GLPG1972 as a Disease Modifying Therapy for Osteoarthritis

Overview of Osteoarthritis (OA) and Clinical Opportunity for GLPG1972

- **No DMOAD approved**
- **GLPG1972 targets ADAMTS-5, aggrecanase, to reduce cartilage degradation**
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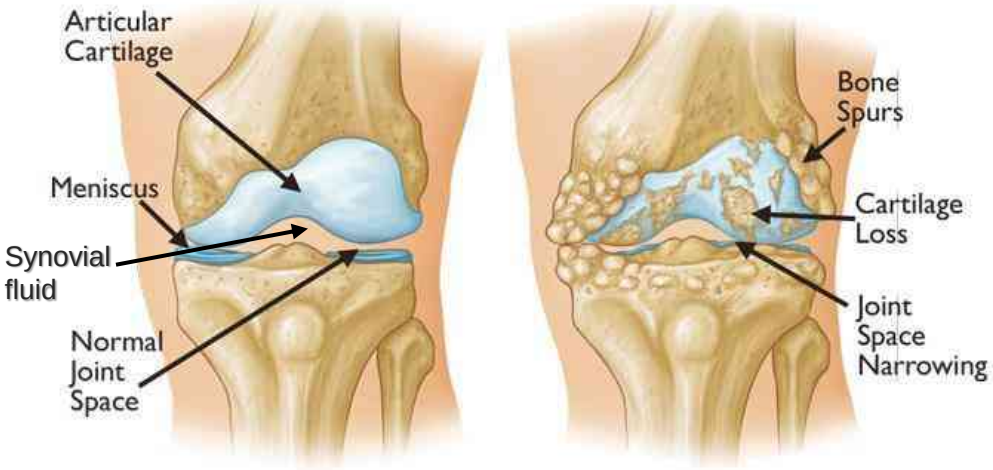

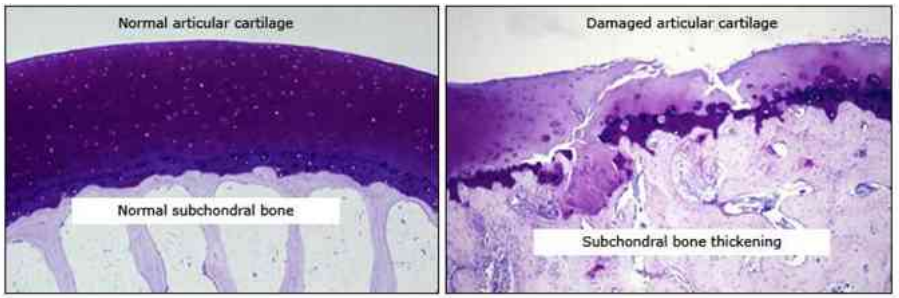

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Why Target ADAMTS5? It Cleaves Aggrecan and is Linked to Cartilage Degradation

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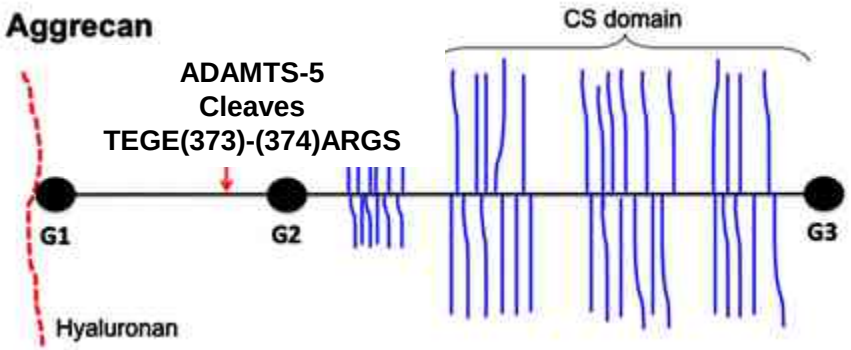

