

Supplementary Information for

Pathogenic Role of Delta 2 Tubulin in Bortezomib Induced Peripheral Neuropathy

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Movies S1 to S15

Supplementary Information Text

Methods

<u>Animals.</u> *In vivo* experiments were carried out on female Wistar rats (Envigo, Udine, Italy), weighing between 175 and 200 g at the beginning of the experimental procedure (n=6-13 rats/group). The rats were housed under constant temperature and lighting conditions with a 12 h light/dark cycle and they received food and water *ad libitum*. Procedures and experimental protocols were compliant with the ethics guidelines described in national (DL. Vo 26/2014, Gazzetta Ufficiale della Repubblica Italiana, permit No1161/2016) and international laws (European Union Directive 2010/63/EU: Guide for the Care and Use of Laboratory Animals, U.S National Research Council, 1996). All the experiments were approved by the Italian State authorities (14/2016). For the *in vitro* experiments, all protocols and procedures used to prepare primary culture of DRG neurons dissected from wild type mice (C57BL/6) were approved by the Committee on the Ethics of Animal Experiments of Columbia University and in agreement with the Guide for the Care and Use of Laboratory Animals distributed by the National Institutes of Health.

Behavioral analysis and neurophysiology. At baseline, 24 h after a single Bort administration and 24 h after the chronic administration of the antineoplastic drug, a blinded examiner performed behavioral tests in random fashion in order to evaluate mechanical and thermal nociceptive thresholds through Dynamic and Plantar tests, respectively, as previously described (1). The Dynamic test used an algesimeter (Ugo Basile, Comerio-Varese, Italy) which generates a linearly increasing mechanical force. Briefly, a metal filament applied a linear increasing pressure under the plantar surface of the hind limb using an electronic Von Frey hair unit. The withdrawal threshold was measured by applying force ranging from 0 to 50 g within 20 s. Mechanical threshold reflex was measured automatically by the grams until withdrawal in response to the applied force. Two h after dynamic test, change in thermal hyperalgesia after single and chronical treatments of Bort were monitored using Plantar test (Hargreaves' method; Ugo Basile, Comerio-Varese, Italy), as described previously (1). Briefly, after habituation, a movable infrared heat source (IR 40) was located directly under the plantar surface on the hind paw, and withdrawal latency (s) was used for data analysis. Sensory conduction studies (sensory nerve action potential amplitude and nerve conduction velocity) of caudal and hind limb digital nerves (extensively used in the classification of peripheral neuropathies) were assessed orthodromically (2) through the Myto2 EGM device (EBN Neuro, Firenze, Italy). Briefly, the recordings were performed by placing the reference recording electrode and the active recording electrode at 1 and 2 cm from the base of the tail, the ground electrode at 2.5 cm from the base of the tail, and cathode and anode at 5 and 6 cm respectively. To study digital nerve, the cathode and the anode were placed at the base and at the tip of the fourth toe of the left hind-limb respectively, the ground electrode subcutaneously in the sole, and active recording electrode and reference recording electrode at the ankle and subcutaneously near the patellar bone, respectively. Intensity, duration and frequency of stimulation were set up in order to obtain supramaximal results. Animals were anesthetized with 2% isoflurane and the body temperature was kept constant at 37 ± 0.5 °C with a temperature-controlled heating pad operated via a thermal rectal probe (Harvard Apparatus, Holliston, US).

Quantitative immunoblotting and immunocytochemistry of tubulin PTMs and MT markers. Whole cell lysates from cultured DRG neurons were obtained by manual homogenization in Laemmli buffer 1x (62.5 mM Tris pH 6.8, 10% glycerol, 5% DTT, 2% SDS, 0.004% bromophenol blue) followed by sonication (Bransor-Sonifier 250 for 15 s), boiling (95 °C for 5 min) and pre-clearing (5 min at 10,000 x g). Proteins were separated by 10% Bis-Tris gel (Invitrogen) and transferred to nitrocellulose membrane. After blocking in 5% milk/TBS, membranes were incubated with primary antibodies at 4 °C overnight or 1 h at 37 °C and 1 h with secondary antibodies at R.T.. Secondary antibodies conjugated to IR680 or IR800 (Rockland Immunochemicals) were used for multiple infrared detection. Image acquisition was performed with an Odyssey imaging system (LI-COR Biosciences, NE) and analyzed with Odyssey software. For immunofluorescence (IF) studies of fixed tissue specimens, DRG and sciatic nerve sections were processed as follows: paraffin embedded blocks of DRG (L4-L5) and sciatic nerve samples were serially cut (5 μ m) and deparaffinized by immersing the slices in xylene (7 min x 2) followed by 100%, 90%, 80%, 60%, 40% EtOH (5 min each) and H₂O (5 min) immersion. Slices were then rinsed with PBS 1x (10 min x 2) and antigen retrieval carried out by boiling the slices in citric acid solution (10 mM, pH 6) for 15 min. Sections

were cooled down for 15 min, rinsed 3 times with PBS 1x, permeabilized with 0.01% Triton X-100 for 10 min and blocked with NGS (Thermofisher) 10% in PBS for 1 h at R.T. Primary antibodies incubations were performed overnight at 4 °C in normal goat serum (NGS) 10% PBS 1x buffer. For IF studies of isolated DRG neurons, cells were fixed with 4% PFA for 10 min, followed by membrane permeabilization with 0.1% Triton X-100, blocking with NGS and then staining overnight with primary antibodies as previously described (3). Alexa Fluor fluorescent dyes-conjugated secondary antibodies were diluted 1:200 in 10% NGS-PBS 1x and added for 1 h at R.T.. Acquisition was performed using a spinning disk confocal microscope (Olympus DSU) coupled to a camera controller Hamatsu (C10600 ORCA-R²) or epifluorescence microscopy (Olympus IX81) coupled to a monochrome CCD camera (Sensicam QE; Cooke Corporation) and all images were analyzed by ImageJ software. Ratiometric analyses of tubulin PTM/bulk tubulin levels on DRG cellular bodies, sciatic nerve and proximal and distal axons of cultured DRG neurons were performed using fluorescence intensity levels of primary antibodies on randomly selected cellular bodies, sciatic nerve and proximal and distal axons of fixed and immunostained specimens using ImageJ software.

Sural nerve biopsies and clinical history of control and BIPN patients. Clinical history of the BIPN patient shown was previously described (4). The patient was administered Bort 1.3 gm/m² and a second dose after 4 d to treat a marginal zone lymphoma. Neurological examination showed distal weakness, which was more severe in the legs, and sensory loss to pin, temperature and vibration distally in the hands and feet. An EMG and nerve conduction study showed signs of a sensorimotor neuropathy, with axonal loss and multifocal demyelination. The patient's sural nerve biopsy, performed 2 and 1/2 months after the second and last dose of Bort, showed a significant axonal loss involving both large and small myelinated fibers, with no robust axonal regeneration. There were scattered histiocytes/macrophages associated with active axonal breakdown in the nerve fascicles, along with perivascular T-cell-dominant lymphocytic inflammation. No overt vasculitis or amyloid deposition was seen. By teased fiber analysis, 22% of the teased myelinated fibers showed Wallerian degeneration and 22% showed myelin changes in the forms of segmental demyelination and remyelination. After stopping Bort, nerve conduction studies after 22 months showed improvement in the compound muscle action potential amplitudes. One control patient had a right sural nerve biopsy for a suspected mitochondrial disease (not specified). The morphology revealed a peripheral nerve with mild changes without significant inflammation, consisting of minimal axonal loss with 10% of the teased fibers exhibiting segmental remyelination. No amyloid deposition was observed. The second control patient was a suspected case of idiopathic peripheral neuropathy, not due to neurotoxic medications. The nerve biopsy, however, showed minimal changes that were indistinguishable from agerelated alteration with minimal axonal loss and 9.3% of the teased fibers exhibiting segmental remyelination. No vasculitis, amyloidosis, and immunoglobulin deposition were detectable. The third control patient underwent a sural nerve biopsy with the symptoms of peripheral neuropathy, parkinsonism, bulbar palsy and history of Lyme disease. The sural nerve revealed minimal changes, without any significant axonal loss. By the nerve teasing, 11% of the fibers showed segmental remyelination. No vasculitis or amyloid deposition was identified. The sural nerve biopsies were performed as previously described (5).

Caspase cleavage assay. Caspase activation was assessed in DRG neurons treated with vehicle (DMSO) or 100 nM of Bortezomib up to 48 h using an *in vitro* caspase-3 like cleavage assay utilizing the chemical substrate DEVD-7-amino-4-methylcoumarin (AMC) (Enzo Life Sciences, Farmingdale, NY #ALX-260-031). At the end of treatment, AMC substrate was added to the wells and neurons were incubated for 30 min at 37 °C in the dark. The generation of the fluorescent AMC cleavage product was measured at 360 nm excitation and 460 nm emissions, using a fluorescence plate reader (SpectraMax i3x multi-mode detection platform, Molecular Devices). Addition of staurosporine at the concentration of 600 nM for 24 h was used as a positive control (6).

Fly stocks and *Drosophila* **larval assays.** *UAS-EB1-GFP* on III (BL 35512) and 477-Gal4 on II (BL 8737) (7) were obtained from the Bloomington Stock Center (Bloomington, IN). *ppk-CD4-tdGFP* (III) has been described previously (8). Bort (LC laboratories) was diluted to 2.5 mM in ethanol, aliquoted and stored in - 80 °C until use. Fresh aliquots of Bort were diluted to a final concentration of 20 μ M in 1x PBS. A matching concentration of ethanol was added as a vehicle control. This solution was used to make food using instant *Drosophila* medium (Formula 4-24 ®, Carolina Biological Supply Company) immediately before starting the larval assay in 1:1 (vol/vol). Embryos were collected on grape plates with yeast paste made with 0.5 %

propionic acid. For acute treatment (3 h and 6 h) for live imaging of EB1, third instar larvae were collected. For chronic treatment, first instar larvae (24-28 h after egg laying) were collected manually with a paintbrush. All collected larvae were washed in 1 × PBS and placed into either Bort or vehicle-containing food. All larvae were reared at 22-25° C. For acute treatment, 2-3 similarly sized larvae from control and Bort treated larvae were collected from each experiment. For chronic treatment larvae were stage-matched to late third instar (based on the morphology of anterior spiracles) at the time of collection. Controls typically reached late third instar by 5-7 d. Any remaining animals that did not reach late third instar by 10 d after starting the treatment were discarded. All animals matching the developmental criteria were collected to avoid any selection bias.

