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(54) Title: METHODS FOR TREATING DISEASES ASSOCIATED WITH TAF1 LOSS OF FUNCTION

(57) Abstract: This disclosure provides compounds, compositions and methods of treatment of diseases and/or disorders associated with TAF1 loss-of-function (LOF). Non-limiting examples of these diseases and/or disorders include X-linked Dystonia Parkinsonism (XDP) X-linked syndromic intellectual developmental disorder-33. Non-limiting examples of compounds useful in the treatment of diseases and/or disorders associated with TAF1 LOF include, and are not limited to, SAK3, pridopidine, and/or lamotrigine.



## METHODS OF TREATING DISEASES ASSOCIATED WITH TAF1 LOSS OF FUNCTION

### CROSS-REFERENCE TO RELATED APPLICATION

5 This application claims the benefit of U.S. Provisional Application Serial No. 63/507,633, filed June 12, 2023, the disclosure of which is hereby incorporated by reference in its entirety, including all figures, tables and amino acid or nucleic acid sequences.

### BACKGROUND OF THE INVENTION

10 X-linked Dystonia Parkinsonism (XDP) is a severe neurodegenerative disease endemic to the Philippines [1] linked to a DNA repeat expansion within an intronic SINE-VNTR-Alu (SVA)-type retrotransposon insertion in the *TAF1* gene [2,3]. The insertion disrupts *TAF1* splicing and reduces levels of the full-length transcript [4]. The discoveries of genetic lesions and molecular defects suggest potential strategies for modeling XDP in animals but bringing  
15 such models to fruition has been challenging. SVAs are large segments of repetitive DNA, and the *TAF1* intron in which this element is inserted is not conserved in lower animals. We have developed *TAF1* loss of function (LOF) tadpoles that have robust phenotypes including developmental delay, swimming deficit, shorter lifespan, and a range of abnormal behavior reminiscent of XDP symptoms in humans. In tadpoles, these symptoms include forced and  
20 uncontrolled mandibular movements, tail spasms ranging from mild to severe, and loss of spatial orientation.

The clinical manifestations of XDP have been documented in multiple XDP cohorts exhibiting a characteristic progression of focal dystonia that generalized over time as parkinsonian features also emerged [10–12]. There are few treatment options for XDP,  
25 consisting of oral medications, chemodenervation by botulinum toxin, and deep brain stimulation [1], which offer limited symptomatic relief, reinforcing the significant need to develop better therapies.

A consistent finding across studies is that TAF1 expression is reduced in XDP cells compared to matched controls [3–9] supporting that a partial loss of TAF1 function may  
30 contribute to XDP pathogenesis and that small molecules that mitigate the effects of this loss could provide therapeutic benefit. This disclosure provides compounds, compositions and methods of treatment of diseases and/or disorders associated with TAF1 LOF. Non-limiting examples of these diseases and/or disorders include X-linked Dystonia Parkinsonism (XDP)

X-linked syndromic intellectual developmental disorder-33. Non-limiting examples of compounds useful in the treatment of diseases and/or disorders associated with TAF1 LOF include, and are not limited to, SAK3, Pridopidine, succinilic acid (4-anilino-4-oxo-butanoic acid) and/or Lamotrigine.

#### BRIEF SUMMARY OF THE INVENTION

This disclosure provides compounds, compositions and methods of treatment of diseases and/or disorders associated with TAF1 LOF. Non-limiting examples of these diseases and/or disorders include X-linked Dystonia Parkinsonism (XDP) X-linked syndromic intellectual developmental disorder-33. Non-limiting examples of compounds useful in the treatment of diseases and/or disorders associated with TAF1 LOF include, and are not limited to, SAK3, Pridopidine, succinilic acid (4-anilino-4-oxo-butanoic acid), and/or Lamotrigine.

#### BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication, with color drawing(s), will be provided by the Office upon request and payment of the necessary fee.

FIGs. 1A-1G. SAK3, Pridopidine, Lamotrigine show distinct and complementary benefits in TAF1 LOF tadpoles. Viability: TAF1 LOF tadpoles (KD) have decreased viability which is apparent starting at 6-8 days post fertilization (dpf). Fig. 1A. Sak3 showed mild viability improvements compared with controls and did not cause significant toxicity. Fig. 1B. Pridopidine showed more dramatic improvement in viability, albeit with some toxicity at the dose tested. Fig. 1C. Lamotrigine proved to be toxic at the concentration tested, however it did delay the initial drop in viability typically by 2 dpf.

Swimming Behavior: TAF1 LOF tadpoles (KD) are developmentally delayed which also delays the dpf at which they start swimming and perdure as a 10 dpf TAF1 LOF tadpoles will tend to rest more often than swim, like a 6 dpf WT tadpoles would do. Fig. 1D. Sak3 mildly rescued developmental delay (not shown) which resulted in a partial rescue of swimming activity by 10 dpf. Fig. 1E. Similarly, both pridopidine and lamotrigine partially rescued the developmental delay, more so with Lamotrigine at 10 dpf. Fig. 1F. Example of tadpoles at 6 dpf (bar = 2 mm). While the differences in development are subtle, the TAF1 LOF tadpoles have less mature muscles in the tail, 5-10% smaller tail, head, eyes, and gut, which has not adopted the twisted shape. Lamotrigine, in particular seems to rescue this developmental delay.

Fig. 1G. Visual output from our tadpole tracker system showing the swimming behavior of each of the 5 tadpoles in a 60 mm dish represented as density map. WT are to very active and swim along the edge in circular motion. The compounds do not impact the behavior of WT animals. We can see that lamotrigine is able to rescue the behavior in the TAF1 LOF, while  
5 SAK3 offer a partial rescue.

FIGs. 2A-2E. Succinanic acid (4-anilino-4-oxo-butanoic acid) shows distinct and complementary benefits in TAF1 LOF tadpoles. Viability: TAF1 LOF tadpoles (KD) have decreased viability which is apparent starting at 15 days post fertilization (dpf). Fig. 2A. Succinanic acid (4-anilino-4-oxo-butanoic acid; RVL2 or RVL002 in the figures) showed  
10 viability improvements compared with controls and did not cause significant toxicity.

Swimming Behavior: Figs. 2B-2E. Succinanic acid (4-anilino-4-oxo-butanoic acid) mildly improves viability (Fig. 2A), swimming behavior (Fig. 2B), swimming mobility (Figs. 2C and 2E) and body orientation (Fig. 2D). The compound did not impact the behavior of WT animals.

FIGs. 3A-3D: Overexpression of HCN2 mRNA aggravates the phenotypes TAF1 Loss-of-Function in tadpoles. FIG. 3A: HCN2 overexpression does not result in a decrease in viability when injected into wild-type (WT) tadpoles. However, it further exacerbates the decrease the viability when injected concomitantly in TAF1 LOF tadpoles. Combined with lamotrigine (RVL27), HCN2 overexpression further decreases their viability. FIG. 3B:  
20 Upright orientation is a measure of spatial awareness and general motor function. WT tadpoles normally adopt a dorso-ventral, i.e. upright position. It is not normal for a tadpole to stay on its side at 15 dpf. HCN2 overexpression does not change the normal upright orientation in WT. However, it shows a non-significant decrease when the tadpoles are dosed with lamotrigine, and a significant decrease in a TAF1 LOF background. FIG. 3C: The overall time spent in the  
25 middle of the dish is a measure of swimming behavior related to both neuro-motor function and cognitive function. WT tadpoles normally spent more time swimming around the edge of the petri dish spending minimal time in the middle, only to cross it briefly without stopping. HCN2 overexpression does not change the normal swimming behavior in WT tadpoles. However, it shows a small but significant increase when the tadpoles are dosed with  
30 lamotrigine, and an obvious and significant increase in a TAF1 LOF background. FIG. 3D: The swimming velocity is a measure of swimming behavior and activity related to neuro-motor function and spatial orientation while swimming. Compared with WT tadpoles HCN2 overexpression does not change the normal swimming behavior in WT. However, it shows a

significant decrease in a TAF1 LOF background. Legend: One-way analysis of variance (one-way ANOVA) are indicated for statistical p-value < 0.05. WT: wild-type tadpoles; HCN2: overexpression of HCN2 with mRNA injection; TAF1: mosaic model of TAF1 loss-of-function using CRISPR; RVL27: Lamotrigine at 25 $\mu$ M; Dpf: Days post fertilization.

FIGs. 4A-4B: Treatment with the Notch agonist Ynhu-3792 or the voltage-dependent calcium channel blocker gabapentin aggravated the phenotypes of TAF1 Loss-of-Function tadpoles. FIG. 4A: Treatment with 50  $\mu$ M gabapentin (RVL66) non-significantly decreased the viability of TAF1 LOF tadpoles, while 1  $\mu$ M of Ynhu-3792 (RVL67) significantly decreased the viability of TAF1 LOF tadpoles at 10 dpf. Gabapentin or Ynhu-3792 did not affect the viability of the WT. FIG. 4B: Upright orientation is a measure of spatial awareness and general motor function. Nearly 100% of WT tadpoles adopt a dorso-ventral, i.e. upright position, by 8 dpf. Both gabapentin and Ynhu-3792 decreased the adoption of an upright position in WT, and even more so in TAF1 LOF tadpoles. Legend: Two-way analysis of variance (Two-way ANOVA) are indicated for statistical p-value < 0.05 compared to WT. WT: wild-type tadpoles; TAF1: mosaic model of TAF1 loss-of-function using CRISPR; RVL66: gabapentin at 50 $\mu$ M; RVL67: Ynhu-3792 at 10  $\mu$ M (viability assay) or at 1  $\mu$ M (spatial orientation); Dpf: Days post fertilization.

FIG. 5: Distribution of Lamotrigine candidate hits based on Thermal Proteome Profiling. TPP values were used to calculate a log2 fold-change and the log2 Z-score. The top proteins with Log2 fold-change and Z-score > 0. were considered hits (boxed area). Hit proteins (PSEN2, U2AF1, PSME3, and HBZ) involved in Notch signaling are indicated in the boxed area.

#### DETAILED DISCLOSURE OF THE INVENTION

The present disclosure relates to compounds and compositions for the treatment of diseases and/or disorders associated with a loss-of-function (LOF) mutation of a gene encoding TATA-box binding protein associated factor 1 (TAF1). Non-limiting examples of such diseases or disorders include, and are not limited to, XPD and/or X-linked syndromic intellectual developmental disorder-33.

