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REVIEW ARTICLE

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Modern approaches for modelling dystonia and Huntington's disease in vitro and in vivo

Olga A. Zhunina[1] | **Nikita G. Yabbarov**[1] | **Alexander N. Orekhov**[2,3] | **Alexey V. Deykin**[4]

[1]JSC "Russian Research Center for Molecular Diagnostics and Therapy", Moscow, Russia

[2]Laboratory of Angiopathology, Institute of General Pathology and Pathophysiology, Moscow, Russia

[3]Institute for Atherosclerosis Research, Skolkovo Innovative Center, Moscow, Russia

[4]Institute of Gene Biology, Moscow, Russia

Correspondence
Alexander N. Orekhov, Laboratory of Angiopathology, Institute of General Pathology and Pathophysiology, 125315 Moscow, Russia.
Email: a.h.opexob@gmail.com

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Summary

Dystonia associated with Huntington's disease, Parkinson's disease or other neurodegenerative diseases substantially affects patients' quality of life and is a major health problem worldwide. The above-mentioned diseases are characterized by neurodegeneration accompanied by motor and cognitive impairment and often have complex aetiology. A frequent feature of these conditions is the abnormal accumulation of protein aggregates within specific neuronal populations in the affected brain regions. Familial neurodegenerative diseases are associated with a number of genetic mutations. Identification of these mutations allowed creation of modern model systems for studying neurodegeneration, either in cultured cells or in model animals. Animal models, especially mouse models, have contributed considerably to improving our understanding of the pathophysiology of neurodegenerative diseases. These models have allowed the study of pathogenic mechanisms and development of new disease-modifying strategies and therapeutic approaches. However, due to the complex nature of these pathologies and the irreversible damage that they cause to the neural tissue, effective therapies against neurodegeneration remain to be elaborated. In this review, we provide an overview of cellular and animal models developed for studying neurodegenerative diseases, including Huntington's disease and dystonia of different origins.

KEYWORDS

dystonia, Huntington disease, neurodegenerative disease models, neuroprotection

1 | INTRODUCTION

Age-related neurodegenerative disorders, especially those associated with motor impairment, have become more frequent worldwide in recent decades, for a large part due to the increase in the elderly population. These disorders represent a major challenge for public health, since they are difficult to treat, and the existing medications can only slow down the pathologic process in some patients, but do not offer a cure.[1] Most common neurodegenerative disorders affecting the general population are Parkinson's disease (PD), Huntington's disease (HD), frontotemporal dementia, amyotrophic lateral sclerosis and spinocerebellar ataxia. Pathophysiology of these diseases includes motor, cognitive and memory impairment.[2-5] Dystonia is one of the main syndromes of the above-mentioned disorders. Given the steady increase in life expectancy in most countries, it is likely that the incidence of these diseases will continue to increase in the future, necessitating the development of new and effective therapies. The search for such therapies can only be successful if based on a clear understanding of the underlying mechanisms of each condition. The key pathogenic mechanisms of the neuronal damage are likely to include protein aggregate formation and chronic neuroinflammation. Among the invaluable tools to

study the disease onset and progression are the cell and animal model systems that are representative of hallmarks of the human pathology. Different experimental models based on yeast, nematode, drosophila, mice, rats and even primates have been developed to study neurodegenerative processes and provided insights into the disease key mechanisms.[6-9]

HD is characterized by a high phenotype heterogeneity. Up to 90% of HD cases are associated with focal or segmental dystonia that contributes to motor impairment. Currently, there are no clear guidelines for dystonia treatment either in the context of HD or as a separate condition. Often, the same drugs are effective in the treatment of phenotypically similar dystonia.

Recently, several protocols of induced-pluripotent stem cells (iPSCs) generation were developed for establishing patient-specific iPSC lines and using them to create disease models.[10] Of special interest are three-dimensional (3D) cell culture systems that can replicate the structure of different tissues, and even whole organs, including the brain.[11,12] It is well known that glial cells can be involved in neurodegeneration and can play a role no less important than that of the neuronal cells.[13] Currently, different cell lines of glial and neuronal origin empowered by 3D cultivation systems and genome sequencing data make it possible to create accurate patient-specific disease models in vitro.[14] However, this approach is not free from drawbacks: limited number of available individual iPSC cell lines and high frequency of line-to-line variation and unstable CAG expansion. Human embryonic stem cells (hESCs) are currently the only type of hPSCs available as clinical grade lines, and further characterization of hESCs and iPSCs is needed.[15]

