

Galápagos



GLPG1972: a potent, selective, orally bioavailable ADAMTS-5 inhibitor for the treatment of OA

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ADAMTS-5 a promising therapeutic target in OA

- ADAMTS-5 plays a key role in aggrecan degradation
- Target validated in human OA cartilage explants (Song - 2007)
- In the DMM model *adams-5^{-/-}* mice showed protection from cartilage degradation and mechanical allodynia (Glasson - 2005 and Malfait - 2010)
- Mice treated with an ADAMTS-5 mAb had attenuated joint damage and were protected from mechanical allodynia (Miller – 2016)
- ARGS levels increased in human knee synovial fluid after joint injuries and in OA (Larsson – 2009)

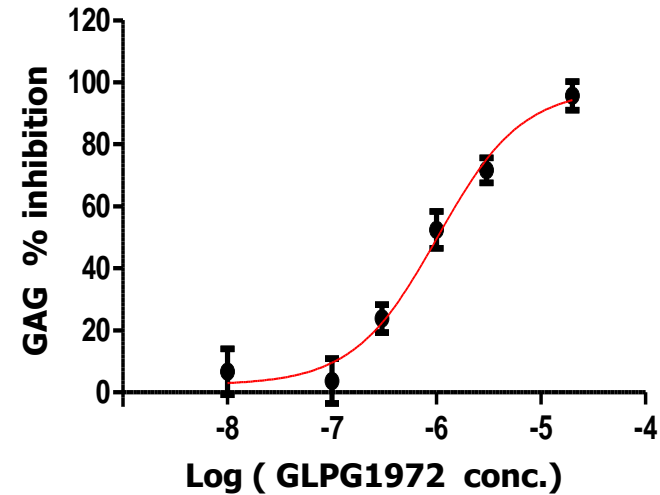
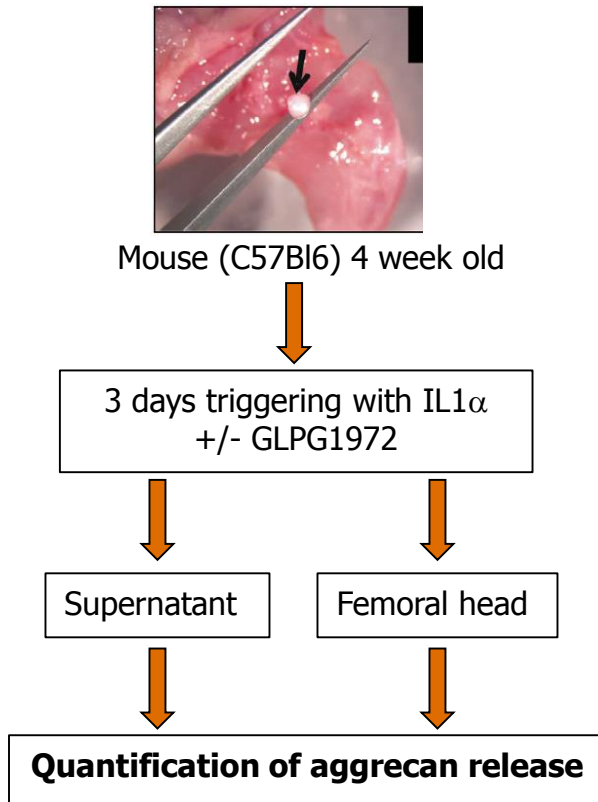


High potency and anti-catabolic activity *in vitro*

	GLPG1972 IC ₅₀ range (nM)
h-ADAMTS-5 potency	<25
r-ADAMTS-5 potency	<25
h-ADAMTS-5 (Aggrecan-ELISA)	<70
GAG release inhibition in mouse cartilage explants	<1,500
AGNx1 release inhibition in human cartilage explants	<1,000

