Más allá de la terapia de reemplazo enzimático en las enfermedades por depósito lisosomal: reducción del sustrato, chaperonas, nanomedicina y terapia génica

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III Reunión de
Enfermedades Minoritarias

Hospital Clínico Universitario
Lozano Blesa de Zaragoza
14 de junio de 2013

Introducción

III Reunión de
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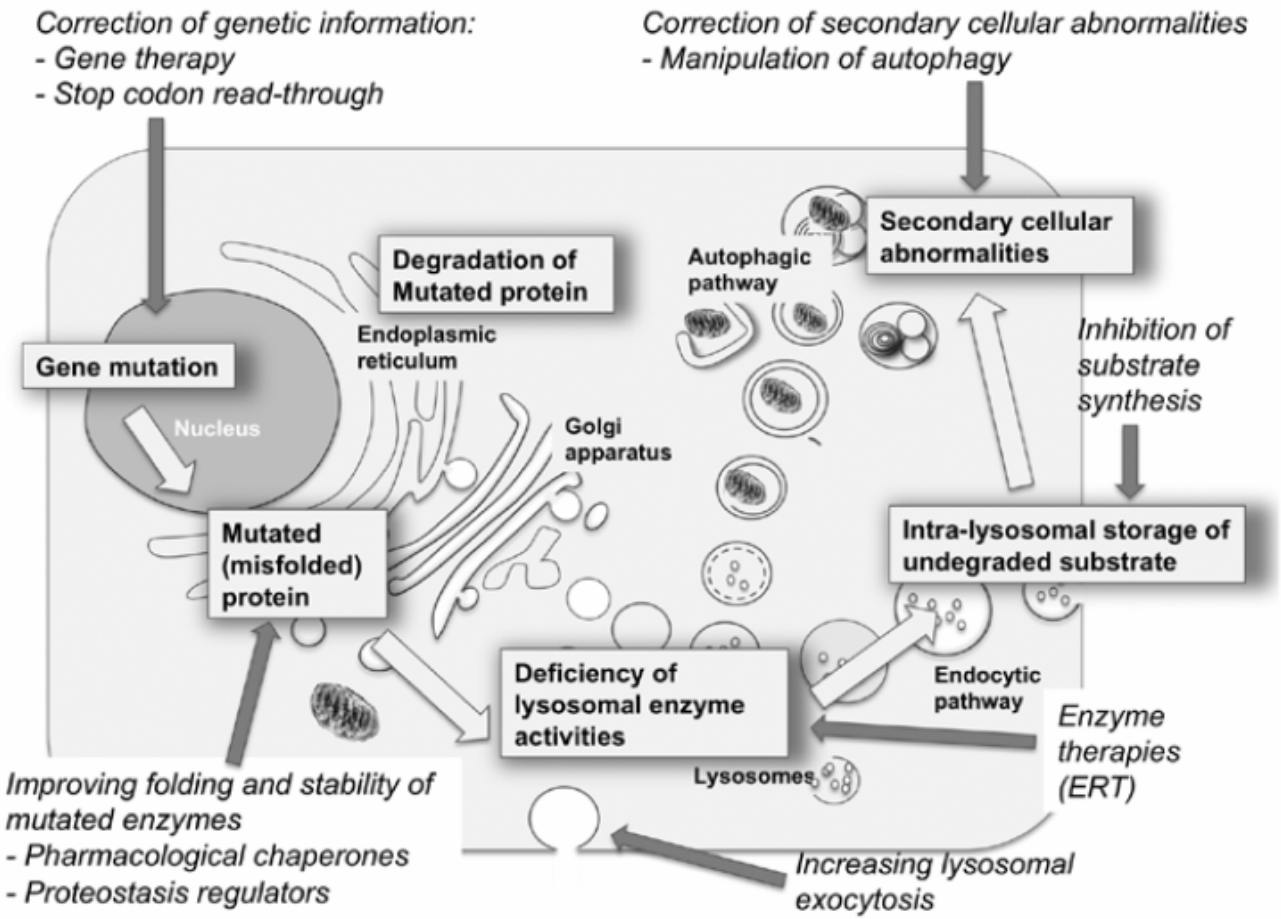
14 de junio de 2013

Introducción

Potenciales estrategias



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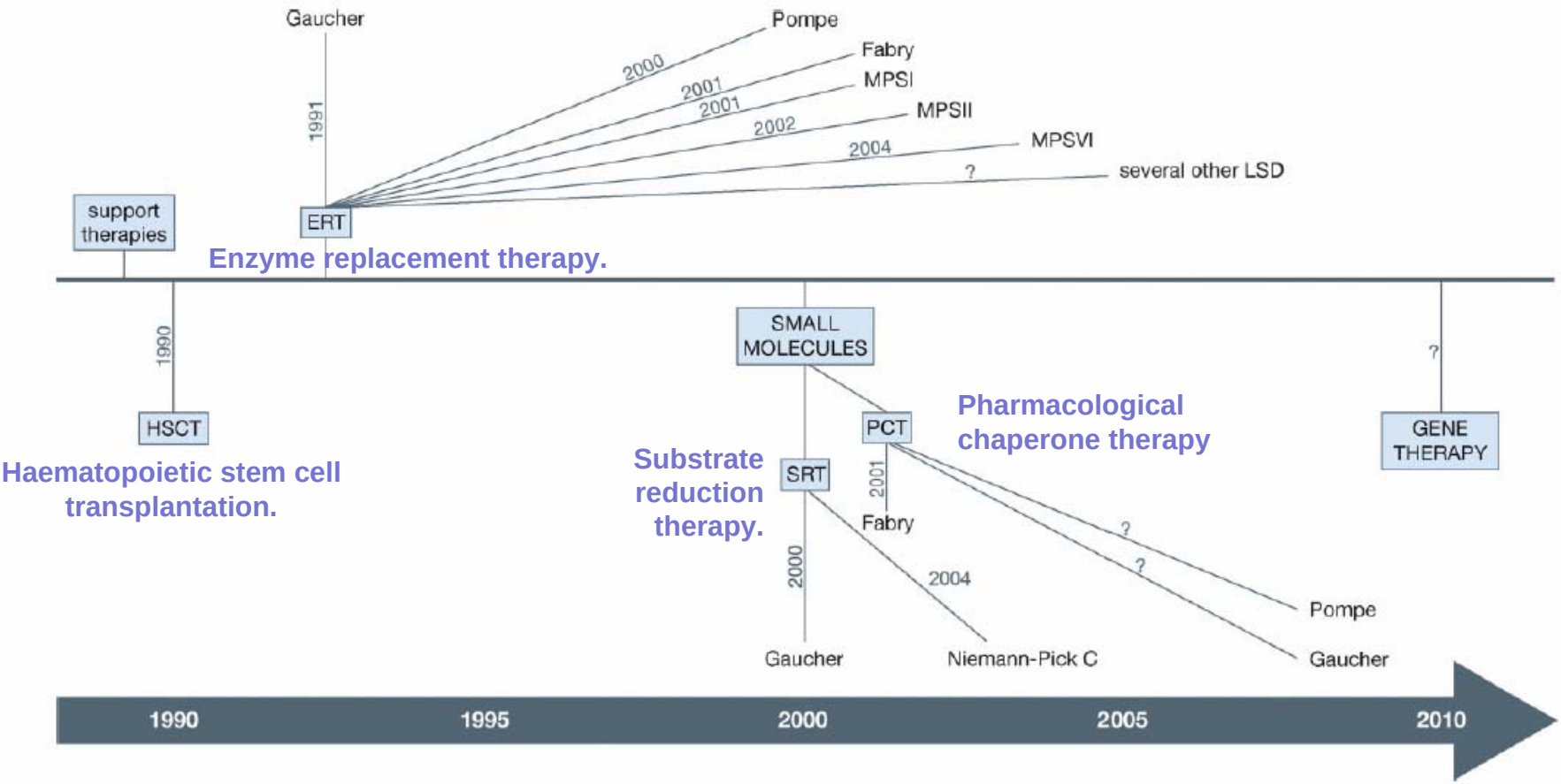
Introducción

Evolutivo histórico (i)



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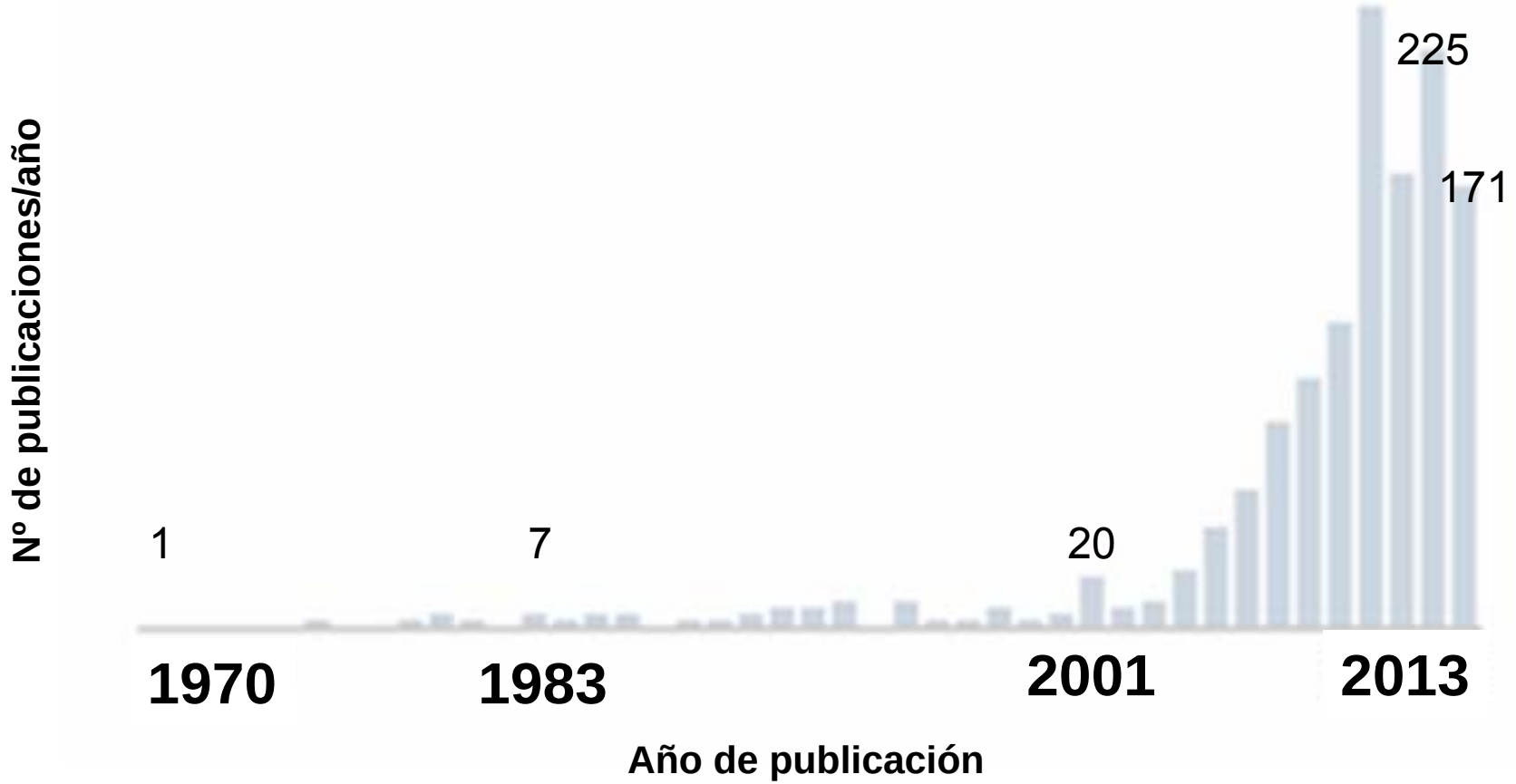
Introducción

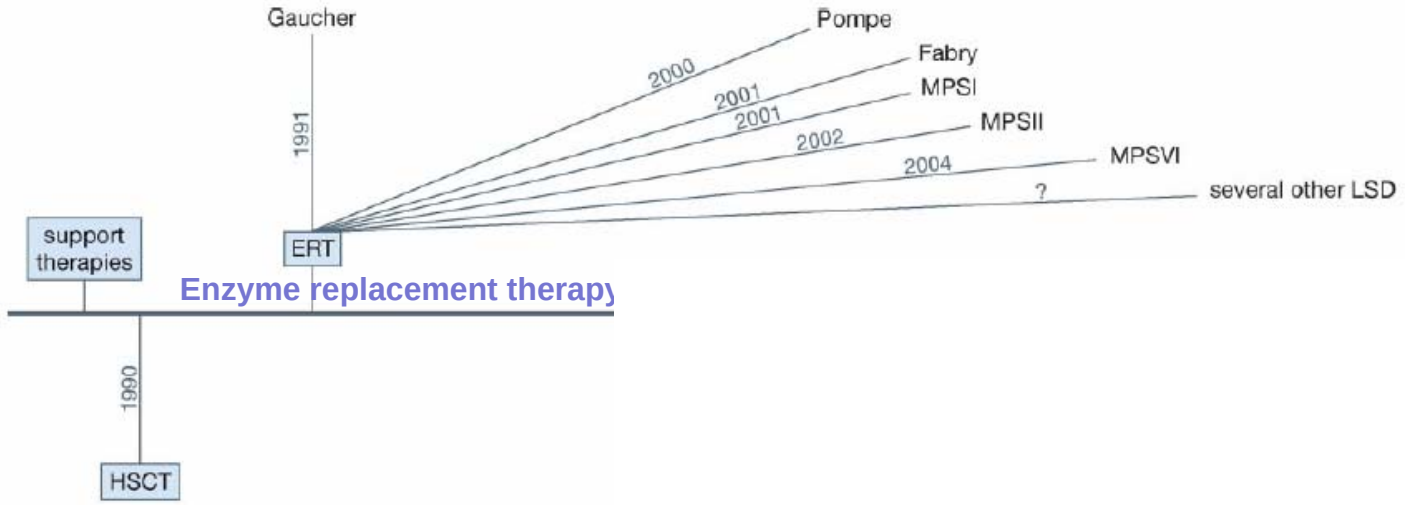
Evolutivo histórico (ii)



http://www.authormapper.com/search.aspx?phr=subject:Medicine%20%26%20Public%20Health&q=lysosomal%20storage%20diseases%20treatment

Introducción

Evolutivo histórico (i)



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Introducción

Estrategias: Sustitución enzimática.