The terms “treat”, “treating”, “inhibiting”, “inhibit”, “suppressing”, “suppress”, “decrease” and “decreasing” are used, in the context of this disclosure, to refer to the reduction, improvement, stabilization and/or elimination of a symptom of disease, or slowing the progression of disease. In the case of this disclosure, the disease or diseases to be treated include

X-linked dystonia parkinsonism (XDP; phenotype MIM number 314250, [omim.org/entry/314250](https://omim.org/entry/314250)) and/or X-linked syndromic intellectual developmental disorder-33 (phenotype MIM number 300966, [omim.org/entry/300966](https://omim.org/entry/300966)). Each of these OMIM entries is hereby incorporated by reference in their entireties.

5 In the context of XPD, the disclosed methods of treatment may result in decreased torsion dystonia and/or reduced spasmodic eye blinking, and/or decreased Parkinsonia symptoms that accompany or precede dystonia. Typically, the clinical course of XPD is highly variable with parkinsonism as the initial presenting sign and, more significantly, dystonia as the disease progresses. Parkinsonian symptoms include, and are not limited to resting tremor, chorea, bradykinesia, rigidity, postural instability, and severe shuffling gait. Dystonia may develop focally, most commonly in the jaw, neck, trunk, and eyes, and less commonly in the limbs, tongue, pharynx, and larynx, the most characteristic being jaw dystonia often progressing to neck dystonia. Some individuals have parkinsonism and non-disabling symptoms that are only slowly progressive. Other individuals develop a combination of parkinsonism and dystonia and can develop multifocal or generalized symptoms within a few years. Most XPD patients are male, although females may also develop XPD. Thus, certain embodiments of this disclosure envision the treatment of male patients only and other embodiments envision the treatment of female patients only. Yet other embodiments envision the treatment of both male and female subjects having XPD.

20 In the context of subjects having X-linked syndromic intellectual developmental disorder-33, the disclosed methods can be used to improve delayed psychomotor development, intellectual disability, delayed speech, spastic diplegia, tremor, and/or dystonic movements. In certain embodiments, the disclosed methods improve symptoms associated with spastic diplegia, tremor, and/or dystonic movement. In other embodiments, the disclosed methods reduce the severity or frequency of spastic diplegia, tremor, and/or dystonic movement in the treated subjects.

25 The term “therapeutically effective amount” is intended to constitute an amount of a compound disclosed herein that treats or suppresses symptoms associated with diseases and/or disorders associated with a loss-of-function (LOF) mutation of a gene encoding TATA-box binding protein associated factor 1 (TAF1). Non-limiting examples of such diseases or disorders include, and are not limited to, XPD and/or X-linked syndromic intellectual developmental disorder-33. In other words, compounds are administered in an amount sufficient to constitute a treatment of the disease and cause a reduction, improvement,

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stabilization and/or elimination of a symptom of a disease or slowing the progression of a disease associated with the loss of function of TAF1. Such amounts could range from about 0.01 to about 1,000 mg/kg of a subject to be treated.

The terms “about” or “approximately” mean a range of  $\pm 0$ -20%,  $\pm 0$  to 10%, or up to  $\pm 1\%$  of a given value. In the context of compositions containing amounts of ingredients where the terms “about” or “approximately” are used, these compositions contain the stated amount of the ingredient with a variation (error range) of 0-10% around the value ( $X \pm 10\%$ ). With respect to periods of time (days, weeks, months), the term is intended to include a period of  $\pm 6$  hours for days,  $\pm 1$  day for weeks, and  $\pm 7$  days for months.

The term “and/or” is used, herein, as a function word to indicate that two words or expressions are to be taken together or individually. As an example, the phrase “a, b, and/or c” be construed as a alone, b alone, c alone, a combination of a and b, a combination of a and c, a combination of b and c, or a combination of a, b, and c.

As used herein, the singular forms “a”, “an” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise. Further, to the extent that the terms “including”, “includes”, “having”, “has”, “with”, or variants thereof are used in either the detailed description and/or the claims, such terms are intended to be inclusive in a manner similar to the term “comprising”. The transitional terms/phrases (and any grammatical variations thereof) “comprising”, “comprises”, “comprise”, include the phrases “consisting essentially of”, “consists essentially of”, “consisting”, and “consists” can be used interchangeably. The phrases “consisting essentially of” or “consists essentially of” indicate that the claim encompasses embodiments containing the specified materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claim.

In the present disclosure, ranges are stated in shorthand, so as to avoid having to set out at length and describe each and every value within the range. Any appropriate value within the range can be selected, where appropriate, as the upper value, lower value, or the terminus of the range. For example, a range of 0.1-1.0 represents the terminal values of 0.1 and 1.0, as well as the intermediate values of 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and all intermediate ranges encompassed within 0.1-1.0, such as 0.2-0.5, 0.2-0.8, 0.7-1.0, etc. When ranges are used herein (such as for dose ranges), specific embodiments of different combinations and subcombinations of these dose ranges (e.g., subranges within the disclosed ranges) are intended to be explicitly included.

“Pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art.

The active agents disclosed herein can be formulated into pharmaceutically acceptable compositions. Such compositions comprise one or more of the disclosed active agents in combination with a pharmaceutically acceptable carrier such as a phosphate buffered saline, a bicarbonate solution, or formulated with a carrier such as starch into a pill to produce a pharmaceutical composition. The carrier must be “acceptable” in the sense that it is compatible with the active ingredient (agent) of the composition, and preferably capable of stabilizing the active agent and not deleterious to the subject to be treated. The carrier is selected on the basis of the mode and route of administration and standard pharmaceutical practice. Suitable pharmaceutical carriers and diluents, as well as pharmaceutical necessities for their use, are described in Remington’s Pharmaceutical Sciences.

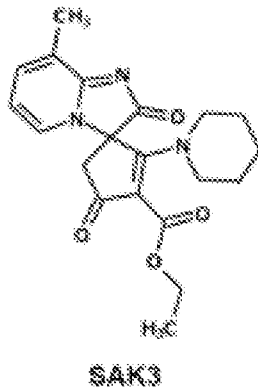
As used herein, “subject”, “patient”, “host” or “organism” refers to any member of the phylum Chordata, more preferably any member of the subphylum vertebrata, or most preferably, any member of the class Mammalia, including, without limitation, humans and other primates, including non-human primates such as rhesus macaques, chimpanzees and other monkey and ape species; farm animals, such as cattle, sheep, pigs, goats and horses; domestic mammals, such as dogs and cats; laboratory animals, including amphibians (e.g., frogs, tadpoles, salamanders, caecilians), rabbits, mice, rats and guinea pigs; birds, including domestic, wild, and game birds, such as chickens, turkeys, ducks, and geese. The term does not denote a particular age or gender. Thus, adult, young, and newborn individuals are intended to be covered as well as male and female subjects. In some embodiments, a host cell is derived from a subject (e.g., tissue specific cells, such as hepatocytes).

By “reduces” is meant a negative alteration of at least 1%, 5%, 10%, 25%, 50%, 75%, or 100%.

By “increases” is meant as a positive alteration of at least 1%, 5%, 10%, 25%, 50%, 75%, or 100%.

As used herein, a “pharmaceutical” refers to a compound manufactured for use as a medicinal and/or therapeutic drug. In the context of this disclosure, the compounds to be used for the treatment of XPD include SAK3 ((ethyl-8-methyl-2,4-dioxo-2-(piperidin-1-yl)-2H-spiro[cyclopentane-1,3-imidazo[1,2-a]pyridin]-2-ene-3-carboxylate), pridopidine,

succinanic acid (4-anilino-4-oxo-butanoic acid), and lamotrigine. The structure of SAK3 is provided below and is disclosed in Xu et al. (Int. J. Mol. Sci., 2021, 22:6185, doi.org/10.3390/ijms22126185), the disclosure of which is hereby incorporated by reference in its entirety, particularly with reference to the structure of SAK3.



The compounds and compositions disclosed herein can be administered by any acceptable route for the treatment of XPD or a subject with a mutation of a gene encoding TAF1 that confers a loss-of-function. Non-limiting examples include administering the compounds and/or compositions disclosed herein orally, by injection, by subcutaneous injection, by intraperitoneal injection, by intravenous infusion, topically, or by inhalation.

The subject compounds can be formulated according to known methods for preparing pharmaceutically useful compositions. In general, the compositions of the subject invention will be formulated such that an effective amount of the subject compounds is combined with a suitable carrier in order to facilitate effective administration of the composition. The compositions used in the present methods can also be in a variety of forms. These include, for example, solid, semi-solid, and liquid dosage forms, such as tablets, pills, powders, liquid solutions or suspension, suppositories, injectable and infusible solutions, and sprays. The preferred form depends on the intended mode of administration and therapeutic application.

The compositions also preferably include conventional pharmaceutically acceptable carriers and diluents which are known to those skilled in the art. Examples of carriers or diluents for use with the subject compounds include, but are not limited to, water, saline, oils including mineral oil, ethanol, dimethyl sulfoxide, gelatin, cyclodextrins, magnesium stearate, sodium croscarmellose, dextrose, cellulose, sugars, calcium carbonate, glycerol, alumina, starch, and equivalent carriers and diluents, or mixtures of any of these. The subject

composition can further comprise one or more pharmaceutically acceptable carriers and/or excipients. The term “pharmaceutically acceptable” as used herein means compatible with the other ingredients of a pharmaceutical composition and not deleterious to the recipient thereof. Carriers and/or excipients according to the subject invention can include any and all solvents, diluents, buffers (such as, e.g., neutral buffered saline, phosphate buffered saline, or optionally Tris-HCl, acetate or phosphate buffers), oil-in-water or water-in-oil emulsions, aqueous compositions with or without inclusion of organic co-solvents suitable for, e.g., IV use, solubilizers (e.g., Polysorbate 65, Polysorbate 80), colloids, dispersion media, vehicles, fillers, chelating agents (e.g., EDTA or glutathione), amino acids (e.g., glycine), proteins, disintegrants, binders, lubricants, wetting agents, emulsifiers, sweeteners, colorants, flavorings, aromatizers, thickeners (e.g. carbomer, gelatin, or sodium alginate), coatings, preservatives (e.g., Thimerosal, benzyl alcohol, polyquaterium), antioxidants (e.g., ascorbic acid, sodium metabisulfite), tonicity controlling agents, absorption delaying agents, adjuvants, bulking agents (e.g., lactose, mannitol) and the like. The use of carriers and/or excipients in the field of drugs and supplements is well known. Except for any conventional media or agent that is incompatible with the target proteins or with the composition, carrier or excipient use in the subject compositions may be contemplated.

