Review of efficacy and safety of cyclodextrin administration in feline NPC1 disease

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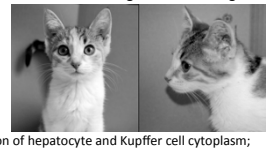
Feline NPC1 – missense mutation 2864G-C

Hepatic signs:
- ↑ serum hepatic transaminase activity
- ↓ serum albumin
- ↑ serum cholesterol

Neurologic signs: intention tremor and truncal ataxia begin at 6 wks of age and progress



Other signs: ↓ weight gain

Survival time: 20.7 ± 5 wks of age

Histological and biochemical evaluation:

Liver: severe and extensive vacuolization of hepatocyte and Kupffer cell cytoplasm; accumulations of cholesterol, sphingomyelin, BMP, sphingosine, sphinganine, minor neutral glycosphingolipids, and GM3 ganglioside.

Brain: diffuse neuronal cytoplasmic vacuolization with intracellular cholesterol storage and severe Purkinje cell loss;
marked accumulation of GM2 and GM3 gangliosides,
lesser increase of free sphingoid bases and minor neutral glycosphingolipids

13 groups of cats evaluated:
3 treated subcutaneously (SC) at 3 weeks of age
6 treated intrathecally (IT) at 3 weeks of age
1 treated SC & IT at 3 weeks of age
1 treated IT at 16 weeks of age

Group	Genotype	Route of Administration	Dose	Dosing Interval	Animal Numbers	
					Males	Females
1	Unaffected	-	-	-		
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3	NPC	SC	1000 mg/kg	7 days	5	1
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* Treatment first began at 16 weeks of age

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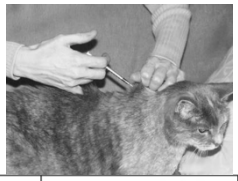
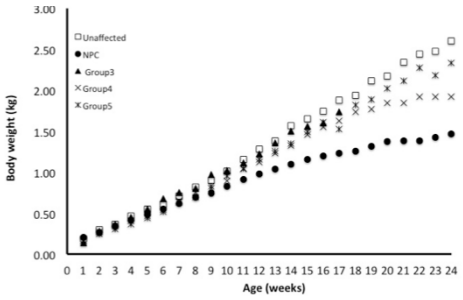
Mean plasma and CSF concentration 1 hr after subcutaneous injection



	Concentration (µg/mL)		
Dose (mg/kg)	Plasma	CSF	Plasma/CSF Ratio
1000	547	<5.00[1]	>109
4000	2570	19.45	132
8000	3485	21.2	164

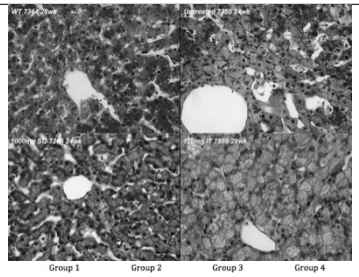
[1]Lowest limit of Quantification (LLOQ) was 5 µg/mL

Efficacy of subcutaneous therapy (1000, 4000, or 8000 mg/kg every 7d)
Increased weight gain occurred in all 3 SC-treated groups



Efficacy of subcutaneous therapy (1000, 4000, or 8000 mg/kg every 7d)
Normalization of hepatic disease occurred in all 3 SC-treated groups

