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AN OVERVIEW ON PARKINSON'S DISEASE ANIMAL MODELS: FROM CLASSIC TO EVOLVING

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ABSTRACT: A progressive neurodegenerative brain disorder with motor & non-motor are signs of Parkinson's disease or idiopathic parkinsonism. Parkinsonism is characterized in striatal region by the deterioration of Substantia nigra pars compacta & dopamine depletion in Dopaminergic neurons. In Parkinsonism research, the prime purpose is to recognize the pathogenesis, strategies & implementation of therapeutic frameworks that regulate the disease progress. Versions of toxins are even starting to be used to anticipate what might arise in individual Parkinson's disease. There is indeed, ton of advancement to be developed especially with reference to the design of experimental models which can precisely determine productive clinical neuroprotective substances. For Parkinsonism research, modern pharmacological, neurotoxin-induced, genetically altered & cellular models become presently accessible. Although caution should be exercised in the initial detection of neurodegenerative illnesses, data imply that future progress is secure, possible and probable to boost clinical care. In this overview, comprehensive information on key features of *in-vivo* & *in-vitro* models presently available has been included.

INTRODUCTION:

Parkinson's disease: Parkinsonism is widespread degenerative brain disease in which hereditary causes, environmental influences, or mixed effect of both emerging from a complicated etiology. Motor disorders like bradykinesia, tremors & muscle rigidity, along with postural dysfunction are the clinical main symptoms, but many patients often suffer from autonomic and cognitive disorders. The important PD symptoms are mediated via selective deterioration of neurons of dopamine within substantia nigra, but in the rest of the regions of the brain, there is also generalized neurodegeneration and pathology, including protein inclusions called Lewy bodies & dystrophic neurites called Lewy neurites.

Around 60-70 percent of the dopamine fibers in the caudate-putamen and at least 50 percent of the dopamine neurons in the SN are already lost by the time clinical manifestations appear. For two main reasons, animal models of human disease are essentially used to study the pathogenic mechanisms of human disease & To test potential clinical treatments. Recognizing pathogenic pathways offers clues to a disease's potential

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etiology & can provide perspectives into therapeutic strategies. Before moving ahead to clinical trials in humans, drug-gene therapy, as well as medical devices, are designed to utilize these routes must then be tested in recapitulative animal models. The significance of laboratory animals is therefore immediately apparent, and it is clear that the better the model, the better the understanding of the human disease is. The ability to predict successful treatments for human disease also depends on the amount of animal study [1].

Animal Models: In medical science, animal models are important tools to better understand human disease pathogenicity. These models should be used once developed to test therapeutic approaches to treat functional disabilities detected in the disease of interest. Parkinsonism was the first degenerative brain disease modelled on the rationale of clinical and experimental findings and subsequently treated with neurotransmission replacement therapy. For implementing PD models, agents were used to selectively interrupt or demolish catecholaminergic systems such as Reserpine, Methamphetamine, 6-hydroxy dopamine, and 1-methyl-4-phenyl- 1, 2, 3, 6-tetrahydro pyridine. Recently, agricultural chemicals such as rotenone and paraquat, when routinely administered, have also been found to be capable of generating specific features of PD in rodents, apparently *via* oxidative damage. To research the function of this protein in dopaminergic degeneration, transgenic animals that over-express alpha-synuclein are used [2].

Pharmacological Animal Models:

Reserpine Model: The first demonstration of clinical effects of L-DOPA, the use of reserpine was critical. Shortly after that, this effect has been observed in living creatures and the Reserpine methodology would be used to validate the potential symptomatic treatment efficacy of new PD drugs. Indeed, in addition to L-DOPA, other current symptomatic anti-parkinson treatments predicted also by the Reserpine method seemed to be: Apomorphine, Pramipexole, Ropinirole, Rotigotine, Pergolide, Bromocriptine & Cabergoline. Similarly, Reserpine-induced motor disorder is also reversed by L-DOPA-associated agents along with: Muscarinic antagonists like Benztropin & trihex yphenidyl; inhibitors of MAO-B or catechol-O-methyltransferase (COMT) such as Selegiline, Rasagiline & Tolcapone; and inhibitors of Amantadine [3].

