New Mechanisms of Cartilage Degradation

A view from proteolytic enzymes and their regulation

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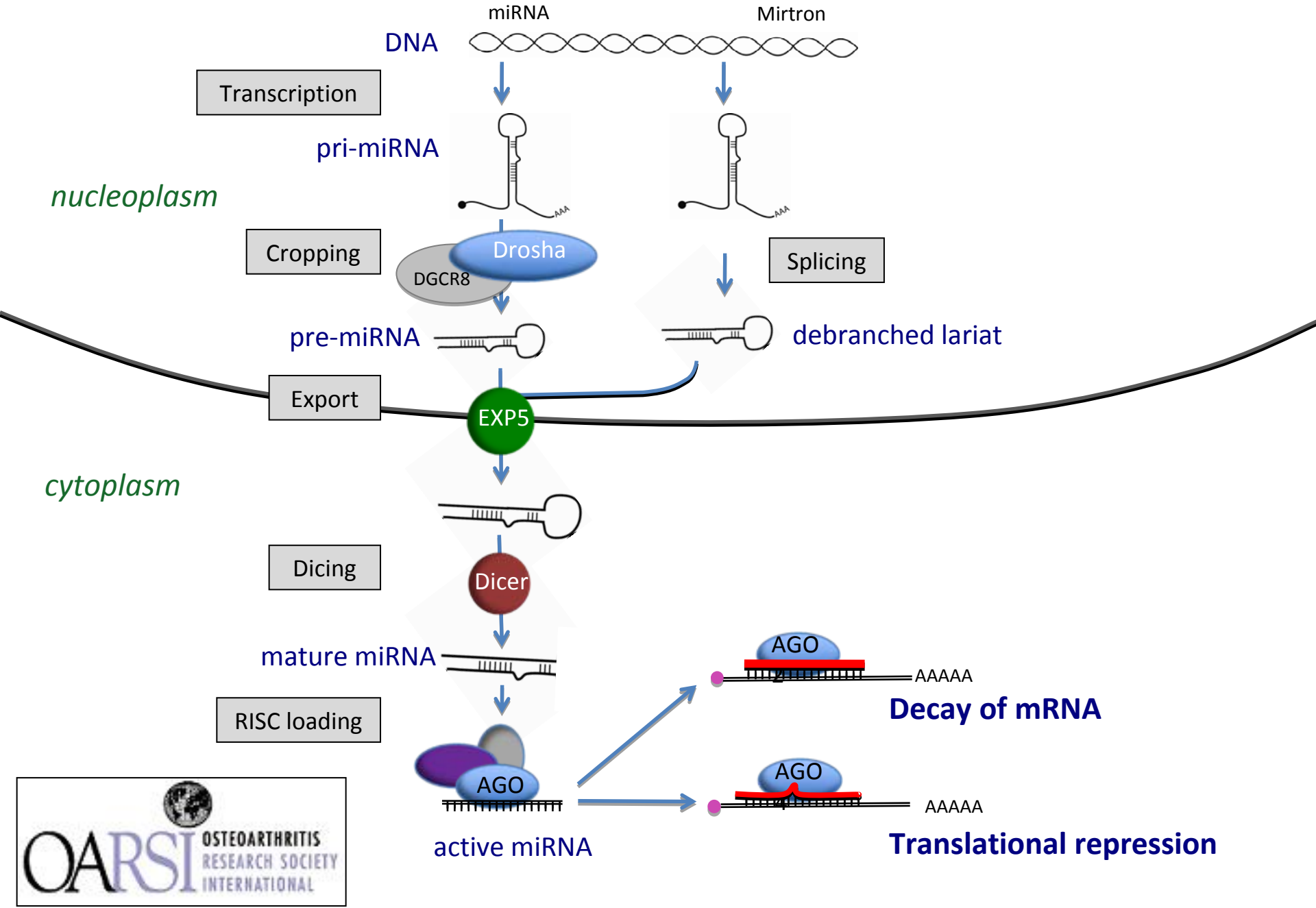
MicroRNA biogenesis and mode of action



