered, including genes involved in EC signaling that promote vascular sprouting and remodeling (Figure 3.4a). Within the parent category of signaling, several components of the Wnt/β-catenin pathway that regulate CNS
angiogenesis and BBB maturation were altered. These include ligands (WNT-3, -4, -6, -7B, -10A), effectors (TCF3, TCF4), and downstream targets (APDCC1, a novel WNT inhibitor upregulated in the HD-BECs (Figure 3.3F & 3.4B) and indicate a possible increase in pro-angiogenic signals. In addition, pro-angiogenic genes such as NOTCH-3 and -4, αv-integrin and SMAD3 were also upregulated (Figure 3.3F & 3.4B). ROBO-1 and -2 which promote downregulation of VEGFR2 during active angiogenesis at the beginning of EC differentiation, were upregulated, correspondingly VEGFR2 was downregulated in the HD cells (Figure 3.3F & 3.4B). These data indicate that HD-BECs are starting to mature by expressing the correct gene cues for maturation, but there is a delay compared to their control counterparts. In support of this hypothesis, GO analysis of cellular compartments determined that the majority of DEGs are localized within the plasma membrane and cytoplasm (Figure 3.5B), therefore DEGs in the HD-BECs could affect EC function through dysregulation of critical surface proteins controlling adhesion, signaling receptors and barrier properties (Figure 3.5B).

**HD iPSC-derived BECs have functional deficits in angiogenesis and barrier properties**

Transcriptomic analysis revealed significant dysregulation in a number of BBB relevant pathways. We next evaluated whether these deficits translated into impaired functional EC barrier properties that can be predicted by altered transcriptional signatures.

**Angiogenesis:** To functionally evaluate whether the transcriptomic findings translate into increased angiogenic potential of the HD-BECs, we conducted a wound-healing assay to assess the angiogenic state of BECs by measuring the distance the cells travel into a
wound area after scratching a monolayer of BECs. HD-BECs showed increased migration into the wound over a 6 hour time period (Figure 3.4C & D), suggesting that intrinsic signals in HD-BECs prime them for increased angiogenesis compared to control BECs.

**Tight junction function:** We next examined whether alterations in adherens and tight junction components present in HD-BECs could result in aberrant paracellular barrier function. One of the key BBB TJ components, CLDN3, was downregulated in HD-BECs. Visualization of the subcellular localization of two other major BBB TJ proteins, CLDN5 and OCLN, in control and HD-BECs with immunofluorescence, did not reveal any overt abnormalities in OCLN localization at EC junctions. However, CLDN5 was localized both at junctions and intracellularly in HD but not control BECs (Figure 3.6A). To determine whether BBB function is impaired, TEER measurements were performed on HD and control-BECs over 96 hours. There was a significant reduction in maximal TEER values in HD samples at 72 hours, (adjusted p-values (60Q 4x10^-2), (66Q 1x10^-3), (71Q 1x10^-6), (109Q 1x10^-9)), particularly with highly expanded repeat lines above 70Qs (e.g. 71Q and 109Q) (Figure 3.6B). These findings indicate that TJs and paracellular barrier function is altered in HD-BECs compared to healthy control-BECs.

**Transporter function:** 74 SLC- and ABC- transporters are differentially expressed between HD and control cells (Table 3.5). We therefore examined whether transporter function was impaired. Among the dysregulated ABC transporters, ABCB1, which encodes the multi-drug resistance protein 1 (MDR1) and plays a crucial role in drug efflux across the BBB, was highly upregulated in the HD-BEC samples, initially suggesting that HD-BECs could
have higher transporter function (Figure 3.7A). To test this hypothesis, we developed a puromycin survival assay that relies on the ability of BECs to extrude puromycin surviving treatment due to the presence of MDR-1. We treated control or HD-BECs with puromycin for 48 hours and found that HD-BECs were unable to survive the antibiotic treatment, even at lower levels of puromycin (Figure 3.7B) (adjusted p-values (60Q 9x10^-3), (109Q 1x10^-2)). Furthermore, the extent of decreased survival correlated with increasing polyQ length (Figure 3.7B), suggesting that although MDR-1 is upregulated in HD-BECs, it is not properly functioning in the presence of chronic mHTT expression. These findings elucidate a functional consequence to transport in the presence of mutant HTT based on the transcriptome analysis.

Transcytosis is impaired in HD-BECs.

Recent findings show mHTT aggregates within the vasculature of HD mice and patients are primarily concentrated in endocytotic vesicles. Pathway analysis of the RNA-Seq data showed that a significant number of affected genes regulate both clathrin- and caveolin-mediated endocytosis, which could lead to abnormal endocytosis or transcytosis. Upregulation of FABP4, DYNAMIN, and FILAMIN, which initiate vesicle formation and scission, F-ACTIN, as well as several INTEGRIN subunits and other receptors that activate endocytosis (TRANSFERRIN & LOW DENSITY LIPOPROTEIN receptors) were identified (Figure 3.3F). Additionally, CAVEOLIN-1 (CAV-1) expression was higher in the HD-BECs (Figure 3.3F, 3.4B & 3.7C). CAV-1-dependent transcytosis is normally downregulated in maturing BECs as compared to peripheral ECs. The presence of higher levels of transcytosis proteins suggests that HD-BECs have not undergone full differentiation to form
mature barrier properties, but instead maintain a more non-CNS transcellular permeability. Albumin can enter the CNS by CAV-1-mediated transcytosis \(^{(64)}\). Since HD-BECs have increased CAV-1 expression, and increased albumin levels are found within the CNS of R6/2 mice after intravenous injections \(^{(55)}\), we examined the possibility of increased transcytosis in our iPSC-derived BECs by CAV-1-mediated endo/transcytosis using the transwell permeability assay. All HD-BECs had increased levels of albumin transcytosis across the monolayer (Figure 3.7D) (adjusted p-values (60Q \(2 \times 10^{-2}\)), (66Q \(1 \times 10^{-3}\)), (71Q \(2 \times 10^{-3}\)), (109Q \(7 \times 10^{-3}\)), suggesting that the transcellular barrier is also impaired in HD-BECs.

**Barrier deficits of HD iPSC-derived BECs are maintained in presence of healthy control astrocytes**

To define whether barrier deficits in the HD-BECs are maintained in the presence of healthy astrocytes, TEER measurements were performed on a representative set of HD versus control lines with a relatively mild TEER phenotype (60Q versus 33Q control) in the presence of control iPSC-derived astrocytes \(^{(245)}\). These astrocytes were co-cultured on the bottom well of transwell plates to test whether signaling from proper soluble factors would be sufficient to rescue barrier deficits. Co-culturing healthy control astrocytes with either control or HD-BECs reduced variability between experiments and allowed ECs to maintain high TEER values, over multiple experiments. Although both control and HD-BECs were able to reach high TEER values, control astrocytes did not rescue the 60Q HD-BECs compared to the 33Q controls (Figure 3.8A) (P-values (72 hours \(3 \times 10^{-2}\)), (96 hours \(6 \times 10^{-3}\))). This difference was even more apparent over time as the HD-BECs could not maintain high TEER values after 3 days in contrast to control-BECs (Figure 3.8A). These results suggest that both
HD and control-BECs can respond to astrocyte signaling to form initial barrier properties; nevertheless barrier properties are intrinsically flawed in HD-BECs.

3.4 Discussion

With the advent of iPSC technology and development of disease relevant models through differentiation of patient cells into cells of the NVU, we have the capability to determine cell-specific contributions to disease pathogenesis. Using iPSCs to generate BECs from HD and unaffected control patients has allowed us to identify transcriptional and functional differences in human HD-BECs. We find primary EC intrinsic deficits that promote barrier dysfunction independent of other cells of the NVU and pathways critical for CNS angiogenesis, EC maturation and maintenance of the BBB altered in HD-BECs. In an accompanying manuscript from the Svendsen and Shusta groups, the authors use a complementary approach to model the BBB from patients with Allan-Herndon-Dudley-syndrome, demonstrating selectively impaired transport of thyroid hormone in the differentiated patient iPSCs. Together, these manuscripts support the use of the iPSC-BEC system to generate robust and clinically relevant models of human BBB-related disorders and represent the first iPSC-derived models of the human BBB in neurological disorders.

A growing number of studies suggests that constituents of the NVU are altered in neurodegenerative diseases, and may contribute to pathogenesis in a cell-intrinsic or extrinsic manner including BBB dysfunction. Classically, it was assumed that there was no overt BBB leakage in HD; however recent data indicates that vascular abnormalities could play a significant role in HD pathogenesis, including BBB dysfunction at multiple levels.
BBB and vascular abnormalities are found in HD subjects and rodent models of HD, including increased cerebral blood volume, increased extravasation of Evan’s blue dye after LPS insult, increased cortical and striatal microvessel density with a corresponding decrease in EC TJs, and decreased GLUT1 transporter levels.

Our transcriptomic analysis of the HD versus unaffected control cells provides insights into the pathways and networks uniquely altered in HD-BECs that are predicted to affect specific BBB functions. The studies described here indicate that the transcriptional differences between control and HD-BECs in BBB-specific genes or signaling do indeed translate into functional barrier impairment in HD-BECs. For instance, WNT signaling which contributes to the proper formation and maintenance of the cerebrovascular network and BBB is altered in HD-BECs. Multiple pro-angiogenic genes such as WNT, NOTCH-3, -4, v-integrin, and SMAD-3 are also upregulated in HD-BECs, suggesting that they are highly angiogenic. In contrast, the increase in ROBO1 and -2 genes with the corresponding downregulation of VEGFR2 indicates that the HD-BECs are also undergoing maturation. These data suggest that Wnt/β-catenin signaling may have a broader impact on the intrinsic aberrant angiogenesis than VEGF signaling. Genes that contribute to the downregulation of VEGF signaling appear to function properly whereas Wnt/β-catenin signaling remains active. These data suggest that intrinsic defects in Wnt/β-catenin signaling are working together with extrinsic astrocyte-mediated VEGF signaling to alter BBB function.
The finding that several dysregulated pathways in HD-BECs play regulatory roles in angiogenesis and barriergenesis provides a potential mechanism to explain vascular defects found in HD patients and mouse models. Albeit previous studies have attributed BBB deficits to increased astrocyte-mediated VEGF signaling, our data suggest that EC-intrinsic activation of pro-angiogenic signals that promote angiogenesis and makes the vasculature of the HD CNS permeable to toxic insults could also contribute to the deficits. The delay in barriergenesis of HD-BECs may be due to high levels of mHTT that uncouples angiogenesis and barriergenesis in CNS endothelium leaving newly sprouting vessels unable to protect the CNS effectively. This aberrant barrier function is reflected in all cell biological mechanisms that form the barrier such as paracellular barrier (altered TJ localization and decreased TEER), transcellular barrier (increased transcytosis of albumin), and decreased transport across the ECs. Moreover, increased expression of genes that contribute to BBB breakdown could contribute to the functional impairment in HD-BECs. For instance, MMP-2 and -9 levels that contribute to basement membrane dissolution and disruption of junctional proteins are increased in HD-BECs. Increased CAV-1 promotes albumin or other serum protein transport across the BBB, and MDR-1, although increased in expression, is nonfunctional and is likely to contribute to overall BBB impairment and HD pathogenesis. Interestingly, a recent study showed an increase in MDR-1 expression in both human HD postmortem tissue and the R6/2 mouse model of HD and an increase in functional activity in HD mice. Our iPSC-derived model recapitulates the elevated levels of MDR-1 in the presence of chronic mHTT expression; however, some differences exist between the functional consequences in mice versus the in vitro system, indicating a need for further
research to elucidate the effects on the human CNS and the precise role of MDR-1 in HD pathogenesis.

Several of the primary pathways that contribute to proper barrier development are also dysregulated in HD neurons and astrocytes \(^{1,13,226,227,249}\), including WNT, TGF\(\beta\), and VEGF (Figure 3.8B) that would impair barrier formation and maturation over time. From a clinical perspective, therapeutic drug delivery into the brain necessitates an understanding of the state of BBB function in neurodegenerative diseases in order to develop effective treatments. The network data and functional outcomes reflecting these deficits in the HD-BECs can help to identify the most critical targets for therapeutic intervention and be a tool for investigating fundamental biological and disease processes in the NVU that affect the human cerebral vascular network. For instance, future studies will evaluate many of the key BBB transporters that are expressed on the BECs and focus on specific transports that are upregulated in the HD-BECs and/or have been shown to be a critical target for therapeutic delivery, including: TRANSFERRIN, Amino Acid Transporter Light Chain, L System (LAT1), Breast Cancer Resistance Protein (BCRP), and Multidrug resistance-associated protein 1 (MRP-1). Next steps also include further developing co-culture studies to assess the effects of HD astrocytes on healthy and diseased BECs, and future “BBB on a chip” technologies. Importantly, the iPSC-derived cell models may be used to assess the potential brain penetrability of drugs under consideration for CNS drug discovery programs and guide future treatments for HD patients.

