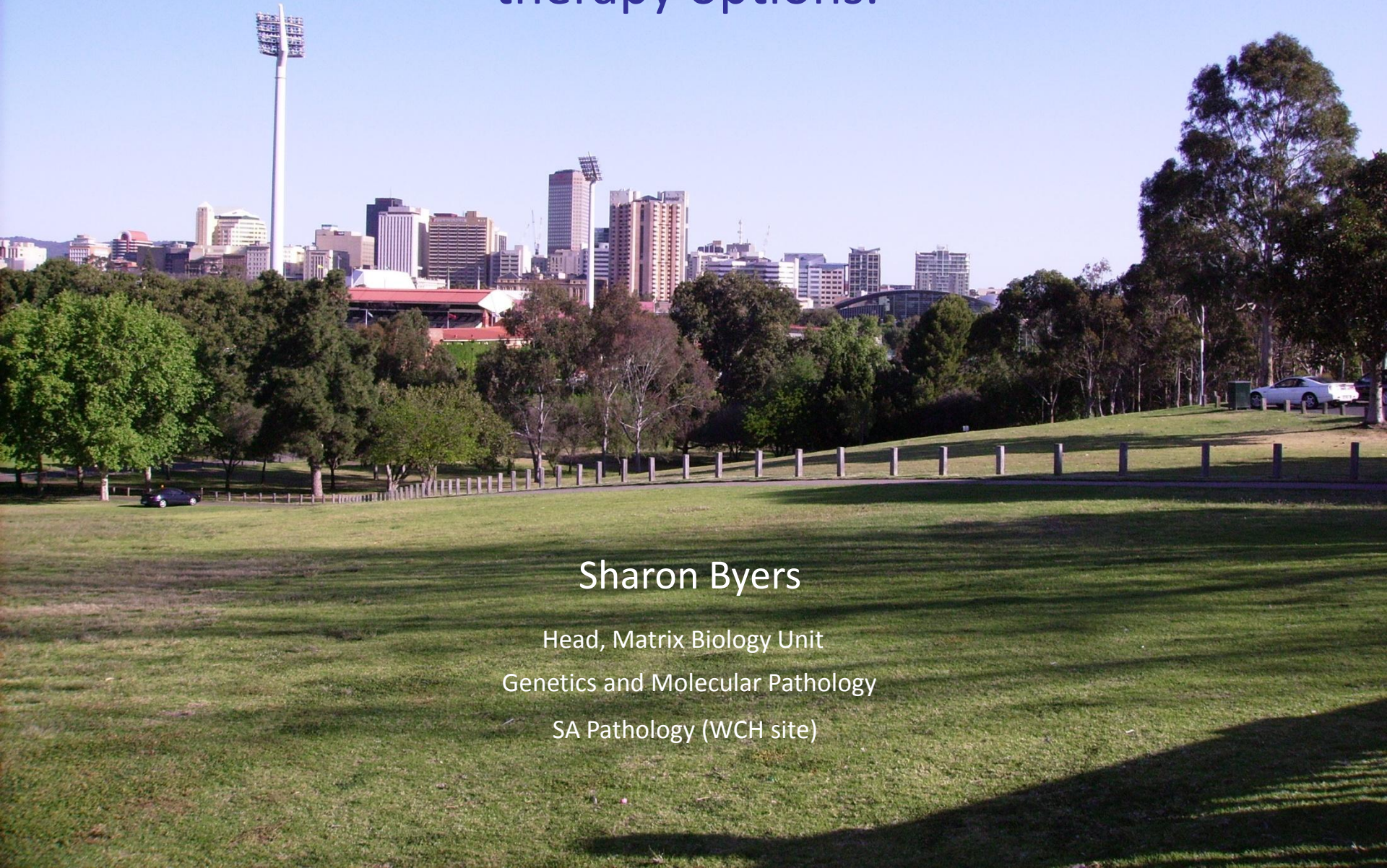


Bone disease in MPS children – current and potential therapy options.