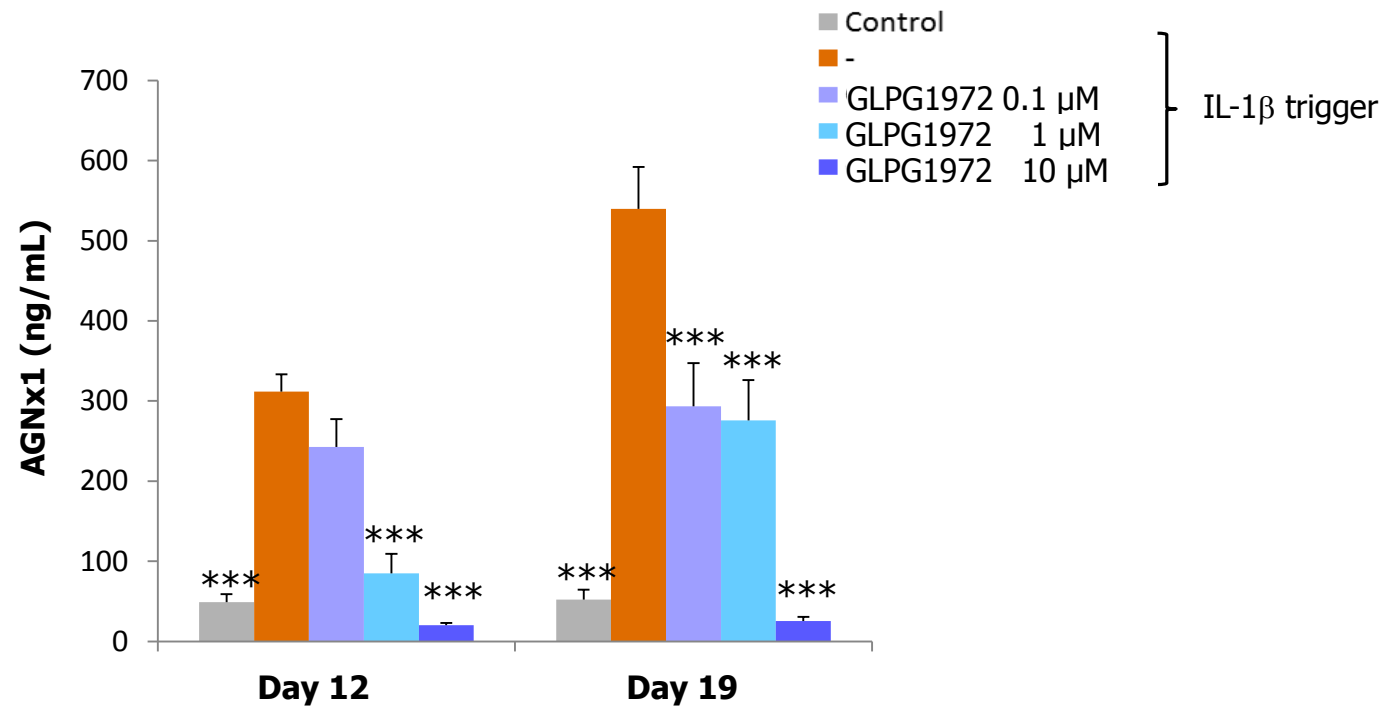
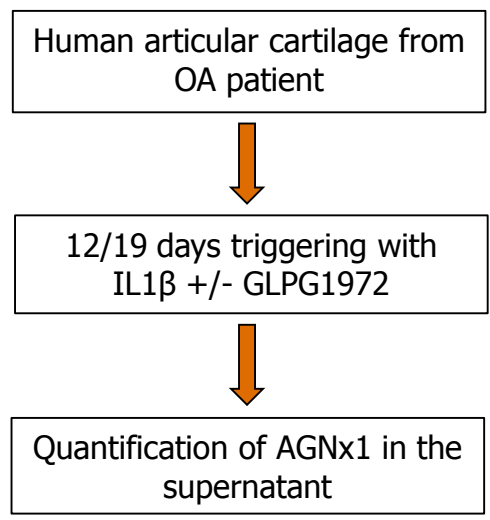