3.5 Figures
Figure 3.1. iPSC-derived BECs from healthy control patients stain for BBB markers and show functional barrier properties. A) Diagram of the human BBB showing restricted transport of cells and molecules from the blood into the brain, and signaling pathways (e.g. WNT/β-catenin) controlling BBB genes. Paracellular transport is prevented by the presence of TJs formed by CLAUDINs (CLDN (blue)), OCCLUDIN (OCLN (red)), and ZONA OCCLUDENS (ZO (purple oval)). Low levels of transcytosis are controlled by a decrease in the number of caveolae (orange circles and light blue CAVEOLIN-1). Lastly, transport and efflux of ions and other molecules are highly regulated by solute carriers, ATP-binding cassette genes, and other ion channels. B) Representative images for healthy control iPSC-derived BEC stained for PECAM1 (CD31), GLUT-1 (SLC2A1), CLDN-5, OCLN, and ZO-1. C) Scatter plot of TEER values from control-BECs over 120 hours, reaching maximal values between 48 and 72 hours. TEER values shown are averaged between two control iPSC lines (28Q and 33Q) over three individual readings taken from triplicate wells, (mean+/SEM). There was no statistical difference in TEER values between the two samples using a two-tailed Student’s T-test ((n) = 14 (33Q) and 16 (28Q), independent experiments/differentiations per sample)
Figure 3.2. Flow cytometry of control and HD iPSC-derived BECs.
Flow data showing percentage of CD31 and GLUT1 positive BECs after subculturing onto collagen and fibronectin. All patient samples show >90% pure BECs by flow analysis with no statistical difference between samples. Statistical analysis was done by one-way ANOVA using n=3, independent experiments, with 3 independent growth replicates per an experiment.
Figure 3.3. Exploratory, pathway, and motif analysis of transcriptomic data from control and HD-BECs reveals the presence of novel genes associated with blood-brain barrier and dysregulation of known BBB genes. A) List of uniquely expressed CLDNs found in RNA-Seq data from healthy iPSC-BECs. B) A Venn diagram of shared SLC- and ABC- transporters between healthy iPSC-BECs data and previously published BEC transcriptomic data. C) Selected results from motif analysis on all SLC- and ABC- transporter genes expressed in control-BECs. P-values represent the likelihood of finding the calculated enrichment of that motif in random sequences with similar GC content. Also see Table 3.3. D) PCA of log2 normalized count data on global expression demonstrates grouping within individual control or HD samples and separation between both groups along PC#2. E) Hierarchical clustering of DEGs using log2 normalized count data show clustering of control versus HD samples and groups. F) Hierarchical clustering of DEGs in signaling pathways affecting BBB function using log2 normalized count data. G) IPA upstream regulator analysis showing transcriptional regulators predicted to be activated or inhibited by calculation of activation z-scores. P-value calculated by Fisher’s exact test from expected and observed genes overlapping in our DEG list and all genes regulated by each transcription factor.
Figure 3.4. HD-BECs show GO biological process enrichment for signaling pathways that regulate angiogenesis. A) Network mapping of binGO biological process analysis showing enrichment for genes that regulate WNT signaling, angiogenesis and vascular development. All enrichment nodes have an adjusted p-value < 0.05. Adjusted p-values were calculated based on overrepresentation of categories over a background sample using a hypergeometric test and adjusted using a Benjamini & Hochberg FDR. B) Gene network showing differentially expressed genes that are involved in angiogenesis and have a direct connection (Edges). Orange denotes genes that are upregulated in HD and blue are downregulated. C & D) Wound-healing assay shows HD cells have increased migration into wound. Images are 0 and 6 hour time points. Plot shows change in area overtime. \( n = 7 \) (control) & 3 (HD) independent experiments/differentiations and p-values (2.2x10^{-2}) were calculated using Student’s T-test. Lines used were 28Q, 33Q, 66Q, and 71Q. (mean±/SEM). (*p< 0.05; **p< 0.01; ***p<0.001).
Figure 3.5. Cytoscape networks displaying GO functional analysis. A) Enrichment mapping of binGO molecular functional analysis shows enrichment of genes that control ion binding which include INTEGRINS and of additional cellular adhesion genes which require cofactors for their function. B) CluGO analysis showing enrichment of specific cellular compartments revealing an enrichment of cytoplasmic and plasma membrane localized genes and lacking enrichment in nuclear genes. A & B) All enrichment nodes have an adjusted p-value < 0.05. Adjusted p-values were calculated based on overrepresentation of categories over a background sample using a hypergeometric test and adjusted using a Benjamini & Hochberg FDR.
Figure 3.6. HD-BECs have abnormal structural and functional endothelial cell tight junctions. A) Representative immunostaining micrographs for CLDN5 and OCLN in control and HD-BECs. There is an increase in intracellular CLDN5 protein inside HD cells. B) A bar graph of TEER values for control (black) and HD (grey) lines at 72 hours post subculture. The TEER is decreased in all HD-BECs. For statistical analysis of TEER, resistance values from each triplicate measurement per well were averaged in each experiment (independent differentiation) containing 3 replicate wells per a condition/sample. ANOVA with Bonferroni correction for multiple comparisons was used to determine differences across multiple experiments (n = independent experiment/differentiation & adjusted p-values (CTLs n=20), (60Q n=20 & 4x10^{-2}), (66Q n=11 & 1x10^{-3}), (71Q n=8 & 1x10^{-6}), (109Q n=16 & 1x10^{-9})). No significant differences were detected between control samples. Control values were then combined for further comparison to HD samples. (mean+/-SEM). (*p< 0.05; **p< 0.01; ***p<0.001).
Figure 3.7. HD-BECs have abnormal function of transporters and transcytosis. A) Bar graphs showing increased PGP protein expression in HD-BECs. B) Puromycin survival assay. There is reduced MDR-1 function in HD-BECs and less cell survival due to decreased efflux of puromycin. For the puromycin assay $n=3$ independent experiments/differentiations with triplicate wells for each condition (adjusted p-values $(60Q \ 9\times10^{-3})$, $(109Q \ 1\times10^{-2})$). C) Bar graphs showing increased CAV1 protein expression in HD-BECs. D) Bar graph of the albumin transcytosis assay shows increased transport of albumin-594 across HD-BEC monolayers compared to controls. ($n =$ independent experiments/differentiations with triplicate wells & adjusted p-values (CTLs $n=10$), $(60Q \ n=4 \ & \ 2\times10^{-2})$, $(66Q \ n=5 \ & \ 1\times10^{-3})$, $(71Q \ n=3 \ & \ 2\times10^{-3})$, $(109Q \ n=3 \ & \ 7\times10^{-3})$). ANOVA and Bonferroni correction for multiple comparisons was used to determine differences across multiple experiments between HD vs Control cells. (mean$\pm$/SEM). (*$p< 0.05$; **$p< 0.01$; ***$p<0.001$).
Figure 3.8. Coculture of HD-BECs with healthy control iPSC-derived astrocytes does not restore paracellular barrier function. A) TEER values from HD and control-BECs co-cultured with control iPSC-derived astrocyte. TEER values over 96 hours. At 72 and 96 hours HD-BECs had decreased TEER compared to control-BECs. ($n=3$, independent experiments/differentiations with triplicate wells (P-values (72hours $3\times 10^{-2}$), (96 hours $6\times 10^{-3}$)). Statistical analysis performed using two-tailed Student’s T-test. B) Model of EC barrier dysfunction in HD. Schematic of NVU in HD select genes that are dysregulated in HD-BECs and HD-astrocytes. These genes can contribute to neuronal dysfunction and death. (mean +/-SEM). (*$p<0.05$; **$p<0.01$; ***$p<0.001$).
Table 3.1. Previous human BEC datasets that we have used for comparison with the healthy control or HD patient iPSC-derived BECs.

<table>
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<th>Study</th>
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<td>Lopez-Ramirez et al., 2013</td>
<td>hCMEC/D3</td>
<td>Culture</td>
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Table 3.2. SLC- genes and anti-sense SLC- genes that are uniquely expressed in iPSC-derived BECs.

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<td>SLC9A4</td>
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Table 3.3. Motif analysis of SLC and ABC genes in iPSC-derived BECs. These sequence motifs are highly enriched when analyzing all SLC and ABC genes that are found in our healthy control iPSC-derived BECs. P-values represent the likelihood of finding the calculated enrichment of that motif in random sequences with similar GC content.

<table>
<thead>
<tr>
<th>motif_name</th>
<th>motif</th>
<th>pvalue</th>
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<tbody>
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<td>NRF-1</td>
<td>yGCGCakGCGC (959)</td>
<td>6.75E-12</td>
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<tr>
<td>GMEB2</td>
<td>t.ACGyam (1490)</td>
<td>7.32E-12</td>
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<tr>
<td>MIZF</td>
<td>c.rCGTCCGC (1352)</td>
<td>1.91E-08</td>
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<tr>
<td>Egr-1</td>
<td>mGcCCACGC. (1128)</td>
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<td>HIC1</td>
<td>ss...TGCCc... (1642)</td>
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<td>s.gGGAGSa.g (1563)</td>
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<td>HINFP1</td>
<td>GCGGACSyks.sRTGCCGC (487)</td>
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<td>ZIC1</td>
<td>grCCCCCyGctGG. (859)</td>
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<td>HINFP1</td>
<td>GCGGACGy.sccrrCTGCCGC (466)</td>
<td>7.43E-05</td>
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<td>AP-2</td>
<td>.gCCy..rGGca (1469)</td>
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<tr>
<td>Sp1</td>
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<td>0.00017753</td>
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<td>TFAP2A</td>
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<td>Egr</td>
<td>gyGGGsGsrrs (1524)</td>
<td>0.00221534</td>
</tr>
<tr>
<td>Whn</td>
<td>...gACGCc. (1313)</td>
<td>0.00287111</td>
</tr>
<tr>
<td>STAT3:STAT3</td>
<td>kTkmcGGGAAmsc (597)</td>
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<td>STAT1</td>
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<td>E2F</td>
<td>ttTsGCCGSm.. (957)</td>
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<td>c-Myc:Max</td>
<td>.rcCACGTGgy. (796)</td>
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<td>HSF</td>
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<td>KLF15</td>
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<td>ETS1</td>
<td>accGGAwryrcwTCCgs. (510)</td>
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<td>AP-2</td>
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<tr>
<td>Hmx3 (Nkx5-1)</td>
<td>CAAGTGCGTG (656)</td>
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<tr>
<td>CREB</td>
<td>y.aCGTCA. (1504)</td>
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<td>g.csgTa.wrCsGTtr (889)</td>
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<tr>
<td>GMEB2</td>
<td>yaCgtaac.saCGya (694)</td>
<td>0.04825038</td>
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Table 3.4. Motif analysis of DEGs in HD-BECs. These sequence motifs are highly enriched in our DEG list. P-values represent the likelihood of finding the calculated enrichment of that motif in random sequences with similar GC content.

<table>
<thead>
<tr>
<th>motif_name</th>
<th>motif</th>
<th>pvalue</th>
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</thead>
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<td>SOX10</td>
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<td>MEF-2</td>
<td>rgyTaTwTTwa. (1197)</td>
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<td>COUP TF</td>
<td>....tGacCyyts..c.y.m (2680)</td>
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<td>HIF1</td>
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<td>SOX10</td>
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<td>Pbx</td>
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<td>BCL6</td>
<td>wrCTTTTcagGraT (969)</td>
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<td>CTCF</td>
<td>..gcCas.aGrkGGrcrs (203)</td>
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<td>Helios A</td>
<td>TTTCCw (291)</td>
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Table 3.5. Differentially expressed SLC and ABC genes. A list of all differentially expressed SLC and ABC genes in HD-BECs versus control BECs.

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Table 3.6. Selected genes that may regulate tight junctions and endothelial transport and fold changes that could contribute to HD pathogenesis.