In one embodiment, the compounds of the subject invention can be formulated for administration via injection, for example, as a solution or suspension. The solution or suspension can comprise suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, non-irritant, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid. One illustrative example of a carrier for intravenous use includes a mixture of 10% USP ethanol, 40% USP propylene glycol or polyethylene glycol 600 and the balance USP Water for Injection (WFI). Other illustrative carriers for intravenous use include 10% USP ethanol and USP WFI; 0.01-0.1% triethanolamine in USP WFI; or 0.01-0.2% dipalmitoyl diphosphatidylcholine in USP WFI; and 1-10% squalene or parenteral vegetable oil-in-water emulsion. Water or saline solutions and aqueous dextrose and glycerol solutions may be preferably employed as carriers, particularly for injectable solutions. Illustrative examples of carriers for subcutaneous or intramuscular use include phosphate buffered saline (PBS) solution, 5% dextrose in WFI and 0.01-0.1% triethanolamine in 5% dextrose or 0.9% sodium chloride in USP WFI, or a 1 to 2 or 1 to 4 mixture of 10% USP ethanol, 40% propylene glycol and the balance an acceptable

isotonic solution such as 5% dextrose or 0.9% sodium chloride; or 0.01-0.2% dipalmitoyl diphosphatidylcholine in USP WFI and 1 to 10% squalene or parenteral vegetable oil-in-water emulsions.

To provide for the administration of such dosages for the desired therapeutic treatment, pharmaceutical compositions of the invention will advantageously comprise between about 0.1% and 99%, and especially, 1% and 15% by weight of the total of the subject compounds based on the weight of the total composition including carrier or diluent.

The subject compounds can also be administered utilizing liposome technology, slow release capsules, implantable pumps, and biodegradable containers. These delivery methods can, advantageously, provide a uniform dosage over an extended period of time.

The subject invention also concerns a packaged dosage formulation comprising in one or more packages, packets, or containers the subject compounds and/or a composition of the subject invention formulated in a pharmaceutically acceptable dosage. The package can contain discrete quantities of the dosage formulation, such as tablet, capsules, lozenge, and powders. The quantity of the subject compounds in a dosage formulation and that can be administered to a patient can vary from about 1 mg to about 1000 mg. In some embodiments, the amount is in the range of 5 mg to 500 mg, to be administered 1, 2, 3, or 4 times per day, for about 2, about 3, about 4, about 5, about 6, about 7, about 10, about 14, about 21, about 28, about 35, about 40, about 45, about 50, about 55, about 60, about 120, about 180, about 365 days or more days.

In some embodiments, the subject compounds or compositions can be administered a certain number of times per week or month (for example, 1, 2, 3, 4, 5, 6, or 7 times per week or between 1 day and x days per month, where x is 28, 29, 30, or 31 days depending on the month or year (if a leap year)). "A week" refers to a period of time of about 5, about 6 or about 7 days. "A month" refers to a period of time of about 28, about 29, about 30, or about 31 days.

As discussed above, therapeutically effective amounts of the subject compositions are administered to a subject in need of treatment of XPD or X-linked syndromic intellectual developmental disorder-33. Thus, the subject compounds can be administered in an amount that ranges from about 0.01 mg/kg to about 150 mg/kg of a subject to be treated; about 1 mg/kg to about 75 mg/kg of a subject to be treated; about 1 mg/kg to about 50 mg/kg of a subject to be treated; about 10 mg/kg to about 100 mg/kg of a subject to be treated; about 10 mg/kg to about 75 mg/kg of a subject to be treated; about 10 mg/kg to about 50 mg/kg of a subject to be treated; about 1 mg/kg to about 75 mg/kg of a subject to be treated; about 10 mg/kg to about 30 mg/kg of a subject to be treated; about 15 mg/kg to about 30 mg/kg of a subject to be treated;

about 15 mg/kg to about 25 mg/kg of a subject to be treated; or in an amount of about 20 mg/kg of a subject to be treated.

In certain embodiments, the subject compositions or compounds can be administered before symptoms of XPD have developed, including, for example, dystonia and/or parkinsonian symptoms such as resting tremor, bradykinesia, rigidity, postural instability, and/or severe shuffling gait. Additionally or alternatively, the subject compositions can be administered after symptoms of XPD have developed or after a subject has been diagnosed XPS. In certain embodiments, diagnosing XPD comprises identifying at least one mutation in the gene encoding TAF1 (OMIM entry 313650, the disclosure of which is hereby incorporated by reference in its entirety).

All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

Following are examples which illustrate procedures for practicing the invention. These examples should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted.

## EXAMPLE 1

### MATERIALS AND METHODS

*Phenotypic rescue in TAF1 LOF tadpoles by SAK3, Pridopidine and Lamotrigine.* TAF1 LOF tadpoles presents robust phenotypes including developmental delays resulting in a delayed start of swimming at 8 days post fertilization (8 dpf) compared with 6 dpf for wild-type tadpoles. They also present abnormal swimming behavior, ~50% lower viability, and a range of abnormal behaviors, including forced and uncontrolled mandibular movements, mild to severe tail spasms, loss of spatial orientation, the frequency of observing any of those last three phenotypes, which we liken to dystonia-like symptoms as far as tadpole goes, being approximately 0.1 event per minute. Highlights are presented below and Figure 1.

Figs. 1A-1G. SAK3, Pridopidine, Lamotrigine show distinct and complementary benefits in TAF1 LOF tadpoles. Viability: TAF1 LOF tadpoles (KD) have decreased viability which is apparent starting at 6-8 days post fertilization (dpf). Fig. 1A. Sak3 showed mild viability improvements compared with controls and did not cause significant toxicity. Fig. 1B. Pridopidine showed more dramatic improvement in viability, albeit with some toxicity at the

dose tested. Fig. 1C. Lamotrigine proved to be toxic at the concentration tested, however it did delay the initial drop in viability typically by 2 dpf.

Swimming Behavior: TAF1 LOF tadpoles (KD) are developmentally delayed which also delays the dpf at which they start swimming and perdure as a 10 dpf TAF1 LOF tadpoles will tend to rest more often than swim, like a 6 dpf WT tadpoles would do. Fig. 1D. Sak3 mildly rescued developmental delay (not shown) which resulted in a partial rescue of swimming activity by 10 dpf. Fig. 1E. Similarly, both pridopidine and lamotrigine partially rescued the developmental delay, more so with Lamotrigine at 10 dpf. Fig. 1F. Example of tadpoles at 6 dpf (bar = 2 mm). While the differences in development are subtle, the TAF1 LOF tadpoles have less mature muscles in the tail, 5-10% smaller tail, head, eyes, and gut, which has not adopted the twisted shape. Lamotrigine, in particular seems to rescue this developmental delay. Fig. 1G. Visual output from our tadpole tracker system showing the swimming behavior of each of the 5 tadpoles in a 60 mm dish represented as density map. WT are to very active and swim along the edge in circular motion. The compounds do not impact the behavior of WT animals. We can see that lamotrigine is able to rescue the behavior in the TAF1 LOF, while SAK3 offer a partial rescue. We are in the process of assessing combinations of these drugs to identify synergistic effects.

Figs. 2A-2E. Succinanic acid (4-anilino-4-oxo-butanoic acid) shows distinct and complementary benefits in TAF1 LOF tadpoles. Viability: TAF1 LOF tadpoles (KD) have decreased viability which is apparent starting at 15 days post fertilization (dpf). Fig. 2A. Succinanic acid (4-anilino-4-oxo-butanoic acid; RVL2) showed viability improvements compared with controls and did not cause significant toxicity.

Swimming Behavior: Figs. 2B-2E. Succinanic acid (4-anilino-4-oxo-butanoic acid; RVL2) mildly improves viability (Fig. 2A), swimming behavior (Fig. 2B), swimming mobility (Figs. 2C and 2E) and body orientation (Fig. 2D). The compound did not impact the behavior of WT animals.

## EXAMPLE 2 - Evaluating HCN2 as potential target.

Notch signaling is triggered when a Notch ligand binds to a transmembrane NOTCH receptor. This binding initiates two successive proteolytic cleavages, through  $\alpha$ - and  $\gamma$ -secretases, releasing the Notch intracellular domain (NICD).

It has been suggested that patients with motor neuron disorders have disrupted Notch signaling. This was demonstrated in patients with Amyotrophic lateral sclerosis (ALS), where

NICD is significantly under expressed in the brain of ALS patients compared with normal subjects, while the Notch1 is over expressed in the same ALS patients (Gómez-Pinedo U, Galán L, Matías-Guiu JA, Pytel V, Moreno T, Guerrero-Sola A, Matías-Guiu J. Notch signalling in the hippocampus of patients with motor neuron disease. *Front Neurosci.* 2019 Apr 5;13:302. PMID: PMC6460507). Furthermore, a recent publication showed that TAF1 upregulates the lncRNA FOXD2-AS1 which then activates the NOTCH1 signaling pathway in glioma stem cells Wang Y, Cheng Y, Yang Q, Kuang L, Liu G. Overexpression of FOXD2-AS1 enhances proliferation and impairs differentiation of glioma stem cells by activating the NOTCH pathway via TAF-1. *J Cell Mol Med.* 2022 May;26(9):2620–2632. PMID: PMC9077300).

Overexpression of NOTCH intracellular domain leads to dysregulation of the NOTCH signaling, resulting in impaired neuronal patterning and bioelectric signals, including in vertebrate animals such *Xeopus laevis* tadpoles (Pai VP, Lemire JM, Paré J-F, Lin G, Chen Y, Levin M. Endogenous gradients of resting potential instructively pattern embryonic neural tissue via Notch signaling and regulation of proliferation. *J Neurosci.* 2015 Mar 11;35(10):4366–4385. PMID: PMC4355204).

It was demonstrated in tadpoles that overexpression of HCN2 in the form of an mRNA was able to rescue the phenotypes associated with NOTCH disruption, similar to lamotrigine (Pai VP, Levin M. HCN2 channel-induced rescue of brain, eye, heart and gut teratogenesis caused by nicotine, ethanol and aberrant notch signalling. *Wound Repair Regen.* 2022 Nov;30(6):681–706. PMID: 35662339).

As such we evaluated if HCN2 overexpression could rescue TAF1 loss-of-function (LOF) in the tadpole model, which would indicate a similar NOTCH signaling disruption. We injected both HCN2 mRNA and TAF1 CRISPR in 4-cell stage *Xenopus* embryos, to generate a TAF1 LOF overexpressing HCN2. We did not observe any phenotypic rescue in TAF1 LOF. We also did not observe synergistic improvement when dosing the HCN2-expressing TAF1-LOF tadpole with lamotrigine. In some cases, HCN2 mRNA aggravated the phenotypes caused by TAF1 LOF.