Sharon Byers

Head, Matrix Biology Unit
Genetics and Molecular Pathology
SA Pathology (WCH site)

Mucopolysaccharidosis (MPS)



Charles Hunter

a lysosomal storage disorder

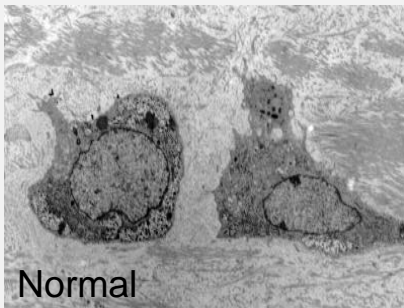
↓ enzyme required for the degradation of glycosaminoglycans

11 known disorders

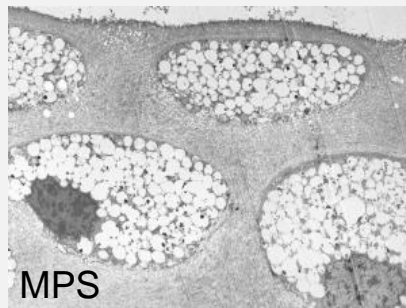
wide range of tissues affected

pathology not always apparent at birth

pathology is progressive



Normal



MPS

characteristic foamy appearance on EM

MPS disorders

| MPS | ENZYME DEFICIENCY | STORED GAG | PATHOLOGY |
|------|--|------------|---------------|
| I | α -L-iduronidase | HS, DS | CNS, skeleton |
| II | iduronate-2-sulphatase | HS, DS | CNS, skeleton |
| IIIA | sulphamidase | HS | CNS |
| IIIB | α -N-acetylglucosaminidase | HS | CNS |
| IIIC | acetyl-CoA: α -glucosamide N-acetyltransferase | HS | CNS |
| IIID | glucosamine-6-sulphatase | HS | CNS |
| IVA | galactose-6-sulphatase | KS | skeleton |
| IVB | β -D-galactosidase | KS | skeleton |
| VI | N-acetylgalactosamine-4-sulphatase | DS | skeleton |
| VII | β -D-glucuronidase | HS, DS, CS | CNS, skeleton |
| IX | hyaluronidase | HA | skeleton |

HS = heparan sulphate

CS = chondroitin sulphate

HA = hyaluronan

DS = dermatan sulphate

KS = keratan sulphate

Development of pathology in MPS VI



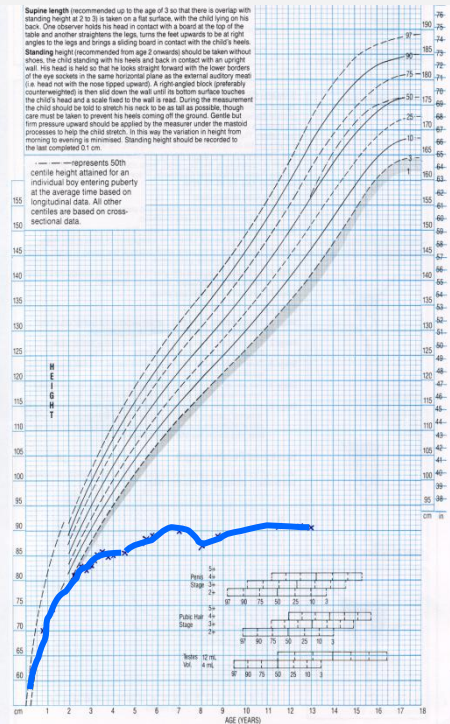
1 yr



10 yrs



16 yrs



Current therapies

- palliative care
- BMT for young (< 1yr) MPS I patients with CNS involvement
- enzyme replacement therapy (ERT) clinically available
 - MPS I in 2003
 - MPS VI in 2005
 - MPS II in 2006
- ERT very effective – gag storage is reduced in liver, spleen, kidney, lung etc
- ERT is expensive - >\$USD 350,000 per patient per year
- mixed response by bone to ERT
 - *“patients continued to experience decline in musculoskeletal and spinal involvement”* Thomas (2006): *J Inherit. Metab. Dis.* 29:762.
 - *“substantial growth was observed for the pre-pubertal patients (27% gain in height)”* Sifuentes (2007): *Molec. Genet. Metab.* 90:171.
 - *“there does not seem to be an obvious trend of increase or decrease in height ..
.....regardless of the age at which ERT was started”* Arora (2007): *J Inherit. Metab. Dis.* 30:821.
- cartilage does not respond to ERT
- “progression of degenerative joint disease is unchanged”



