Kísérleti terápia a mucopolysaccharidosis csont és ízuleti manifesztációira: háttér és vizsgálatok

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Experimental treatment for bone and joint disease in MPS: background and current studies

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Disclosures

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Background: Storage

- Glycosaminoglycan (GAG) storage:

  dermatan, heparan, keratan, chondroitin sulfate

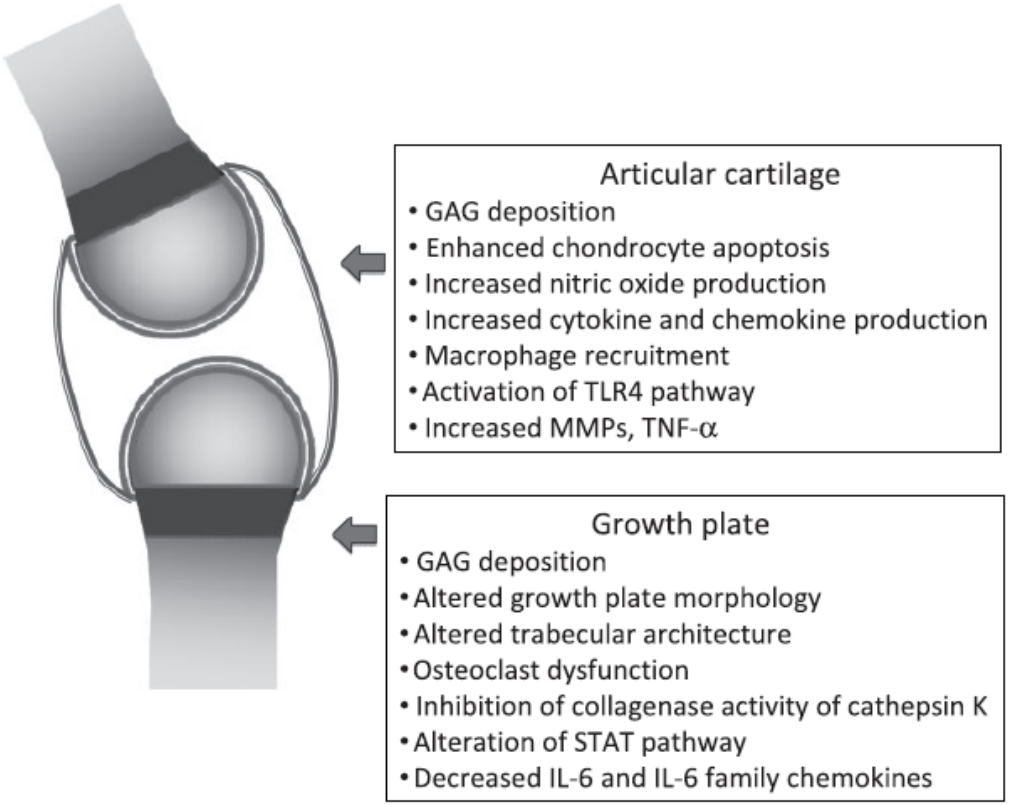
  - Depends on MPS type
  - Known association with manifestations / phenotype
- Questions:
  - Why differences between tissues and organs?
  - Why is ERT not effective in treating all manifestations if GAG levels are reduced effectively?

Background: Inflammation

(Dr. Calogera Simonaro)

- GAG storage:
  - TLR4 activation (innate immune system)
    - Dermatan sulfate similar to bacterial (LPS).
    - TNF-α, IL-1B, RANKL, and other inflammatory cytokines.
- Animal models:
  - MPS VI rats:
    - Dermatan sulfate storage
    - Bone and joint disease
  - MPS I dogs:
    - Dermatan sulfate storage
    - Cardiovascular disease

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.
Frohbergh M, et al. Dose Responsive Effects of Subcutaneous Pentosan Polysulfate Injection in Mucopolysaccharidosis Type VI Rats and Comparison to Oral Treatment. PLoS One. 2014. 9;6:e100882



Clarke, L., Pathogenesis of skeletal and connective tissue involvement in the mucopolysaccharidoses: glycosaminoglycan storage is merely the instigator. Rheumatology, 2011, 50:v13-v18.