Recently, promising results were obtained using antisense oligonucleotides (ASO) to correct the splicing and restore functional SMN protein for spinal muscular atrophy treatment in infants.[16] These inspiring results suggest the possibility of developing ASO drugs in the near future to cure such diseases as amyotrophic lateral sclerosis and HD. Cannabinoids revealed promising results in symptomatic treatment of adult dystonia in HD and as a separate condition.[17] Preliminary data are often encouraging, but, in most cases, final results obtained in large controlled trials are disappointing. In this review, we will summarize the information on current models of HD and/or dystonia and the main results obtained (Table 1).

2 | ANIMAL MODELS OF NEURODEGENERATIVE DISORDERS

Transgenic mouse strains were developed for modelling of HD, PD and dystonia of different origin. Mice expressing mutant human huntingtin, α-synuclein and torsinA (expression product of *DYT1* gene) have been created, but none of them allowed replication of the pathophysiology of these diseases fully enough.[18,19] In particular, neuronal death and protein aggregate formation in HD, neurofibrillary tangles formation, generation of Lewy bodies and dopaminergic neurons intensive death in PD could not be reproduced. More recently, rat models were created that possess superior properties in comparison with mouse models. However, despite the larger size of the brain and relatively complex behaviour, rat models shared the common disadvantage of rodent models consisting in the lack of neurodegeneration, and the results obtained with these models were not very useful for clinical applications.[20,21] Despite that, contribution of rodent models to the understanding of neurodegenerative diseases and the drug development is invaluable.

Nonhuman primates are better suited for modelling neurodegenerative processes due to genetic proximity, large brain size and age-related formation of lesions. Development of transgenic nonhuman primate models of neurodegenerative diseases has great promise for diagnostics and treatment due to better replication of human physiological conditions.[22] However, the results obtained with these models so far are limited: only few cases have been reported to date, and only scarce behavioural data are available.[23] Moreover, contemporary transgenic models lack major neuronal degeneration and are not easily available. On the other hand, models elaborated using somatic gene transfer have other disadvantages such as restricted neuronal degeneration in the injected areas and therefore limited mimicking to the time-course development characteristics of the neurodegeneration process observed in humans. In models of HD, motor impairment (dyskinesia, chorea and dystonia) could be replicated, but cognitive impairment was more difficult to demonstrate.[24]

3 | HUNTINGTON'S DISEASE

Unlike AD and PD, which are characterized by high frequency of sporadic cases, HD is an inherited autosomal dominant neurological disorder caused by a mutation in the *IT15* gene. In HD, progressive cell death in the striatum and cortex is accompanied by cognitive and motor impairment and behavioural changes ultimately followed by death.[25] Common pattern of classical symptoms is known as "The Huntington's triad." Current animal models of HD induced by toxic agents have been previously used for studying mitochondrial impairment (mitochondrial toxin 3-nitropropionic acid) and excitotoxicity-induced cell death (excitotoxins like kainate, ibotenate and quinolinate). These models are still used widely in HD studies, alongside the genetic models. The toxins used for the generation of HD models lead to selective loss of striatal GABAergic projection neurons, but do not affect striatal interneurons, representing the neurological lesions of HD.[26]

A wide range of transgenic animal and in vitro models targeting the huntingtin (*HTT*) gene was developed after

