Letter to Editor

HIV Peptide-Inspired Synthetic Polymer Hybrids against Huntington's Disease: Are We Closer to a Therapeutic Breakthrough?

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Dear Editor,

From George Huntington's initial observations of chorea in the people of Long Island to the discovery of chromosome 4 as its genetic source, the journey toward treating Huntington's disease (HD) has been filled with both enlightenments and dilemmas. The Htt gene plays an indispensable role in many cellular processes, which itself becomes a complexity that makes finding a cure quite difficult.

Among the pathways Htt engages in, the RE1-Silencing Transcription Factor (REST) pathway is particularly crucial. REST silences neuron-specific genes in non-neuronal cells by recruiting co-repressors and histone-modifying enzymes [1]. In neurons, Htt suppresses REST, enabling neuronal genes to function freely and allowing neurons to retain their neuronal identity. Another key pathway is the cAMP Response Element-Binding (CREB) pathway, which, with its coactivator CBP, activates survival-promoting genes in neurons. This CREB-CBP interaction is enabled by Htt [2].

In HD, patients possess both normal and mutant Htt (mHtt) gene, making complete Htt removal unfeasible, as its normal form is essential as explained earlier. This dual role of Htt introduces layered complexity in the search for a cure. Thus, instead of aiming for a cure, we are left managing symptoms—a task that, in recent times, has also become increasingly troublesome. While3 promising solutions like gene silencing with antisense oligonucleotides (ASOs)—small nucleotide sequences that bind to and silence disease-causing RNA—show potential, significant obstacles remain. These obstacles are difficulties in crossing the blood brain barrier (BBB), concerns over toxicity, and the multifaceted nature of HD itself.

A key obstacle is the rapid clearance of these therapeutic molecules, as their small size makes them prone to easy excretion. The brief half-life of such therapeutics has prompted the recent exploration of a new avenue. Valosin-containing protein (VCP) is a component of ubiquitin-proteasome system (UPS) that clears protein debris. Mosfolded mHtt protein aggregates interact with VCP disrupting its typical role. This leads to accumulation of VCP in mitochondria triggering subsequent neuronal death [3]. An invention of peptide HV3, derived from the HIV-TAT sequence, targets VCP/mHtt interaction and avoids its neuro-disruptive fate [4]. However, HV3's low molecular weight results in its clearance just like ASOs [5]. This low half-life of HV3s has now carried us to a novel discovery of synthetic HV3-mimicking protein-like polymers (PLPs) for enhanced therapeutic potential [6].

To generate PLPs, the HV3 sequence is modified by: (i) substituting cysteine with serine, (ii) adding arginine or lysine residues, and (iii) conjugating with a norbornene-hexanoic derivative [6]. Among four PLP variants made (P 1-4), P1 exhibited the highest efficacy, significantly improving viability in HdhQ111 cells ($P < 0.0001$) under stress conditions and effectively inhibiting VCP-mHtt binding in HEK 293T cells. It also demonstrated superior cellular uptake and stability, establishing it as a promising candidate for in vivo studies at a therapeutic dose of 3 mg/kg, comparable to HV3-TAT [6].

This discovery of HV3-like PLPs mark an intriguing leap forward, yet several limitations warrant careful consideration. The true measure of these modifications will be how well they perform in more complex in vivo environments as mHtt's cellular manifestations are notoriously tricky. The relatively direct strategy of targeting VCP/mHtt aggregation might overlook the broader and perhaps more consequential Htt-mediated dysregulations at fundamental level. Such therapy that manages mitochondrial survival might still fall short in addressing the full spectrum of HD pathophysiology.

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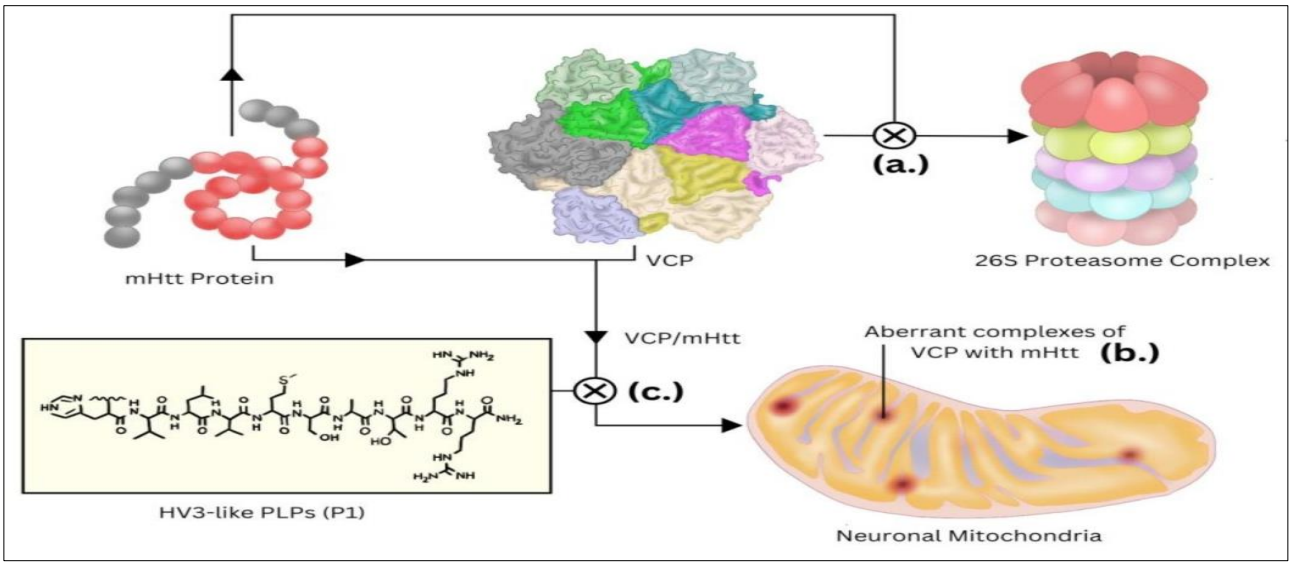

Figure 1: PLPs in mitigating mHtt-mediated mitophagy. (a) VCP's natural role in facilitating proteasome-assisted protein degradation is disrupted by mHtt. (b) mHtt-VCP complexes accumulate within neuronal mitochondria, triggering mitophagy. (c) PLPs inhibit MHtt-VCP interactions, preserving VCP's normal function and preventing mitochondrial accumulation and subsequent neuronal loss.

This, in turn prompts critical questions: Can systemic delivery of PLPs achieve sufficient therapeutic effect across the BBB? Will the peptides' engineered stability endure long-term? Most importantly, can targeting VCP/mHtt yield meaningful impact in a disease as complex as HD? While early results are promising, the clinical viability of these strategies remains uncertain.

Definitions, Acronyms, Abbreviations

ASOs: Antisense Oligonucleotides, BBB: Blood Brain Barrier, CBP: CREB-Binding Protein, CREB: cAMP Response Element-Binding, HD: Huntington's Disease, HEK 293T: Human Embryonic Kidney 293T cells, HdhQ111: Mouse model for Huntington's Disease, HV3: HIV-TAT-derived peptide, Htt: Huntingtin, mHtt: Mutant Huntingtin, PLPs: Protein-like Polymers, P1-4: PLP variants from 1 to 4, REST: RE1-Silencing Transcription Factor, TAT: Trans-Activator of Transcription (HIV), UPS: Ubiquitin-Proteasome System, VCP: Valosin-containing Protein.

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