

www.mps2012.eu

MPS Betegtársaság Találkozó és Tudományos Szimpózium

Június 28- Július 1, 2012
Noordwijkerhout, Hollandia

Sólyom Alexander
PTE KK Gyermekklinika, Pécs

Betegtársaság Hálózat

- 21 ország MPS, illetve lizoszómális tárolási betegség betegtársaság képviselte magát:

USA, Anglia, Hollandia, Kanada, Törökország, Olaszország, Spanyolország, Schweiz, Ausztria, Németország, Lengyelország, Brazília, Japán, Indonézia, Taiwan, Belgium, Írország, Norvégia, Svédország, Ausztrália, Magyarország.

- 2013, Osaka, Japan
- 2014, Bahia, Brazilia
- 2016, Hamburg, Németország

TRANSITION PASSPORT FOR LSD PATIENTS

PAEDIATRIC

TO

ADULT





National MPS Society Interaction/Relationship with Pharmaceutical Companies Policy

Gyógyszeripar és Betegtársaságak

The National MPS Society recognizes the importance of maintaining relationships with the pharmaceutical companies that have FDA approved or developing treatments for individuals with MPS and related diseases. Ethical relationships with the companies are critical to ensuring that the Society provides accurate and unbiased education to families about available and future treatments.

The role of the company is to inform the Society about the benefits and risks of treatments and to provide scientific and educational information. Through the interaction with the Society, the companies gain a unique perspective about the diseases, direct access to the patient population, information about the needs and priorities of Society members, disease knowledge to assist in clinical trial design, advance patient education, feedback on new treatments, and support during the regulatory approval process.

This interaction provides the opportunities for project collaboration including but not limited to general and medical education about the diseases and advocacy for product (treatment) approval and reimbursement.

The Society's Executive Director and President are the primary liaisons between the company and the Society and submit requests for targeted or operating financial grants. The grants must be given without conditions, and no *quid pro quo* arrangement will be accepted. Monies received benefit all Society members, not just the subset served by the product of the company.

The Society will accept company funds for company sponsored meetings. The Society recognizes that the companies are legally limited to services they can provide for meetings where patients are present, such as speakers, meals and travel to the meetings. These funds are available for any family in that region to attend the meeting, regardless of the disease. The Society assumes no responsibility for meeting planning or determination of attendance.

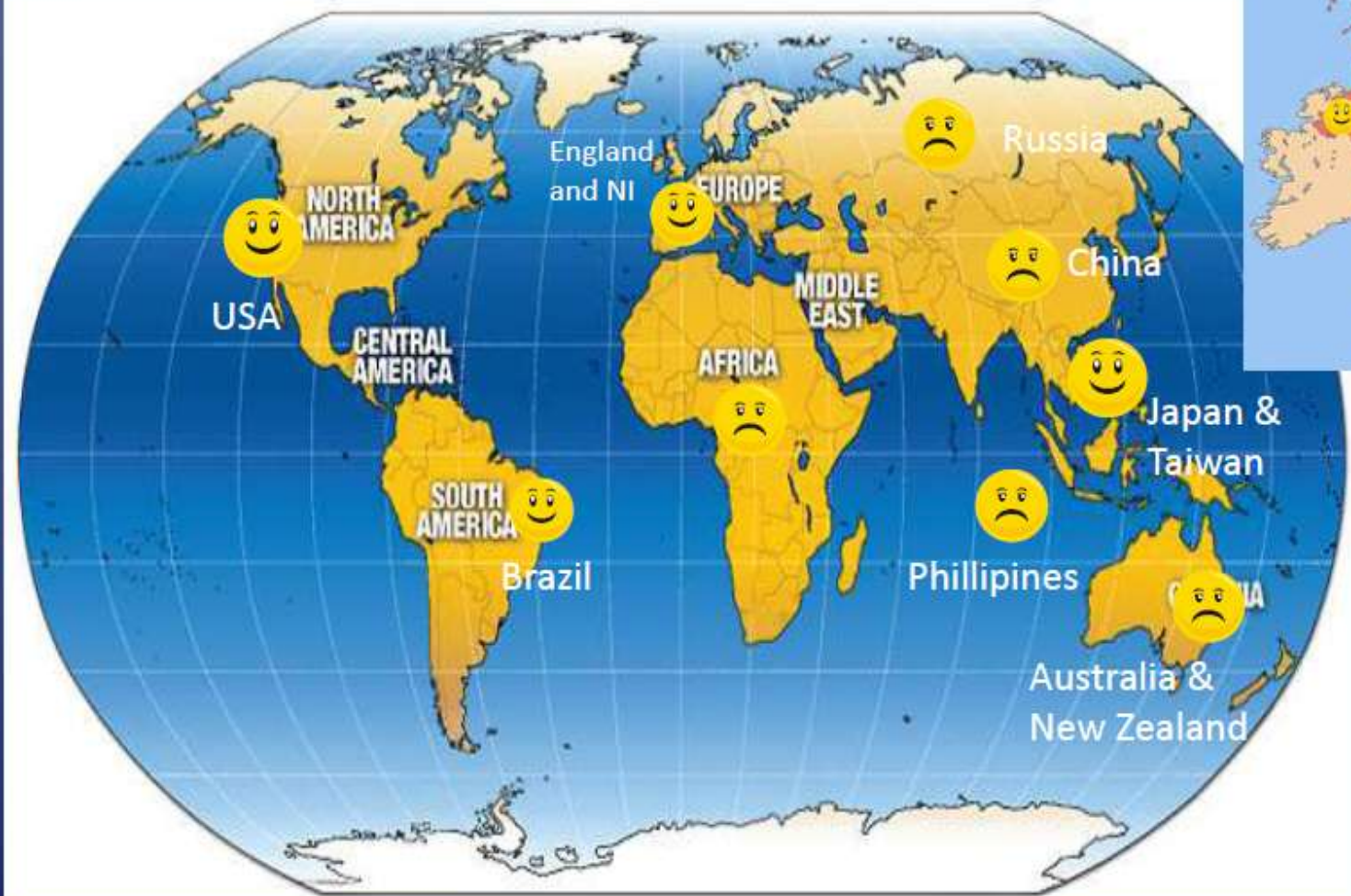
The Society also accepts company funds for collaborative educational projects. Although these are branded projects between or among the companies and the Society, the Society is responsible for payment of services associated with the projects.

Society staff may serve as consultants or working members on committees, or members of a speakers' bureau. Any consulting work, including presentations, for which the staff receives compensation, must be scheduled as a vacation time. Alternatively, staff can request that compensation be paid directly to the Society, whereby that consulting is considered work time.