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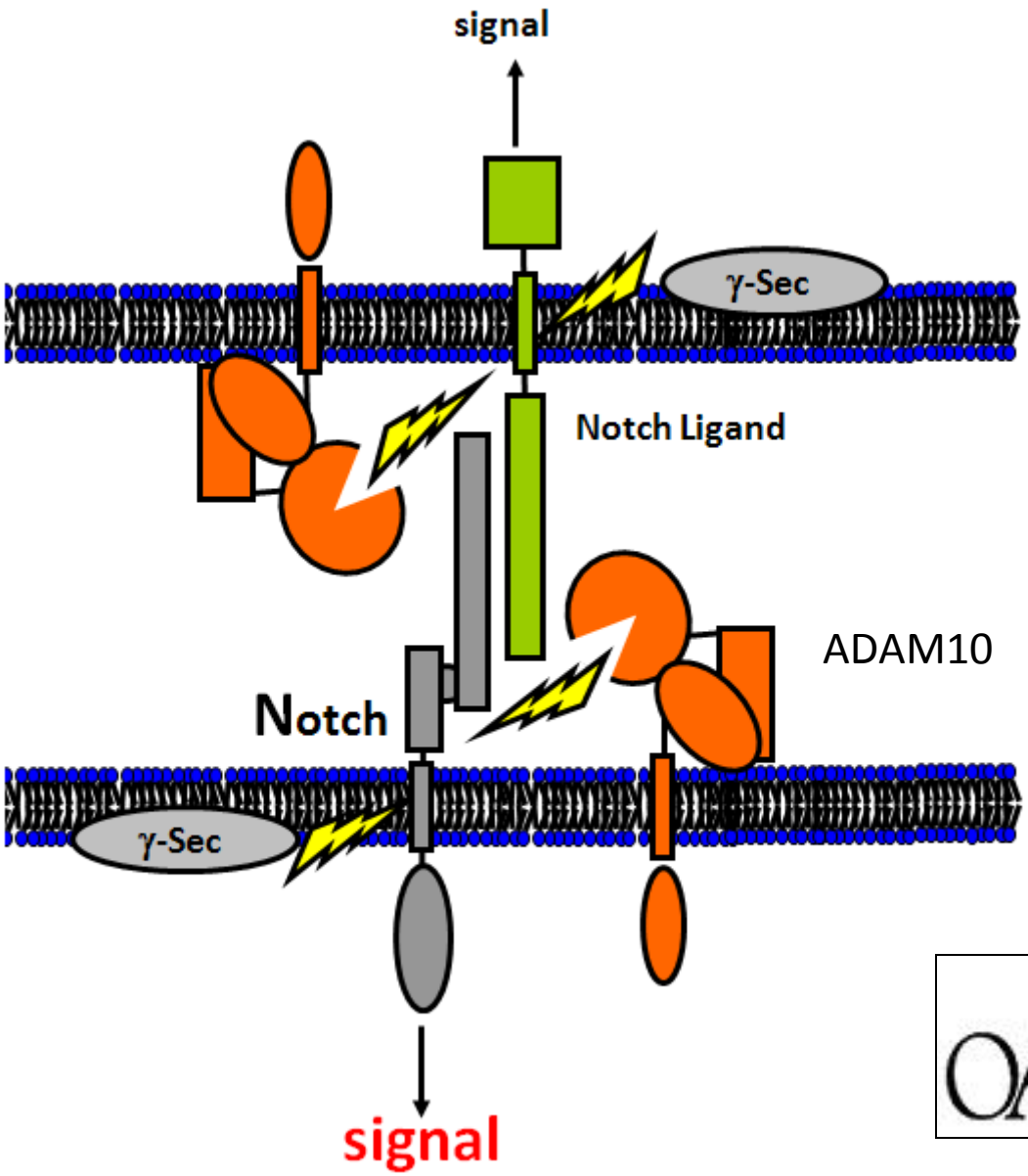
MicroRNAs in cartilage

