Tempo and Mode of Peto's Paradox

Comparative Genomics and the Evolution of Cancer Suppression

Tuatara (*Sphenodon punctatus*), Auckland Zoo

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School of Informatics, Computing and Cyber Systems
College of Engineering, Informatics and Applied Sciences
Northern Arizona University





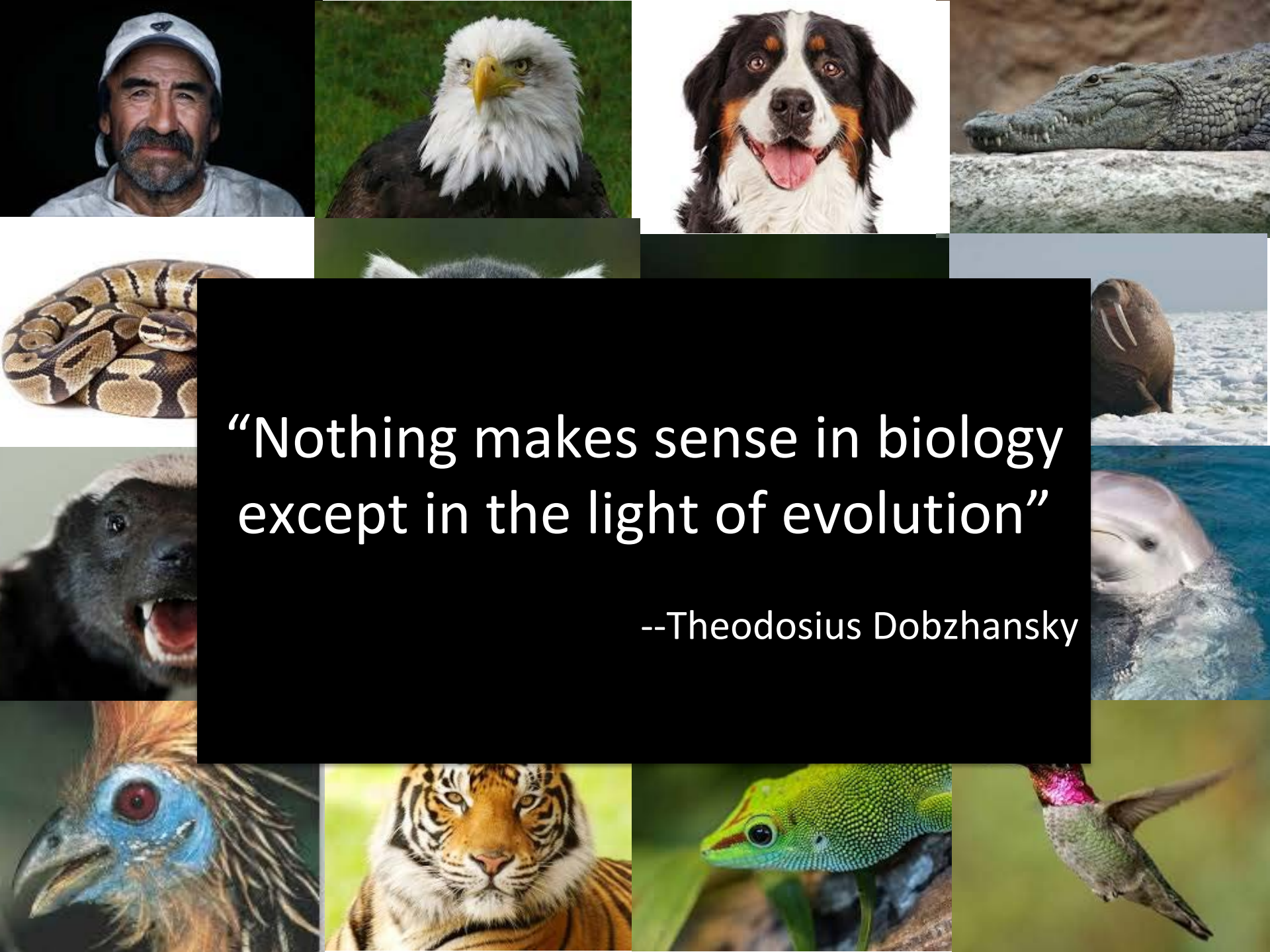








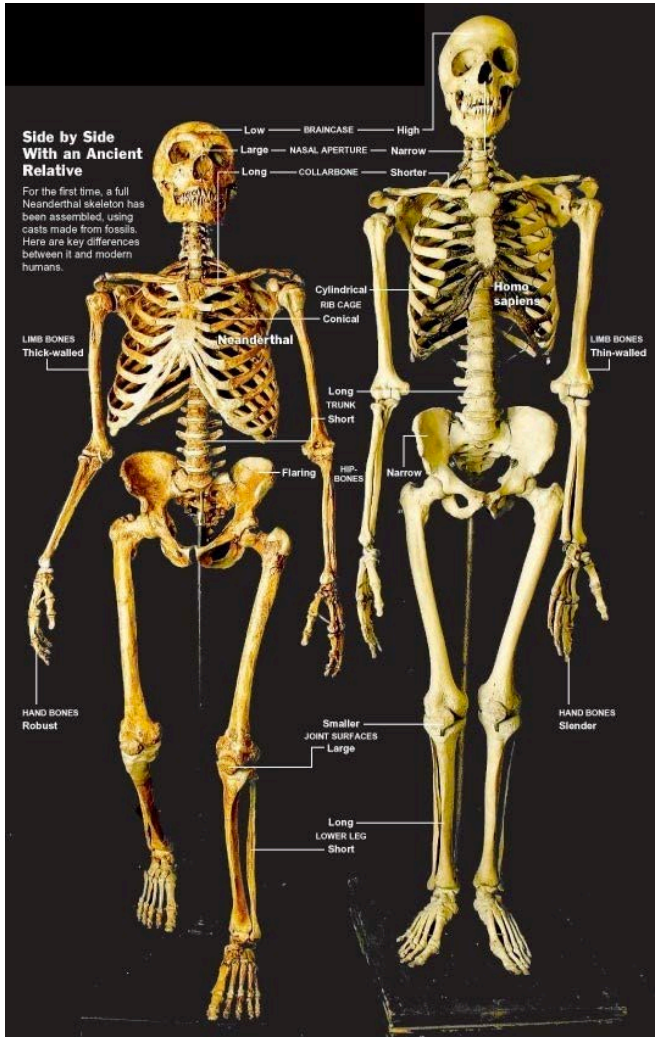


"Nothing makes sense in biology except in the light of evolution"

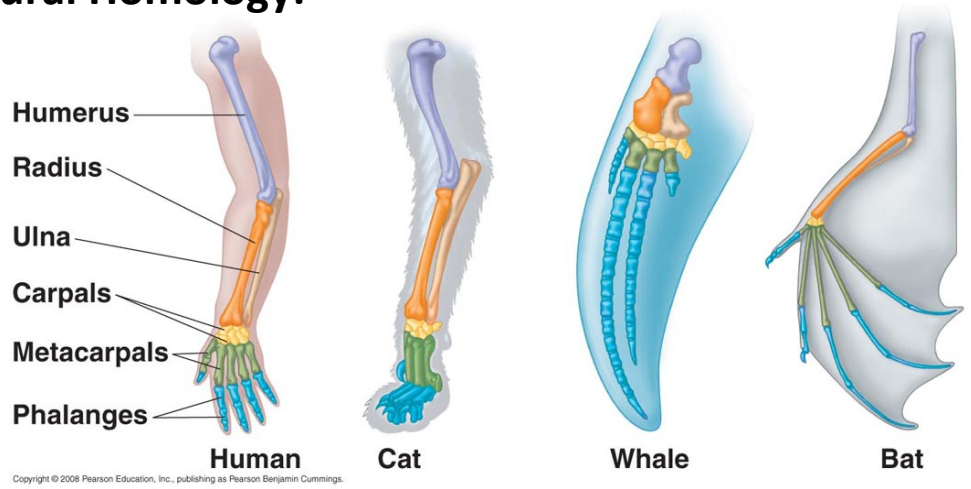
--Theodosius Dobzhansky

Explaining Diversity:
From Morphology to Genomics



Homology and Bioinformatics

Structural Homology:



Sequence Homology:

```
Human KKASKPKKAASKAPTKKPKATPKATPVKKAKKKLAAT