Degeneration index in sensory neurons of Drosophila larvae. Immunolabeling of Drosophila larvae was performed largely as described previously (9). Briefly, late third instar larvae were dissected in 1 × PBS, fixed in 4% paraformaldehyde (PFA, Electron Microscopy Sciences) in 1 × PBS for 15 min, rinsed three times in 1 × PBS + 0.3% Triton X-100 (PBS-TX), and blocked for 1 h at R.T. or overnight at 4 °C in 5% normal donkey serum (NDS) in PBS-TX (Jackson ImmunoResearch). Primary antibodies were chicken anti-GFP (1:1000; Abcam) diluted in 5% NDS in PBS-TX. Tissue was incubated overnight in primary antibodies at 4 °C and then washed in PBS-TX for 3 × 15 min at R.T.. Species-specific, fluorophoreconjugated secondary antibodies (Jackson ImmunoResearch) were used at 1:1000 in 5% NDS in PBS-TX, and incubated overnight 4 °C. Tissue was rinsed in PBS-TX for 3 × 15 min with a final rinse in PBS. Tissue was mounted on poly-L-lysine coated coverslips, dehydrated 5 min each in an ascending ethanol series (30, 50, 70, 95, 2 × 100%), cleared in xylenes (2 × 10 min), and mounted in DPX (Fluka). Drosophila sensory neurons were imaged on a Zeiss 510 Meta laser scanning confocal microscope (25x objective, glycerol, 1.4 NA, Plan-Neofluar). Entire body walls were imaged in tiles, and then stitched using Grid/Collection stitching plugin in Fiji software (10) to capture all ddaC nociceptive neurons in abdominal segments in each animal. All images were randomized and blinded before single cells were cropped out for further analysis. Images containing single cells were batch processed using automatic global threshold (default method), made binary, and the particle analyzer plugins of Fiji was used to calculate degeneration index as described previously in the neurodegeneration index measurements of DRG neurons (11).



Fig. S1. Behavioral tests and neurophysiological studies in control and bortezomib-treated rats after 24 h or 8 wk of treatment. (A) Hind-paw withdrawal response to mechanical stimulus (Dynamic Test) and plantar withdrawal latency response to heat source (Plantar Test) were recorded before chemotherapy administration (baseline value), after 24 h and at the end of treatment (8 wk) with bortezomib (Bort). Mechanical allodynia and thermal hyperalgesia were observed only at the end of chronic administration of Bort in treated animals (Bort) compared to controls (Contr). (B) Digital and caudal nerve conduction velocity (NCV) and amplitude were measured before chemotherapy administration (baseline value), after 24 h and at the end of treatment (8 wk) with Bort. Only after 8 w of treatment with Bort significant decrease of caudal and digital NCV and potential amplitude were evident in treated rats vs controls (Contr). Data are expressed as medians plus interquartile range and analyzed by Mann-Whitney test, n=6-13 animals per condition.



Fig. S2. De-tyrosinated, acetylated and polyglutamylated tubulins in rats treated with acute doses of bortezomib. (A, B) Representative tubulin PTM immunofluorescence staining of dorsal root ganglia (DRG) cell bodies and sciatic nerve (SN) isolated from rats acutely treated with bortezomib (Bort) as in Fig. 1B. DeTyr, de-tyrosinated tubulin; polyGlu polyglutamylated tubulin (GT335); Acetyl, acetylated tubulin; βIII, βIII tubulin. Scale bar, 20 μm.



Fig. S3. D2, De-tyrosinated, acetylated and polyglutamylated tubulins in rats treated with chronic doses of bortezomib. (A, B) Representative tubulin PTM immunofluorescence staining of DRG cell bodies and sciatic nerve (SN) isolated from rats chronically treated with bortezomib (Bort) as in Fig. 1C. D2, delta 2 tubulin; deTyr, de-tyrosinated tubulin; polyGlu, polyglutamylated tubulin (GT335); Acetyl, acetylated tubulin; βIII, βIII tubulin. Scale bar, 50 µm.



Fig. S4. Bortezomib does not increase caspase-3 enzymatic activity in cultured DRG neurons at the onset of axonal degeneration. Caspase-3 enzymatic activity was measured in DRG neurons plated on 96 well dishes and treated with 100 nM bortezomib (Bort) at the concentration for indicated times. Staurosporine (600 nM) was added for 24 h as a positive control. Data are reported as medians plus interquartile range, (n=3 triplicates; 3-9 wells per condition) and analyzed by Kruskal-Wallis test.



Fig. S5. CCP1 and TTL levels are not affected by bortezomib at onset of neurodegeneration. (A) Immunoblot analyses of carboxypeptidase 1 (CCP1), tubulin tyrosine ligase (TTL) and D2 levels in whole cell lysates from DRG neurons (12 DIV) treated with DMSO (Control) or 100 nM for the indicated times. (B) Quantification of GAPDH normalized CCP1 and TTL levels as in A. Data are shown as medians plus interquartile range and analyzed by Mann-Whitney test.



Fig. S6. Additional MT dynamics parameters in the peripheral nerve fibers of zebrafish exposed to **bortezomib.** MT dynamics parameters in the peripheral nerve fibers of zebrafish treated as in Fig 4B. Data were pooled from 3 individual fish containing 4 to 5 neurites with up to 80-220 comets and analyzed by Mann-Whitney test. Data are shown as median plus interquartile range.



Figure S7. CCP1 depletion affects D2 levels. (A) Schematic of the experimental strategy for 7 and 10 d infection to analyze axonal degeneration as in Fig. 6. (B) Immunoblot analyses of CCP1, D2 and polyglutamylated tubulin levels from whole cell lysates of DRG neurons infected for 7 or 10 d with shCCP1 or shNC lentivirus. (C) Quantification of normalized CCP1, D2 and polyglutamylated tubulin levels as in B. Data are pooled from 4-7 experiments. (D) Schematic of the 5 d infection strategy with shCCP1 or shNC lentivirus and pLVX-EGFP-D2- or WT- α -tubulin lentivirus to analyze mitochondria motility as in Fig. 7. (E) Immunoblot analyses of CCP1. D2 and polyglutamylated tubulin levels of whole cell lysates of DRG neurons infected for 5 d with shCCP1 or shNC lentivirus. (F) Quantification of normalized CCP1, D2 and polyglutamylated tubulin levels as in E. Data are pooled from 5-7 experiments. (G) Immunoblot analyses of CCP1 and D2 levels of whole cell lysates of DRG neurons infected for 7 d with shCCP1 or shNC lentivirus plus and minus bortezomib (Bort) as in Fig. 6. (H) Quantification of normalized D2 levels as in G. Data are pooled from 5 experiments. (I) Immunoblot analyses of CCP1 and D2 levels of whole cell lysates of DRG neurons infected for 5 d with shCCP1 or shNC lentivirus plus and minus bortezomib (Bort) as in Fig. 7. (J) Quantification of normalized D2 levels as in I. Data are pooled from 4 experiments. PolyGlu, polyglutamylated tubulin (polyE); GAPDH, loading control. All data in C, F, H and J are shown as medians plus interquartile range and statistics analyzed by Mann-Whitney test.



Fig. S8. Bortezomib does not affect lysosome motility in DRG neurons at the onset of neurodegeneration. (A) Representative kymographs of lysosome movement in DRG neurons (5 DIV) infected at 1 DIV with Lamp1-mRFP-FLAG lentivirus followed by bortezomib (Bort) treatment (100 nM for 24 h). Videos (10s/frame for 30 min). Scale bar, 10 μ m. (B) Quantification of lysosome dynamic states, Dynamic Pause (DP), Stationary (ST), Anterograde Running (AR), Retrograde Running (RR), in DRG neurons treated as in A. Data are shown as medians plus interquartile range from 12-15 neurites and analyzed by Mann-Whitney test.



Fig. S9. Proposed pathogenic role of D2 in BIPN. Bortezomib exposure promotes premature tubulin longevity and D2 accumulation at a prodromal stage of the disease. Soluble D2 accumulation may induce axonal degeneration by selective inhibition of mitochondria motility that might occur through at least four non mutually exclusive modalities: a) by interfering with mitochondria bioenergetics through direct D2 binding to the VDAC; b) by raising intracellular Ca²⁺ levels causing Miro-dependent mitochondria/motor complex detachment from MTs; c,d) by increasing the affinity of the anchoring proteins Syntaphilin (c) or Myosin V (d) to mitochondria and either MTs (c) or F-actin (d).