EXAMPLE 3 - Evaluating treatment with NOTCH agonist Ynhu-3792 or with voltage-dependent calcium channel blocker gabapentin in tadpoles.

Based on our HCN2 results we evaluated a NOTCH agonist. Ynhu-3792 (5-(3-methoxyphenoxy)-*N*<sup>2</sup>-[4-(1-methylethyl)phenyl]-2,4-quinazolinediamine hydrochloride; CAS Registry No. 2624336-93-0) activates Notch signaling pathway and expression of Hes3 and Hes5. It was shown to promotes neurogenesis in the hippocampal dentate gyrus, and to increases the spatial and episodic memory abilities of mice (Lu H, Cheng G, Hong F, Zhang L, Hu Y, Feng L. A Novel 2-Phenylamino-Quinazoline-Based Compound Expands the Neural Stem Cell Pool and Promotes the Hippocampal Neurogenesis and the Cognitive Ability of Adult Mice. Stem Cells. 2018 Aug;36(8):1273–1285. PMID: 29726088).

We first tested that 10  $\mu$ M was a safe dose in tadpoles. However, we observed that while it was safe in wild-type tadpoles, it was acutely toxic in the TAF1 LOF background. Reducing the dose to 1  $\mu$ M remained toxic in TAF1 LOF tadpoles.

Looking at the spatial orientation of young tadpoles, Ynhu-3792 did have a negative effect in WT tadpoles, which was even more pronounced in the TAF1 LOF.

Gabapentin is known to block the voltage-dependent calcium channels activation by binding to the  $\alpha 2\delta$  subunit (CACNA2-D1, -D2, -D3 and -D4). Voltage-dependent calcium channels are regulated by Notch signaling, such as when constitutively expressing Notch intracellular domains (NICD). It has been shown that Gabapentin would have similar benefit than lamotrigine in rescuing the effect of sustained NICD expression in tadpoles (Pai VP, Levin M. HCN2 channel-induced rescue of brain, eye, heart and gut teratogenesis caused by nicotine, ethanol and aberrant notch signalling. Wound Repair Regen. 2022 Nov;30(6):681–706. PMID: 35662339}. However, based on our observations we seek to verify that Gabapentin would instead aggravate the phenotypes of TAF1 LOF tadpoles. Treatment with gabapentin did decrease both the viability and the spatial orientation in the TAF1 LOF background.

**EXAMPLE 4 - Identification of Notch signaling proteins targeted by lamotrigine using thermal proteome profiling.**

Tadpoles at 15 dpf where dosed for 2 hours with 50  $\mu$ M of lamotrigine, then submitted to one-pot thermal proteome profiling (TPP). Tadpoles samples were snap-frozen in dry ice/methanol (4 cycles of snap-freezing). Then samples were centrifuged, and 11.1  $\mu$ L of each of the 9 temperature treatments of a single condition were pooled in a new tube (total 100  $\mu$ L). The 16 pool samples were centrifuged for 75 minutes at a max speed and at 4°C, then 80  $\mu$ L were transferred to new tubes. The protein content of each pool was determined and completed to 100  $\mu$ L with 50 mM Tris pH 8. The protein content of each sample was then reduced with

10  $\mu\text{L}$  of 110 mM DTT for 15 minutes at 65°C and alkylated with 10  $\mu\text{L}$  of 180 mM iodoacetamide for 30 minutes in the dark. Proteins were then precipitated with 8 volumes of ice-cold acetone and 1 volume of ice-cold methanol overnight at -80°C, and the pellet was washed 3 times with 250  $\mu\text{L}$  of cold methanol. Protein pellets were resolubilized in 100  $\mu\text{L}$  of  
5 50 mM Tris pH 8.0 + 0.75M + 0.1% NaDOC and digested with 3.3  $\mu\text{g}$  of Trypsin/LysC at 37°C with agitation. Samples were then acidified with 2% formic acid, and the peptides were purified by reversed-phase SPE. Each sample was analyzed in SWATH mode on a 30-minute LC-MS/MS gradient (GPF mode). The ion library is composed of a pool of the 16 samples. The ion library was analyzed in IDA mode on a 30-minute LC-MS/MS gradient.

10 The acquisition was performed with a Sciex ZenoTOF 7600 (Sciex, Foster City, CA, USA) equipped with an OptiFlow Turbo V ion source using the micro probe and an electrode 1-10  $\mu\text{L}/\text{min}$ . Sciex OS 3.0 software was used to control the instrument and for data processing and acquisition. The acquisition was performed in Zeno Dependant Data Acquisition (Zeno-DDA or IDA) mode for the ion library. The samples were analyzed in Zeno SWATH (Zeno-DIA) acquisition mode. The source voltage was set to 4.5 kV and maintained at 200°C; curtain  
15 gas was set at 35 psi, gas one at 20 psi, and gas two at 60 psi. A Waters ACQUITY UPLC M-class system was used (Waters, Milford, MA, USA) with a reversed-phase Kinetex XB C18 column 0.3 mm i.d., 2.6  $\mu\text{m}$  particles, 150 mm (Phenomenex), which was maintained at 60°C. Samples were injected in direct-inject mode using a 5  $\mu\text{L}$  loop (full loop mode with overfilling).  
20 For the 30 minutes LC gradient, the mobile phase consisted of the following solvent A (H<sub>2</sub>O 0.2% FA 3% DMSO) and solvent B (EtOH 0.2% FA 3% DMSO) at a flow rate of 5  $\mu\text{L}/\text{min}$ .

Peptides and proteins for the ion library were identified using Protein Pilot (Sciex). We used an ion library constructed with the IDA samples for SWATH peptide quantification. Peptides were quantified using DIA-NN (version 1.8.1). Peptide areas were then corrected  
25 using the RT-LOESS algorithm from the NormalizerDE package and summed for each protein. TPP value were used to calculate a log<sub>2</sub> fold-change and the log<sub>2</sub> Z-score. The top proteins with Log<sub>2</sub> fold-change and Z-score > 0.58 were considered a hit.

TPP revealed 4 proteins that are part of the NOTCH signaling pathways likely interact directly with Lamotrigine: The Hemoglobin subunit zeta (HBZ), Presenilin-2 (PSEN2),  
30 Proteasome activator complex subunit 3 (PSME3), and Splicing factor U2AF 35 kDa subunit (U2AF1). With the exception of PSEN2, a subunit of the gamma-secretase complex involved in Notch processing, the interaction between either HBZ, PSME3 or U2AF1 has not been

specifically characterized. Based on Reactome pathway annotations, we can provide an initial evaluation of the likely interaction between Notch and these lamotrigine target candidates:

HBZ interacts with several regulators of NOTCH expression, including Jun, ATF2, CREBP1, MAFB and MAFG (Sanalkumar R, Indulekha CL, Divya TS, Divya MS, Anto RJ, Vinod B, Vidyanand S, Jagatha B, Venugopal S, James J. ATF2 maintains a subset of neural progenitors through CBF1/Notch independent Hes-1 expression and synergistically activates the expression of Hes-1 in Notch-dependent neural progenitors. *J Neurochem.* 2010 May;113(4):807-18. doi: 10.1111/j.1471-4159.2010.06574.x. Epub 2010 Jan 8. PMID: 20067572.)(Reinke AW, Grigoryan G, Keating AE. Identification of bZIP interaction partners of viral proteins HBZ, MEQ, BZLF1, and K-bZIP using coiled-coil arrays. *Biochemistry.* 2010 Mar 9;49(9):1985-97. doi: 10.1021/bi902065k. PMID: 20102225; PMCID: PMC2841013.).

PSEN2, a subunit of the gamma-secretase complex along with PSEN1, is known to be involved in processing and cleaving of NOTCH. (Arber C, Lovejoy C, Harris L, Willumsen N, Alatz A, Casey JM, Lines G, Kerins C, Mueller AK, Zetterberg H, Hardy J, Ryan NS, Fox NC, Lashley T, Wray S. Familial alzheimer's disease mutations in PSEN1 lead to premature human stem cell neurogenesis. *Cell Rep.* 2021 Jan 12;34(2):108615. PMCID: PMC7809623)(Kostyszyn B, Cowburn RF, Seiger A, Kjaeldgaard A, Sundström E. Distribution of presenilin 1 and 2 and their relation to Notch receptors and ligands in human embryonic/foetal central nervous system. *Brain Res Dev Brain Res.* 2004 Jul 19;151(1-2):75-86. PMID: 15246694).

PSME3, part of the 26S and 20S proteasome-ubiquitination systems, which are involved in ubiquitination of NOTCH (Wu G, Lyapina S, Das I, Li J, Gurney M, Pauley A, Chui I, Deshaies RJ, Kitajewski J. SEL-10 is an inhibitor of notch signaling that targets notch for ubiquitin-mediated protein degradation. *Mol Cell Biol.* 2001 Nov;21(21):7403-15. doi: 10.1128/MCB.21.21.7403-7415.2001. PMID: 11585921; PMCID: PMC99913.)(Oberg C, Li J, Pauley A, Wolf E, Gurney M, Lendahl U. The Notch intracellular domain is ubiquitinated and negatively regulated by the mammalian Sel-10 homolog. *J Biol Chem.* 2001 Sep 21;276(38):35847-53. doi: 10.1074/jbc.M103992200. Epub 2001 Jul 18. PMID: 11461910.).

U2AF1 (Splicing factor U2AF 35 kDa subunit) is involved in both the expression of NOTCH genes and CSL transcription factors who also regulates NOTCH genes. Notch and CSL form a Coactivator Complex, which includes CREBBP, p300, HATs, HDACs, NCORs. (Laaref AM, Manchon L, Bareche Y, Lapasset L, Tazi J. The core spliceosomal factor U2AF1 controls cell-fate determination via the modulation of transcriptional networks. *RNA Biol.*

2020 Jun;17(6):857–871. PMID: 30030832).  
PMCID: PMC7549707)(Oswald F, Kovall RA. CSL-Associated Corepressor and Coactivator Complexes. Adv Exp Med Biol. 2018;1066:279–295. PMID: 30030832).

5           It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims. In addition, any elements or limitations of any invention or embodiment thereof disclosed herein can be combined with any and/or all  
10 other elements or limitations (individually or in any combination) or any other invention or embodiment thereof disclosed herein, and all such combinations are contemplated within the scope of the invention without limitation thereto.

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5 12. Lee LV, Rivera C, Teleg RA, Dantes MB, Pasco PMD, Jamora RDG, et al. The unique phenomenology of sex-linked dystonia parkinsonism (XDP, DYT3, “Lubag”). *Int J Neurosci* 2011;121 Suppl 1:3–11.