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<th>Gene Symbol</th>
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<td>CLDN15</td>
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<td>CLDN3</td>
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<td>CDLN4</td>
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<td>BBB permeability and Ion Flux</td>
</tr>
<tr>
<td>SLC1A6</td>
<td>1.32</td>
<td>Excitotoxicity</td>
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<tr>
<td>SLC22A17</td>
<td>1.31</td>
<td>Iron and Ferritin Accumulation</td>
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<td>ABCB1</td>
<td>2.38</td>
<td>Drug Efflux</td>
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<tr>
<td>SLC16A8</td>
<td>-1.58</td>
<td>Metabolic Dysfunction</td>
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</table>
3.6 References


61 Duran-Vilaregut, J. *et al.* Role of matrix metalloproteinase-9 (MMP-9) in striatal blood-brain barrier disruption in a 3-nitropropionic acid model of Huntington’s


3.7 Methods and Materials

**Generation and characterization of human non-integrating iPSCs using episomal plasmids**
Fibroblasts were reprogrammed into non-integrating and virus-free iPSC lines as described
using the Amaza Human Dermal Fibroblast Nucleofector Kit to express episomal plasmids
with six factors: OCT4, SOX2, KLF4, L-MYC, LIN28, and p53 shRNA (Addgene) 142. Nomenclature reflects the 1) last two digits of parental lines identifier, 2) non-disease or HD line, 3) CAG repeat number, and 4) clone number 142. Human iPSCs were rigorously characterized at the Cedars-Sinai iPSC core. G-Band karyotyping ensured normal a karyotype and genomic DNA PCR confirmed the absence of episomal plasmid genes, as described 210-212. Pluripotency was assessed by immunostaining with surface and nuclear pluripotency markers for subsequent flow cytometry quantification (> 80% SSEA4 and Oct3/4 double positivity), by quantitative RT-PCR of endogenous pluripotency genes, and by gene-chip and bioinformatics-based PluriTest assays. Spontaneous embryoid body differentiation confirmed the capacity to form all germ layers.

**Maintenance and differentiation of human iPSC-derived BECs or Astrocytes.** Briefly, iPSCs underwent spontaneous differentiation for 6 days in unconditioned medium (UM). The mixed cultures were then switched to human endothelial cell medium (Life Technologies) with bFGF (R&D Systems) and 1% platelet-poor plasma derived bovine serum (Alfa Aesar) to select for BEC colony expansion and maturation for 2 days. During this time the samples were treated with retinoic acid (RA, Sigma). All cells were then plated onto collagen-IV (Sigma) and fibronectin (Corning) coated tissue culture plates or 0.4 µM 12 well transwell filters for 2-3 days to reach confluence before characterization and use in various assays.
**Immunofluorescence.**

After 2-3 days of growth on collagen IV and fibronectin coated chamber slides, cells were washed once with PBS and fixed in either 4% paraformaldehyde, 100% ice-cold methanol, or ice-cold 95% ethanol followed by 80% ice-cold acetone. Following fixation cells were blocked in 10% goat serum with 1% BSA and 0.1% triton X-100 (where applicable) for 1 hour at room temperature. Cells were then labeled with primary antibody overnight at 4 degrees, washed three times with PBS and treated with a fluorescently labeled secondary antibody for 1 hour at room temperature. Cells were counterstained with DAPI to visualize nuclei.

**Wound Healing Assay.** Following differentiation BECs were plated in collagen/fibronectin coated 12 well plates. After 24 hours the cells would reach 100% confluence and the initial scratch/wound was made. Images were taken on an EVOS microscope at time 0 and 6 hours. Two images were taken per a well and 6 wells were used for each experiment/differentiation. ImageJ software was used to quantify the area of the wound and the changes in area were calculated for each time point.

**Transendothelial Electrical Resistance.** Trans-endothelial electrical resistance (TEER) measurements were performed using an EVOM voltohmmeter (World Precision Instruments). The resistance value (Ωxcm^2) of an empty filter coated with collagen/fibronectin was subtracted from each measurement.
**RNAseq and DE Statistics.**

Total RNA was isolated from cells with the Qiagen RNeasy Kit using a QIAshredder for cell lysis and all RIN values were >9. RNA-Seq libraries were made with 1ug of RNA using the Illumina TruSeq mRNA v2 protocol. Libraries were quantified using the KAPA library quant kit and sequenced on the HiSeq 2500 using 75 cycles to obtain paired-end reads 75 base pairs in length. Paired-end reads were trimmed using a base quality score threshold of >20 and aligned to the hg19 genome with Tophat 2. RNA-Seq data were analyzed using quality control metrics, including: quality score trimming, base composition, k-mer content, and 5’ and 3’- bias. Counts per gene were quantified using HTseq and analyzed with the R package DESeq2, or Partek Flow, to identify differentially expressed genes. 10% and 5% false discovery rate cutoffs were used for significance for DESeq2 and Partek Flow, respectively.

**Exploratory, pathway, and motif analysis of DEGs.**

For exploratory analysis plots GENE-E and Partek GS 6.6 were used for hierarchical clustering (Spearman’s Ranked Correlation) and heatmap generation, and PCA of log2 transformed global expression values, respectively. Data were analyzed through the use of QIAGEN’s Ingenuity® Pathway Analysis (IPA®, QIAGEN Redwood City, www.qiagen.com/ingenuity) for pathway analysis and upstream regulator analysis. Cytoscape was used to visualize GO analysis networks from BinGO, Enrichment Map, and CluGO \(^{241,250-252}\). Motif analysis was performed on a 1000bp region upstream of each gene's TSS, as reported by RefSeq, which were taken from the hg19 genome. Background sequences
were created by sampling the genome for the same number of random 1000bp regions of matched GC content (in the case of the healthy BEC analysis) or by using the upstream regions from the opposite treatment group (when comparing HD patient-derived cells to healthy-patient derived cells). THEME \(^{176}\) was used to find enriched motifs in the upstream regions over the background sequences. The set of motif hypotheses is derived from all vertebrate-specific scoring matrices (PSSMs) from TRANSFAC \(^{219}\) and the human HT-SELEX compendium \(^{239}\), filtered for sufficient information content (>9 total bits). Motif hypotheses were then clustered according to similar binding site motifs, and the top p-value for all motifs in a cluster is reported. These data were then filtered for transcription factors that are expressed in the RNA-Seq dataset in order to generate a list of related motifs where these factors bind.

**Efflux and transporter Assays.** For transwell assays cells were allowed to reach confluence on 12 well 0.4µM tranwell inserts over 3days post subculture. After TEER measurements the medium in the lower chamber was brought to 1mL and the upper chamber medium was replaced with medium containing either 10 µM rhodamine 123 (Life Technologies) or 10 mM albumin-594 (Life Technogies) and incubated for 1 hour at 37 degrees C. After incubation 100µL of medium was taken from the bottom and upper chambers and placed into a 96 well plate in duplicate. Fluorescence was read using a plate reader. Values were normalized to readings from a blank well containing cells and medium without the fluorescent molecules. Puromycin efflux was measured based on cell death by allowing the BECs to grow for 48 hours post subculture in normal 12 well TC plates with subsequent
treatment with either 0.5 or 1 µM puromycin. After 48 hours of treatment cells were washed once with PBS and fixed with 4% PFA. After fixation cells were then washed and DAPI stained to visualize cell nuclei. ImageJ software was used to quantify cell counts from five images per a well using 3 wells per an experimental set and over 4 experiments.

**Statistical Analysis.** Multiple statistical models were used to test the data based on data parameters. For each experiment a description of the statistical model used can be found within the figure legend or methods. Statistical significance is denoted by * < 0.05, ** < 0.01, *** < 0.001. Sample sizes and statistical tests for each experiment were chosen based on previous expertise and knowledge from past experiments using similar model systems, mice and iPSCs, and current accepted standards based on literature review. An estimation of variation within control or HD samples was assessed based on the statistical model used or data acquired, and accounted for in each experiment.
Chapter Three

Aberrant gene expression and alternative splicing drive cellular pathologies in ALS
4.1 Summary of Chapter 3: This chapter is taken from unpublished data still in progress for use in preparing a manuscript from the NeuroLINCS consortium.

The following chapter outlines some of the current work being conducted by the NeuroLINCS consortium. Our focus is on iPSC modeling of ALS, differentiating patient-derived iPSCs into motor neurons. The NeuroLINCS consortium uses a similar “multi-omic” approach as the HD iPSC consortium to gain further insight into the pathogenic mechanisms of ALS. For this dissertation, I will focus on the data identified specifically from the transcriptomic analyses conducted by our lab. These data include changes in mRNA expression levels as well as alternative splicing using total RNA-seq analysis. We identified several regulators that alter gene expression and alternative splicing in ALS, and I propose novel mechanisms that may lead to genomic instability in ALS motor neurons.

4.2 Introduction

Since the discovery of the C9orf72 (C9) gene mutation in 2011, there has been extensive scientific progress in understanding the contribution of this mutation to ALS\textsuperscript{253}. This mutation is the most common genetic cause of ALS, a disease where 90% of all cases are sporadic\textsuperscript{254}. The C9 version of the disease accounts for ~34% of the familial cases and ~6% of sporadic cases\textsuperscript{254}. As in HD, this form of ALS also is caused by a repeat expansion, but the expansion is in the intronic region of the gene and is a hexanucleotide expansion of GGGGCC. This repeat can expand into the 1000s, while unaffected individuals typically have between 2 and 10 repeats\textsuperscript{255,256}. It is not yet known the threshold repeat length for disease causation. ALS patients can have as few as 20 repeats, but some individuals with up to 30 repeats show
no disease manifestation\textsuperscript{255,256}. Furthermore, researchers do not know how the repeat length correlates with the disease onset, progression, or exact phenotype.

The C9 version of ALS shares some pathological features of the sporadic disease including mislocalization of RNA binding proteins (RBPs), but there are unique pathologies that seem to be specific to the expansion itself, including the presence of RNA foci and dipeptide repeat proteins which are generated from RAN translation. Similar to HD, the C9 form of ALS is dominant, with a possible contribution from LOF consequences. C9 ALS also manifests with abnormal transcriptional regulation and RNA processing\textsuperscript{253,254}. Aberrant RNA processing is observed in sporadic forms of ALS as well and this has been linked to the sequestration of RBPs. However, an understanding of the specific transcriptional changes and networks impacted are just beginning to emerge. I have utilized transcriptomic analysis on differentiated ALS iPSC-derived motor neurons to elucidate pathogenic signatures in C9 ALS.

4.3 Results

\textit{Changes in gene expression reveals TGFB, ERBB2, and NRG1 pathogenic network activation in C9ORF72 iPSC-derived motor neurons.}

Using transcriptomic analysis (e.g. analysis methods described in Chapters 1 and 2), we identified 828 differentially expressed genes and 1889 differential exon usage events (Figure 4.1A). Upstream analysis of the 828 DEGs identified a pathogenic network that included TGF-\( \beta \), ERBB2, and NRG1 (Figure 4.1B). Both TGF-\( \beta \) and ERBB2 signaling have been implicated previously in ALS\textsuperscript{257-260}, supporting the validity of the model and approach from
our network, TGF-β appears to be functioning as the most upstream dysregulated pathway. Figure 4.1C shows a mechanistic network with TGF-β driving changes for TNF, ERBB2, and IFNG signaling. Downstream of these signaling pathways JUN, STAT1 and 3, and SMAD2, and 3 are each predicted to be activated, and of these, JUNB and STAT1 also show an increase in gene expression in ALS samples compared to control. NRG1 and PLAU signaling are also predicted to be activated (Figure 4.1B & 4.2A). Target genes of this network include MMPs which have also been identified as potentially driving pathology and are upregulated by gene expression analysis (Figure 4.2A & B).

**RNA binding proteins and alt-splicing in ALS**

Using our list of differential exon usage genes, we used DeepBind software to predict which RBPs bind to our genes and possibly be involved in alternative splicing. These data are predicted by motif analysis across the genes sequence. Of the 102 RBPs that are found in the DeepBind database, we identified 18 RBPs that bind our gene list with a score > 5 (Figure 4.3). Interestingly, among these RBPs we discovered HNRNPA1 and SRSF1 among the top hits. Both of these genes contribute to ALS pathology, and specifically mislocalize in the C9 form of ALS261.

Upstream analysis of our alt-spliced gene list showed many of our genes to be regulated by NEUROG1 and TGF-β, both of these genes are predicted regulators of the set of differentially expressed genes as well. Further indicating a role for these genes in ALS, NEUROG1 is predicted as downregulated in the DEG list and is also predicted to be highly inhibited at the protein level. These alternatively spliced genes and upstream regulators are
involved in caveolae-mediated endocytosis and translational elongation. Alterations to RNA translation are observed in ALS, and are linked to the RBPs previously implicated in ALS. Strikingly, these hits are among the top RBPs identified DeepBind analysis\textsuperscript{262}. These data are illuminating some of the underlying pathology in the transcriptomic profile of these ALS samples.