Wild type | Untreated

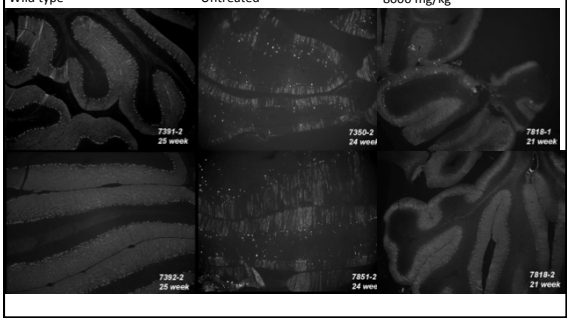


1000 mg/kg | 120 mg IT

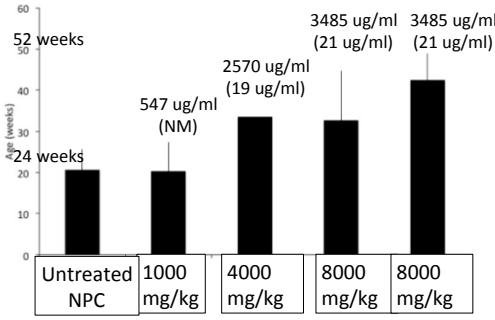
	Group 1	Group 2	Group 3	Group 4	Group 5
ALT	58.9+/- 13.3	341.2 +/- 188.6 *p=.0005	142.2 +/- 165	37.5	77 +/- 66.9
Albumin	2.87+/- .24	2.59 +/- .26 *p=.03	2.78 +/- .28	3.0	3.4 +/- .41 *p=.007
Cholesterol	124.7+/- 29.9	259.1 +/- 102.2 *p=.0008	189.6 +/- 57.6	131	166 +/-20.5

Efficacy of subcutaneous therapy (8000 mg/kg every 7d)
Significant positive effect on Purkinje cell survival at 8000mg/kg

Wild type | Untreated | 8000 mg/kg

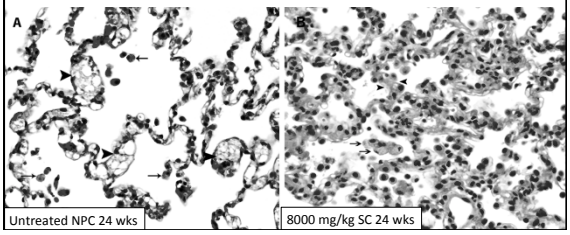


Survival times with subcutaneous therapy
Increased survival time occurred at 8000 mg/kg



Toxicity of subcutaneous therapy (8000 mg/kg every 7d)
Pulmonary toxicity resulted in death in 2/5 treated cats

2/5 cats in Group 5 (8000 mg/kg) developed severe dyspnea resulting in death.



6 groups treated intrathecally (IT) at 3 weeks of age

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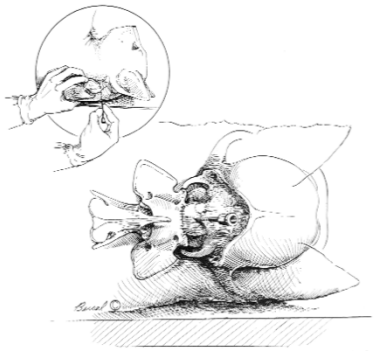
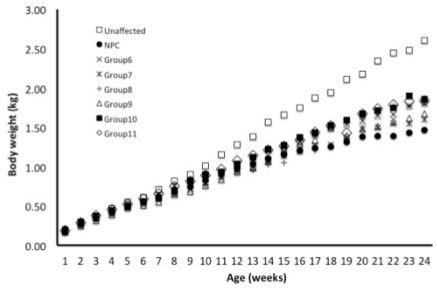


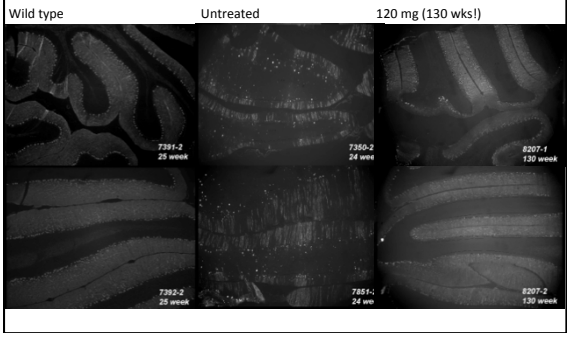
Pharmacokinetic parameter estimates following 120 mg IT dose

PK Parameters	Units	Plasma	CSF
C_{max}	(μg/mL)	125.4	11645
T_{max}	(h)	0.25	0.25
$AUC_{0\text{-}24h}$	(μg*h/mL)	173	20300
$AUC_{0\text{-}inf}$	(μg*h/mL)	215	20400
CL/F	(mL/h)	557	5.89
$T_{1/2}$	(h)	1.77	3.93
V_z/F	(mL)	1420	33.3

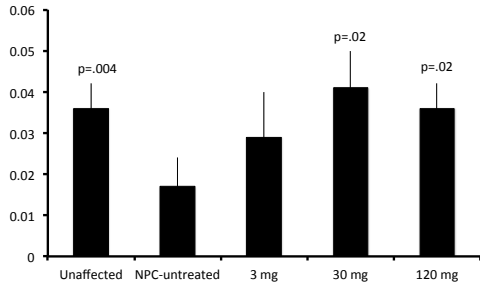
Efficacy of intrathecal therapy (3.8, 7.5, 15, 30, 60, or 120 mg q14d)
No effect on weight gain
No effect on liver disease (data not shown)

