ARTIGO DE REVISÃO/REVIEW ARTICLE

Branaplam as a Promising Splicing Modulator: From Spinal Muscular Atrophy to Huntington's Disease

Branaplam como um Promissor Modulador de *Splicing*: Da Atrofia Muscular Espinhal à Doença de Huntington

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Abstract

RNA-targeting splicing modulators have revolutionized modern medicine by allowing reversible regulations of gene expression. Branaplam was the first molecule found to specifically modulate a splicing behaviour at a particular splice site. Originally, branaplam was developed as a splicing modulator for spinal muscular atrophy (SMA), the second most common autosomal recessive disease and the primary cause of genetic infant mortality. More recently, its use in Huntington's disease (HD), a fatal autosomal dominant neurodegenerative disease with limited symptomatic control, has been investigated. This review comprehensively analyzes branaplam's development program in both clinical conditions mentioned, projecting some of the aspects that may require further investigation when considering splicing modulators, as a therapeutic class, in these diseases.

Resumo

Os moduladores de *splicing*, que têm como alvo o RNA, revolucionaram a medicina moderna ao permitirem a regulação de expressão genética de forma reversível. A primeira molécula encontrada com a capacidade de alterar um processo de *splicing* particular num local específico foi o branaplam. Inicialmente, o branaplam foi desenvolvido como um modulador de *splicing* para a atrofia muscular espinhal (AME), a segunda doença autossómica recessiva mais comum e a principal causa de mortalidade infantil genética. Mais recentemente, foi investigada a sua utilização na doença de Huntington (DH), uma doença neurodegenerativa autossómica dominante fatal, com controlo sintomático limitado. Nesta revisão analisa-se, de forma abrangente, o programa de desenvolvimento do branaplam em ambas as situações clínicas mencionadas, projetando-se alguns dos aspetos que podem carecer de investigação futura, quando se consideram os moduladores de *splicing*, como classe terapêutica, nestas doenças.

1. Introduction

The approval of several RNA-targeting compounds in the past two decades has broken new ground in drug development territory by expanding the therapeutic range to the previous "undruggable" RNA transcripts which comprise 90% of the human genome.[1] A major perk of RNA-targeting therapies stems from their ability to act upon an early step in disease expression without permanently altering the genome. Belonging to this novel therapeutic class are splicing modulators. They operate upon precursor messenger RNA (pre-mRNA) and its processing and have already been approved for the treatment of several genetic diseases, including Duchenne muscular dystrophy and spinal muscular atrophy (SMA).[2]

Two main classes have been used in clinically validated splicing modulation: antisense oligonucleotides (ASOs), short single stranded oligonucleotides which act by binding directly to RNA transcripts through Watson-Crick base-pairing, and small molecules, organic compounds with a low molecular weight that act by binding to structural pockets of folded higher-order RNAs.[3] ASOs were the first splicing modulators invented as well as the first approved for the treatment of human diseases.[4] However, since they are neither orally available nor accessible to the central nervous system (CNS) they fall short in the long-term treatment of diseases, particularly in the treatment of neurological conditions, where they require invasive administrations. On the other hand, small molecule splicing modulators have been increasingly sought after given their oral bioavailability and systemic distribution.[5]

Branaplam is an orally bioavailable, systemically acting, small molecule and the first compound found to specifically modify a splicing behaviour at a particular splice site.[6] To date, branaplam has been explored for the treatment of two distinct diseases: first SMA, and more recently Huntington's disease (HD). There are few of considerable therapeutic options available for these conditions, with only three approved disease modifying therapies (DMTs) for SMA, them being two splicing modulators and a gene therapy, and no approved DMTs for HD.[7,8] Despite the unique aspects surrounding the discovery and development of this RNA-targeting small molecule, there is a lack of branaplam-focused reviews. This review aims to address this gap, at the same time highlighting, with the case of branaplam, the potential for RNA-targeting small molecules to reform the DMTs' arsenal.

2. Methodology

A review of literature was conducted using the PubMed, ScienceDirect and ClinicalTrials.gov databases. The keywords used were "RNA splicing", "splicing modulators", "branaplam", "LMI070", "NVS-SM1", "spinal muscular atrophy", and "Huntington´s disease". Articles were retrospectively searched from April 2023 to August 1988. The applied time frame was chosen due to splicing modulators being first discovered in August 1988. A first screening was performed based on article type (reviews, journal articles, clinical trials and conference abstracts), language (English), year of publication, title and abstract. The identified articles were further selected according to the quality and relevance of content, with 21 being ultimately included.

