



A Bout With Gout

An Play in Three Acts

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Adapted from the work:

Evolutionary history and metabolic insights of ancient mammalian uricases

James T. Kratzer, Miguel A. Lanaspa, Michael N. Murphy, Christina Cicerchi, Christina L. Graves, Peter A. Tipton, Eric A. Ortlund, Richard J. Johnson, and Eric A. Gaucher
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NB. Conflict of interest statement: E.A.G. declares financial interest because a patent related to this research has been filed by the Georgia Institute of Technology, and this technology is licensed to General Genomics, LLC, which is a start-up founded by E.A.G.. R.J.J. is an inventor on several patents and patent applications related to lowering uric acid as a means for treating hypertension, diabetic nephropathy, and renal disease, and is a founder of XORT, Inc., which is a start-up company that has licensed these applications.

Act I

(In which we introduce the main characters)

*Q1: What do we know
about gout?*

Gout

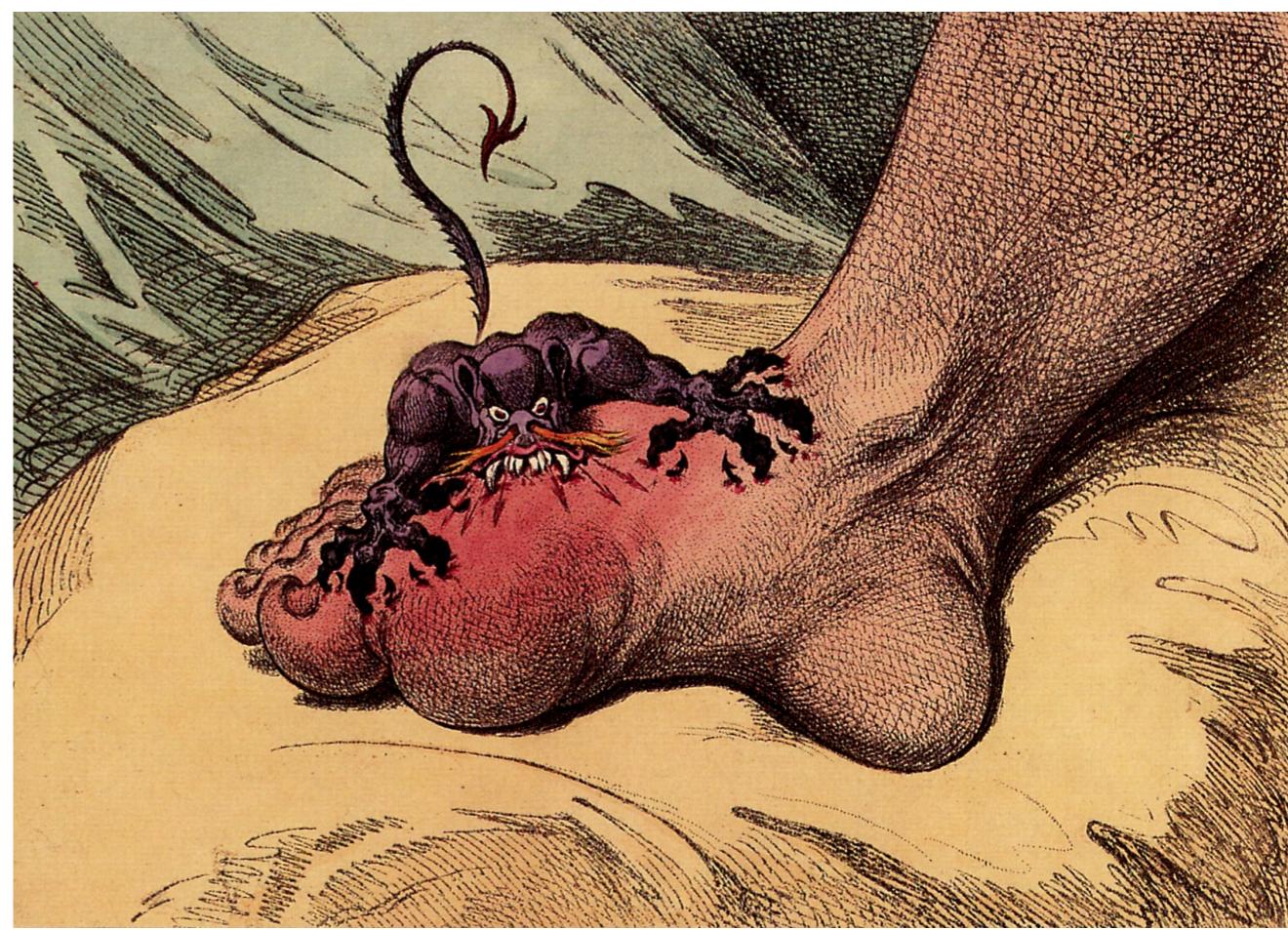
- Accumulation of uric acid crystals in joints (insoluble!)
- Crystals trigger immune reaction - inflammation mediated by IL-1 β)
- Natural byproduct of purine metabolism
- Common (3.9%) and commonly treated (allopurinol)
- Causes: excess production, insufficient excretion, overindulgence of purines
- Risk factors: FHx, ♂, weight, alcohol, lead, meds, niacin