4.4 Discussion

TGF-\(\beta\) is implicated in ALS as having both neuroprotective and deleterious effects. Depending on the cell type, TGF-\(\beta\) signaling may reduce neuroprotection by peripheral immune cells and microglial, while a decrease in signaling in motor neurons due to mislocalization of pSMAD prevents proper TGF-\(\beta\) signaling in motor neurons\textsuperscript{257,259}. Activation of TGF-\(\beta\) signaling directly in motor neurons is also protective by helping to clear sequestered RBPs\textsuperscript{259}. Our data suggest a role for TGF-\(\beta\) in the pathogenesis of ALS by directly contributing to the dysregulation of genes and to alternative splicing, however this pathway could be upregulated in our cells as a compensatory mechanism. Regardless of the precise role TGF-\(\beta\) plays, it is clearly an important pathway and should be further investigated to understand ALS pathogenesis. Future studies are in progress to both further activate and inhibit TGF-\(\beta\) signaling and assess whether pSMADS are mislocalized in the ALS cells. Alternatively, several of the other pathways that converge upon the TGF-\(\beta\) pathway, including: ERBB2, NRG1, IFNG, and PLAU signaling, might be critical for the transcriptional dysregulation. It is unclear how each these pathways contributes to the disease and it will
take pathway perturbation and functional analysis of known ALS cellular phenotypes to unravel the role of each.

Much less is known about how NEUROG1 affects ALS motor neurons. This transcription factor has been utilized in mesenchymal transplantations studies of ALS mouse models as a neuroprotective agent\textsuperscript{263}. The normal function of NEUROG1 is in the initiation of neuronal differentiation. NEUROG1 interacts with NEUROD1 during neuronal development and neurogenesis. These data indicate a potentially important role for NEUROG1 in motor neuron development and function and to ALS. Downregulation of NEUROG1 in ALS patient could be altering neurogenesis and normal motor neuron function.

Through our analysis, we've identified potentially important pathogenic networks which may contribute to transcriptional dysregulation and alternative splicing in ALS, potentially through interactions with RBPs and have generated a potential disease signature that might be relevant to the development of small molecule therapeutics for ALS.

4.5 Figures
Figure 4.1. Hierarchical clustering and upstream regulator analysis of differentially expressed genes in ALS iPSC-derived motor neurons. A) Clustering of 828 DEGs identified by DEseq2 statistical analysis of gene expression from ALS versus control iPSC-derived motor neurons. Clear separation can be seen in the gene expression profiles of the ALS and control samples. B & C) Upstream regulator analysis identifies transcription factors that regulate the gene expression changes seen in ALS motor neurons. Interactome analysis identifies a mechanistic network connecting several of these factors.
**Figure 4.2.** NRG1 interacts with other predicted upstream regulators to drive MMP overexpression in ALS motor neurons.  

**A)** Interactome network showing NRG1, TGFB, ERBB2, and PLAU signaling driving gene changes and MMP expression.  

**B)** Log2 Fold change of MMPs upregulated in ALS iPSC-derived motor neurons.
Figure 4.3. RNA binding proteins identified by DeepBind analysis of alternatively spliced genes in ALS motor neurons. The frequency of identifying the top scoring RBPs which bind to alternatively spliced mRNAs in ALS iPSC-derived motor neurons.
4.6 References


4.7 Methods and Materials

**Generation and characterization of human non-integrating iPSCs using episomal plasmids**

ALS and non-disease repeat iPSCs were generated and characterized as described above in chapters 1 and 2.

**iPSC Motor Neuron Differentiation**

induced motor neurons were generated as described here.\(^\text{264}\).

**RNA-Seq**

Total RNA was isolated from cell pellets with a Qiagen RNeasy Kit and QIAshredder. rRNA were depleted using the Ribo-Zero Gold rRNA removal kit. Total RNA-Seq libraries were made with 1µg of RNA using the Illumina Truseq stranded total RNA library prep kit. Final PCR products were run on 2% agarose E-Gels (Invitrogen) and libraries were size selected at 300 bases. Libraries were sequenced on the Hi-Seq 2500 at 100 bases. Reads were trimmed by quality scores and mapped to the hg19 genome with Tophat 2. Counts per gene were quantified by HTseq then analyzed with the R package DESeq 2 and DEXseq to identify differentially expressed genes and differential exon usage, respectively, with a single comparison of ALS versus non-disease. A 10% false discovery rate cutoff was used for significance. Data were analyzed through the use of QIAGEN’s Ingenuity® Pathway Analysis (IPA®, QIAGEN Redwood City, [www.qiagen.com/ingenuity](http://www.qiagen.com/ingenuity)), Cytoscape, BINGO, and DeepBind.\(^\text{241,250,251,265}\).
Chapter Four

Conclusions and Future Directions
5.1 Transcriptional Dysregulation in HD

Transcriptomic analyses of animal models of HD, postmortem brain tissue, and now iPSC models of HD all show transcriptional dysregulation as one of the earliest and reproducible pathological features of HD. Our iPSC model of HD has provided us with the ability to analyze multiple cells of the CNS over time. Our previously published data mainly focused on neural stem cells, a cell type which would be found during development or in specialized regions of the brain. These cells recapitulated the transcriptional dysregulation in genes that were functionally relevant to neurons.

We expanded these studies to a more mature neural population and used both transcriptomic and epigenomic analyses to gain a better understanding of the mechanisms in which transcriptional dysregulation occurs. These data recapitulate known abnormalities in the HD brain, but also discovered novel aspects of pathology. Pathways such as calcium signaling, REST, and BDNF were altered, as expected, but also a novel pathogenic network involved in neuronal development was identified. NEUROD1 was a major hub in this network, and due to the role it plays in overall neuronal development and function, and in adult neurogenesis, we decided to target this gene as a possible point of therapeutic intervention. As a proof of concept, we used a small molecule, ISX9, which upregulates NEUROD1 by calcium influx. This treatment reversed expression of genes we found to be downregulated in HD that I propose restores normal levels of gene expression, and recovers many functional properties. Epigenomic analysis of these cells also showed a possible underlying histone profile that marks genes that are ultimately dysregulated in HD. Future studies are needed to assess whether upregulation of NEUROD1 by ISX9 can change these
profile of histone modification. Additionally, it will be important to determine the direct gene targets of NEUROD1, in these cells, using ChIPSeq, as well as looking at binding partners of NEUROD1. NEUROD1, in part, functions by direct interaction with HATs to upregulate genes targets. These data would further our understanding of the mechanisms at play during pathogenesis and that may contribute to rescue.

Using our iPSCs, we were able gain insight into the effect of mHTT expression on BECs function. Previous studies have shown mHTT expression in other non-neuronal cell types can contribute to pathogenesis, but it was unclear if HD BECs acquired cell autonomous defects. I was able to show that BECs from HD patients indeed had intrinsic deficits and these may be partially due to mHTT altering the transcriptional profile in these cells. Signaling pathways that regulate angiogenesis and the BBB were altered at the transcriptional level changing the expression pattern in HD-BECs. What is unclear is whether these changes may be regulated by similar epigenomic profiles as described for neuronal cells. Using similar ChIPSeq methods or ATAC-SEQ would be the next steps to determine the exact mechanism in this cell type. Moreover, there is no evidence to suggest that treatment with ISX9 would help to rescue the deficits in the BEC transcriptome as NEUROD1 does not have a role in the development and function of BECs. However, if BECs have comparable epigenomic profiles, one may be able to identify strategies that could target a similar profile with a single drug such as a histone-modifying agent. Even if there are distinct epigenomic profiles, understanding the underlying mechanisms in each cell type could provide a rationale for combination drug targeting of upstream pathways, such as upregulating NEUROD1 and downregulating WNT.
5.2 Neurodevelopmental deficits in HD

HD and other neurodegenerative diseases have historically not been considered as developmental diseases. The data I present here and evidence from other studies demonstrate that some aspects of HD could involve an impact on the normal development of the CNS. These alterations might not manifest with overt phenotypes as the brain has many compensatory mechanisms. Rather these effects might impact when the disease occurs as the individual ages and how the diseased gene overcomes these compensatory mechanisms. The effects of aging on the CNS are still emerging but studies have shown an increase in inflammation, DNA damage, alterations to histones, and changes in adult stem cell populations during aging. These changes might be the nudge that the disease gene needs in order to overpower the cognitive reserve and compensatory mechanisms of the CNS. I have provided evidence that neurodevelopment and neurogenesis could be altered at the transcriptional level in HD. A slight delay in the temporal expression of key genes during neurodevelopment could be responsible for the CNS abnormalities seen in the prodromal stages of HD, which then contribute to the overall pathogenic progression in HD.

5.3 Altered BEC function in HD

Studies that have focused on changes in the CNS vasculature have identified abnormalities in the number of vessels and even changes to the BBB. With our patient iPSC-derived BECs I have been able to decipher some of the mechanisms that are contributing to these changes. Due to an altered transcriptional pattern, there seems to be an increase in angiogenesis and a delay in maturation of the BBB. Similar to the neuronal impairments, these changes might
manifest as the cells become less able to manage the effects of mHTT. The BECs become more angiogenic and this leads to the increase in small vessel density. As angiogenesis occurs, barriergenesis is usually tightly coupled with this process but the presence of mHTT stress may cause these two processes to become uncoupled and the delay maturation of the BBB (Figure 5.1). This delay could allow for leakage of the BBB, which would contribute to neuronal dysfunction and death.

The altered tight junction localization and corresponding reduced TEER levels indicate that the paracellular barrier of the HD-BECs is compromised. This could lead to an influx of small molecules that are toxic to the CNS in HD patients. Small ions like potassium, which has been shown to contribute to neuronal death in HD, could be accumulating in the CNS of HD patients through a paracellular leak and directly contributing towards the increase in potassium regulated excitotoxicity. The increase in transcellular permeability could also directly be contributing to HD pathogenesis by transcytosis of larger blood solutes, antibodies, and immune cells, as well as a decrease in the efflux of toxic lipophilic molecules due to the decrease in PGP function.

These data provide evidence that BECs are key cell types that are contributing to the dysfunction and loss of neuronal cells in HD, and provide a rationale for directly targeting BECs to treat neurodegenerative diseases.

5.4 Neuronal and BEC signaling

Alterations in gene expression that impact neurodevelopment could also indicate changes in neurogenesis, a mechanism that occurs throughout adult life. This mechanism can help to
compensate for CNS damage arising from mHTT chronic expression. Animal models have shown an increased activation of neurogenesis through increased proliferation, however analysis of HD patient brain shows decreased levels in mature neurons arising through this mechanism in the striatum. It is possible that the neurogenesis program is overactive in HD patients and this leads to a premature depletion of the NSC population. Ultimately, we do not know how these processes may be contributing to HD pathogenesis which can be the focus of future studies. Moreover, the changes in HD-BECs might also affect the specialized vascular niche that surrounds the NSC populations. This could also change the normal function of NSCs in HD patients and needs to be further investigated.

**Neural Stem Cell and Brain endothelial cells interactions**

The signals between neural cells and the BECs continues into the adult CNS with signaling between all of the cellular members of the NVU responsible for maintaining the BBB and to regulate homeostasis of the CNS and its metabolic profile. Adult neural stem/progenitors continue to provide signals to the BECs that live near their residence within the subventricular zone (SVZ)\(^{266}\). These unique signals generate a specialized vascular niche which helps to regulate the self-renewal and differentiation of the NSCs. In contrast to the majority of the vasculature in the CNS these vessels lack astrocyte endfeet and pericyte coverage, allowing NSCs to directly contact the vasculature. Progeny of the dividing NSCs are found closest to the vasculature. The BECs in this area seem to have altered BBB properties allowing small molecules to enter the SVZ, in part due to a lack of tight junctions\(^{266}\). The specialized state of the BBB in this region is particularly relevant to a recent
finding in HD which shows a potential alteration to neurogenesis and our recent findings, which are described in chapter 2, showing abnormal expression of genes involved in neurodevelopment and neurogenesis that are also involved in survival and morphology of the HD neural cells\textsuperscript{119,120}.