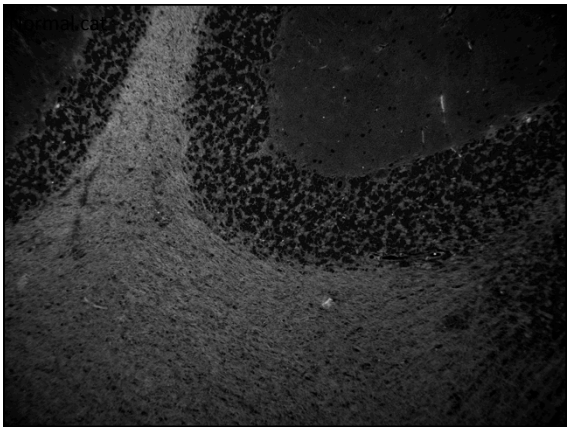


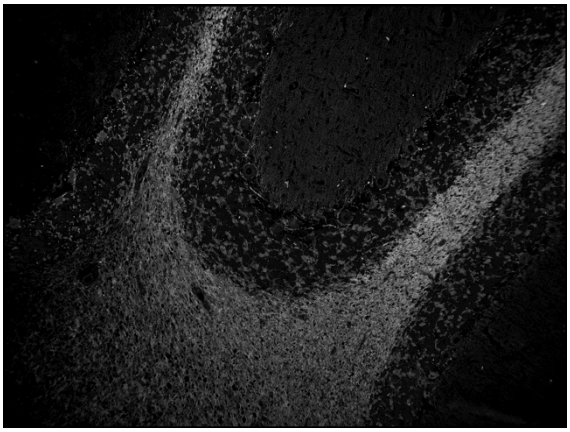
Efficacy of intrathecal therapy (3.8, 7.5, 15, 30, 60, or 120 mg q 14d)
Significant positive effect on Purkinje cell survival occurred



Efficacy of intrathecal therapy (3.8, 7.5, 15, 30, 60, or 120 mg q 14d)
Cats treated with =/> 30 mg showed increased Purkinje cell numbers per pixel in the cerebellar hemispheres at 24 weeks of age







Efficacy of intrathecal therapy (3.8, 7.5, 15, 30, 60, or 120 mg q 14d)

Cats treated with =/> 30 mg had greatest improvements in neurological function and survival time

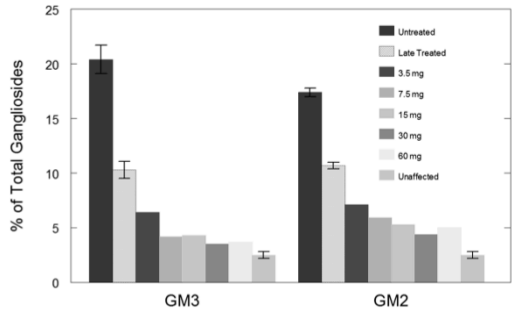
Onset of signs of neurological dysfunction

Treatment group	Age of onset of signs (wks)	Neurological dysfunction at 24 wks
1 (unaffected)	NA	NA
2 (untreated)	6.4 +/- 0.8	+3 ataxia, +3 tremors
6 (3.8mg)		
8555	10	+2 ataxia; +1 tremors
8645	9	+2 ataxia; +1 tremors
8721	12	+1 ataxia
7 (7.5 mg)		
8552	14	+1 ataxia; +1 tremors
8644	23	+2 ataxia; +1 tremors
8689	12	+2 ataxia; +1 tremors
8 (15 mg)		
8546	17	+1 ataxia
8640	18	+1 ataxia
8722	17	+1 ataxia

Survival time

Treatment group	Longest individual survival time (wks)
6 (3.8 mg)	49
7 (7.5 mg)	62
8 (15 mg)	66
9 (30 mg)	> 77 (still alive)
10 (60 mg)	> 95 (still alive)
11 (120 mg)	> 121 (still alive)

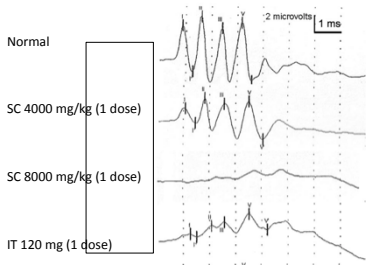
Brain gangliosides in 24 wk old NPC cats after intrathecal CD- therapy