MPS VI cat

- naturally occurring feline model of MPS VI
- similar pathology to human MPS VI
 - severe bone disease
 - enlarged liver and spleen
 - corneal clouding
 - lysosomal storage in most soft connective tissues eg heart, lung, liver, kidney, hip capsule



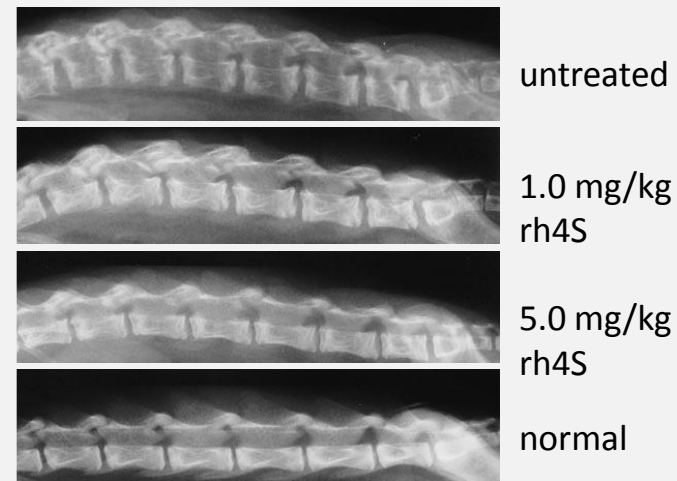
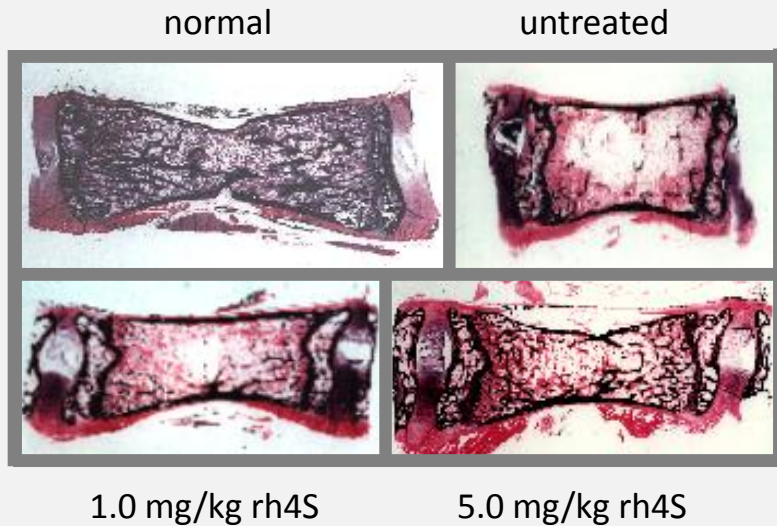
bone response to ERT is dose dependent