…the usefulness of ERT is limited due to the fact that enzyme distribution is insufficient...

Urbanelli L. Recebt Pat CNS Drug Discov. 2011; 6: 1-19..

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Introducción

Estrategias: Sustitución enzimática.

Table 3 Easy- and hard-to-reach tissues for in vivo delivery of intravenously administered enzymes

Disease	Subtype(s)	Easy to reach	Hard to reach
Gaucher disease	Type 1	Spleen, liver, bone marrow	Bone
	Types 2 and 3	Spleen, liver, bone marrow	Bone, brain
Fabry disease	Both classic and later onset	Vascular endothelium	Kidney, heart
Mucopolysaccharidoses	All	Spleen, liver, bone marrow	Bone, brain, cartilage
α-Mannosidosis	—	Spleen, liver, bone marrow	Bone, brain
Niemann-Pick disease	Type B	Spleen, liver, bone marrow	Alveolar macrophages
Pompe disease	Infantile onset	—	Heart, smooth muscle, skeletal muscle
	Later onset	—	Smooth muscle, respiratory skeletal muscle

Desnick RJ. Annu. Rev. Genomics Hum. Genet. 2012.; 13: 307–35

Introducción

Estrategias en desarrollo

Enzyme targeted drugs

Include substances that modify the enzyme to make it:

*1.- **more accessible to organs** such as the bone or the brain (nanomedicina).*

*2.- **enhance enzyme activity** (chaperonas)*

*3.- **activate enzyme synthesis** by small molecules that induce read-through of premature stop codons of genes that bear a nonsense mutation.*

Substrate targeted drugs

Substances that inhibit the synthesis or modify the structure of the substrate (substrate deprivation or substrate optimization, respectively).

Trasplante de progenitores hematopoiéticos

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Trasplante de céls. hematopoiéticas

Fundamento

HSCT was the first therapeutic approach introduced in the treatment of LSDs.

Bone marrow has been traditionally the graft source for this procedure.

However, in recent years, a number of patients have been treated with unrelated donor umbilical cord blood transplant, allowing rapid and increased access to transplantation.

Parenti G. Int J Mol Med.2013; 31:11-20.

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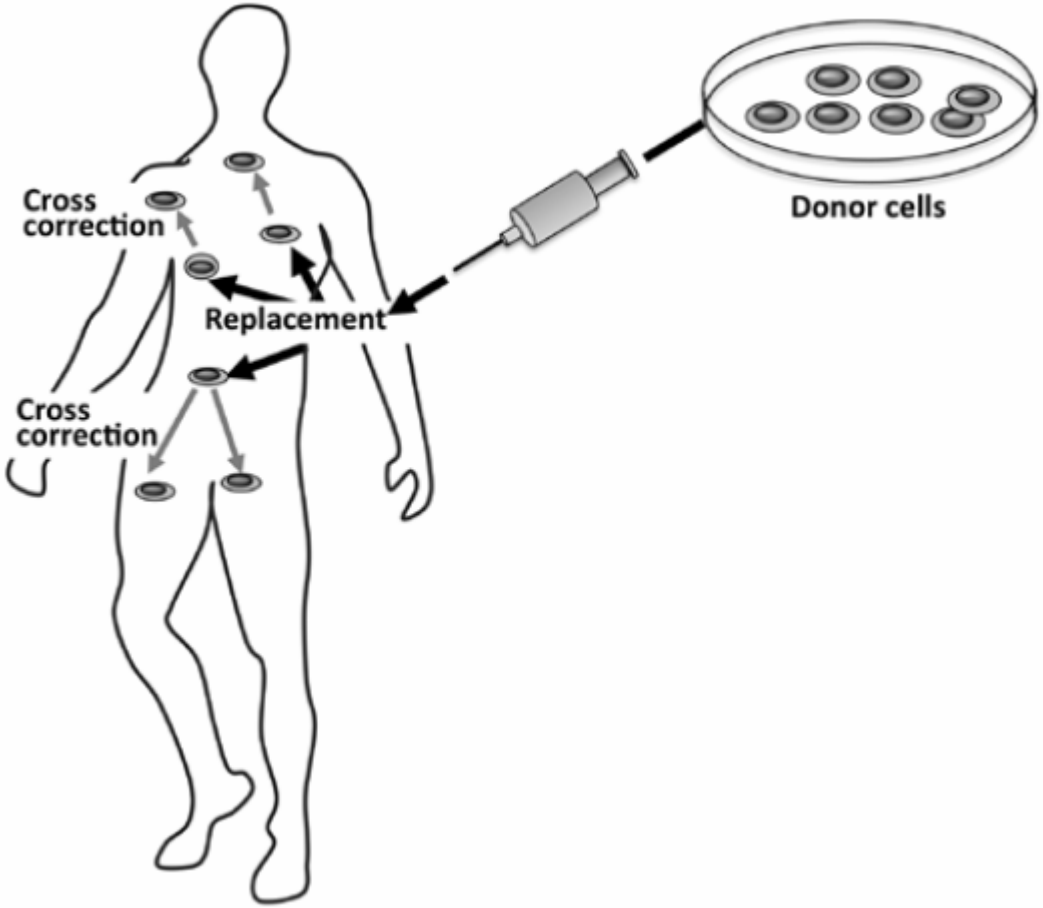
Trasplante de céls. hematopoiéticas

Fundamento



1.- Repopulate specific tissues by the donor's healthy cells.

2.- Secretion of functional lysosomal hydrolases by the donor's cells in the extracellular space and into the blood circulation.
The secreted normal enzyme may be taken up by the recipient cells and may cross-correct the enzyme defect in these cells.

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Trasplante de céls. hematopoiéticas

Experiencia actual

Utilized in over 900 patients suffering from various LSDs, and in some instances with dramatic success.

Rovelli AM, Steward CG. Hematopoietic cell transplantation activity in Europe for inherited metabolic diseases: open issues and future directions. Bone Marrow Transplant 2005; 35 Suppl 1: S23-6.

Transplantation procedures have been performed specifically on patients affected by MPS I patients (Hurler syndrome) [*Polgreen LE, Tolar J, Plog M, et al. Growth and endocrine function in patients with Hurler syndrome after hematopoietic stem cell transplantation. Bone Marrow Transplant 2008; 41: 1005-11*.], Krabbe disease [*Escolar ML, Poe MD, Provenzale JM, et al. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. N Engl J Med 2005; 352: 2069-81*.], Gaucher's disease [*Rappeport JM, Ginns EI. Bone-marrow transplantation in severe Gaucher's disease. N Engl J Med 1984; 311: 84-8. Boelens JJ. Trends in haematopoietic cell transplantation for inborn errors of metabolism. J Inherit Metab Dis 2006; 29: 413-20*]., or Pompe disease [*Watson JG, Gardner-Medwin D, Goldfinch ME, Pearson AD. Bone marrow transplantation for glycogen storage disease type II (Pompe's disease). N Engl J Med 1986; 314: 385*.].

Bone marrow transplantation has been shown to be beneficial in patients affected by a mucopolysaccharidosis (MPS) type I (Hurler syndrome) if performed in an early age.

Beck M. Expert Opin Emerg Drugs. 2010; 15: 495-507.

Trasplante de céls. hematopoiéticas

Experiencia actual

HSCT is indicated for the treatment of mucopolysaccharidosis **(MPS) I** (*Valayannopoulos V and Wijburg FA: Therapy for the mucopolysaccharidoses. Rheumatology (Oxford) 50 (Suppl 5): v49-v59, 2011.*) and has beneficial effects on the visceral manifestations of **MPS VI**, in pre-symptomatic or late-onset **Krabbe disease**, and in the attenuated forms of **metachromatic leukodystrophy** (*Orchard PJ, Blazar BR, Wagner J, Charnas L, Krivit W and Tolar J: Hematopoietic cell therapy for metabolic disease.J Pediatr 151: 340-346, 2007*.).

HSCT is considered the preferred treatment for patients with severe MPS I diagnosed before the age of 2.5 years, and may be considered in individual patients with intermediate phenotypes if there is a suitable donor.

For Krabbe disease and metachromatic leukodystrophy, disease phenotype and the extent of disease at the time of transplantation are of fundamental importance in determining outcomes.

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Trasplante de céls. hematopoiéticas

Experiencia actual

TPH. EXPERIENCIA LIMITADA O CONTROVERTIDA

- Gaucher III: considerar si deterioro neurológico o pulmonar a pesar de TES (Peters, BMT03)
- Alfa-manosidosis: parece frenar la progresión (Grewal, JPediatr04; Albert, BMT03; Wall, JPediatr98)
- Fucosidosis: podría ser útil muy precoz (Krivit04; Miano, BMT01)
- Aspartilglucosaminuria: mal resultado en 4 pacientes (Arvio, JPediatr01). ¿Quizás precoz? (Laine, BMT04)
- Mucolipidosis II: cardiopulmonar estable y cierta mejoría neurocognitiva. ¿Precoz? (Grewal, BMT03)
- Niemann-Pick: mal resultado en A y C. Bueno en B (Victor, JIMD03; Shah, Pediatrics05)
- Farber: Buen resultado en el tipo II/III sin afectación neurológica; malo en el tipo I (Vormoor, JPediatr04; Yeager, BMT00)
- Wolman: si precoz, buen resultado (Krivit, BMT00; Stein, EurJPediatr07; Tolar, BMT09)
- Mucopolisacaridosis VII o Sly: puede ser útil (Peters, BMT03; Yamada, BMT98)

Trasplante de céls. hematopoiéticas

Experiencia actual

TPH. EXPERIENCIA DESFAVORABLE

- MPS II o síndrome de Hunter (grave) (McKinnis, J Pediatr 96; Li, Am J Med Genet 96; Vellodi, JIMD 99; Guffon, J Pediatr 09)
- MPS III o síndrome de Sanfilippo (Vellodi, JIMD 92; Cleary, Arch Dis Child 93; Sivakumur, JIMD 99; Prasad, Blood 08) ¿Neonatal?
- MPS IV o síndrome de Morquio (Peters, BMT03; Tomatsu07) ¿Más precoz?
- GM1 gangliosidosis (Shield, JIMD 05)
- GM2 gangliosidosis (Jacobs, BMT05)

Trasplante de céls. hematopoiéticas

Experiencia actual

high
mortality rates in the most difficult of transplant scenarios (10-25%)

Sergey S . Current Pharmaceutical Design, 2011, 17, 2558-74.

Trasplante de céls. hematopoiéticas

Experiencia actual

A significant advantage of HSCT is that, as **donor-derived, enzyme-producing cells are able to migrate to the brain**. This procedure has the potential to improve neurocognitive function and quality of life, particularly when performed early in the course of the disease.

On the other hand, HSCT is burdened by a significant mortality related to the procedure, by the limited availability of suitable donors, by the limited number of disorders that can be treated by this approach and by insufficient engraftment and correction of pathology in some tissues, such as bone or heart.

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Tratamiento de la Enf. Lisosomales

Estrategias

	Enzima	SNC	Ac	Alternativa
Gaucher	Imiglucerasa (Cerezyme®) Velaglucerasa (Vpriv®)	No No	Sí No	❶ Reducción del sustrato *(Zavesca®).: Ausencia ensayos extensos (Schiffman, 2008).* ❷ Experimental: AT335 (chaperona), Eliglustat (análogo ceramida).
Fabry	Agalsidasa α *(Replagal®)* Agalsidasa β *(Fabrazyme®)*	No No	No datos	❶ AT1001 (Chaperona) en ensayos fase II-III.
MPS I (Hurler)	Laronidasa *(Aldurazyme®)*	No	Sí	❶ Trasplante ❷ Enz. Intratecal (Casos aislados).
MPS II (Hunter)	Idursulfasa *(Elaprase®)*	No	Sí	❶ Enz. Intratecal (Ensayos fase II).
MPS VI (Maroteaux-Lamy)	Galsulfasa *(Naglazyme®)*	No	Sí	
Pompe	Aglucosidasa α *(Myozime®)*	-	Neutralizantes	❶ preTto, inmunomodulador. ❷ AT220 (chaperona). ❸ Terapia génica.