## CLAIMS

We claim:

1. A method of treating a subject with a loss-of-function (LOF) mutation of a gene encoding TATA-box binding protein associated factor 1 (TAF1) comprising administering a compound selected from the group consisting of SAK3, Pridopidine, Lamotrigine, succinilic acid (4-anilino-4-oxo-butanoic acid), and combinations thereof or a composition comprising a compound selected from the group consisting of SAK3, Pridopidine, Lamotrigine, succinilic acid (4-anilino-4-oxo-butanoic acid) and combinations thereof to a subject having a LOF mutation of the gene encoding TAF1.
2. The method according to claim 1, wherein said subject has X-linked syndromic intellectual developmental disorder-33 or X-linked Dystonia Parkinsonism (XDP).
3. The method according to any one of claims 1 or 2, wherein a pharmaceutical composition comprising a compound selected from the group consisting of SAK3, Pridopidine, Lamotrigine, and combinations thereof is administered to said subject and said pharmaceutical composition comprises between about 0.1% and 99% by weight of said compound or combination of compounds based on the weight of the total composition including carrier or diluent.
4. The method according to any one of claims 1 or 2, wherein a pharmaceutical composition comprising a compound selected from the group consisting of SAK3, Pridopidine, Lamotrigine, and combinations thereof is administered to said subject and said pharmaceutical composition comprises between about 1% and 15% by weight of said compound or combination of compounds based on the weight of the total composition including carrier or diluent.