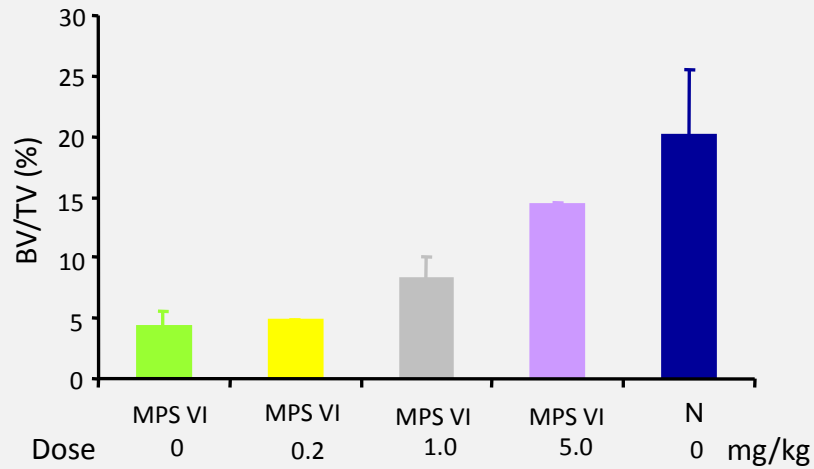
MPS VI

MPS VI treated

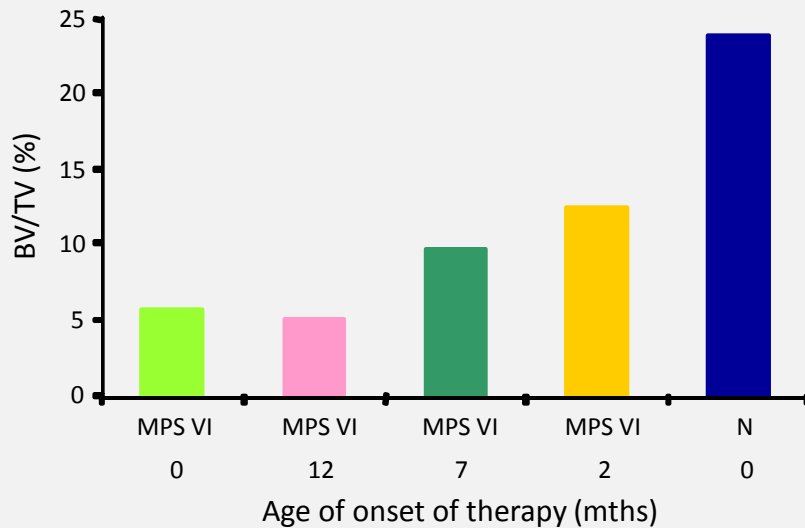
Normal



Crawley et al (1997): *J. Clin. Invest.* 99: 651-662.
Byers et al (1997): *Bone* 1: 425-431.



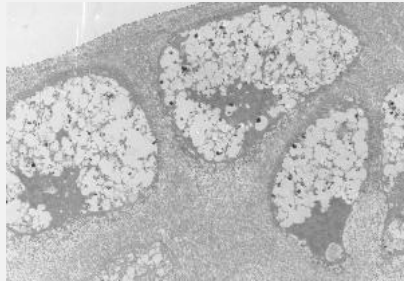
- the most effective dose for bone is higher than that required for most other tissues



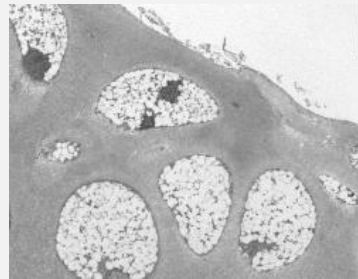
- early initiation of therapy is crucial for optimal bone response

Crawley et al (1997): J. Clin. Invest. 99: 651-662.
 Byers et al (1997): Bone 1: 425-431.

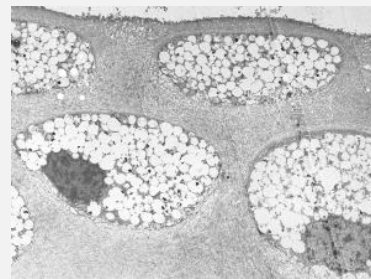
- cartilage does not respond to intravenous ERT at any dose
- progression of degenerative joint disease unchanged



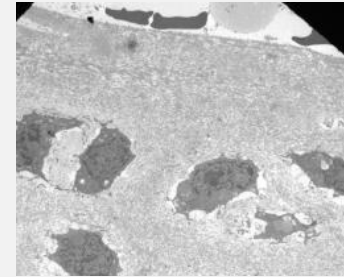
untreated



1.0 mg/kg

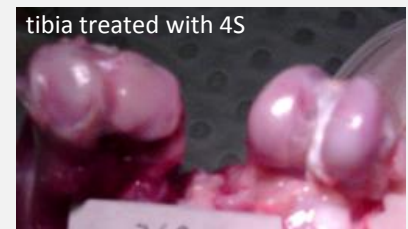


5.0 mg/kg



intra-articular
ERT

- cartilage does respond to localised ERT in the joint
- progression of degenerative joint disease is slowed