Mouse cartilage explants: $IC_{50} < 1.5 \mu M$





Human cartilage explants: $IC_{50} < 1\mu M$





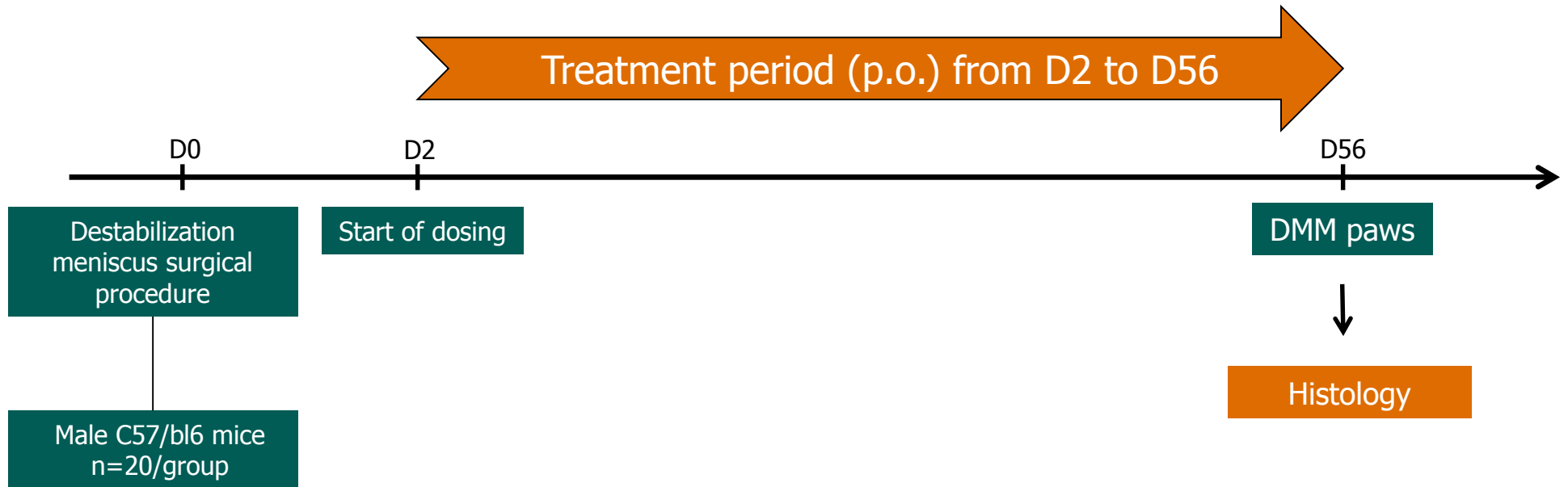
High *in vitro* selectivity vs. other metalloproteinases

Target	Selectivity (fold)
ADAMTS-5	-
ADAMTS-4	> 5
ADAMTS-1	>150
ADAMTS-13	> 5,000
ADAM17 (TACE)	> 1,000
MMP-1	> 1,500
MMP-2	> 50
MMP-7	> 1,500
MMP-9	> 500
MMP-13	> 1,000
MMP-14	> 150



GLPG1972 in mouse DMM model

Experimental design

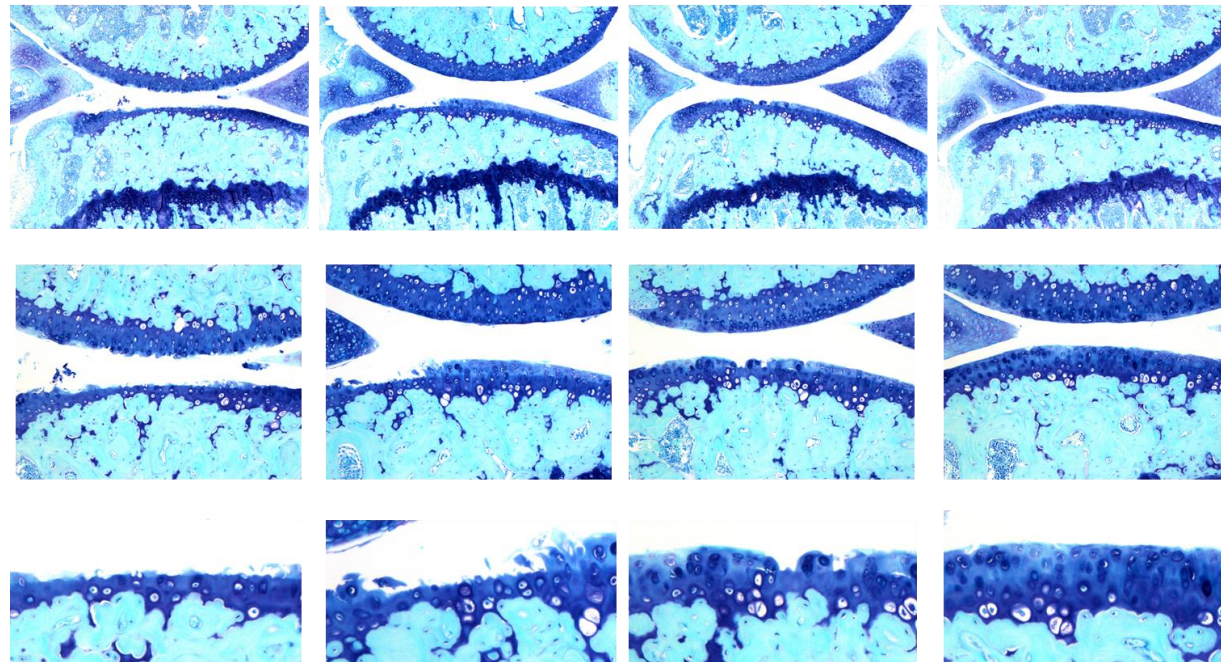


Mouse model of destabilization of the medial meniscus adapted from:
Glasson *et al.*, Osteoarthritis Cartilage, 2007