TABLE 1 Overview of animal models of Huntington's disease and dystonia

Model organism	Disease mechanism	Advantages	Disadvantages	Research impact
Huntington's disease models				
C. elegans	*Htt* expression with glutamate expansions of various length	Cheap enough for big scale drug/genetic and behavioural screening	Low predictive efficacy with regard to clinical trials	Identified pathways that either suppress or enhance mutant *Htt*-induced neuronal degeneration Identified genetic modifiers of *Htt* aggregation
D. melanogaster	*Htt* expression with glutamate expansions of various length	Cheap enough for big scale drug/genetic and behavioural screening	Low predictive efficacy in regard to clinical trials	Identified pathways involved in mutant *Htt* induced neuronal degeneration Identified genetic modifiers of *Htt* aggregation
Rodent (mice, rats)	Mainly transgenic *Htt* expression with glutamate expansions of various length	Appropriate for behavioural tests Exhibit behavioural and physiological symptoms associated with disease Wide range of mice and rats transgenic strains Low to satisfactory predictive efficacy with regard to clinical trials	Disease symptoms not always reproduce human pathology Various factors (eg strain, supplier, gender) documented to affect experimental outcomes	Most common HD models are based on rodents Rodent models generated the predominant amount of data concerning HD origin and development
Nonhuman primates	Pharmacologically induced neuronal loss or transgenic *Htt* expression	Anatomy similar to human and useful for testing drug delivery Appropriate for behavioural tests	Expensive and highly regulated Complicated technology Not appropriate for large-scale drug screening	Clinically predictive models Testing drug delivery mechanisms
Dystonia models				
Invertebrate models (*C. elegans* and *D. melanogaster*)	Transgenic animals expressing various lengths of *Htt*	Amenable to large-scale forward drug/genetic and behavioural screening Large-scale RNAi screen can identify modifiers of *Htt* protein aggregation	Low predictive efficacy with regard to clinical trials	Data obtained using these models mainly contributed understanding of mechanisms of DYT1 dystonia development, especially identifying the function of torsinA, such as a role chaperone-mediated protein folding, protection of dopaminergic neurons from neurotoxicity, and the endoplasmic reticulum stress, as well as the effects of modulating the expression or introducing mutations on behaviour
Rodent (mice, rats)	DYT1 mice models expressing mutated torsinA or animals expressing wild-type torsinA at different levels using artificial promoters DYT11 mice models expressing mutated ε-sarcoglycan DYT12 mice models expressing Na^+, K^+-ATPase α3 isoform.	Exhibit behavioural and physiological symptoms associated with the disease Amenable to behavioural tests Lesions are similar to human pathology Wide variety of transgenic models Most of these transgenic rodent models showed an impairment of motor behaviour, especially gait defects	Difficult to generate proper control animals due to differences in the transgene insertion site, copy number, expression level and pattern of expression	These genetic animal models are useful to study the pathophysiology of dystonia and develop novel therapies

(Continues)

TABLE 1 (Continued)

Model organism	Disease mechanism	Advantages	Disadvantages	Research impact
Nonhuman primates	Pharmacologically induced	Lesion anatomy similar to human and useful for testing drug delivery	Very expensive and highly regulated Methodologies can be technically challenging Not appropriate to large-scale drug screening	The results obtained using these models revealed pathoanatomic features of the disease and suggested that dystonia is associated with aberrant sensory representations interfering with motor control.

discovering the genetic nature of HD in 1993. The single gene mutation causing HD leads to polyglutamine expansion in the amino-terminus of the protein. The polyglutamine tail length directly correlates with HD symptoms severity and disease onset age. This circumstance made it possible to develop HD models that closely represent original disease pathophysiology.[27] Despite the clear origin of HD development, the underlying mechanism of mutated *HTT* toxicity still remains obscure.[28]

Small organism *in vivo* HD models based on *Drosophila melanogaster* and *Caenorhabditis elegans* are widely used and possess some advantages over rodent and primate models, namely a short lifespan and reproduction time of the model organism, which allows the performance of a broad panel genetic and drug screening.[29,30] Distinctive features of Drosophila-based models include the easily detectable neurodegeneration in the eye, aggregate overexpression caused by overexpression of mutant HTT, neuronal death and reduced lifespan. Importantly, these models replicate motor, learning and memory impairments associated with HD.[31-34]

Caenorhabditis elegans expressing mutant HTT in aggregates were also developed. These transgenic nematode models revealed neuronal toxicity and paralysis in an age- and polyglutamine length-dependent manner.[35,36] *Caenorhabditis elegans* strains expressing HTT with expanded polyglutamine tail in sensory and mechanosensory neurons and characterizing by age and polyglutamine tail-length selective neuronal degeneration have also been created.[37,38]