Figure 1						
	DRG	Control vs Bort	D2 vsPTMs	SN	Control vs Bort	D2 vs PTMs
Panel B	Acute Treatment in Rat	pValue	pValue	Acute Treatment	pValue	pValue
- "	Acetvlated	0.99	0.03	Acetvlated	0.99	0.22
	PolyGlu	0.62	0.01	PolyGlu	0.22	0.02
	deTyr	0.4	0.01	deTyr	0.3	0.62
Panel C	Chronic Treatment in Rat	pValue	pValue	Chronic Treatment	pValue	pValue
- "	Acetvlated	0.2	0.057	Acetvlated	0.057	0.057
	PolyGlu	0.11	0.9	PolyGlu	0.88	0.88
	deTyr	0.02	0.02	deTyr	0.99	0.48
Panel E	Acute Treatment in Rat	pValue				
"	NE200 neurons positive to D2	0.01				
	Peripherin vs NF200	0.002				
Panel G	Sural Nerve Biopsy in Human	Patient 1 vs Patient 4	Patient 2 vs Patient 4	Patient 3 vs Patient 4		
I IF	D2	pValue 0.001	pValue	pValue		
Figure 1S	Acute Treatment in Rat	Baseline	24h	Chronic Treatment	Baseline	8w
Panel A	Behavioural Test	Control vs Bort	Control vs Bort	Behavioural Test	Control vs Bort	Control vs Bort
	Durania Test	pValue	pValue	Dunamia Trat	pValue	pValue
	Plantar Test	0.34	0.86	Dynamic Test Plantar Test	0.16	0.0002
Panel B	Electrophysiology	pValue	pValue	Electrophysiology	pValue	pValue
	Caudal Nerve conduction velocity	0.23	0.91	Caudal Nerve Conduction Velocity	0.09	0.0003
	Digital Nerve conduction velocity	0.08	0.12	Digital Nerve conduction velocity	0.84	0.002
	Potential Amplitude Caudal Nerve	0.59	0.55	Potential Amplitude Caddal Nerve	0.21	0.003
Figure 2						
Panel B	In vitro DRG neurons	-	100nM Bort			
		Control vs 6h	Control vs 12n	Control vs 24n		
	D2/BIII	0.63	0.02	0.002		
Panel C	In vitro DRG neurons	-	100nM Bort			
Degeneration	1	control vs 6h	ontrol vs 12n	control vs 24h	control vs 48h pValue	Control 72h
	Neurofilament	0.41	0.07	0.03	0.03	0.03
Panel E	In vitro DRG neurons	Or start up 0.4h	100nM Bort	Ocastal un 70h		
В		control vs 24h pValue	control 48h pValue	pValue	I	
	D2	0.01	0.004	0.004		
Panel G	In vitro DRG neurons	Central up 12h	100nM Bort	Control up 49h		
В	Soluble tub/M1 pellet	control vs 12h pValue	ontrol 24h pValue	Dontrol vs 48h	ł	
1	D2	0.53	0.16	0.02	1	
_	βΙΙΙ	0.9	0.3	0.15	1	
Figure 3	la vita DDO nome					
Stability Assay	In vitro DRG neurons	Contr vs Contr+NZ	3h vs 3h +NZ	6h vs 6h +NZ	Control vs 3h Control vs 6h	3h vs 6h
		pValue	pValue	pValue	pValue pValue	pValue
IF Downl D	ßIII	<0.0001	<0.0001	0.14	0.99 0.8	0.57
Panel D	In Vitro DRG neurons	Control vs 2h	Contr vs 3h	Control vs 6h		
		pValue	pValue	pValue		
IB	Acetlated	0.34	0.02	0.0006		
Panel F	del YR	0.99	0.39 100nM Bort	0.01		
MT Dynamics		Control vs 1h	Control vs 2h	Control vs 3h	Control vs 6h	Control vs 24h
	Consultants	pValue	pValue	pValue	pValue	pValue
	Comet density	0.001	0.004	< 0.0001	< 0.0001	< 0.0001
	Output when the feature of the					
	Catastrophe frequency	0.009	0.17	0.002	0.0008	0.17
	Length of growth	0.009	0.17 0.08	0.002 0.22	0.0008 < 0.0001	0.17 0.002
	Length of growth Comet life time Rescue or nucleation	0.009 0.55 < 0.0001 0.0008	0.17 0.08 < 0.0001 0.001	0.002 0.22 < 0.0001 < 0.0001	0.0008 < 0.0001 < 0.0001 < 0.0001	0.17 0.002 0.001 0.0005
Figure 4	Catastrophe inequency Length of growth Comet life time Rescue or nucleation	0.009 0.55 < 0.0001 0.0008	0.17 0.08 < 0.0001 0.001	0.002 0.22 < 0.0001 < 0.0001	0.0008 < 0.0001 < 0.0001 < 0.0001	0.17 0.002 0.001 0.0005
Figure 4 Panel C	Catastrophe requency Length of growth Comet life time Rescue or nucleation In vivo in Zebrafish	0.009 0.55 0.0001 0.0008 1.3 uM Bort	0.17 0.08 < 0.0001 0.001 Panel G	0.002 0.22 < 0.0001 < 0.0001 < 0.0001 In vivo in Drosophila Control in 2h	0.0008 < 0.0001 < 0.0001 < 0.0001 < 0.0001	0.17 0.002 0.001 0.0005
Figure 4 Panel C MT Dynamics	Carastrophe requency Length of growth Comet life time Rescue or nucleation In vivo in Zebrafish	0.009 0.55 < 0.0001 0.0008 1.3 uM Bort Control vs 6h pValue	0.17 0.08 < 0.0001 0.001 Panel G	0.002 0.22 < 0.0001 < 0.0001 In vivo in Drosophila Control vs 3h DValue	0.0008 < 0.0001 < 0.0001 < 0.0001 < 0.0001 20 uM Bort Control vs 6h	0.17 0.002 0.001 0.0005 3h vs 6h
Figure 4 Panel C MT Dynamics	Catastrophe requency Length of growth Cornet life time Rescue or nucleation In vivo in Zebrafish Growth rate	0.009 0.55 < 0.0001 0.0008 1.3 uM Bort Control vs 6h pValue < 0.0001	0.17 0.08 < 0.0001 0.001 Panel G Growth rate	0.002 0.22 < 0.0001 0.0001 In vivo in Drosophila Control vs 3h pValue 0.27	0.0008 < 0.0001 < 0.0001 < 0.0001 < 0.0001 20 uM Bort Control vs 6h pValue 0.001 0.001	0.17 0.002 0.001 0.0005 3h vs 6h pValue 0.006
Figure 4 Panel C MT Dynamics Figure S6	Catastrophe requency Length of growth Cornet life time Rescue or nucleation In vivo in Zebrafish Growth rate Cornet density Cottactrophe Growth or State	0.009 0.55 < 0.0001 0.0008 1.3 uM Bort Control vs 6h pValue < 0.0001 0.87 0.7	0.17 0.08 < 0.0001 0.001 Panel G Growth rate Comet density Comet density	0.002 0.22 < 0.0001 < 0.0001 In vivo in Drosophila Control vs 3h pValue 0.27 0.23 0.27 0.03 - 0.0001	0.0008 < 0.0001 < 0.0001 < 0.0001 20 uM Bort Control vs 6h pValue 0.001 0.04 < 0.0001	0.17 0.002 0.001 0.0005 3h vs 6h pValue 0.006 0.46 0.2
Figure 4 Panel C MT Dynamics Figure S6	Latastrophe requency Langth of growth Camet life time Rescue or nucleation In vivo in Zebrafish Growth rate Camet density Catastrophe frequency Length of growth	0.009 0.25 < 0.0001 0.0006 1.3 uM Bort Control vs 6h pValue < 0.0001 0.87 0.7 0.85 0.85	0.17 0.08 < 0.0001 0.001 Panel G Growth rate Comet density Catastrophe frequency Length of growth	0.002 0.22 < 0.0001 (0.0001 0.0001 Control vs 3h pValue 0.27 0.03 < 0.0001 < 0.0001 < 0.0001	0.0008 0.0001 0.0001 0.0001 0.0001 20 uM Bort Control vs 8h 0.001 0.04 0.001 0.04 0.001 0.04 0.001	0.17 0.002 0.001 0.0005 3h vs 6h pValue 0.006 0.46 0.3 0.0002
Figure 4 Panel C MT Dynamics Figure S6	Latastrophe requency Length of growth Rescue or nucleation In vitvo in Zebrafish Growth rate Camet density Catastrophe frequency Length of growth Camet life time time	0.009 <0.0008 <0.0008 13.04 Bort Control vs 6h pValue <0.0001 0.87 0.7 0.85 0.059 0.89 0.059	0.17 0.08 < 0.0001 0.001 Panel G Growth rate Comet density Catastrophe frequency Length of growth Comet if entre accession	0.002 0.22 < 0.0001 4.0001 (a).0001 (b).0001 (c).0001 0.27 0.03 < 0.0001 < 0	0.0006 4.0007 4.0007 2.0007 2.0007 2.0007 2.0007 2.0007 2.007 0.04 4.0007 2.007 4.0007 4.	0.17 0.002 0.001 0.0005 3h vs 6h pValue 0.006 0.46 0.3 0.0002 0.0002 0.070
Figure 4 Panel C MT Dynamics Figure S6	Latastrophe requency Langth of growth Comet life time Rescue or nucleation In vivo in Zebrafish Growth rate Comet density Catastrophe frequency Catastrophe frequency Comet life time Rescue or nucleation Rescue or nucleation	0.009 0.25 < 0.0001 0.0008 1.3 LiM Bort Control vs 6h pValue < 0.0007 0.67 0.75 0.75 0.059 0.23 0.059 0.23 0.059 0.23 0.059 0.23 0.059 0.23 0.059 0.23 0.059 0.23 0.059 0.059 0.059 0.059 0.059 0.057 0.057 0.0007 0.007 0.	0.17 0.08 < 0.001 0.001 Panel G Growth rate Comet density Catastrophe frequency Length of growth Catastrophe frequency Length of growth Rescue for the uncleation Panel F	0.002 0.22 < 0.0001 < 0.0001 Control vs 3h pValue 0.27 < 0.0001 < 0.	0.0006 4.0.001 4.0.001 2.0.001 2.0.001 Control vs 8h PValue 0.001 0.04 4.0.001 4.0.001 4.0.001 4.0.001 6.005 6.05 6.005	0.17 0.002 0.001 0.0005 3h vs 6h pValue 0.006 0.46 0.3 0.0002 0.07 0.28
Figure 4 Panel C MT Dynamics Figure S6	Latashophe frequency Latashophe frequency Comet life inem Rescue or nucleation In vivo in Zebrafish Growth rate Comet density Catashophe frequency Catashophe frequency Catashophe frequency Comet life inem Rescue or nucleation Rescue or nucleation Retrograde comets	1.009 1.0008 1.0008 Control vs 6h pValue 4.0001 0.67 0.75 0.059 0.23 0.69	0.17 0.08 < 0.001 2.001 Panel G Growth rate Comet density Catastrophe frequency Length of growth Comet Ife Lime Rescue or nucleation Panel E Degeneration Index	0.002 0.22 < 0.0001 < 0.0001 Control vs 3h pValue 0.27 0.03 < 0.0001 < 0.0000	0.0006 0.0001 0.0001 0.0001 20 LM Bort Control vs 6h pValue 0.001 0.04 0.001 0.04 0.0001 0.04 0.0001 0.0	0.17 0.002 0.001 0.0005 3h vs 6h PValue 0.006 0.46 0.3 0.0002 0.3 0.0002 0.07 0.28
Figure 4 Panel C MT Dynamics Figure S6 Figure 5	Latastrophe requency Langth of growth Comet life time Rescue or nucleation In vitvo in Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Comet life time Rescue or nucleation Retrograde comets	0.009 0.05 0.5 0 0.000 1.3 uN Bort Control vs 6h pValue 4.0.000 0.7 0.8 0.7 0.8 0.009 0.2 0.6 0 0.6 0 0.6 0 0.6 0 0.6 0 0 0 0 0 0	0.17 0.08 0.08 0.001 Panel G Growth rate Comet density Catastrophe Requency Length of growth Comet if le time Rescue or nucleation Panel E Degeneration Index	0.002 0.22 < 0.0001 < 0.0001 2.0001 2.0001 2.0001 0.0001 0.0001 < 0.0001 < 0.00001 < 0.0001 < 0.0001 < 0.0001 <	0.0009 4.0.001 4.0.001 20.0001 20.0001 20.0001 20.001 0.001 0.001 0.04 4.0.001 4.0	0.17 0.002 0.001 0.0005 3h vs 6h pValue 0.006 0.46 0.3 0.0002 0.002 0.007 0.28
Figure 4 Panel C MT Dynamics Figure S6 Figure 5 Panel D Degeneration	Latastrophe requency Langth of growth Comet life time Rescue or nucleation In vivo in Zebrafish Growth rate Comet density Catestrophe frequency: Length of growth Comet life time Rescue or nucleation Retrograde comets In vitro DRG neurons	0.009 0.05 0.55 0.0001 0.0000 13 aM Bort Control vis 6th 9-0.0001 0.87 0.85 0.000 0.7 0.85 0.059 0.23 0.69 shNC vis shTTL1	0.17 0.08 < 0.001 0.001 Panel G Growth rate Comet density Catasthe frequency Catasthe frequency Catasthe or nucleation Rescue or nucleation Panel E Degeneration Index Lentiviral shRNA Delivery ShNC vs ShTT2	0.002 0.22 < 0.0001 < 0.0001 Control vs 3h pValue 0.27 < 0.0001 < 0.0001 < 0.0001 < 0.0001 < 0.0001	0.0009 4.0001 4.0001 4.0001 20 uM Bort C Control vs 6n private 0.001 0.04 4.0001 4.0	0.17 0.002 0.001 0.0005 3h vs fih pValue pValue 0.006 0.46 0.3 0.0002 0.07 0.28