Haloperidol Model: Haloperidol is an effective & representative antipsychotic medication with a powerful potential for Dopaminergic receptors & is extensively used in the laboratory to trigger extrapyramidal outcomes in rodents, involving stiffness & in specific catalepsy; actions triggered by suppression of Striatum Dopaminergic receptors [5]. Due to the absence of disease imitating biology, Haloperidol method was assumed as a poor Parkinson's disease-like methodology. Haloperidol injections stimulate Parkinsonism like face validity behaviours such as Akinesia & Rigidity, which corresponds to enhanced Glutamate amounts in Entopeduncular nucleus [4]. The innovative therapeutic substances with anti-parkinsonian effects are tested by alteration of rigidity or catalepsy as in the animal model using haloperidol. A common bar test is used to measure catalepsy, although it is still necessary to compare data with similar laboratories for alterations in bar height (5 to 10 cm), cut-off time (60 sec to 5 min), & haloperidol dose, along with animal sensitivity. Similar to the Reserpine method, any pathological correlation associated with parkinsonism is also not observed. However, it is still essential for the assessment of Non-Dopaminergic Substance[s 5].

A-Methyl-Para-Tyrosine: Alpha-methyl-p-tyrosine is a pharmacological substance used to deplete dopamine as the antagonist of Tyrosine - hydroxylase, an enzyme associated in the synthesis of dopamine. Similar to reserpine, the impact of alpha-methyl-p-tyrosine on the depletion of dopamine in the nigrostriatal structure is temporary and without neurodegenerative disorders. This molecule consequently shares the same weaknesses as the reserpine model. Alpha-methyl-p-tyrosine is frequently used in conjunction with reserpine to attenuate dopamine deficiency effects [6].

Neurotoxic Models: Parkinson's disease is considered a multifactorial intermittent condition in which other probable risk factors such as comorbid conditions (*e.g.,* diabetes & hypertension), lifestyle variations (*e.g.,* smoking & diet pattern), and working surrounding are of considerable importance apart from age and family history.

The most important class of working environment substances associated with PD and purposely released to eliminate or control pests from agricultural land is agricultural chemicals like pesticides [5]. Most of the structural dopamine analogues, such as 6-Hydroxy Dopamine & MPTP, have been known to destroy dopamine neurons & generate Parkinson-like phenotypes selectively. Epidemiological findings had reported that prolonged exposure to agricultural chemicals (Herbicide paraquat & Pesticide rotenone) tends to increase the danger of developing Parkinson's disease. These effects allow the neuro-toxins to be used by multiple groups to generate Parkinsonism models and also to explore the mechanisms. The following are most specific neurotoxins used to produce Parkinsonism model. For the identification of the pathophysiology underlying Parkinson's disease and the creation of therapeutic strategies to control its motor symptoms, the usage of toxin-induced animal models has also been essential [7].

6-Hydroxy-Dopamine (6-OHDA): 6-Hydroxy dopamine is neuro-toxin which have been effectively used in Parkinsonism induction experimental models. In 1971, Ungerstedt identified 6-OHDA's powerful neurotoxic effects, in a study that provided the first example of using a chemical substance to generate a Parkinson's disease animal model. Since 6-Hyroxdoxy dopamine is unable to cross Blood-Brain Barrier, Parkinsonism is not mediated by systemic administration. This model of induction includes its injection of 6-Hydroxy dopamine in the Substantia Nigra medial forebrain bundle & striatum. Interestingly, intra-striatal 6-Hydroxy dopamine injection in the substantia nigra & ventral tegmental network induces significant retrograde neuronal degeneration (ST-VTA).

Dopaminergic nerves get destroyed, as in parkinsonism and the non-Dopaminergic neurons are retained. Although the lewis bodies do not build. Usually, 6-Hydroxy dopamine is used as a concept in hemi-Parkinson, in which its unilateral injection through Substantia Nigra triggers asymmetric motor behaviour (turning, rotation) while systemically injecting apomorphine, a Dopaminergic receptor agonist, either amphetamine, as a dopamine-releasing substance. The measurable motor activity in this model is a significant improvement in monitoring pharmacological screening substances for their influence on the Dopaminergic process and in assessing cell replacements treatments [8].

1-Methyl-4- Phenyl-1, 2, 3, 6-Tetra Hydropyridine (Mptp): In 1982, in a development phase that went wrong, MPTP was unintentionally found &, while in certain circles it may have caused some chaos, today it represents the most significant and most commonly used Parkinsonian toxin applied in animal experiments. Along with an intravenous treatment for this compound, young opioid users developed idiopathic Parkinsonian syndrome. Since investigating the genetic cause of their disease, the neurotoxic toxin responsible for the Parkinsonism effect was found to be MPTP.