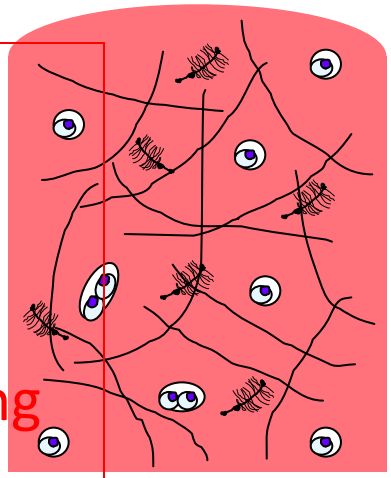
- miR-140: Increase during chondrogenesis
  - » Correlate with expression of *SOX9, AGGRECAN and COL2A1*
  - » Down-regulated by IL-1
  - » Reduced in OA cartilage
  - » 9 potential target genes
  - » Down-regulate ADAMTS-5
- miR-146: Increase in response to IL-1 and TNFα
  - » Down-regulated in OA cartilage
  - » Mediating NFκB signalling (IRAK1, TRAF6)
- miR-9: Up-regulated in OA cartilage and bone
  - » Overexpression in chondrocytes decrease MMP-13 secretion
  - » Inhibition of miR-9 increases MMP-13 production.
- miR-27a: Down-regulate MMP-13 and IGFBP-5

ADAM10 and Notch regulates cell-cell signalling



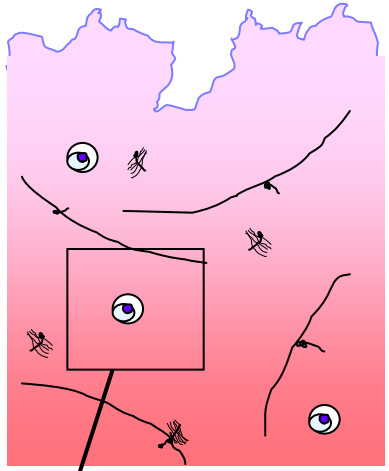
Injury, Aging, ROS,
Mechanical stress
Degraded ECM
Abnormal ECM synthesis
Genetics
Inflammatory cytokines

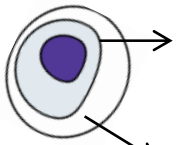
microRNA
Sulfation
Syndecan 4
DDR-2
Notch signalling



Cartilage

OA





proMMPs

TIMPs

ADAMTSs

Chondrocytes

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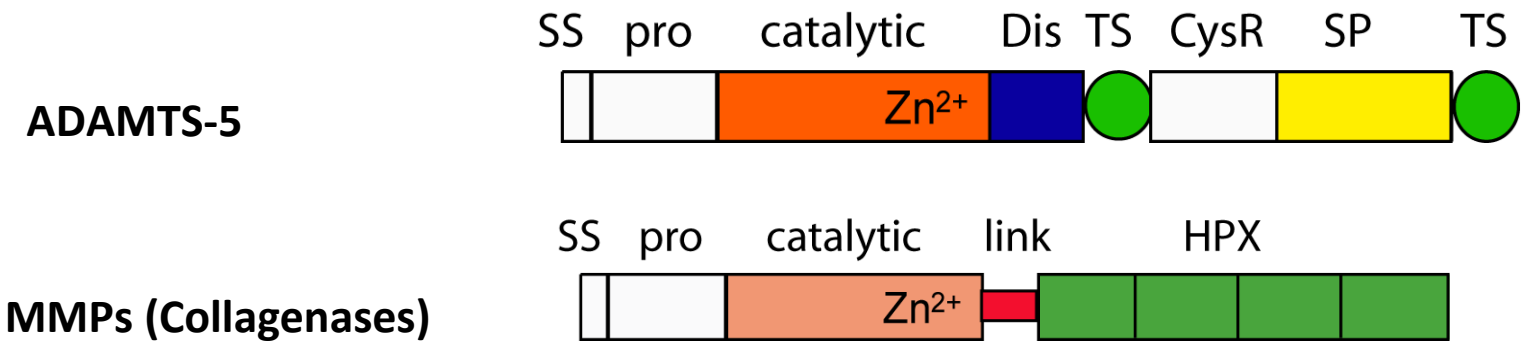
Common features between aggrecanases and collagenases



- Blocking the function of non-catalytic domains may specifically inhibit the target metalloproteinase