Figure 4 Panel C MT Dynamics Figure 56 Figure 5 Panel D Degeneration Index	Latashopin Indunicy Latashopin Indunicy Latashopin Indunication Rescue or nucleation In vitvo in Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Rescue or nucleation Retrograde cornets In vitro DRG neurons	2.009 2.009 2.0008 2.0008 1.3 uM Bort Control vs 6h pValue Control vs 6h 2.3 0.6 2.4 0.6 2.5 2.5 0.6 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5	0.17 0.0001 0.0001 Panet G Growth rate Comet density Catastrophe frequency Length of growth Comet life lime Comet die lime Comet die lime Degeneration Index Lentiviral shRNA Delivery ShNC vs shTTL2 pylaue	0.002 0.22 < 0.0001 < 0.0001 Control vs 3h pValue 0.27 < 0.0001 < 0.	0.0008 4.0001 4.0001 2.0001 2.0001 2.0001 Control vs 6h PV8lue 0.01 0.04 4.0001 4.0	0.17 0.002 0.001 0.0005 3h vs 6h pValue 0.006 0.46 0.30 0.000 0.006 0.46 0.30 0.000 0.000 0.007 0.28
Figure 4 Panel C MT Dynamics Figure 56 Figure 5 Panel D Degeneration Index	Latastrophe requency Langth of growth Comet life time Rescue or nucleation In vivo in Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Comet life time Rescue or nucleation Retrograde comets In vitro DRG neurons Neurofilament	0.009 0.55 0.55 0.0008 13.uM.Bort Control vs 6h pValue 0.0001 0.7 0.87 0.7 0.85 0.009 0.23 0.69 0.69 0.01 0.69 0.01 0.69 0.01 0.69 0.01 0.69 0.01 0.69 0.01 0.69 0.01 0.69 0.01 0.69 0.01 0.69 0.01 0.69 0.01 0.69 0.001 0.69 0.6	0.17 0.08 0.08 0.001 Panel G Growth rate Comet density Catastrophe frequency Length of growth Comet life time Rescue or nucleation Panel E Degeneration Index Lentiviral shRNA Delivery ShNC vs shTL2 pValue 0.007	0.002 0.22 < 0.0001 2.0001 2.0001 2.0001 2.0001 2.0001 0.000 0.000 0.0001 < 0.0001 < 0.0001 0.0000000000	0.0008 4.0001 4.0001 4.0001 20.0001 20.0001 20.0001 20.0001 0.04 4.0001 4.00	0.17 0.002 0.001 0.005 3h vs 8h pValue 0.006 0.46 0.3 0.0002 0.07 0.28
Figure 4 Panel C MT Dynamics Figure 56 Figure 5 Panel D Degeneration Index Figure 6 Panel B	Latashopin Inductory Latashopin Inductory Latashopin Inductory Comet life time Rescue or nucleation In vivo in Zebrafish Growth rate Comet density Comet density Comet density Comet density Comet life time Rescue or nucleation Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons	0.009 0.05 0.25 0.0001 0.0000 13 uM Bort Control vs 6h P 0.0000 0.00000 0.00000 0.0000 0.0000 0.0000 0.0000 0.00	0.17 0.08 < 0.001 0.001 Panel G Growth rate Comet density Catastrophe frequency Longth of growth Rescue or nucleation Panel E Degeneration Index Lentiviral shRNA Delivery ShNC vs shTTL2 pValue ShCC Vt ss fCPL + SnCCPH+And	0.002 0.22 < 0.0001 in vivo in Drosophila Control vs 3h pValue 0.27 < 0.0001 <	0.0009 4.0001 4.0001 4.0001 20.001 20.001 120 uM Bort C Control vs Bn PValue 0.001 4.0001 4	0.17 0.002 0.001 0.0005 3h vs 6h pValue 0.006 0.46 0.3002 0.46 0.3002 0.28
Figure 4 Panel C MT Dynamics Figure 56 Figure 5 Panel D Degeneration Index Figure 6 Panel B Degeneration	Latastrophe requency Langth of growth Rescue or nucleation In vitro in Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Comet life time Rescue or nucleation Rescue or nucle	2009 2009 20008 20008 1.3 uM Bort Control vs 6h pValue < 0.0001 0.87 0.7 0.85 0.23 0.69 5hNC vs shTTL1 pValue 0.01 shNC vs shNC+Bort	0.17 0.0001 0.0001 Panel G Growth rate Comet density Catastrophe fequency Length of growth Comet if e time Rescue or nucleation Density in the second Density in the second Lentiviral stRNA Delivery Lentiviral stRNA Delivery Lentiviral stRNA Delivery Lentiviral stRNA Delivery (7D) shCCP1 vs shCP1-Bort	0.002 0.22 < 0.0001 (a),0001 (a)	0.0008 0.0001 0.0001 0.0001 0.0001 0.001 0.001 0.001 0.04 0.0001 0.04 0.0001 0.04 0.0001 0.001 0.001 0.0000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000 0.000000 0.00000000	0.17 0.002 0.001 0.0005 3h vs 6h pValue 0.006 0.46 0.3 0.002 0.3 0.002 0.28
Figure 4 Panel C MT Dynamics Figure 56 Panel D Degeneration Index Figure 6 Panel B Degeneration Index Figure 6 Panel B Degeneration Index	Latastropie reduncy Langth of growth Comet life time Rescue or nucleation In vivo in Zebrafish Growth rate Comet density Catastrophe fequency Length of growth Comet life time Rescue or nucleation Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons Neurofilament	0.009 0.05 0.05 0.0008 13 uN Bort Control vs 6h pValue 0.0001 0.7 0.87 0.7 0.85 0.009 0.37 0.85 0.009 0.37 0.85 0.059 0.23 0.69 ShNC vs shTTL1 pValue 0.01 shNC vs shNC+Bort 0.02	0.17 0.08 0.08 0.001 Panel G Growth rate Comet density Catastrophe frequency Length of growth Comet life time Rescue or nucleation Panel E Degeneration Index Lentiviral shRNA Delivery pValue 0.007 Lentiviral shRNA Delivery (7D) shCCP1 vs shCCP1+Bort Desting a shCP1 Abuttory (7D) shCCP1 vs shCCP1+Bort Desting a shCP1 Abuttory (7D) shCCP1 vs shCCP1+Bort	0.002 0.22 < 0.0001 2.0001 2.0001 2.0001 2.0001 2.0001 0.001 0.001 2.0001 2	0.0008 0.0001 0.0001 0.0001 20.0001 20.0001 20.0001 0.004 0.004 0.004 0.0001 0.0000 0.0001 0.0000	0.17 0.002 0.001 0.0005 0.0005 0.0005 0.0005 0.006 0.46 0.3 0.0002 0.3 0.0002 0.28
Figure 4 Panel C MT Dynamics Figure 56 Panel D Degeneration Index Figure 6 Panel D Degeneration Index Figure 7 Panel B	Latashopine inducincy Latashopine inducincy Latashopine inducincy Comet life interne Rescue or nucleation In vitvo in Zebrafish Growth rate Comet leansity Catashopine frequency Catashopine In vitro DRG neurons In	2.009 2.009 2.0008 2.0008 1.3 UM Bort Control vs 6h pValue Control vs 6h pValue Cort 2.3 Co	0.17 0.0001 0.001 Panel G Growth rate Comet density Catastrophe fequency Length of growth Rescue or muchation Panel E Degeneration Index Lentiviral shRNA Delivery (7D) shCOP1+sbCOP1-Bort 0.57 Lentiviral shRNA Delivery (7D) shCOP1+bort	0.002 0.22 < 0.0001 in vivo in Drosophila Control vs 3h pValue 0.27 < 0.0001 <	0.000 0.0001 0.0001 0.0001 2.0001 2.0001 1.0001 0.001 0.001 0.001 0.001 0.001 0.001 0.000	0.17 0.002 0.001 0.0005 0.0005 0.006 0.006 0.46 0.3 0.000 0.3 0.000 0.28
Figure 4 Panel C MT Dynamics Figure 56 Panel D Degeneration Index Figure 6 Panel B Degeneration Index Figure 7 Panel B	Latastropie requency Langth of growth Rescue or nucleation In vitro in Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Comet life time Rescue or nucleation Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons Neurofilament In vitro DRG neurons Neurofilament	0.009 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.00 0	0.17 0.0001 0.0001 Panel G Growth rate Comet density Catastrophe Fequency Length of growth Comet life time Comet life time Comet differ Banal E Degeneration Index Lengthraf sRNA Delivery EshtCus shTTL2 Pikule 0.007 Lentiviral sRNA Delivery (TD) shCCP1 +shCCP1+Bort 0.57 Lentiviral sRNA Delivery (5D) shCCP1+BortP1+Bort Pikule	0.002 0.22 < 0.0001 20.0001 20.0001 20.0001 20.0001 0.027 0.03 < 0.0001 < 0.0001 < 0.0001 < 0.0001 < 0.0001 0.02 Control vs Bort 0.04 20.0001 20.00001 20.0001 20.0001 20.0001 20.0001 20.0001 20.0001 20.0	0.0008 0.0001 0.0001 0.0001 20.0001 20.0001 20.0001 0.001 0.001 0.04 0.0001 0.04 0.0001 0.001 0.0000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000 0.000000 0.00000000	0.17 0.002 0.001 0.0005 30 vs 6h pValue 0.006 0.46 0.3 0.0002 0.3 0.0002 0.28
Figure 4 Panel C MT Dynamics Figure 56 Figure 5 Pamal D Degeneration Index Figure 6 Panel B Degeneration Index Figure 7 Panel B Degeneration Index Figure 6 Panel B Degeneration Index	Latastropie reducincy Langth of growth Rescue or nucleation In vivo in Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Comet life time Rescue or nucleation Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons Neurofilament In vitro DRG neurons Neurofilament In vitro DRG neurons Neurofilament In vitro DRG neurons Neurofilament	0.009 0.05 0.55 0.0001 0.0008 13 uN Bort Control vs 6h pValue 0.000 0.7 0.87 0.7 0.85 0.009 0.69 0.69 0.69 0.69 0.69 0.69 0.69 0.61 ShNC vs shTL1 pValue 0.01 ShNC vs shNC+Bort 0.02 ShNC vs shNC+Bort 0.02	0.17 0.08 0.08 0.001 Panel G Growth rate Comet density Catastrophe fequency Length of growth Comet life time Rescue or nucleation Panel E Degeneration Index Lentiviral shRNA Delivery pValue DiCP1 vs shCCP1+Bort 0.007 Lentiviral shRNA Delivery (5D) shCCP1 vs ShCCP1+Bort 0.001 0.01	0.002 0.22 0.22 0.22 0.0001 0.0001 0.0001 0.0001 0.000 0.000 0.000 0.000 0.000 0.000 0.00 0	0.0009 4.0001 4.0001 2.0001 2.0001 2.0001 2.0001 2.0001 0.04 0.04 0.04 4.0001 4.0001 4.0001 6.09 No Virus vs pLVX-EGFP-WT tub- pValue 0.009	0.17 0.002 0.001 0.0005 0.0005 0.0005 0.0005 0.005 0.005 0.005 0.03 0.0002 0.03 0.007 0.28