The major elements of Parkinsonism, Oxidative Stress, ROS, energy depletion, and inflammation have been consistently pointed to. It's been routinely demonstrated that MPTP is essentially the gold specification among Parkinsonism researchers for modifying any of these toxin-based animal methods of parkinsonism. MPTP is intensely lipid-soluble & quickly crosses through BBB following systemic administration. MPTP enters astrocytes while in its brain & is metabolized by monoamine oxidase-B B into MPP+, its active metabolite (MAO-B) [9]. Different mammalian organisms have been controlled with MPTP to model parkinsonism, including Sheep, Dogs, Guinea pigs, Cats, Mice, Rats & Monkeys.

MPTP specifically causes injury to the dopaminergic neuronal system in both monkeys and mice. The significance of this system is the specific and measurable neuro-toxic influence mostly on nigrostriatal system. In contrast, Lewy-like intra-neuronal components have been generally described in whereas Lewy-like intra-neuronal components have been commonly identified in mice. Similarly, when rodents are injected with a chronic lower drug dose of MPTP over an interval of 30 d with osmotic mini pumps, it's been reported that immune responsive inclusions for both ubiquitin and alpha-synuclein can be observed behaviourally; both Monkeys & Mice have been specifically categorized by MPTP induced motor dysfunction. L-dopa or a dopamine stimulant are reversible in such abnormal mutations, confirming

a connection between such symptoms & nigrostriatal system harm [6].

Paraquat: Paraquat (N, N'-dimethyl-4-4-4'-bypiridinium) is an agricultural herbicide that is structurally identical to MPTP/MPP+ and is used in Parkinsonism research irrespective of its use. With the support of the Na+ dependent channel, paraquat can penetrate through the Blood Brain Barrier and it reaches the Pentose Phosphate Pathway instead of linking to Mitochondrial Complex I and enhances NADPH minimizing variants. In contrast, intracellular antioxidants systems such as Glutathione and Thioredoxin were disrupted, which raises Oxidative Stress inside the cells & demolishes the structure of Lipids, Proteins, DNA & RNA. The BCl_3 community, tumour necrosis component receptor, the cell destruction of DFF45-like effector, and the caspase family are all involved in paraquat by regulating apoptosis-related genes. It stimulates apoptosis *via* intrinsic pathways for cell death, such as activation of Cytochrome c, Caspase-3 and JNK, leading to apoptosis. Few findings have shown that paraquat has uncertain effects on the nigrostriatal Dopaminergic system, such as dose-dependent loss of TH-Positive striatal fibers & decreased motor activity [5].

Its possible significance to environmental pollutants as a trigger factor for generating Parkinson's disease is the intensity of the Paraquat or Paraquat/ Maneb method. Both of these compounds are being used in geographic locations which overlap. An elevated threat for Parkinson's disease after exposed to paraquat has been identified by epidemiological experiments. Moreover, Paraquat treatment enhances aggregates of alpha-synuclein resembling of Parkinsonism like Lewy Bodies. Paraquat has also been revealed to suppress nor-adrenergic neurons in the locus coeruleus in one experiment. Consequently, the absence of a significant impact of paraquat in the broadly used therapies on striatal dopamine degradation can limit its use using this approach to test Neuroprotective strategies for Parkinsonism [6].

Retonone: Insecticide like rotenone has been widely used to kill fish and is a material typically found in many plant types' roots. It is probably the strongest antagonist for the selective mitochondrial complex I. Rotenone is extremely lipid-soluble and can get through the Blood-Brain Barrier easily. The systemic mechanism I suppression was found in Parkinsonism patients. Thus, the metabolites that develop complex I suppression, both probable pathogenic substances and required modelling equipment, also received significant recognition. With the exception of MPTP, which only in Catecholaminergic Neurons induces blockade of specific Complex I, Rotenone causes Systemic inhibition.

The first documented endeavour to use rotenone model of parkinsonism was conducted at a concentration 500 000 times significantly higher than its IC50, Complex I through surgical infusion into the parenchyma. Human evidence on Systemic complex I impairment for parkinsonism led investigators to investigate its rotenone administration in peripheral passages. Similarly, it generated strongly selective Nigro-striatal deterioration when rotenone was induced chronically at lower doses to obtain complex I suppression similar to those reported in Parkinsonism patients' platelets. Exceptionally, cytoplasmic alpha-synuclein positive additions identical to LBs were recorded in sustaining Dopaminergic Neurons for the first time in an experimental animal. Rotenone methodology also made available the first evidence that significant nigro-striatal deformation could be developed through systemic Mitochondrial Impairment; it further demonstrated that dopaminergic neurons do have distinctive responsiveness to suppression of the complex I. Systemic chronic treatment in the Lewis Rat, which may be more prone than certain varieties of strains, becomes the most widely accepted method in system 1.