Valayannopoulos V. Enzyme replacement therapy and substrate reduction therapy in lysosomal storage disorders with neurological expression. En: Handbook of Clinical Neurology, Vol. 113 (3rd series) Pediatric Neurology Part III O. Dulac, M. Lassonde, and H.B. Sarnat, Editors. Chapter 190. pp. 1851-7.

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Tratamiento de la Enf. Lisosomales

Estrategias

	Enzima	SNC	Ac	Alternativa
Gaucher	Imiglucerasa (Cerezyme®) Velaglucerasa (Vpriv®)	No No	Sí No	❶ Reducción del sustrato *(Zavesca®).: Ausencia ensayos extensos (Schiffman, 2008).* ❷ Experimental: AT335 (chaperona), Eliglustat (análogo ceramida).
Fabry	Agalsidasa α *(Replagal®)* Agalsidasa β *(Fabrazyme®)*	No No	No datos	❶ AT1001 (Chaperona) en ensayos fase II-III.
MPS I (Hurler)	Laronidasa *(Aldurazyme®)*	No	Sí	❶ Trasplante ❷ Enz. Intratecal (Casos aislados).
MPS II (Hunter)	Idursulfasa *(Elaprase®)*	No	Sí	❶ Enz. Intratecal (Ensayos fase II).
MPS VI (Maroteaux-Lamy)	Galsulfasa *(Naglazyme®)*	No	Sí	
Pompe	Aglucosidasa α *(Myozime®)*	-	Neutralizantes	❶ preTto, inmunomodulador. ❷ AT220 (chaperona). ❸ Terapia génica.

Valayannopoulos V. Enzyme replacement therapy and substrate reduction therapy in lysosomal storage disorders with neurological expression. En: Handbook of Clinical Neurology, Vol. 113 (3rd series) Pediatric Neurology Part III O. Dulac, M. Lassonde, and H.B. Sarnat, Editors. Chapter 190. pp. 1851-7.

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Terapia de reducción del sustrato

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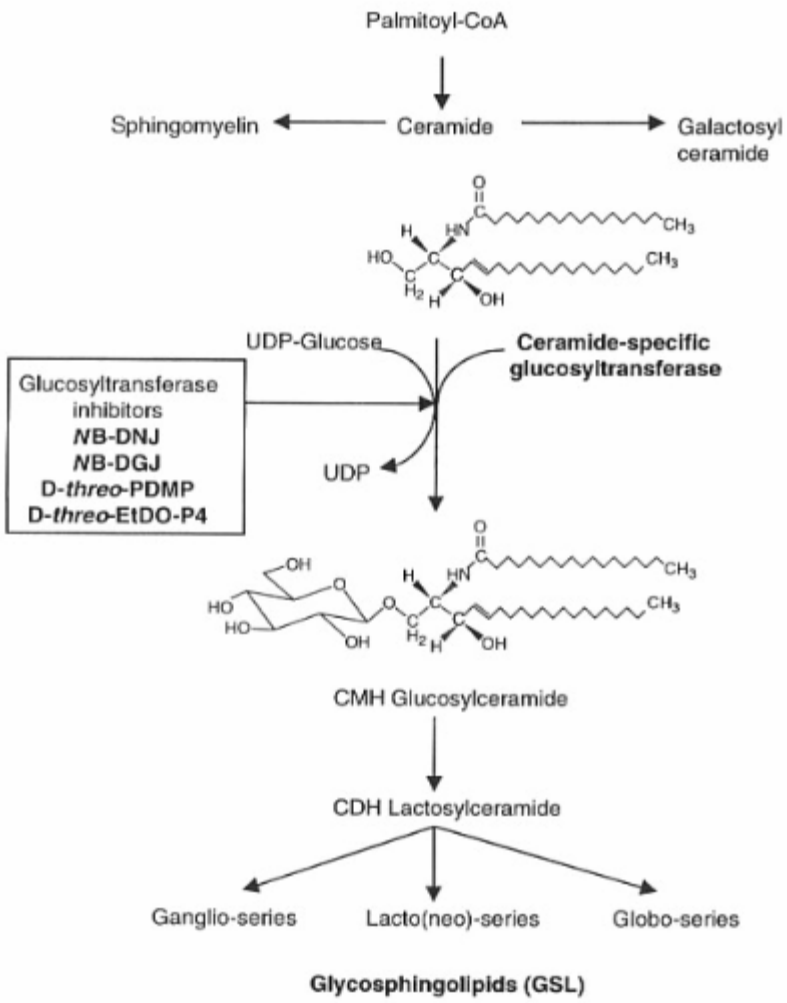
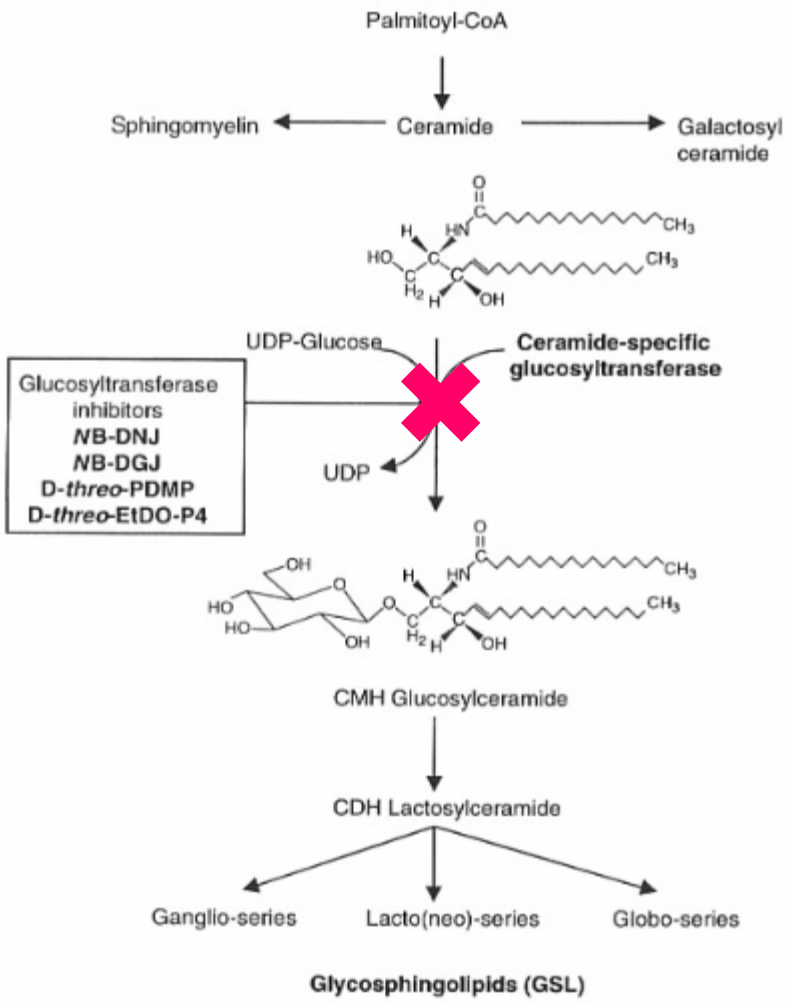
Terapia de reducción del sustrato

Fundamento



Terapia de reducción del sustrato

Fundamento



Terapia de reducción del sustrato

Miglustat

Is a small **iminosugar** molecule that acts as a competitive inhibitor of the enzyme, glucosylceramide synthase, which catalyzes the first committed step in glycosphingolipid synthesis and is able to cross the bloodbrain barrier.

Miglustat was shown to reduce glycosphingolipid accumulation and cellular pathology in the brain, delay onset of neurological symptoms, and prolong survival during pre-clinical studies (Zervas et al., 2001).

Valayannopoulos V. Enzyme replacement therapy and substrate reduction therapy in lysosomal storage disorders with neurological expression. En: Handbook of Clinical Neurology, Vol. 113 (3rd series) Pediatric Neurology Part III O. Dulac, M. Lassonde, and H.B. Sarnat, Editors. Chapter 190. pp. 1851-7.

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Terapia de reducción del sustrato

Miglustat

During developmental clinical trials, miglustat induced sustained reductions of liver and spleen volumes, with increased hemoglobin concentrations and platelet counts; the plasma activity of the biomarker, chitotriosidase, also decreased:

Cox T, Lachmann R, Hollak C, Aerts J, van Weely S, Hrebicek M, Platt F, Butters T, Dwek R, Moyses C, et al: **Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis.** Lancet 2000, 355:1481–1485.

Elstein D, Hollak C, Aerts JM, van Weely S, Maas M, Cox TM, Lachmann RH, Hrebicek M, Platt FM, Butters TD, et al: **Sustained therapeutic effects of oral miglustat (Zavesca, N-butyldeoxynojirimycin, OGT 918) in type I Gaucher disease.** J Inherit Metab Dis 2004, 27:757–766.

Heitner R, Elstein D, Aerts J, Weely S, Zimran A: **Low-dose Nbutyldeoxynojirimycin (OGT 918) for type I Gaucher disease.** Blood Cells Mol Dis 2002, 28:127–133.

Pastores GM, Barnett NL, Kolodny EH: **An open-label, noncomparative study of miglustat in type I Gaucher disease: efficacy and tolerability over 24 months of treatment**. Clin Ther 2005, 27:1215–1227.

Terapia de reducción del sustrato

Miglustat

Similar effects have been observed in ‘real-world’ clinical practice settings:

Giraldo P, Alfonso P, Atutxa K, Fernandez-Galan MA, Barez A, Franco R, Alonso D, Martin A, Latre P, Pocovi M: **Real-world clinical experience with long-term miglustat maintenance therapy in type 1 Gaucher disease: the ZAGAL project.** Haematologica 2009, 94:1771–1775.

Giraldo P, Latre P, Alfonso P, Acedo A, Alonso D, Barez A, Corrales A, Franco R, Roldan V, Serrano S, Pocovi M: **Short-term effect of miglustat in every day clinical use in treatment-naive or previously treated patients with type 1 Gaucher's disease.** Haematologica 2006, 91:703–706.

Pastores GM, Elstein D, Hrebicek M, Zimran A: **Effect of miglustat on bone disease in adults with type 1 Gaucher disease: a pooled analysis of three multinational, open-label studies**. Clin Ther 2007, 29:1645–1654.

Cox TM. Orphanet Journal of Rare Diseases 2012, 7:102

Terapia de reducción del sustrato

Miglustat

Cox *et al. Orphanet Journal of Rare Diseases* 2012, **7**:102
http://www.ojrd.com/content/7/1/102

RESEARCH **Open Access**

Evaluation of miglustat as maintenance therapy after enzyme therapy in adults with stable type 1 Gaucher disease: a prospective, open-label non-inferiority study

Timothy M Cox[1*], Dominick Amato[2], Carla EM Hollak[3], Cecile Luzy[4], Mariabeth Silkey[4], Ruben Giorgino[4], Robert D Steiner[5] for the Miglustat Maintenance Study Group

Terapia de reducción del sustrato

Miglustat

Methods:

Adult type 1 Gaucher disease patients stabilized during at least 3 years of previous enzyme therapy were included in this 2-year, prospective, open-label non-inferiority study.

The primary endpoint was percent change from baseline in liver volume.