Mouse KKAAKPKKAASKAPSKKPKATPKATPVKKAKKKPAAT
  Rat KKAAKPKKAASKAPSKKPKATPKATPVKKAKKKPAAT
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      ***:**********:******************** ***
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Homology and Bioinformatics

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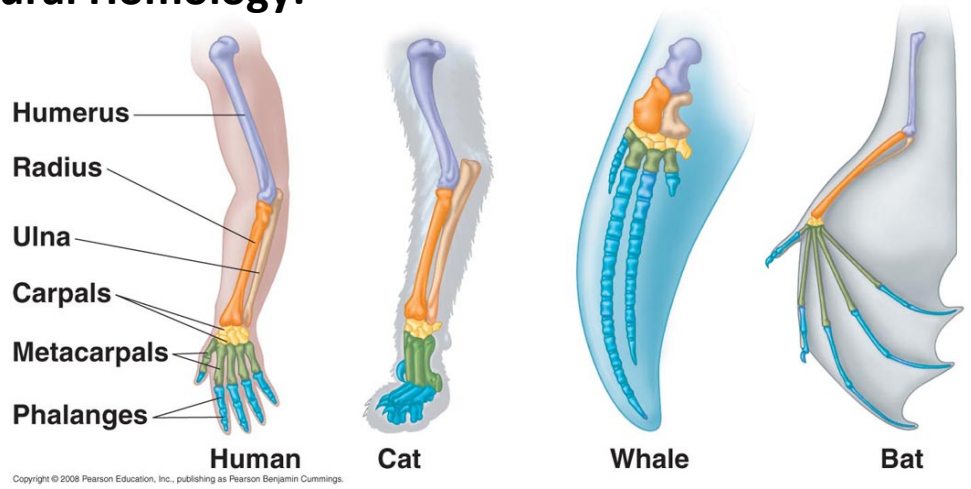

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      ***:**********:********************  ***
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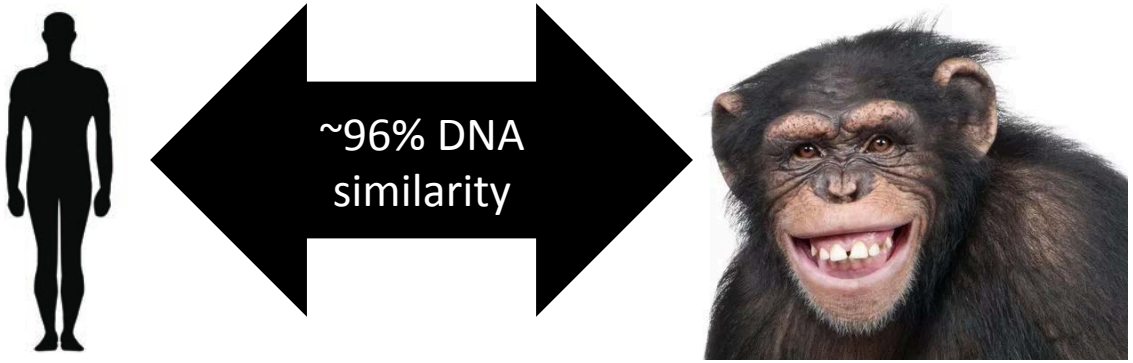
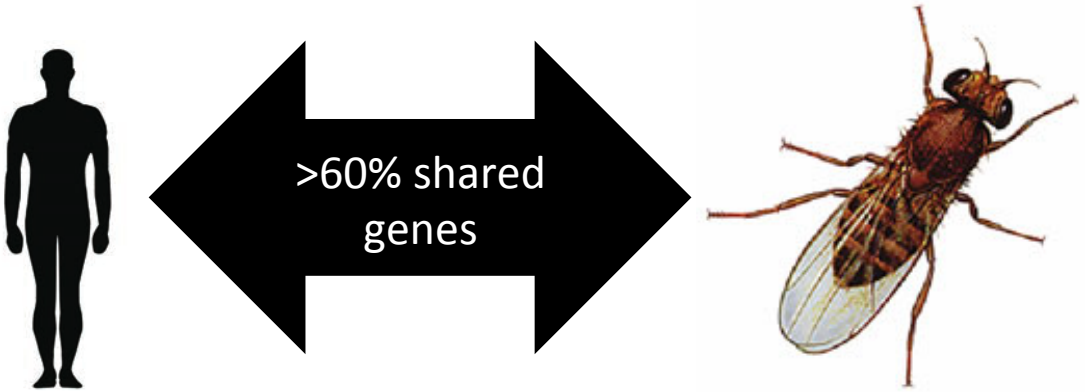
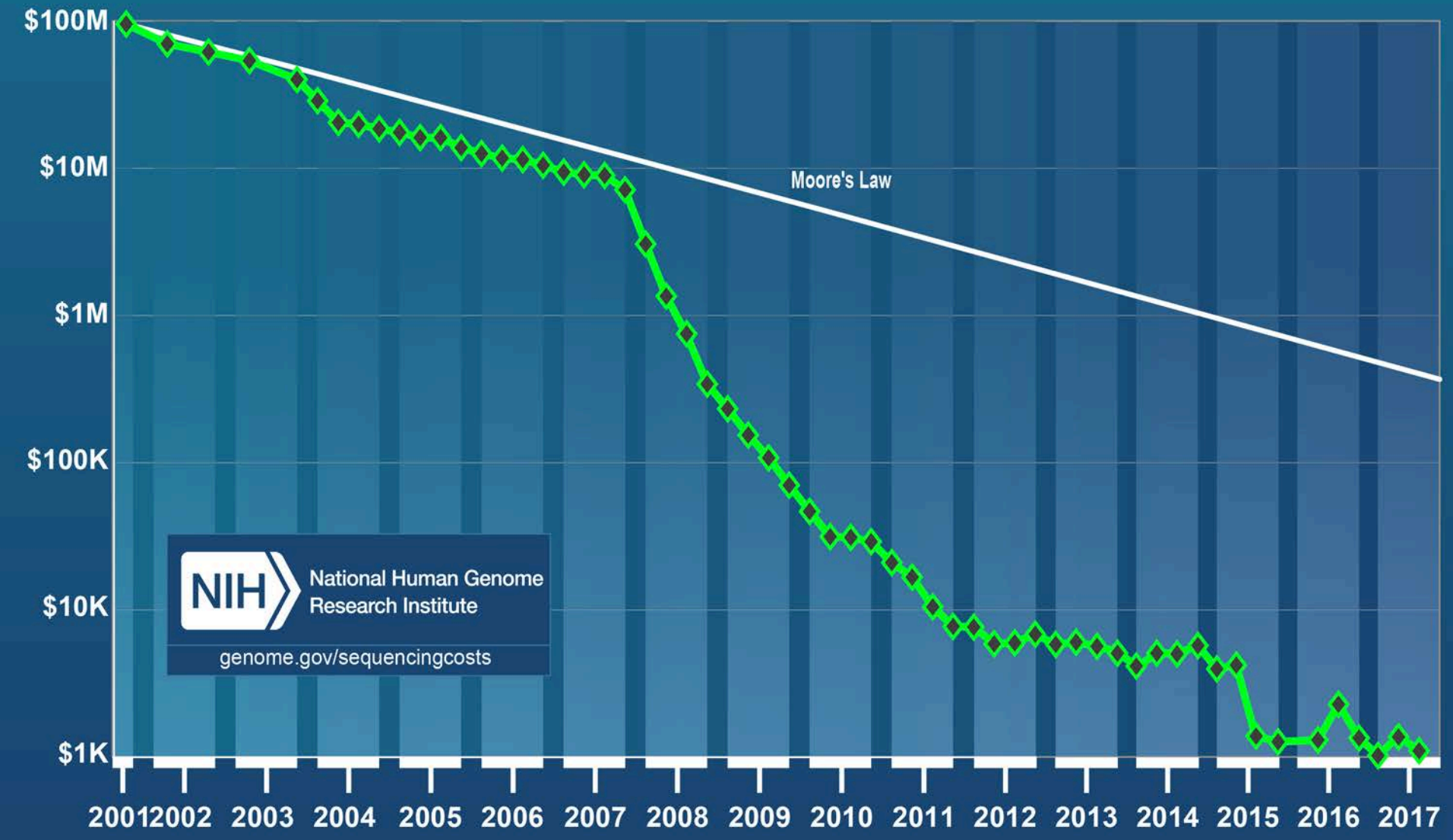
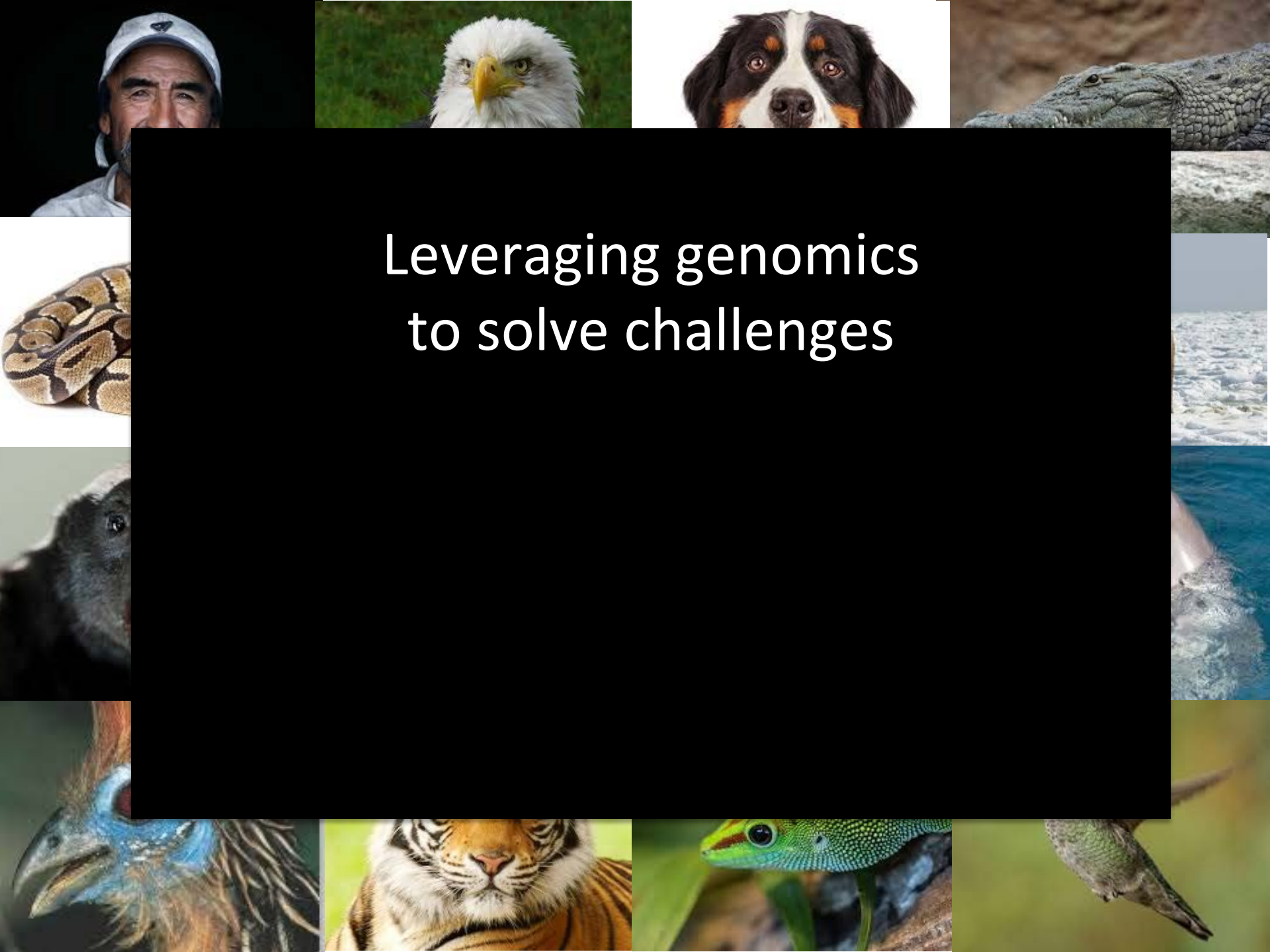
What is comparative genomics?