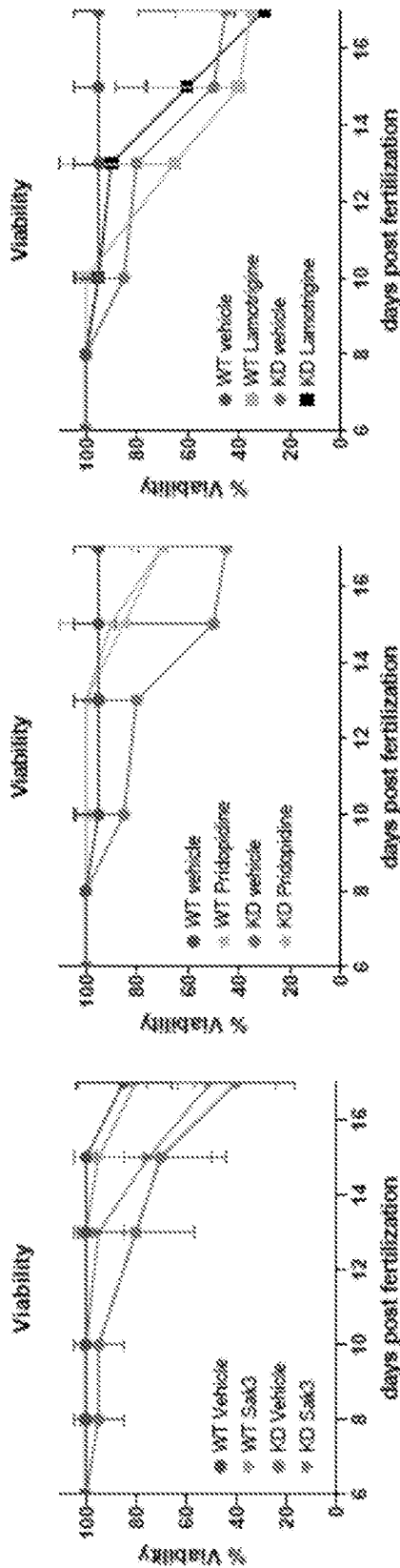


FIG. 1A

FIG. 1B

FIG. 1C

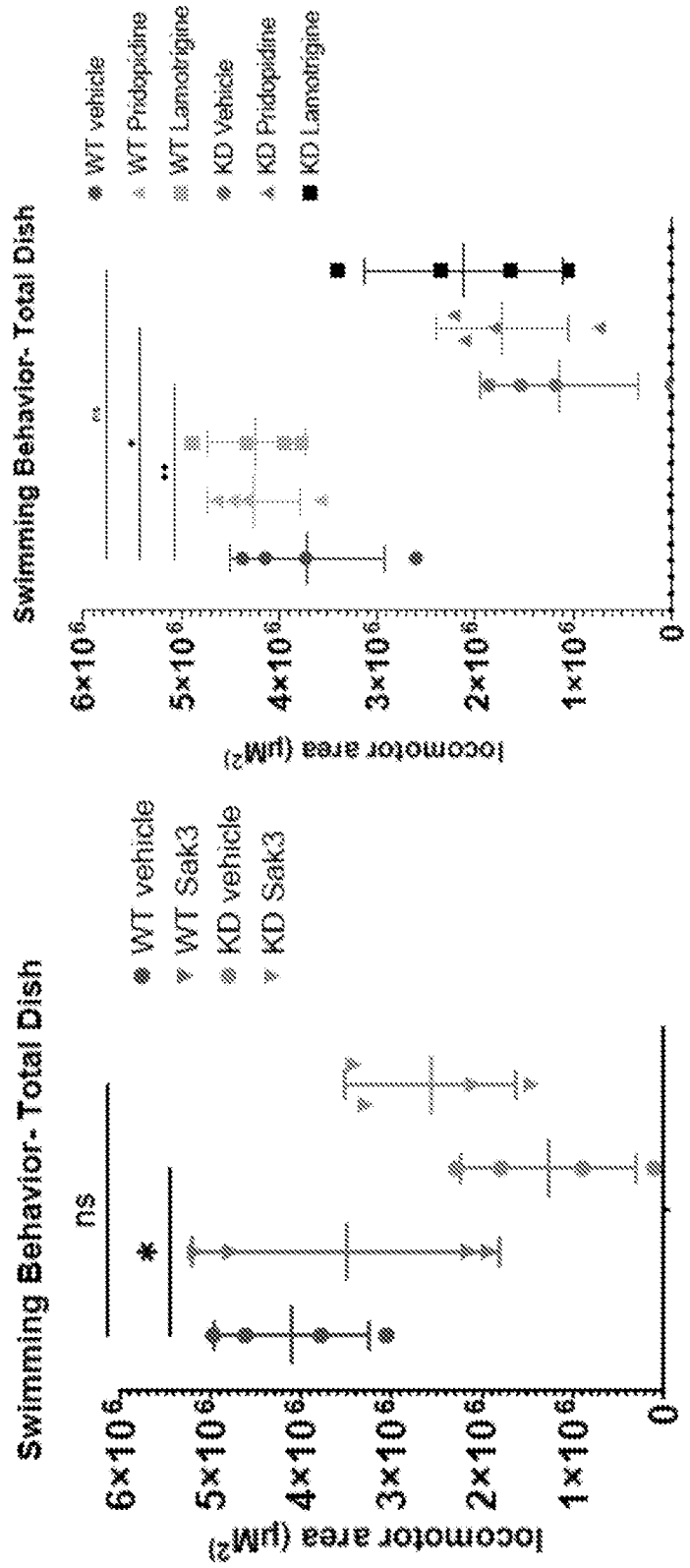


FIG. 1E

FIG. 1D

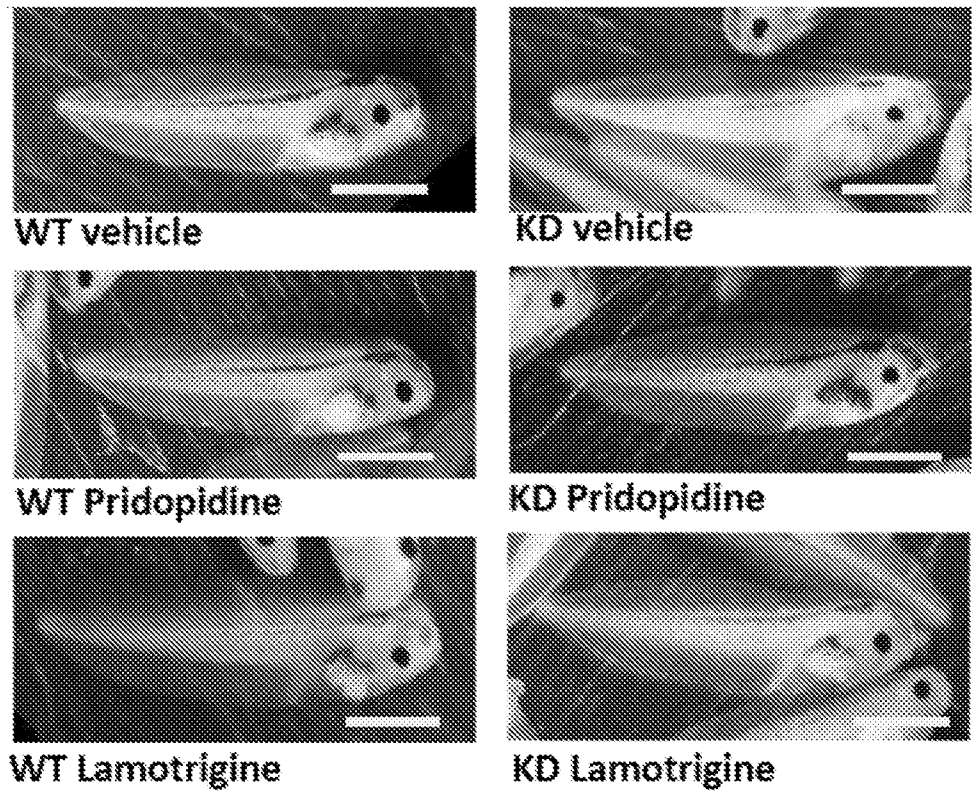


FIG. 1F

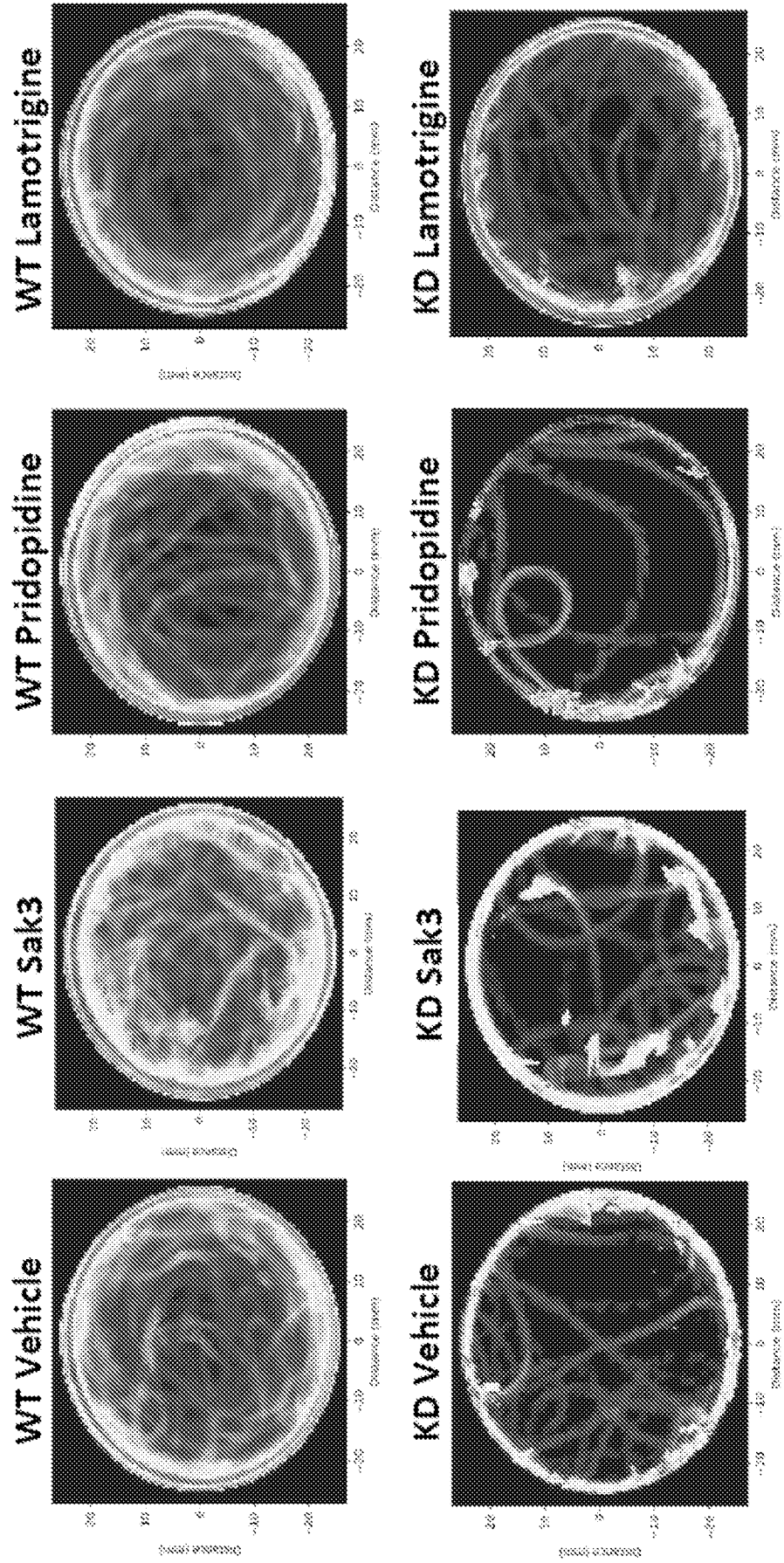


FIG. 1G

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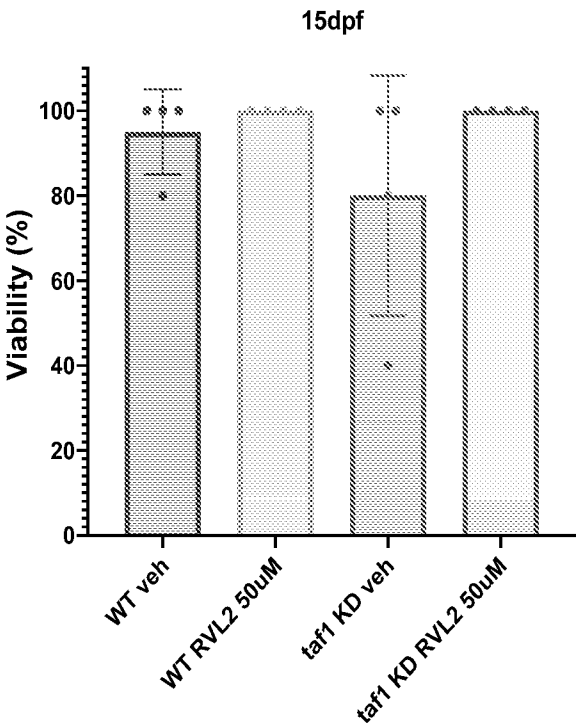


FIG. 2A

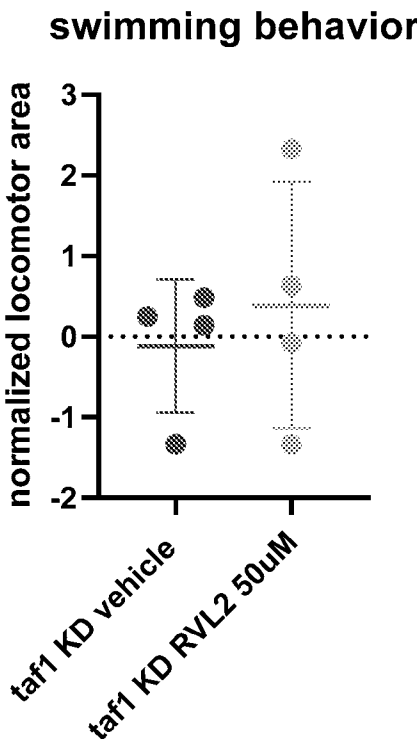


FIG. 2B

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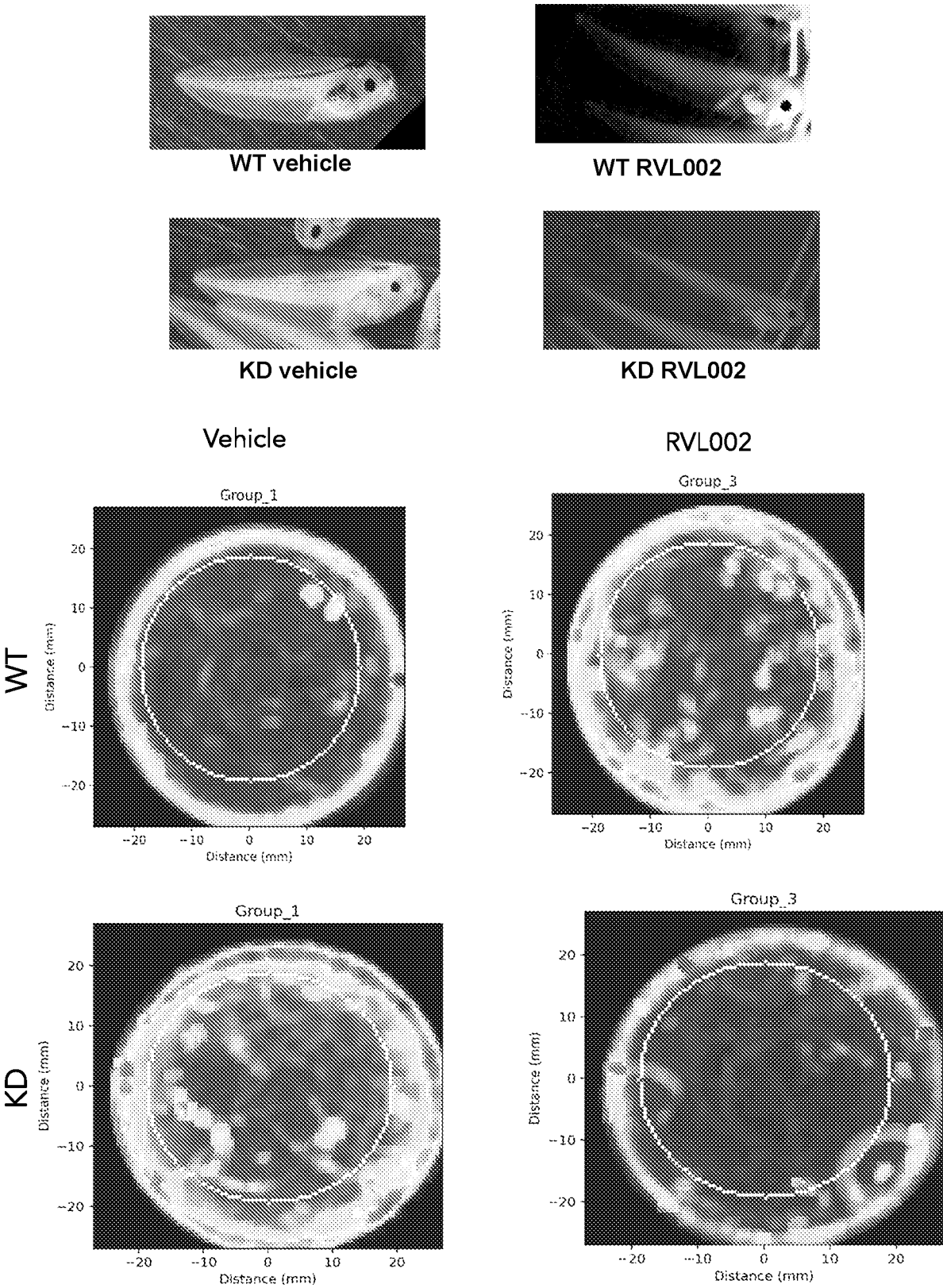