Gout

Gout



Gout

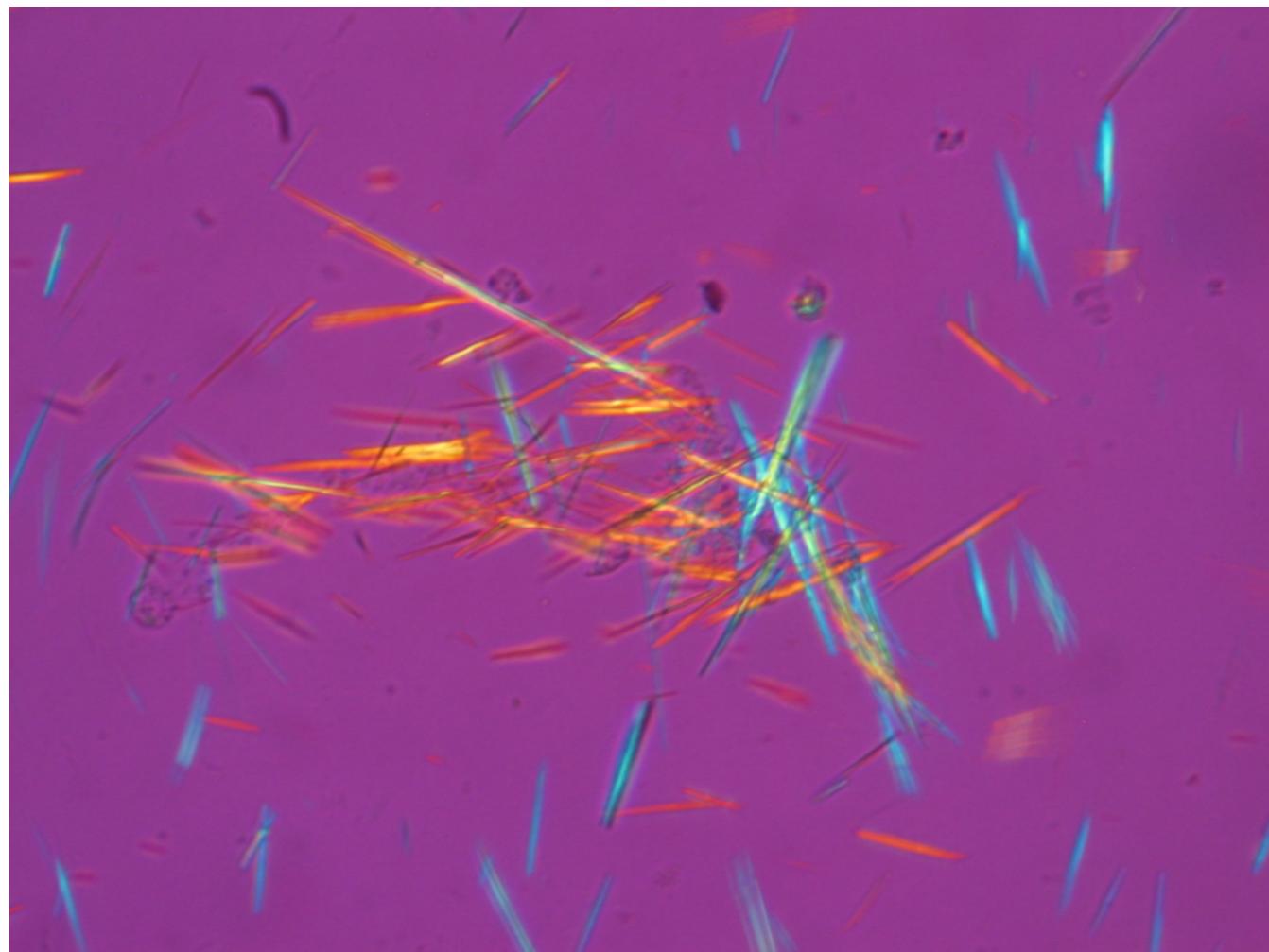


Gout

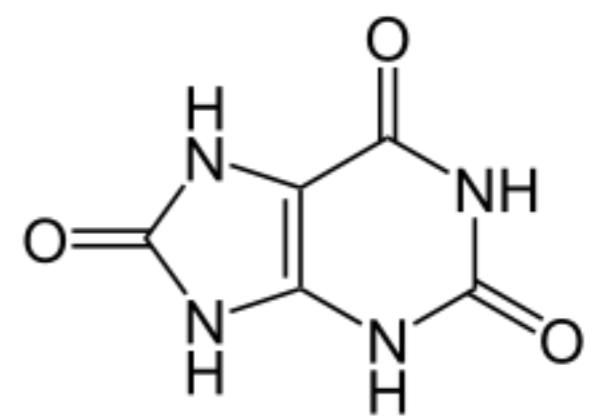
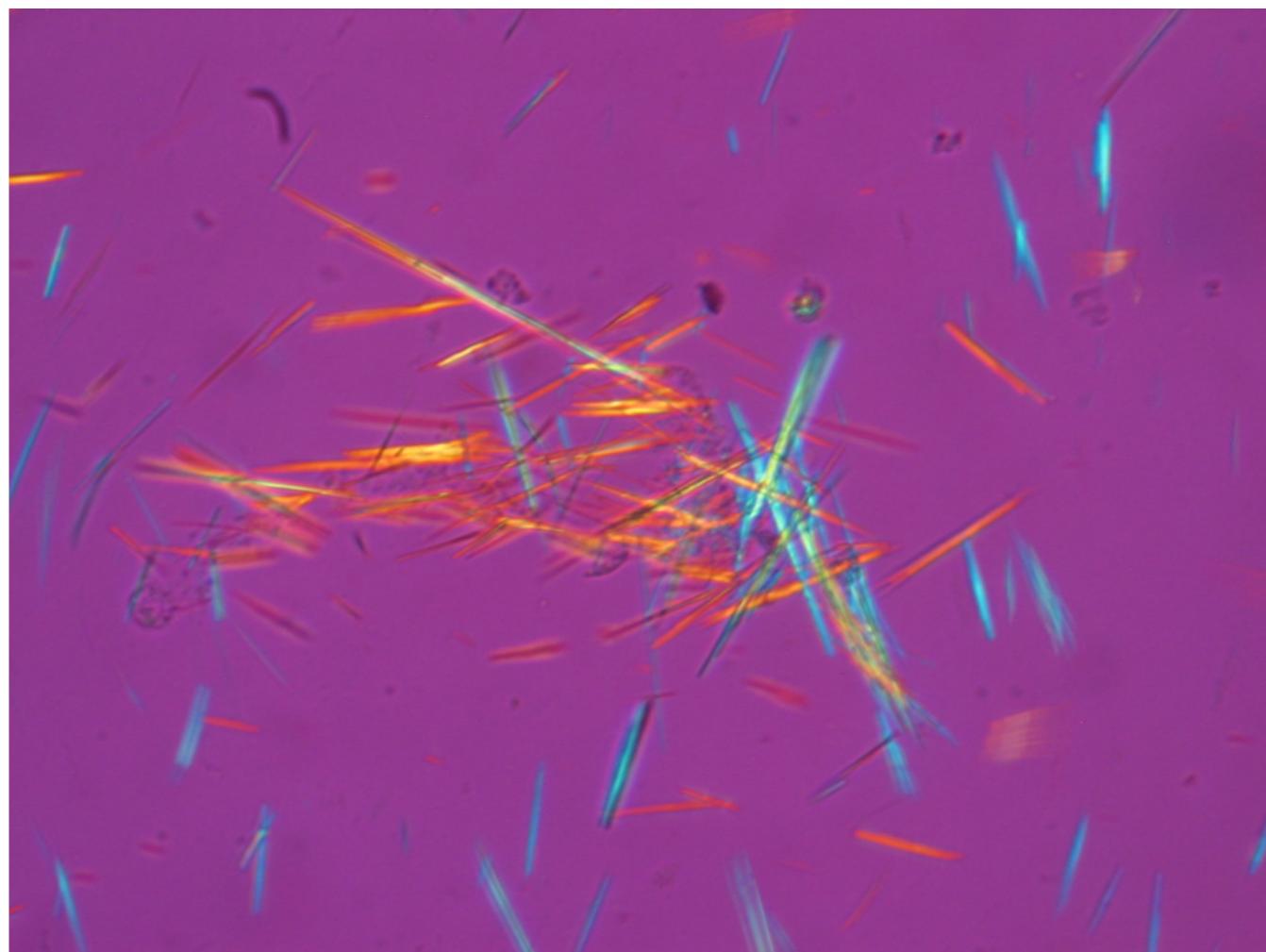
Gout



Gout



Gout



*Q2: Why do we get gout
but not other animals?*

A: Uricase!