### 5.5 Transcriptional Dysregulation in ALS

Alterations to the transcriptome at the gene expression level and the level of RNA processing have a role in the pathogenesis of ALS. Previously published data has shown sequestration of RBPs that are thought to be contributing to the alt-splicing seen in ALS patients. The data in chapter 3 shows our patient iPSC-derived motor neurons recapitulate some of these features seen in patient samples. We have identified a mechanistic network driven by TGFB and NRG1 signaling which may, at least in part, be responsible for the majority of gene changes in the ALS samples, and are even responsible for the expression of genes that are later found to be alternatively spliced. Currently, we are pursuing these data by reanalyzing the transcriptome after chemical activation and inhibition of the TGFB signaling pathway. These experiments will be complemented with functional assays and integration with other ‘omics’ assays to help define mechanisms underlying the gene expression changes.

Our functional assays will also look to determine the role of RBP localization in regulating alt-splicing. Many of the RBPs identified by DeepBind analysis of alt-spliced genes have been previously implicated in ALS and our data may shed light on the specific mechanism causing these changes. Interestingly, many of these RBPs have been found to be involved in R loop formation. R loops are RNA-DNA hybrids that are mainly formed to help
regulate gene transcription and DNA methylation at the sites of the R loops. The formation of R loops has been linked to disease and genomic instability, including ALS. It is not clear how much of a role R loops have in ALS pathology, nor is it known which regions of the genome are affected by their formation. Recent studies have shown an important role for proteins that modify DNA damage and neurodegeneration, but again how they function in the disease is unclear. Better knowledge of the exact players and contributions of genomic instability towards pathology will overall help our understanding of these diseases. Future work will focus on identifying the genomic regions most affected by R loop formation, possibly using DNA–RNA immunoprecipitation followed by sequencing (DRIP-seq) and investigating how RBPs could be increasing their formation.

The results outlined in chapter 3 are only from the transcriptomic analysis of these cells. Our collaborators in the NeuroLINCS consortium have also looked at functional assays and other ‘omic’ analyses, including: proteomics, whole genome sequencing, and epigenomics. Additional analysis using metabolomics and lipidomics will be added to this analysis. Our future work will focus on integrating all of these unique datasets and to identify subnetworks, or signature, that drive the pathology in ALS. We will utilize different perturbations including knockdown of the C9 mRNA to assess if these signatures are specific to C9 pathology and whether they can be reversed. This effort will help us to understand ALS pathology at a global level, allowing us to define specific signatures as primary or secondary features driving pathogenesis and others that are compensatory.

5.6 Conclusions
The overarching goal of each of the studies presented in this dissertation has been to determine if patient iPSCs can be successfully used to model aspects of neurodegenerative disease biology. Utilizing patient-derived iPSCs and RNA-seq has proven to be an effective method of modeling HD and using transcriptomic analysis we have identified novel mechanisms that may be involved in driving disease pathology. Moreover, some of the mechanisms that have been identified in these studies are reversible by small molecule intervention, not only by reversing the transcriptomic disease signature, but also by rescuing some of the associated functional deficits. Additional work is needed to determine how each of the novel disease features contributes to both of the diseases. Careful consideration of the timing of therapeutic administration needs to be assessed for any future therapeutics developed for HD or ALS. Furthermore, a combinatorial approach may be necessary to target each of the cell types and functions affected by the disease.

5.7 Figures
**Figure 5.1 Proposed model of cell autonomous deficits in HD BECs.** Left panel shows proper epigenetic and transcriptional control of signaling pathways that are induced in the BECs by signaling from the NVU. This lead to BBB maturation and proper BBB function. The right panel shows mHTT expression in the BECs which prevents the proper signaling and increases pathways related to angiogenesis. This leads to increased angiogenic sprouting, and uncoupling of barrier maturation. Newly formed vessels have impaired barrier function due to decreased BBB maturation.
5.8 References


Appendix One

A novel structural scaffold of polypharmacological compounds with therapeutic activity in Huntington’s disease models

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**Summary**

There are currently no disease-modifying therapies for the neurodegenerative disorder Huntington’s disease (HD). This study identified novel thiazole-containing inhibitors of the deacetylase sirtuin-2 (SIRT2) with neuroprotective activity in ex vivo brain slice and Drosophila models of HD. A systems biology approach revealed an additional SIRT2-independent property of the lead-compound, MIND4, as an inducer of cytoprotective NRF2 (nuclear factor-erythroid 2 p45-derived factor 2) activity. Structure-activity relationship studies further identified a potent NRF2 activator (MIND4-17) lacking SIRT2 inhibitory activity. MIND compounds induced NRF2 activation responses in neuronal and non-neuronal cells and reduced production of reactive oxygen species and nitrogen intermediates. These drug-like thiazole-containing compounds represent an exciting opportunity for development of multi-targeted agents with potentially synergistic therapeutic benefits in HD and related disorders.

**Introduction**

Mammalian NAD+-dependent sirtuin deacetylases (SIRT1-SIRT7) regulate diverse physiological functions in cells and are implicated as potential modifiers of age-related human diseases (Liu et al., 2013). The second family member, sirtuin-2 (SIRT2), was originally identified as α-tubulin deacetylase (North et al., 2003). Later studies, however, indicated that SIRT2 deacetylates a broad variety of protein substrates and regulates multiple cellular processes, including histone remodeling and gene transcription (Rauh et al., 2013; Taylor et al., 2008). SIRT2 is a highly abundant protein in the adult CNS, including
in neurons, although its precise function(s) remains uncertain (Luthi-Carter et al., 2010; Maxwell et al., 2011). We previously identified neuroprotective properties associated with several selective inhibitors of SIRT2 deacetylase (Chopra et al., 2012; Luthi-Carter et al., 2010; Outeiro et al., 2007).

Huntington's disease (HD), an autosomal dominant and progressive neurodegenerative disorder, is caused by expansion of a polymorphic trinucleotide repeat sequence (CAG)n within the gene encoding the large, highly conserved protein, Huntingtin (HTT) (1993). The expression of mutant HTT induces complex pathogenic mechanisms and alterations in multiple cellular pathways, including but not limited to protein misfolding and aggregation, transcriptional dysregulation, mitochondrial dysfunction and elevation reactive oxygen species. In particular the harmful role of oxidative stress has been described in both HD patients and in experimental models (Browne and Beal, 2006; Sorolla et al., 2012), and is potentially due to inherent sensitivity of neurons to an excess of reactive oxygen species (ROS) (Johri and Beal, 2012; Li et al., 2010; Moller, 2010; Quintanilla and Johnson, 2009; Tsunemi et al., 2012). However, no single neurodegenerative mechanism has emerged as the predominant mechanism and this complex disease pathology challenges effective development of neurotherapies.

The initial goal of the present study was to identify a new scaffold(s) of potent and selective SIRT2 inhibitors and to assess the therapeutic potential of these compounds in models of neurodegenerative diseases (Chopra et al., 2012; Luthi-Carter et al., 2010; Outeiro et al., 2007; Pallos et al., 2008). We identified and characterized a novel structural scaffold
MIND4, which transpired to contain compounds with dual SIRT2 inhibition and antioxidant NRF2 (nuclear factor-erythroid 2 p45-derived factor 2) activation properties.

Results

Identification of a lead series of novel SIRT2 inhibitors

To identify novel SIRT2 inhibitors, a scaffold-hopping approach was taken. We used derivatives of 8-nitro-5-R-quinoline and 5-nitro-8-R-quinoline, previously identified as substructures of bioactive compounds, as starting templates to create an initial focused library for screening compound activities in biochemical acetylation assays with human recombinant SIRT2 protein (Outeiro et al., 2007). Compounds were screened at a single concentration (10 μM) in triplicate in biochemical SIRT2 assays and counter-screened against SIRT3 activity to assess target selectivity. Using iterative structure-activity chemical modifications to improve potency and selectivity, we identified compound 5-nitro-8-\{(5-(phenoxymethyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio\}quinoline, henceforth MIND4 (Fig. 1A, B). In vitro activity tests of MIND4 showed selective concentration-dependent inhibition of human recombinant SIRT2 deacetylase activity (Fig. 1C-E). A structure-activity relationship (SAR) study identified additional thiazole analogs with selective SIRT2 inhibition activity, however with lower potency than the parent compound MIND4 (Fig. 1G). Intriguingly, a close structural analog 5-nitro-2-\{(5-(phenoxymethyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio\}pyridine, henceforth MIND4-17 (Fig. 1G), lacked any SIRT2 inhibition activity in the tested concentration range of 0.1-10 μM (Fig. 1F).
Characterization of a selective SIRT2 inhibition mechanism of the lead inhibitor MIND4

The precise potency of SIRT2 inhibition by MIND4 was determined as IC50=1.2±0.2 μM in a concentration-dependent activity test with human recombinant SIRT2 deacetylase (Fig. 2A). A subsequent mechanistic study revealed competitive inhibition with NAD+ and non-competitive inhibition with the peptide substrate with Ki of 2.1±0.2 μM (Fig. 2B, C). We used these results and molecular docking to generate a model of a SIRT2/MIND4 complex, which defines a molecular basis for compound selectivity against SIRT2 (Fig. 2D). The model shows partial MIND4 overlap with the NAD+ binding site but not with the acetyl lysine site. Superimposition of the complex with SIRT1 and SIRT3 shows that MIND4 fits the larger SIRT2 active site. SIRT1 isoleucine-316 (Ile316) and SIRT3 leucine-395 (Leu395) and the corresponding helices would clash with MIND4, providing a rationale for SIRT2 selectivity.

Bioactivity of SIRT2 inhibitor MIND4

The activity of MIND4 was tested in rat embryonic striatal ST14A cells stably expressing a 546 amino acid HTT fragment containing either a wild-type (26Q) or expanded (128Q) polyglutamine repeat (Ehrlich et al., 2001; Quinti et al., 2010). Consistent with the properties of a SIRT2 deacetylase inhibitor, MIND4 treatment increased acetylation of β-tubulin lysine-40 (K40) in both wild-type and HD cells (Fig. 3A, B, C) (North et al., 2003). Next, MIND4 activity was examined in wild-type primary cortical neurons (DIV11), which preferentially express full-length SIRT2 (isoform SIRT2.1) and are enriched in the brain SIRT2.2 isoform (Fig. 3E) (Maxwell et al., 2011). Transient 6 h treatment with MIND4 did not increase
acetylation of cytoplasmic $\alpha$-tubulin (K40), but upregulated acetylation of known nuclear H3 histone substrates lysine-56 and lysine-27; acetylation levels of lysine-14 of H3 histone were unchanged (Rauh et al., 2013), (Fig. 3E, F). An increase in histone acetylation suggests that such SIRT2 inhibition could influence gene transcription as reported in previous work (Luthi-Carter et al., 2010).

**Treatment with MIND4 is neuroprotective in HD models**

Next, rat corticostriatal brain slice explants were used to test the neuroprotective potential of MIND4 in a complex neural tissue system expressing HTT exon 1 with expanded CAG repeats (mHTTex1) (Reinhart et al., 2011). Treatment with MIND4 significantly protected against mHTTex1-induced neurodegeneration in a concentration-dependent manner (Fig. 3G). Neuroprotection at the highest 10 $\times$ M concentration of MIND4 was comparable to the efficacy of a reference compound, the pan-caspase inhibitor Boc-D-FMK (C) at 100 $\mu$M (Varma et al., 2007). MIND4 was further tested in an additional in vivo setting using a Drosophila model of HD, in which neuroprotective effects of SIRT2 inhibition has been established in previous studies (Marsh et al., 2003; Pallos et al., 2008). In this model, degeneration of photoreceptor neurons is visually scored by the presence of surviving rhabdomeres in the eyes of Drosophila expressing mHTTex1 (Steffan et al., 2001). Flies treated with 10 $\times$ M MIND4 had significantly more surviving rhabdomeres than untreated controls (Fig. 3H). The neuroprotective effects of MIND4 were confirmed in an independent second trial conducted at the 10 $\times$ M dose (data not shown). Relative rescue was estimated as 22.6% and 20.7% for the first and second trials, respectively.
MIND4 induces transcriptional activation of the NRF2 pathway in HD and wild-type neuronal cells

Next we sought to determine whether MIND4 treatment could alter gene expression, possibly restoring or compensating for transcriptional dysregulation in HD models as a possible neuroprotective mechanism (Crook and Housman, 2011; Luthi-Carter et al., 2002; Luthi-Carter et al., 2010). We thus performed gene expression profiling to determine the impact of MIND4 on transcriptional readouts in wild-type and HD ST14A cells.