Background: Inflammation

(Dr. Calogera Simonaro)

- MPS VI rats:
  - anti-TNF-α and ERT simultaneous use showed reduction of inflammatory cytokines and improvement of bone and joint tissue structure and function.
  - Pentosan polysulfate treatment (PPS – Sp54) showed similar reductions in inflammatory cytokines, with improvement in bone and joint structure and function WITHOUT simultaneous ERT.
  - PPS treatment also resulted in decreased GAG levels.
- MPS I dogs:
  - Inprovement in carotid artery and aorta intima-media thickness
  - Reduction in GAG levels

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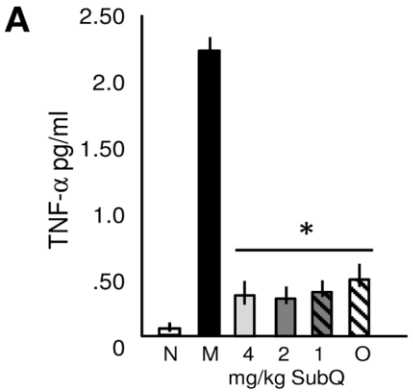
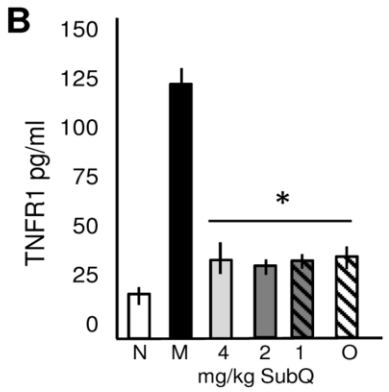
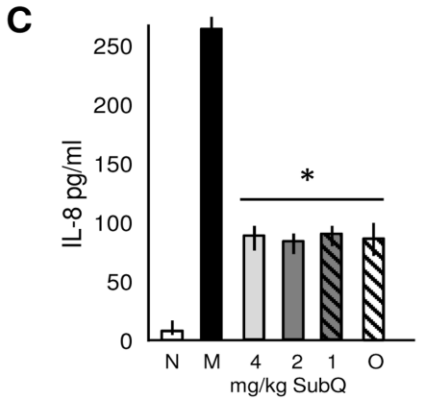
Biomarkers - cytokines

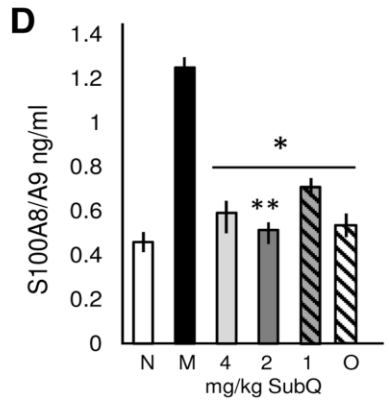
PPS treatment:
MPS VI rats

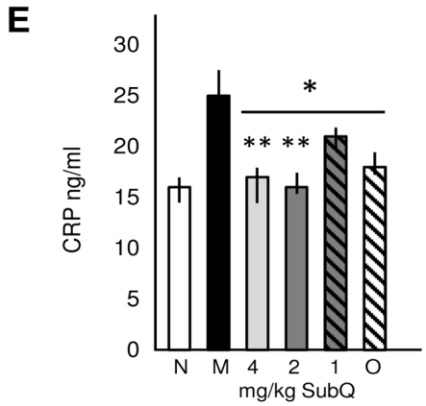
N = normal
M = MPS VI
4 = 4mg/kg/week sc
2 = 2mg/kg/week sc
1 = 1mg/kg/week sc
O = 4mg/kg/die po