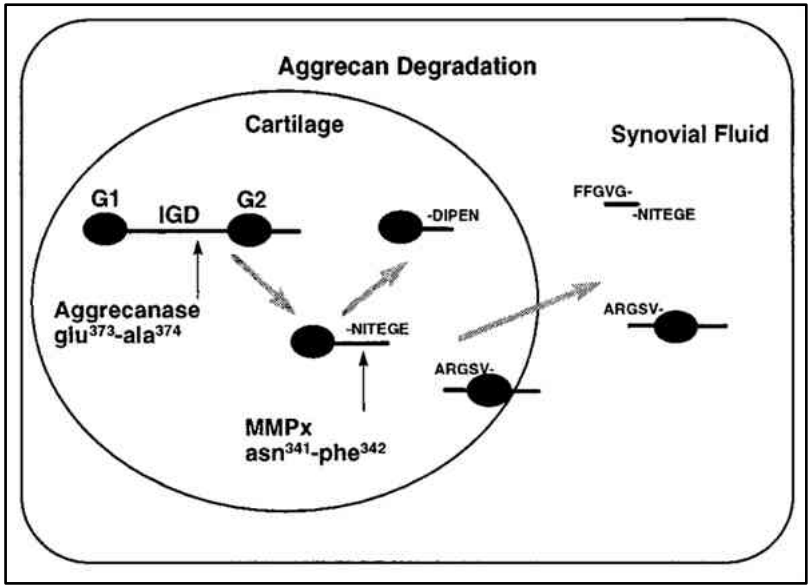

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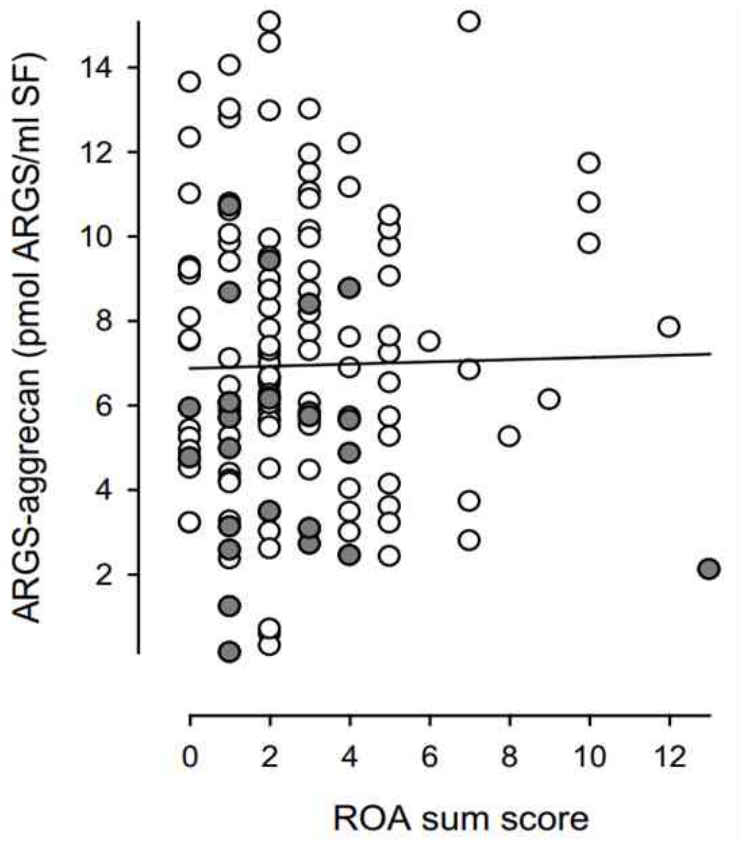

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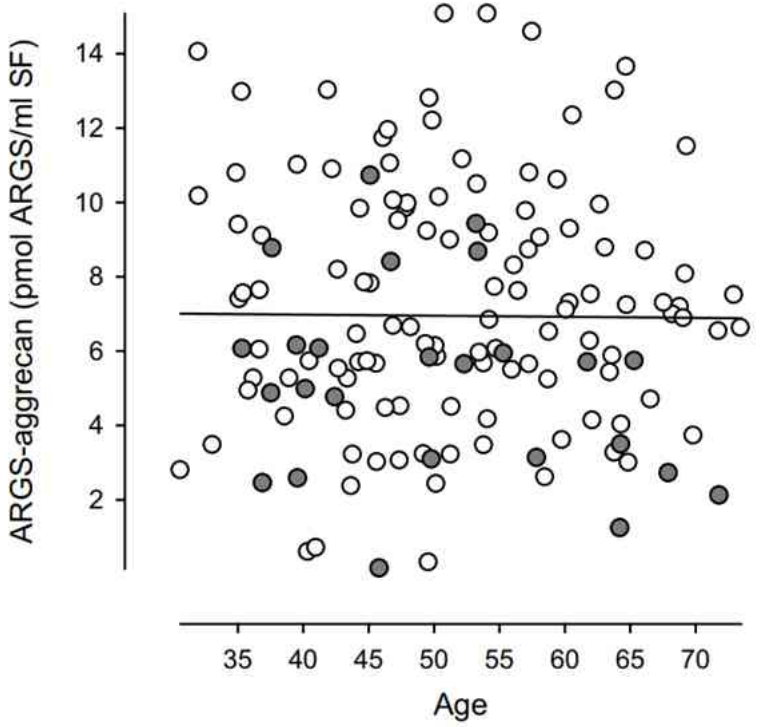

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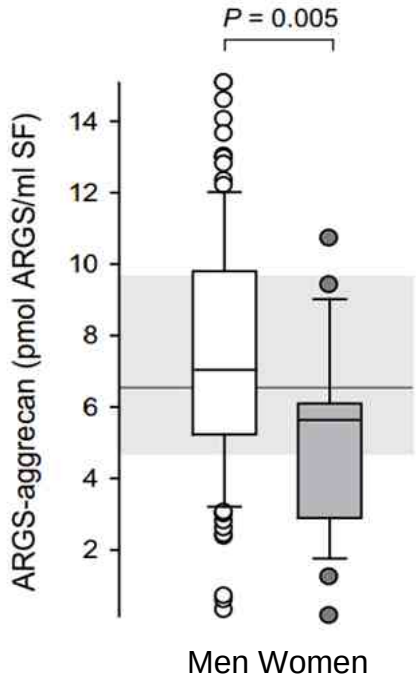
Men have higher amounts of ARGS, but women have a higher incidence of OA



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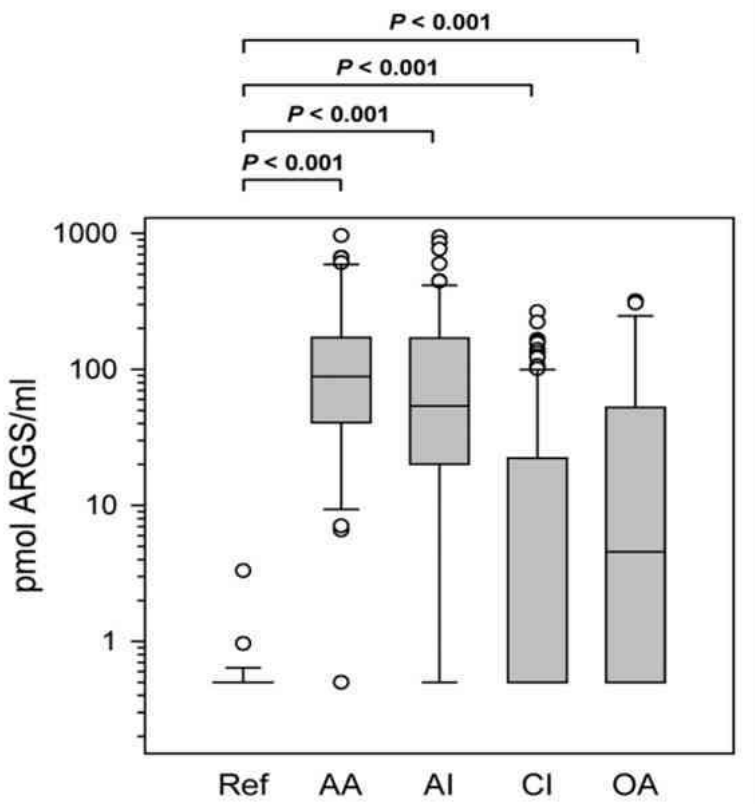

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Bottom line—Serum ARGS Might Not Be the Best Marker for OA