Betegtársasági Példák

- Csak feltétel nélkül
- Csak a betegek érdekeit szolgálhatja
- Pénz a gyógyszercégektől
 - Ausztrália: 1/3
 - UK: kb. 10%
 - Hollandia: max. 25%

April 1980	First Bone Marrow Transplant for MPSI at Westminster Children's Hospital, London
May 1982	UK MPS Society founded
1983 	24 MPS Societies founded globally
2000	
April 2003	Aldurazyme for MPSI received marketing approval in the USA
April 2005	National Specialist Commissioning granted in England for provision of clinical management and ERT for MPS diseases
January 2006	Naglazyme for MPSVI received marketing approval in Europe
January 2007	Elaprase for MPSII received marketing approval in Europe



The human cost and impact to MPS patients and their families

- Living with the reality of a lost opportunity of a life that could be saved. Feeling they can't look to the future, life has no purpose, mental decline.
- Divided communities – the 'have's' and 'have not's'. Maybe this is emphasized by the closeness of the MPS International Community and access to social media?
- The mental health problems related to being denied access to treatment from the patient, parent, partner, sibling or extended family member.
- Living with a degenerative disease and getting worse and worse when access to treatment is denied.
- Caring for a loved one with a degenerative disease and the consequences when access to treatment is denied.

Cégek

- Genzyme – újszülöttkori szűrés
 - Pár USA államban (MPSI, Krabbe, Niemann-Pick, Pompe, Fabry) populáció 31%-a,
 - 2-3 mutáció, 1 hordozó / 58,000
- Shire – MPS II, MPS IIIA/B
 - IT-ERT vizsgálatok
 - MPS IIIB – epidemiológiai vizsgálat
 - MPS IIIA - epidemiológiai vizsgálat, IT-ERT
 - MPS II
 - Szelekció, IQ csökkenés (15-30 pt/3 év, vagy IQ<77)
 - Havonta, 6 hónapig (2012 végéig)
 - Biomarkerek vizsgálata (LAMP fehérje)

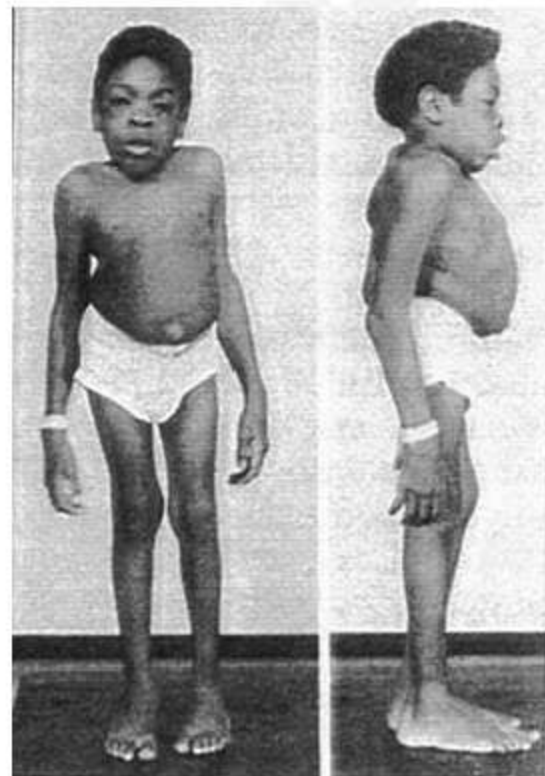
Shire humanitárius program

- Bizonytalan – csak tervezési fázisban van és a kommunikáció nem volt megfelelő
 - Szakértői bizottságok döntenének cég által támogatott terápiáról.
- Mobil/számítógépes app.
 - gyógyszer, kontroll vizsgálatok, gyógytorna, stb.
- Internetes fórumok létrehozása
 - Személyes info. megszerzése?
 - Olaszoknál a betegtársaság működteti...
- Fizoterápiás trainingek személyenként
 - Német/oszták példa: inkább a „saját” gyógytornászt tanitatása
- Váróterem kérdőívek
 - orvos megtudhatja: milyen információra van szükség még
- Nyomtatott MPS típus specifikus tájékoztatók
 - Saját nyelv, ország specifikus
- Paciens támogató rendszer:
 - Telefonos segítő-információs szolgálat

UX003 rh-GUS for MPS 7 (Sly Syndrome)

- Recombinant human β -glucuronidase (GUS) as Enzyme Replacement Therapy
- Multisystem lysosomal storage disorder similar to MPS 1 (Hurler-Scheie Syndrome)
- Estimated ~200 patients in world
- Excellent and extensive preclinical data
- Enters clinic in ~12 months
- Product easy to manufacture

Original patient diagnosed
With Sly Syndrome



Cégek

- Biomarin
 - MPS IV „patient outcome study”
 - Eredmények az életminőség függvényében
 - MPS IV A study, phase III (176 gyermek)
 - „jó eredmények”, adatok 2012 vége
 - www.morquiobmrn.com
 - 5 év alatti Phase II
 - „non-ambulatory”, „nem járás képes” study terv



How to get involved?

Morquio B Registry

www.morquioB.org

Priest family website

www.morquioB.com

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Tudományos szimpózium

- MPS VI – HSCT és ERT hasonló
 - Vizelet GAG csökkent
 - Fizikális teljesítmény nőtt
 - 12 perces járás teszt
 - 3 perces lépcsőzés
 - Kardiológiai eltérések javultak
 - Csont eltérések, szemészeti eltérések kevésbé javultak

Early Initiation of Therapy



- Siblings, aged 8 weeks and 3.6 years,
- Absence of scoliosis; preserved joint movement, cardiac valves and facial morphology
- In favor of a clear benefit of early initiation of ERT