Biomarkers - GAGs

PPS treatment:
MPS VI rats

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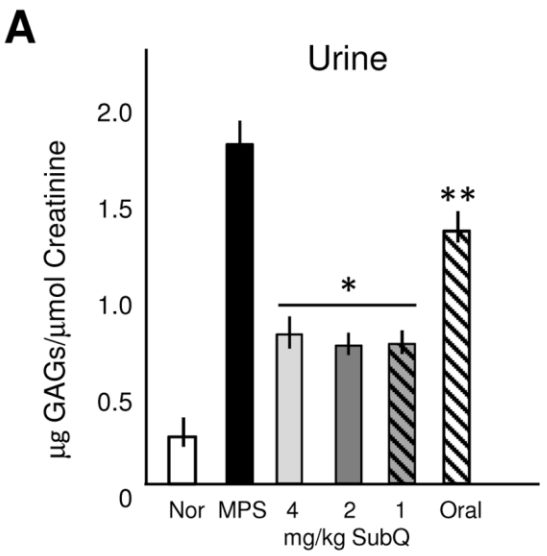
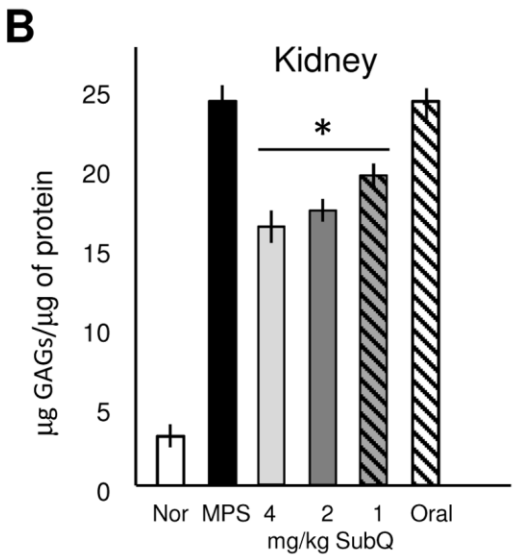
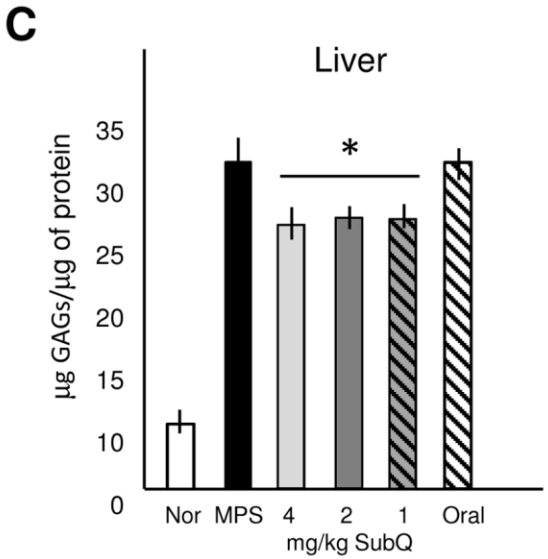
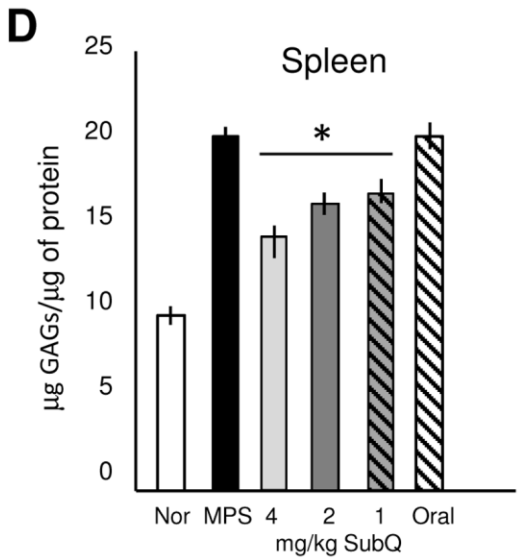