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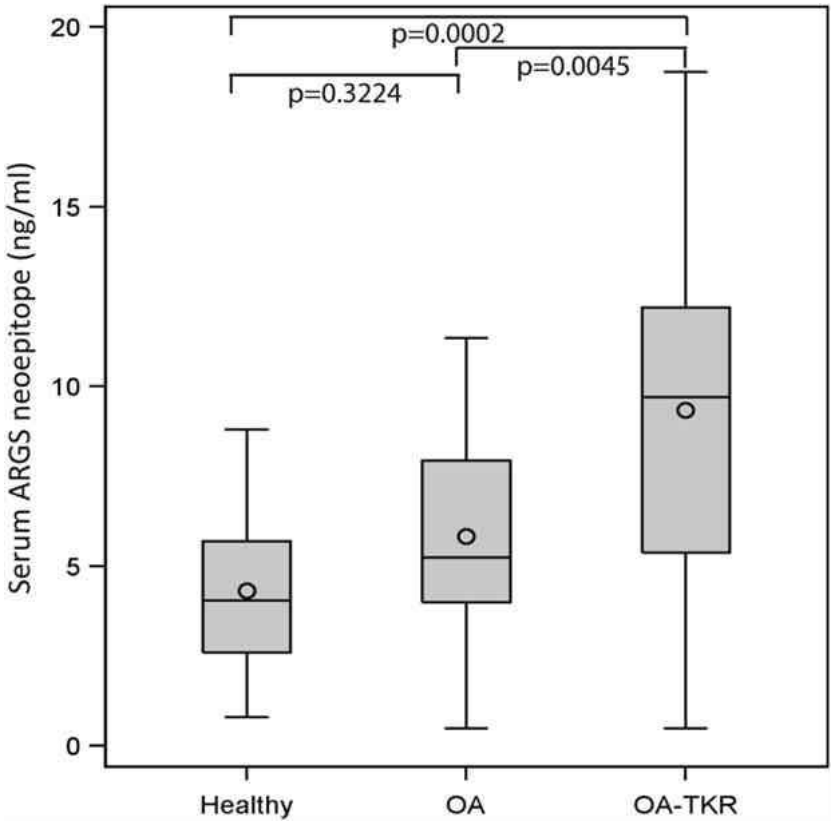

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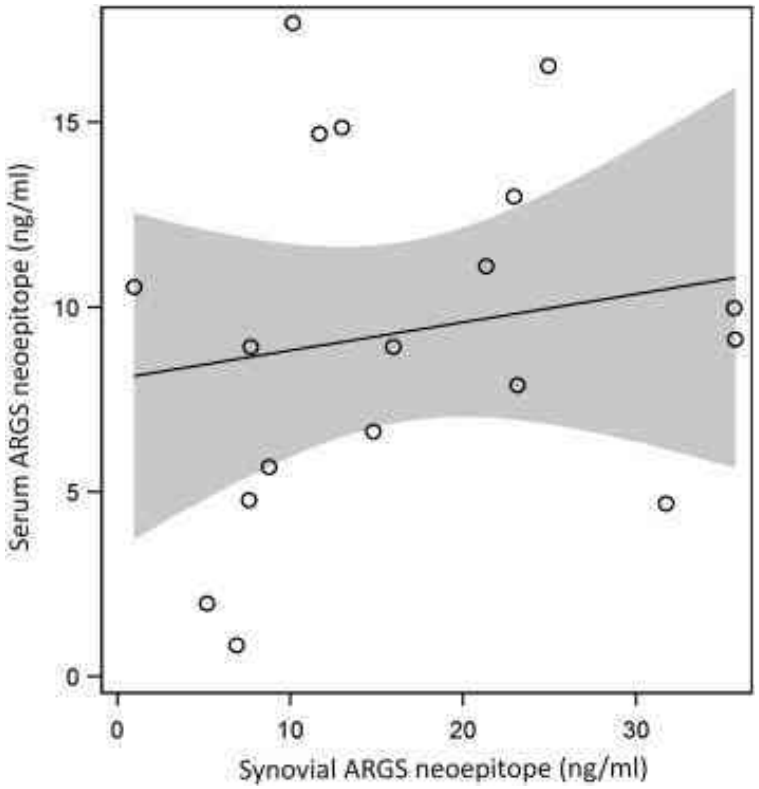

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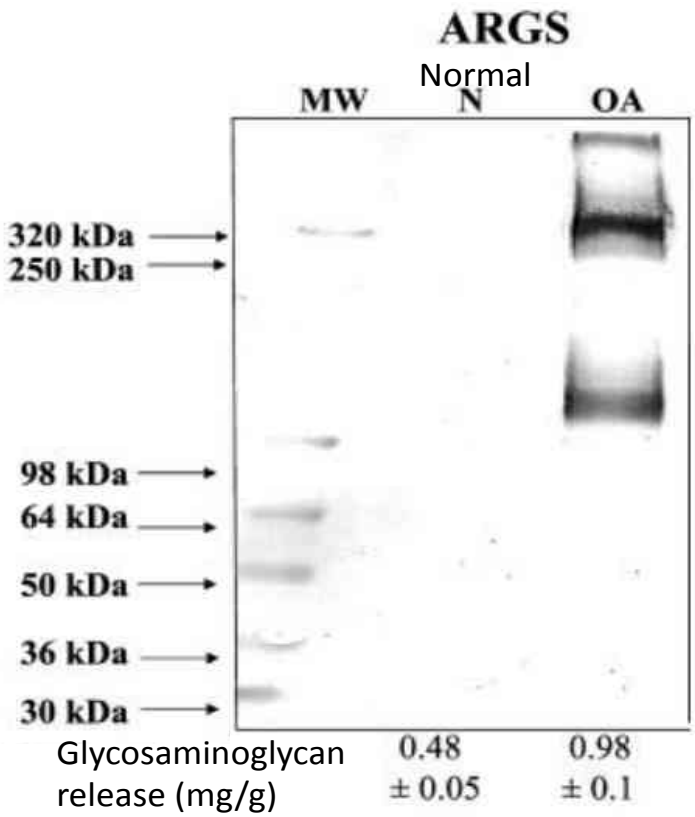