Mc Gill et al. 2010

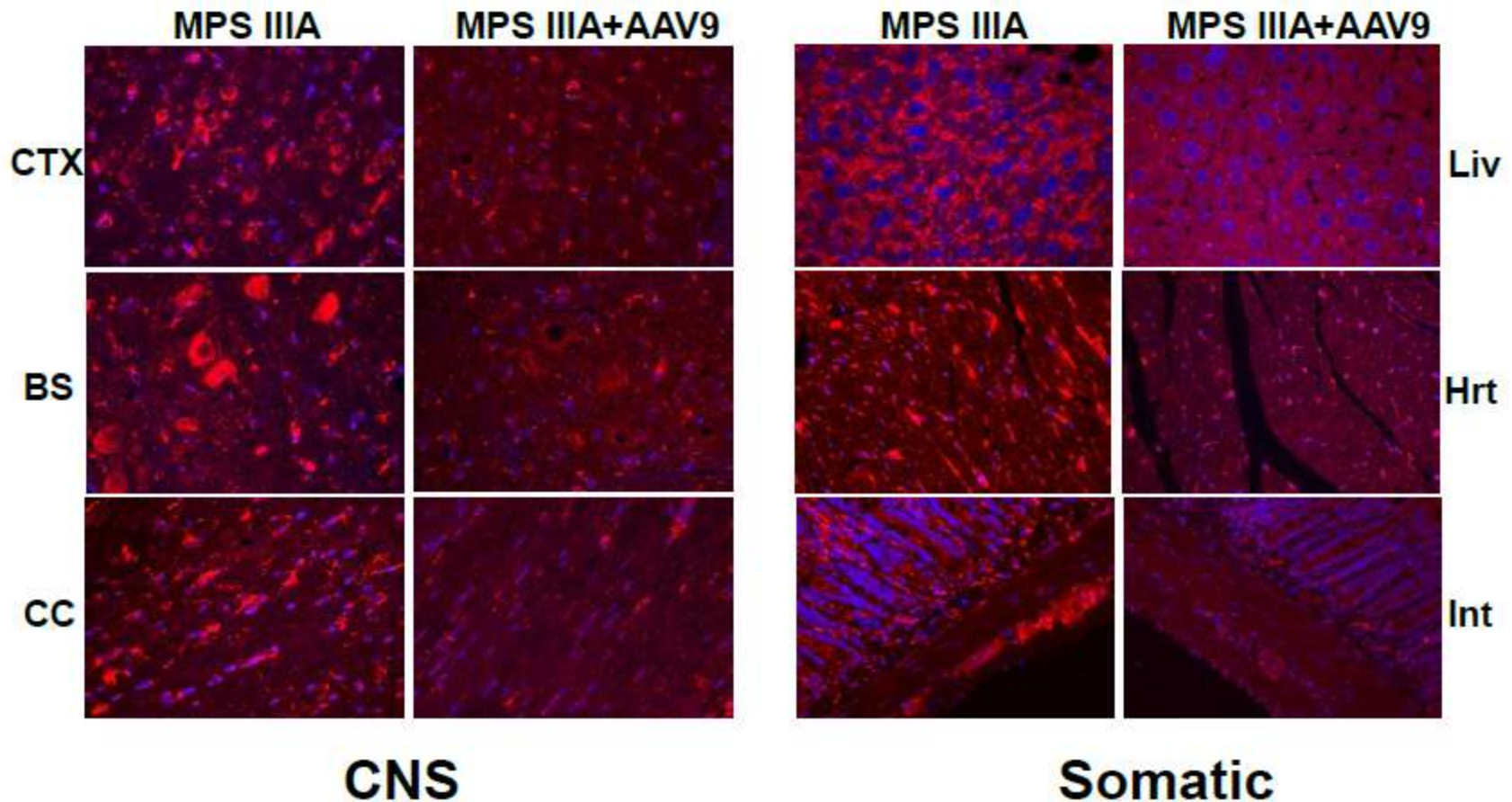
Take Home Messages

- Overall positive outcome for the 2 treatment modalities: ERT and HSCT
- HSCT remains an option when ERT unavailable or in cases with significant cognitive impairment
- Bone disease, growth, cardiac valve disease, corneal clouding and cervical spine compression remain partially addressed
- Place for early treatment- place for NBS
- Place for new treatment strategies (small molecules, gene therapy...)

Génterápia

- „előállított” DNS/gén szakasz a véráramba
- MPS VI (Nápoly), MPS IIIB (USA)
- virális vektor
 - AAV (adeno associated viral) vektor terápia (metakromasiás leukodystrophia - Arylsulfatáz def. egerek).
 - Várható kezdés emberekben 2012 július. (Ankara, Nápoly, Rotterdam).
 - AAV vektor jó mivel nem patogén, sejtekben látens, így hosszú távú expresszio.
 - Probléma: korábbi infekciók miatt antitest termelés/jelenlét, így hatástalan lehet. Nem tudni hányan esnének ebbe a csoportba.

Reduction of LAMP1 in the CNS and Somatic Tissues (10 days pi)



NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.™





Phenotypic improvement in MPS VI cats injected with AAV2/8-TBG-ARSB

NR



Untreated MPS VI



MPS VI + AAV (P50)

MPS VI + AAV (P5)



6×10^{13}



6×10^{13}



6×10^{12}



2×10^{12}



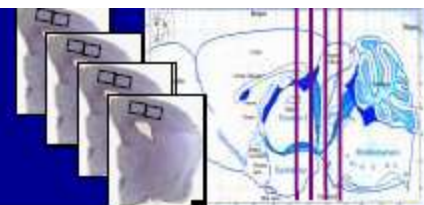
6×10^{11}



2×10^{11}

- Szubsztrát redukciós terápia (SRT)
 - Heparan szulfát redukciós gyógyszer fejlesztés alatt (Zacharon Pharma)
 - Genistein aglycone „tisztá szintetikus forma” – Genistin (sója extrátum) kevésbé hatékony
 - GAG termelést (en bloc) gátolja, minden MPS-ben
 - Vér-agy gáton átmegy 10%-a
 - Max 15mg/ttkg/nap emberekben eddig
 - 150-160mg/ttkg/nap – Manchester
 - » Estrogen hatást figyelik

MPSIIIB Brain pathology improved



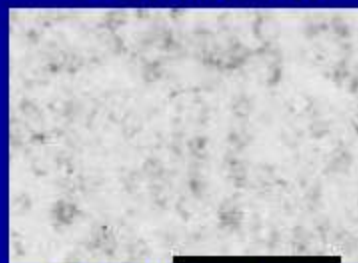
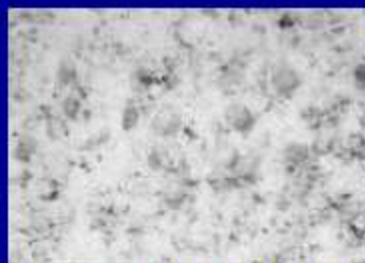
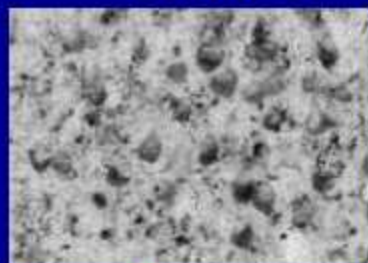
MPS IIIB