Cost per Genome

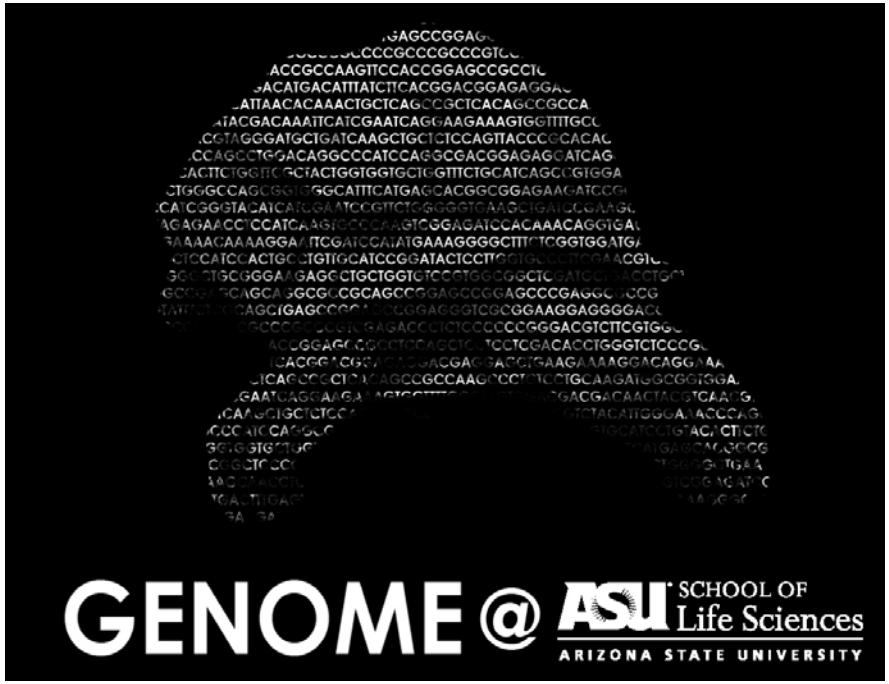




Leveraging genomics to solve challenges

Leveraging genomics to solve challenges

CONSERVATION



Tollis, DeNardo et al. (2017) *PLoS ONE*

WHOLE GENOME SHOTGUN SEQUENCING

<u>DNA:</u>
147X coverage
3,319,764,020 reads
335 Gbytes

<u>RNA-Seq:</u>
286,596,459 reads

DE NOVO ASSEMBLY

<u>Three de Bruijn assemblers</u>

- ABySS
- SOAPdenovo
- Platanus

(run iteratively)
32 CPUs, 1TB RAM

GENOME ANNOTATION

<u>Align to assembly:</u>
RNA-Seq Data
UniProtKB
NCBI proteomes

RepeatMasking

Ab-initio gene prediction

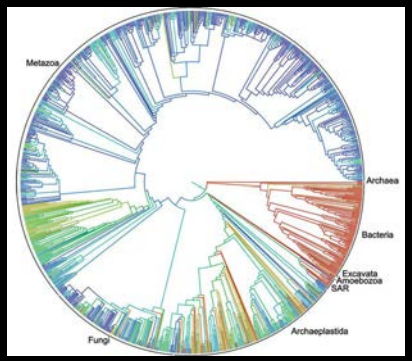
(run iteratively)
100s of CPUs

Gopherus evgoodei

Edwards, **Tollis** et al. (2016) *Ecology and Evolution*
Edwards et al. (2016) *ZooKeys*

Leveraging genomics to solve challenges

CONSERVATION



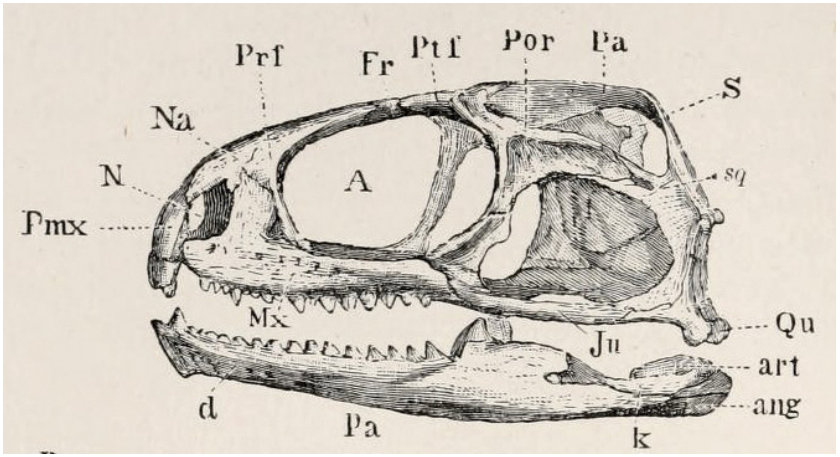
THE TREE OF LIFE

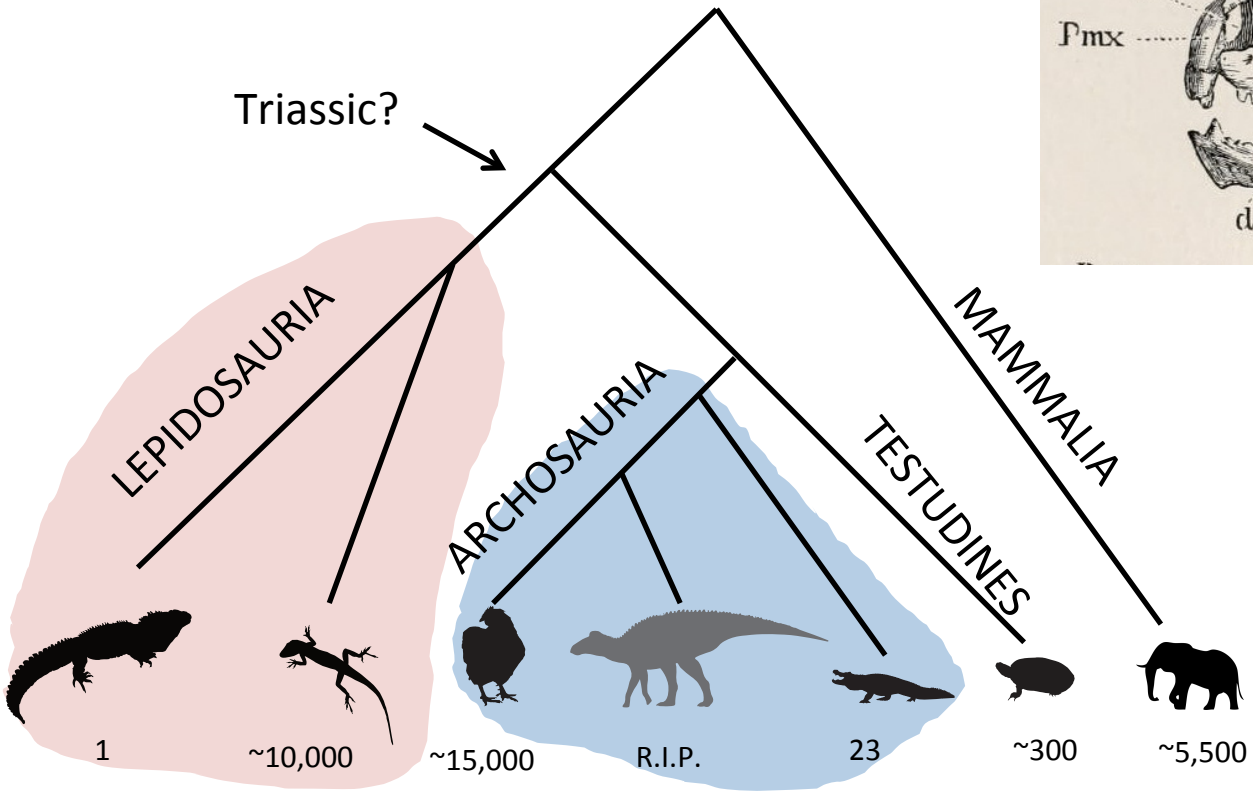

Tuatara (*Sphenodon punctatus*)
#150NotALizard

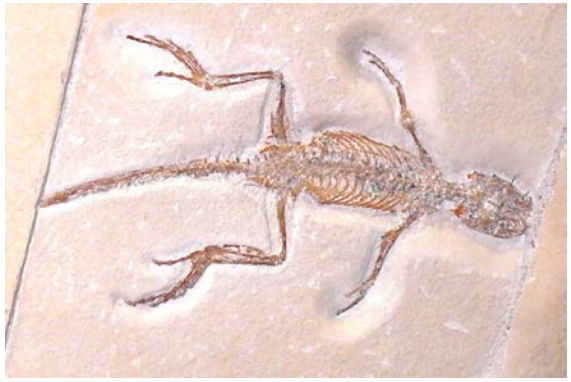
Why is the tuatara genome important?

Rhynchocephalia: Sphenodontidae: *Sphenodon punctatus*

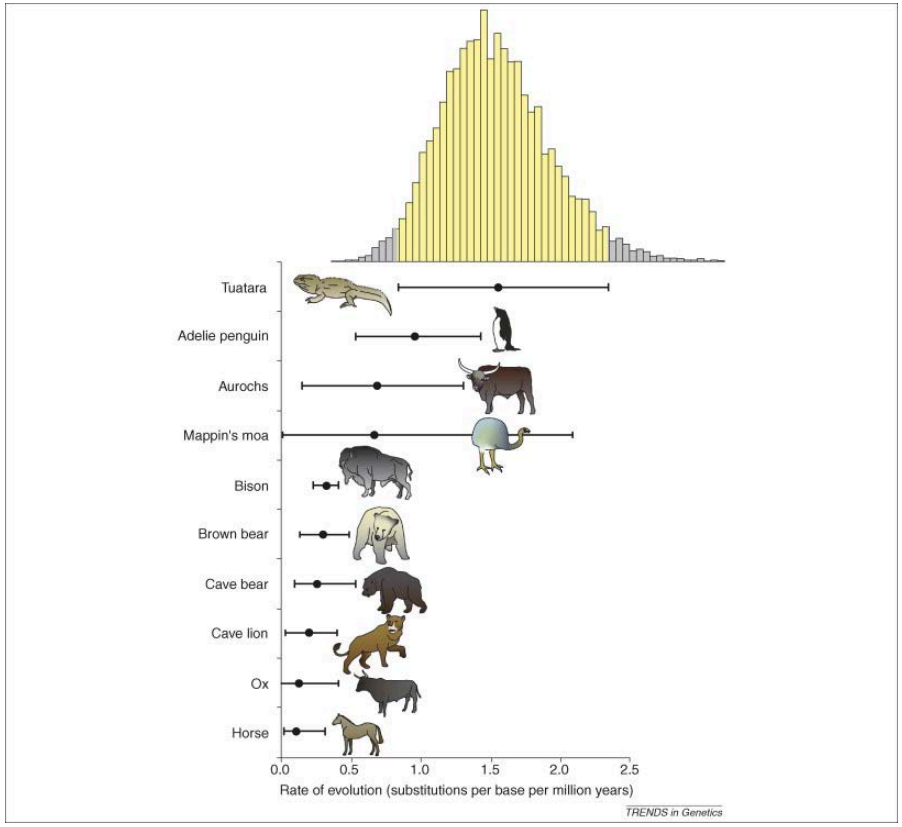
"It's a livin' fossil, silly!"







The great tuatara rate debate (2008-2009)



"Molecular and morphological evolution in tuatara are decoupled."
Subramanian et al. 2009. Trends in Genetics. Vol 25:16-18

Hay et al. (2008) *Trends in Genetics*
Subramanian et al. (2009) *Trends in Genetics*

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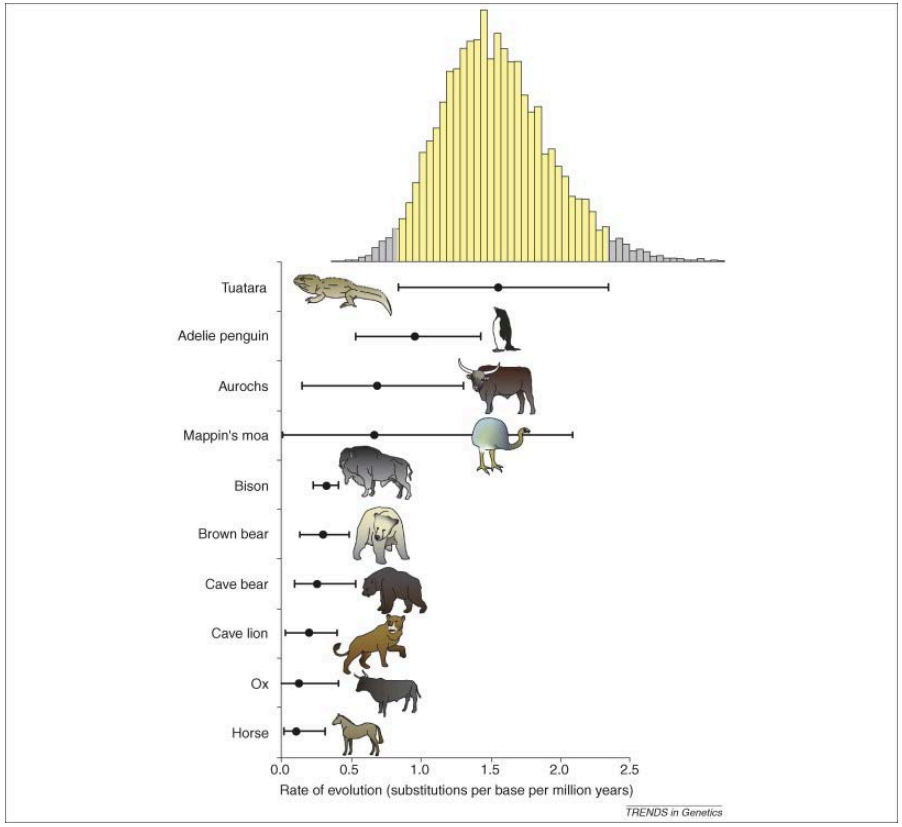

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Subramanian et al. (2009) *Trends in Genetics*

nature International weekly journal of science

comments on this story

Stories by subject

- Evolution and paleontology

Published online 27 March 2008 | Nature | doi:10.1038/news.2008.695

News

The rapid evolution of tuatara

Study of the 'living fossils' may challenge theory of rate of evolution in cold-blooded organisms.