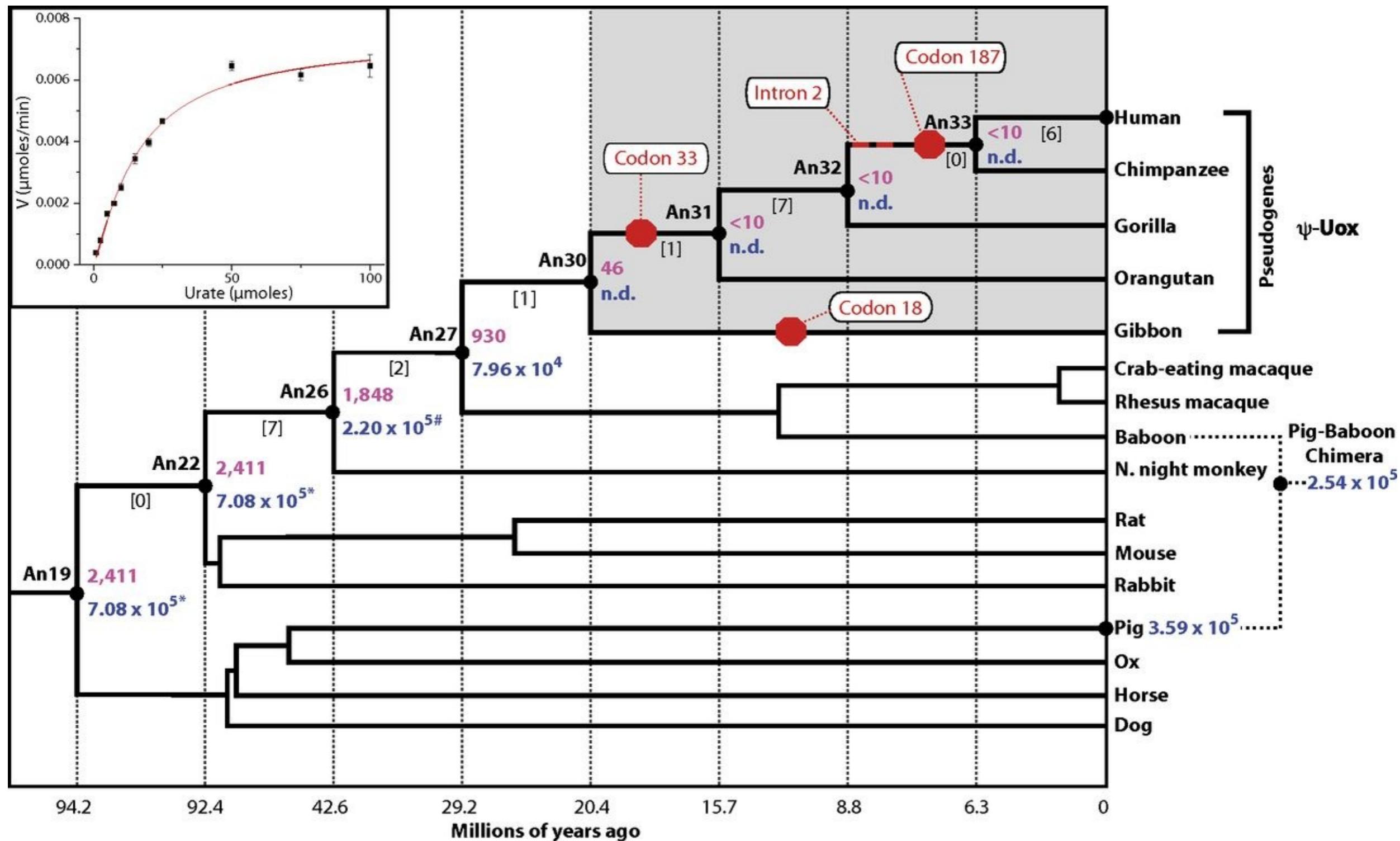
Some Facts About Uricase

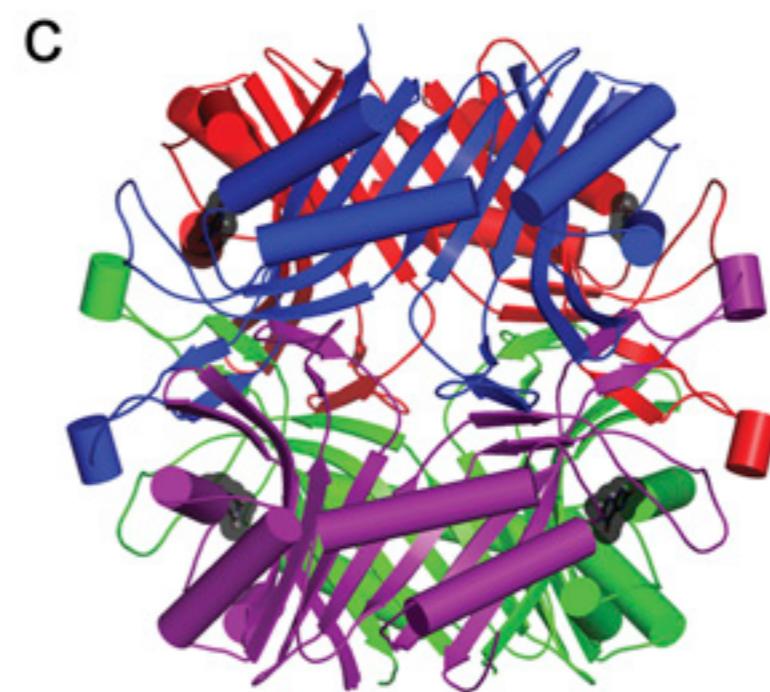
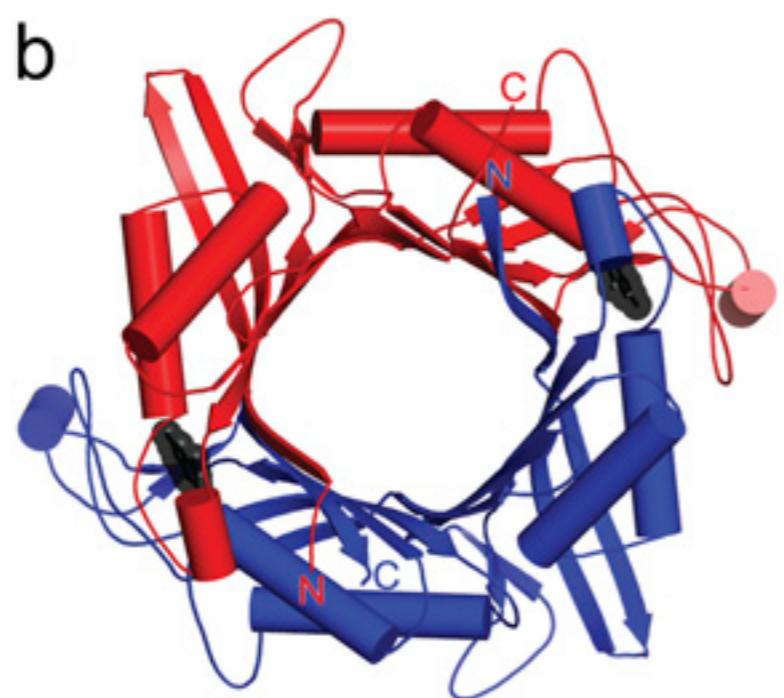
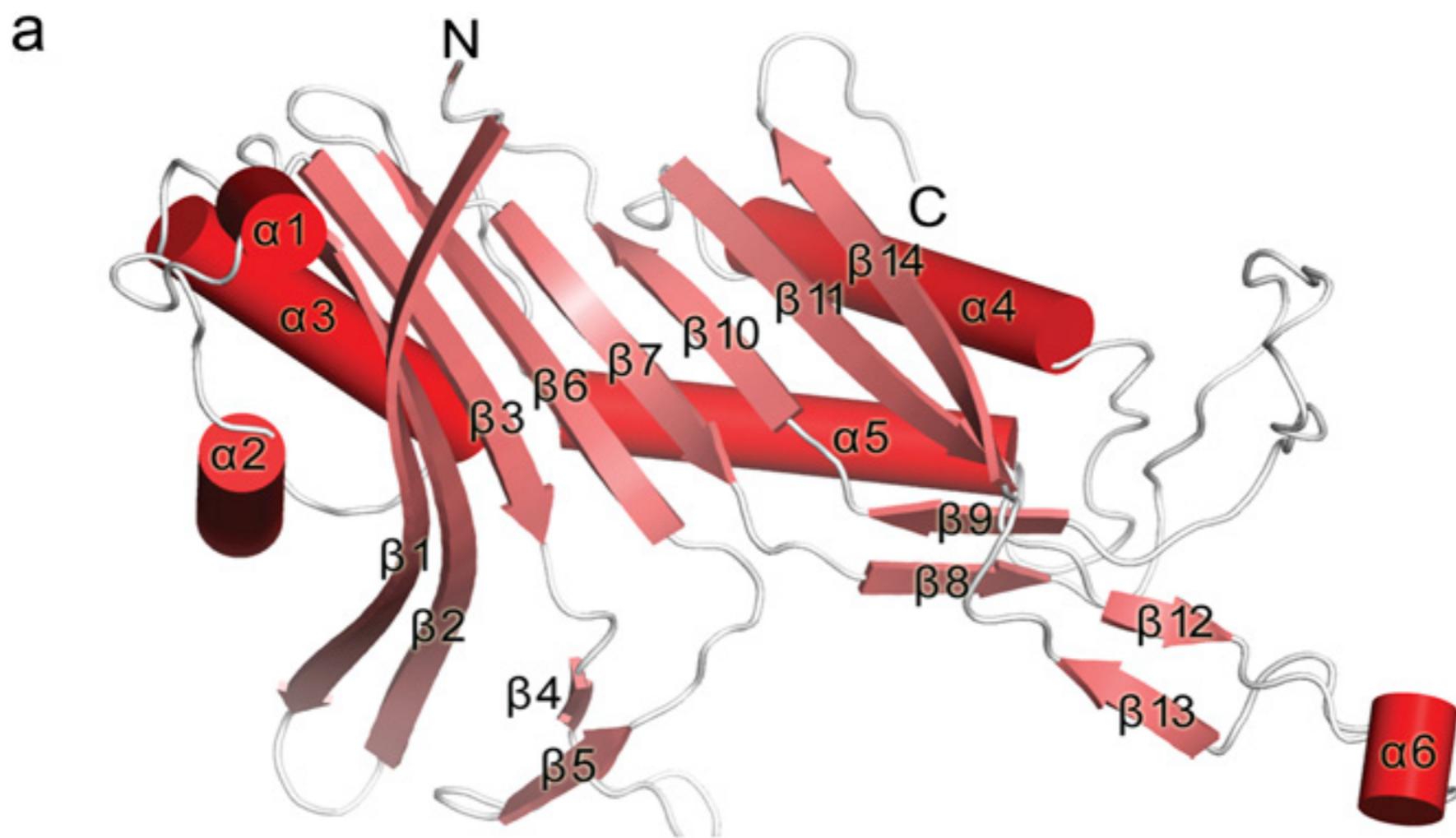
- Liver enzyme
 - Converts uric acid to 5-hydroxyisourate
 - Converted to allantoin and excreted by kidneys
- *Aspergillus*: 301 AA, 33.4 kDA
- Homotetramer (dimer-of-dimers)