Figure 4 Panel C MT Dynamics Figure 56 Figure 5 Panel D Degeneration Index Figure 6 Panel B Organet B Panel B Mitochondria Dynamics	Latastropie requency Latastropie requency Longh tiegrowth Rescue or nucleation In vitro in Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Rescue or nucleation Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST AR	0.009 0.009 0.0008 0.0008 1.3 UM Bort Control vs 6h pValue Control vs 6h pValue Coot 0.67 0.7 0.83 0.69 0.23 0.69 0.23 0.69 0.02 0.01 0.02 0.02 0.02 0.02 0.02 0.02	0.17 0.0001 0.0001 Panel G Growth rate Comet density Catastrophe fequency Length of growth Comet ife time Rescue or nucleation Degeneration Index Begeneration Index Lentiviral shRNA Delivery ShNC vs shTTL2 pYalue 0.007 DiscP1+sbnCP1+Bort 0.57 DiscP1+sbnCP1+Bort 0.57 0.501 0.57 0.501 0.57 0.501 0.57 0.501 0.57 0.501 0.57 0.501 0.57 0.501 0.57 0.501 0.57 0.501 0.57 0.501 0.50	0.002 0.22 < 0.0001 In vitro in Drosophila Control vis 3in Pvilue 0.27 0.33 < 0.0001 < 0.0001 < 0.0001 < 0.0001 < 0.0001 ShNC+Bort vis shCCP1+Bort Pvilue 0.22 ShNC+Bort vis shCCP1+Bort Pvilue 0.0001 < 0.0001 < 0.0001	0.0008 0.0007 0.0007 0.0007 0.0007 0.0007 0.007 0.001 0.04 0.007 0.007 0.007 0.007 0.007 0.0009 0.0000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000 0.00000000	0.17 0.002 0.001 0.0005 0.0005 0.006 0.46 0.3 0.000 0.3 0.002 0.28
Figure 4 Panel C MT Dynamics Figure 56 Panel D Degeneration Index Figure 6 Panel B Degeneration Index Figure 7 Panel B Mitochondria Dynamics	Latastropie requency Latastropie requency Length of growth Rescue or nucleation In vitvo in Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Comet life time Rescue or nucleation Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST AR AR AR	0.009 0.05 0.5 0.0008 1.3 uM Bort Control vs 6h pValue 0.0001 0.87 0.85 0.0001 0.87 0.85 0.000 0.89 0.000 0.87 0.85 0.0001 0.87 0.0001 0.0001 0.0001 0	0.17 0.08 0.08 0.001 Panel G Growth rate Comet density Catastrophe fequency Length of growth Comet if elime Panel E Degeneration Index Degeneration Index	0.002 0.22 < 0.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.20 ShNC+Bort vs shCCP1+Bort 0.02 ShNC+Bort vs shCCP1+Bort 0.00 0.001 0	0.0008 0.0001 0.0001 0.0001 20.0001 20.0001 0.001 0.001 0.04 0.0001 0.04 0.0001 0.04 0.0001 0.000 0.0000 0.00000 0.0000 0.00000 0.00000 0.00000 0.00000 0.0000 0.00000 0.00000 0.0000000	0.17 0.002 0.001 0.0005 0.0005 0.0006 0.006 0.46 0.3 0.0002 0.07 0.28
Figure 4 Panel C MT Dynamics Figure 56 Figure 5 Panel D Degeneration Index Figure 6 Panel B Degeneration Index Figure 7 Panel B Mitochendria Dynamics Panel D	Latashopine indujency Latashopine indujency Latashopine indujency Comet life inem Rescue or nucleation In vitro IZebrafish Growth rate Comet idensity Catashopine frequency Catashopine frequency Catashopine frequency Catashopine frequency Comet life time Rescue or nucleation Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST ST ST RR In vitro DRG neurons	0.029 0.030 0.0008 0.0008 0.0008 0.0008 0.000 0.000 0.000 0.000 0.000 0.00 0	0.17 0.08 0.08 0.001 Deal C Growth rate Cornet density Catastrophe frequency Length of growth Cornet if le time Rescue or nucleation Panel E Degeneration Index Lentiviral shRNA Delivery pValue DirCP1+30:CD1+Bort DirCP1+30:CD1+Bort DirCP1+0:CD1+Bort DirCP1+0:CD1+Bort 0.001 0.001 0.001 No Winx sy pLVX-EGFP-D2 pValue	0.002 0.22 0.22 0.22 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001 0.000 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.000 0.0001 0.000 0.0001 0.000	0.0009 4.0001 4.0001 2.0001 2.0001 2.0001 1.0001 2.0001 4.0001	0.17 0.002 0.001 0.0005 0.0005 0.0005 0.0005 0.0005 0.0005 0.03 0.0002 0.03 0.0002 0.07 0.28
Figure 4 Panel C MT Dynamics Figure 56 Figure 5 Panel D Degeneration Index Figure 6 Panel B Degeneration Index Figure 7 Panel B Mitochondria Dynamics Panel D	Latastropie reducincy Latastropie reducincy Langth of growth Rescue or nucleation In vitro In Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Comet life time Rescue or exclusion Rescue or exclusion In vitro DRG neurons In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP T	2.009 2.009 2.0008 2.0008 2.0008 2.0008 2.0008 2.0001 2.0001 2.7 2.8 2.0001 2.7 2.8 2.0 2.3 2.3 2.3 2.3 2.3 2.3 2.3 2.3 2.3 2.3	0.17 0.0001 0.0001 Panel G Growth rate Comet density Catastrophe fequency Length of growth Comet ife time Rescue or nucleation Panel E Degeneration Index Lentiviral sRRNA Delivery Lentiviral sRRNA Delivery Lentiviral sRRNA Delivery Lentiviral sRRNA Delivery Data Data Data Data Data Data Degeneration Data	0.002 0.22 < 0.0001 2.0001 2.0001 2.0001 2.0001 0.27 0.3 0.27 0.3 0.3 0.3 0.3 0.0001 0.0001 0.001 0.001 0.001 0.001 0.0000 0.0001	0.0008 0.0001 0.0001 0.0001 120.004 Bort Control vis dh pValue 0.001 0.04 0.001 0.04 0.001 0.04 0.0001 0.000 0.001 0.000 0.001 0.000 0.001 0.000 0.000 0.000 0.001 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000 0.00000 0.00000 0.00000 0.00000 0.00000000	0.17 0.002 0.001 0.0005 3h vs 6h pVelue 0.006 0.46 0.3 0.0002 0.3 0.0002 0.3 0.002
Figure 4 Panel C MT Dynamics Figure 56 Final D Degeneration Index Figure 6 Panel B Degeneration Index Figure 7 Panel B Degeneration Index Figure 6 Panel B Degeneration Index Figure 7 Panel B Mitochondria Dynamics State	Latastrophe requency Langth of growth Ceret life tim velocition Ceret life tim velocition Rescrie or nucleation In vitro Izebrafish Growth rate Comet density Catastrophe frequency Length of growth Comet life time Rescrie or nucleation Retrograde cornets In vitro DRG neurons Neurofilament In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST AR Rescrief Cometant In vitro DRG neurons DP ST AR	0.009 0.05 0.05 0.0001 0.0001 1.3 uM Bort Control vs 6h pValue 0.0001 0.7 0.87 0.7 0.85 0.000 0.69 0.69 0.69 0.69 0.69 0.69 0.69 0.61 0.62	0.17 0.08 0.08 0.001 Panel G Growth rate Comet density Catastrophe frequency Length of growth Comet life time Rescue or nucleation Panel E Degeneration Index Degeneration Index Lentiviral shRNA Delivery plaine 0.0017 JaNC vs shTL2 plaine 0.0017 JaNC vs shTL2 plaine 0.0017 JaNC vs shTL2 plaine 0.0017 JaNC vs shTL2 plaine 0.0017 JaNC vs shTL2 plaine 0.001 0.0001 0.	0.002 0.22 0.22 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001 0.00 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.000 0.0001 0.000 0.0001 0.000 0.0001 0.000 0.0001 0.000 0.0001 0.000 0.00	0.0008 0.0001 0.0001 0.0001 20.0001 20.0001 20.0001 0.004 0.004 0.004 0.004 0.0001 0.0001 0.0001 0.0001 0.0001 0.0000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.0	0.17 0.002 0.001 0.0005 0.0005 0.0006 0.46 0.3 0.0002 0.07 0.28
Figure 4 Panel C MT Dynamics Figure 56 Panel D Degeneration Index Figure 5 Panel D Degeneration Index Figure 5 Panel D Degeneration Index Figure 5 Panel D Degeneration Index Figure 5 Panel B Mitochondria Dynamics State	Latastrophe frequency Latastrophe frequency Latastrophe frequency Rescue or nucleation In vitro in Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Rescue or nucleation Retrograde cornets In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST AR R In vitro DRG neurons DP ST AR RR In vitro DRG neurons	0.009 0.009 0.0008 1.3 uM Bort Control vs 6h pValue Control vs 6h pValue 0.75 0.85 0.75 0.85 0.75 0.85 0.23 0.69 2.24 0.60 0.62 2.44 0.60 0.44 0.60 0.65 0.6	0.17 0.17 0.0001 Panel G Growth rate Comet if density Catastrophe frequency Length of growth Comet life lime Comet life lime Comet life lime Comet life lime Degeneration Index Degeneration Index Degeneration Index Lentiviral shRNA Delivery (7D) shCCP1 + ShRCA Delivery (7D) shCCP1 + ShCCP1+Bort 0.007 Lentiviral shRNA Delivery (7D) ShCCP1 + ShCCP1+Bort 0.001 0.001 0.001 0.001 0.001 0.001 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001	0.002 0.22 < 0.0001 (a), where in Drosophila Control vis 3in pValue 0.27 0.33 < 0.0001 < 0.0001	0.0008 0.0001 0.0001 0.0001 120.0M Bort Control vs 6h PValue 0.001 0.04 0.04 0.001 0.04 0.001 0.04 0.0001 0.001 0.09 No Vinus vs pLVX:EGFP-WT lub PValue 0.009	0.17 0.002 0.001 0.0005 0.0005 0.006 0.46 0.3 0.000 0.3 0.000 0.28
Figure 4 Panel C MT Dynamics Figure 56 Panel D Degeneration Index Figure 6 Panel B Degeneration Index Figure 7 Panel B Mitochondria Dynamics State Figure S4	Latastropie requency Latastropie requency Length of growth Rescue or nucleation In vitro In Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Comet (If time Rescue or nucleation Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR	0.009 0.009 0.0008 0.0008 1.3 uM Bort Control vs 6h pValue 0.0001 0.87 0.7 0.85 0.000 0.87 0.7 0.85 0.00 0.69 0.03 0.69 0.03 0.69 0.03 0.69 0.03 0.60 0.60 0.60 0.60 0.60 0.60 0.60	0.17 0.08 0.09 0.08 0.09 0.09 0.001	0.002 0.22 < 0.0001 2.0001	0.0008 0.0008 0.0007 0.0007 0.0007 0.0007 0.0007 0.001 0.001 0.04 0.0007 0.04 0.0007 0.04 0.0007 0.04 0.0007 0.00 10.0 10.0 10.0 10.0 10.0 10	0.17 0.002 0.001 0.0005 0.0005 0.0005 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0005 0005 00005 00005 000005 00000000
Figure 4 Panel C MT Dynamics Figure 56 Panel D Degeneration Index Figure 6 Panel B Degeneration Index Figure 7 Panel B Mitochondria Dynamics State Dynamics State	Latashopine indujency Latashopine indujency Latashopine indujency Cornet life time Rescue or nucleation In vitro Izebrafish Growth rate Cornet density Catashopine frequency Catashopine frequency Catashopine frequency Catashopine frequency Cornet life time Rescue or nucleation Retrograde cornets In vitro DRG neurons Neurofilament In vitro DRG neurons DP T AR RR In vitro DRG neurons DP ST AR RR In vitro DRG neurons	0.00 0.00 0.0008 1.3.uM Bort Control vs 6h pValue Control vs 6h pValue 0.75 0.059 0.23 0.69 2.23 0.69 2.23 2.25 2.55 2.25 2.55 2.55 2.55 2.55 2.55	0.17 0.08 0.08 0.001 Deals Growth rate Comet density Catastrophe frequency Length of growth Comet life time Rescue or nucleation Panel E Degeneration Index Lentiviral shRNA Delivery plalue 0.007 JaiNC vs shTL2 plalue 0.007 JaiNC vs shTL2 JaiNC v	0.002 0.22 0.22 0.22 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001 0.00 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.000 0.000	0.0008 0.0009 0.0007 0.0007 0.0007 0.0007 0.0007 0.0007 0.004 0.004 0.004 0.004 0.004 0.0007 0.000 0.09 0.00 0.09 0.00 0.09 0.00 0.00 0.	0.17 0.002 0.001 0.0005 0.0005 0.0006 0.006 0.46 0.3 0.0002 0.07 0.28