Mutant HD and wild-type ST14A cells (Ehrlich et al., 2001; Quinti et al., 2010) were treated with MIND4 at 5 \( \mu \text{M} \) for 24 h. RNA from MIND4-treated and untreated HD mutant and wild-type ST14A cells was extracted and run on Affymetrix rat microarrays (Affy GeneChip Rat Genome 230 2.0 array) (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE49392). Duplicates for each experimental condition were imported into Partek Genome Suite for biostatistical analysis. Genes showing significant differential expression were identified by ANOVA for three contrasts resulting in three gene-lists: mutant HD (MT) vs. wild-type (WT) = Case I (Disease Phenotype); MT/MIND4 treated vs. WT = Case II (Treatment Phenotype), and MT/MIND4 treated vs. MT = Case III (Mutant Drug-Dependent Phenotype) (Table 1). These represented transcriptional alterations in MT compared to WT cells (Case I), in MT treated compared to WT cells (Case II), and in MT treated cells compared to untreated MT cells (Case III). The lists, Cases I-III, were then imported into Ingenuity Pathway Analysis (IPA - Ingenuity Systems, www.ingenuity.com) for pathway and network analyses.
Surprisingly, in treated MT cells compared to untreated MT cells (Case III), all top seven of the most significant canonical pathways activated by MIND4 treatment were either directly or indirectly related to NRF2; in decreasing order of significance, these were: 1) the NRF2-mediated oxidative stress response itself, 2) glutathione-mediated detoxification, 3) LPS/IL-1 mediated inhibition of RXR function, 4) aryl hydrocarbon receptor signaling, 5) xenobiotic metabolism signaling, 6) glutathione redox reactions, and 7) glutathione biosynthesis (Fig. 4A; please see Discussion for more details). Fig. 4B shows a portion of the IPA canonical pathway of NRF2 colored by intensity correlated to fold-change of gene expression in treated versus untreated MT cells.

Next we tested whether MIND4 could also induce transcription of ARE genes in primary neurons. Wild-type rat primary striatal neurons were treated with MIND4 at a 5 µM dose for 24 h and subjected to transcriptional microarray analysis as described (Luthi-Carter et al., 2010). The analysis of transcriptional changes shows that treatment with MIND4 induced a robust expression of canonical NRF2 gene targets in primary neurons as well (Table S1, Supplemental Information). These results suggested the intriguing possibility that MIND4 is an inducer of NRF2, acting through a SIRT2 inhibition-dependent or -independent mechanism.

**MIND4 induces NRF2 activation response in SIRT2-independent manner**

To validate the transcriptional microarray data, wild-type and mutant HD ST14A cells were treated with MIND4 for 24 h, and the expression levels of two canonical NRF2-responsive
proteins, NQO1 and GCLM, were examined. Concentration-dependent increases in these proteins were observed in both cell lines, consistent with activation of NRF2 (Fig. 5A, B).

Next, we examined the effects of MIND4 on the stabilization of NRF2 protein, a well-known step in the cascade of pathway activation. The effects of MIND4 on NRF2 levels were compared with the reference NRF2-inducer sulforaphane (SFP) (Zhang et al., 1992). Compounds were tested in COS1 cells transfected with plasmid constructs encoding NRF2-V5 proteins and ß-galactosidase to normalize transfection efficiency between samples as described (McMahon et al., 2010). Treatment with both compounds resulted in stabilization of NRF2, as determined by the clear increases in protein levels (Fig. 5C). These results further support the finding that MIND4 is an inducer of the NRF2 pathway.

Treatment with the structural analog MIND4-11, also a SIRT2 inhibitor (IC50=4 μM), had no effect on induction of the NRF2 response (Fig. 5D), further supporting a SIRT2-independent mechanism of NRF2 activation for MIND4. In contrast, treatment with the close structural analog MIND4-17, lacking SIRT2 inhibition activity, led to an even more potent induction of the NRF2-responsive proteins NQO1 and GCLM compared to MIND4 in both wild-type and HD mutant ST14A cells (Fig. 5E, F). Together, the findings suggest that the parent compound MIND4 is also an inducer of NRF2, activating this pathway via a SIRT2 inhibition-independent mechanism.

Thiazole analogs MIND4 and MIND4-17 induces NRF2 activation response in primary mouse neurons and astroglia
To extend evaluation of the NRF2 activation properties of MIND4 and MIND4-17 analogs, compound effects were tested in primary mouse neurons. A concentration-dependent induction of NQO1 and GCLM proteins in wild-type mouse cortical neurons (6 DIV) treated with MIND4-17 for 24 h supported a direct induction of the NRF2 pathway (Fig. 6G). These results showed that treatment with MIND4-17 can induce canonical NRF2 activation responses in mouse neurons.

Next, we examined whether MIND4-17 similarly to MIND4 could mediate transcriptional activation of canonical NRF2-responsive ARE genes. To that end we first used an ARE response element transcriptional reporter assay in a rat corticostriatal neuronal co-culture system (Kaltenbach et al., 2010). As shown in Fig. 5H, MIND4-17 significantly increased the transcriptional rate of a 5x-ARE-luciferase reporter construct transiently transfected into corticostriatal co-cultures. As would be expected for direct activation of NRF2, an almost saturating transcriptional response was already observed within 4 h of compound treatment.

Next, we determined whether MIND4-17 activates downstream ARE-dependent transcription of endogenous NRF2-target genes in native corticostriatal co-cultures. Treatment with MIND4-17 for 6 h significantly and concentration-dependently increased the expression of the canonical ARE genes Nqo1, Hmox1, Srx1, and to a lesser degree Gclc (Fig. 5I-L). These same genes were activated in primary rat neuronal cultures by MIND4 (Table S1). Finally, we compared the effects of MIND4 and MIND4-17 on transcriptional activation of NRF2 pathway in the context of the HD mutation (Fig. 5M, N). Both compounds showed similar concentration-dependent activation of the 5x-ARE-luciferase reporter in
corticostriatal co-cultures derived from wild-type vs. an HD mutant knock-in mouse model (Q175/+) (Menalled et al., 2012). Treatment of cultures with MIND4-17 for 24 h was not significantly cytotoxic for striatal (5 DIV) or cortical (5 DIV) neurons, differentially labeled in co-culture (Fig. S1). To extend the validation of NRF2 activation properties in non-neuronal cells, we tested MIND4 and MIND4-17 in primary mouse astroglia. Treatment with both compounds resulted in concentration-dependent increases of NRF2-responsive NQO1 and GCLM protein levels, demonstrating that effects of these inducers are not restricted to neuronal cells (Fig. 5O, P).

**NRF2 inducer MIND4 and its structural analog MIND4-17 reduce ROS levels in microglia**

We next performed functional studies evaluating properties of MIND4 and MIND4-17 in a well-characterized microglia model of NRF2 activation (Innamorato et al., 2008; Koh et al., 2011) using lentiviral transduction of SIRT2 shRNA or a scrambled control (Fig. 6A). The effects of both compounds on the levels of reactive oxygen species (ROS) were examined in microglia activated with LPS/TNF-α as described (Pais et al., 2013). Treatment with MIND4 or MIND4-17 resulted in a decrease of ROS levels in wild-type microglia (Fig. 6B). Notably, the effect of MIND4-17 was more pronounced than the effect of MIND4 and in agreement with the difference in inducer potencies of NRF2 activation. SIRT2 knockdown in microglia caused a significant elevation of ROS levels as previously described (Fig. 6 B, C) (Pais et al., 2013). Nonetheless, treatment with MIND4-17 was still able to decrease ROS levels, albeit with lower magnitude than in wild-type microglia (Fig. 6C). The effects of MIND4 treatment on ROS levels were undetectable and likely due to its lower potency of NRF2 activation.
Since SIRT2 knockdown led to an increase, not a decrease, in ROS levels in microglia (Pais et al., 2013), SIRT2 inhibitory activity of MIND4 is presumably irrelevant for the observed antioxidant effects of MIND4 in wild-type microglia. Moreover, the antioxidant effects of MIND4-17 in wild-type and SIRT2-null microglia are clearly independent from SIRT2 since this compound lacks SIRT2 inhibitory activity. Together, these findings indicate that the antioxidant effects of both MIND4 and MIND4-17 are attributable to the NRF2-activating properties of these compounds.

**NRF2 inducers MIND4 and MIND4-17 reduce levels of reactive nitrogen intermediates (RNI) in microglia**

Finally, we examined whether induction of NRF2 thru SIRT2-independent mechanism could inhibit release of neurotoxic nitric oxide, produced by iNOS in activated microglia (Aguilera et al., 2007). Treatment with MIND4 and MIND4-17 reduced production of nitric oxide in a concentration-dependent manner in activated microglia, where the effect of MIND4-17 was again more pronounced (Fig. 6 D). The reduction of nitric oxide levels was similar in control cell (white bars) vs. those transduced with SIRT2 shRNA (black bars), and irrespective of the presence or absence of SIRT2 inhibitory activity in MIND4 vs. MIND4-17, respectively. These results were again consistent with a SIRT2-independent mechanism for NRF2 activation, here resulting in the reduction of nitric oxide levels in activated microglia.

**Discussion**
We have identified a novel scaffold of thiazole-containing compounds which exhibits selective SIRT2-inhibition activity at various potencies. Mechanistic studies with the most potent compound elucidated an NAD+-competitive mechanism of SIRT2 inhibition. MIND4 acts as a bioactive SIRT2 inhibitor, and is neuroprotective in ex vivo brain slice and in vivo Drosophila models of HD. Through a systems biology approach, we unexpectedly found that MIND4 is also a transcriptional inducer of the NRF2-mediated oxidative stress response and modulates multiple pathways (see Fig. 4A) all centrally regulated by NRF2 activation: in glutathione-mediated detoxification, NRF2 regulates the expression of multiple members of the glutathione transferase (GST) supergene superfamily, the enzymes that catalyse the conjugation of numerous xenobiotics with glutathione (Hayes and Dinkova-Kostova, 2014; Wu et al., 2012). In LPS/IL-1 mediated inhibition of RXR function, NRF2 binds directly to RXR through its Neh7 domain (Chorley et al., 2012; Wang et al., 2013). In aryl hydrocarbon receptor signaling, NRF2 is often required for induction of classical AhR battery genes, e.g. by dioxin (Yeager et al., 2009). In xenobiotic metabolism signaling, NRF2 regulates genes encoding multiple drug-metabolizing enzymes (Pratt-Hyatt et al., 2013; Wu et al., 2012). In glutathione redox reactions, NRF2 regulates the enzymes that are responsible for regenerating and keeping glutathione in its reduced state (Hayes and Dinkova-Kostova, 2014). Finally, in glutathione biosynthesis, NRF2 regulates the expression of both subunits of the enzyme that catalyzes the rate-limiting step in glutathione biosynthesis (Moinova and Mulcahy, 1999). Moreover, MIND4 effects on gene transcription were confirmed to be translated into increased expression of NRF2-responsive proteins in both HD mutant and
wild-type cells. Together, these results strongly implicate NRF2 as a central target of MIND4 activation.

The follow-up experiments with a close structural analog of MIND4, MIND4-17, suggested that the mechanism of NRF2 activation is SIRT2-independent. This conclusion was supported by results demonstrating similar effects of MIND4 and the known inducer SFP (Zhang et al., 1992) on stabilization of NRF2 protein, a well-defined step in the pathway activation by NRF2 inducers. A functional study showed that MIND4 and MIND4-17, the latter lacking detectable SIRT2 inhibition activity, both reduce production of ROS and RNI in microglia, consistent with the properties of NRF2 inducers. Together, these findings suggest that MIND4 and MIND4-17 represent a novel class of NRF2 activators.

The molecular mechanism of NRF2 activation was elucidated as targeting cytoplasmic KEAP1 adapter protein through covalent modification of major sensor-cysteine C151. That modification is resulted in conformational change and arrest of NRF2/KAEP1 complex, unable to target NRF2 for proteasome degradation, which leads to accumulation and nuclear translocation of de novo synthesized NRF2, and subsequent activation of ARE gene transcription. This NRF2 activation mechanism is described in depth in an accompanying manuscript.

Antioxidant activities mediated by the transcription factor NRF2 have emerged as a potential therapeutic approach to combat age-dependent neurodegeneration (Johnson et al., 2008; Joshi and Johnson, 2012; Tufekci et al., 2011; van Muiswinkel and Kuiperij, 2005; Xiong et al., 2015). Overexpression of NRF2 provides protection for primary neurons from expression of mutant HTT fragment (Tsvetkov et al., 2013), and the efficacy of
pharmacological activation of NRF2 has been shown in HD mice and is associated with induction of broad antioxidant effects in brain (Ellrichmann et al., 2011; Stack et al., 2010).