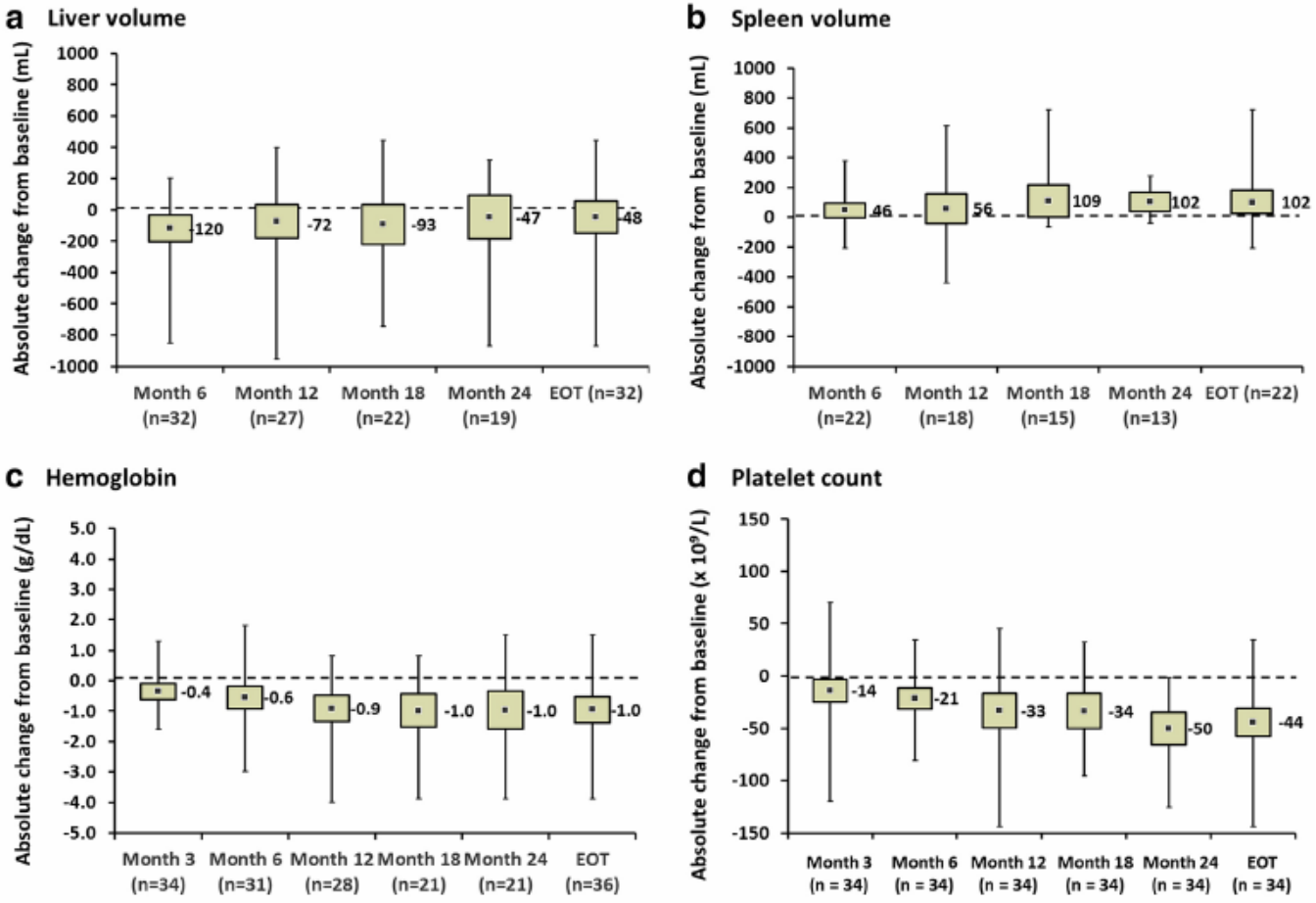
Secondary endpoints included changes in spleen volume, hemoglobin concentration and platelet count.

Results:

Forty-two patients were enrolled.

Terapia de reducción del sustrato

Miglustat



Cox TM. Orphanet Journal of Rare Diseases 2012, 7:102

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Terapia de reducción del sustrato

Miglustat y hueso

It has also been suggested that miglustat **improves cortical and trabecular bone mineral density** (BMD) during 6 months to 2 years of therapy, and can reduce the frequency of bone pain in a sustained manner

Pastores GM, Elstein D, Hrebicek M, Zimran A: **Effect of miglustat on bone disease in adults with type 1 Gaucher disease: a pooled analysis of three multinational, open-label studies**. Clin Ther 2007, 29:1645–1654.

Terapia de reducción del sustrato

Miglustat y hueso

METHODS:

This was a pooled analysis of data collected prospectively over an observation period of 2 years from patients who participated in 3 multinational, open-label clinical trials evaluating the efficacy and tolerability of miglustat 100 mg TID (the currently approved therapeutic dose). Bone manifestations were assessed qualitatively and in relation to treatment and spleen status. The effects of miglustat on BMD were assessed by dual-energy x-ray absorptiometry at the lumbar spine and/or femoral neck. Bone response was defined as a positive change in BMD, based on the change in BMD Z-score from baseline to months 6, 12, and 24. Changes in BMD were also analyzed according to spleen status and baseline severity of osteopenia.

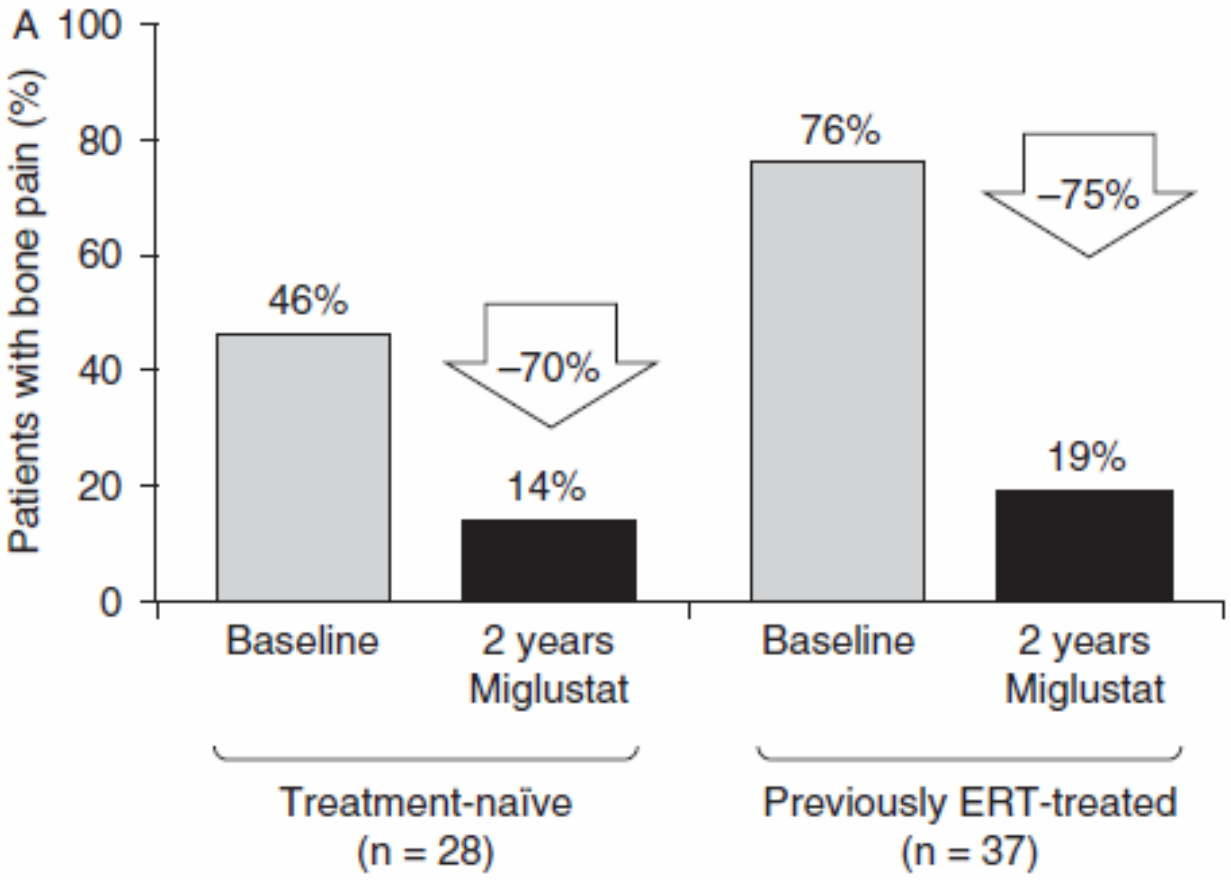
RESULTS:

The analysis involved 72 patients, including 41 (57%) who had received previous ERT

Pastores GM. Clin Ther. 2007;29:1645-54.

Terapia de reducción del sustrato

Miglustat y hueso



Pastores GM. Clin Ther. 2007;29:1645-54.

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Terapia de reducción del sustrato

Miglustat y SNC

Enfermedad de Niemann-Pick C.

Efecto de Miglustat 18 meses.

Cambio* en la velocidad de los movimientos oculares sacádicos horizontales a los 12 meses (el cambio negativo representa una mejora)

* MOSH, movimientos oculares sacádicos horizontales fue elegido como variable principal en base a su correlación con la progresión de la enfermedad

Patterson MC. Lancet Neurol 2007; 6: 765-72.

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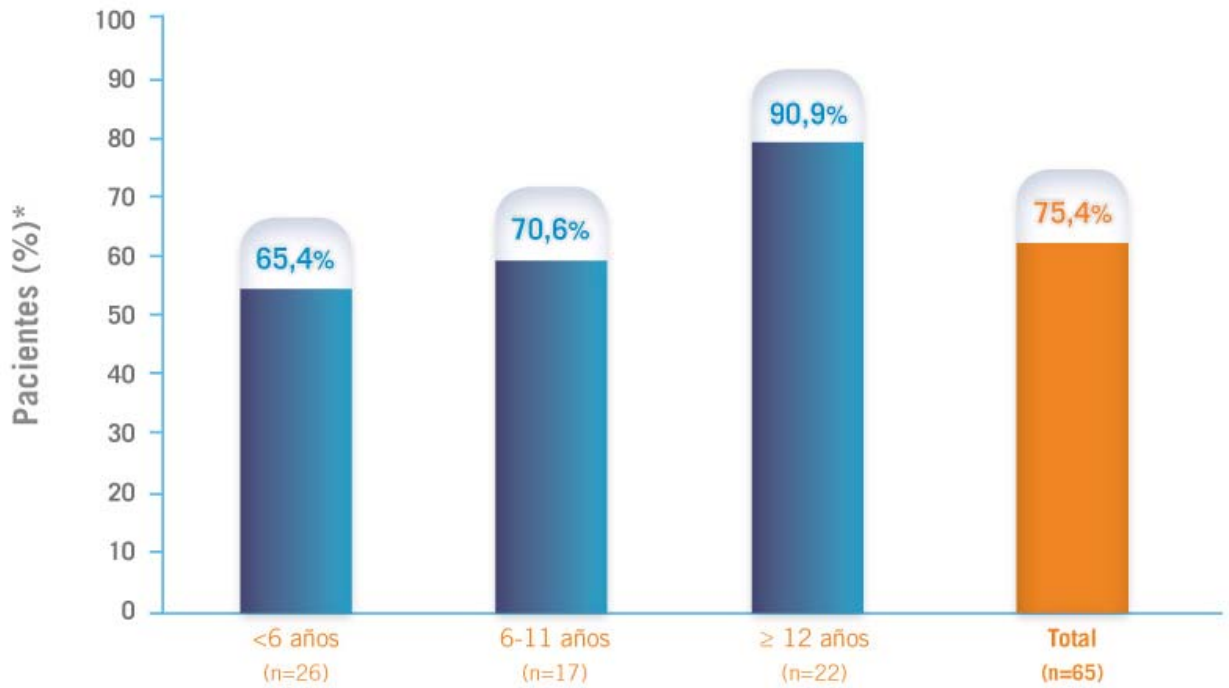
Miglustat y SNC

Porcentaje* de pacientes con mejora o estabilidad de 3 o más parámetros después del tratamiento con miglustat, por grupo de edad



* Porcentajes calculados de acuerdo con el número de pacientes evaluables por grupos; sólo un paciente tuvo datos de respuesta no disponibles.

Patterson MC. Annual Lysosomal Disease Network (LDN) World Symposium, 18-20 Febrero 2009, San Diego, EEUU.

Terapia de reducción del sustrato

Miglustat y SNC

Patterson MC. Annual Lysosomal Disease Network (LDN) World Symposium, 18-20 Febrero 2009, San Diego, EEUU.

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Efecto chaperona de Miglustat

Por otro lado, miglustat también es capaz de inhibir en mayor o menor grado los enzimas *glucosidasa I y II*, implicadas en los procesos de plegamiento y funcionamiento de las proteínas.

Terapia de reducción del sustrato

Efecto chaperona de Miglustat

Mikosch P, Reed M, Baker R, Holloway B, Berger L, Mehta AB, Hughes DA:
Changes of bone metabolism in seven patients with Gaucher disease treated consecutively with imiglucerase and miglustat.
Calcif Tissue Int. 2008, 83:43–54.

Abian O, Alfonso P, Velázquez-Campoy A, Giraldo P, Pocoví M, Sancho J.
Therapeutic Strategies for Gaucher Disease: Miglustat (NB-DNJ) as a Pharmacological Chaperone for Glucocerebrosidase and the Different Thermostability of Velaglucerase Alfa and Imiglucerase
Mol. Pharmaceutics, 2011; 8: 2390-7.

Terapia de reducción del sustrato

Miglustat como insulino sensibilizador

Además, también inhibe a *sucrasa* y *maltasa* (dos disacaridasas), lo que posiblemente se relaciona con algunos de los efectos adversos digestivos observados con miglustat, especialmente la diarrea osmótica.