Numerous transgenic mouse models of HD have been created, including YAC46, YAC72, YAC128, BACHD, HdhQ97/Q97, HdhQ111/Q111 and HdhQ150/Q150, R6/1, and the two most commonly used models R6/2 and N171-82Q that express the amino-terminal expansion of human mutant HTT.[39] R6/2 is one of the widely used strains carrying 115-156 CAG repeats and displaying a robust phenotype with learning and severe motor impairment characterized by abnormal gait and hypodynamia with pronounced neurodegeneration at the age of 10 weeks. The animals die early, typically between 12 and 14 weeks of age.[40,41] Character and pathophysiology of HTT aggregates formation resembles the biopsy material from patients with HD.[42] The above-mentioned features made this model useful for drug screening.[43] N171-82Q strain expresses a 171 amino acid fragment of human HTT with 82 CAG repeats. Animals bearing this mutation fail to gain weight at the age of 8-10 weeks, reveal mild motor impairments at 12 weeks, have signs of neurodegeneration at 16-20 weeks and die at 24-30 weeks.[44] YAC128 and BACHD transgenic mice express full-length human mutant HTT with 128 and 97 residue-long polyglutamine in the amino-terminal region, respectively, and present with milder neurological impairments than R6/2 strain.[45] At the same time, YAC46 and YAC72 mice did not show any clear behavioural impairments.[46] HdhQ97/Q97, HdhQ111/Q111 and HdhQ150/Q150 knock-in mice were generated by replacing the first exon of the murine HTT gene by the first exon of the mutant human HTT gene. HdhQ150/Q150 expressing mutant HTT with a longer polyglutamine tail expansion revealed late-onset behavioural changes. These animals presented with motor and gait abnormalities and more severe impairments as compared to HdhQ111/Q111 strain expressing HTT with a shorter expansion. In general, mice strains with expanded polyglutamine repeats (YAC128, BACHD, HdhQ97/Q97, HdhQ111/Q111 and HdhQ150/Q150) reveal clear HTT aggregates formation only at an older age and have a prolonged lifespan similar to wild-type animals. Both BACHD and YAC128 exhibit striatal atrophy at the age of 12 months. At the same time, BACHD reveals cortical atrophy and neurodegeneration at the age of 12 months versus YAC128, which has cortical atrophy at the age of 18 months.[45] HdhQ150/Q150 and HdhQ111/Q111 strains exhibit neuronal intranuclear aggregates formation mainly in the striatum at the age of 15 to 22 months.[47,48] In summary, genetic knock-in HD model mouse strains replicate the HD genetic defects with precision, but do not display the robust disease phenotype unlike BACHD and YAC128 models, which could be regarded as a better option for drug screening.

Rat models of HD have been created by several groups independently. One of the transgenic rat models, tgHD51, carries 51 CAG repeats and survives up to two years. This model represents the late-onset HD similar to the human disease.[49] Another recent rat model, BACHD, is characterized by progressive neurodegenerative impairments and extensive loss of striatal neurons.[50]

Recently, the interest in transgenic nonhuman primate modelling of human diseases was renewed.[51] Current research efforts are focused mainly on establishing a self-sustainable population core and therefore producing HD monkeys for the research purposes. One of the obstacles to that research is the fact that rhesus macaques express only 10-11 CAG repeats, while transition point for CAG repeats in humans is about 35.[52] Currently, data from 8 HD monkey lines have been reported, five of them being tested in a longitudinal study.[24] Monkey lines rHD1, rHD2, rHD3, rHD4 and rHD5 expressing 29 (single gene copy), 83 (two gene copies), 84 (two gene copies), 27 (two gene copies) and 88 (two gene copies) have been created.[54] rHD6, rHD7 and rHD8 lines carry exons 1-10 of the hHTT gene coding N-terminal 508 amino acids with 67-72 CAG repeats under control of the human HTT promoter.[24,53,55]

4 | DYSTONIA

Apart from HD, dystonia may develop as an independent disorder, revealing the same phenotype as HD-associated impairment. Dystonia is a neurological disorder characterized by constant spasmodic muscular contraction. Muscle spasms are often unpredictable and change the normal position of the body. Spasms can be chronic and cause considerable discomfort, pain and disability. Currently, dystonia of different origins is often treated with the same drugs: botulinum toxin, anticholinergic agents, tetrabenazine, baclofen, cannabinoids and others. At present, many forms of dystonia have been described that vary in aetiology, manifestations and optimal methods of therapy. It should be noted that in 2006, the official recommendations of the European Federation of Neurological Societies and the Society of Motor Disorders (EFNS/MDS) were adopted on the issue of dystonia.[56] Undoubtedly, the success of studying the pathogenesis and, as a consequence, the choice of strategies for treating dystonia should be based on developing models that fully reflect the symptoms of this disorder.[57]