FIG. 2C

Body orientation measures tadpole ability to maintain upright swimming position

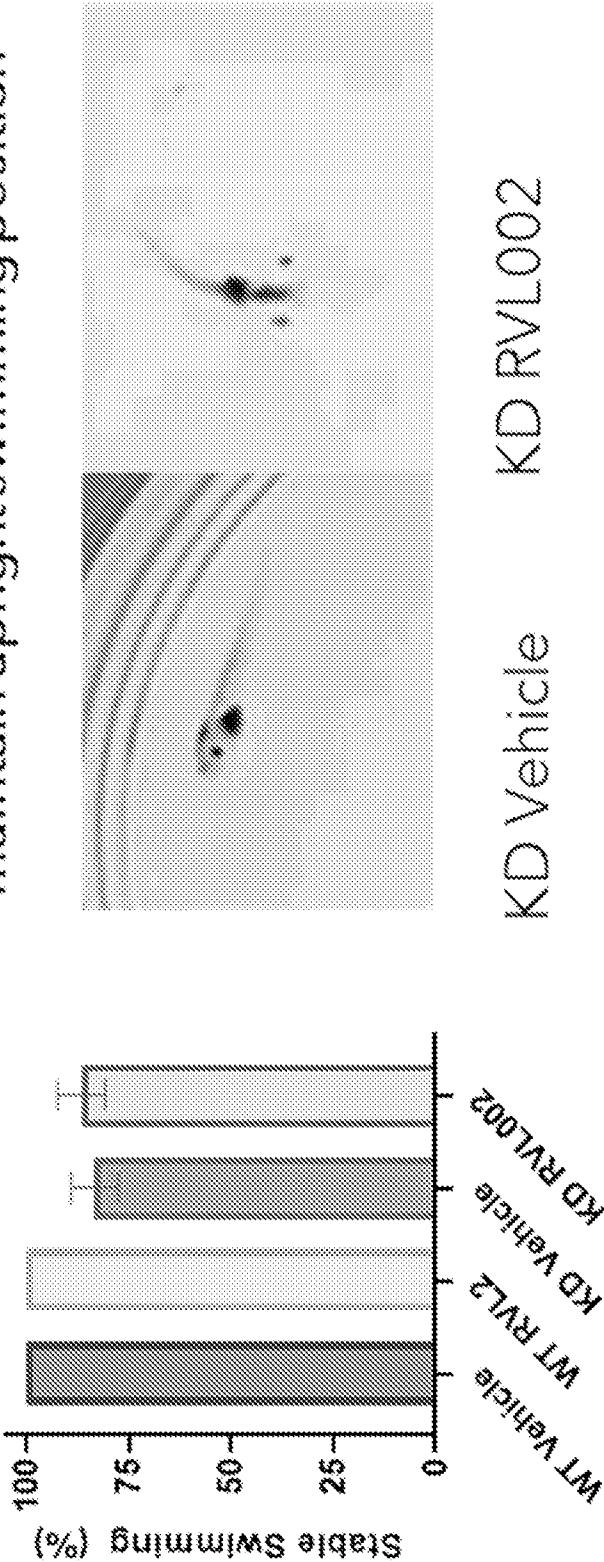


FIG. 2D

Velocity over time shows RVL002 dosed Taf1  
KD tadpoles have increased mobility compared  
with vehicle treated Taf1 KD tadpoles

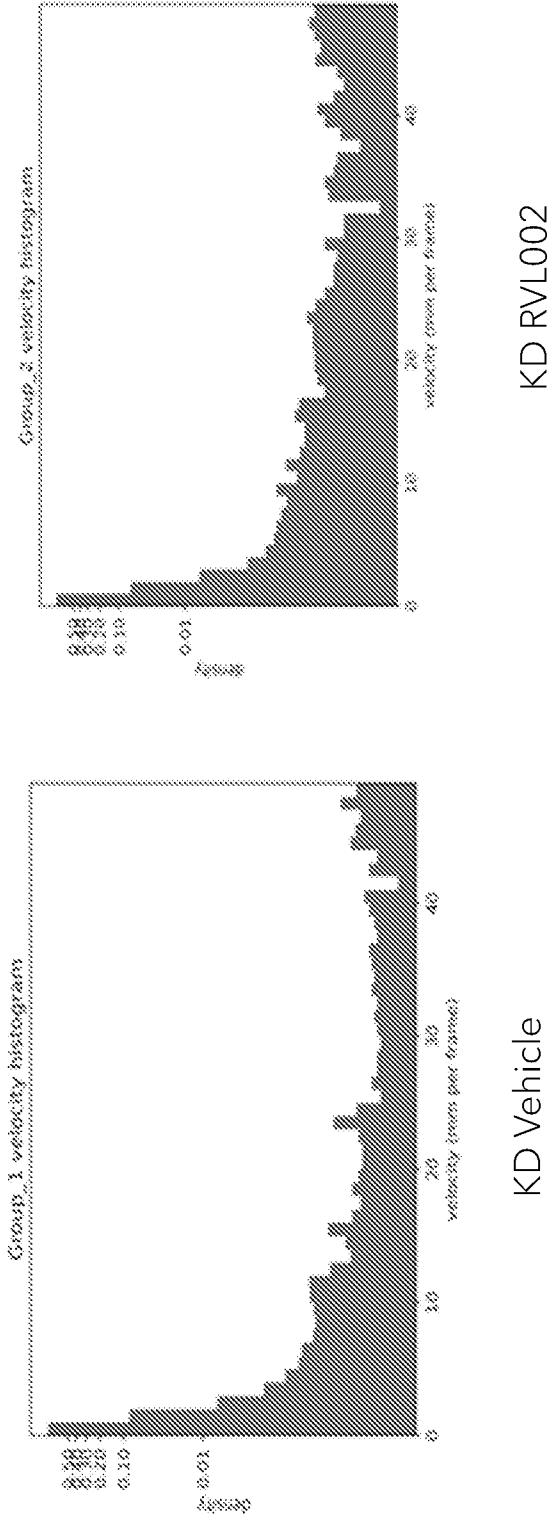


FIG. 2E

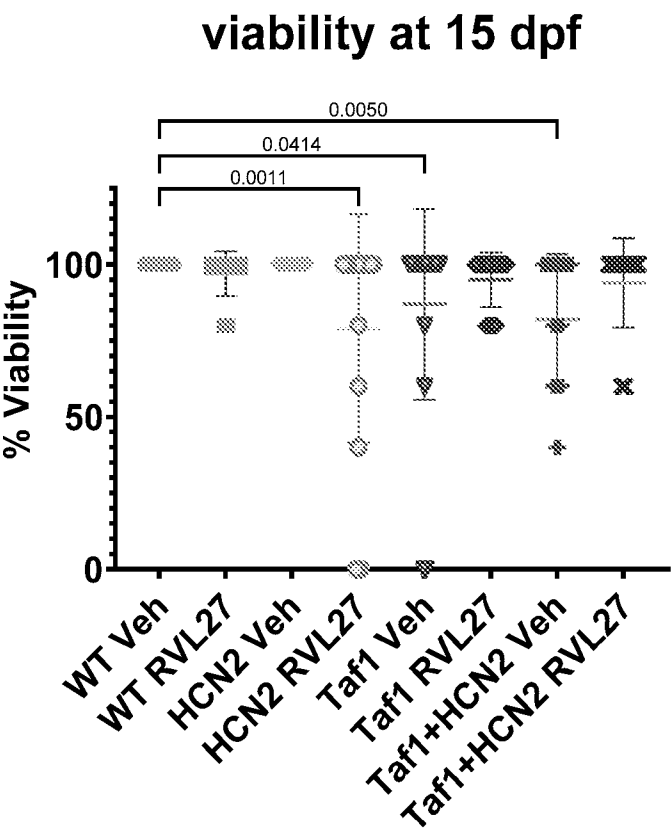


FIG. 3A

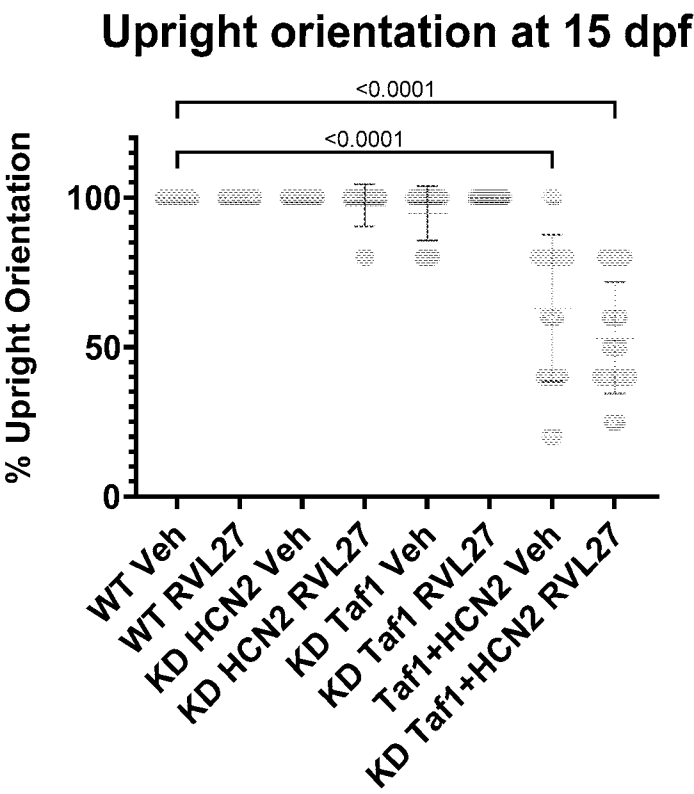


FIG. 3B

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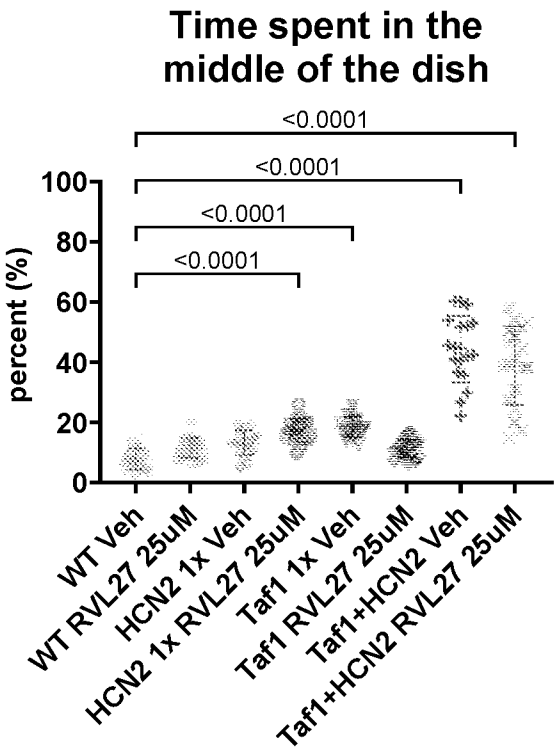