Pharmacokinetic parameters for HPβCD in the plasma and CSF of cats

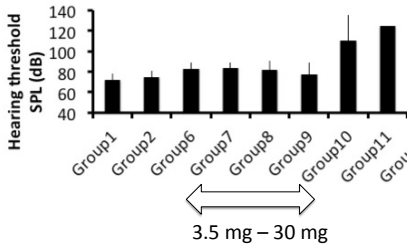
Analyte	Route	Dose	Matrix	C_0	$AUC_{0-\infty}$	$AUC_{0\text{-}24h}$	$t_{½}$	CL/F	Vd_{ss}
				(μg/mL)	(μg•h/mL)	(μg•h/mL)	(h)	(mL/h×kg)	(mL/kg)
HP-ß-D Kleptose	IT	30 mg	CSF	15,400	23,300	23,100	3.22	1.29	4.14
HP-ß-D Kleptose	IT	30 mg	Plasma	25.7[1]	-	-	-	-	-
									([1] from one cat)
HP-ß-D Kleptose	IT	120 mg	CSF	11,645	20,400	20,300	3.93	5.89	33.3
HP-ß-D Kleptose	IT	120 mg	Plasma	125.4	215	173	1.77	557	1,420

Safety of intrathecal therapy (3.8, 7.5, 15, 30, 60, or 120 mg every 14d)
Wildtype cats treated with cyclodextrin showed increased hearing threshold



Ward et al 2010

Safety of intrathecal therapy (3.8, 7.5, 15, 30, 60, or 120 mg every 14d)
NPC cats treated with >30m showed increased hearing threshold



3.5 mg – 30 mg

1 group treated SC & IT at 3 weeks of age

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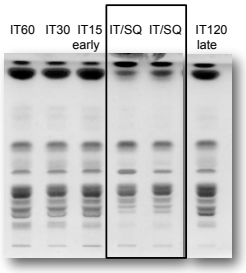
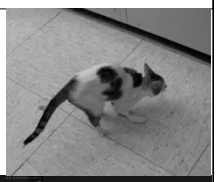
Liver lipids in NPC cats treated with both SC and IT HPBCD

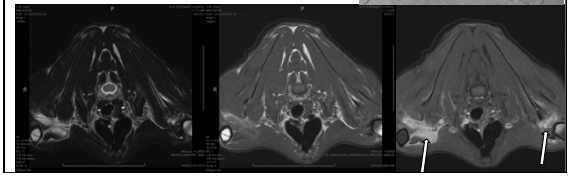


- IT route alone does not reduce the lipid accumulation in liver
- Combination IT/SQ does

Efficacy and safety of combination of SC and IT therapy

- Combination therapy resulted in amelioration of both hepatic and neurologic disease.
- Oldest cat is >139 weeks of age.
- Subcutaneous therapy resulted in cellulitis, myositis, and arthritis which result in a non-disease related abnormal gait (IT-treated cats do not walk this way)





1 group treated IT at 16 weeks of age

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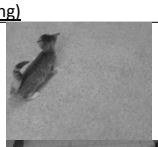
Efficacy of intrathecal therapy after onset of clinical signs
5 cats began treatment at 16 wks of age and are living >42 weeks (still living)

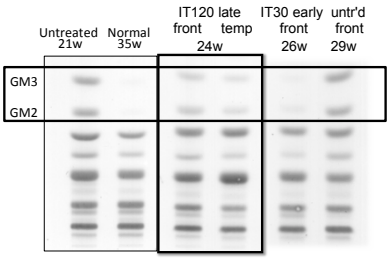
16 wk old untreated NPC cat



24 wk old untreated NPC cat

24 wk old NPC cat which began IT CD at 16 wks of age

Brain gangliosides in the NPC1 cat brain
Effect of IT HPBCD begun at 16 weeks of age



Very significant reduction of GM2 and GM3

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- IT and SC therapy combined have positive effect on both neurological and hepatic disease.
- SC cyclodextrin alone had negative effects on the respiratory system as well as on muscle and subcutaneous tissue, and was not as effective as IT cyclodextrin.

Questions to follow-up on

- Do biomarker data predict clinical outcome?
- Is there a more effective dosing frequency for HPBCD?
- Is there a better way to administer HPBCD?
- What are the long-term effects of HPBCD administration?