A supplemental manual search was conducted on Google Search to identify further relevant data from companies' announcements and news releases, of which 11 were selected. A recent conference held on March 2022 by the Huntington's Disease Youth Organization, where updates on branaplam's development were provided, was also included.

3. Branaplam: a splicing modulator of two genetic diseases

Since genetic diseases are generally brough on by mutations in specific genes, they are attractive candidates for molecular-based therapies, such as splicing modulation. One way in which splicing modulation can be used in the treatment of genetic diseases is by manipulating alternative splicing (AS). The manipulation of AS is particularly interesting, as it can both be used to increase or decrease the amount of a specific protein isoform. This is because, while splicing modulators can preponderate the production of a certain protein isoform, they can also suppress the expression of a particular gene by introducing premature stop codons (PTCs) in its messenger RNA (mRNA) and thus triggering nonsense-mediated mRNA decay (NMD).[2]

The small molecule branaplam has been explored for the treatment of two very different neurogenetic diseases – SMA, and, more recently, HD (**Fig. 1**). Branaplam is an intriguing example amongst splicing modulators, as it can modulate AS in the two mentioned ways for the

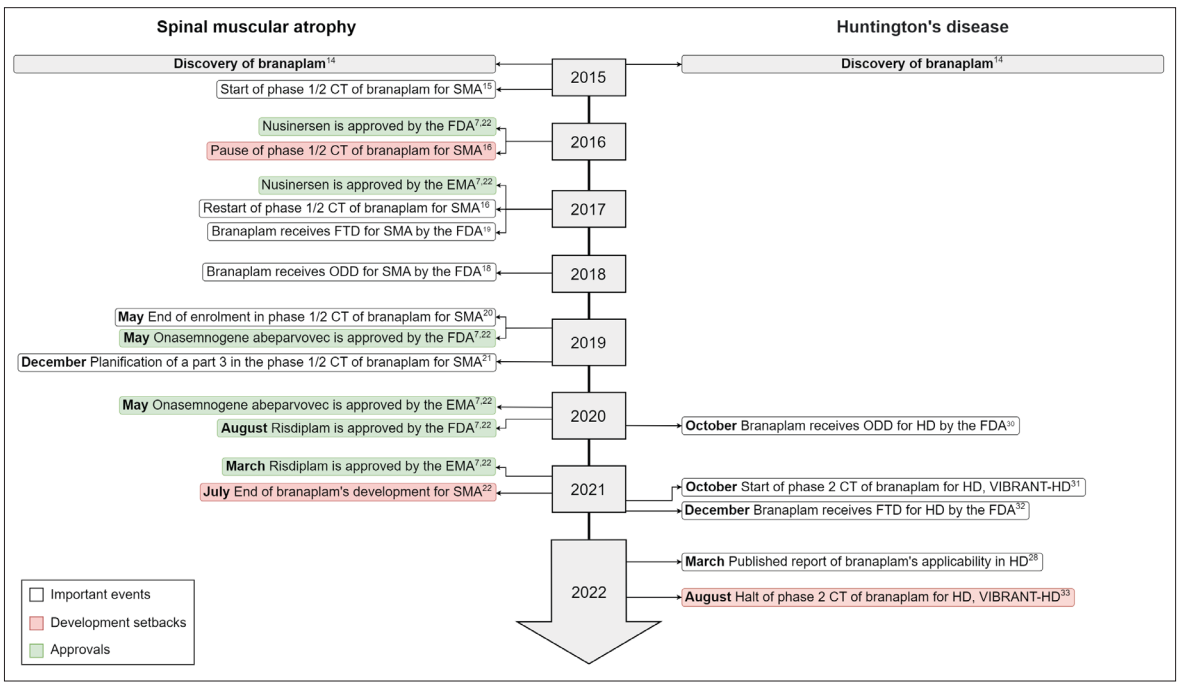

Figure 1. Timeline of branaplam's development and other relevant events.

CT – clinical trial; EMA – European Medicines Agency; FDA – Food and Drug Administration; FTD – fast track designation; HD – Huntington's disease; ODD – orphan drug designation; SMA – spinal muscular atrophy.

potential treatment of the two distinct diseases. Whereas in SMA branaplam has been shown to increase the amount of deficient full-length survival motor neuron protein (FL-SMN), in HD it could reduce the production of toxic mutant huntingtin (mHTT) protein.