FIG. 3C

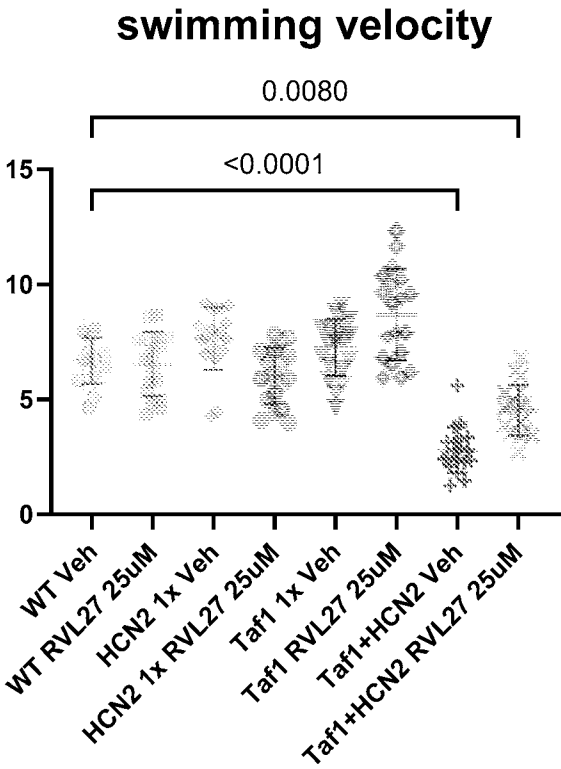


FIG. 3D

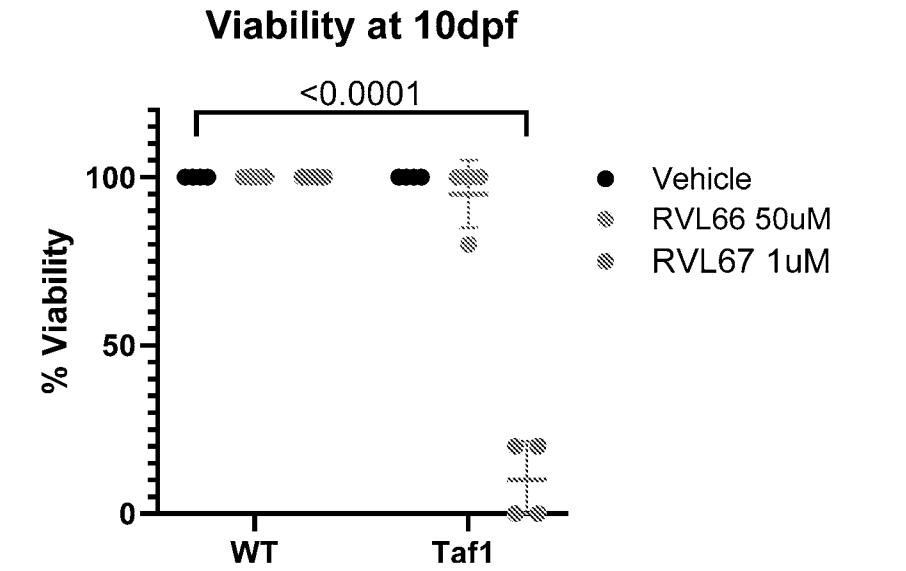


FIG. 4A

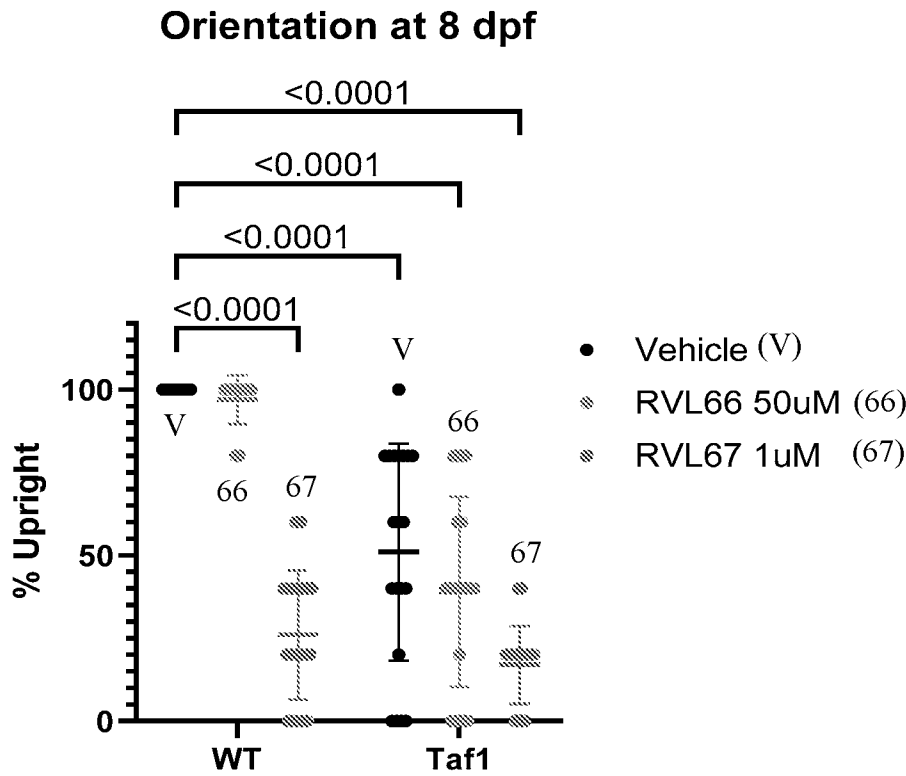


FIG. 4B

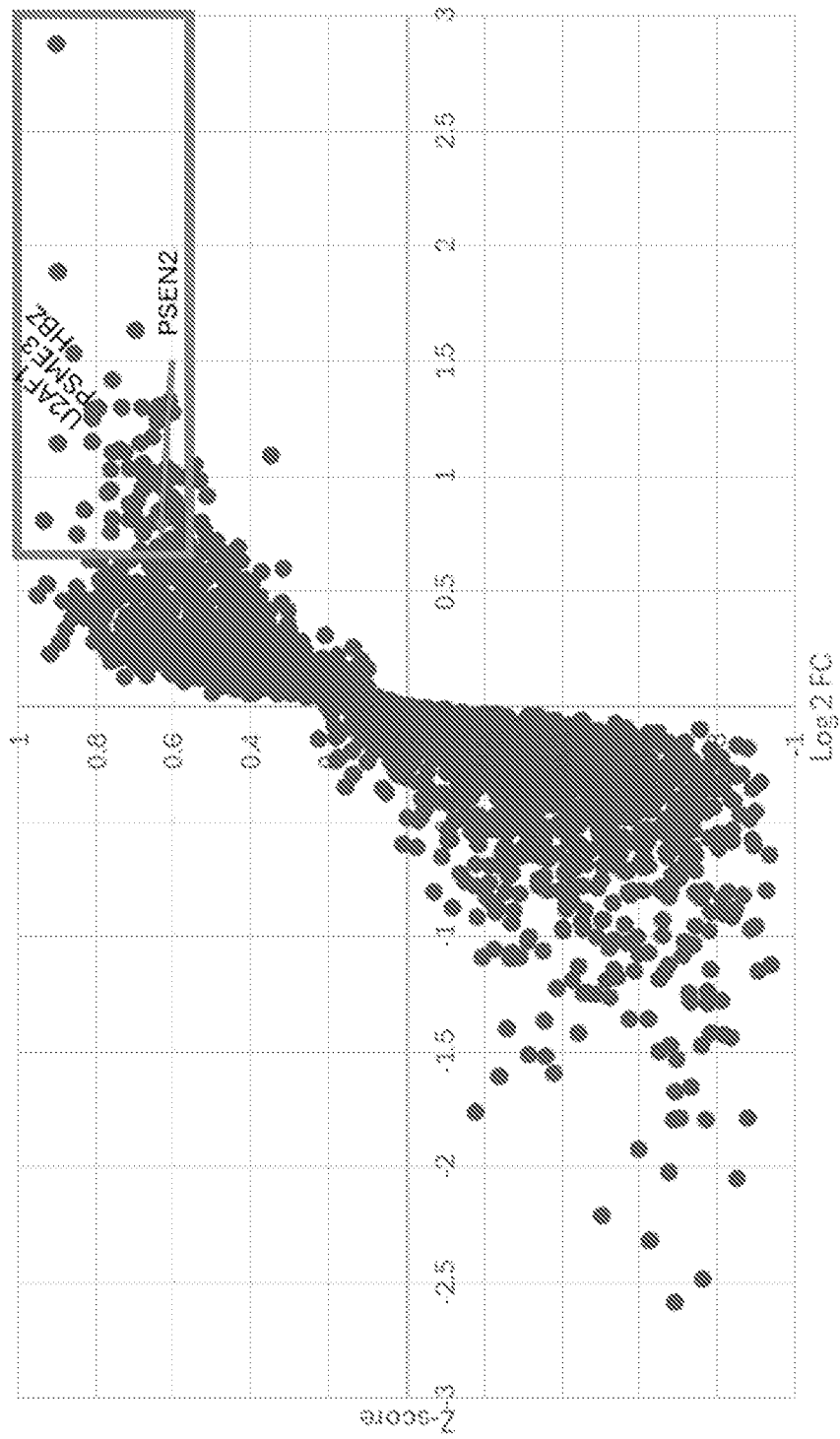


FIG. 5

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/033552

**A. CLASSIFICATION OF SUBJECT MATTER**IPC: **A61K 31/4184** (2024.01); **A61K 31/437** (2024.01); **A61K 31/438** (2024.01); **A61K 31/451** (2024.01); **A61K 31/4545** (2024.01); **A61P 25/14** (2024.01); **A61P 25/28** (2024.01); A61P 21/00 (2024.01)CPC: **A61K 31/4184**; **A61P 25/14**; **A61P 25/28**; **A61K 31/4545**; **A61K 31/437**; **A61K 31/438**; **A61K 31/451**; A61P 21/00; A61K 2300/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                   | Relevant to claim No. |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | WO 2021/252950 A2 (ARIZONA BOARD OF REGENTS ON BEHALF OF THE UNIVERSITY OF ARIZONA) 16 December 2021 (16.12.2021)<br>entire document | 1, 2                  |
| X         | US 2019/0192496 A1 (PRILENIA THERAPEUTICS DEVELOPMENT LTD.) 27 June 2019 (27.06.2019)<br>entire document                             | 1, 2                  |
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| Y         | WO 2015/112601 A1 (IVAX INTERNATIONAL GMBH et al.) 30 July 2015 (30.07.2015)<br>entire document                                      | 3, 4                  |
| A         | US 2004/0192690 A1 (BUXTON et al.) 30 September 2004 (30.09.2004)<br>entire document                                                 | 1-4                   |



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Date of the actual completion of the international search

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Date of mailing of the international search report

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## INTERNATIONAL SEARCH REPORT

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PCT/US2024/033552

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                                                                            | Relevant to claim No. |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A         | ITO et al., Decreased N-TAF1 expression in X-linked dystonia-parkinsonism patient-specific neural stem cells, Disease Models & Mechanisms, Vol. 9, 2016, Pgs. 451-462, [retrieved on 02 August 2024]. Retrieved from the internet: <URL: <a href="https://journals.biologists.com/dmm/article/9/4/451/3769/Decreased-N-TAF1-expression-in-X-linked-dystonia">https://journals.biologists.com/dmm/article/9/4/451/3769/Decreased-N-TAF1-expression-in-X-linked-dystonia</a> >. entire document | 1-4                   |