WT

Control

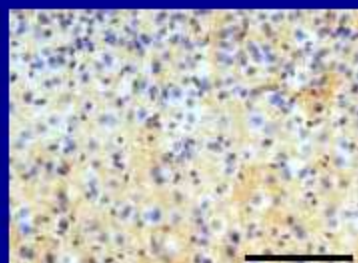
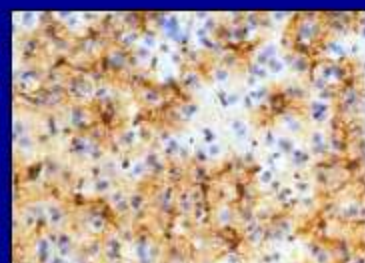
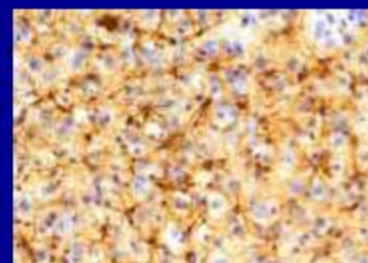
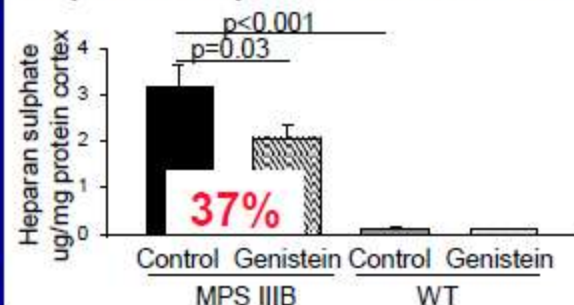
Genistein

Genistein

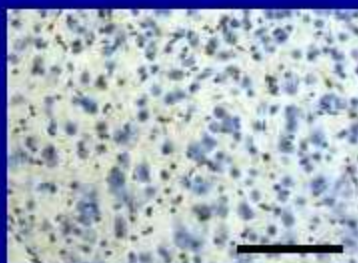
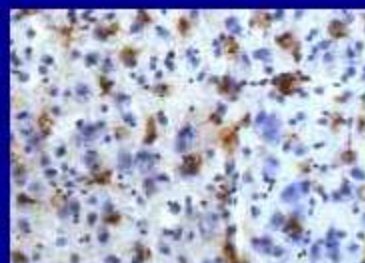
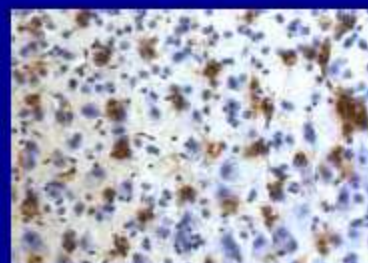
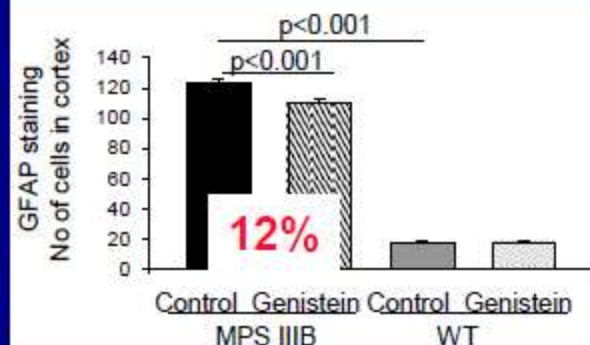


Lysosomal size (LAMP2) Cerebral cortex

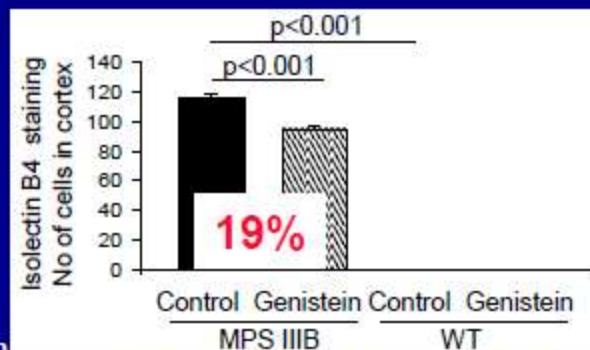
Heparan Sulphate substrate - brain



Astrocytes (GFAP) Cerebral cortex



Microglia (ILB4) Cerebral cortex Bar = 100μm



- Intratecalis enzim pótló terápia (IT-ERT)
 - Bejut az agyszövetbe is.
 - Dura vastagság csökkentés - szűkület ↓.
 - Emberi klinikai kísérletek:
 - MPS I (Minnesota - Csontvelő + IT-ERT, UCLA)
 - MPS II (North Carolina, Birmingham, Phase I/II)
 - MPS IIIA (Manchester, Amsterdam, Phase I/II – Intratecalis adagoló eszköz)
 - MPS VI (Phase I/II)
 - MPS II, IIIA intratecális alkalmazásra gyártott.
 - MPS I, VI hígított 2-3x-ra.

Treatments for neurodegenerative MPS



Many neuropathic MPS patients are now:

- receiving treatment **or**
- their disorder is the subject of a clinical trial (NCT# - see www.clinicaltrials.gov)

- **MPS I (Hurler)**

- HSCT In clinical use
- HSCT with i.v. ERT NCT# 01572636
- HSCT with intra-CSF ERT NCT # 00638547
- Intra-CSF ERT NCT# 00852358

- **MPS II**

- Intra-CSF ERT NCT#00920647 and # 01506141

- **MPS IIIA**

- Intra-CSF ERT NCT# 01155778 and # 01299727
- Intracerebral gene therapy NCT# 01474343
- High-dose genistein Trial planned – Wegryzn, Bigger et al – Poland, Manchester UK

- **MPS IIIB**

- Intracerebral gene therapy Trial planned - Heard et al – Institut Pasteur, Paris, France
- i.v. gene therapy (AAV9) Trial planned - Fu et al – Nationwide Children’s Hospital, Ohio, USA

- **MPS VII**

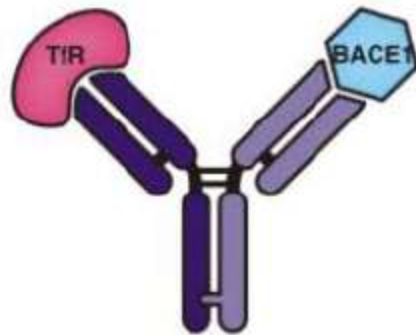
- ERT with UX003 (orphan drug) Trial planned – Sly et al with Ultragenyx – St Louis & California, USA

Állatmodellek ritkán mérik fel a funkcionális javulást károsodott egyéneknél.
Kérdéses a követésre alkalmas eszköztár?

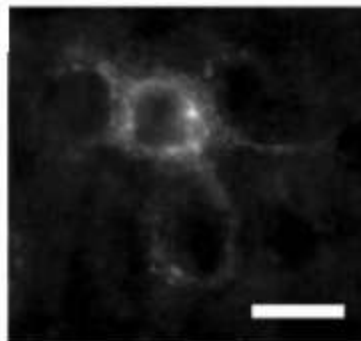
Dr. Kim Hemsley, Ausztrália

- KIR (központi idegrendszer) és a vér-agy gát
 - A legtöbb GAG lerakódás a perivascularis terekben van.
 - Mannóz-6-foszfát mediált „nagy molekula” transcytosist kihasználva „csomagolási” módszerekkel ERT átjuthat.