The Fact About Uricase

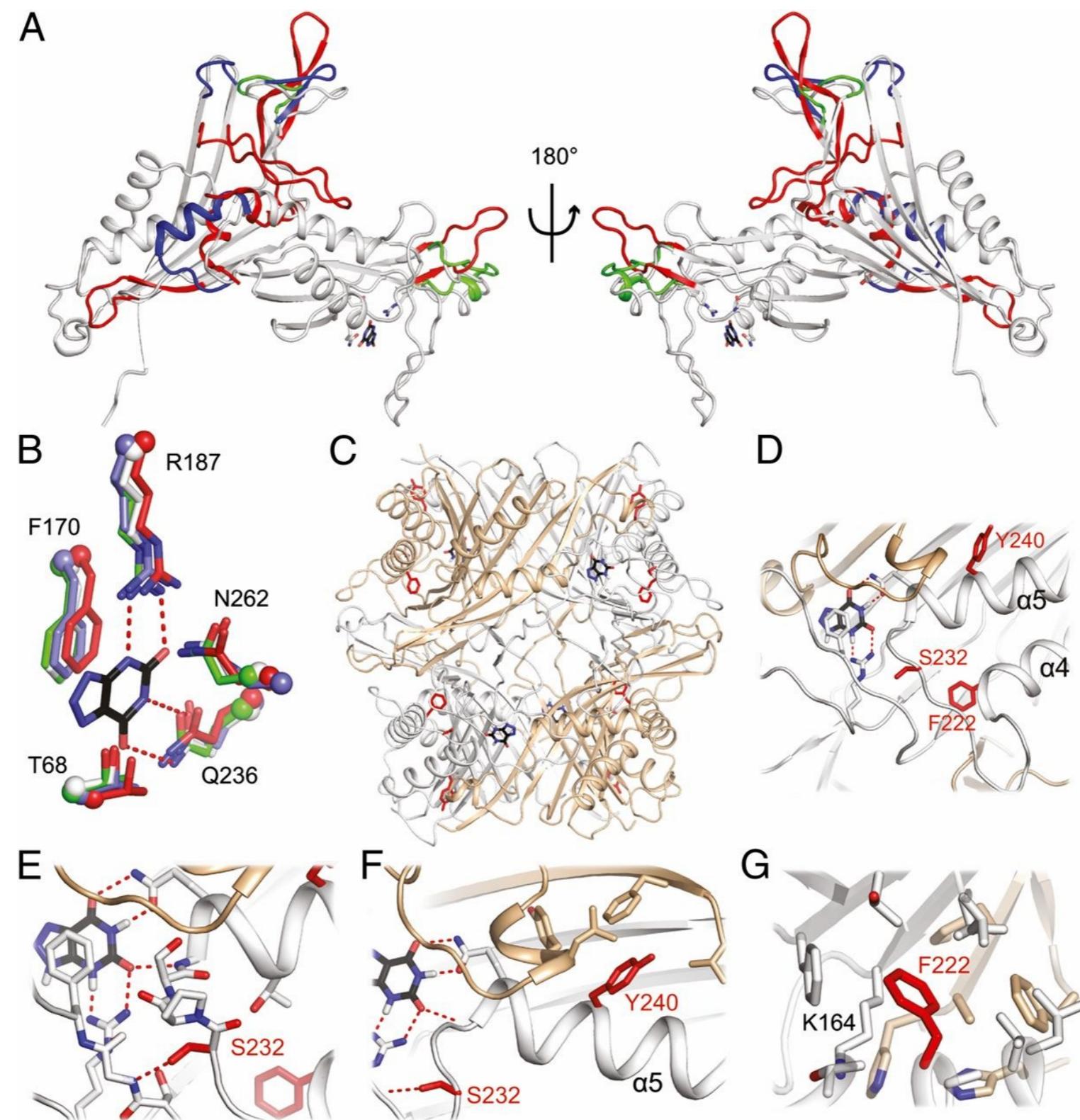
Humans have lost this enzyme!

Phylogeny of the uricase gene family and enzymatic properties of inferred ancestral uricases.





Structural features of an ancient mammalian uricase.



Act II

(In which we pit the main characters against each other)