SCIENTIFIC METHOD —

Living ~~dinosaur~~ found to be fastest evolving creature

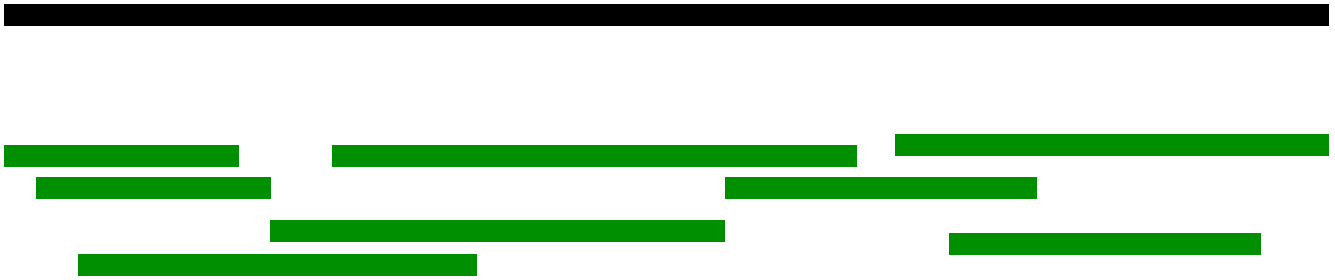
Researchers in New Zealand have found that the Tuatara, a ~~lizard~~ native to the ...

MATT FORD - 3/25/2008, 8:23 AM

6.9 L turbocharged V8, 1350 hp, top speed 276mph (444 km/h)

Just align the whole genome: local alignments using LASTZ

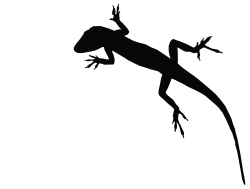
Anolis reference (AnoCar2.0)

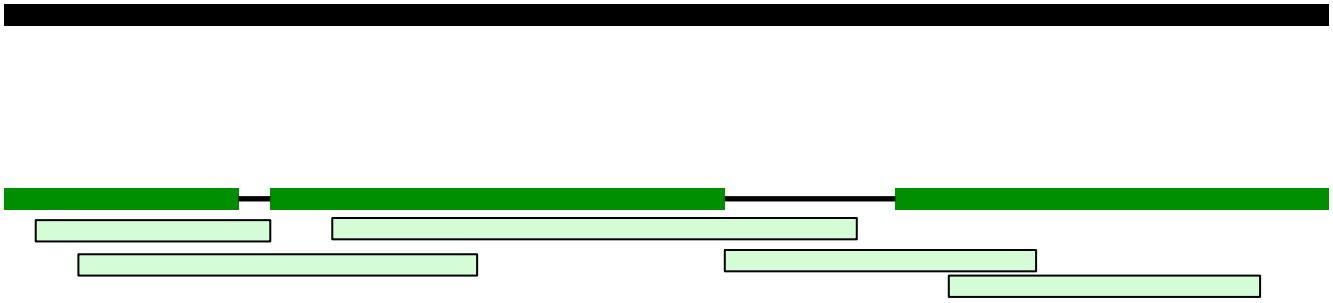


Sphenodon query

Chaining: form gapless blocks

Netting: rank and collect highest scoring chains

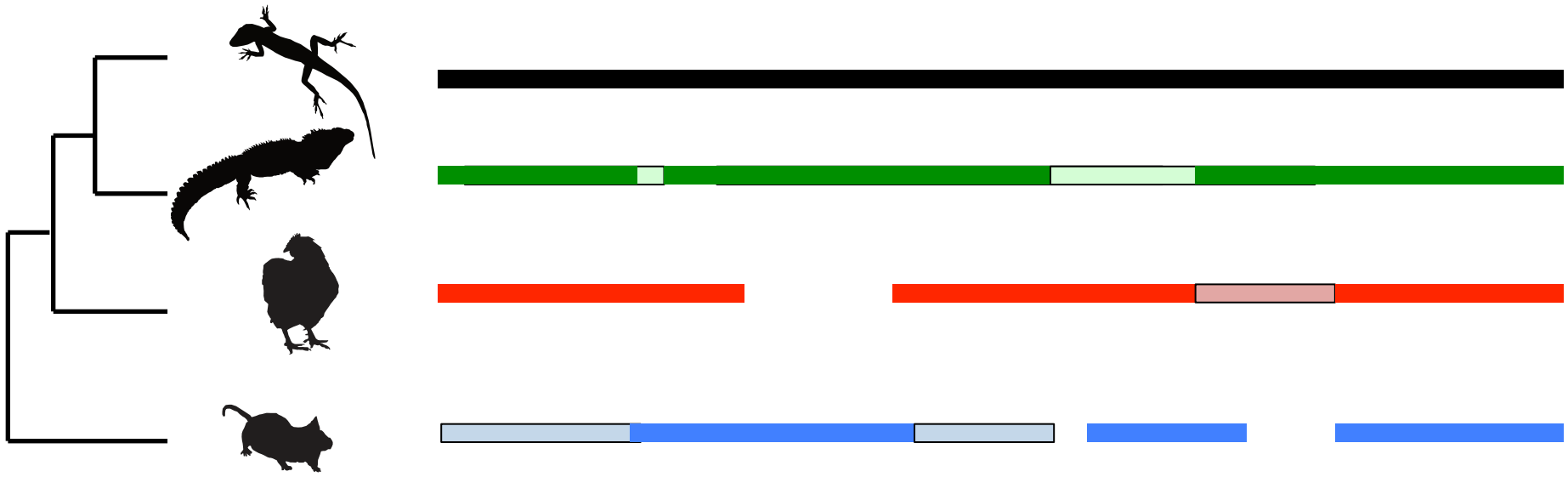




Netting: fill in with lower-scoring chains

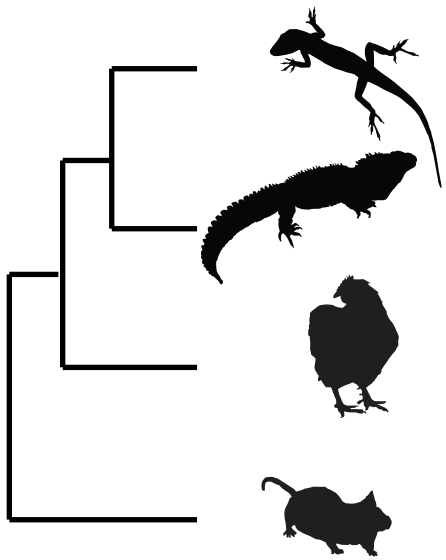
- Result: Pairwise syntenic net