Chaperonas

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Chaperonas

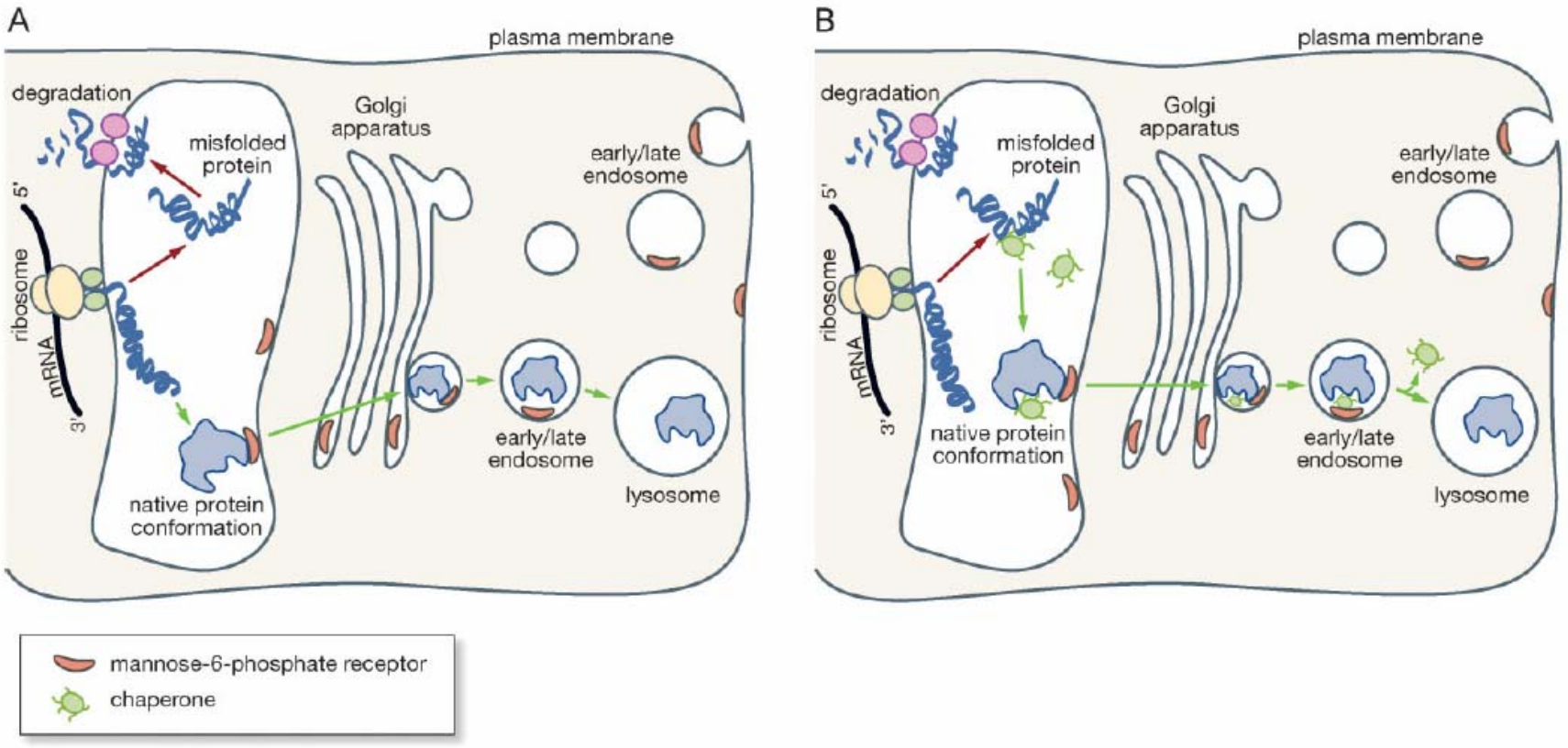
Fundamento

Enzyme Stabilization Therapy

ability of certain molecules to associate with, and then allow abnormally folded LSD enzymes to either assume a more normal tertiary structure, or be trafficked more efficiently to lysosomes, thereby increasing the overall enzymatic capability of the respective LSD enzyme.

Chaperonas

Fundamento



Parenti G. EMBO Mol Med 1, 268–279

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Chaperonas

Fundamento

For several reasons, LSDs can be considered excellent candidates for chaperone-mediated PCT.

It is assumed that a **threshold activity of approximately 10%** is sufficient to prevent storage in LSDs

Parenti G. EMBO Mol Med 1, 268–279

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Chaperonas

Fundamento

One of the disadvantages of a chemical chaperone, however, is the fact that its treatment effect is restricted to patients with missense mutations, and based on the analysis of molecular surveys of a large number of Pompe patients it may be assumed that only 10 -15% of these patients are amenable to enhancement therapy.

Porto C. The pharmacological chaperone n-butyldeoxynojirimycin enhances enzyme replacement therapy in pompe disease fibroblasts. Mol. Ther. 2009; 17, 964-71.

Chaperonas

Fundamento

En la Enfermedad de Gaucher se ha asociado mayor respuesta a las chaperonas en presencia del alelo N370S.

Kelly JW. Chemical chaperones increase the cellular activity of N370S beta -glucosidase: a therapeutic strategy for Gaucher disease. *Proc Natl Acad Sci USA 2002; 99:* 15428-33.

Chaperonas

Experiencia actual

Table 2. Animal Models of LSDs Amenable to Evaluating Pharmacological Chaperones

Disease	Deficient Enzyme	Animal Model		References
		Mutation	Species	
Fabry disease	α-Galactosidase A	hR301Q TgM	*GLA* KO mouse	136
		hR301Q Tg	*GLA* KO mouse	131
		hR301Q TgG3S(+/−)M(+/−)	*GLA* KO mouse +GB3 synthase	188
Gaucher disease	β-Glucocerebrosidase	mL444P	KI mouse	189, 190
		mV394L	KI mouse	191
		mD409H	KI mouse	191
		M4L/PS-NA	mV394L KI mouse crossed with prosaposin KO mouse (PS-NA)	192
		M9H/PS-NA	mD409H KI mouse crossed with prosaposin KO mouse	192
		C381Y/P467L	Sheep (spontaneous mutation)	193
Pompe disease	Acid α-glucosidase	hP545L Tg	*GAA* KO mouse	132
		1639delG	Japanese quail (spontaneous mutation)	194
Tay Sach's disease	β-Hexosaminidase A	P469AL	Flamingo (spontaneous mutation)	195
GM1 gangliosidosis (Morquio B)	β-Galactosidase	hR201C Tg	*GLB1* KO mouse	138
Krabbe disease	Galactocerebrosidase	mH168C	Mouse (spontaneous mutation)	196
		cC158S	Dog (spontaneous mutation)	197
MPS IIIA (Sanfillippo disease)	α-*N*-Acetylglucosaminidase	mD31N	Mouse (spontaneous mutation)	198, 199
MPS VI (Maroteaux-Lamy)	*N*-Acetylgalactosamine-4-sulfatase	fL476P	Cat (spontaneous mutation)	200

Valenzano KJ. Assay Drug Development Tech. 2011; 9: 213-25.

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Chaperonas

Experiencia actual

Hospital Verge dels Lliris. Alcoy. http://alcoi.san.gva.es

Table 1. Approved Therapies and Pharmacological Chaperones for Lysosomal Storage Disorders

Disease	Deficient Enzyme	Approved Drug(s)[a]	Pharmacological Chaperones		
			Name	Status	References
Fabry	α-Galactosidase A	Fabrazyme® (agalsidase beta) Replagal™ (agalsidase alpha)	Galactose	Preclinical	164
				Case Study	165
			DGJ (AT1001; Amigal™)	Phase 3	40, 75, 131, 166
Gaucher	Acid β-Glucosidase	Cerezyme® (imiglucerase) VPRIV™ (velaglucerase alfa) Zavesca® (miglustat; NB-DNJ)	α-*allo*-HNJ; α-galacto-HNJ; β-1-*C*-butyl-DGJ	Preclinical	167
			DIA	Preclinical	168
			NN-DNJ	Preclinical	64, 126, 127, 169, 170
			N-(7-oxadecyl)DNJ	Preclinical	127
			N-(*n*-octyl)DNJ	Preclinical	127, 170
			NOV	Preclinical	161
			Castanospermine; *N*-(*n*-octyl)IFG; PDMP; morpholine- and piperazine-substituted alkylated nitrogen heterocycles; *N*-octyl-2,5-dideoxy-2,5-imino-D-glucitol	Preclinical	126
			CO-DNJ and CN-DNJ	Preclinical	170
			N-hexanoic acid adamantyl amide DNJ	Preclinical	64
			Calystegine derivatives; DIX	Preclinical	171
			IFG (AT2101)	Phase 2	65, 70, 76
			5-[(4-methylphenyl)thio)-quinazoline 2,4-diamine	Preclinical	108
			5-(3,5-dichlorophenoxy)-*N*-(4-pyridinyl)-2-furamide	Preclinical	108
			NOI-NJ, 6S-NOI-NJ, 6N-NOI-NJ, 6S-NOI-GNJ	Preclinical	172
			Diltiazem	Preclinical	107
			Ambroxol	Investigator-initiated pilot study	61, 173, www.Gaucher.org
			NB-DNJ, Aminocyclitol 1, Aminocyclitol 4	Preclinical	169
			Dansyl-capped *N*-substituted DNJ derivatives 10 and 11	Preclinical	173
			6S-NDI-NJ	Preclinical	174
			2-*O*-alkly iminoxylitol derivatives	Preclinical	175

(*continued*)

Valenzano KJ. Assay Drug Development Tech. 2011; 9: 213-25.

Chaperonas

Experiencia actual

Hospital Verge dels Lliris. Alcoy. http://alcoi.san.gva.es

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				Case Study	165
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Gaucher	Acid β-Glucosidase	Cerezyme® (imiglucerase) VPRIV™ (velaglucerase alfa) Zavesca® (miglustat; NB-DNJ)	α-*allo*-HNJ; α-galacto-HNJ; β-1-*C*-butyl-DGJ	Preclinical	167
			DIA	Preclinical	168
			PDMP; morpholine- and piperazine-substituted alkylated nitrogen heterocycles; *N*-octyl-2,5-dideoxy-2,5-imino-D-glucitol		
			CO-DNJ and CN-DNJ	Preclinical	170
			N-hexanoic acid adamantyl amide DNJ	Preclinical	64
			IFG (AT2101)	Phase 2	65, 70, 76
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(*continued*)

Valenzano KJ. Assay Drug Development Tech. 2011; 9: 213-25.

Chaperonas

Experiencia actual

Table 1. (Continued)

Disease	Deficient Enzyme	Approved Drug(s)[a]	Pharmacological Chaperones	
			Name	Status
GM1 Gangliosidosis (Morquio B)	Acid β-Galactosidase	None	NOEV	Preclinical
			DGJ, NB-DGJ	Preclinical
			Galactose	Preclinical
			DLHex-DGJ	Preclinical
			DGJ derivatives (compounds 17, 18, 22)	Preclinical
			Fluorous iminoalditols 6–8	Preclinical
GM2 Gangliosidosis (Tay-Sachs / Sandhoff)	Acid β-Hexosaminidase	None	NGT	Preclinical
			AdDNJ; ADNJ; ACAS	Preclinical
			M-22971 (nitro-indan-1-one); M-45373 (pyrrolo[3,4-d]pyridazin-1-one); M-31850 (bisnaphthalimide)	Preclinical
			Pyrimethamine	Phase 2
			N-benzyl LABNAc	Preclinical
Pompe	Acid α-Glucosidase	Myozyme® (alglucosidase alfa) Lumizyme® (alglucosidase alfa)	DNJ (AT2220)	Phase 2
			NB-DNJ (miglustat)	Preclinical
			NO-DNJ	Preclinical
Krabbe	Galactocerebrosidase	None	α-Lobeline	Preclinical
Batten	Palmitoyl:protein thioesterase	None	CS38	Preclinical
MPS I (Hurler / Hurler-Scheie)	α-L-iduronidase	Aldurazyme® (laronidase)	None	
MPS II (Hunter)	Iduronate sulphate sulphatase	Elaprase® (idursulfase)	None	
MPS IIIC (Sanfilippo Syndrome type C)	Heparan sulfate acetyl-CoA: α-glucosaminidine *N*-acetyltransferase	None	Glucosamine	Preclinical
MPS VI (Maroteaux-Lamy)	*N*-acetylgalactosamine-4-sulfatase	Naglazyme® (galsulfase)	None	

Valenzano KJ. Assay Drug Development Tech. 2011; 9: 213-25.

Chaperonas

Experiencia actual

Table 1. (Continued)

Disease	Deficient Enzyme	Approved Drug(s)[a]	Pharmacological Chaperones	
			Name	Status
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			AdDNJ; ADNJ; ACAS	Preclinical
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			N-benzyl LABNAc	Preclinical
Pompe	Acid α-Glucosidase	Myoz Lumi	DNJ (AT2220)	Phase 2
			NO-DNJ	Preclinical
Krabbe	Galactocerebrosidase	None	α-Lobeline	Preclinical
Batten	Palmitoyl protein thioesterase	None	CS38	Preclinical
MPS I (Hurler / Hurler-Scheie)	α-L-iduronidase	Aldurazyme® (laronidase)	None	
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MPS VI (Maroteaux-Lamy)	*N*-acetylgalactosamine-4-sulfatase	Naglazyme® (galsulfase)	None	

Valenzano KJ. Assay Drug Development Tech. 2011; 9: 213-25.