Pyrethrins/Pyrethroids: Pyrethrins are substances containing insecticidal characteristics which arise naturally. Sometimes offered as mixtures for industrial & household use, these substances are have been using in many domestic insecticides, flea sprays, Animal shampoos, Head Lice therapies & Mosquito Repellents. Pyrethroid toxicity has long been observed to trigger neurological symptoms, relying on the distinct exposure involving Salivation, Tremor, Choreoathetosis, or Coma. The potential for Pyrethroids, such as Permethrin & Deltamethrin, to enhance DAT-mediated 3 H-

dopamine uptake or trigger neurotransmitter release has been reported across several studies. Given the relevance of the dopaminergic neuron's DAT activity, this is an area of investigation that deserves additional exposure. While Pyrethroids became a comparatively latest insecticide class and are generally unusual to be implicated in Parkinsonism cases diagnosed before the 1970s & 1980s, additional investigation requires the potential for generalized human exposures & the capability to modify dopaminergic homeostasis [10].

Genetic Models: While multiple cases of idiopathic parkinsonism are unpredictable, several variations in genes that cause hereditary variants of parkinsonism have currently been revealed & several vulnerability variants have also been detected, contributing to modern theories and research of disease driving processes. Multiple experimental models are dependent on null mutated genetically modified rodents, an additional genetic version, or point gene variants positioned within various PARK loci. Genetic mouse models would safely be generated by null mutations of predefined genes (knockout mice) for the recessively inherited impairment mutations in Parkin, DJ-1 & PINK1, all of which trigger the beginning of Idiopathic Parkinsonism. Transgenic mouse model experiments have been designed through the dominantly inherited gain of function variants such as alpha-Synuclein & Leucine-rich repeat-kinase 2 (LRRK2), wherein additional iterations of the genes are imported into the genome of the animal or released by Lente or Adeno associated viruses. Multiple mouse varieties have been established for alpha-Synuclein, where instead of human wild type genes is over expressed against distinct Heterologous modifiers for replication of gene duplication & triplication documented in Parkinsonism family A30P or A53T idiopathic parkinsonism causing alpha-Synuclein variations have been expressed through Transgenic mice. For example, a persistent phenotype with intra-neuronal additions, degradation & Mitochondrial DNA disruption in neuronal cells was mediated via elevated amounts of mutated alpha-synuclein expression within the animal prion Protein Transmitter [11].

A-Synuclein: Alpha-Synuclein is indeed small but abundant Neuronal Proteins for ex, 140 Amino acids that is specifically intensified throughout the pre-synaptic interfaces & whereas alpha-specific synuclein's physiological purpose seems to be investigated, numerous experiments have demonstrated a regulating feature in membrane & vesicular dynamics for certain protein. Genetic variations throughout the alpha-synuclein gene, arising as replacements (A53T, A30P & E46K), replication or triplication, are presently firmly founded to be causative of dominantly inherited variants of idiopathic Parkinsonism. Relevantly, a massive structural element of Lewis Bodies has been recognized as alpha-synuclein. Collaboratively, certain conclusions make convincing evidence for idiopathic Parkinsonism modelling through overexpression among Animals of wild type or mutant variants of alpha-synuclein. Cause of Autosomal Dominant forms of familial Parkinsonism has been recognized by Point mutations (A30P, A53T & E46K) or multiplexing (duplication & triplication) of the SNCA gene (alpha-synuclein & PARK1). While there is proof that alpha-synuclein connects with Tubulin & SNARE Network, however, there is still a weak understanding of its Physiological Function & exact mechanisms through which its mutations contribute to impairment & Death of cells are indeed uncertain.

The reality that multiplications of SNCA genes are connected with idiopathic parkinsonism led to the hypothesis that the alpha-syncluein level is significant for its toxicity & accordingly, multiple models are focused on the over-expression of alpha-synuclein wild type (occasionally truncated) from murine or individual origins. Certain models transmit one or multiple mutated SNCA gene variants or combine alpha-synuclein mutations or overexpression with some mutations connected with Parkinsonism. In common, although models of alpha-synuclein seem optimistic & important to Parkinson’s disease, neither of those demonstrate the evident deterioration of Nigrostriatal pathway & Motor symptoms, while others in SNc & other brain domains are certain to evolve alpha-synuclein aggregates [8].