Significance

The discovery of a novel drug-like scaffold of thiazole-containing compounds as described here presents an opportunity to develop clinical lead candidates with distinct as well as combined/synergistic mechanisms of SIRT2 inhibition and/or NRF2 activation for treatment Huntington’s disease and other neurodegenerative disorders.

Acknowledgements

This work was supported by grants from the NIH U01-NS066912, R01NS04528, NIH NS078370, NIH NS080514, and NIGMS grant GM080356, the Biotechnology and Biological Sciences Research Council (BB/J007498/1, BB/L01923X/1), Alzheimer Forschung Initiative (grant 14834 to C.S.) and Cancer Research UK (C20953/A18644). We also acknowledge support from RJG foundation to L.Q and A.G.K and from the American Heart Association to R.G.L. This work was made possible in part by the availability of the Optical Biology Shared Resource of the Cancer Center Support Grant (CA-62203) at the University of California, Irvine. We thank Michael McMahon (University of Dundee) for plasmids encoding wild-type Keap1.

Figures
Figure 1. Identification potent and selective SIRT2 inhibitor MIND4. A, B) Primary and counter screening of focused library of 8-nitro-5-R-quinoline and 5-nitro-8-R-quinoline derivatives using SIRT2 (A) and SIRT3 (B) biochemical deacetylation assays. Compounds were screened at single 10 μM concentration in triplicates. Selection of active inhibitors was set at indicated threshold (dotted lines) of <50% of SIRT2 remaining activity; >75% of SIRT3 remaining activity. MIND4 (compound #4) was preliminary identified as a potent selective SIRT2 inhibitor. C-E) Concentration-response tests in SIRT1 (C), SIRT2 (D) and SIRT3 (E) biochemical deacetylation assays showed a selective inhibition of SIRT2 by MIND4. F) Concentration-response activity test showed no detectable SIRT2 inhibition activity of structural analog MIND4-17. G) Structures and SIRT2 inhibition activities of MIND4 analogs. Compound SIRT2 IC50s were established in concentration-response tests in vitro.
**Figure 2. MIND4 mechanism of SIRT2 inhibition.** A) Concentration-dependent inhibition of SIRT2 activity by MIND4. B-C) Competition of MIND4 with the SIRT2 co-substrate NAD+ and with acetylated substrate, respectively. Deacetylase activity of SIRT2 was measured at several MIND4 concentrations: 0 µM (empty circles), 0.625 µM (filled circles), 1.2 µM (empty squares), 2.5 µM (filled squares), and 5 µM (triangles). Reactions were conducted at increasing concentrations of NAD+ (B) or peptide substrate (C). The best fitting inhibition model is competitive for NAD+ and non-competitive for the peptide substrate. D) Docking model of the SIRT2/MIND4 complex rationalizes isoform selective inhibition. Overlaid structures of SIRT1 (yellow) (PDB ID 4KXQ), SIRT2 (blue) (3ZGV), and SIRT3 (pink) (4FVT) are presented as cartoons. MIND4, docked in SIRT2, is shown as balls-and-sticks in light blue. Acetylated lysine peptide and non-hydrolyzable NAD+ analog (carba-NAD+), shown SIRT3-bound, are presented as pink sticks. The large SIRT2 active site cavity is displayed as a transparent blue surface.
Figure 3. Bioactivity and neuroprotective properties of MIND4. A-B) MIND4 treatment increases acetylation of $\beta$-tubulin lysine-40 (K40) in wild-type (A) and HD mutant (B) rat embryonic ST14A cells. Cells were treated with compound for 6 h, then lysates prepared and resolved by SDS-PAGE, and immunoblotted with antibodies specific to acetylated K40 acetylated and total $\beta$-tubulin. C) Quantification of $\beta$-tubulin acetylation from (A) and (B). Ratio of acetylated/total $\beta$-tubulin in wild-type (black line) and mutant HD (grey lane) was plotted against compound concentration. E-F) Effects of MIND4 on increase acetylation of SIRT2 substrates, cytoplasmic $\beta$-tubulin and histone 3 (H3), in wild-type primary cortical mouse neurons (DIV 11) treated with compound for 6 h; protein levels analyzed by immunoblotting with respective antibodies. E) Effects of MIND4 on acetylation of $\beta$-tubulin K40. Total $\beta$-tubulin levels were used as loading control. A putative compound target is preferentially expressed as a full-length SIRT2 protein (SIRT2.1 isoform). F) Effects of MIND4 on acetylation of H3 lysine-56 (K56), lysine-27 (K27), lysine-9 and lysine-14 (K9/K14). Total H3 levels used as loading control. G) MIND4 treatment protects medium spiny neurons (MSNs) in rat ex vivo brain slices against toxicity of transiently transfected mutant (73Q) N-terminus HTT fragment (mHTTex1). Yellow fluorescent protein (YFP) was used as a neuronal viability marker and co-transfected with mHTTex1 constructs (black bars). Effects are compared with survival of neurons expressing YFP plasmid alone (open bar) and expressed as the number of healthy YFP-positive MSNs per brain slice. MIND4 at the indicated concentrations (black bars) and the positive control pan-caspase inhibitor Boc-D-FMK at 100 μM (grey bar) were added directly to the tissue culture media. Statistically significant effect of MIND4 treatment was observed at 10 μM by ANOVA followed by Dunnnett’s post hoc comparison test at the p<0.05 confidence level. H) MIND4 enhanced survival of photoreceptor neurons in a Drosophila model of HD. Relative rescue of photoreceptor neurons, expressing mutant HTTex1 fragment, in flies treated vs. untreated with MIND4 at the 10 μM dose was estimated as 22.6%. * = p <0.001.
A

B

C

D

E

F

G
Figure 4. Gene expression profile and IPA analysis. Gene expression profiling and IPA analysis revealed NRF2 as the major pathway impacted by MIND4 in mutant HTT-expressing cells (Case III). A) Pathway analysis resulted in lists of IPA “Canonical Pathways,” sorted according to Fisher’s exact test right-tailed p-value. The top Canonical Pathway was the NRF2-mediated Oxidative Stress Response. This pathway had a highly significant log(p-value) = 13.496. Other pathways are shown in decreasing order of significance to the right. The orange boxes are ratios of the number of MIND4 affected genes in the pathway to the total number in the pathway altogether. B) In Case III a fold-change increase of expression of NRF2-responsive genes is shown as a function of color intensity. Large fold-changes are shaded with dark red and decreasing values are shown in lighter red. The pathway shows differential expression in NRF2 downstream targets in mutant HTT expressing cells in the presence and absence of MIND4.
A

![Graph showing various biological responses and their effects](image)

B

![Diagram illustrating the transcription factor Nrf2 pathways](image)
Figure 5. NRF2 activation properties of thiazole analogs MIND4 and MIND4-17. A-B) Treatment with MIND4 increased expression of NRF2-responsive proteins NQO1 and GCLM in wild-type (A) and in HD mutant (B) rat embryonic ST14A cells. Levels of GAPDH were used as loading control. C) Treatment with MIND4 increased stability of NRF2. COS1 cells were co-transfected with plasmids encoding NRF2-V5, KEAP1, and ß-galactosidase to monitor transfection efficiencies, and treated for 24 h with MIND4 at 10 μM or the classical NRF2 inducer sulforaphane (SFP) at 5 μM. Cell extracts were prepared, proteins were resolved on SDS-PAGE, and NRF2 levels were detected by immunoblotting with a V5 antibody. D) Comparative analysis of NRF2 activation response of NQO1 expression by the SIRT2 inhibitors MIND4 and MIND4-11 in HD mutant ST14A cells. Cells were exposed to compounds for 24 h. Levels of ß-tubulin were used as loading control. E, F) Treatment with MIND4-17 for 24 h increased expression of the NRF2-responsive proteins NQO1 and GCLM in wild-type (E) and in HD mutant (F) ST14A cells. Levels of GAPDH used a loading control. G) Concentration-dependent induction of the NRF2-responsive proteins NQO1 and GCLM in wild-type mouse cortical neurons (6 DIV) treated with MIND4 or MIND4-17 as indicated for 24 h. Protein expression was detected by immunoblotting. Levels of ß-tubulin were used as loading control. H) Treatment of primary mouse corticostriatal co-cultures with 5 μM of MIND4-17 induced time-dependent increases in the transcriptional rate of a 5x-ARE promoter-luciferase reporter. *p<0.05 by a Student’s t-test with respect to DMSO-only controls. I-L) MIND4-17 induces concentration-dependent increases in transcription of the ARE genes Nqo1 (I), Hmox1 (J) Gclc (K), and Srx1 (L) as quantified by qPCR. *p<0.05 by a Student’s t-test with respect to DMSO-only controls (“0”). M, N) Similar concentration-dependent increases in the transcription of a 5x-ARE-luciferase reporter transfected into wild-type (light grey) vs. mutant HD Q175/+ mouse neurons (black) in corticostriatal co-cultures were induced by treatment with MIND4 (M) and MIND4-17 (N) for 24 h. *p<0.05 by a Student’s t-test with respect to DMSO-only controls (“0”). O-P) Concentration-dependent induction by MIND4 (O) and MIND4-17 (P) of the NRF2-responsive NQO1 and GCLM proteins in primary mouse astroglia. Cultures were treated for 24 h with MIND4 or MIND4-17 at indicated concentrations. GFAP protein levels were used as the loading control.
Figure 6. NRF2 activating properties of MIND4-17 in microglia cells with intact or knocked down SIRT2 protein. NRF2 activation properties were tested functionally by measuring production of reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI) in LPS/TNF\textsuperscript{1} induced microglia. A) N9 microglial cells were lentivirally-transduced with shRNA for SIRT2 knock-down (sh2.1) or with a scrambled control shRNA (shCtr). SIRT2 levels were detected by immunoblotting. B-C) ROS levels in stimulated microglia with intact SIRT2 (B) or after SIRT2 knockdown (C) treated with vehicle (DMSO), MIND4 or MIND4-17. Microglia cells were stimulated with LPS and TNF for 20 h in medium supplemented with compounds at the indicated concentrations. Representative histograms of the fluorescence intensity for the ROS probe showing the overlays of vehicle (DMSO)-treated cells (filled light gray), treated with MIND4 (5 \text{M}) (dotted line) or with MIND4-17 (2.5 \text{M}) (filled dark gray). D) RNI production in stimulated microglia cells with functional SIRT2 (white bars) and SIRT2 knockdown (black bars). Cells were treated with vehicle (DMSO), MIND4, and MIND4-17 at the indicated concentrations. RNI was assessed by measurement of iNOS-dependent release of nitrates in the culture supernatants and quantified as percent of control (DMSO-treated cells). Data are presented as mean ± SD of four independent experiments. *p<0.05 and **p<0.01 by a Student's t-test.
Table 1 Legend. Gene expression analysis of MIND4-treated cells. Statistically significant expression changes of genes for Cases I-III: listed genes in bold font are upregulated; listed genes in normal font (not bold) are downregulated. Top seven Canonical Pathways are shown based on significance calculated by IPA for case III (MIND4-treated cells). Note that in Case III transcripts were predominately upregulated.