3.1. Branaplam and spinal muscular atrophy

3.1.1. Spinal muscular atrophy pathophysiology

SMA is an autosomal recessive neuromuscular disease where there is a progressive degeneration of alpha motor neurons in the spinal cord, due to biallelic loss-of-function mutations of the *SMN1* gene. In 95% of cases, loss-of-function is caused by a homozygous deletion of *SMN1*, with the remaining 5% cases being compound heterozygous at the *SMN1* locus.[9] When present, the *SMN1* gene is the main producer of survival motor neuron (SMN) protein, a ubiquitously expressed 294-aminoacid polypeptide vital for survival of all cell types, though being more abundant in certain tissues, such as the brain and spinal cord.[10]

The *SMN1* gene, approximately 20kb in length, is composed by 9 exons, that is exon 1, 2a, 2b, 3, 4, 5, 6, 7 and 8, with exon 8 remaining untranslated.[9] Located on chromosome 5q13, it belongs to a 500kb inverted duplication termed SMA region, a region of high genomic instability containing numerous protein-coding genes and pseudogenes.[11] The protein-coding gene *SMN1*, telomeric, and its mirrored copy *SMN2*, centromeric, are 99% homologous, only differing in 5 nucleotides, one being the exchange of a cytosine for a thymine in codon 280 in the sixth position of *SMN2* exon 7. Despite being transcriptionally silent, this C-to-T transition is believed to enhance an extended inhibitory context at the splicing sites of exon 7, affecting the already compromised recruitment of U1 small nuclear RNA (snRNP) to the suboptimal exon 7 5' splice site (5'ss). The hindered binding of U1 snRNP, which interacts by complementarity with the sequence of the 5'ss to initiate splicing, favours an AS where exon 7 is excluded in about 90% of the *SMN2* transcripts.[9,12] These incomplete transcripts, produce a truncated protein lacking exon 7 (SMNΔ7), which in unstable and has a reduced functionality. Because around 10% of *SMN2* transcripts do retain exon 7, thus producing FL-SNM, *SMN1* loss-of-function can be partially rescued by the presence of *SMN2* (**Fig. 2**). Therefore, even though SMA patients have at least one copy of *SMN2* gene, they are still unable to produce the necessary amount of SMN protein to prevent disease. SMA's severity is, in general, inversely correlated with the amount of SMN production and the number of *SMN2* genes.[9]

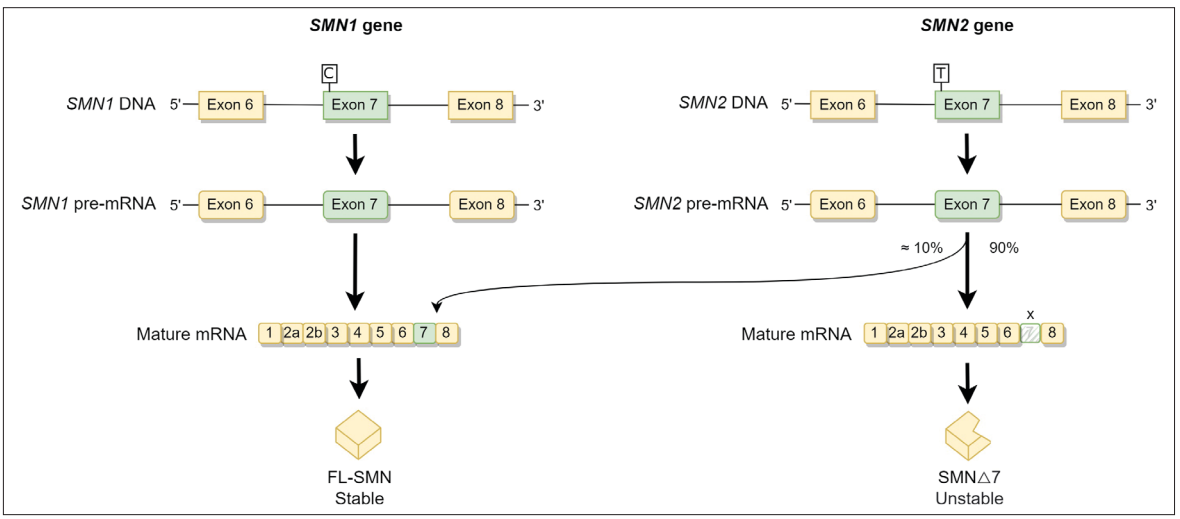

Figure 2. Effect of the C-to-T transition in splicing of exon 7.
FL-SMN – full-length SMN; SMNΔ7 – SMN protein lacking exon 7.