GLPG1972 in mouse DMM model

Representative images



Vehicle

**GLPG1972
30 mg/kg bid**

**GLPG1972
60 mg/kg bid**

**GLPG1972
120 mg/kg bid**

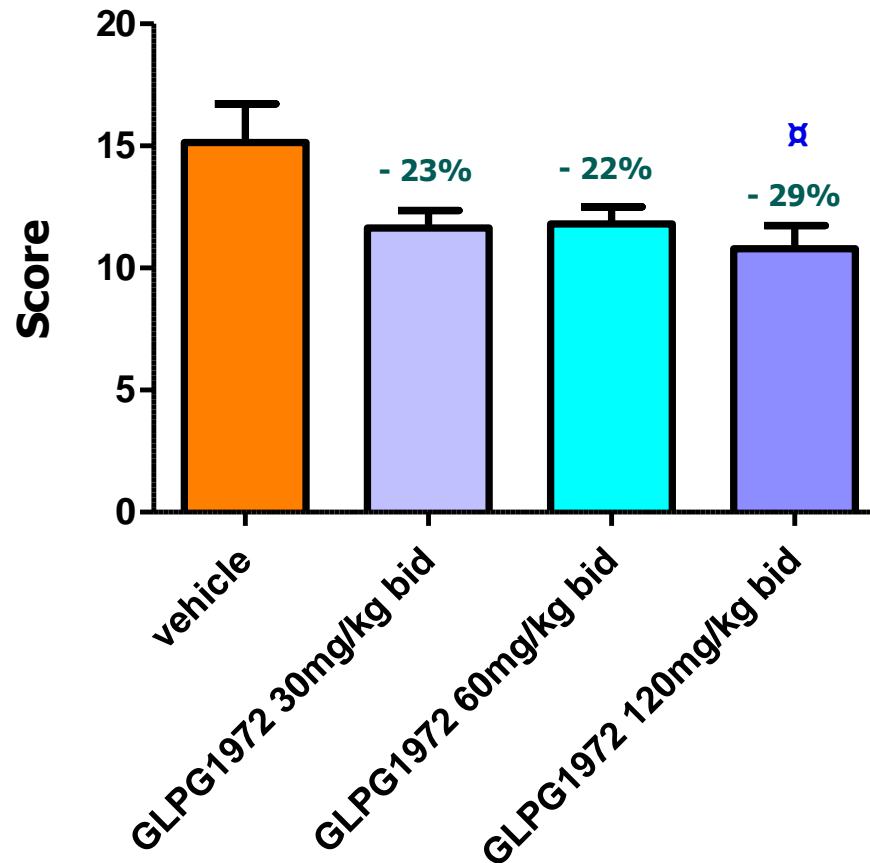
Scoring system modified from
Shu *et al.*, Arthritis Rheum. 2016