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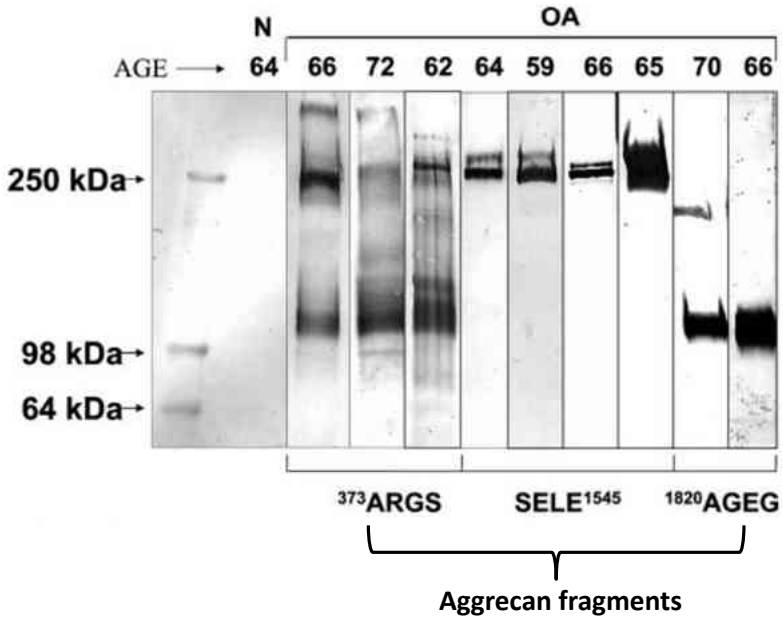

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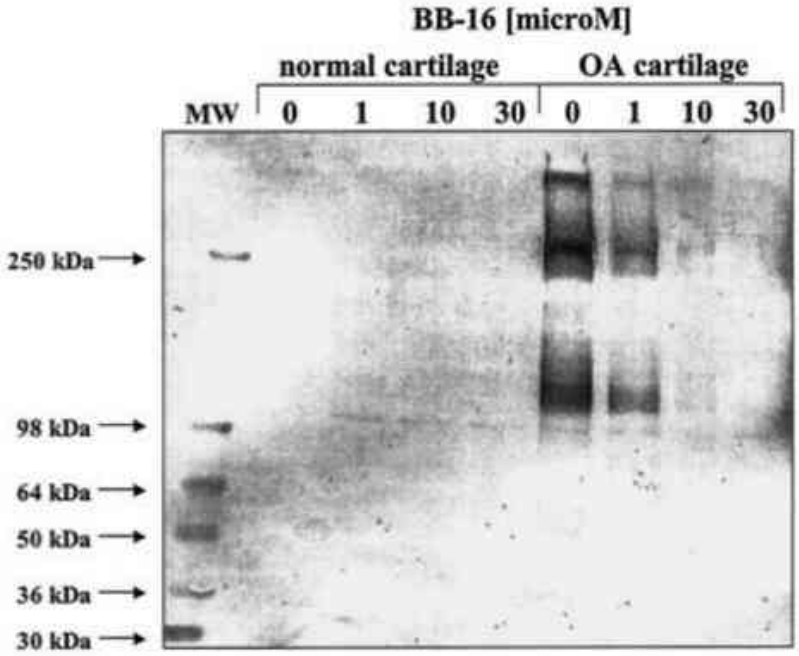

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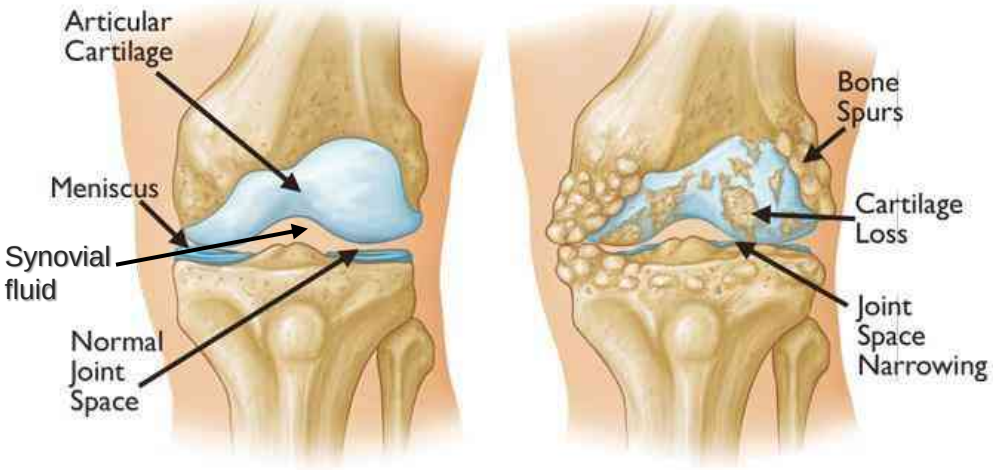

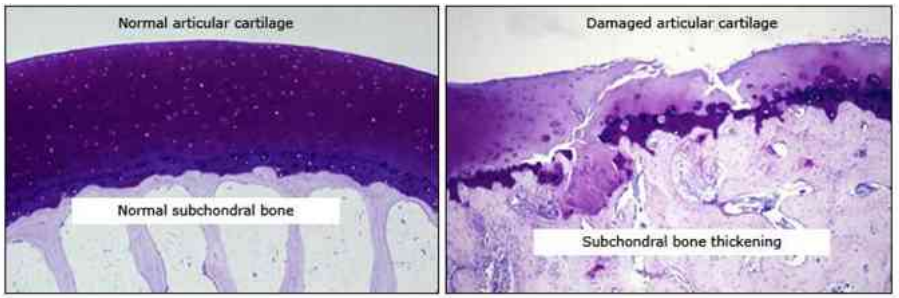

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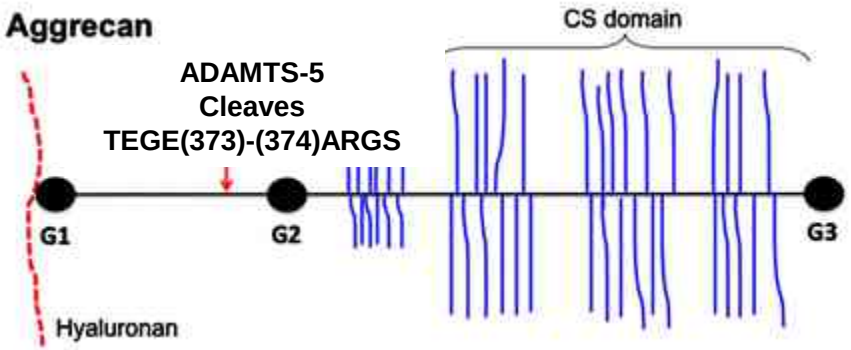