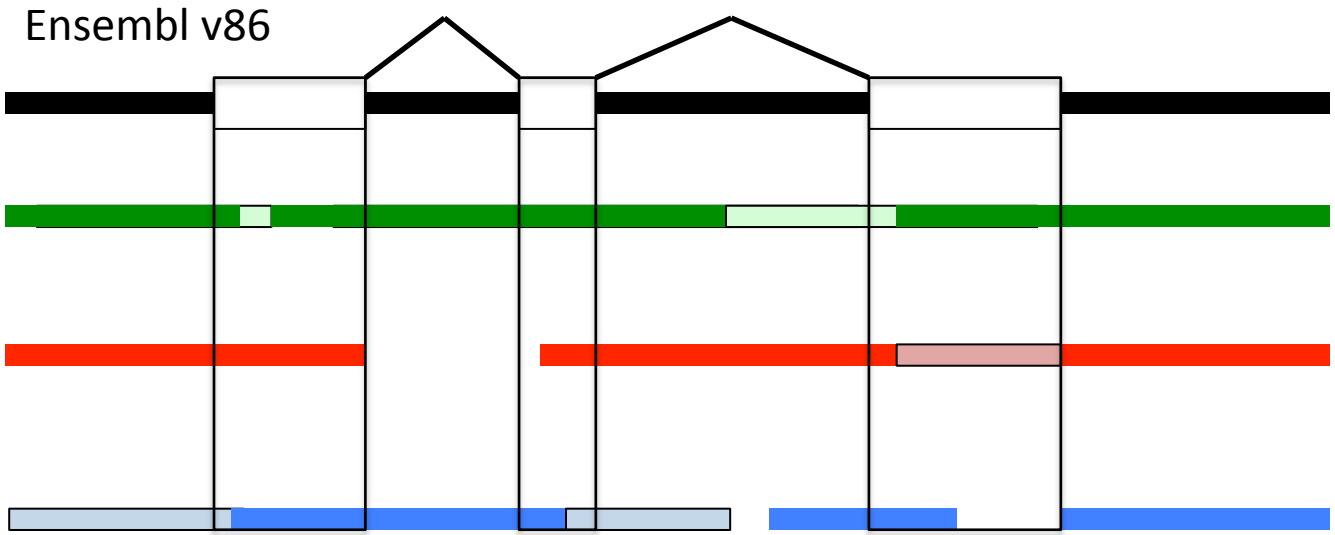
MULTIZ: create multiple alignment



- 28 vertebrates
- ~270Mbp of aligned sequence
- ~25% of the *Anolis* lizard genome = HOMOLOGY

Extract annotations using reference





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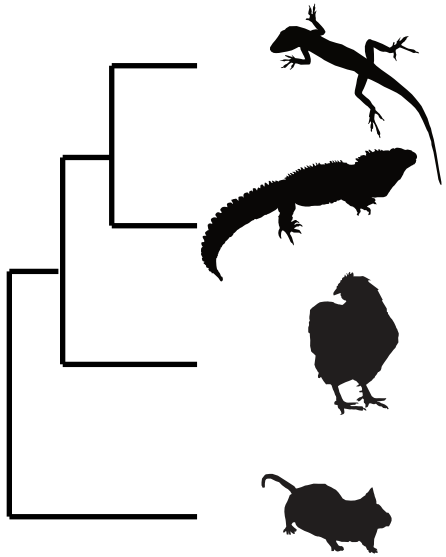
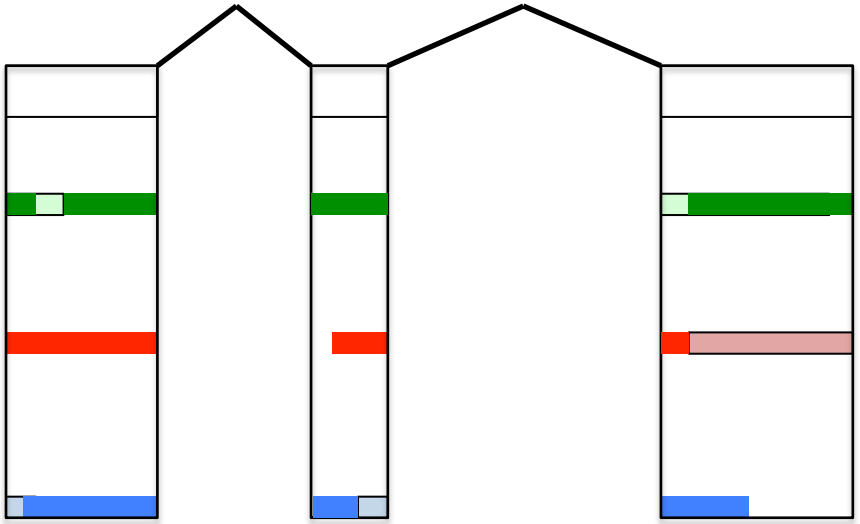
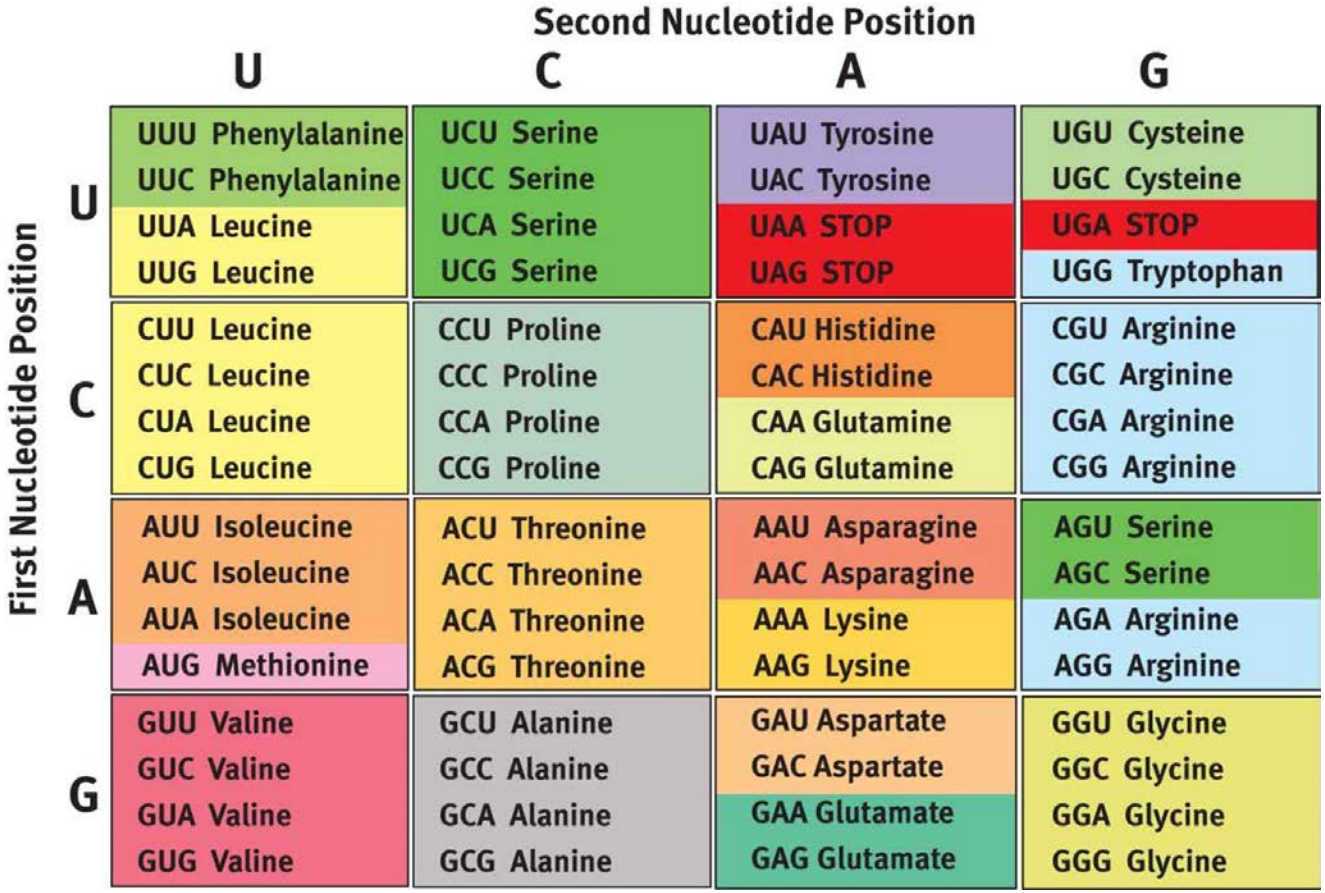
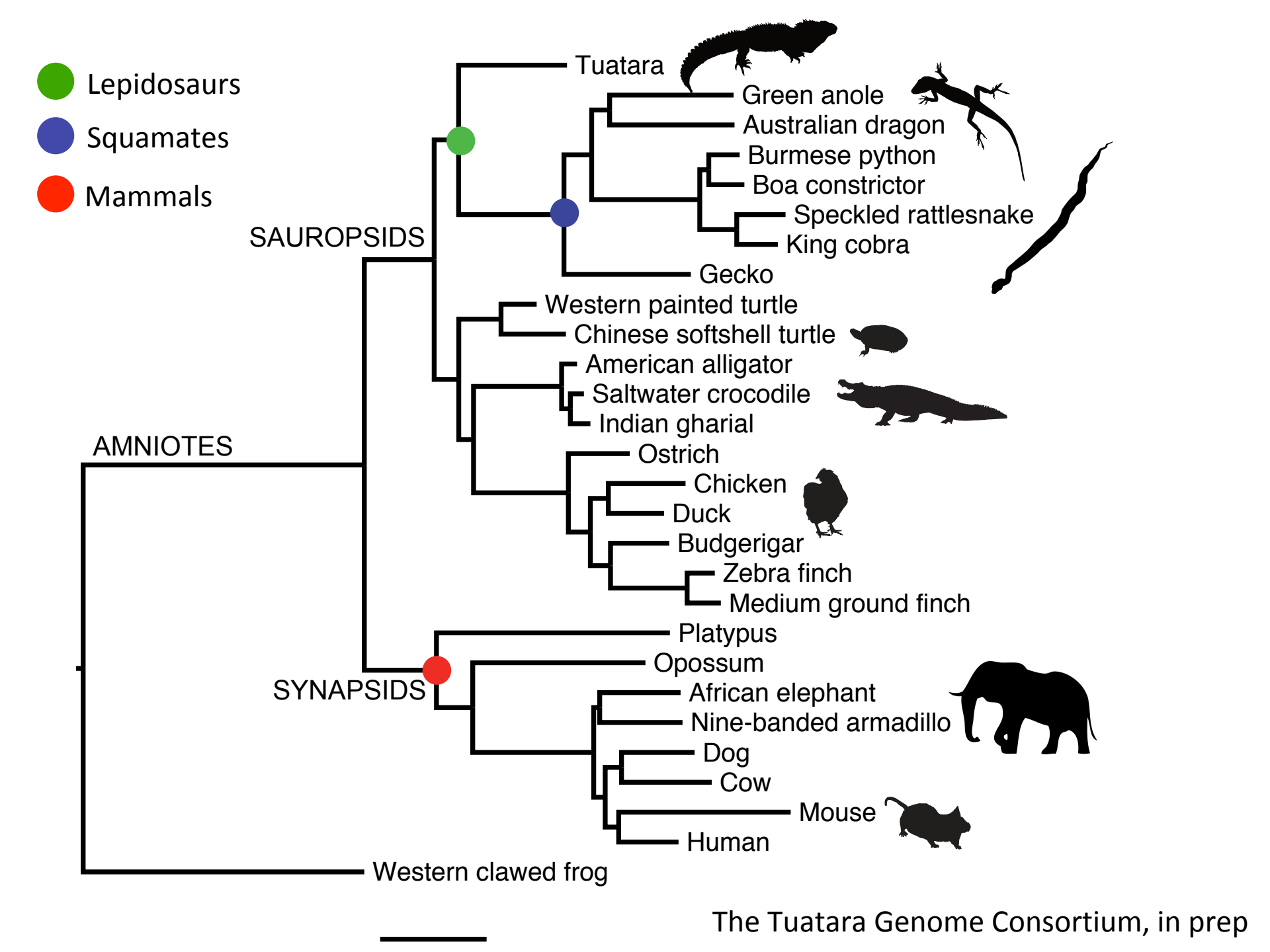




- To generate a ***neutral*** model of vertebrate evolution, we focused on fourfold degenerate sites.

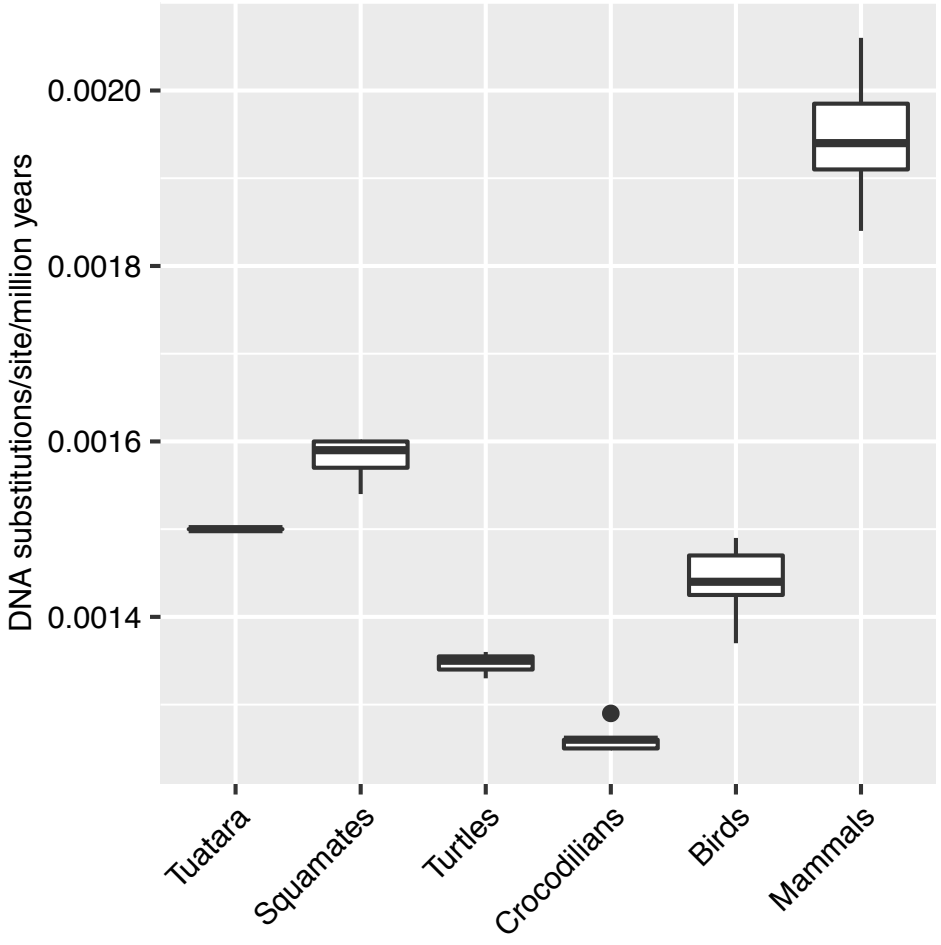
Fourfold Degenerate Sites





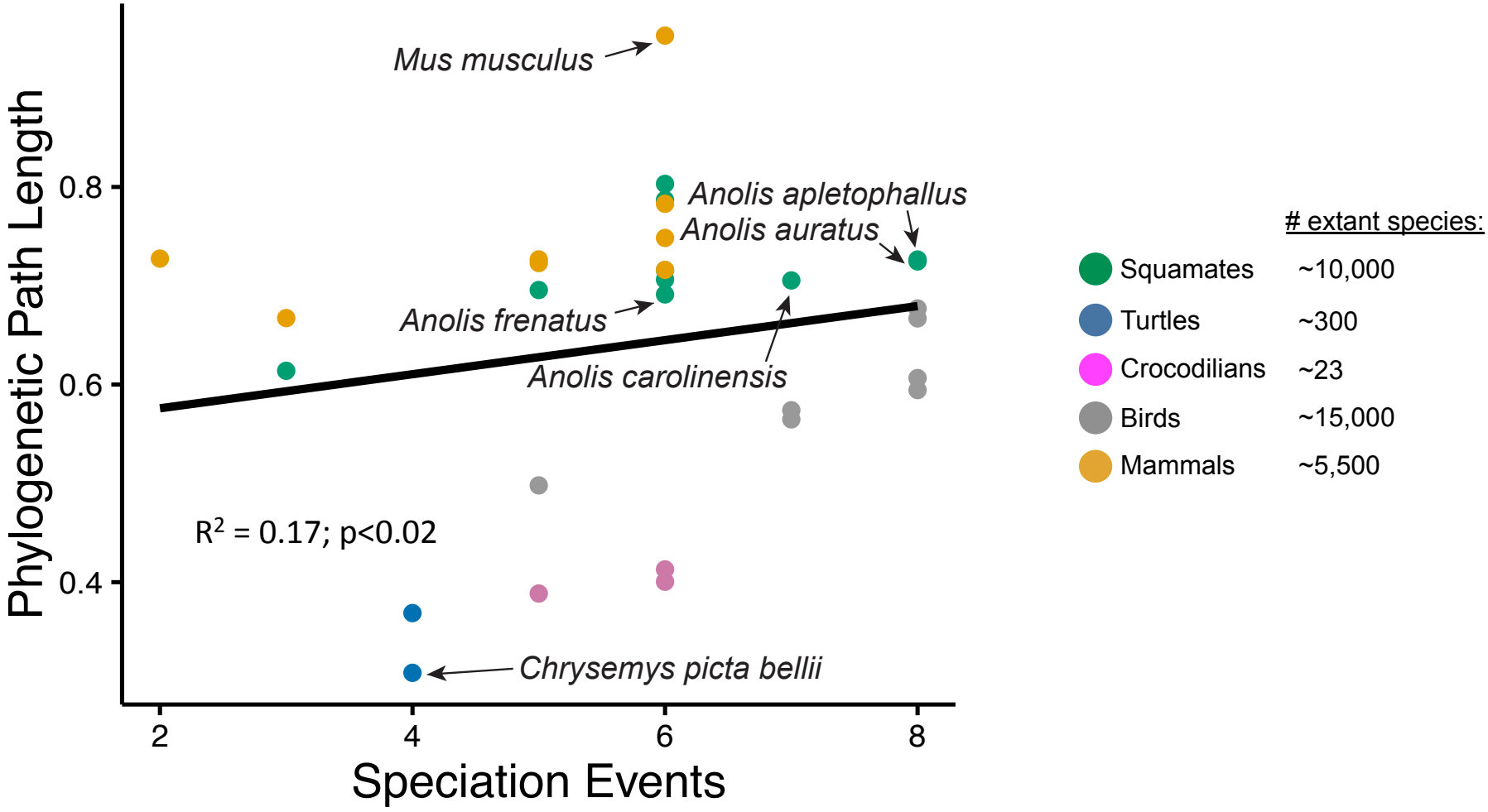
The Tuatara Genome Consortium, in prep

Tuatara is the slowest evolving living lepidosaur