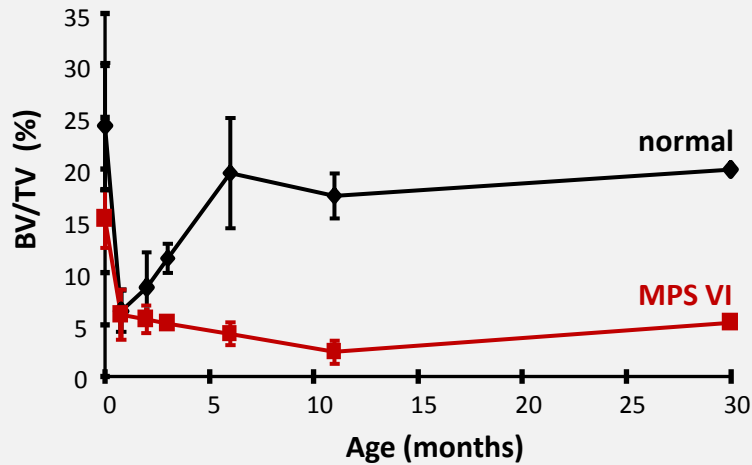


inj every month

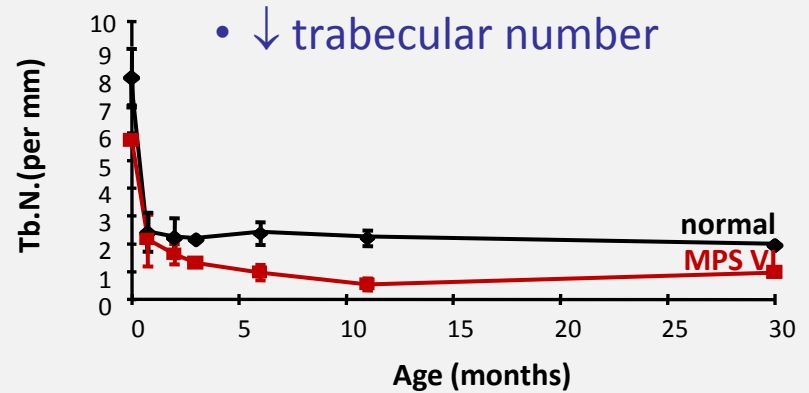
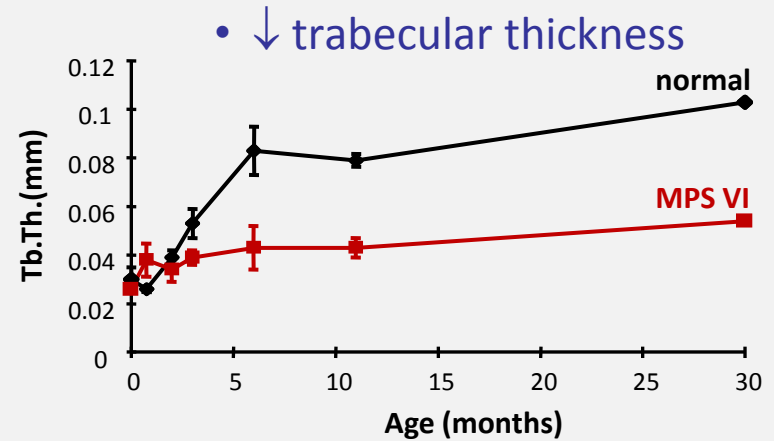
Auclair et al (2006): *Pediatr. Res.* 59: 538-543.

Auclair et al (2007): *Molec. Genet. Metab.* . 91: 352-361.

bone mass is reduced in MPS VI

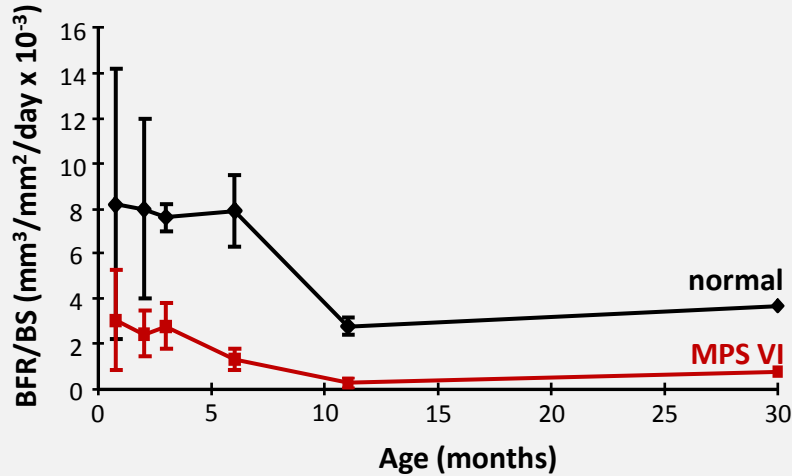


- bone mineral volume falls within the normal range at birth
- ↓ bone mass with age