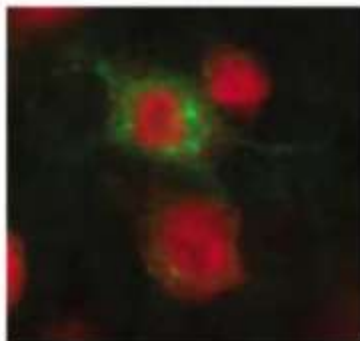
Hybrid Mab with low Affinity to TfR and high To β -secretase



Anti-TfR^D



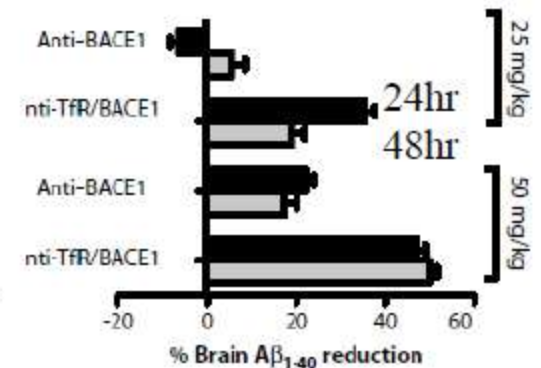
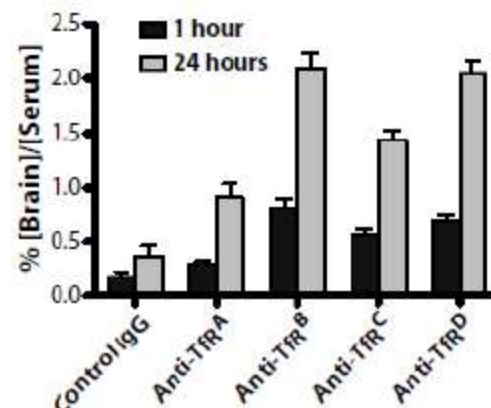
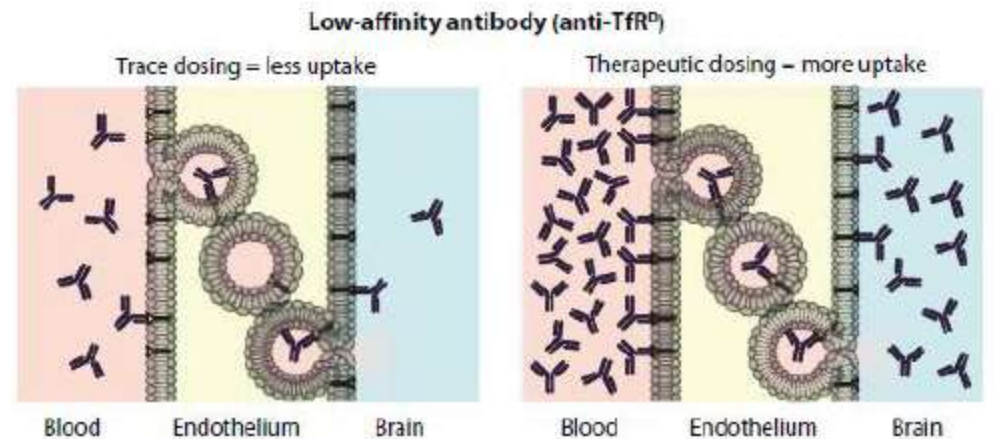
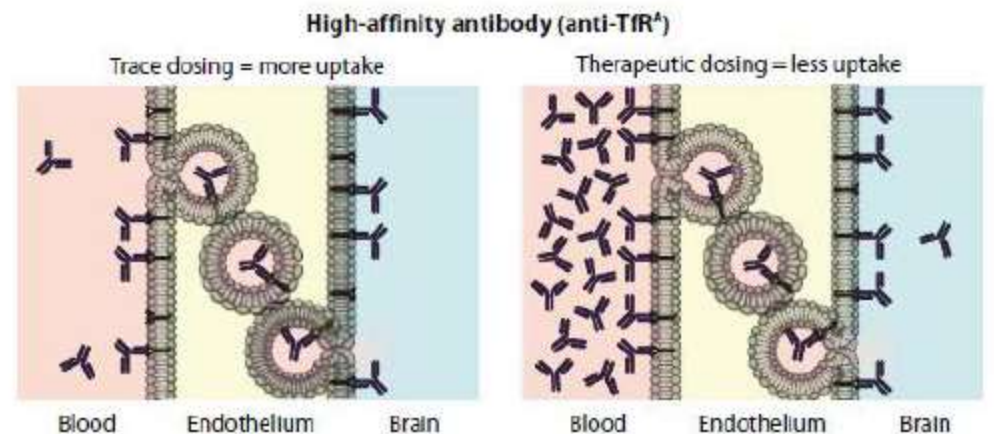
Anti-TfR^D/NeuN