SMN is a ubiquitously expressed protein vital in numerous cellular processes and pathways, with a highest expression during fetal development. The first and most studied function of SMN protein was its role in the assembly, metabolism, and transport of diverse classes of ribonucleoproteins, such as the snRNPs implicated in pre-mRNA spicing by the spliceosome. Recent studies have shown SMN to be involved in other processes including the trafficking and transport of RNA transcripts, local protein translation, cytoskeletal dynamics, endocytosis and autophagy.[10]

With SMN being present in all cell and tissues, the systemic nature of SMA disease is understandable. In effect, besides the neurons, abnormally low levels of SMN in humans have been shown to affect the skeletal muscle, heart, autonomic nervous system, vasculature, gastrointestinal tract, liver, kidney, pancreas, spleen and even the immune system.[13] A remaining question is why the reduction of a protein with a such broad functionality ends up predominantly impacting the motor neurons. Possible explanations suggest this may be due to the unique nature and homeostasis of neuron cells, given that many functions of the SMN are notably involved in neuronal activity. For instance, SMN's involvement in transcript transportation can, in SMA patients, lead to a deficient mRNA transportation along dendrites and axons, hindering the rapid protein turnover required in the distal regions of the motor neurons. Furthermore, problems in the cytoskeleton may impede the formation of growth cones during neuronal development. Also, it is easy to see how the role of SMN in endocytosis could influence the functionality of motor neurons, as it is particularly important for the function of synapses, such as the ones positioned at the neuromuscular junctions.[10]

3.1.2. The rise and fall of branaplam's development for SMA

Discovery and exploration

In 2015, the continuous search for small molecule splicing modulators of *SMN2* led to the identification of four orally available small molecules by Novartis: NVS-SM1, NVS-SM2, and inactive analogues NVS-SM3 and NVS-SM4. These resulted from a compound optimization following a high-throughput screening of around $1.4x10^6$ compounds, with a hit rate less than 1%, where an identified pyridazine class of orally active small molecules was found to elevate levels of FL-SMN via exon 7 inclusion. The two active compounds, NVS-SM1 and NVS-SM2, which had already shown a significant increase of exon 7 inclusion and SMN protein expression in both SMA patient fibroblasts and SMNΔ7 mouse myoblasts during compound optimization, then went through pharmacokinetic (PK) profiling in rodents, exhibiting high plasma exposure, good bioavailability, and good brain distribution.[14]

NVS-SM1, now mostly known as branaplam, displayed efficacy at lower doses and exposures, thus being the chosen analogue for additional studies. In the severe phenotype SMNΔ7 mouse models, branaplam showed a dose-dependent increase of FL-SMN production in

the brain, as well as durable phenotype improvements following early postnatal administrations. Additional evaluation of possible off-target effects was conducted by analysing junction-level and gene expression changes following branaplam treatment of human fibroblasts. Splicing was altered in 35 genes of which only five had gene-level changes in expression (*ADAM12*, *ANXA11*, *APPL2*, *RCC1* and *SREK1*), revealing branaplam to be a highly selective splicing modulator.[14]

Subsequent studies were performed aiming to understand the compounds' mechanism of action. First, since the splicing modulation by branaplam acted upon a restricted number of genes, efforts focused on finding a cis-acting element common among them. The first region in question was the 5' end of exon 7, around the location of the C-T polymorphism. However, a minigene with a similar exon-skiping polymorphism was not responsive to NVS-SM2 (branaplam analogue chosen for its superior *in vitro* potency). Later chimeric constructs coupled with analysis of mutations causing NVS-SM2-mediated splicing disruption, established NVS-SM2-responsiveness to be dependent upon sequences around the exon-intron junction, particularly at the 5'ss. This suggested an association between branaplam and the RNA:RNA duplex involved in U1 snRNP interaction with the exon 7 5'ss.[14]