The Tuatara Genome Consortium, in prep

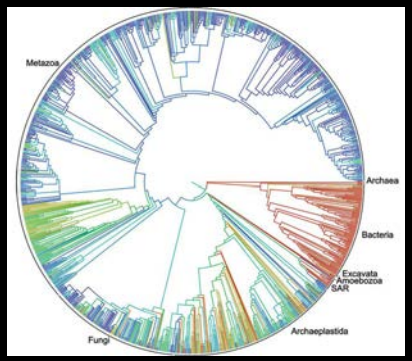
Rates of molecular evolution are coupled with rates of speciation



Tollis et al. (2018) *Genome Biology and Evolution*

Leveraging genomics to solve challenges

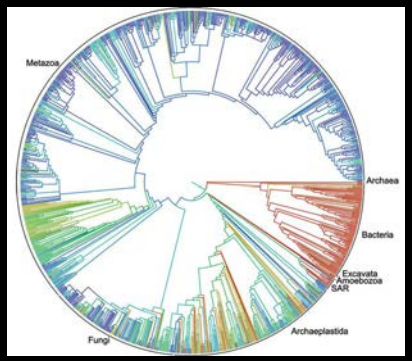
CONSERVATION



THE TREE OF LIFE

Leveraging genomics to solve challenges

CONSERVATION



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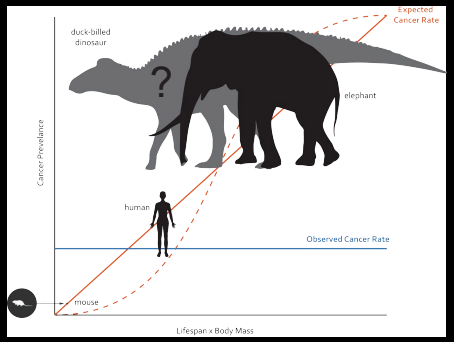
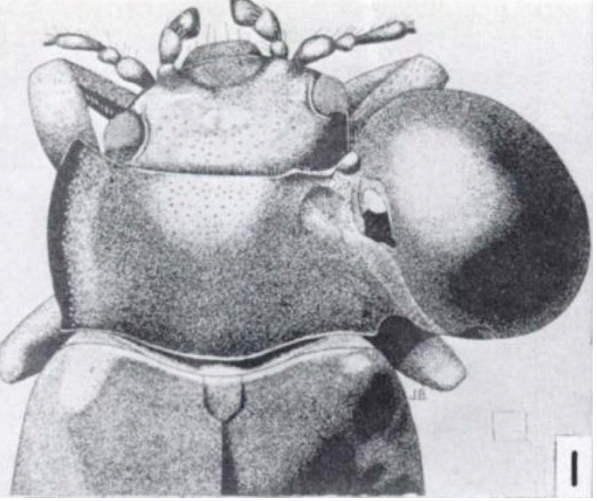
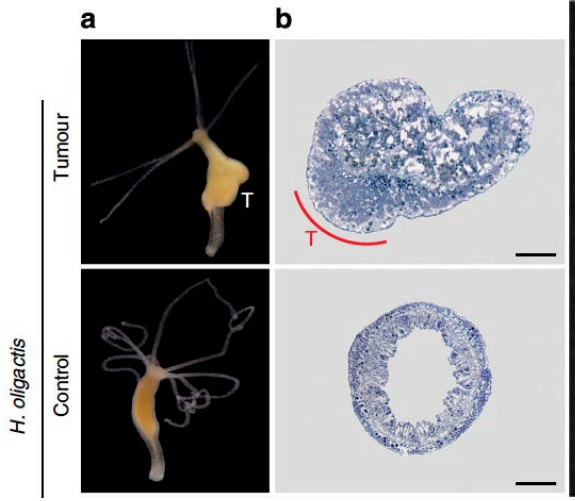
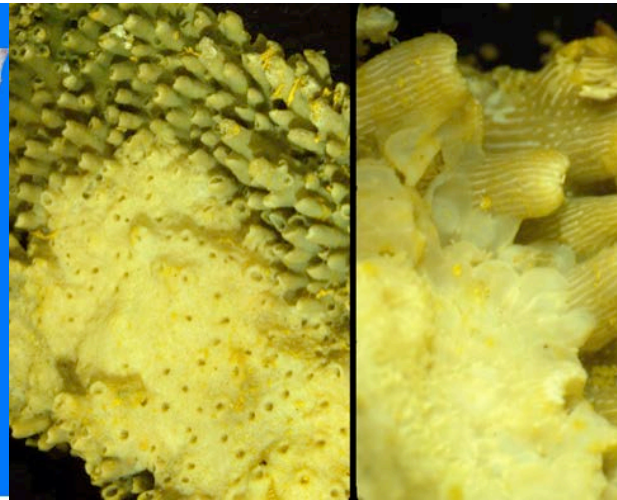


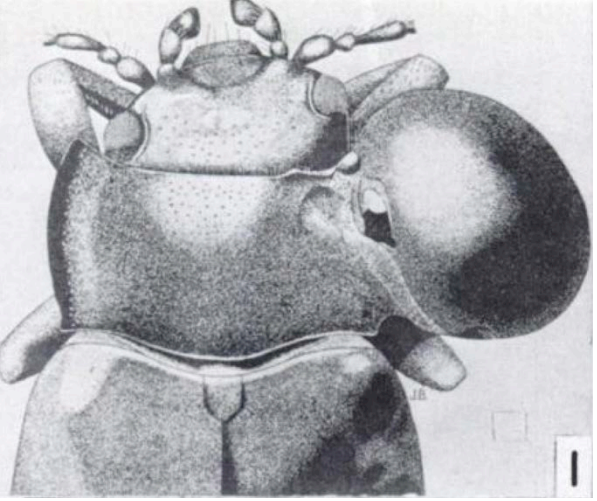
CANCER EVOLUTION

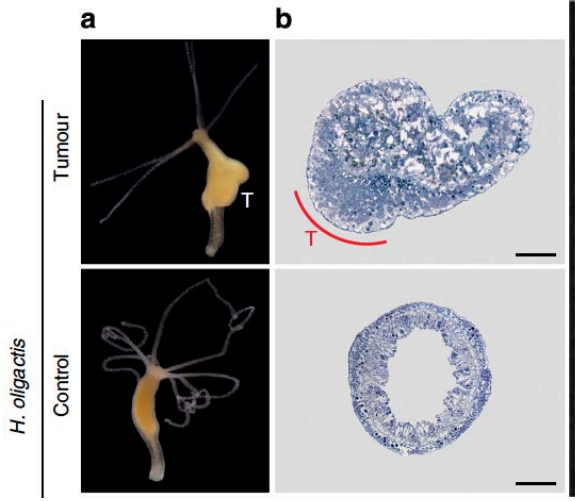




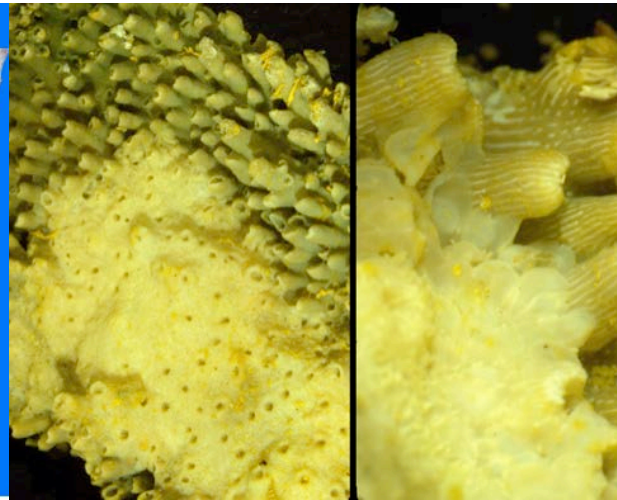