Invertebrate models developed on the base of *C elegans* and *D melanogaster* are especially appropriate for large-scale drug and genetic screens aimed at bolstering our understanding of the molecular mechanisms and disease symptoms development.[58]

Studies performed in cultured cells indicated that defects in *DYT1* gene can lead to both transcription impairment caused by abnormal interaction of the mutant protein torsinA with nuclear envelope proteins, and the loss of its function in the endoplasmic reticulum, where it is localized. To determine which of these possibilities actually takes place, a transcriptional and proteomic profiling was conducted using neuronal cell lines inducing wild-type or mutant torsinA expression. It was shown that, although mutant torsinA accumulates in the nuclear envelope, this amount is clearly not enough to disturb the regulation of transcription. However, changes in the expression at the protein level were detected, indicating the potential effect of torsinA on the regulation of the redox state and energy metabolism. It should also be noted that some of the identified proteins were known to be associated with other forms of dystonia. Thus, the results obtained confirmed the hypothesis of a transcription disorder in *DYT1* dystonia.[59]

Rodent models of dystonia have been developed since 1960 and include mouse-, rat- and hamster-based models. A homozygous mouse model of dystonia, *DYT1*, is characterized by a generalized dystonia caused by trinucleotide deletion (n. DelGAG, p. ΔE 302/303) in the *Tor1a* gene. Homozygous F205I mice had motor deficiency, reduced steady-state torsinA levels, altered cortico-striatal synaptic plasticity and apparent brain imaging abnormalities in the areas associated with motor function. Therefore, F205I was shown to cause anomalies in the areas affected by *DYT1* Tor1a mutation (ΔE). The obtained results demonstrated the pathological significance of F205I Tor1a and allowed the creation of a model that has aetiological and phenotypic significance for further study of the mechanisms of this disease.[60]

Another in vivo model of *DYT1* dystonia was developed for studying the functional connectivity of large-scale cortical and subcortical networks in mice such as Dyt1 KI and wild type using functional magnetic resonance imaging (MRI). The relationship between the structural integrity of the basal ganglia and the cerebellum with impaired functional connectivity was investigated using diffusion MRI. Unlike wild-type mice, Dyt1 KI mice demonstrated increased functional connectivity through striatum, thalamus and somatosensory cortex, as well as decreased functional connectivity in the motor and cerebellar cortex. In addition, Dyt1 KI mice, like wild-type mice, showed increased free-water in the striatum and cerebellum, while an increase in this index correlated with impaired functional connectivity between the basal ganglia, the cerebellum and the sensorimotor cortex. The in vivo MRI data confirmed the hypothesis that the deletion of the 3-base (ΔGAG) pair in the Dyt1 gene encoding torsinA affects the level of functional connectivity and the microstructural integrity of the sensorimotor cortex, basal ganglia and cerebellum.[61]

Transgenic rat models carrying a complete human mutant and a wild-type *Tor1A* genes have been developed. In these models, a mutation in the coding region of the Tor1A gene caused a deletion of the glutamic acid residue in the protein torsinA (ΔETorA). The conducted complex phenotypic approach with classical behavioural tests and analysis of electrophysiology and neuropathology revealed a progressive neurological phenotype in ΔETorA expressing rats. A number of pathological features, such as the pathology of the nuclear envelope, behavioural anomalies and changes in ductility, could be reproduced. Based on these results, the

model was proposed for further studies of the pathophysiology of ΔETorA, as well as for exploration of therapeutic approaches.[62,63]

Another *DYT1* dystonia mouse model, which was originally intended to study manifestations of "dystonic-like" postures, was described. In this work, several behavioural tests could not reveal significant differences between the control and transgenic mice. Transgenic animals registered "dystonic-like" posture in almost all cases, which could, however, be attributed to a constrictive reflex since they were also observed in the control animals. Based on the fact that the presence of dystonia should always lead to dopaminergic dysfunction, the effect of dopaminergic substances (L-DOPA in combination with carbidopa) on motor behaviour was studied in transgenic mice. The obtained results did not provide clear answers, since chronic treatment with these drugs improved hindlimb clasping only in the transgenic mice, and in acute treatment of such reaction was observed in animals being in the control group.[64]