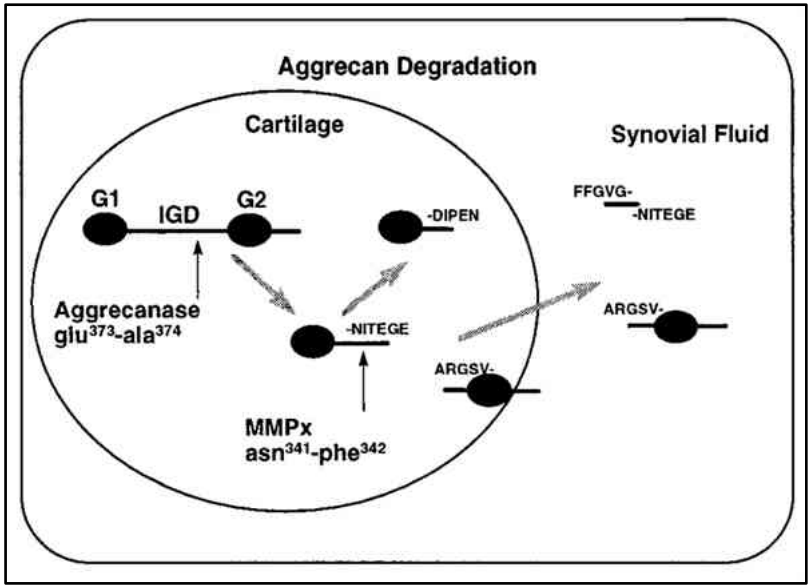

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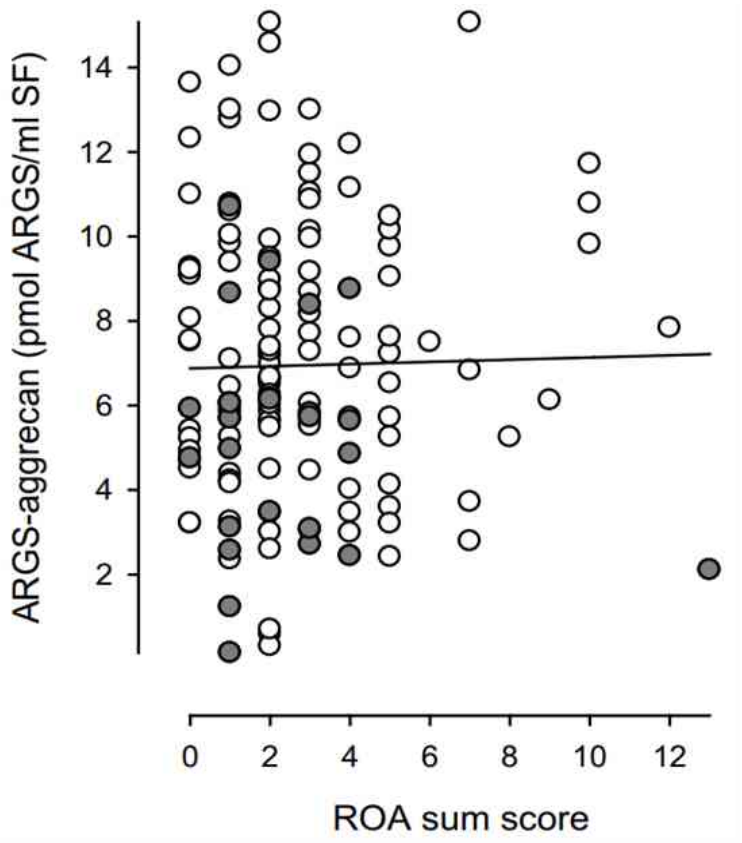

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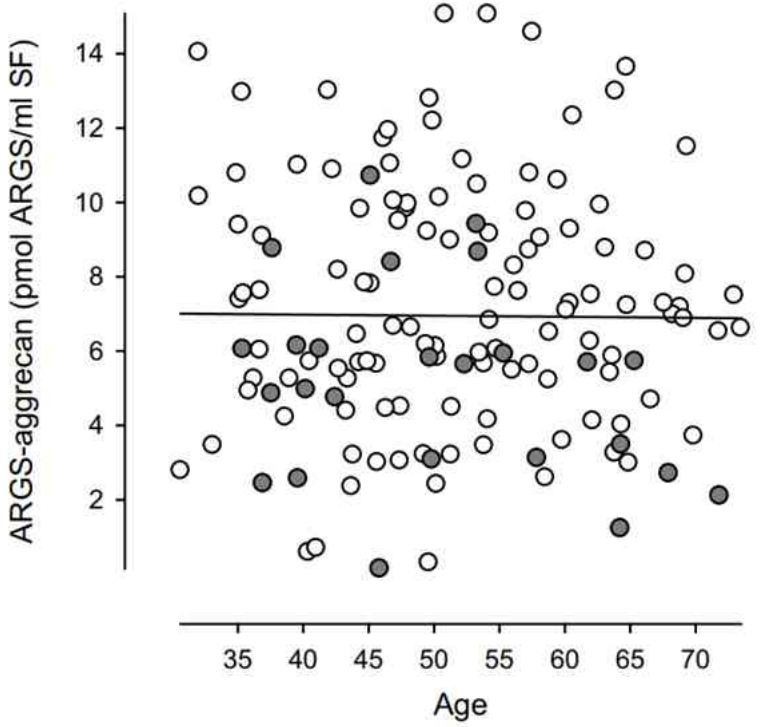