Figure 4 Panel C MT Dynamics Figure 56 Figure 57 Panel D Degeneration Index Figure 6 Panel B Degeneration Figure 7 Panel B Mitochondria Dynamics State Figure 54 Caspase activity	Latastropie requency Latastropie requency Langth of growth Rescue or nucleation In vitro in Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Generative muchaelion Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR In vitro DRG neurons	2.009 2.009 2.0008 2.0008 2.0008 2.0008 2.0008 2.0007 2.0001 2.000	0.17 0.17 0.0001 Panel G Growth rate Comet density Catastrophe fequency Length of growth Comet ife time Rescue or nucleation Density of the second Comet density Comet de time Rescue or nucleation Density of the second Density of the seco	0.002 0.22 < 0.0001 2.0001 2.0001 2.0001 2.0001 0.001 0.27 0.3 2.0001 < 0.0001 2.0	0.0008 0.0001 0.0001 0.0001 0.0001 0.001 0.001 0.001 0.04 0.0001 0.04 0.0001 0.000 0.001 0.000 0.001 0.0000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000 0.00000000	0.17 0.002 0.001 0.0005 0.0005 0.006 0.46 0.3 0.000 0.46 0.3 0.002 0.07 0.28
Figure 4 Panel C MT Dynamics Figure 56 Panel D Degeneration Index Figure 6 Panel D Degeneration Index Figure 7 Panel B Mitochondria Dynamics State Figure 54 Caspase activity Elou:	Latastropie requency Latastropie requency Length of growth Rescue or nucleation In vitro in Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Comet life time Rescue or nucleation Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons Dev ST AR AR In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR	0.009 0.05 0.55 0.55 0.55 0.55 0.55 0.55 0.0001 0.7 0.85 0.69	0.17 0.08 0.08 0.001 Panel G Growth rate Comet density Catastrophe fequency Length of growth Comet iffe line Panel E Degeneration Index Degeneration Index	0.002 0.22 < 0.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.0001 2.20 ShNC+Bort vs shCCP1+Bort 2.20 ShNC+Bort vs ShCP1+Bort 2.20 ShNC+Bort vs ShCP1+Bort vs ShCP1	0.0008 0.0001 0.0001 0.0001 20.0001 20.0001 0.001 0.001 0.04 0.0001 0.04 0.0001 0.04 0.0001 0.000 0.001 0.000 0.001 0.0000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000000	0.17 0.002 0.001 0.0005 0.0005 0.0005 0.0006 0.46 0.3 0.0002 0.07 0.28
Figure 4 Panel C MT Dynamics Figure 56 Panel D Degeneration Index Figure 6 Panel D Degeneration Index Figure 6 Panel D Mitochondria Dynamics State Figure S4 Caspase activity Figure S4 Caspase activity	Latashopine induces view of the second tile international second tile international second se	2.009 2.009 2.0008 2.0008 2.0008 2.0008 2.0008 2.0001 2.0001 2.000	0.17 0.17 0.0001 Panel G Growth rate Comet if density Catastrophe frequency Length of growth Comet life lime Degeneration Index Degeneration Index Degeneration Index Lentiviral shRNA Delivery (TD) ShCC Vs shTTL2 PValue 0.007 Lentiviral shRNA Delivery (TD) shCCP1+Bort PValue 0.007 Lentiviral shRNA Delivery (SD) shCCP1+Bort PValue 0.001 0.00	0.002 0.02 0.22 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.00 0.27 0.03 0.27 0.03 0.27 0.03 0.001 0.001 0.00 0.00 0.00 0.00 0.	0 0008 0 0008 0 0001 0 0001 20 004 Bort Control vs 8/h PV8/ue 0 001 0 04 0 04 0 04 0 04 0 04 0 001 0 04 0 001 0 04 0 001 0 04 0 000 0 001 0 04 0 000 0 001 0 000 0 001 0 000 0 001 0 000 0 001 0 000 0 0000 0 0000 0 000 0 000 0 0000 0 0000 0	0.17 0.002 0.001 0.0005 0.0005 0.006 0.46 0.3 0.000 0.46 0.3 0.000 0.28
Figure 4 Panel C MT Dynamics Figure 56 Figure 56 Panel D Degeneration Index Figure 6 Panel B Degeneration Index Figure 7 Panel B Mitochondria Dynamics State Figure 54 caspase activity Figure 55 Panel B	Latastropie requirely Langth of growth Rescue or nucleation In vitro In Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Comet life time Rescue or nucleation Rescue or nucleation Neurofilament In vitro DRG neurons DP ST AR RR In vitro DRG neurons DEVD-AMC cleavage In vitro DRG neurons	2.009 2.009 2.0008 2.0008 2.0008 2.0008 2.0007 2.0007 2.0001 2.7 2.7 2.8 2.000 2.7 2.7 2.8 2.0 2.0 2.0 2.0 2.0 2.0 2.0 2.0 2.0 2.0	0.17 0.08	0.002 0.02 0.22 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.00 0.001 0.00 0.001 0.00	0.0008 0.0007 0.0007 0.0007 0.0007 0.0007 0.001 0.000 0.001 0.000 0.000 0.001 0.0000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000 0.000000 0.00000000	0.17 0.002 0.001 0.0005 30 vs 6h pValue 0.006 0.46 0.3 0.0002 0.3 0.0002 0.28
Figure 4 Panel C MT Dynamics Figure 56 Panel D Degeneration Index Figure 6 Panel D Degeneration Index Figure 6 Panel B Mitochondria Dynamics State Figure 54 Caspase activity Figure 55 Panel B	Latashopine inducery Latashopine inducery Latashopine inducery Cornet life time Rescue or nucleation In vivo in Zebrafish Growth rate Cornet density Cornet density Cornet life time Rescue or nucleation Retrograde cornets In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP Latashopine DP Latashopine DP Latashopine La	0.00 0.00 0.000 0.0008 1.3 uM Bort Control vs 6h pValue Control vs 6h pValue 0.7 5 0.059 0.23 0.69 2.23 0.69 2.23 2.25 2.55 2.	0.17 0.08 0.08 0.001 Panel G Growth rate Comet density Catastrophe Requency Length of growth Comet life time Rescue or nucleation Panel E Degeneration Index Lentiviral shRNA Delivery plain Diffice as hTL2 plain Diffice as hTL2 plain Diffice as hTL2 plain Diffice as hTL2 plain Diffice as hTL2 plain CP1 vas ARNA Delivery (ID) aftCP1 vas ARCP1+Bort 0.57 0.57 0.57 0.001 0.31 0.001 0.	0.002 0.02 0.22 0.0001 0.001 0.0001 0.0001 0.0001 0.0001 0.000 0.0001 0.000 0.0001 0.00 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.02 0.0001 0.000 0.0001 0.000 0.0001 0.000 0.0001 0.000 0.	0.0008 0.0007 0.0007 0.0007 0.0007 20.0007 120 uM Bort Control vs 6h privation 0.04 0.04 0.04 0.0007 0.04 0.0007	0.17 0.002 0.001 0.0005 0.0005 0.0005 0.0005 0.0005 0.0005 0.0005 0.0005 0.000 0.000 0.000 0.007 0.28
Figure 4 Panel C MT Dynamics Figure 56 Panel D Degeneration Index Figure 6 Panel B Degeneration Index Figure 6 Panel B Degeneration Index Figure 8 Panel B Mitochondria Dynamics State Figure 84 Caspase activity Figure 85 Panel B	Latastropie requency Latastropie requency Longh tiegrowth Rescue or nucleation In vitro in Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Rescue or nucleation Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP TT L	0.009 0.009 0.0008 0.0008 1.3 UM Bort Control vs 6h pValue Control vs 6h pValue Control vs 6h pValue Control vs 5hNC+Bort DValue Control vs 5hNC+Bort DValue Control vs 5hNC+Bort DValue Control vs 12h pValue Control vs 12h DValue Control vs 12	0.17 0.08 0.09 0.09 0.09 0.09 0.09 0.09 0.00	0.002 0.02 0.22 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.00 0.001 0.00 0.001 0.00 0.001 0.00 0.0	0.0008 0.0008 0.0007 0.0007 0.0007 120.0M Bort Control vs 6h 0.001 0.04 0.04 0.001 0.04 0.001 0.04 0.001 0.04 0.0001 0.0 0.001 0.0 0.0 0.001 0.0 0.0	0.17 0.002 0.001 0.0005 0.0005 0.006 0.46 0.3 0.000 0.46 0.3 0.002 0.07 0.28 0.07 0.28
Figure 4 Panel C MT Dynamics Figure 56 Panel D Degeneration Index Figure 6 Panel D Degeneration Index Figure 6 Panel B Degeneration Index Figure 64 Panel D Mitochondria Dynamics State Figure 54 Caspase activity Figure 54 B	Latastropie requency Latastropie requency Length of growth Rescue or nucleation In vitro I Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Comet file time Rescue or nucleation Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST AR RR In vitro DRG neurons	0.009 0.009 0.009 0.0009 0.0009 0.0009 0.0009 0.000 0.000 0.000 0.000 0.000 0.00	0.17 0.08 0.08 0.08 0.08 0.09 0.001 0.001 0.001 0 0.001 0 0.001 0 0 0 0	0.002 0.22 0.001 0.021 0.001 0.0	0.0008 0.0008 0.0007 0.0007 0.0007 0.0007 0.0007 0.001 0.001 0.04 0.0007 0.04 0.0007 0.04 0.0007 0.04 0.0007 0.00 0.00	pValue 0.42 0.002 0.0005 0.005
Figure 4 Panel C MT Dynamics Figure 56 Panel D Degeneration Index Figure 6 Panel D Degeneration Index Figure 6 Panel D Mitochondria Dynamics State Figure 84 Caspase activity Figure 85 Panel B IB	Latashopine indunicy Latashopine indunicy Latashopine indunicy Latashopine indunicy Rescue or nucleation In vitro IZebrafish Growth rate Comet idensity Catashopine frequency Latashopine frequency Catashopine frequency Comet idensity In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP Latashopine DP Latashopine	0.009 0.009 0.009 0.009 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.00	0.17 0.17 0.00 0.001 Panel G Growth rate Comet density Catastrophe fequency Length of growth Comet de lane Degeneration Index Degeneration Index Lentiviral shRNA Delivery ShNC vs ghTL2 Pylaue 0.007 Lentiviral shRNA Delivery (7D) shCCP1-Bort 9/Sue 0.001 0.01 0.01 0.01 0.01 0.01 0.00	0.002 0.02 0.22 0.001 0.001 0.001 0.001 0.001 0.001 0.00 0.27 0.03 0.02 0.02 0.02 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0.02 0.00 0 0.00 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0 0008 0 0008 0 0001 0 0001 0 0001 0 001 0 0001 0 0000 0 0001 0 0000 0 0001 0 0000 0 0000 0 0001 0 0000 0 00000 0 0000 0 00000 0 000000 0 00000 0 00000 0 00000 0 00000000	0.17 0.02 0.001 0.0005 0.0005 0.006 0.46 0.3 0.000 0.46 0.3 0.000 0.28 0.000 0.28 0.000 0.28 0.000 0.28