In effect, further studies of the flaking sequences surrounding the 5'ss of branaplam-sensitive genes, found them to be enriched for a rare nGA motif at the 5'ss's exon portion. Combination of data from biophysical studies, computional models and high-resolution crystallography finally consolidated that the active compounds, NVS-SM2 and branaplam, acted by binding to the U1 snRNP–pre-mRNA complex in a sequence selective manner. Ultimately, this enhanced affinity of U1 snRNP for the 5'ss of exon 7, thus promoting exon 7 inclusion and enhanced of FL-SMN mRNA and FL-SMN protein production (**Fig. 3**).[14] As a result, branaplam became the first molecule known to specifically alter a splicing behaviour at a particular splice site.[6]

Clinical trials

In 2015, in view of the preclinical studies, Novartis launched an open-label, multi-part, first-in-human clinical trial (CT) of branaplam for SMA (NCT02268552) which is currently ongoing though not recruiting. This phase 1/2 CT aimed to assess branaplam's safety, tolerability, and early effectiveness as well as its PK and pharmacodynamics (PD). In part 1 of the CT, the enrolled participants, required to be type I SMA patients younger than 6 months, were administered weekly ascending doses. The purpose was to establish a maximum tolerated dose that would in turn determine the weekly doses (up to three) that would be tested in part 2, in a new set of patients.[15]

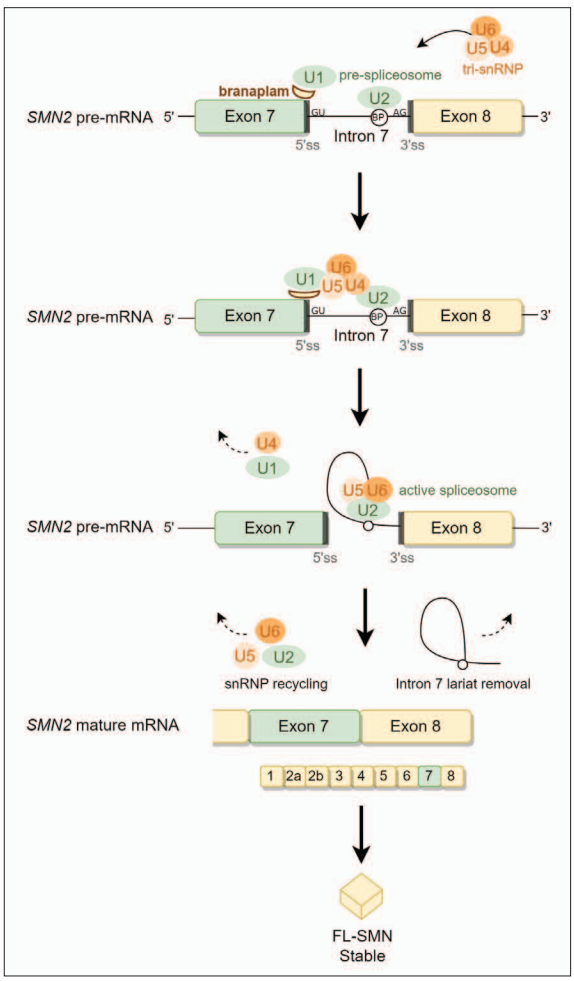

Figure 3. Effect of branaplam in *SMN2* splicing.

BP – branch point adenosine; FL-SMN – full-length SMN; snRNP – small nuclear ribonucleoproteins; ss – splice site; tri-RNP – triple small nuclear ribonucleoprotein.

In 2016, this trial was paused due to safety concerns raised following the results of an animal safety study: animals treated with a daily regimen of branaplam began to show signs of nerve injury as well as damage to the spinal cord, testes, and kidney blood vessels. The CT was later resumed in 2017 ensuring a close monitoring of enrolled patients and adding routine nerve tests as a safety precaution.[16] Interim results revealed most ad-

verse effects to be mild, manageable, and reversible. It was reported a loss of motor function following dose lowering precipitated by the preclinical toxicology findings. Notwithstanding, motor function was restored in some patients after the resumption of the previous dose.[17] Similarly, in 2017, the US Food and Drug Administration (FDA) granted branaplam a fast track designation (FTD) in type 1 SMA and in 2018 an orphan drug designation (ODD) for the treatment of SMA.[18,19]

In May 2019, Novartis announced the termination of the enrolment in the phase 1/2 CT with a total of 32 patients, 25 having been enrolled in phase 2.[20] In December, an update was issued informing that the trial was progressing well, with a total of 29 participants receiving study treatment. Furthermore, Novartis mentioned the planification of a part 3 intended to evaluate long-term safety, tolerability, and effectiveness of extended treatment, meant to include participants from parts 1 and 2 that had received treatment for at least 52 weeks.[21]