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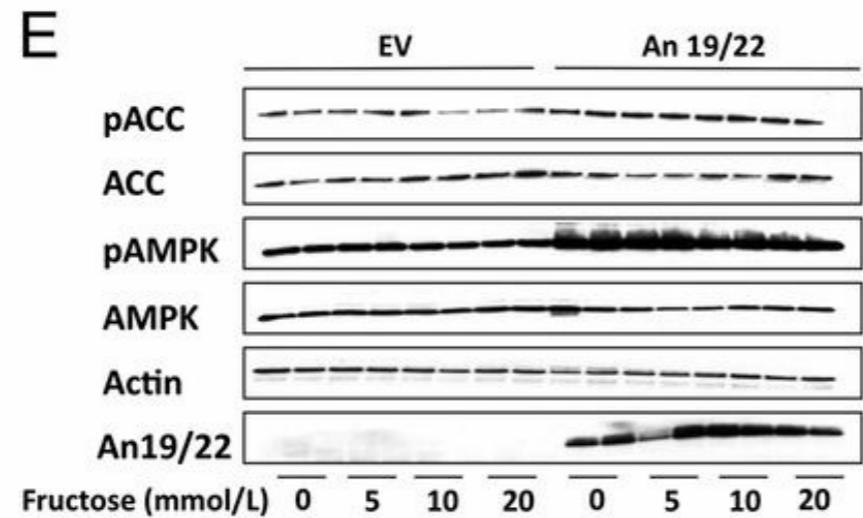
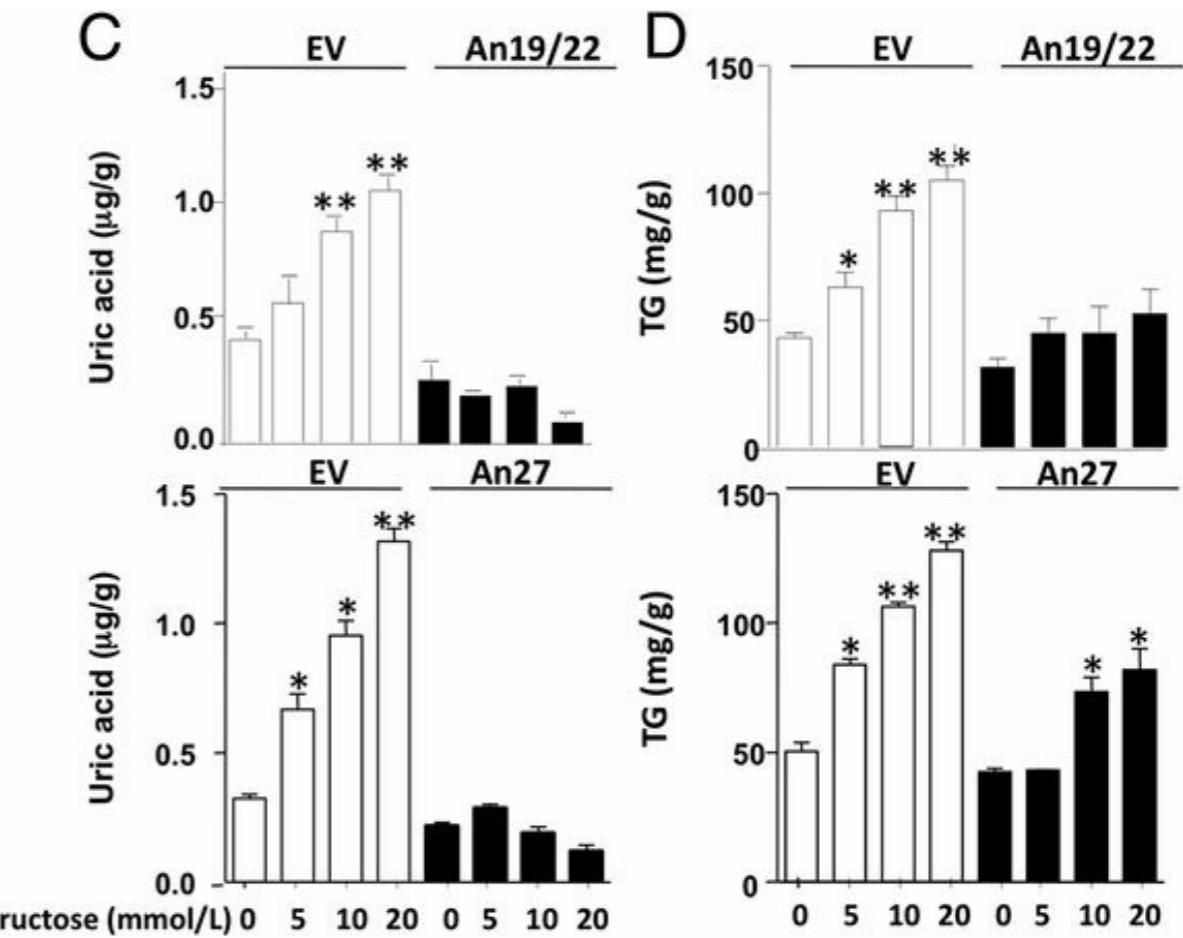
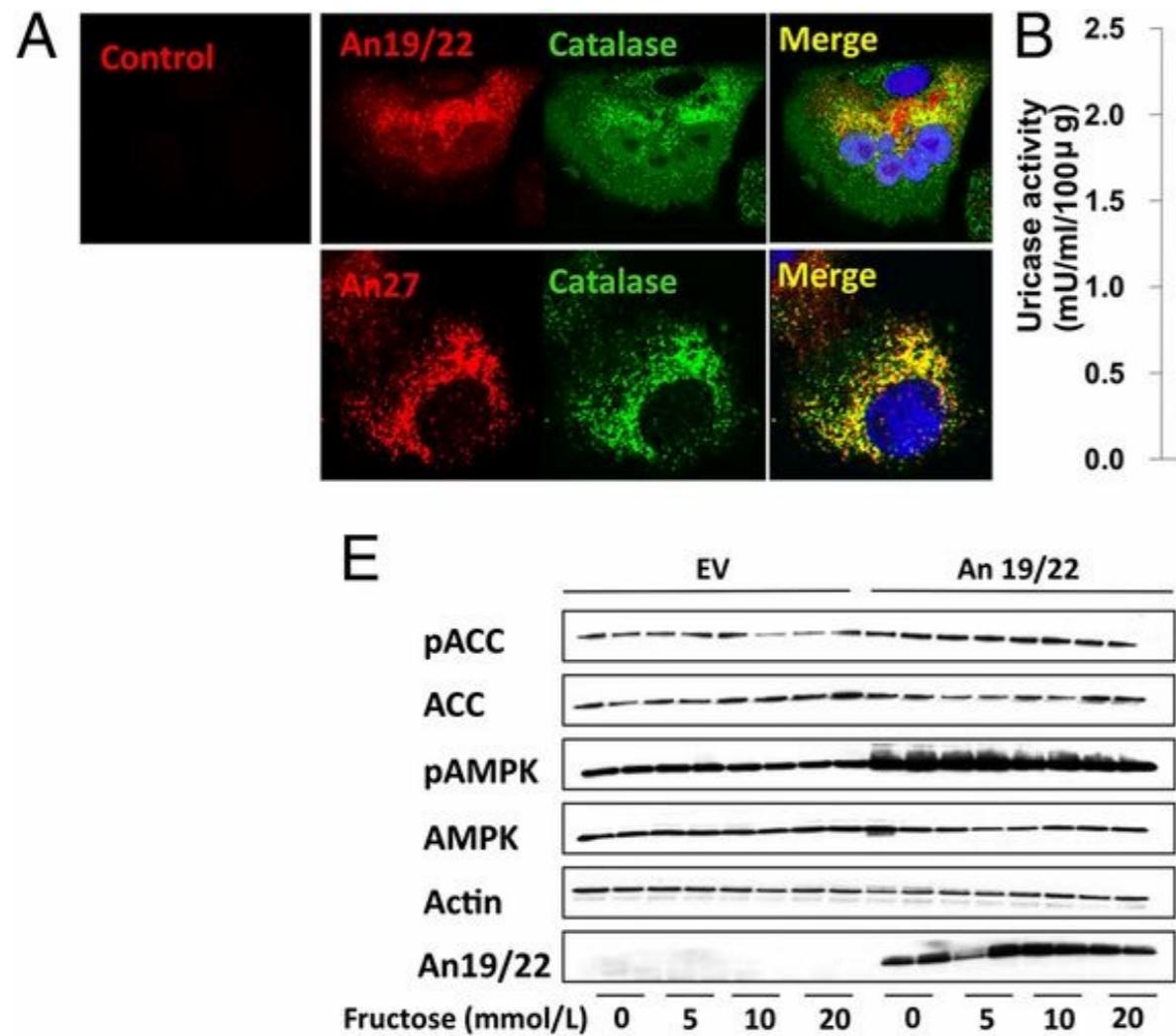
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- Prevailing theory: uric acid is a potent antioxidant
- New hypothesis: lack of uricase facilitates fat accumulation from fructose

Expression and function of ancestral uricases in human HepG2 cells.



Act III

(In which we look to the future)

Gout Treatment

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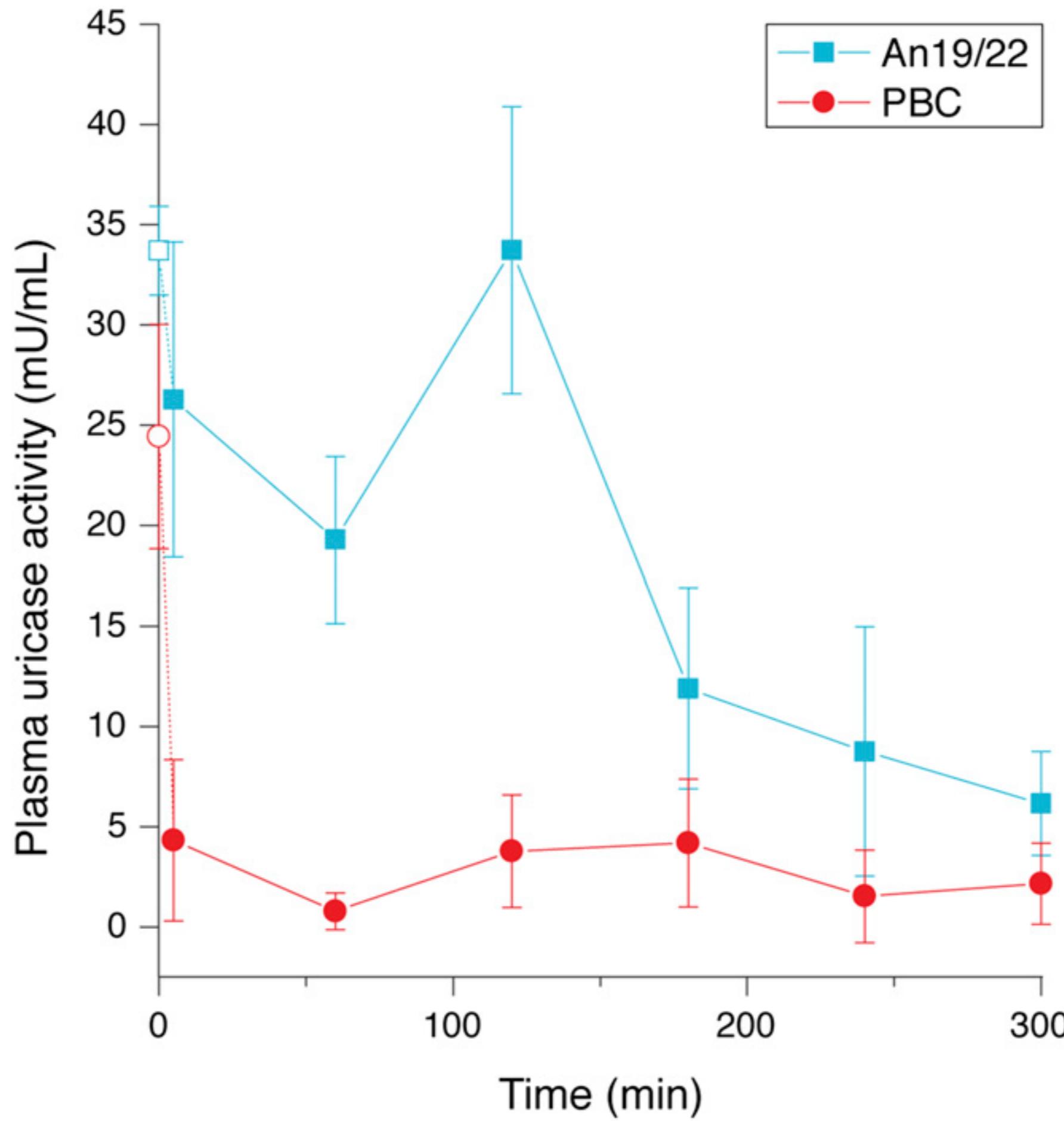
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 - Pegloticase: PEGylated baboon-pig chimera