<table>
<thead>
<tr>
<th>Biochemical Pathways</th>
<th>Case I</th>
<th>Case II</th>
<th>Case III</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFK2-mediated oxidative stress response pathway</td>
<td>ACTG2, ACTC1, CAT, GSTA4, DNAJ1, KDRB3, MACC1, PKRCC2, SOL</td>
<td>ABCD4, HKMX1, ACTG2, ADAM1, MAP2K1, GATA5, KSR2, GSTA3, DNAJ1, DNAJC15</td>
<td>ABCD4, GSTP1, ADAM1, GST72, GST18, CAT, HKMX1, DNAJC15, DNAJB1, KDRB3, GSTA3, DNAJ1, DNAJC15</td>
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<tr>
<td>Glutathione-mediated detoxification</td>
<td>GSTA3, GSTG1, GSTA1, GSTT3, GSTF2</td>
<td>GSTA2, GSTA3, GSTT3, GSTP1, GST17</td>
<td>GSTA2, GSTA3, GSTT3, GSTP1, GST17</td>
</tr>
<tr>
<td>LPS1-1 mediated inhibition of ROR function</td>
<td>ACOX1, GSTA4, ALDH1A2, ALDH1B1, ALDH1A1, NADPH</td>
<td>ACOX1, ACOX4, GSTP1, ACOX1, ACOX4, GSTP1</td>
<td>ACOX1, ACOX4, GSTP1, ACOX1, ACOX4, GSTP1</td>
</tr>
<tr>
<td>Aryl/hydrocarbon receptor signaling</td>
<td>ALDH1A2, NR1F2, ALDH1A1, NFIA, ALDH1A1, NR1F2, CYP1A1, GSTA4, TOP8,</td>
<td>ALDH1A2, GSTA1, GSTT1, NR1F2, ALDH1A1, NFIA, CYP1A1, NR1F2, CYP1A1,</td>
<td>ALDH1A2, GSTA1, GSTT1, NR1F2, ALDH1A1, NFIA, CYP1A1, NR1F2, CYP1A1,</td>
</tr>
<tr>
<td>Xenobiotic metabolism signaling</td>
<td>ALDH1A2, GSTA4, ALDH1A1, NFIA, ALDH1A1, NR1F2, CYP1A1, GSTA4, TOP8,</td>
<td>ALDH1A2, GSTA4, GSTA5, NR1F2, CYP1A1, GSTA4, TOP8,</td>
<td>ALDH1A2, GSTA4, GSTA5, NR1F2, CYP1A1, GSTA4, TOP8,</td>
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Statistically significant expression changes of genes for cases I-III: genes that are underlined are upregulated; genes not underlined are downregulated. The top seven canonical pathways are shown based on significance calculated by IPA for case III (MIND4-treated cells). Note that in Case III transcripts were predominately upregulated.
References


18. Liu, L., Arun, A., Ellis, L., Peritore, C., and Donmez, G. (2013). Sirtuin 2 (SIRT2) enhances 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced nigrostriatal damage via deacetylating forkhead box O3a (Foxo3a) and activating Bim protein. The Journal of biological chemistry 287, 32307-32311.

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Materials and Methods

Compound source and storage
Compounds were procured from ChemBridge Corp. San Diego (purity QC ensured by provided NMR), dissolved in molecular biology grade dimethyl sulfoxide (DMSO) from Sigma-Aldrich to 10 mM stock concentration, aliquoted, and stored at -80 °C.

Characterization of compound-dependent inhibition of SIRT2 deacetylase activity

Compound-dependent modulation of sirtuin activity was initially assessed using the Fluor de Lys fluorescent biochemical assay (BioMol International, LP) in a 96-well format as described (Outeiro et al., 2007). Deacetylation reaction was performed at 37 °C for 1 h in the presence of human recombinant enzymes: SIRT1 (BioMol-SE-239) 1 unit/per reaction, SIRT2 (BioMol-SE-251) 5 units/per reaction, or SIRT3 (BioMol-SE-270) 5 units/per reaction, compound of interest, standard buffer, 50 μM substrate, and 500 μM NAD+ according to the manufacturer's protocol.

For analyzing the SIRT2 inhibition mechanism of MIND4 in a continuous coupled enzymatic assay with an α-tubulin peptide substrate, the recombinant enzyme was prepared and its activity analyzed as described previously (Moniot et al., 2013). The IC50 for MIND4 was determined using α-tubulin and NAD+ at 150 μM and 500 μM, respectively. The titration with NAD+ was performed at 150 μM α-tubulin peptide, and the peptide titration at 1 mM NAD+. Data analysis and fitting was done in Grafit 7 (Erithacus Software, Horley, UK).

Docking model for selective binding of MIND4 to SIRT2

For generating the SIRT2/MIND4 complex model, the compound was docked using the program FlexX of the LeadIT suite (BioSolveIT, Germany) and a SIRT2/ADP-ribose structure
(PDB ID 3ZGV) (Moniot et al., 2013); ligand omitted for the calculation) as the receptor. The MIND4 molecule, generated as a 3D SDF file in MarvinSketch (ChemAxon, Budapest, Hungary), was docked with FlexX using default parameters, i.e., hybrid enthalpy and entropy driven ligand binding, hard penalty on protein ligand clashes (maximum allowed overlap volume 3.2 Å³), and average penalty on intra-ligand clashes (clash factor 0.6). The best pose was exported and visualized in Pymol (Schrödinger LLC, Portland, USA). The overlay with SIRT1 (PDB ID 4KXQ) and with SIRT3 in complex with carba-NAD and acetylated peptide (PDB ID 4FVT) was generated using the build-in align command of Pymol.

**NRF2 stabilization assay**

COS1 cells were plated 16 h before transfection. Cells were co-transfected with plasmids encoding wild-type KEAP1 and NRF2-V5 (generous gifts from Dr. M. MacMahon and Dr. John D. Hayes, University of Dundee) at 1:1 ratio. A plasmid encoding β-galactosidase was transfected as well to monitor transfection efficiency. 24 h post-transfection cells were exposed to MIND4 or sulforaphane for 24 h, harvested, lysed, and extracts were prepared and loaded on SDS-PAGE normalized to β-gal expression activity. Samples were resolved on SDS PAGE and immunoblotted with V-5 antibody.

**Rat embryonic striatal ST14A cells**

Compound bioactivity was tested in the rat embryonic striatal cell lines ST14A, which stably express either a mutant expanded repeat (128Q) or wild-type (26Q) 546 amino acid huntingtin (HTT) fragment (generous gift of E. Cattaneo) (Ehrlich et al., 2001). ST14A cells
were propagated at 33 °C in the presence of serum. To induce neuronal differentiation cells were serum deprived and cultured at 37 °C in presence of N2 supplement (Invitrogen). Cells were treated with compounds for 24 h, unless stated otherwise, as described (Quinti et al., 2010). Please see detailed information on antibodies and immunoblotting protocol in Extended Experimental Procedures.

**Microarray data analysis**

RNA was extracted from HD mutant and wild-type ST14A cells, differentiated for 24 h and treated with vehicle (DMSO) or with 5 × M MIND4, using the RNeasy kit (Qiagen). Labeled cRNAs were prepared and hybridized to Affymetrix GeneChip Rat Genome 230 2.0 microarrays according to the manufacturer's instructions. Affymetrix CEL (intensity) files from hybridized arrays were imported into the Partek Genome Suite, Partek Incorporated, for biostatistical analysis. 2 CEL files were used for each experimental condition: wild-type (WT) untreated, MIND4 treated (WT/MIND4), mutant (MTT) untreated, and mutant (MTT) MIND4-treated (MTT/MIND4). Two-way ANOVA was performed with interaction term included and evaluated three contrasts of interest (Case I, II, and III). Gene lists were created for each of the three contrasts using the thresholds of absolute value of fold-change > 1.5 and p-value with False Discovery Rate (FDR) < 0.05. The gene list included for Case I -1765 genes, for Case II -1797 genes, and for Case III-268 genes, which were imported into Ingenuity IPA for pathway and network analyses. These analyses provided Networks (graph structures of molecules connected by relationships in the IPA knowledgebase), Functions (lists of molecules grouped together due to their contribution to a biological function) and Canonical
Pathways (molecules and relationships that participate in a biological pathway). Scores are assigned according to the probability that the genes from the user’s list might appear in the function or pathway by chance (right-tailed Fisher’s Exact Test).

**Compound tests in acutely transfected rat brain slice culture assay**

Coronal brain slices (250 μm thick) containing both cortex and striatum were prepared from CD Sprague-Dawley rat pups (Charles River) at postnatal day 10 and placed into interface culture as previously described (Reinhart et al., 2011). A biolistic device (Helios Gene Gun; Bio-Rad) was used to co-transfect the brain slices with YFP visual reporter and a mutant huntingtin plasmid containing human HTT exon-1 harboring a 73 CAG repeat to induce neurodegeneration of medium spiny neurons (MSNs). MIND4 and positive control the pancaspase inhibitor Boc-D-FMK (Sigma-Aldrich, Inc.) at 100 μM (Varma et al., 2007) were added to cultures wells at the time of slice preparation. YFP co-transfected MSNs were identified 4 days after incubation by their location within the striatum and by their characteristic dendritic arborization as previously described (Crittenden et al., 2010; Reinhart et al., 2011). Please see Extended Experimental Procedures for detailed protocol and analysis.

**Transcriptional assays in primary corticostriatal neuronal co-cultures**

Primary corticostriatal neuronal co-cultures were prepared from E18 WT or Q175/+ (Menalled et al., 2012) mouse brains as previously described (Kaltenbach et al., 2010). For 5x-ARE-luciferase reporter assays, neurons were transfected with 2.5 μg Cignal Antioxidant
Response Reporter dual luciferase plasmids (Qiagen/SABiosciences). For quantitative RT-PCR (qPCR) of ARE target genes, corticostriatal co-cultures were prepared as described (Kaltenbach et al., 2010) and after 4 days in culture treated for 6 h with the indicated compounds followed by RNA harvesting. Please see Extended Experimental Procedures for detailed protocol. Ct values were determined using primer sets against ARE genes Hmox1, Srx, Gclc and Nqo1 (Yang et al., 2012). Each sample was run in technical triplicate and relative expression expressed as fold-change over control after normalizing each sample to Ct values for GAPDH.

**Compound tests in a Drosophila model of HD**

Treatment of a Drosophila HD model with compound and efficacy analysis of the effects of MIND4 on photoreceptor neurons was performed as described (Pallos et al., 2008). The indicated numbers of flies were scored for each condition (n) with the number of ommatidia scored indicated in parentheses. Trial 1: DMSO=11(449); MIND4 1 μM=3(112); MIND4 10 μM=9(337); MIND4 30 μM=9(364). Trial 2: DMSO=8(361); MIND4 10 μM=8(292). Relative rescue of photoreceptor neurons in flies treated vs. untreated with MIND4 at 10 μM dose was estimated for Trial 1 and Trial 2 as 22.6% and 20.7%; t-test significance for Trial 1 was p <0.001 and for Trial 2 was p<0.02.

**Compound tests using ROS/RNI assays in stimulated microglia cells**

N9 microglial cells lentiviral-transduced with shRNA for SIRT2 knock-down or with a scrambled control shRNA were cultured in RPMI medium containing Glutamax (Invitrogen)
and supplemented with 10% FBS (endotoxin levels lower than 10 EU/ml). Cells were plated in 96-well plates (5x10⁴/well) and cultured overnight before stimulation with LPS (100 ng/ml) and TNF (10 ng/ml) for 20 h in medium supplemented with DMSO or with the tested compounds. ROS levels were detected by flow cytometry after microglia incubation with 10 μM 5-(and-6)-chloromethyl-2’,7’-dichlorodihydrofluorescein diacetate, acetyl ester (CM-H₂DCFDA) (Invitrogen) for 20 min. The production of NO by iNOS was measured indirectly by assaying nitrites in the culture supernatant using the Griess reaction. Briefly, 100 μl of supernatants was incubated with an equal amount of Griess reagent (1% sulphanilamide, 0.1% naphthylethlenediamine in 2% phosphoric acid solution) and the absorbance read at 550 nm after 20 min of incubation at room temperature.

Author Contributions.

L.Q. conducted identification, characterization, and analysis of compound properties, was involved in manuscript preparation; D.L. and N.A.R. assisted with in vitro experiments; M.M.M. supervised compound characterization studies in primary neurons and astroglia; M.C. performed IPA and identified NRF2 activation property of MIND4, R.G.L. assisted with gene expression analysis; J.E.L. performed the microarray experiment and assisted with analysis; H.R. and R.L.C. performed microarray analysis in primary neurons; A.D.K. and S.D.N, planned and performed the experiments in NRF2 stabilization, A.D.K. participated in writing and editing of manuscript; T.F.P. tested compound effects on ROS/RNI in microglia; M.J.V.K. performed compound NRF2 transcriptional profiling in primary neuronal culture, L.S.K. tested MIND4 in brain slices; D. C. L. supervised the experiments, analyzed data, and edited
the manuscript; J.P and J.L.M. were involved in the Drosophila studies; J.L.M. edited the manuscript; S.M., C.S. characterized compound SIRT2 inhibition activity, assisted by L.M.; C.S. edited manuscript; E.S. analyzed compound structures and provided chemistry expertise; R.B. performed the docking and modeling studies; L.M.T. was involved in planning transcriptional studies, data analysis, manuscript preparation; A.G.K. planned, organized, was involved in data mining and analysis, manuscript writing and preparation. L.Q., M.C., and S.M. contribute equally to the work.
Appendix Two

Tables
Table 3.7: HD vs CTL neural RNA-Seq DEGs and highlighted mouse striatal development genes.

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Adjusted p-value</th>
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