Figure 4 Panel C MT Dynamics Figure 56 Figure 56 Panel D Degeneration Index Figure 6 Panel B Degeneration Index Figure 7 Panel B Mitochondria Dynamics State Figure 54 Caspase activity Figure 55 Panel B IB	Latastophe requency Latastophe requency Length of growth Rescue or nucleation In vitro In Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Comet life time alaion Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP CDF TD ST CDF TD ST CDF TT CDF CDF TTL In vitro DRG neurons	2.009 2.009 2.0008 2.0008 2.0008 2.0008 2.0008 2.0007 2.0007 2.0001 2.7 2.8 2.000 2.7 2.8 2.0 2.3 2.0 2.3 2.3 2.3 2.3 2.3 2.3 2.3 2.3 2.3 2.3	0.17 0.08 0.08 0.09 0.09 0.09 0.001	0.002 0.02 0.22 0.001 0.02 0.001 0.001 0.001 0.001 0.02 0.001 0.02 0.00 0.02 0.00 0.02 0.00 0.00	0.0008 0.0008 0.0007 0.0007 0.0007 0.0007 0.0007 0.001 0.001 0.04 0.0007 0.04 0.0007 0.04 0.0007 0.00 0.0 0.00 0.0	0.17 0.002 0.001 0.0005 0.0005 0.0005 0.0005 0.0002 0.00000000
Figure 4 Panel C MT Dynamics Figure 56 Figure 57 Panel D Degeneration Index Figure 6 Panel D Degeneration Index Figure 6 Panel B Degeneration Index Figure 54 Mitochondria Dynamics State Figure 54 Caspase activity Figure 55 Panel B IB	Latashopine inducincy Latashopine inducincy Latashopine inducincy Comet life time Rescue or nucleation In vitvo in Zebrafish Growth rate Comet density Catashopine frequency Catashopine frequency Catashopine frequency Comet life time Rescue or nucleation Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST ST RR In vitro DRG neurons DP ST ST RR In vitro DRG neurons DP Latashopine DP Latashopine La	0.00 0.00 0.0008 0.0008 1.3 UM Bort Control vs 6h pValue Control vs 6h pValue 0.7 5 0.89 0.02 ShNC vs shTTL1 pValue 0.02 ShNC vs shNC+Bort 0.02 ShNC vs sh	0.17 0.17 0.0001 0.001 Panel G Growth rate Comet density Catastrophe fequency Length of growth East of a growth Bageneration Index Lentiviral shRNA Delivery (7D) shCCP1+3bcrCP1+3bcrt 0.007 Lentiviral shRNA Delivery (7D) shCCP1+3bcrt Delivery (7D) shCCP1+3bcrt Delivery (7D) shCCP1+3bcrt Delivery (7D) shCCP1+3bcrt Delivery (7D) 0.001	0.002 0.22 < 0.0001 2.0001	0.0008 0.0009 0.0001 0.0001 0.0001 20.0001 0.001 0.04 0.0001 0.04 0.0001 0.04 0.0001 0.001 0.001 0.001 0.001 0.00001 0.0001 0.0001 0.0001 0.0001 0.0001 0.0001	pValue 0.12 pValue 0.000 0.000 0.000 0.000 0.000 0.46 0.3 0.000 0.28 0.000 0.28 0.000 0.28 0.000 0.28 0.000 0.28
Figure 4 Panel C MT Dynamics Figure 56 Figure 56 Panel D Degeneration Index Figure 6 Degeneration Index Figure 6 Degeneration Index Figure 6 Panel B Mitochondria Dynamics State Figure 54 Caspase activity Figure 55 Panel B IB	Latastropie requency Latastropie requency Longan tilgrowin Rescue or nucleation In vitro in Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Rescue or nucleation Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP T T L In vitro DRG neurons DP T T CCPT TTL	2.009 2.009 2.0008 2.0008 2.0008 2.0008 2.0007 2.0007 2.0007 2.007	0.17 0.08 0.09 0.09 0.09 0.09 0.09 0.09 0.09	0.002 0.02 0.22 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.00 0.001 0.00 0	0.0008 0.0008 0.0001 0.0001 0.0001 0.0001 0.001 0.001 0.04 0.001 0.04 0.001 0.04 0.001 0.04 0.001 0.04 0.001 0.0 0.001 0.0 0.0 0.0 0.0 0.0 0.0	0.17 0.002 0.001 0.0005 0.0005 0.006 0.46 0.3 0.000 0.46 0.3 0.002 0.07 0.28 0.07 0.28 0.07 0.28
Figure 4 Panel C MT Dynamics Figure 56 Pamal D Degeneration Index Figure 6 Panel D Degeneration Index Figure 6 Panel B Degeneration Index Figure 6 Panel B Mitochondria Dynamics Figure 54 Caspase activity Figure 54 Figure 54 Fi	Latastropie requency Latastropie requency Length of growth Rescue or nucleation In vitro IZebrafish Growth rate Cornet density Catastrophe frequency Length of growth Cornet life time Rescue or nucleation Retrograde contest In vitro DRG neurons In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST AR RR In vitro DRG neurons DEVD-AMC cleavage In vitro DRG neurons CCP1 TTL In vitro DRG neurons	2.009 2.000 2.0000 2.0000 2.0000 2.0000 2.0000 2.0000 2.000	0.17 0.08 0.08 0.08 0.08 0.08 0.09 0.001 0.001 0 0.001 0 0.001 0 0 0 0 0 0	0.002 0.22 0.020 0.021 0.0000000 0.0000000000	0 0008 0 0008 0 0001 0 0001 0 0001 0 001 0 000 0 001 0 000 0 0000 0 0000 0 0000 0 000 0 000 0	pValue 0.12 pValue 0.002 p1 state p2 state 0.000 p2 state 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.000000
Figure 4 Panel C MT Dynamics Figure 56 Figure 57 Panel D Degeneration Index Figure 6 Panel D Degeneration Index Figure 6 Panel D Mitochondria Dynamics State Figure 84 Caspase activity Figure 85 Panel B IB Figura 87 Panel C and F IB	Latashopine indunity Latashopine indunity Latashopine indunity Latashopine indunity Rescue or nucleation In vitro IZebrafish Growth rate Comet idensity In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP CCP1 TTL In vitro DRG neurons CCP1 TTL In vitro DRG neurons D2 CCP1 TTL In vitro DRG neurons D2 CCP1 TTL	2.009 2.009 2.0008 2.0008 2.0008 2.0008 2.0008 2.0001 2.0001 2.000	0.17 0.17 0.0001 Panel G Growth rate Comet density Catastrophe fequency Length of growth Comet die lune Comet die lune Comet die lune Comet die lune Degeneration Index Degeneration Index Degen	0.002 0.02 0.22 0.001 0.001 0.001 0.001 0.001 0.001 0.00 0.27 0.03 0.02 0.00 0.02 0.00 0.00 0.00 0.00	0 0008 0 0008 0 0001 0 0001 0 0001 0 001 0 000 0 001 0 001 0 0001 0 0000 0 0001 0 0000 0 0001 0 0000 0 0000 0 0001 0 0000 0 00000 0 000000 0 00000 0 00000 0 00000 0 00000000	0.17 0.02 0.001 0.0005 0.0005 0.000 0.006 0.46 0.3 0.000 0.46 0.3 0.000 0.28 0.000 0.28 0.000 0.28 0.000 0.28 0.000 0.28 0.000 0.28 0.000 0.28 0.000 0.28 0.000 0.28 0.000 0.28 0.000 0.28 0.0000 0.0000 0.0000 0.0000 0.000000
Figure 4 Panel C MT Dynamics Figure 56 Figure 57 Panel D Degeneration Index Figure 6 Panel B Degeneration Figure 7 Panel B Mitochondria Dynamics State Figure 54 caspase activity Figure 55 Panel B IB Figure 37 Panel C and F	Latastophe requency Latastophe requency Length of growth Rescue or nucleation In vitro In Zebrafish Growth rate Comet density Catastrophe frequency Length of growth Comet life time aairon Retrograde comets In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP ST AR RR In vitro DRG neurons DP T AR RR In vitro DRG neurons DP T CCP1 TTL In vitro DRG neurons	2.009 2.009 2.0008 2.0008 2.0008 2.0008 2.0008 2.0008 2.0007 2.00	0.17 0.17 0.0001 0.001 Panel G Growth rate Comet density Catastrophe fequency Length of growth Comet de time Rescue or nucleation Panel E Degeneration Index Degeneration Index Lentiviral sRNA Delivery (TD) shCCP1 vs shCCP1+Bort 0.007 Lentiviral sRNA Delivery (SD) shCCP1 vs ShCCP1+Bort 0.001 0.00 0.001 0.00 0.001 0.00 0.001 0.00 0.0	0.002 0.22 0.001 1n vive in Drosophila Control vs 30 0.27 0.37 0.37 0.37 0.30 0.27 0.30 0.30 0.30 0.0001 0.00001 0.0001 0.0001 0.0001 0.0001 0.0001 0.000	0.0008 0.0008 0.0007 0.0007 0.0007 0.0007 0.001 0.001 0.001 0.04 0.0007 0.04 0.0007 0.04 0.0007 0.04 0.0007 0.00 0.0 0 0.00 0.0	0.17 0.02 0.001 0.0005 0.0005 0.0005 0.000 0.000 0.46 0.3 0.0002 0.07 0.28 0.002 0.07 0.28 0.002 0.07 0.28 0.002 0.07 0.28 0.002 0.07 0.28 0.002 0.07 0.28 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.005 0
Figure 4 Panel C MT Dynamics Figure 56 Figure 57 Panel D Degeneration Index Figure 6 Panel D Degeneration Index Figure 67 Panel B Mitochondria Dynamics State Dynamics State Figure 54 Caspase activity Figure 55 Panel B IB Figure 37 Panel C and F IB	Latashopine inducincy Latashopine inducincy Latashopine inducincy Latashopine inducincy Cornet life intem Rescue or nucleation In vitro IZebrafish Growth rate Cornet density Cornet life intem Rescue or nucleation Retrograde cornets In vitro DRG neurons Neurofilament In vitro DRG neurons DP ST ST RR In vitro DRG neurons DP ST ST RR In vitro DRG neurons DP Latashopine DP ST Latashopine CCP1 TTL In vitro DRG neurons DEVD-AMC cleavage In vitro DRG neurons CCP1 TTL D2 D2 CCP1 D0/PGLU D D D D D D D D D D D D D D D D D D D	2.009 2.0008 2.0008 2.0008 2.0008 2.0008 2.0008 2.0008 2.0008 2.0001 2.001 2.001 2.001 2.00 2.001 2.00 2.00	0.17 0.17 0.0001 0.001 Panel G Growth rate Comet density Catastrophe fequency Length of growth Comet density Comet density Comet density Comet density Comet density Degeneration Index Lentiviral shRNA Delivery (TD) ShCCP 1+30CP1+30rt 0.007 Lentiviral shRNA Delivery (TD) ShCCP 1+30CP1+30rt 0.001	0.002 0.22 0.22 0.0001 1. vivo in Drosophila Control vs 37 0.0001 2. 0.0001 2. 0	0 0008 0 0008 0 0001 0 0001 0 0001 0 0001 0 004 0 004 0 0001 0 04 0 0001 0 04 0 0001 0 04 0 0001 0 04 0 0001 0 00 0 04 0 0001 0 00 0 00	pValue 0.12 0.002 0.001 0.0005 0.0005 0.006 0.46 0.3 0.0002 0.28 0.0002 0.28 0.0002 0.28 0.0002 0.28 0.0002 0.28 0.0002 0.28 0.0002 0.28 0.0002 0.28 0.0002 0.28 0.0002 0.28 0.0002 0.000 0.28 0.0002 0.0002 0.0002 0.0002 0.0002 0.0002 0.0002 0.0002 0.0002 0.0005 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.000000
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Table S1. Table showing p values derived from statistical analysis of quantitative data included in Figures and Supplementary Figures.