In 2021, after an almost decade long investment, the discontinuation of branaplam's clinical development for SMA was announced, citing two main motives. First, the broadening of available approved DMTs for SMA, that is two splicing modulators, the ASO nusinersen by Biogen and the daily administered orally available small molecule risdiplam, by Roche, and its own one-shot gene therapy, onasemnogene abeparvovec. Second, the belief that branaplam would not offer a significantly distinct therapeutic solution for SMA, unlike the company's gene therapy. Onasemnogene abeparvovec is a viral vector-based *SMN1* gene replacement therapy. It received approval from the FDA in 2019 and from the European Medicines Agency in 2020 for the treatment of children under two years old.[7,22]

Since the decision to terminate branaplam's development in SMA was unrelated to safety or efficacy issues, the continuation of treatment of the enrolled patients was encouraged, until an alternative therapy could be arranged.[22] Branaplam's phase 1/2 CT is currently anticipated to conclude in 2023.[15] Even though results have not yet been disclosed, in the International Young Adult Virtual Congress held in March 2022 by the Huntington´s Disease Youth Organization, a senior clinical development director stated branaplam has been well-tolerated and effective in type 1 SMA infants, with treatment being carried out for over 6 years in some patients.[23]

3.2. Branaplam and Huntington's disease

3.2.1. Huntington's disease physiopathology

HD is caused by the production of mHTT, a mutated form of Huntingtin (HTT) protein derived from an expansion of CAG repeats in exon 1 of the *HTT* gene. HTT is a ubiquitously expressed 350 kDa protein, present in higher levels in the neurons of the CNS, especially in striatal and corticostriatal neurons. It contains a polyglutamine sequence at the NH2 terminus and multiple HEAT repeats sequences, important for protein–protein interactions, such as the ones implicated in intracellular trafficking.[24]

HTT has been tied to a multitude of physiological functions. First, it is crucial in embryonic development, namely neurogenesis. For instance, HTT knockout mice die prior to birth, before the development of the CNS. Second, HTT is a well-characterized scaffolding protein, vital in the regulation of several intracellular trafficking processes, as well as signalling pathways. Third, it functions as a transcription regulator of several targets, the most known being the brain-derived neurotrophic factor, a factor which promotes striatal neuron survival. And finally, HTT plays an important role in synaptic connectivity, particularly in the correct formation of excitatory synapses.[24]

The number of expanded *HTT CAG* repeats in HD is both somatically and meiotically unstable, with a tendency to gradually expand over a lifetime and between generations. The degree of instability varies. For instance, meiotic expansion is more frequently observed in paternal line of inheritance, as spermatogenesis is more unstable compared to oogenesis.[25] Somatic expansion also differs between tissues, being particularly noticeable in the neurons of the striatum and cortex, where trinucleotide repeats can become greater than a thousand, whilst being relatively stable in other tissues such as in the cerebellum and blood cells.[24,26]

The mHTT protein has been linked to several mechanisms of pathogenesis. Characteristically, in HD there is an accumulation of pathogenic N-terminal fragments, derived from the proteolysis of mHTT by caspases or other proteases. Another major pathogenic mechanism in HD is transcription dysregulation. Namely, mHTT has been shown to interact with transcription regulators involved in cell proliferation, cell survival and metabolism. In fact, the increased susceptibility of the striatum could be related to the impaired transcription of the brain-derived

neurotrophic factor, which is reduced in HD. Besides, mHTT motivates alterations in gene expression by deregulating histones, triggering DNA methylation, and influencing gene expression through modifications in miRNA production. Moreover, it impacts synaptic plasticity by impairing the delivery of synaptic and postsynaptic vesicles. Additional mHTT-associated functional defects include axonal transport deficiencies, mitochondrial and neuroglia dysfunction, and impairment of protein degradation systems. Even though peripheric tissues have been less explored than the CNS, other organ dysfunctions are often present in HD patients, such as skeletal muscle wasting and cardiac failure. These are most likely due to the ubiquitous expression of mHTT and reinforce the importance of future systemically acting DMTs.[24,27]