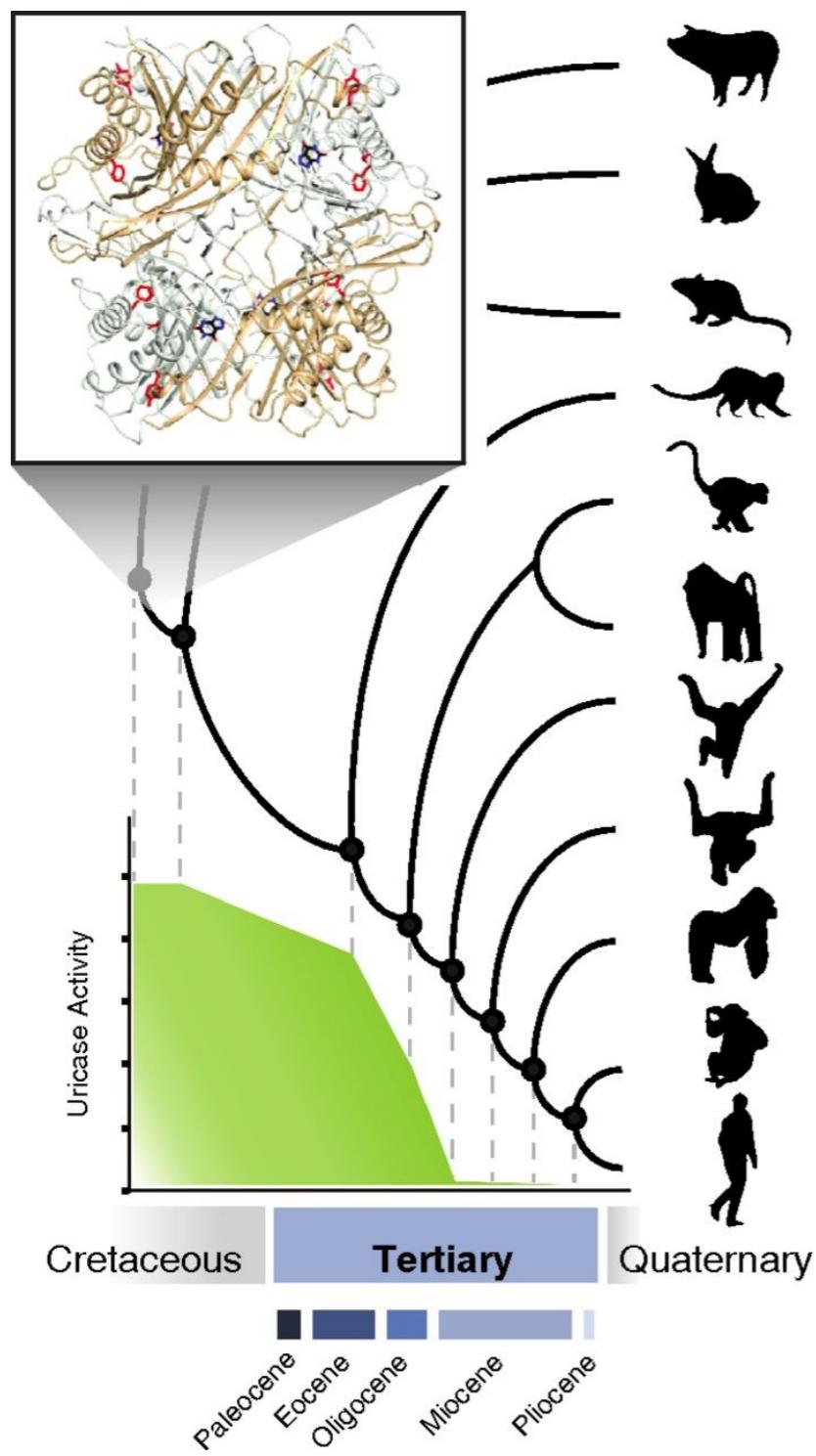
The Uricase of the Future

An19/22 is more catalytically active than modern mammalian uricases, has 100-fold increased half-life, and has greater sequence identity to human uricase than pegloticase (93% vs 90%)

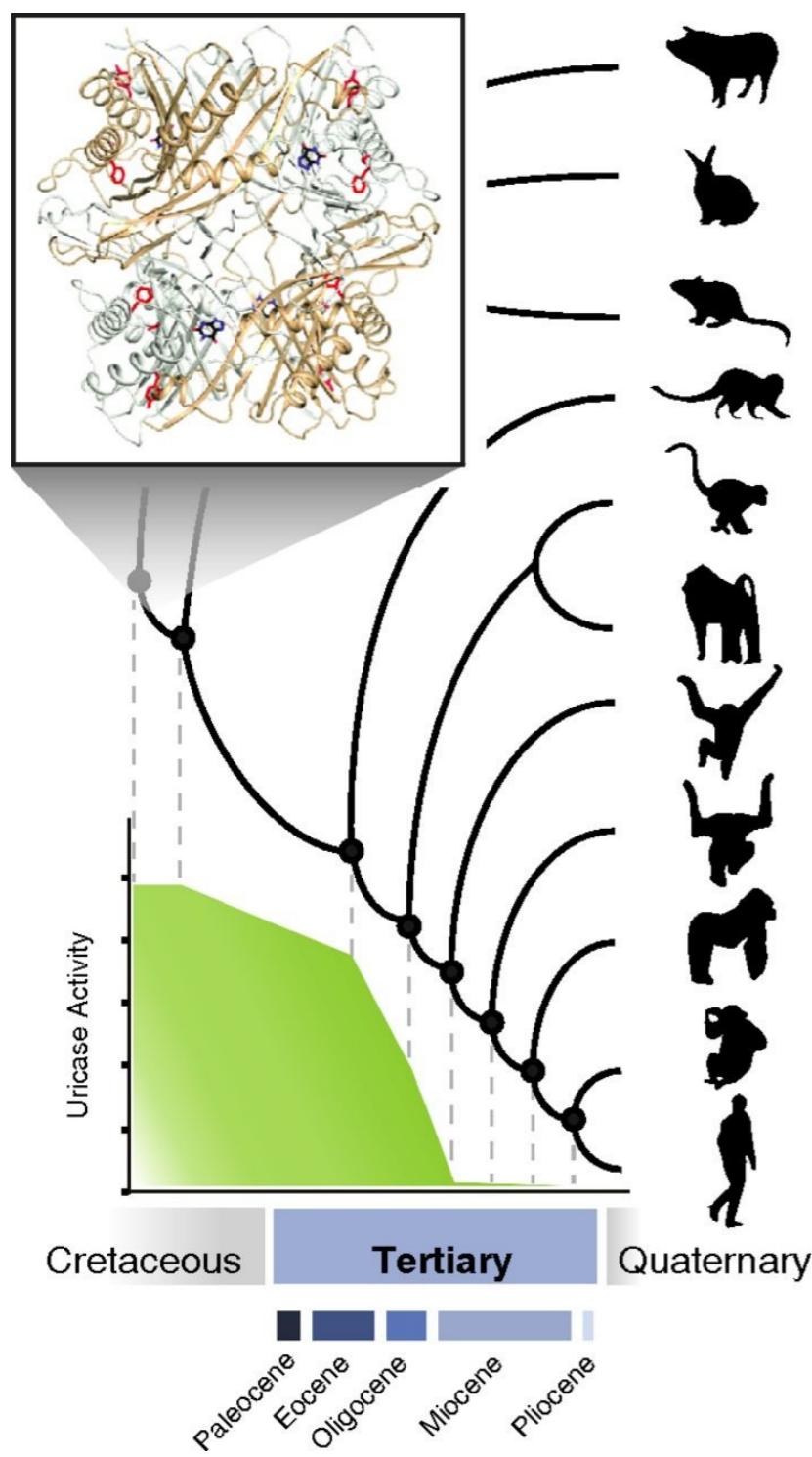
Epilogue

(In which we tie up some loose ends)

Why Did This Happen?