Cancer has been a selective pressure since the origin of multicellularity



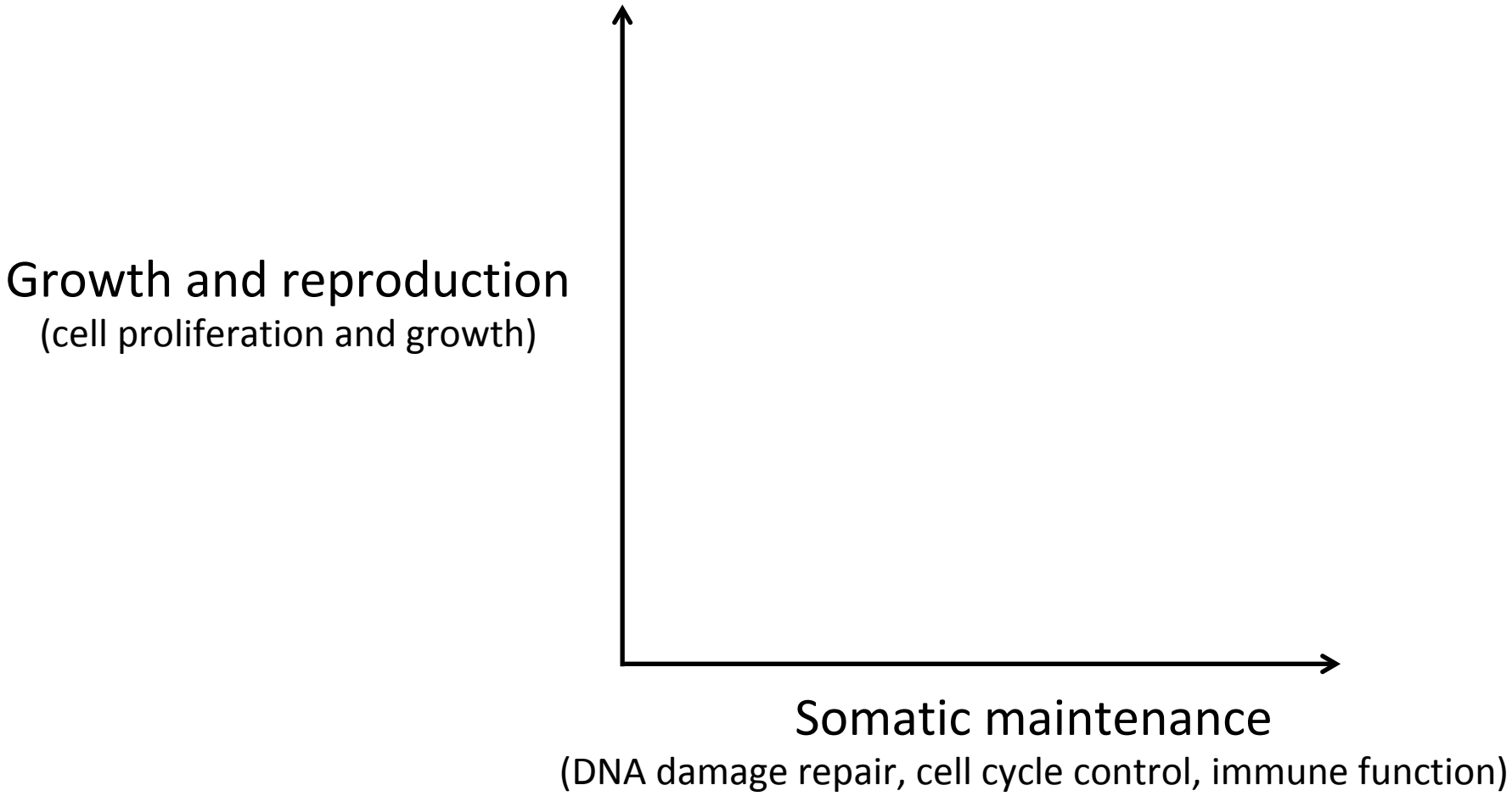




So why is there still cancer?



There are trade-offs with cancer defenses



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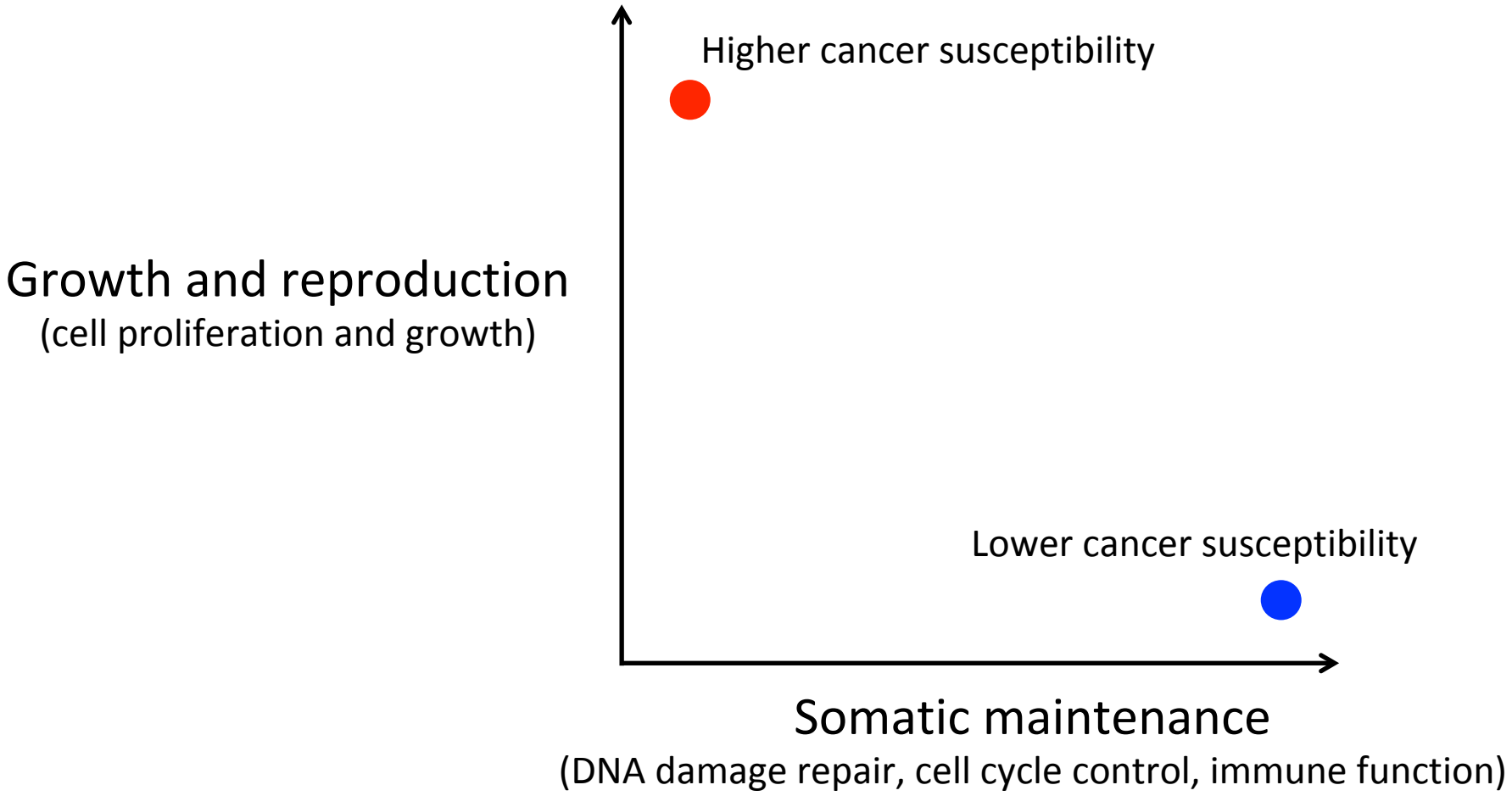
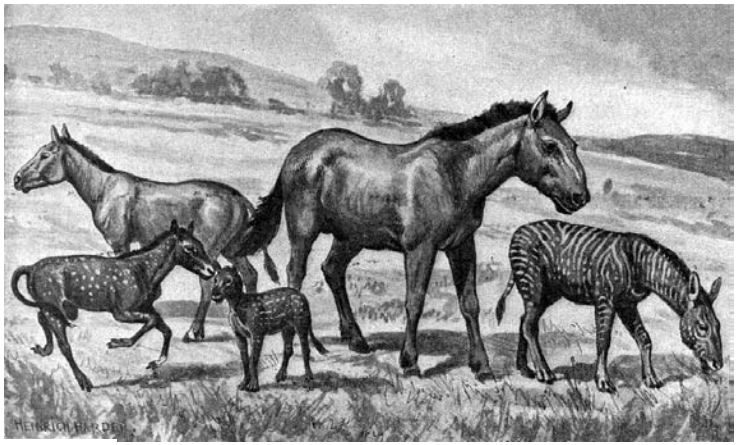
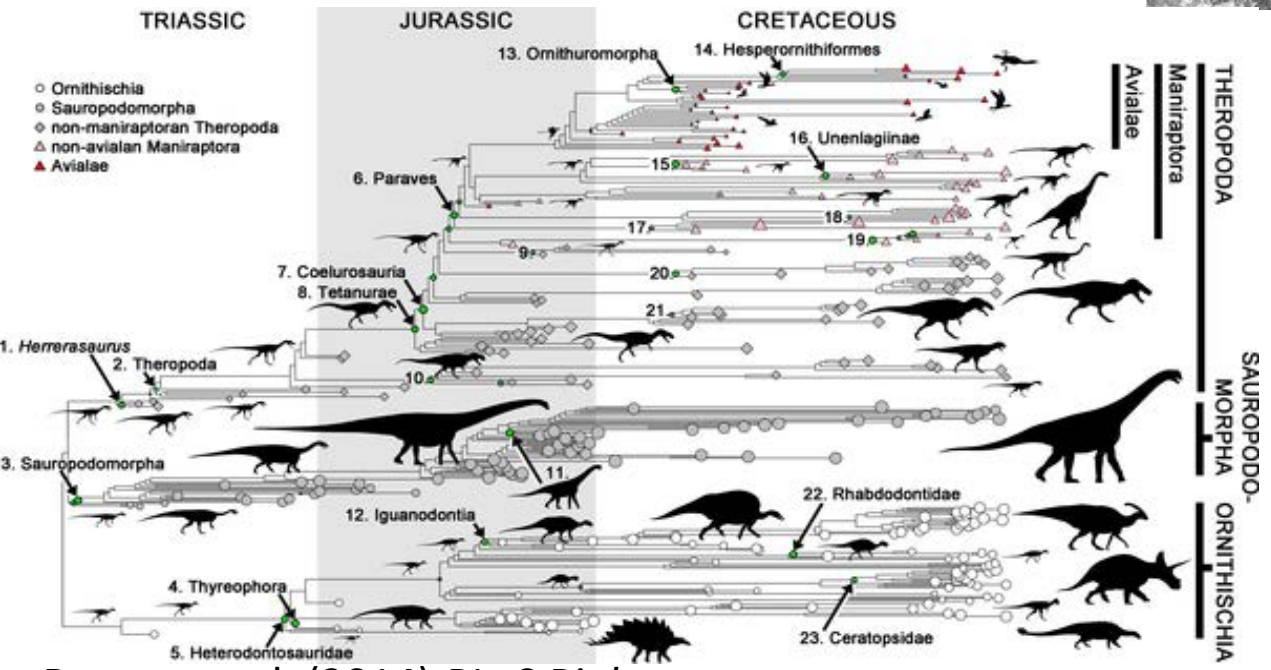


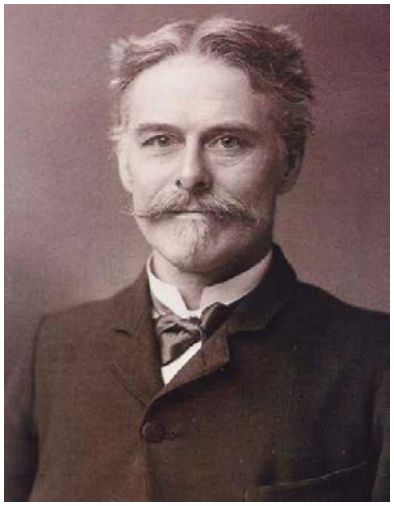
Body Size and Macroevolution

- Cope's Rule





Benson et al. (2014) *PLoS Biology*

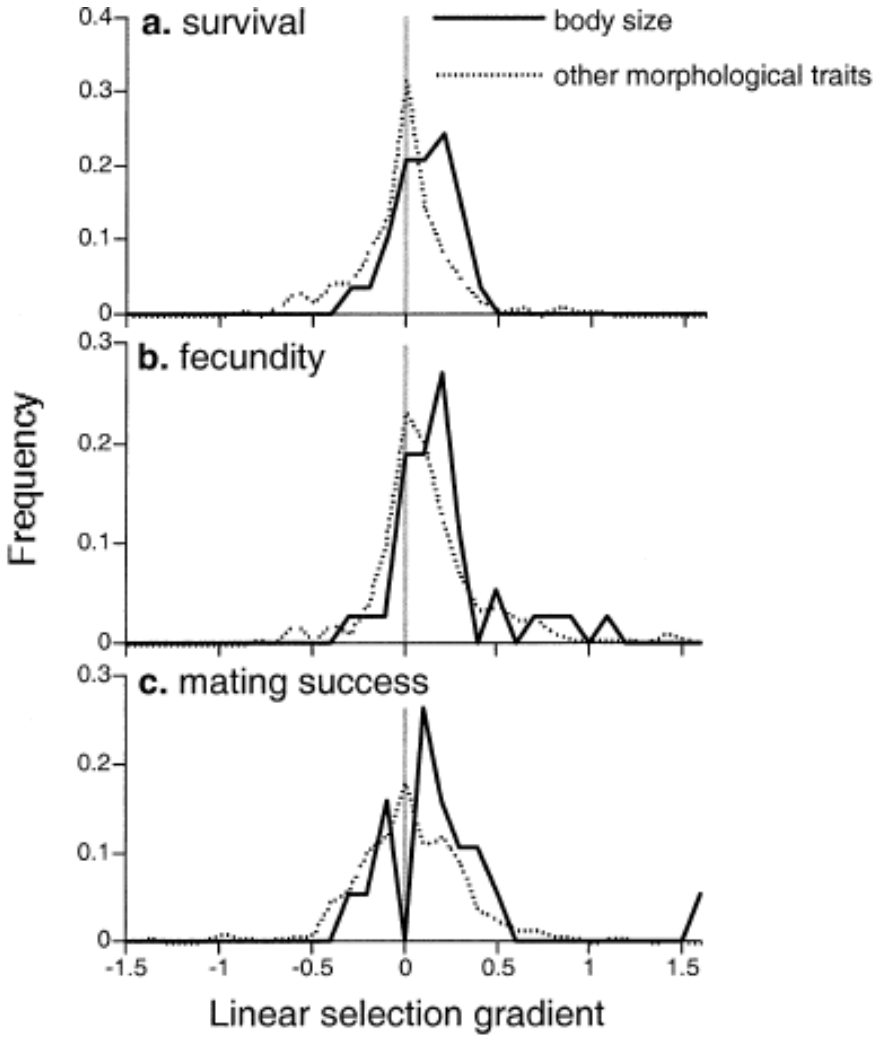


Edward Drinker Cope

Cope's Rule and Mammals

Large Body Size at the Population Level

- → directional selection



Kingsolver and Pfennig (2004) *Evolution*

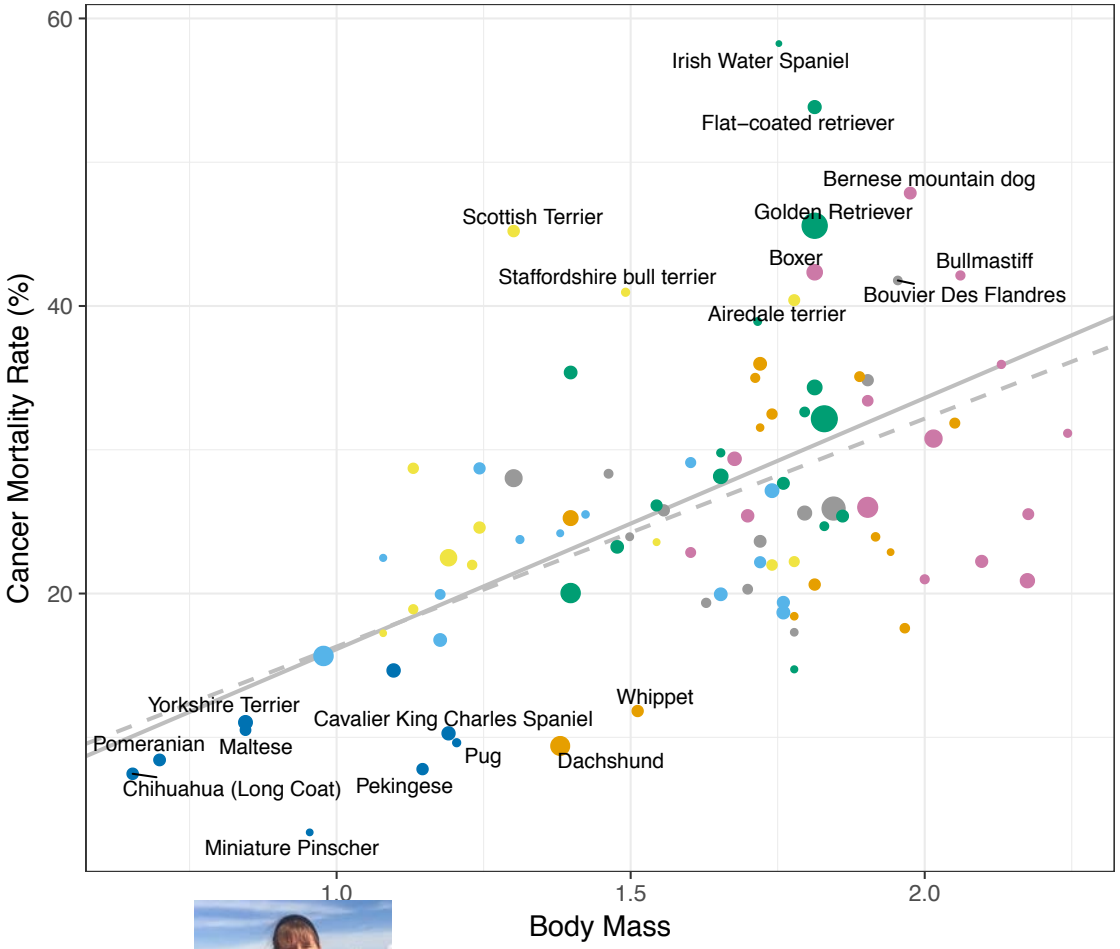