GLPG1972 in mouse DMM model

Reduction in proteoglycan loss

Articular Cartilage PG Cumulative Score

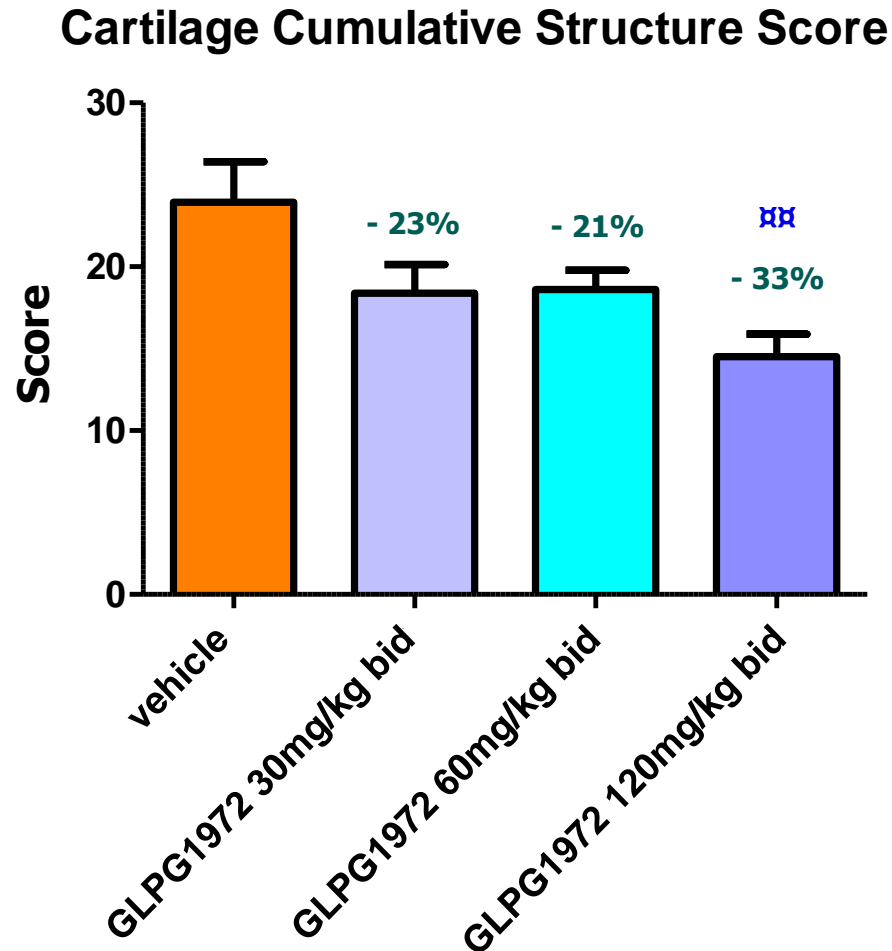


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GLPG1972 in mouse DMM model

Reduction in structural cartilage damage

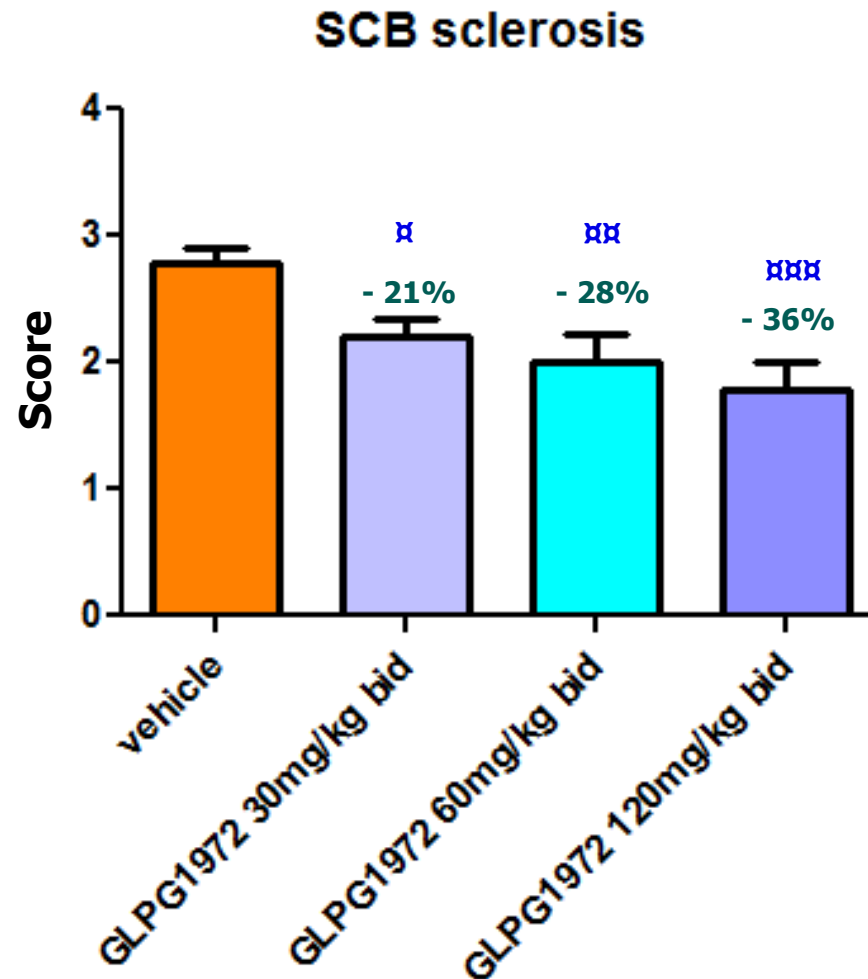


Scoring system modified from
Shu *et al.*, Arthritis Rheum. 2016



GLPG1972 in mouse DMM model

Reduction in subchondral tibia sclerosis



Scoring system modified from
Shu *et al.*, Arthritis Rheum. 2016



Conclusions

- `1972 is a potent and selective chondroprotective ADAMTS-5 inhibitor
- `1972 is orally available and showed a significant protective effect in the DMM model
- `1972 features a robust preclinical pharmacology package with good drugability characteristics

`1972 has been progressed to First-in-Human studies



Acknowledgements

Galápagos



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