Chaperonas

Experiencia actual: Terapia combinada.

Although pharmacological chaperone therapy (PCT) has been developed as a strategy to rescue mutant enzymes from degradation, recent studies showed that chaperones are also able to enhance physical stability and potentiate the therapeutic action of the enzymes used for ERT .

- Porto C. The pharmacological chaperone N-butyldeoxynojirimycin enhances enzyme replacement therapy in Pompe disease fibroblasts. Mol Ther 2009; 17: 964-971.

-Porto C. Synergy between the pharmacological chaperone 1-deoxygalactonojirimycin and the human recombinant alphagalactosidase A in cultured fibroblasts from patients with Fabry disease. J Inherit Metab Dis 2012; 35: 513-20.

-Benjamin ER. Co-administration with the pharmacological chaperone AT1001 increases recombinant human α-galactosidase A tissue uptake and improves substrate reduction in Fabry mice. Mol Ther. 2012; 20: 717-26.

- Khanna R. The pharmacological chaperone AT2220 increases recombinant human acid α-glucosidase uptake and glycogen reduction in a mouse model of pompe disease. PLoS One 7: e40776, 2012.

Chaperonas

Experiencia actual: Terapia combinada.

It is **mutation independent**, and may thus be exploited in any patient on ERT.

Porto C. Synergy between the pharmacological chaperone 1-deoxygalactonojirimycin and the human recombinant alphagalactosidase A in cultured fibroblasts from patients with Fabry disease. J Inherit Metab Dis 35: 513-520, 2012.

Chaperonas

Experiencia actual: Terapia combinada.

Initiation of phase 2a PC/ERT coadministration clinical studies in **Fabry** (NCT01196871) and **Pompe** (NCT01380743) patients.

Boyd RE. J. Med. Chem. 2013, 56, 2705-25.

Terapia génica

III Reunión de
Enfermedades
Minoritarias

Hospital Clínico Universitario
Lozano Blesa de Zaragoza
14 de junio de 2013

Terapia génica

Fundamento

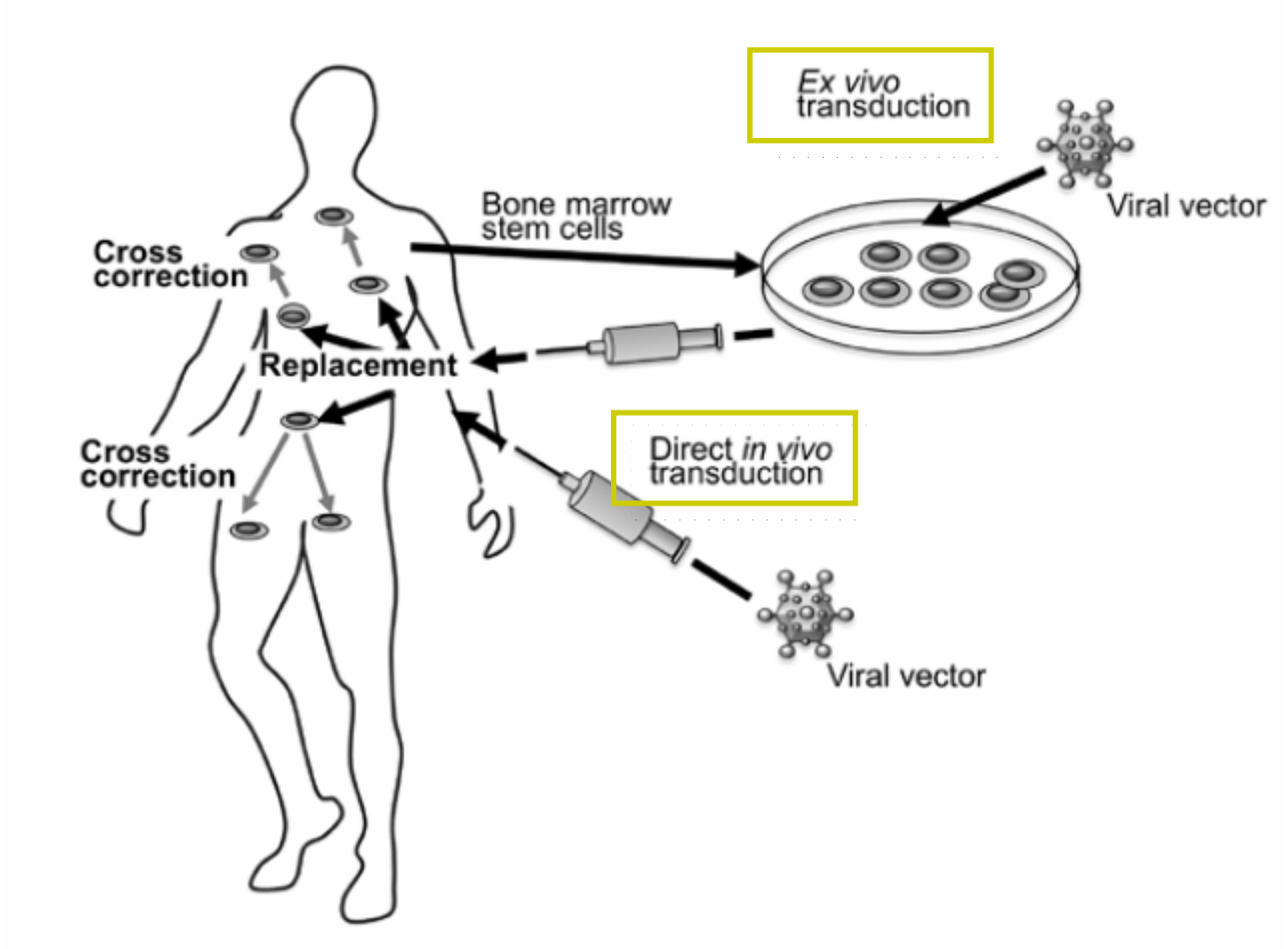
Enfermedades monogénicas.
Tratamiento potencialmente curativo al corregir la mutación.

Fenómeno de corrección cruzada (*cross-correction*).
No hace falta modificar todas las células.

Suficiente con 10% de actividad enzimática
No hace falta modificar todas las células.

Terapia génica

Fundamento



Parenti G. Int J Mol Med. 2012;

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Terapia génica

Fundamento

Modelos animales

Platform	Animal Models	LSDs	Main Results	Prognosis for Human LSD Applications
Adenovirus +: capacity, scalability, efficacy -: Ad-specific innate and adaptive immune responses, pre-existing immunity	Quail Mouse Mouse Mouse Mouse	Pompe [88] Pompe [87, 89] Pompe [82] Fabry [80, 90] MPS IIIa [92], MPS VII [91]	[E1-,E2b-]Ad5, IV, transient efficacy, anti-GAA, anti-Ad response. [E1-,E2b-]Ad5, LSP, IV, efficacy for 6 months, blunted anti-GAA response. HDAd, LSP, IV, efficacy for 6 months, no anti-GAA / minimal Ad response. [E1-]Ad5, IV, transient efficacy, Ad response / Oral, some efficacy (4 dpi). Ad5, canine Ad2, efficacy up to 20 weeks in neonatal, but not adult mice.	HDAd vectors for systemic gene therapy, with use of liver specific-promoters, possibly with immunomodulation therapy. Gene Therapy/ERT combinations.
Adeno-Associated Virus +: efficacy, persistence -: AAV-specific innate and adaptive immune responses, difficulty in production, small cloning capacity, pre-existing immunity	Mouse Mouse Mouse Mouse Mouse Mouse Mouse Cat	Fabry [83, 84] Fabry [183] Pompe [86] Pompe [85] Pompe [106] Pompe [107] Gaucher's [108] MPS VI [109]	AAV2(or 8),IV,LSP,anti-CD40L,1 year efficacy, tolerance, high AAV antibodies. AAV1, IV, up to 25 weeks partial efficacy (adult). AAV2/8 GAA/SCID, IV, up to 24 weeks efficacy (adult). AAV1, IV, up to 11 month efficacy in neonatal (supra-normal). AAV2/8, IV,LSP, modified-signal, 24 weeks efficacy, no anti-GAA antibody (adult). AAV2/8, IV, LSP, MSP, efficacy up to 18 months, tolerance to ERT. AAV8, IV, LSP, up to 6 months efficacy in juvenile. AAV2/8, IV, LSP, up to 1 year efficacy (neonatal, juvenile), no antibody response.	Liver, muscle (Pompe) and CNS targeted therapy with use of tissue specific promoters. Gene Therapy/ERT combinations (Gene Therapy induces tolerance).
Lentivirus +: efficacy, promise in HSC applications, minimal incidence of pre-existing immunity -: insertional mutagenesis, innate immune responses	Mouse Mouse Mouse Mouse Mouse Mouse Mouse Mouse	MPS I [126] MPS I [129] MPS IIIa [135] Pompe [136] MPS I [141] Gaucher's [142] Fabry [143] Pompe [144, 145]	IV, efficacy in neonatal for 20 weeks, increased survival; transient in adults. IV, LSP, efficacy in adults for 6 months, minimal transgene antibodies. IV, up to 7 months partial correction of phenotype in adults. IV, efficacy in neonatal up to 24 weeks. HSCT, supra-normal activity in adults for 6 months, complete correction. HSCT, efficacy up to 24 weeks in adults. HSCT, supra-normal activity in adults for 24 weeks. HSCT, supra-normal activity in adults for 1.5 years; GT mediated tolerance.	High potential for HSC applications (combination of Gene Therapy/HSCT); possibly can be used to treat CNS complications;
Retrovirus +: efficacy, minimal incidence of pre-existing immunity -: insertional mutagenesis, CTL responses, innate immune responses	Mouse Mouse Dog Dog Cat	MPS I [128] MPS I [131] MPS I [132] MPS VII [125, 134] MPS I [133]	IV, LSP, efficacy in neonatal for 8 months, in adults for 1 month. IV, LSP, HGF, efficacy in adults for up to 8 months. IV, LSP, efficacy in neonatal for up to 1.8 years. IV, LSP, HGF, efficacy in neonatal for 17 months, RV persistence for 4 years. IV, LSP, CTLA4-Ig, efficacy in neonatal for 300 days; CTL responses.	Self-inactivating RV for systemic gene therapy with use of liver specific promoters and immunosuppressive regimens
Non-viral +: "relatively safe" -: lack of efficacy	Mouse Mouse Mouse Mouse Mouse	Fabry [155] MPS I [157] Fabry [184] MPS I [159] MPS I [158]	IV, Cationic Lipid/DNA, DEX, anti-CD40L, 3 months minimal efficacy. IV, pDNA, no efficacy (RNA but no activity). Into kidney, pDNA, up to 4-8 weeks partial efficacy in adult. IV, transposon, SCID, up to 18 weeks efficacy. IV, minicircle, LSP, immunomodulation, 3 months partial efficacy.	Lack of substantial pre-clinical efficacy date does not allow for full potential to be commented upon at this time

Sergey S. Current Pharmaceutical Design, 2011, 17, 2558-2574

Terapia génica

Eficacia

Ex-vivo

Se suelen emplear células hematopoiéticas propias (menor rechazo).

Ensayos en varios modelos animales.

Humanos: tres casos de Gaucher tipo I sin resultados.

In-vivo

Inyección intratecal exitosa en modelos animales de MPS VII y IIIB, GM2 y CLN2.

10 niños con lipofucsinosis CLN2 moderada/grave: 12 inyecc. Intracerebrales produjo a los 10 meses retardo evolutivo de la enfermedad.

Parenti G. Int J Mol Med. 2012;

Terapia génica

Seguridad

Potencial mutagénesis

Desconocemos riesgo de desarrollo de **neoplasias** a largo plazo.

Potencial inmunogenicidad en pacientes con déficit enzimático severo.

Pacientes CRIM + vs. CRIM -.

Posibilidad de inducir Ac anti enzimas.

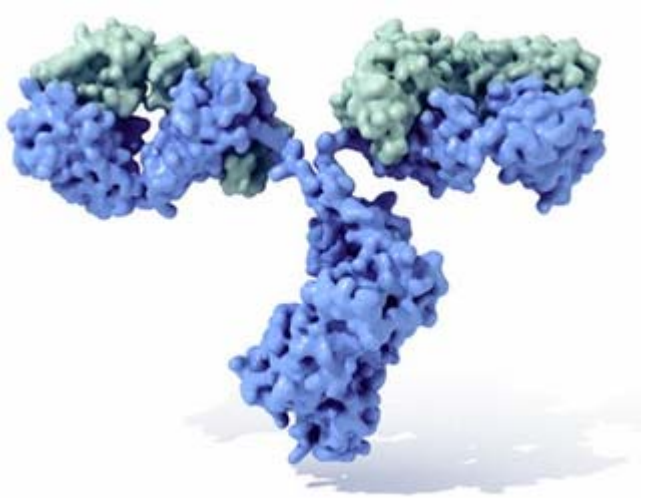
Posibilidad de activar inflamación asociada al proceso lisosomal.