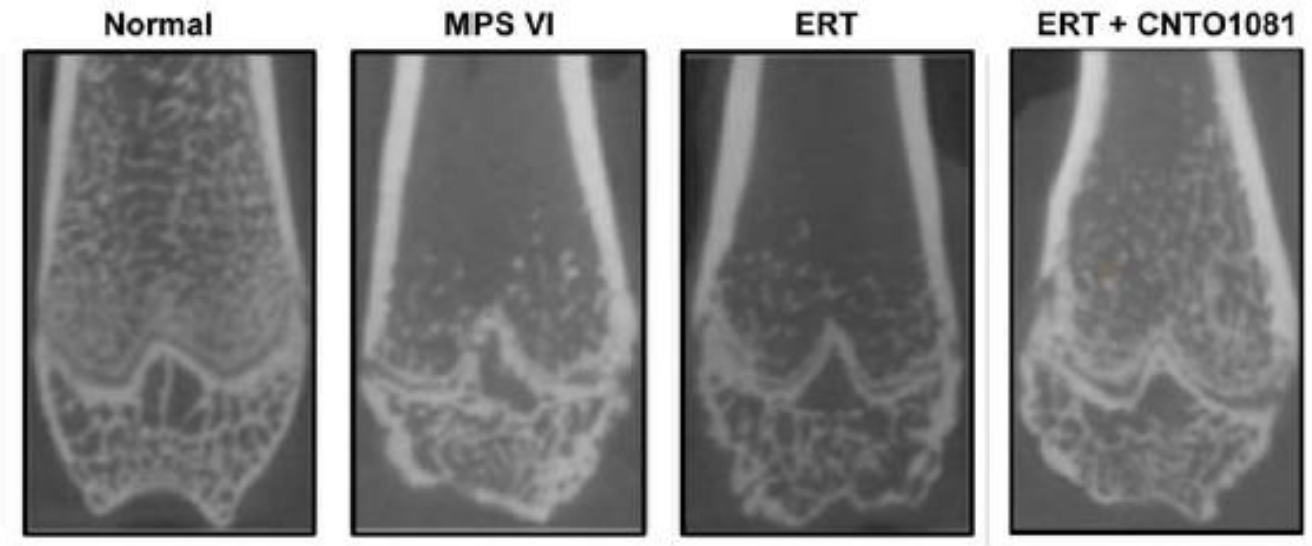


MicroCT

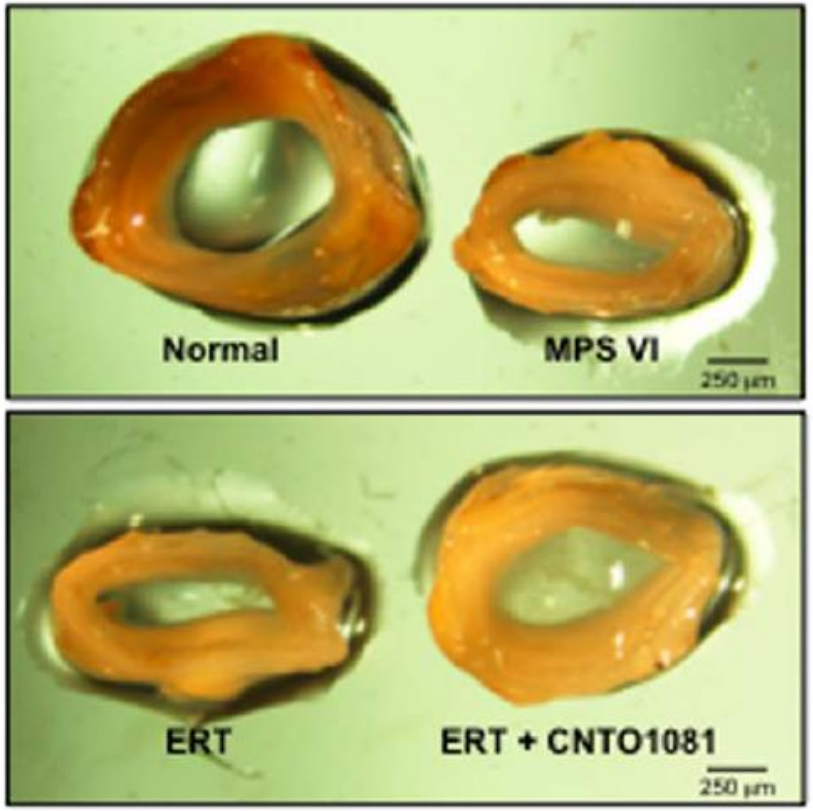
PPS

A- norm
B- MPS VI
C- 1mg/kg
D- 2mg/kg
E- 4mg/kg

Anti-TNFa



Trachea - results similar in antiTNFa and PPS treatment



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Clinical Trials

- MPS I ERT (adult) trial : October 2014, Mainz, Germany
  - 6 months, subcutaneous
  - Safety + Efficacy
- MPS II ERT (adult) trial: September 2014, Gifu, Japan
  - 6 months, subcutaneous
  - Safety + Efficacy
- MPS I HSCT (pediatric) trial: March 2015 – Europe
- MPS I ERT (pediatric) trial: 2015 – Europe
- Also planned:
  - Fabry study
  - MPS VI study

Köszönöm a figyelmet!

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