Dystonic phenotype was obtained in the mutant hamster dtsz (paroxysmal dystonia model), based on the deficiency of erythrocyte interneurons of g-aminobutyric acid (GABA) and changes in the GABAA-benzodiazepine receptor in the striatum. In this experiment, the striatal microinjections were made to the animals, after which the effect of the compounds binding to the sites of the GABAA receptor was determined. The comparison was systemic treatment in dtsz mutants. It was noted that after striatal and systemic injections, flurazepam (benzodiazepine) and muscimol (GABAA receptor agonist) reduced the dystonia severity. In this work, striatal and intraperitoneal administration of phenobarbital resulted in weaker antidystonic effects; intrastriatal injections of GABA resulted in a delay in dystonic attacks; and in systemic and intrastriatal injections of flumazenil (benzodiazepine receptor antagonist), the course of dystonia was aggravated. Therefore, the obtained results substantiated the relevance of striatal GABAergic disinhibition in the pathogenesis of paroxysmal dystonia in dtsz mutants.[65]

A more recent study conducted by the same group demonstrated that microinjection of the GABAA receptor agonist caused only mild antidystonic effects, while bicuculline did not significantly affect the dystonia severity. These data suggested that the disruption of GABAergic inhibition is not relevant for dystonia manifestation in the dtsz mutant.[66]

A spontaneous mutation resulting in motor symptoms similar to muscles of dystonia musculorum has been described in mice. The mutant mice inherited the mutant (dt) phenotype in an autosomal recessive manner. The causative gene was located on chromosome 1—near the D1Mit373 and D1Mit410 microsatellite markers (close to the locus of the dystonin gene (Dst)). The mutant was crossed with Dst trap DstGt mice to prove that Dst is the causative gene of the new mutant phenotype.[67] The resulting heterozygote had a characteristic phenotype for dt, in particular, presented with progressive motor symptoms and sensory degeneration. A nonsense mutation was detected in the spectrin repeats of the plakin domain by DNA sequencing. The new mutant allele was named dt23Rbrc. Abnormal accumulation of neurofilament (NF) was observed in the neurons in homozygous dt23Rbrc/dt23Rbrc mice. NF mainly accumulated in axons (spheroids) and cytoplasm of neurons. Neurons with NF accumulation were detected in the spinal cord, as well as in the areas that determine the motor function and coordination of the posture (red nucleus, reticular nucleus, vestibular nucleus). Therefore, the studied hypomorphic allele of dt caused histological disturbances in the central nervous system. It was suggested that the described spontaneously emerging mutant can become a good model of hereditary sensory and vegetative neuropathy type 6, which is caused by mutations in the human DST gene.[67,68]

Autopsy studies of the brains from dystonia patients carried out using traditional histopathological methods revealed some structural abnormalities. These observations were combined with the results of studying the brain tissues of *DYT1* mouse models of dystonia. Many anomalies were detected by using a combination of quantitative stereologic indices of immunohistochemical stains for specific populations of neurons, morphometric studies of Golgi-stained neurons and immunoelectron microscopy of the synaptic connection. There was no visible loss of striped neurons in Dyt1 mutant mice. Nevertheless, the mutants showed increased immunoreactivity for choline acetyltransferase or parvalbumin interneurons, compared with the control group. Conversely, mutants had fewer interneurons immunoreactive for nitric oxide synthase than control mice. Golgi-histochemical studies of average spiny projection neurons in the mutant mice revealed the loss of dendritic spines. The use of electron microscopy showed a reduction in the ratio of axostimulate to axodendritic synaptic inputs from glutamatergic and dopaminergic sources in mutant mice compared with control mice. The obtained results suggest that there are specific anatomical substrates for altered signalling in the striatum and potential correlates of the abnormalities observed in human imaging studies of *DYT1* dystonia.[69,70]

5 | CONCLUSIONS

Despite the recent advances in disease model creation, there is still no effective cure for HD patients. In the search for novel therapeutic approaches, a number of HD animal models from fruit fly to nonhuman primates have been created and are used today extensively. Different model organisms serve different purposes, with large animals with complex behaviour, such as nonhuman primates, allow to study the pathology more precisely, while small and relatively simple organisms can be used for fast drug screening. Development of novel animal models that more closely recapitulate the pathophysiology of HD patients provides

the information necessary for making the next step towards clinical trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Alexander N. Orekhov https://orcid.org/0000-0002-6495-1628

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