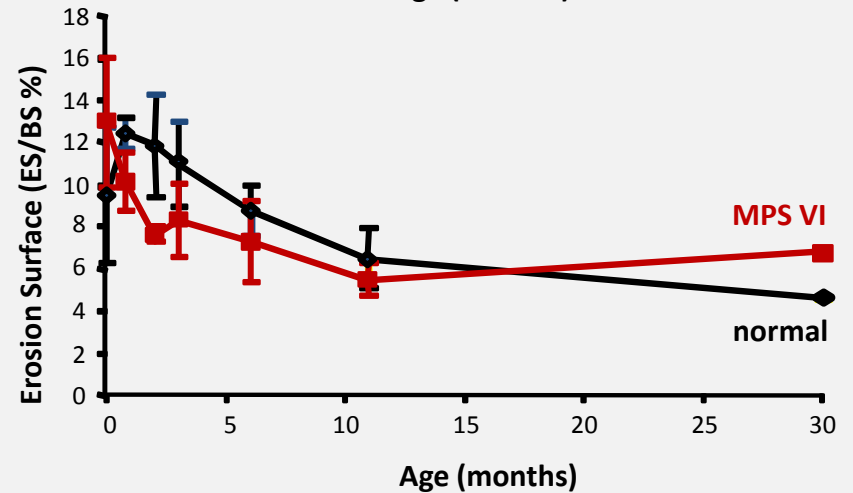
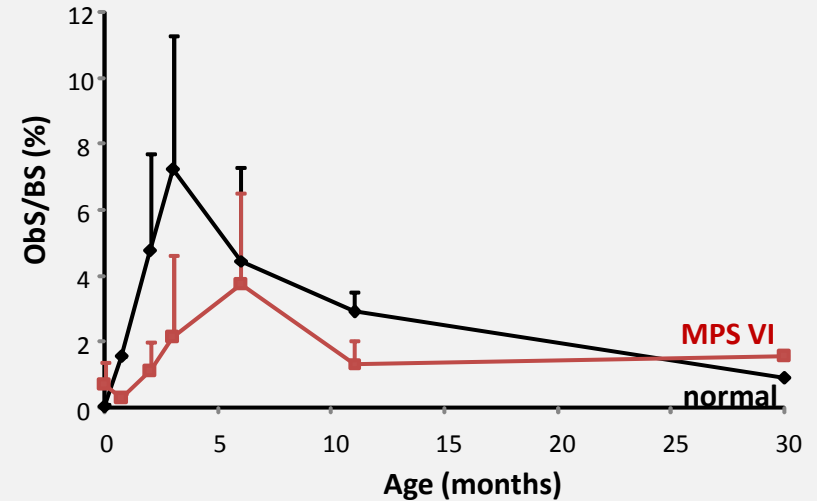