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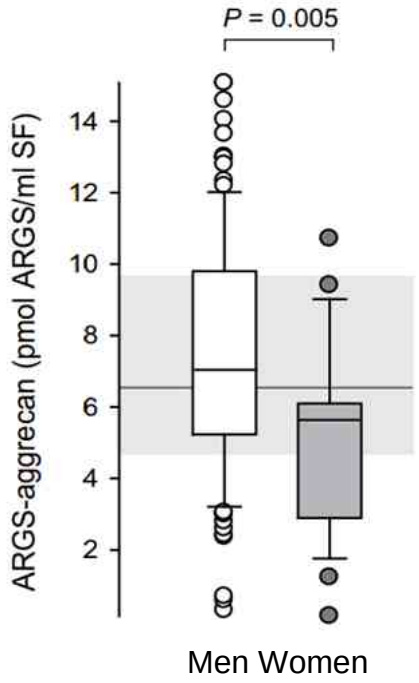

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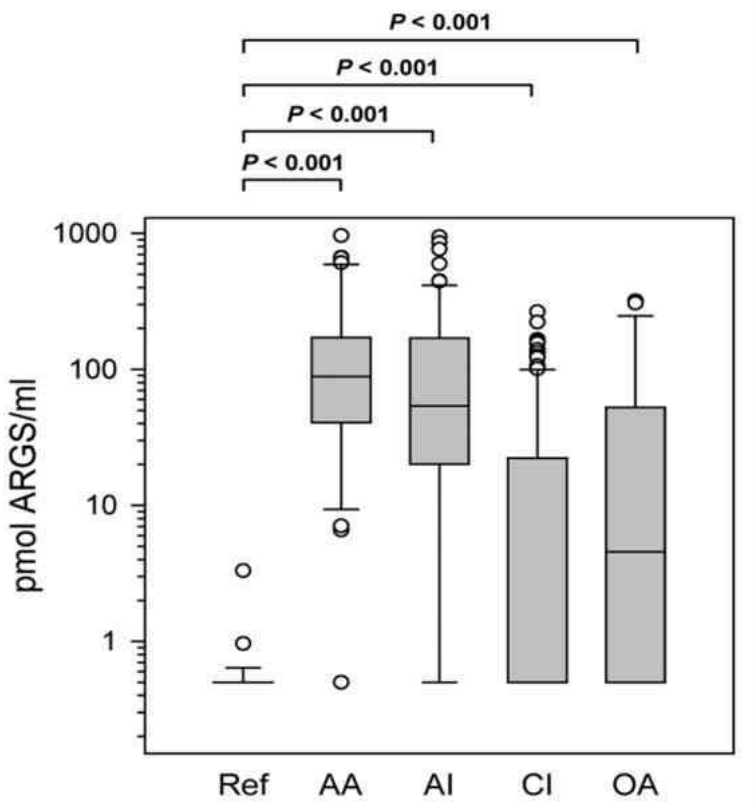

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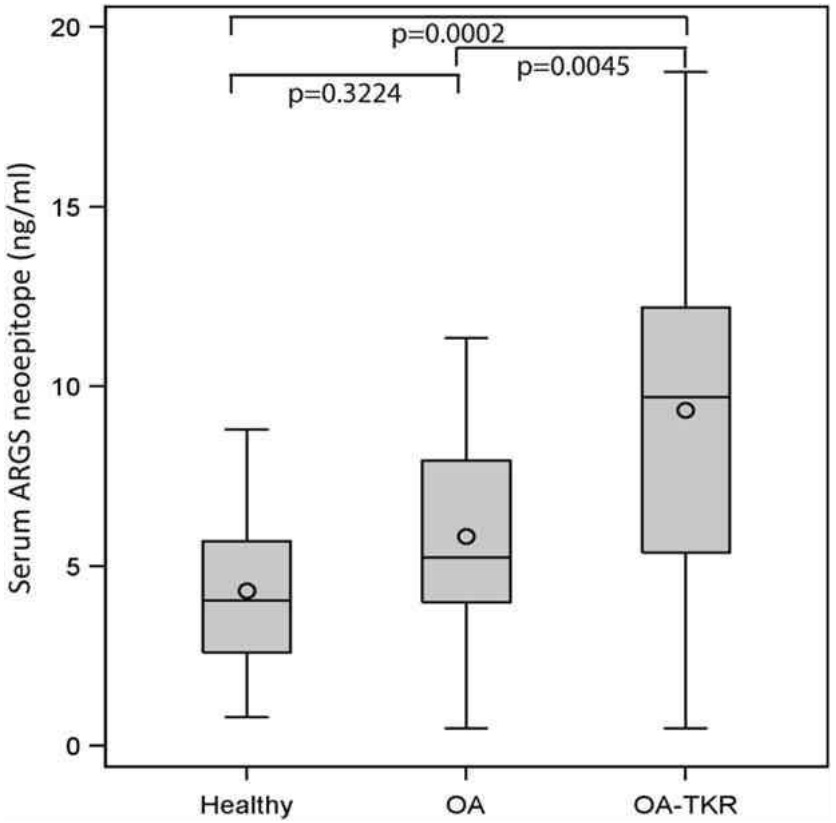

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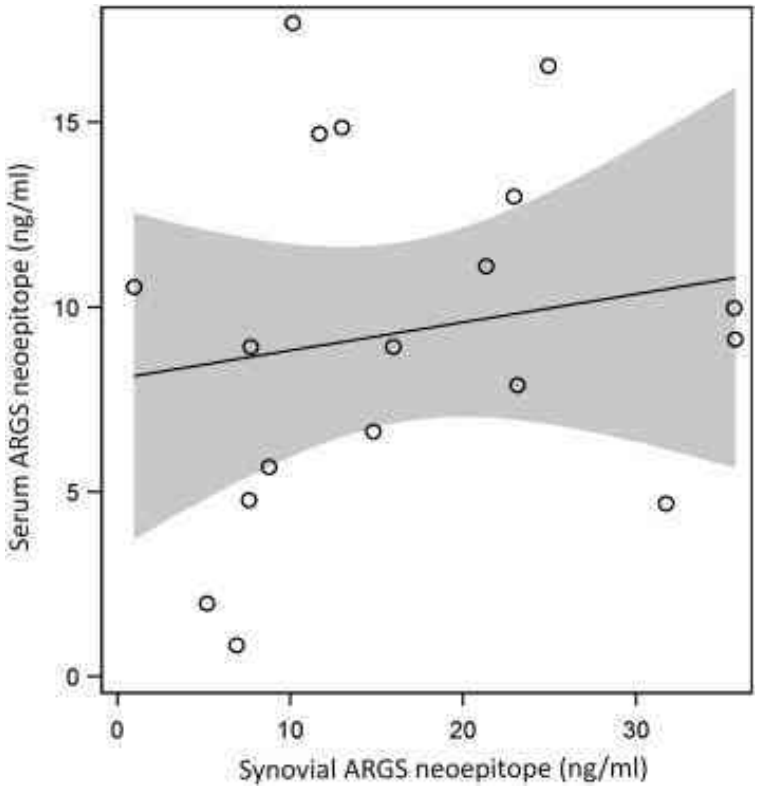