Science Translational Medicine 2011

3: 84a44

Begley, Receptor Mediated Membrane Transport





CONCLUSIONS ¹

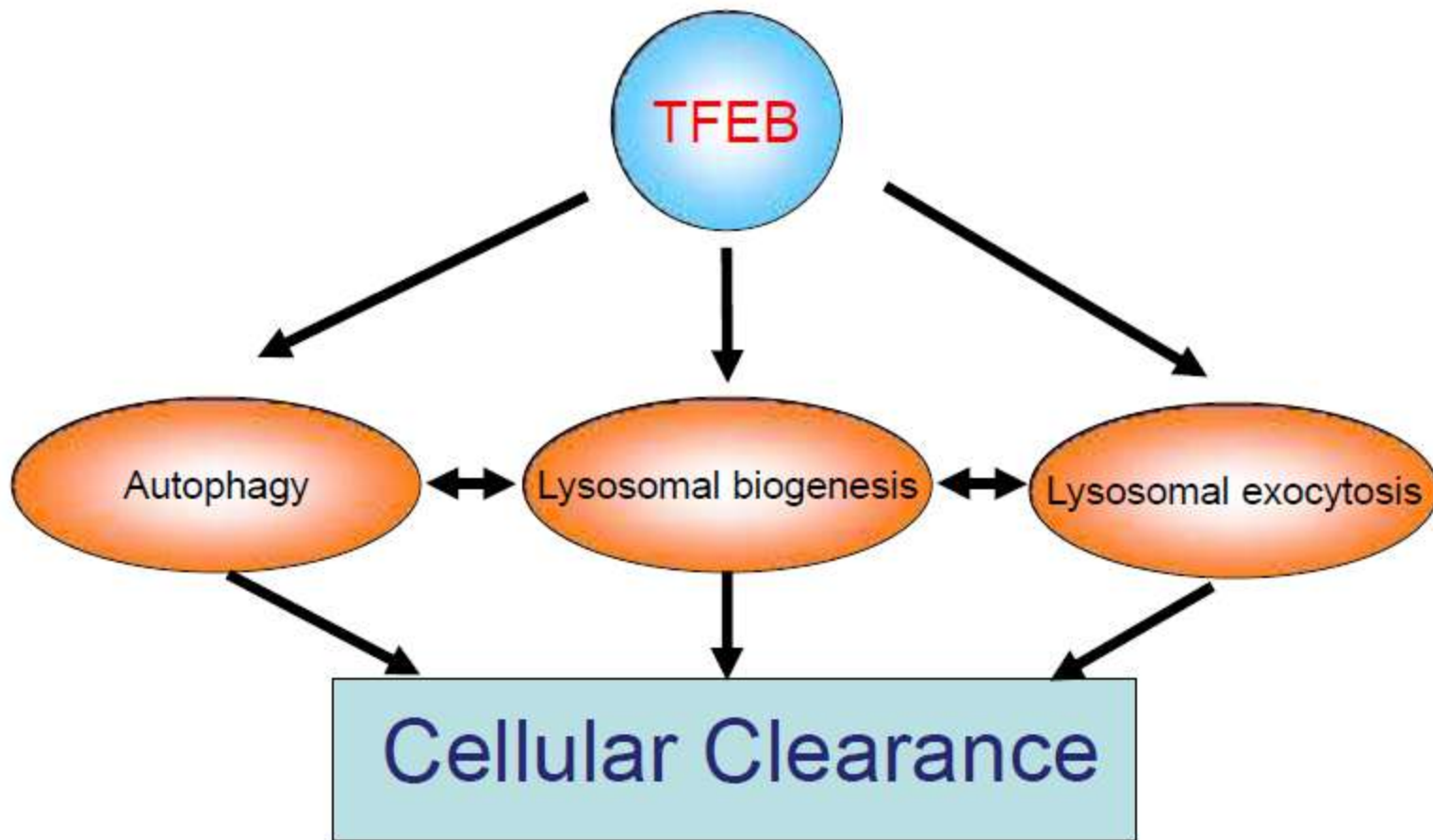
- CNS disease represents a significant burden to patients and their families and cost to society.
- Secondary cascade events together with the primitive storage are responsible for CNS disease
- Fifty percent of patients are affected by CNS involvement by the age of 5.
- All the major CNS signs and symptoms can be expected in MPSII. However Cognitive and Developmental problems are the major issues in the first 3 y of age.
- Behavioural manifestation is a major issue in MPS, in particular MPSII and III, which should be studied in more detail. Therapy in particular is still far to come.
- Cognitive and behavioural studies are mandatory soon after diagnosis.



CONCLUSIONS ₂

- Imaging is a very important tool to properly follow up the progression of the disease and possibly be used as surrogate marker of cognitive functions.
- NMR and TC scans may reserve surprises when read by very experienced neuroradiologists.
- “Closed Meningoencephalocele” is a new specific sign for MPSII. More data on MPSs and other LSDs to understand its value as disease marker and/or specificity.
- I propose to organize online coordinated facilities for NMR and TC scans reading since we still might find brain modifications relevant for the management of the patient (i.e. anesthesia, surgery).
- This coordinated action will help all the programmes related to CNS therapy and natural history studies.

- Lizoszóma aktiváció
 - TFEB gén kódolja a fehérjét amitől:
az autophagia fokozódik, lizoszomák száma nő,
és a lizoszómák „kiürülnek” (exocytosis).
 - MPS IIIA
 - MPS I
 - Pompe
 - Nem tudni mi a kiürített anyagok sorsa.



**CAN WE USE TFEB TO PROMOTE
CELLULAR CLEARANCE IN LSDs?**

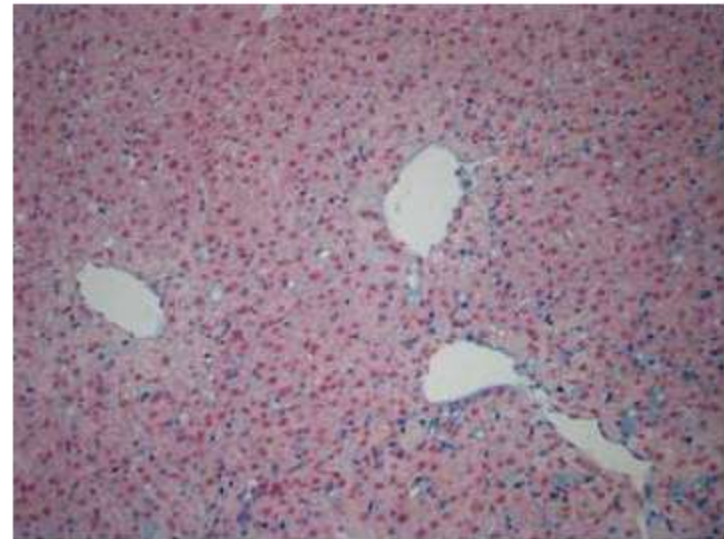
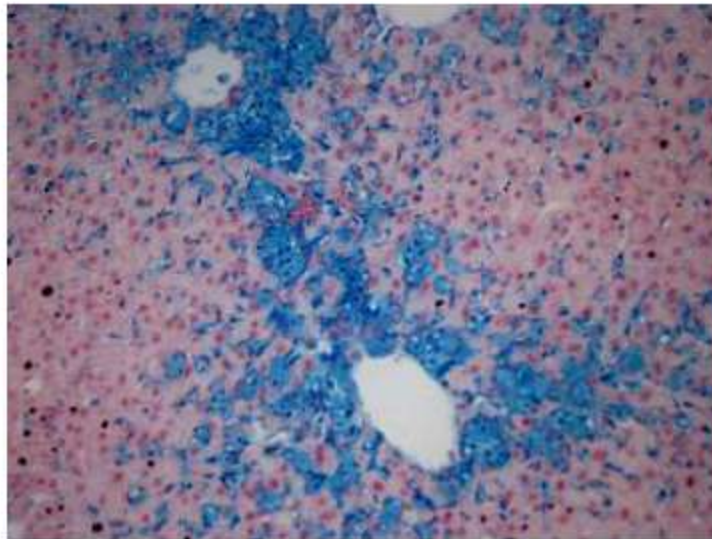
TFEB reduces pathologic lysosomal storage in vivo