bone formation is reduced in MPS VI

- ↓ osteoblast number at early ages

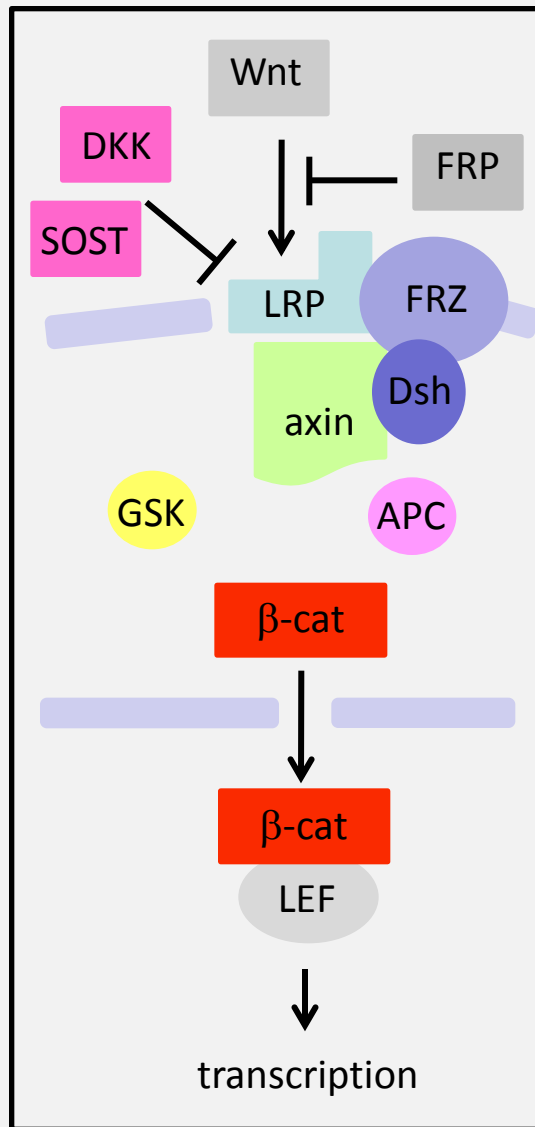


- ↓ bone formation rate in MPS VI
- (mineral apposition rate is normal)



- no change in resorption observed

Wnt signalling pathway is suppressed in MPS VI



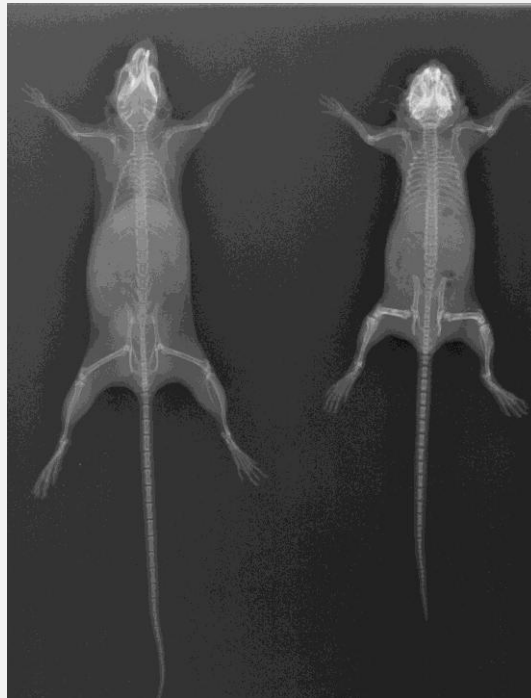
- ↓ co-receptors Frz, LRP5/6
- ↓ DSH
- ↑ FRP

- osteoblasts isolated from normal and MPS VI bone
- affimetrix 1.0 ST human gene array