3.2.2. The rise and halt of branaplam's development for HD

Discovery and exploration

In a study published in March 2022, Novartis described the discovery of branaplam's applicability in HD, as it was able to reduce levels of HTT and mHTT. It was first noticed following the revaluation of splicing changes in SH-SY5Y human neuroblastoma cells treated with 10nM of branaplam, a dose 5 times higher than the half maximal concentration effect for SMN *in vitro*.[28] Notably, there were 94 more pseudoexon splice-in events than in the previous report. Pseudoexons are a type of sequences present in the pre-mRNA that despite looking like exonic sequences are usually ignored by the splicing machinery. These sequences are sometimes implicated in disease pathogenesis and have partaken in novel therapeutic strategies.[29] Still, in this experiment, their splicing appeared to be mostly reversible.[28]

A second experiment aiming to reassess the reversibility of such events in SH-SY5Y cells, re-demonstrated mostly temporary and reservable pseudoexon splice-in events, except for the events concerning the HTT and the tubulin folding cofactor A genes. In parallel, HTT was one of the genes documented to be downregulated by branaplam. Further *in vitro* analyses of branaplam's actions in SH-SY5Y cells documented a dose-dependent increase in exon 50a inclusion, as well as a dose-dependent decrease of HTT transcripts, up to 30 to 95%, with concomitant reduction of HTT protein of up to 55%. Comparably, there was also pseudoexon 50a inclusion in HD patient cell lines, resulting in a down-regulation of mHHT protein, reaching a maximum reduction of 70%.[28]

In common, the spliced-in pseudoexons were highly enriched with a nGA motif at their 3'-end and were mainly predicted to introduce frameshifts or PTCs. In HTT specifically, branaplam triggered the splice-in of pseudoexon 50a (a pseudoexon between exons 49 and 50). The inclusion was later confirmed to induce a frameshift with subsequent introduction of several PTCs both in the pseudoexon and downstream exons,

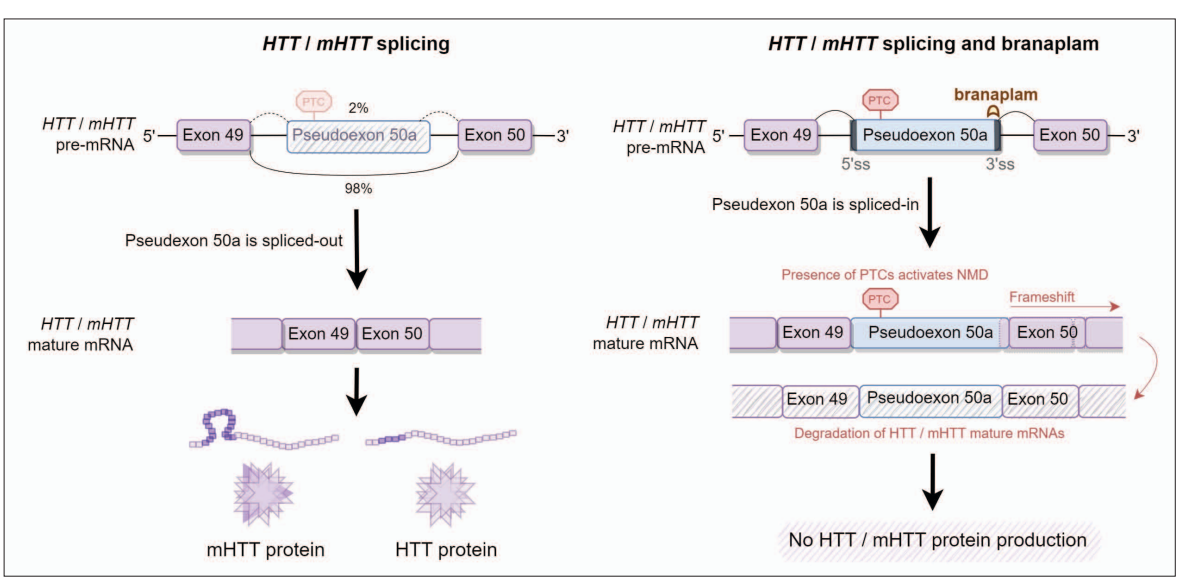

Figure 4. Effect of branaplam in *HTT* and *mHTT* splicing.