Significant GAG reduction in MSD mice injected systemically with AAV-TFEB

MSD-CTR

MSD-AAV-TFEB

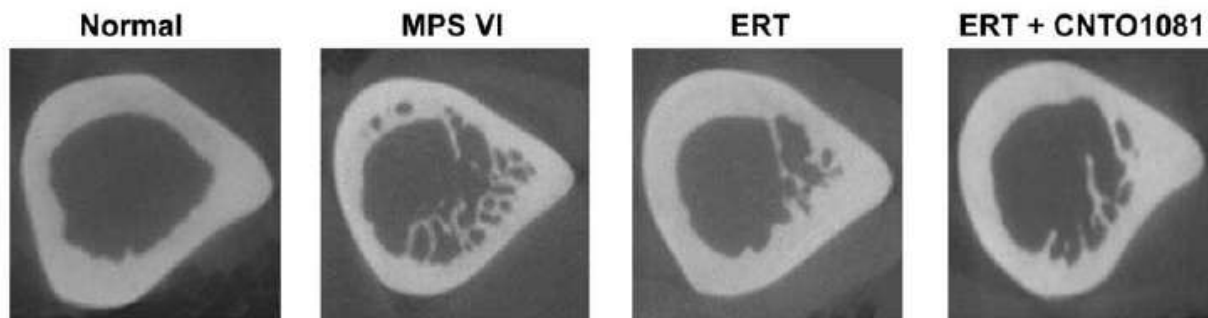
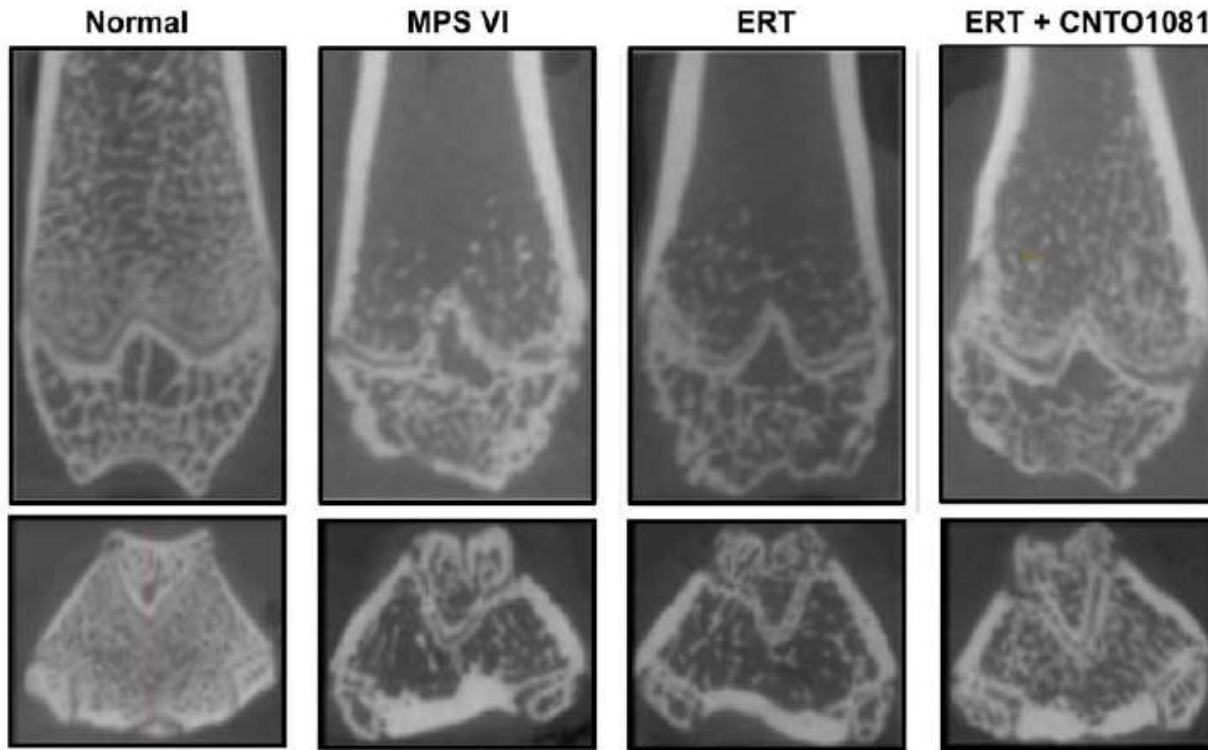
LIVER



- Őssejt transzplantáció
 - A köldökzsínór vér használatát találták hatékonyabbnak (magasabb enzim szintek).
 - Heparán szulfát gátolja a beültetett sejtek migrációját a csontvelőbe.
 - Ez lehet egy tovább vizsgálendő tényező a sikertelen transzplantációnál
- Somaticus őssejtek „újraprogramozása”
 - Saját sejtekben „génetikai mentés” (rescue).
 - Autológ transzplantáció.

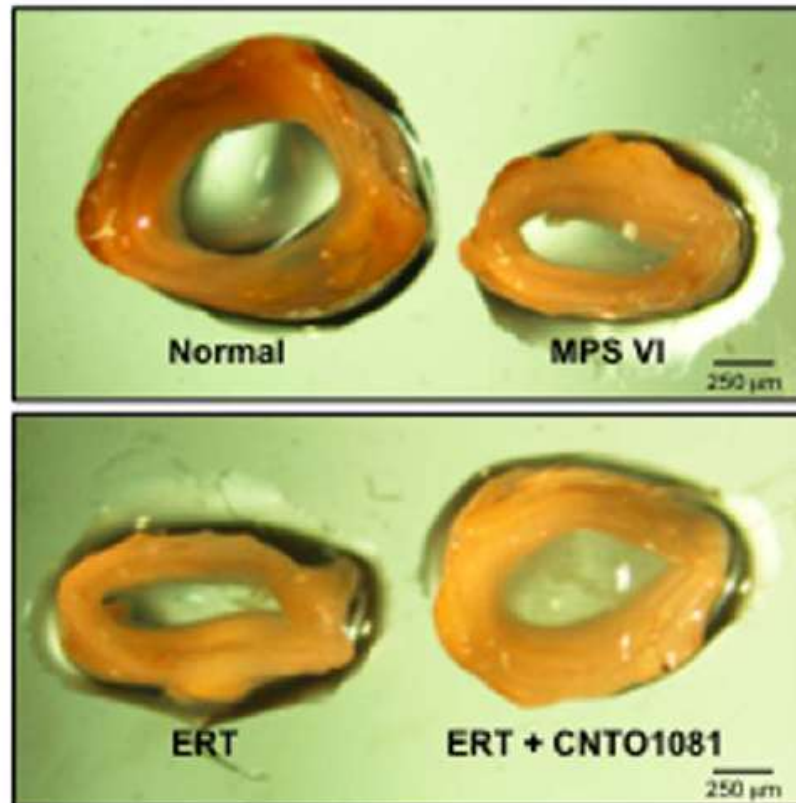
Gyulladás

- GAG tárolás:
 - TLR4 aktiváció
 - TNF- α , IL-1 β , RANKL, és más gyulladásos citokinek.
- Állatmodellek:
 - anti-TNF- α és ERT (enzim pótló terápia) együttes alkalmazása.
 - gyulladásos markerek csökkentek, porc és csontszerkezet kevésbé károsodott, funkcionális javulást mértek, de a növekedésben nem volt lényeges változás.