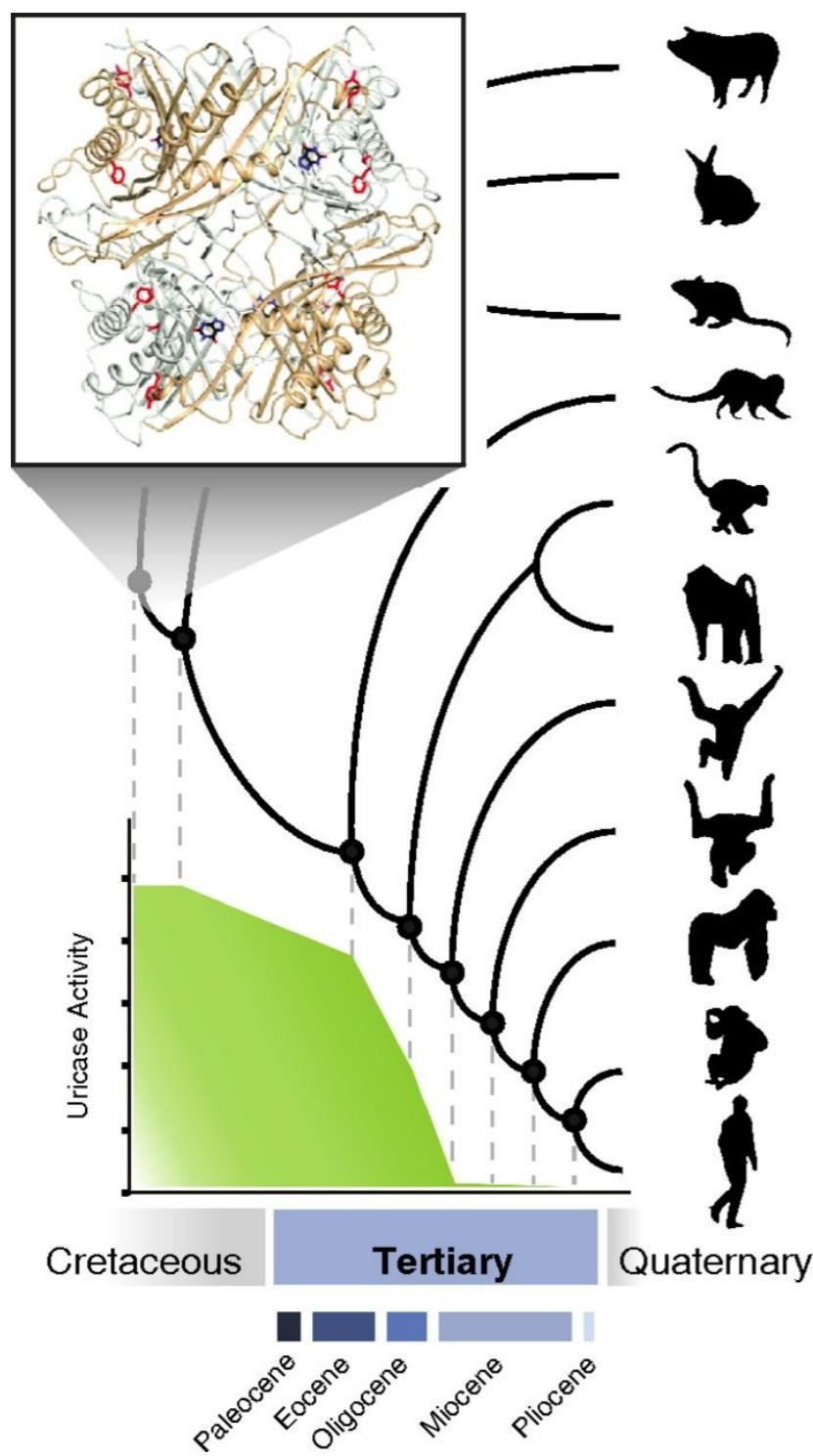


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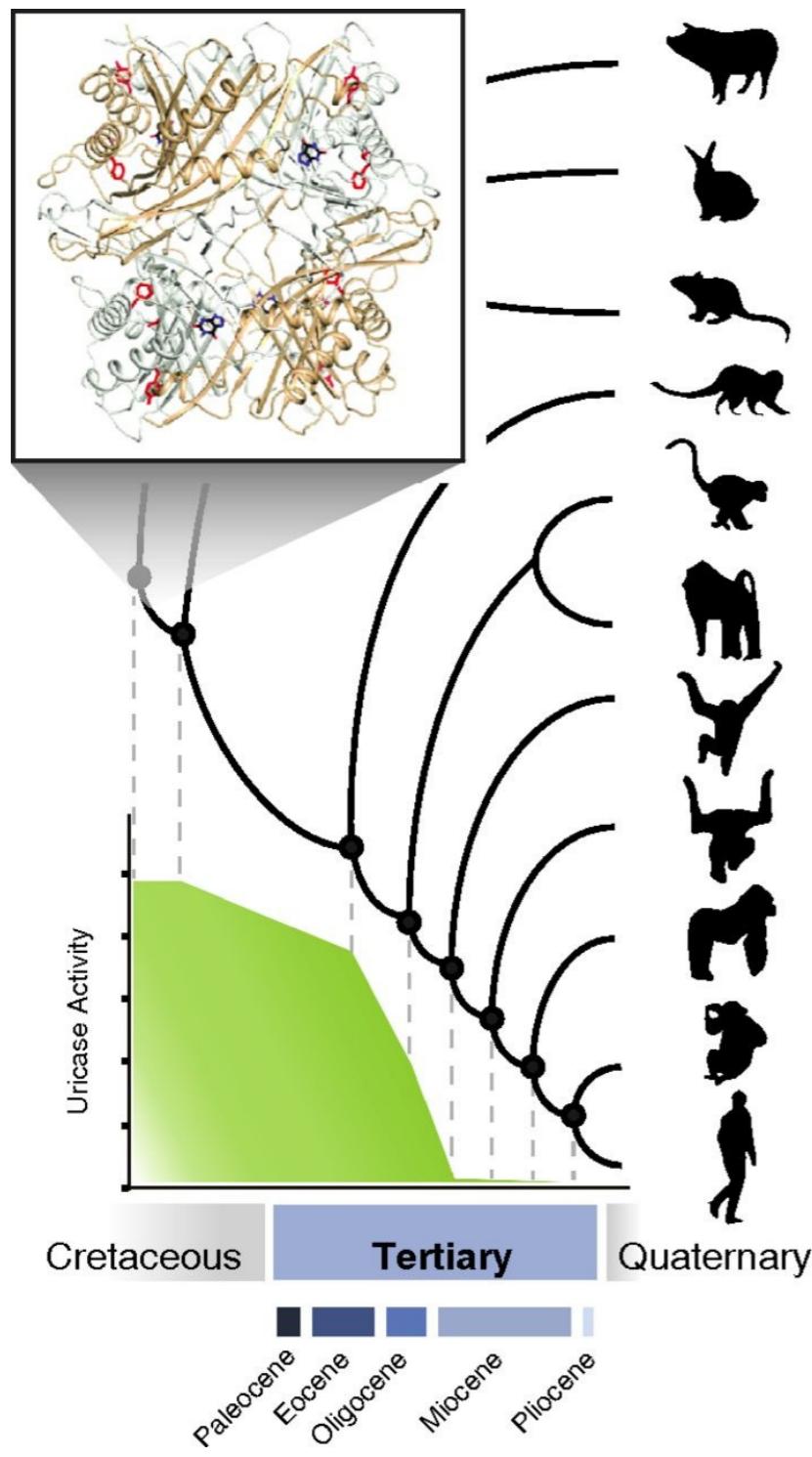
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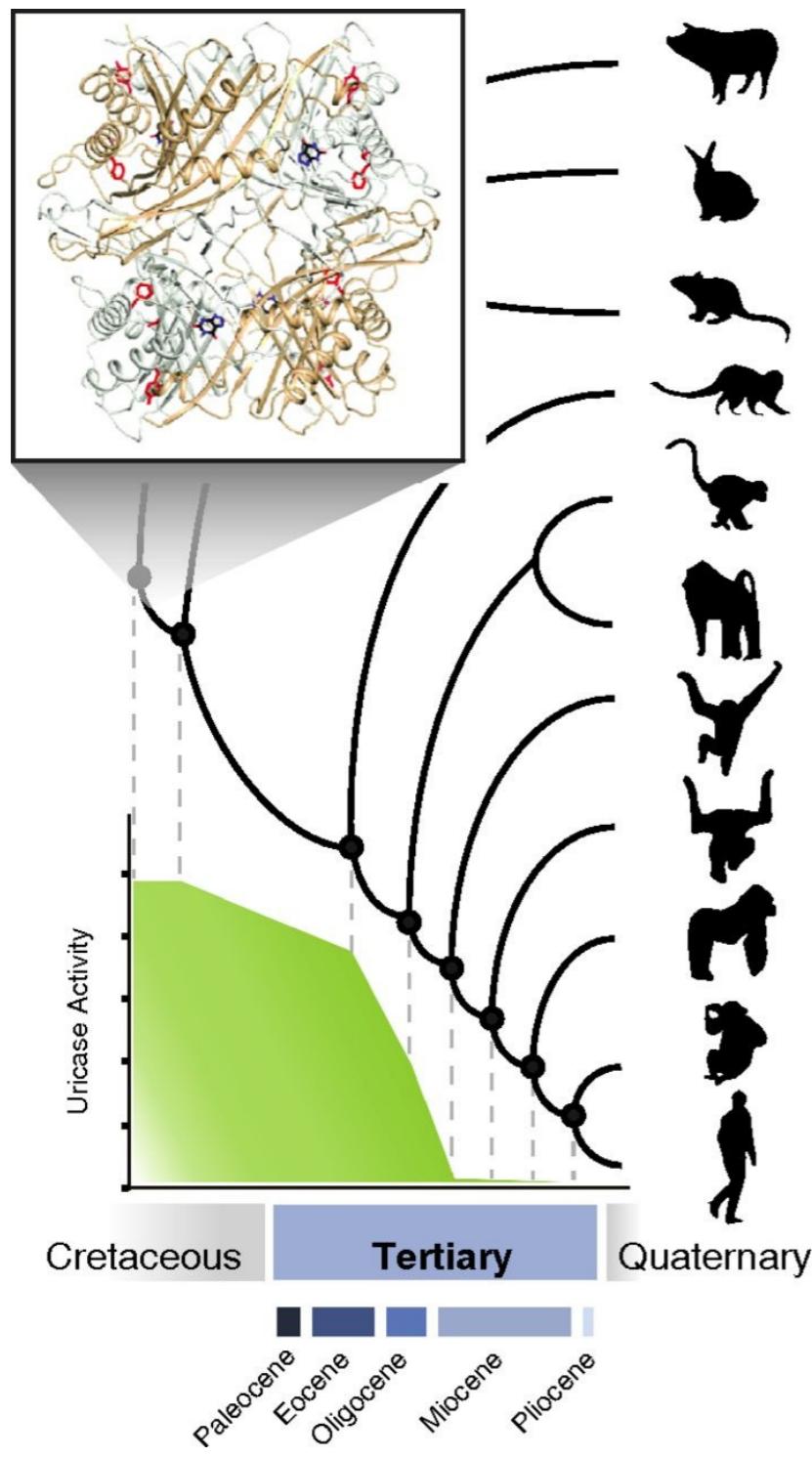
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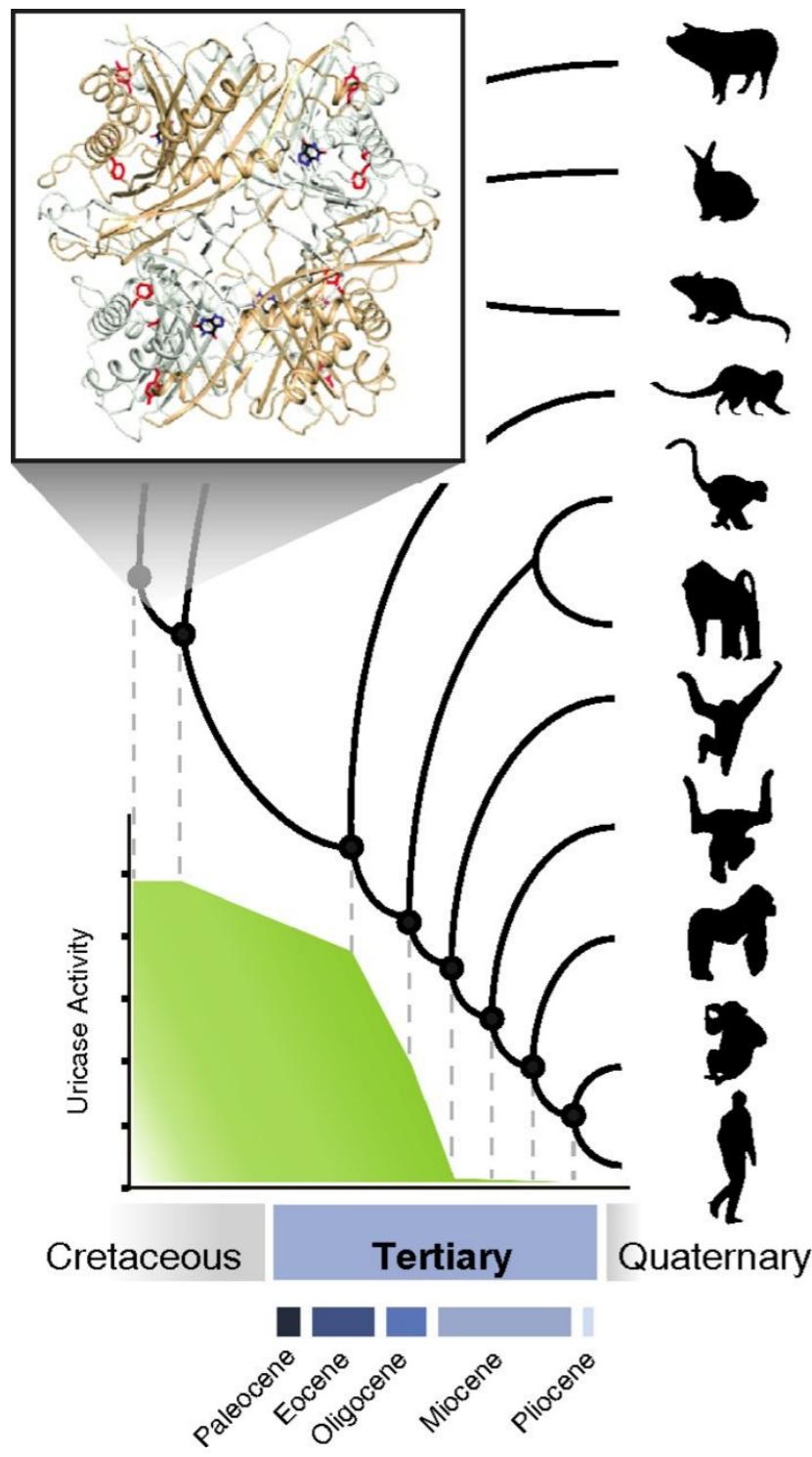
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 - Trichromacy, olfactory decline, etc.
 - Similar impacts seen in birds and other mammals
- The loss of uricase suggests broader physiological adaptations occurred in response to changing vegetation