MPS VII mouse

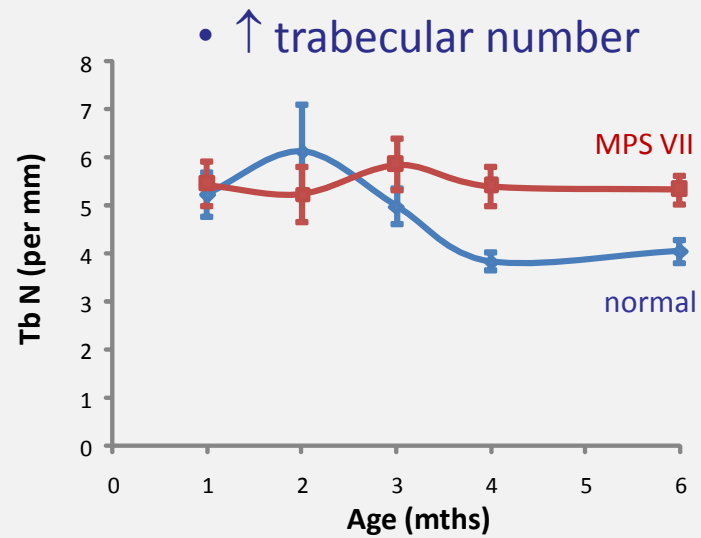
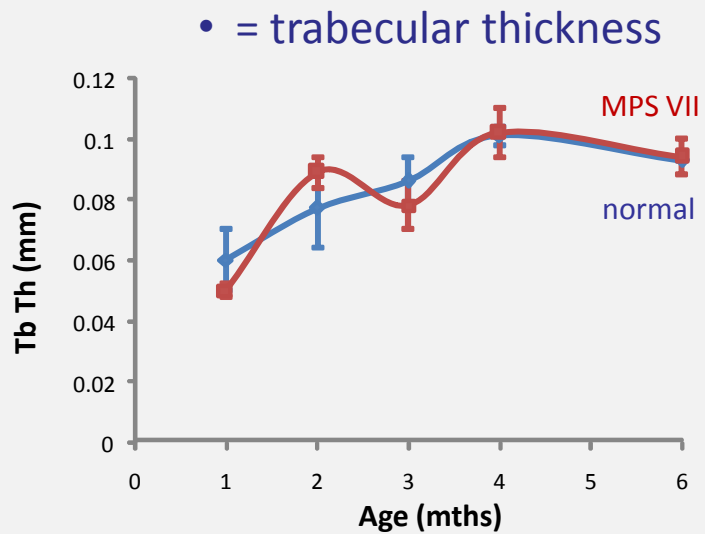
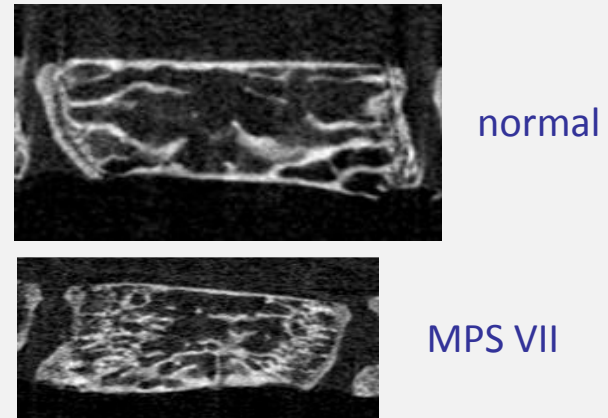
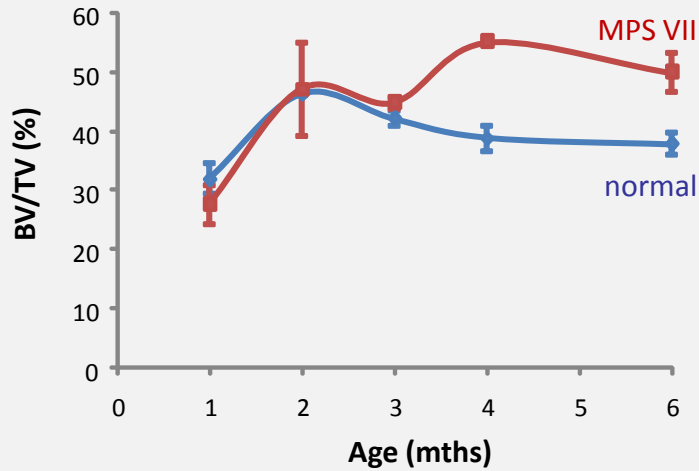


- naturally occurring murine model of MPS VII
- similar pathology to human MPS VII
 - severe bone disease
 - CNS deterioration
 - lysosomal storage in most soft connective tissues eg heart, lung, liver, kidney



MPS VII mouse on left
3mths old

bone mass is increased in MPS VII



summary

- bone responds well to replacement enzyme but is dependent on
 - dose
 - age at which therapy is initiated
- current ERT doses are suboptimal for bone response
- cartilage is unresponsive to intravenous ERT

MPS VI

- ↓ bone mass due to loss of trabeculae number and ↓ thickness
 - ↓ bone formation rate
 - ↓ osteoblast number
 - suppression of the Wnt signalling pathway
- no apparent defect in erosion
- ↓ bone deposition leading to an incremental loss of bone with each (re)modeling cycle

MPS VII

- ↑ bone mass due to persistence of ↑ number of trabeculae
- mechanism unknown
 - ↑ bone formation ??
 - ↓ osteoclast formation and/or function ??

conclusions

- need to target therapies towards bone and cartilage separately
- combination therapies may be more effective
 - ERT + substrate deprivation therapy
 - iv ERT + intra-articular ERT or gene therapy
 - ERT + supplemental therapies
- therapy must start early in life before irreversible pathology develops

- pathogenesis of bone disease differs between MPS types necessitating different approaches to treatment

MPS VI

- enhance osteoblast proliferation and function
- inhibit osteoclast function

MPS VII

- promote osteoclast formation/function ??
- suppress bone formation ??

Acknowledgements



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