Eliyahu, E, et al., Anti-TNF-Alpha Therapy Enhances the Effects of Enzyme Replacement Therapy in Rats with Mucopolysaccharidosis Type VI. PLoS One, 2011, 6:8.

Szimpórium 14

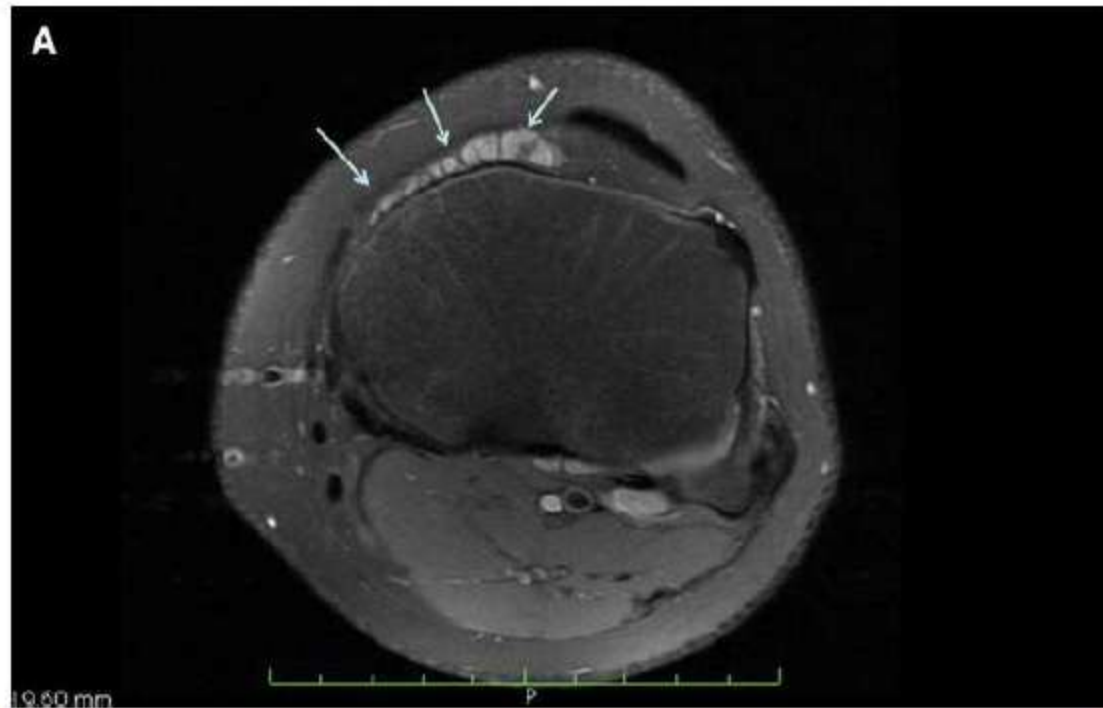


Eliyahu, E, et al., Anti-TNF-Alpha Therapy Enhances the Effects of Enzyme Replacement Therapy in Rats with Mucopolysaccharidosis Type VI. PLoS One, 2011, 6:8.

- MPS IX (familiáris arthritis)
 - Hyaluronidáz hiány
 - Tünetek:
 - Ízületi effúziók
 - Synovialis proliferáció
 - Baker cysták, ganglionok
 - Nincs erózió (kivéve csípő)
 - Visceralis, szemészeti, idegrendszeri érintettség nincs
 - Kifejezett gyulladásos jelek nincsenek

MRI of Knee

- A. Left Knee Ganglion



Radiographic Imaging- MPS IVA

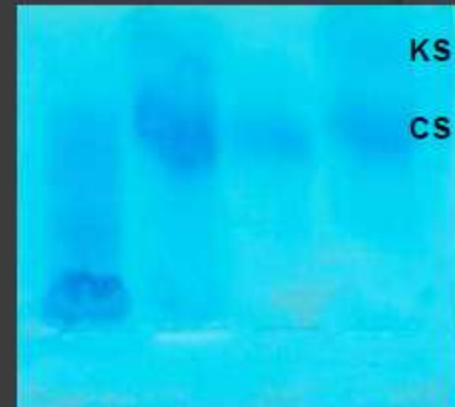
- ⦿ Findings vary and can be subtle
 - Image multiple areas



Urinary Screening- MPS IVA

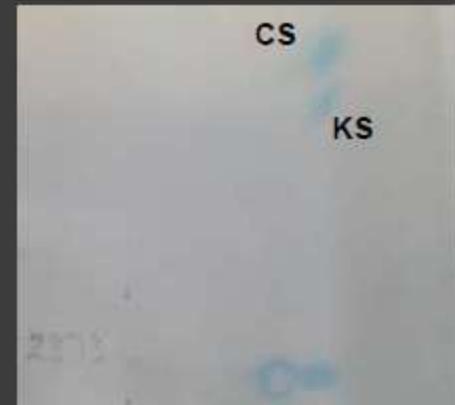
● Test Types

- Quantitative: total urinary GAG
- Qualitative: determination of GAG identity
 - 1D electrophoresis
 - 2D electrophoresis



● Considerations

- Dilute samples problematic
- Excretion decreases with age
- False-negatives
 - Total urinary GAG not always elevated even if KS is excreted
 - KS not always excreted at detectable levels



Enzyme Activity Analysis- GALNS

N-acetylgalactosamine-6 sulfatase

● Best Practices

- Confirm sample integrity by measuring a reference enzyme with similar stability
- Rule out the following conditions:
 - **MPS IVB**: measure β -galactosidase
 - **MSD**: measure a second sulfatase
 - **I-cell disease** (if fibroblasts were used): measure a second mannose-6-phosphate targeted enzyme
- Report normal/affected reference ranges along with patient results

„Life for MPS Award”

Michaela Weigl !

Prof. Michael Beck

Köszönöm a figyelmet!

www.mps2012.eu