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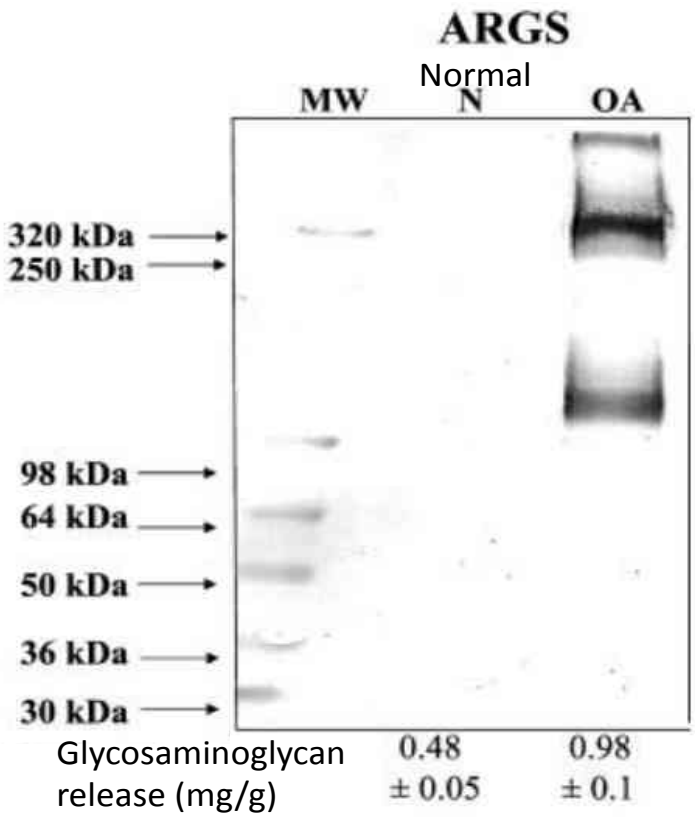

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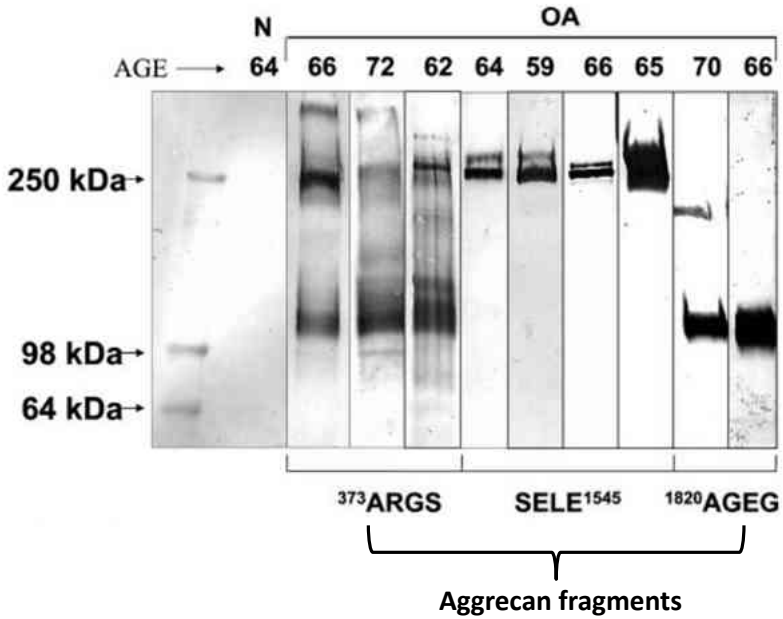

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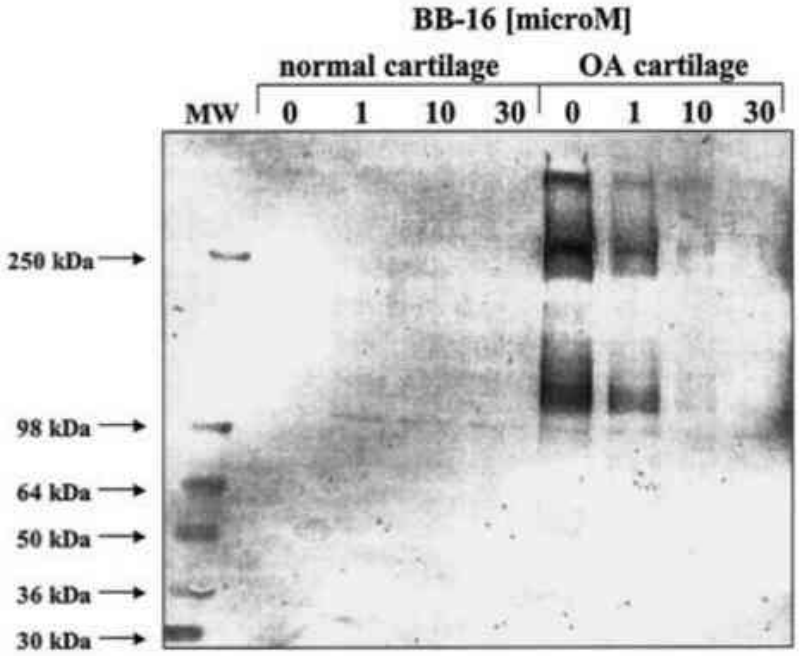