Parkin: Parkin is 465 Amino acid E 3 Ubiquitin ligase that transforms ubiquitin for degradative, *i.e.*, through Proteasome system or Non-degradative *i.e.*, signalling purposes to target proteins.

The majority of early-onset familial idiopathic Parkinsonism cases contribute for Mutations in Parkin. Either through manipulating the normal operation of the Ubiquitin Proteasome system in passage of the aggregated proteins or by disrupting the mitochondrial protective pathway facilitated by Parkin's signaling operation, resulting in mitochondrial dysfunction & can correspond to the etiology of Parkinsonism [12]. Parkin comprises almost 1.3 Mb of Genomic DNA & is a causative factor for adolescent Parkinsonism representative AR (PARK2). In 20 % of young-onset intermittent Parkinson's disease cases, alterations in Parkin are indeed a cause of familial Parkinsonism but are also identified.

Parkin is E 3 Ubiquitin ligase in the Ubiquitin-Proteasome System that works. It is suspected that deprivation of Parkin's activity leads in excessive estimations of substances of Parkin. In Drosophila, overexpression of human variant parkin induces Dopaminergic neurons to influence an age-dependent selective deterioration of Progressive motor disability. There are often numerous delayed onset & Progressive Hypokinetic Motor abnormalities in Parkin Q311X rodents. Stereological research demonstrated that mutant mice exhibit Substantia nigra age-dependent Dopaminergic Neuronal degeneration & a notable decline in the Striatal dopamine level characterized by substantial depletion of striatum Dopaminergic neuronal branches. These discoveries signify that in the dominant-negative etiological processes of idiopathic Parkinsonism, Parkin mutants can perform a pivotal importance [8].

Pink1: Mutations in the PARK6 locus of PINK1 cause a form of early-onset autosomal PD. PINK1 codes for a mitochondrial kinase, which recruits Parkin from the cytosol to the mitochondria, increases the ubiquitination activity of Parkin, and induces Parkin-mediated mitophagy. Since PINK1 and the Parkin function in the same pathway, the phenotypes of PINK1 and Parkin KO mice are very similar. Genetic variations in PINK1's & PARK6 locus cause a kind of early-onset autosomal Parkinsonism. PINK1 rules for a mitochondrial l kinase that employs Parkin through Cytosol to the mitochondria enhances Parkin's ubiquitinating efficiency & induces mitophagy mediated through Parkin. The alleles of PINK1 & Parkin Knock Out mice are quite identical, whereas PINK1 & Parkin run throughout the identical mechanism 13.

LRRK2: There are numerous domains & features of the massive LRRK-2 protein, *i.e.*, leucine-rich repeat kinase-2, usually identified as Dardarin & PARK8, including a kinase, RAS & GTPase domains, and it associates through Parkin. In late-onset & Autosomal dominant cases of idiopathic parkinsonism, Missense & Point mutations in LRRK2 genes have been revealed & are specifically intensified, *i.e.,* 20 % & 40 %, respectively) in Parkinsonism patients among Ashkenazi Jews & Berber Arab ancestors. Kinase (G2019S) or GTPase (R1441C/G) represent the most prominent variants of the LRRK-2 Gene & both have been expressed in animal experiments where mild Dopaminergic deterioration is very often recorded & also the changes in Dopamine release & uptake, while LRRK-2 Knock Out mice do not demonstrate Dopaminergic abnormalities or any other Neuropathological manifestations.

For alpha-synuclein, with varying hereditary & molecular interventions, numerous distinct LRRK2 animal models have been generated. BAC genetically modified mice possessing mutated LRKK-2 have also been established, showing age-dependent & progressive motor deterioration & slightly decreased Striatal Dopamine release. As a whole, mainly mild Dopaminergic disabilities or other Pathological processes significant to Parkinsonism are developed through LRRK-2 animal methods so it is uncertain that they will be beneficial for quantifying therapeutic interventions or investigating the pathophysiology of Parkinson's disease. On either end, Rat LRRK-2 variant has been devised in Nigrostriatal mechanism with Neuron-specific adenoviral-mediated expression of LRRK-2G2019S that demonstrates a Progressive degeneration of Nigral Dopaminergic neurons 14.