Parenti G. Int J Mol Med. 2012;

Terapia génica

Seguridad

Patients lacking any production of endogenous protein (nonsense mutations and whole gene deletions) have been historically referred to as cross-reactive immunologic material (CRIM) negative (CRIM-) while those producing a protein that is entirely enzymatically inactive, or partially active as CRIM positive (CRIM+).



Sergey S. Current Pharmaceutical Design, 2011, 17, 2558-2574

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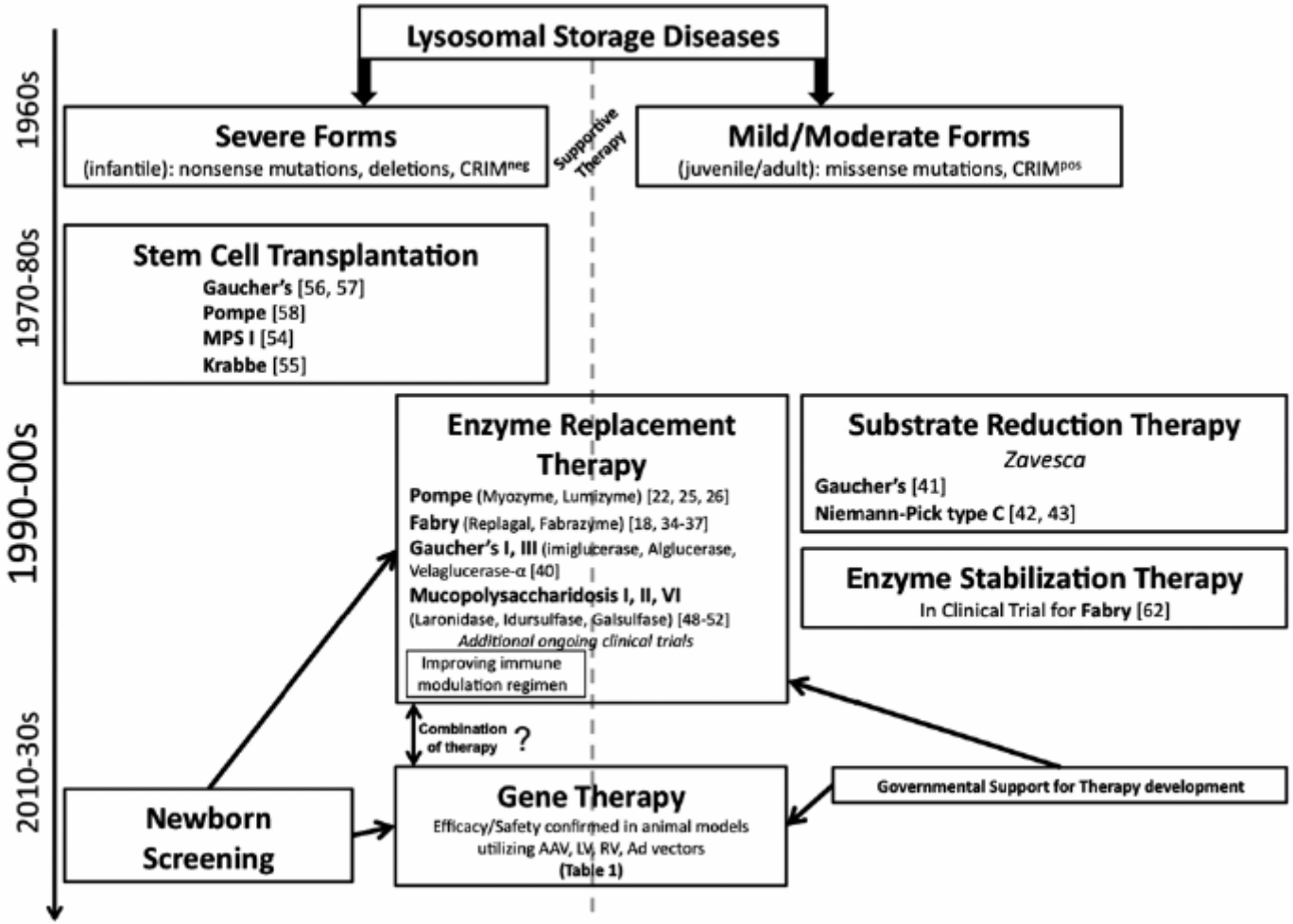
Terapia génica

Eficacia



Sergey S. Current Pharmaceutical Design, 2011, 17, 2558-2574

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Nanomedicina

III Reunión de
Enfermedades
Minoritarias

Hospital Clínico Universitario
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14 de junio de 2013

Nanomedicina

Concepto

Aplicación con fines médicos de **nanopartículas** con fines terapéuticos y/o diagnósticos.

Desde el punto de vista terapéutico permiten una acción celular más específica de los fármacos, protegiéndolos de la degradación (*Ambisome*®), facilitando su acceso a las células diana respetando las sanas.

Nanomedicina

Componentes

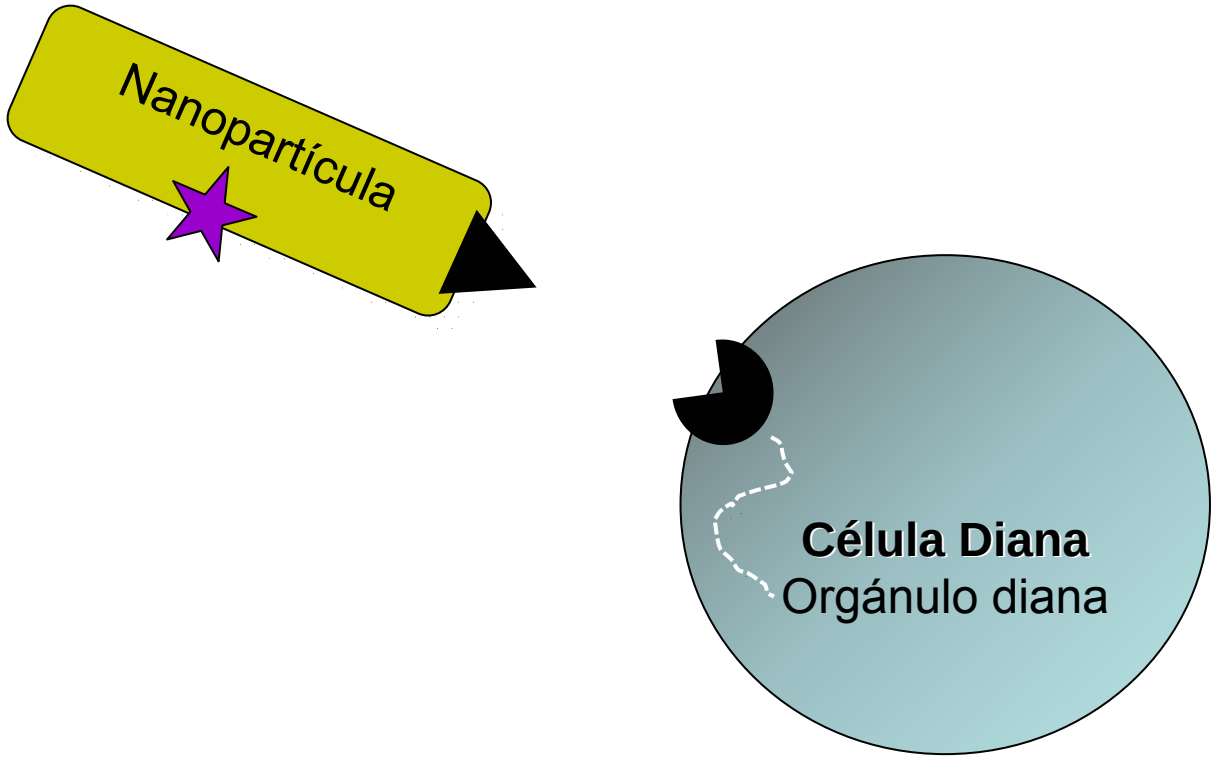
1.- **Vía** de transporte celular (endocitosis).

2.- **Nanopartícula**: Transporta fármaco así como sustrato del receptor de la superficie celular que activa la vía específica de la endocitosis elegida para el fin perseguido.

3.- **Sustrato del receptor** de superficie celular.