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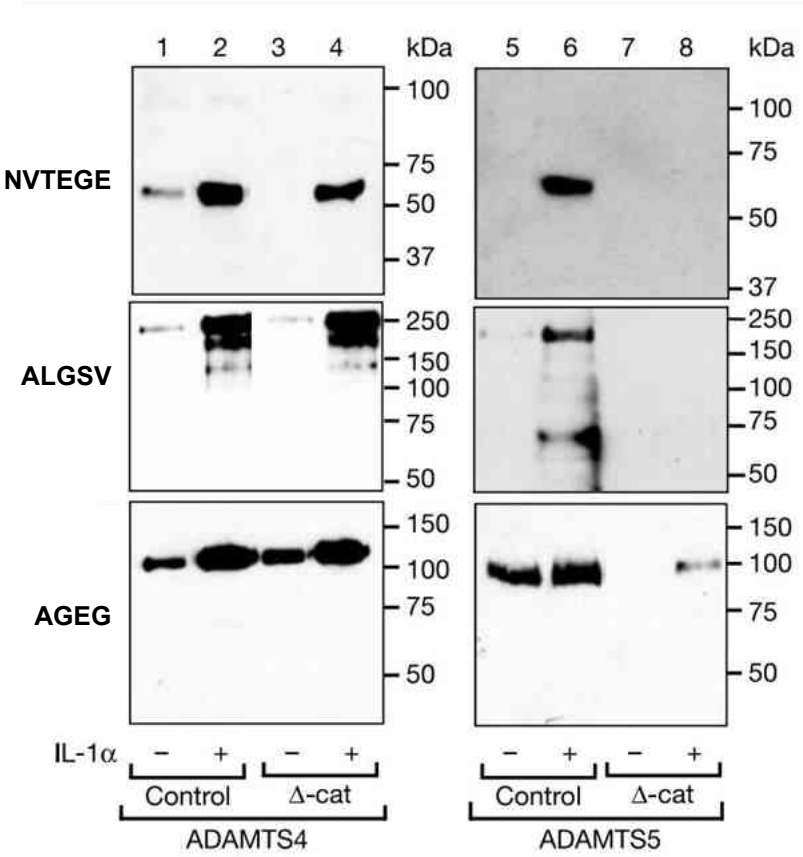
ADAMTS-5 Activity Is Required for Aggrecan Release in Mice

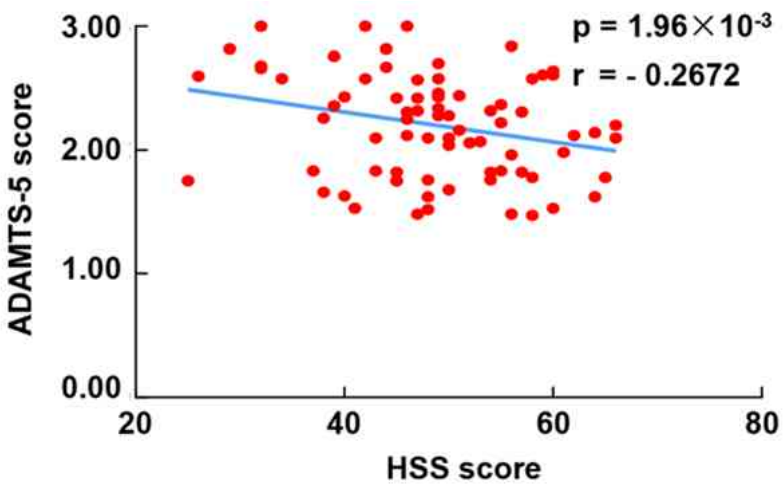
- **IL-1α stimulates mouse cartilage explants to release different aggrecan fragments**
- **Release dependent on ADAMTS5 catalytic activity**
- **However, the precise cytokine responsible for stimulating cartilage degradation in humans is unknown**



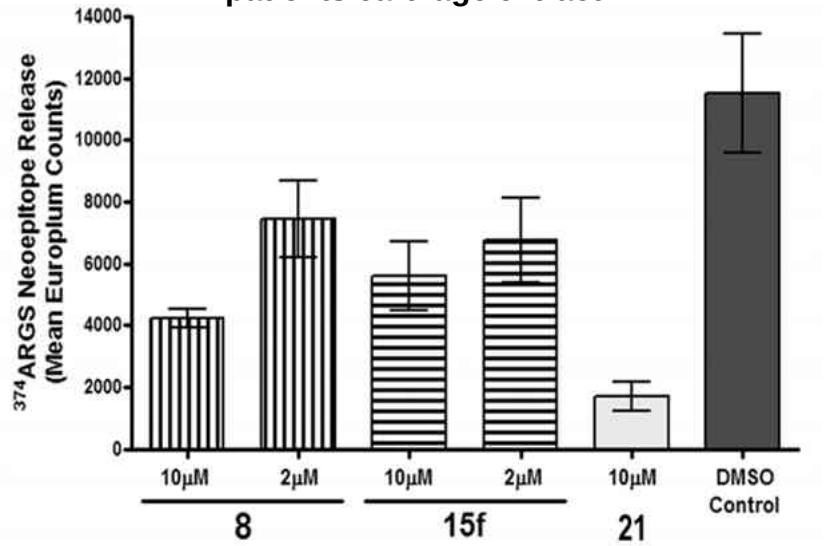
Source: Nature, 2005 (434) https://www.nature.com/articles/nature03417.

ADAMTS5 Expression and Inhibition Correlates With ARGS Activity—Bodes Well for GLPG1972

ADAMTS-5 expression is positively correlated with worse OA diagnosis



ADAMTS-5 inhibition reduces ARGS release in OA patients cartilage extract



Source: J Mol Med 2016 (94) DOI: 10.1007/s00109-016-1418-z and Journal of medicinal chemistry 2012 (55;16) DOI: 10.1021/jm300449x.

- **Compound 15f is a specific ADAMTS-5 (IC_{50}=30 nM) & ADAMTS-4 (IC_{50}=1300 nM) small molecule inhibitor developed by GSK**
- **15f inhibits ARGS release by 50% in a human OA cartilage explant**
- **Compound 21 is a non-specific MMP inhibitor reduces ARGS by 83%**
- **GLPG1972 has lower IC_{50}s**

Our Take—ADAMTS5 Inhibition With GLPG1972 Might Correlate With Disease Stabilization

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- **GLPG1972 has lower IC50s compared to the discontinued GSK effort, 15f**