

1 **Supplementary Figure 1. Graphs of the immunofluorescence quantifications by experiment.** (A)  
2 HC and NPA fibroblasts were fixed and immunostained using an anti-p-c-Abl Tyr412 antibody (green)  
3 and Hoechst staining for nucleus (blue). For each condition, three independent experiments were  
4 performed; 15 cells /experiment were analyzed. Student's t-test. (B) HC and NPA fibroblasts were  
5 treated with imatinib (10  $\mu$ M) for 24 h, fixed, and immunostained using an anti-p62 antibody (green)  
6 and (C) anti-Lamp1 (green). Hoechst staining for the nucleus (blue). For each condition, three  
7 independent experiments were performed; 10-18 cells by experiment were analyzed. ANOVA, Tukey  
8 post-hoc. (D) ) Primary neurons were 7 days in vitro, fixed, and immunostained using anti-p-c-Abl  
9 Tyr412 antibody (red) and Hoechst staining for nucleus (blue). For each condition, three independent  
10 cultures were performed; 10-20 neurons were measured by culture. Student's t-test. (E) Primary  
11 hippocampal neurons were treated with imatinib 5  $\mu$ M by 24 h. Sphingomyelin accumulation was  
12 analyzed by BODIPY-SM. For each condition, three independent cultures were performed; 10-20  
13 neurons were measured by culture. (F) WT and NPA mice received nilotinib (200 ppm) and neurotinib  
14 (67 ppm) supplemented diets or control diet starting at p21 until 7 months of age. Astrocyte area was  
15 measured from GFAP positive cells. 3 mice were used per group and 10 cells were analyzed per mouse.  
16 (G) Microglia shape was determined from Iba-1 fluorescence. 3 mice were used per group and 5-10  
17 cells were analyzed per mouse. ANOVA, Tukey post-hoc. In the box-and-whisker plots, the center  
18 line denotes the median value, edges are upper and lower quartiles and whiskers show minimum and  
19 maximum values and points are individual experiments or number of animals used.

20 **Supplementary Figure 2. Characterization of an NPA neuronal pharmacologic model.** SHSY5Y  
21 cells were treated with 5, 10 and 20  $\mu$ M of desipramine for 24 h. (A) Cholesterol accumulation was  
22 detected with Filipin staining. As a positive control we used cells treated with U18666 (0.5  $\mu$ g/mL),  
23 which induces cholesterol accumulation. (B) ASM activity was measured through a fluorimetric  
24 method in SHSY5Y cells treated with desipramine 5  $\mu$ M and 20  $\mu$ M. Other controls include: LSM, a  
25 competitive substrate, heated proteins, NPA human fibroblasts and vehicle (Ctrl). Mean  $\pm$  SEM of  
26 three independent experiments are shown. \*\* $p \leq 0.01$ ; \*\*\* $p \leq 0.001$ .

27 **Supplementary Figure 3. c-Abl is activated in a pharmacological NPA model.** SHSY5Y cells were  
28 treated with 5, 10 and 20  $\mu$ M of desipramine for 24 h. p-c-Abl levels were analyzed by western blot  
29 (A) and immunofluorescence (B). (A) Three independent experiments were performed. (B) For each  
30 condition, n=15-20 neurons were measured by experiment; three independent experiments. ANOVA,  
31 Tukey *post-hoc*: \* $p \leq 0.05$ ; \*\* $p \leq 0.01$ ; \*\*\* $p \leq 0.001$ ; \*\*\*\* $p < 0.0001$ . In the box-and-whisker plots, the  
32 center line denotes the median value, edges are upper and lower quartiles and whiskers show minimum  
33 and maximum values.

34 **Supplementary Figure 4. Weight gain in mice treated with i.p injections of imatinib.** WT and NPA  
35 mice were treated with imatinib and vehicle from 3 weeks of age until 7 weeks of age. Gain of weight  
36 was recorded during all treatment. The numbers of animals was: WT control=11; WT imatinib=10;  
37 NPA control =8; NPA imatinib=9.

38 **Supplementary Figure 5. Pharmacokinetics and distribution of c-Abl inhibitors.** (A)  
39 Pharmacokinetic parameters of single dose intra venous (IV), oral administration (PO) and intra  
40 peritoneal (IP) administration of neurotinib in plasma and brain. (B) Distribution after 14-day  
41 administration of chow diet containing 67 ppm (10mg/kg) neurotinib and 200 ppm (30 mg/kg) nilotinib  
42 in plasma and brain (B).

44 **Supplementary Figure 6. Weight gain during chronic treatment with c-Abl inhibitor**  
45 **supplemented diets.** WT and NPA mice were treated with nilotinib and neurotinib supplemented diets  
46 from 3 weeks of age until 11 months of age. Gain of weight was recorded during all treatment. The  
47 numbers of animals was: WT control diet=10; NPA control diet=:10; NPA Nilotinib diet=11; NPA  
48 Neurotinib diet=10.

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