Exosite inhibitors or neutralizing antibodies

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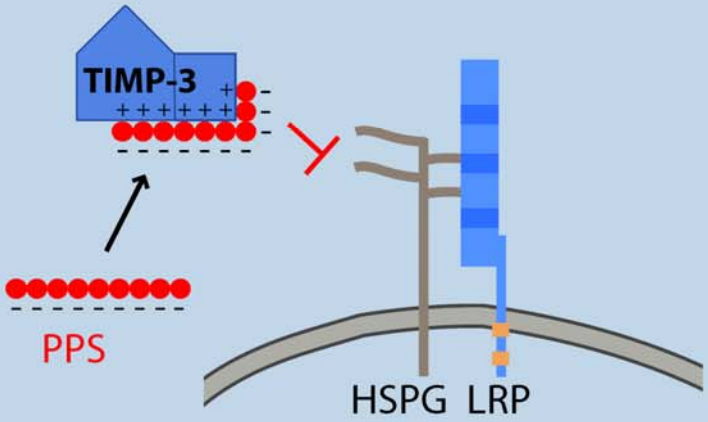
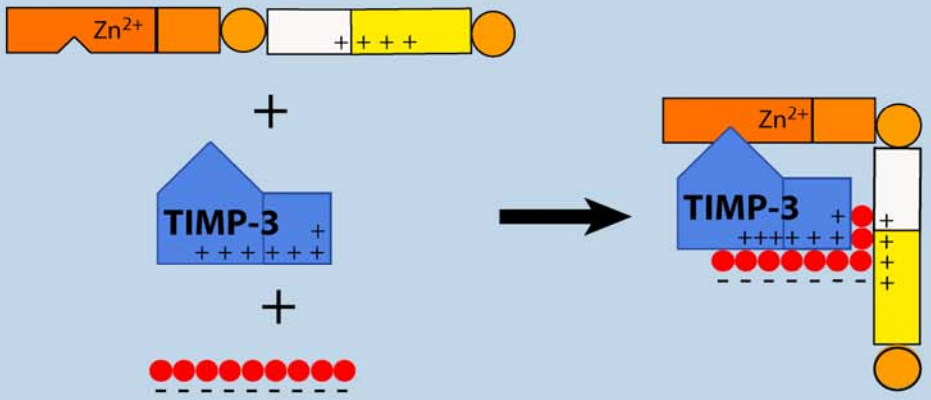
PPS: Three modes of action to block ADAMTS-5

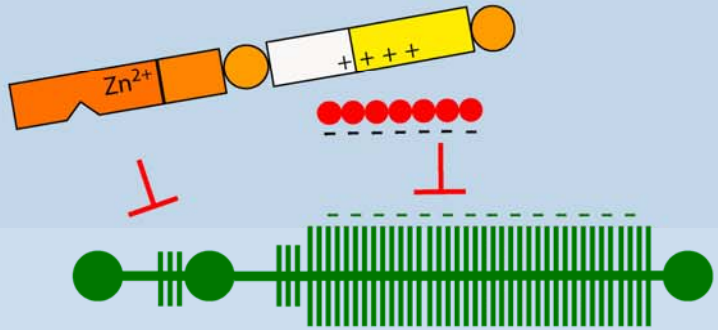
(i) Prevents TIMP-3 internalization



(ii) Enhances TIMP-3 reactivity



(iii) Competes with aggrecan (allosteric inhibitor)