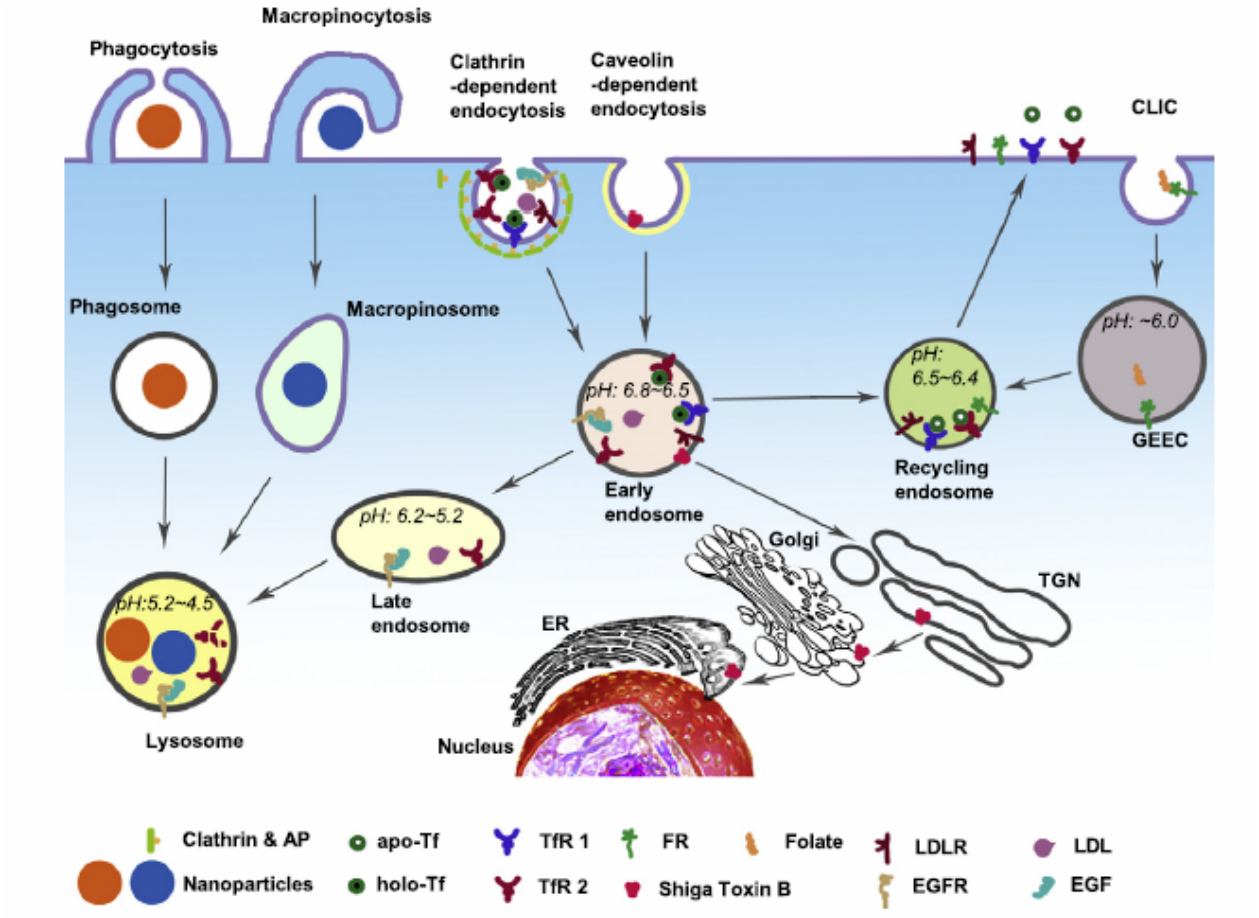
Nanomedicina

Componentes



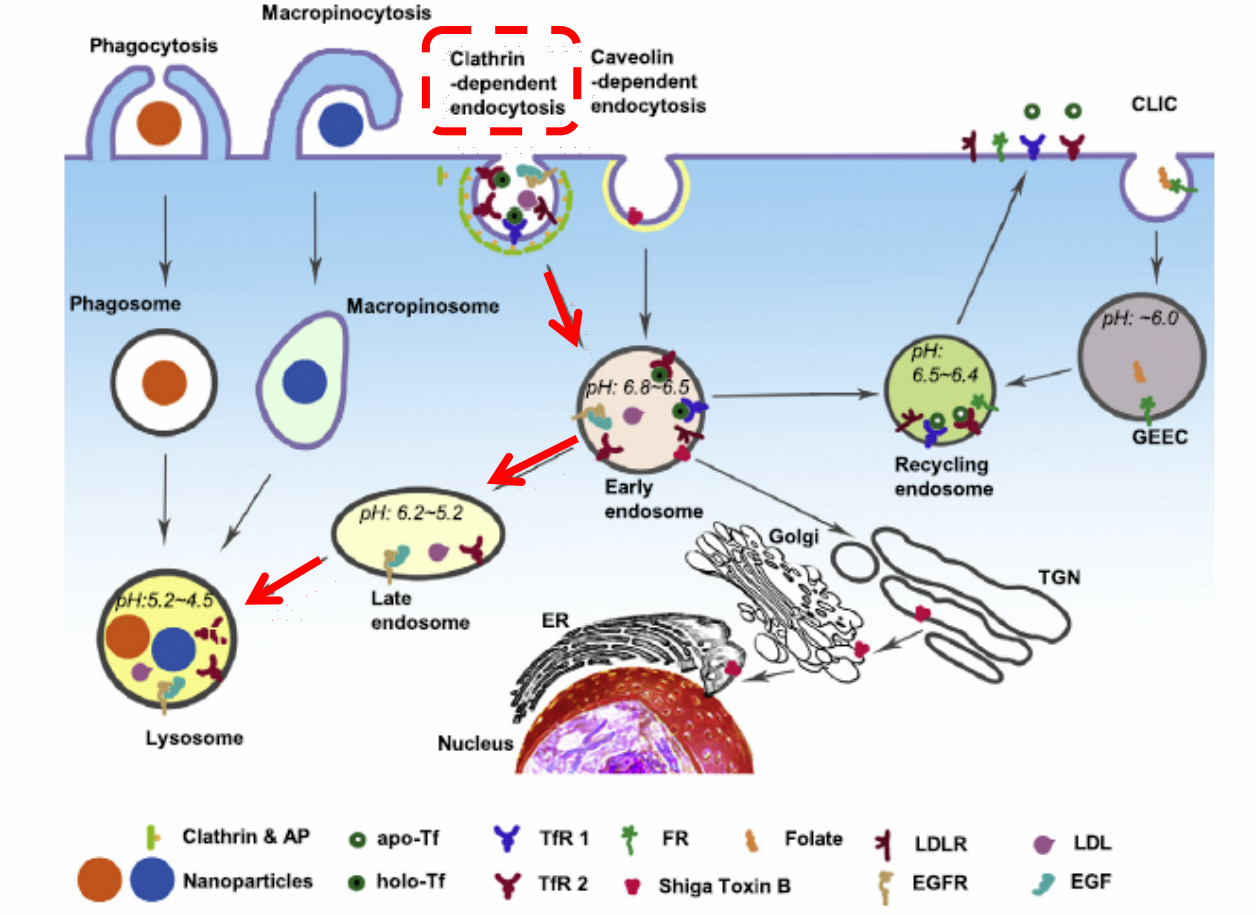
Nanomedicina

Sistemas de transporte celulares



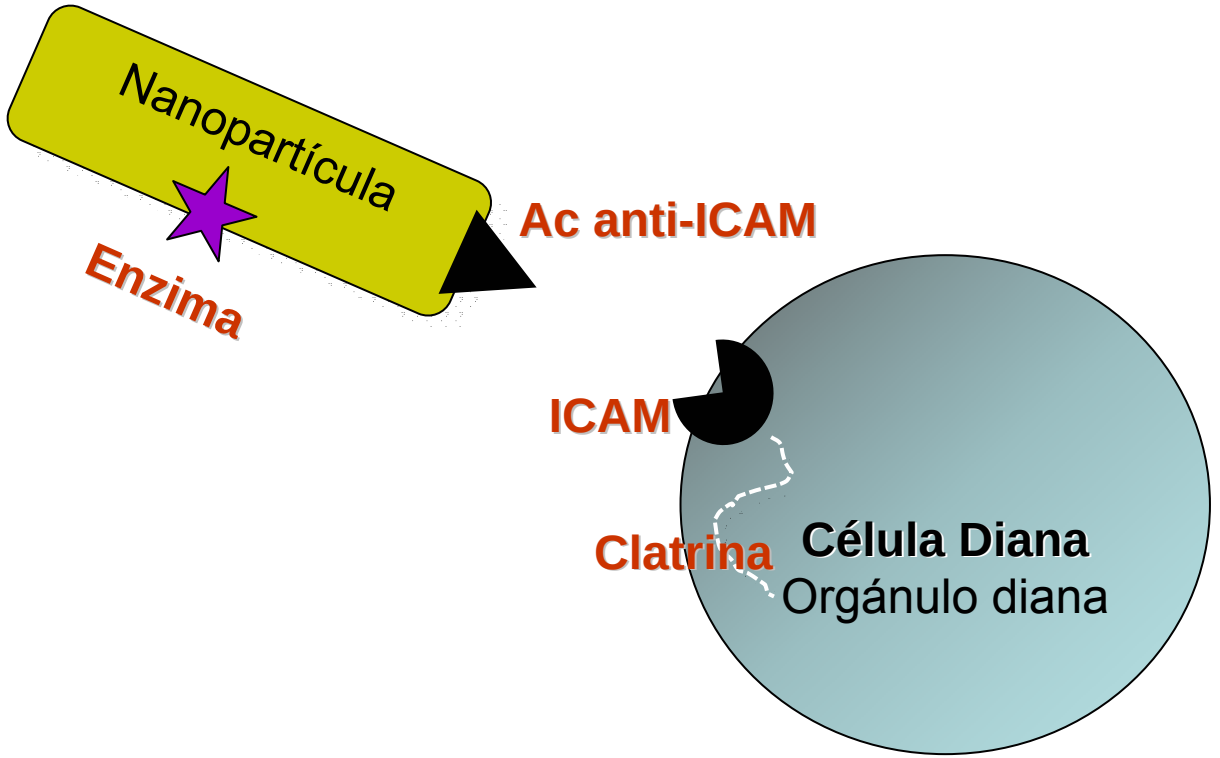
Nanomedicina

Sistemas de transporte celulares



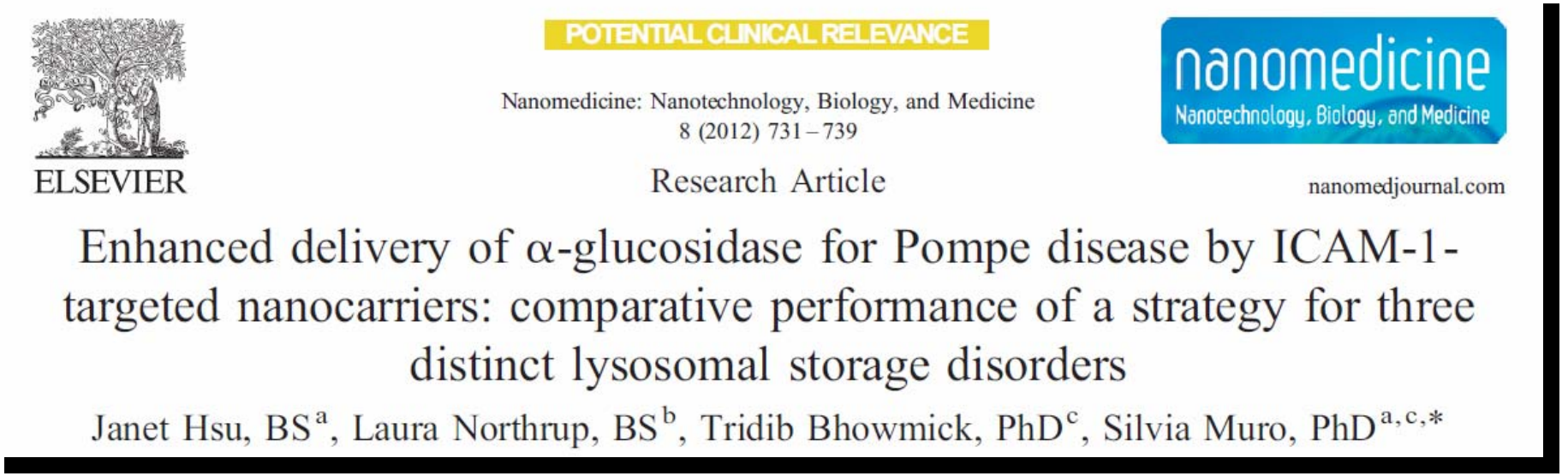
Nanomedicina

Sustrato del receptor



Nanomedicina

Experiencia actual



ELSEVIER

POTENTIAL CLINICAL RELEVANCE

Nanomedicine: Nanotechnology, Biology, and Medicine
8 (2012) 731–739

Research Article

nanomedicine
Nanotechnology, Biology, and Medicine

nanomedjournal.com

Enhanced delivery of α-glucosidase for Pompe disease by ICAM-1-targeted nanocarriers: comparative performance of a strategy for three distinct lysosomal storage disorders

Janet Hsu, BS[a], Laura Northrup, BS[b], Tridib Bhowmick, PhD[c], Silvia Muro, PhD[a,c,*]

Along with improved delivery of **Niemann-Pick** and **Fabry** enzymes, previously described, these results indicate that ICAM-1 targeting holds promise as a broad platform for lysosomal enzyme delivery.

Otras estrategias

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Enfermedades
Minoritarias

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14 de junio de 2013

Tratamiento de las enf. lisosomales

Otras estrategias

Stop-codon read-through

In a large number of lysosomal storage disorders, **nonsense mutations** have been identified that lead to **premature translation termination** and to the synthesis of a **truncated and non-functional enzyme**.

Gentamicina en MPS I (Hurler) útil en fibroblastos humanos.

Tratamiento de las enf. lisosomales

Otras estrategias

Proteostasis regulators

Small molecules that have the potential to restore the normal balance between protein folding, trafficking, and degradation.

Two proteostasis regulators have been reported to restore the function of two mutant lysosomal enzymes in **Gaucher** disease and **GM2 gangliosidosis** .

Co-administration of a pharmacological chaperone and a proteostasis regulator exhibited synergy and resulted in further enhancement of enzyme activity. This approach remains largely experimental.

Conclusiones

III Reunión de
Enfermedades
Minoritarias

Hospital Clínico Universitario
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14 de junio de 2013

Tratamiento de la Enf. Lisosomales

Pros y contras

Table 1. Advantages and limitations of therapies for LSDs

	Advantages	Limitations
HSCT	• Sustained correction after a single procedure • Cross-correction of host's cells by secreted enzymes	• Procedure-related risks and mortality • Not effective in some diseases • Time required to identify compatible donors • Poor engraftment in tissues like bone, cartilage and heart
ERT	• Long-term experience and documented efficacy in thousands of patients treated (*e.g.* Gaucher disease) • Registries available to document natural history of disease and efficacy	• Poor distribution of recombinant enzymes in specific tissues • Inability of recombinant enzyme to cross the BBB; • Frequent infusions required, with high impact on quality of life • High costs
SRT	• Oral administration • Little impact on quality of life	• Limited clinical experience (with the exception of Gaucher disease) • Long-term adverse effects unknown
PCT	• Better biodistribution of therapeutic agents • Possibility to target neurodegeneration in LSDs • Oral administration • Little impact on quality of life	• Limited clinical experience • Long-term adverse effects unknown • Only patients with specific 'responsive' mutations amenable to treatment
Gene therapy	• Sustained correction after a single procedure • Cross-correction by enzymes secreted by 'factory' organs	• Very limited clinical experience, still under development

Parenti G. EMBO Mol Med 1, 268–279

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Alcoi (Alacant).

Tratamiento de la Enf. Lisosomales

Conclusiones

- **Creciente número** de estrategias terapéuticas nuevas.
- **Marcada heterogeneidad** entre enfermedades.
- Grandes potenciales, pero la **mayoría preclínicos**.
- Actualmente **TSE y TRS con algunas chaperonas**, lo que plantea la posibilidad de plantearse **tratamientos combinados**.
- **Elevado coste** de técnicas más recientes (terapia génica).

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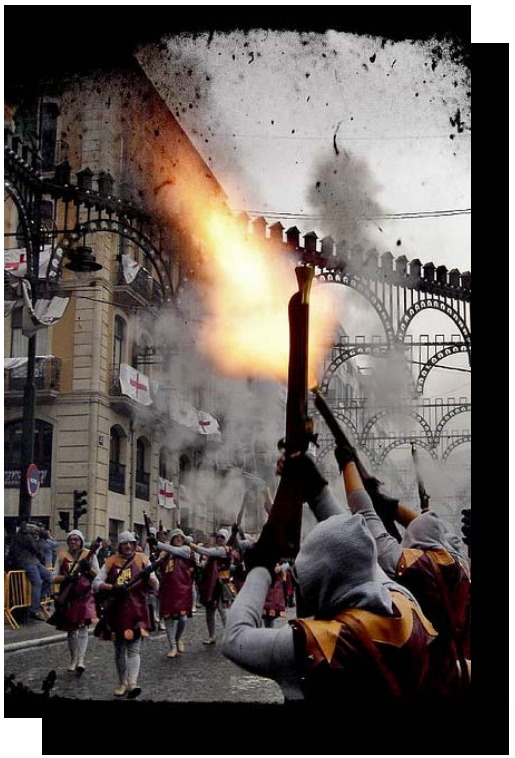
http://alcoi.san.gva.es



Muchas Gracias

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