Nurr1 (NR4 A2): Nurr-1 is a component of the superfamily of nuclear receptors & is implicated in Nigrostriatal Dopaminergic neuron transformation & progression. Idiopathic Parkinsonism was accompanied by the discovery of dual variations in Nurr-1 (-291Tdel & -245TG), which applied to the first NR4A2 exon & affected One allele - 10 of 107 participants with familial Parkinsonism. Nurr-1 alterations modify transcription of TH &

transporter of Dopamergic neurons, signifying that Nurr-1 modifications may cause chronic alterations of dopamine that may enhance Parkinsonism susceptibility. For the proliferation of mesencephalic ventral Dopaminergic neurons, Nurr-1 is crucial because homozygous Nurr-1 Knockout mice do not generate Dopamine neurons in Substantia nigra & die after formation. A substantial decline in Rotarod intensity &Loco motor movements is illustrated by Heterozygous Nurr-1 Knockout mice.

Similar Phenotypes are accompanied by diminished Striatum Dopamine levels, reduced Dopaminergic neuron quantities & decreased Substantia nigra activity of Nurr-1 & DAT. In contrast, Le *et al.* documented that even after MPTP implementation; heterozygous Nurr-1 Knockout mice demonstrated a Substantial decline in an overall number of TH positive neurons in substantia nigra & lowered dopamine in the striatum region. Consequently, such rodents demonstrate a progressive mutation of dopamine that shows a certain similarity to that measured in expressing & mutant rodents of alpha-synuclein over. Consequently, a good method for examining the later phases of idiopathic Parkinsonism characterized by extreme Dopamine neuron loss may be established by Nurr-1 knock-down mice [8].

DJ-1: Two n's diseases were recognized as DJ-1 consanguineous pedigrees in Autosomal recessive Parkinsogenetic variations. One family carried a predictable termination to eradicate & One family carried a predetermined dismissal to abolish mutation that results in proline been incorporated into an alpha-helical region. Development of this Proline variant type of DJ-1 tends to correspond to its mitochondrial deposition & DJ-1 has been implicated as cellular monitoring of Oxidative Stress [15].

Future Perspectives: Several experiments recently demonstrated that the accumulation of alpha-synuclein irregular protein removal, mitochondrial dysfunction, & neuro- inflammation plays a fundamental role in the development of disease initiation & Parkinsonism pathogenesis. By suppressing the operation of Mitochondrial complex-I & further triggering neurotoxicity throughout the brain, neurotoxins predominantly act on Dopaminergic neurons across dopamine carriers dosages, lesion types, neuro toxins used to trigger Parkinson's disease & timing of behavioural interventions are all significant variables in Parkinson's studies to evaluate the treatment/management feasibility of medications. Evidently, no particular experimental model invented to date for Parkinson's disease mimics all Parkinsonism's key elements. In idiopathic Parkinson's study, hazardous experimental models & genetically modified animal models are accessible, but they also have limitations. Nigro striatal deterioration is rare in certain genetically modified mice. It is also expensive to cure. However, there is a severe lack of stable & accurate neurodegenerative experimental animal models in Parkinson's disease studies in the nigrostriatal pathway. For a compelling investigation to recognize innovative clinical strategies or diagnoses, potential experiments based on minimum neurotoxic dose models that imitate all Parkinson's symptoms seem identical. Similar human Parkinsonism needs to be recognized [16].

CONCLUSION: There is a long history of analysing Parkinson's disease using toxins, contributing to the discovery of the presence of dopamine in Parkinsonism & the assessment of the therapeutic efficacy of L-DOPA; still it is the most appropriate treatment for Parkinson's disease. There has been continuous improvement in toxin systems & we now have capacity to emulate the maximum of Parkinsonism pathogenic attributes.

Toxin designs are also beginning to be used in human Parkinsonism to determine what could occur. There is, indeed, a great deal of advancement to be made in establishing models that can accurately identify beneficial neuroprotective substances in individuals. There are strengths & drawbacks of both toxin and genetic-based models. The use of two in contrast, however, would be very advantageous. Thus, in collaboration with a reliable & appropriate neurotoxin, a multi-gene encoded transgenic system may improve the models for Parkinson's disease phenotype. We expect to see enhanced systems for both fundamental interpretation of idiopathic Parkinsonism & for optimized increased drug development in upcoming years.

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