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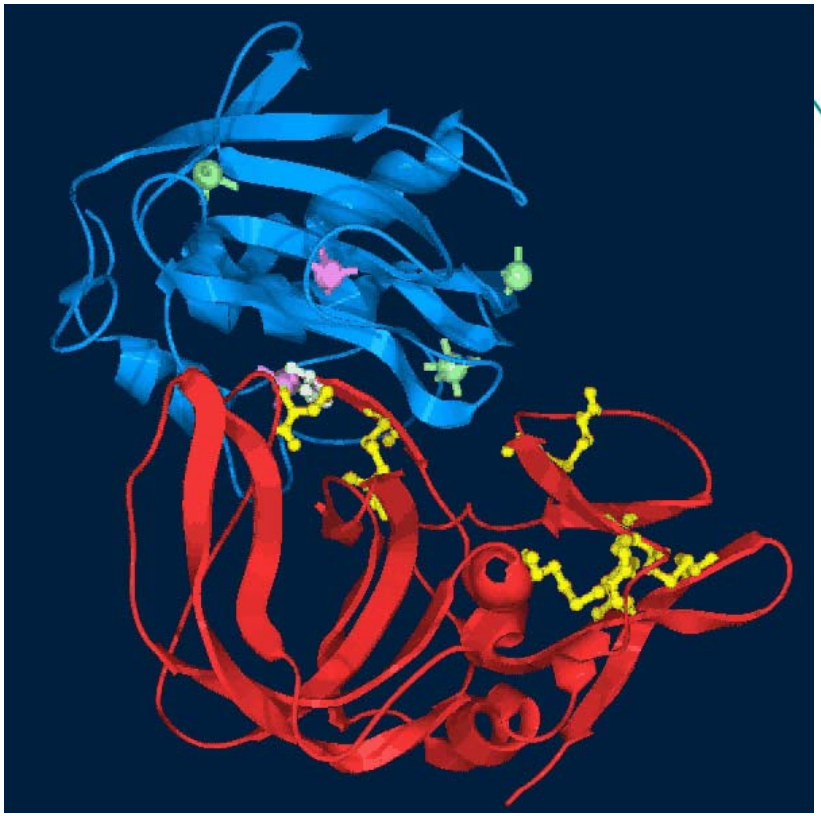
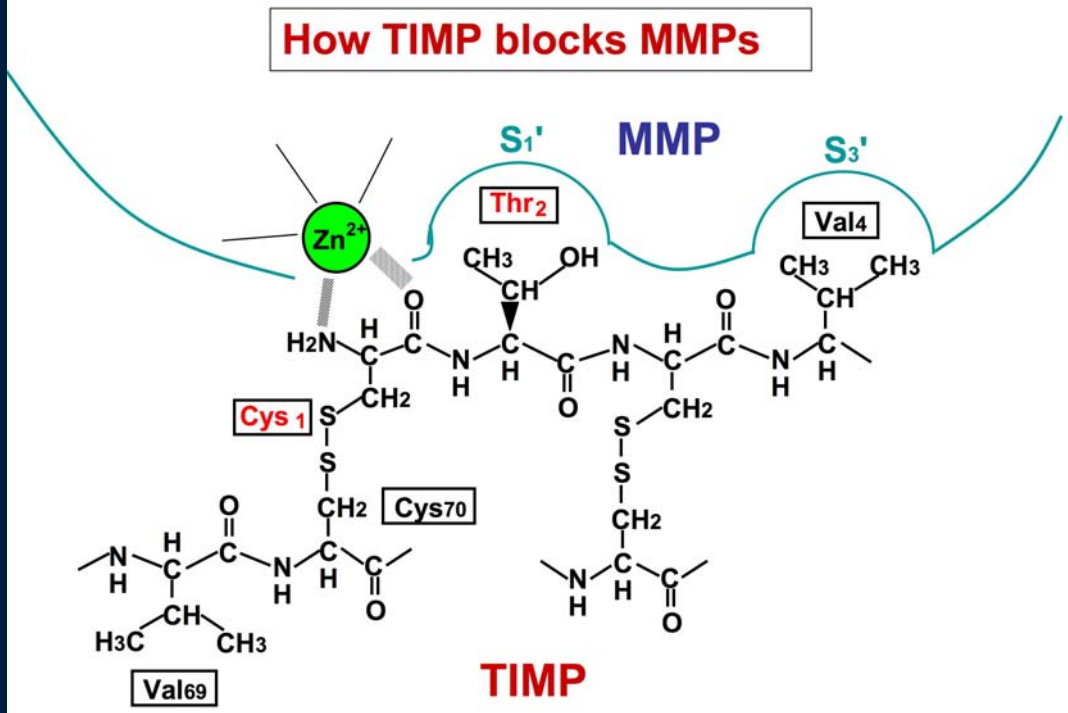
Inhibition mechanism of TIMPs





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