Supplementary Movies

Movie S1. EB3-EGFP dynamics in axons of cultured mouse DRG neurons treated 0 h with bortezomib (Figure 3E).

Movie S2. EB3-EGFP dynamics in axons of cultured mouse DRG neurons treated 6 h with bortezomib (Figure 3E).

Movie S3. EB3-GFP dynamics in adult zebrafish skin nerve endings treated 0 h with bortezomib (Figure 4B).

Movie S4. EB3-GFP dynamics in adult zebrafish skin nerve endings treated 6 h with bortezomib (Figure 4B).

Movie S5. EB1-GFP dynamics in a nociceptive neuron of third star *Drosophila* larva treated with vehicle control (Figure 4F).

Movie S6. EB1-GFP dynamics in a nociceptive neuron of third star *Drosophila* larva treated 6 h with bortezomib (Figure 4F).

Movie S7. LAMP1- mRFP-FLAG dynamics in axons of untreated cultured mouse DRG neurons (SI Appendix, Figure S8A).

Movie S8. LAMP1- mRFP-FLAG dynamics in axons of cultured mouse DRG neurons treated with 100 nM Bort (24 h) (SI Appendix, Figure S8A).

Movie S9. Mito-dsRed dynamics in axons of cultured mouse DRG neurons infected with control shNC lentivirus (Figure 7A).

Movie S10. Mito-dsRed dynamics in axons of cultured mouse DRG neurons infected with control shNC lentivirus plus 100 nM Bort (24 h) (Figure 7A).

Movie S11. Mito-dsRed dynamics in axons of cultured mouse DRG neurons infected with shCCP1 lentivirus (Figure 7A).

Movie S12. Mito-dsRed dynamics in axons of cultured mouse DRG neurons infected with shCCP1 lentivirus plus 100 nM Bort (24 h) (Figure 7A).

Movie S13. Mito-dsRed dynamics in axons of non-infected cultured mouse DRG neurons (Figure 7C).

Movie S14. Mito-dsRed dynamics in axons cultured mouse DRG neurons infected with control EGFP- α -tub lentivirus (Figure 7C).

Movie S15. Mito-dsRed dynamics in axons of cultured mouse DRG neurons infected with EGFP-D2-tub lentivirus (Figure 7C).

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