HTT – huntingtin gene; *mHTT* – mutated huntingtin gene; NMD – nonsense mediated decay; PTC – premature stop codon; ss – splice site.

ultimately leading to NMD and HTT lowering. Through an RNA sequencing search engine, scientist found pseudexon 50a inclusion to be a rare splicing event, occurring at a 2% rate (**Fig. 4**). As it was only noted the existence of a single, very rare, SNP in the exon-intron section of compound sensitive region, which had a low estimated frequency of around 0.0026, branaplam's applicability in the HD population was reinforced.[28]

Pseudoexon 50a inclusion was also observed in animal models. In BacHD mice, there was pseudoexon 50a inclusion both in central and peripheral tissues, along with a reversible, dose-dependent reduction of mHTT up to 40%-45% in the striatum and cortex. The concentration ratio between the cerebellum and the plasma was 1.5, indicating a good brain distribution. Similarly, in dog and non-human primates branaplam was found to distribute into crucial regions of HD's pathology, such as the caudate and the putamen. Functional rescue was observed following the intermittent treatment of BacHD mice. In fact, branaplam-treated BacHD mice showed a comparable performance to the vehicle-treated wild-type mice in the narrow beam test, a test used in mice to reveal subtle motor deficits in coordination, gait, and balance.[28]

Further solidifying the potential of branaplam for HD was the confirmation of pseudoexon 50a inclusion and HTT mRNA reduction to about 40% baseline in the blood samples of once-weekly treated Type I SMA infants. Hence transactability, along with tolerability, would be likely in branaplam treated HD patients.[28]

Clinical trials

Even though the initial report on branaplam's research for HD was only published in the year 2022, Novartis had already announced in October 2020 branaplam's granting of ODD for HD by the FDA.[30] Prior to phase 2 CTs, despite having comparable data from branaplam's development in SMA, Novartis performed a phase 1 placebo-controlled CT with 32 healthy volunteers aiming to evaluate safety, tolerability, PK and PD. Since a single dose of branaplam was able to significantly reduce both HTT and *HTT* mRNA levels for about a week, similar to SMA, a weekly dosing of branaplam for HD was supported.[23]

In October 2021, Novartis started a phase 2b, randomized, double blinded, placebo-controlled CT, VIBRANT-HD (NCT05111249), to evaluate branaplam in HD patients.[31] The main goals were to further evaluate safety, tolerability, PK and PD of weekly administrations of branaplam in 75 individuals between the ages of 25 and 75 years with greater than 40 CAG repeats and early HD. The trial also aimed to find a safe and well-tolerated dose of branaplam capable of decreasing mHTT in the cerebrospinal fluid enough to provide a therapeutic benefit, a reduction estimated to be between 35 and 50%.[23] The CT is currently active, though not recruiting, and is predicted to complete in February 2025.[31]

In December 2021, Novartis announced branaplam had received a FTD from the FDA for the treatment of HD and that it would be a part of the company's pipeline investigational program.[32]

In August 2022, branaplam suffered yet another setback. Novartis announced a temporary dose suspension of VIBRANT-HD following a recommendation from the Data Monitoring Committee which had documented several findings of potential peripheral neuropathy in some of the enrolled participants. Patient monitoring continued until, in December 2022, the promoter announced the formal cessation of the clinical trial,[33] suspending, for the time being, the investigation of branaplam as a therapeutic option for HD.

4. Conclusion and future perspectives

Targeting RNA is a growing therapeutic opportunity for several diseases. Within this new field lies mRNA targeting by splicing modulators, where branaplam is included. Despite its setbacks, evidence encourage the further exploration of branaplam as a DMT for SMA and HD, most likely in a clinical context different from the one studied so far. First, both are devastating neurogenetic diseases with lifelong implications, therefore an orally available, CNS-penetrant small molecule would fit their chronic needs. Second, both diseases have demonstrated systemic dysfunctions, therefore benefiting from systemically acting compounds, as opposed to ASOs, which exclusively target the CNS. Third, despite the recent halt in HD research due to toxicity concerns, there were no major safety concerns on the treatment of type I SMA patients, with some being treated for over 6 years. This, along with the significant lowering of *HTT* mRNA blood levels in chronically treated patients, raises hopes for its long-term transactability and tolerability.[34] Lastly, a future combination of branaplam with other compounds, such as risdiplam[35] could be advantageous, as it would not only provide multi-system acting

therapies, but also potentially minimize the impact of off-target dose-dependent adverse effects by reducing each of the treatment doses.

Ultimately, branaplam remains a breakthrough in splicing modulation. The future may bring new perspectives for this pharmacological class. ■

Contributorship Statement / Declaração de Contribuição

BG: Design and execution of the study, elaboration of the manuscript.

JAR: Manuscript review and approval.

FP: Design and supervision of the study, manuscript review and final approval.

Responsabilidades Éticas

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