Body Size and Cancer in Humans

Kabat et al. (2013) Adult Stature and Risk of Cancer at Different Anatomic Sites in a Cohort of Postmenopausal Women.

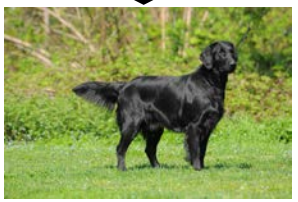
Batty et al. (2006) Adult height in relation to mortality from 14 cancer sites in men in London (UK): evidence from the original Whitehall study.

Cancer Risk is Related to Breed Body Size in Purebred Dogs

Low Cancer Risk Breeds



High Cancer Risk Breeds



Tollis, Balsley et al. in prep

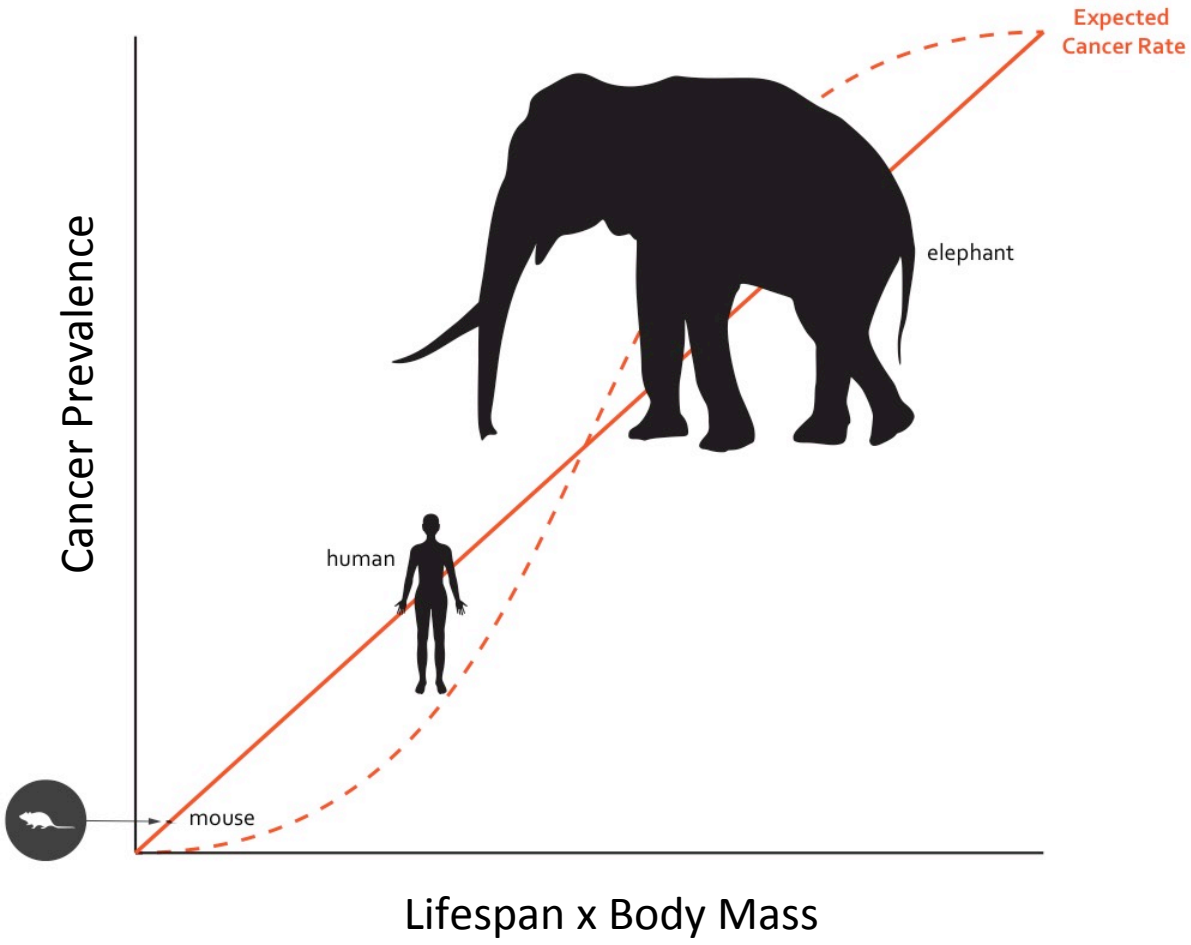
Body Size and Cancer

- Caloric intake?
- Growth factors?
- More cells?

Kabat et al. (2013) Adult Stature and Risk of Cancer at Different Anatomic Sites in a Cohort of Postmenopausal Women.

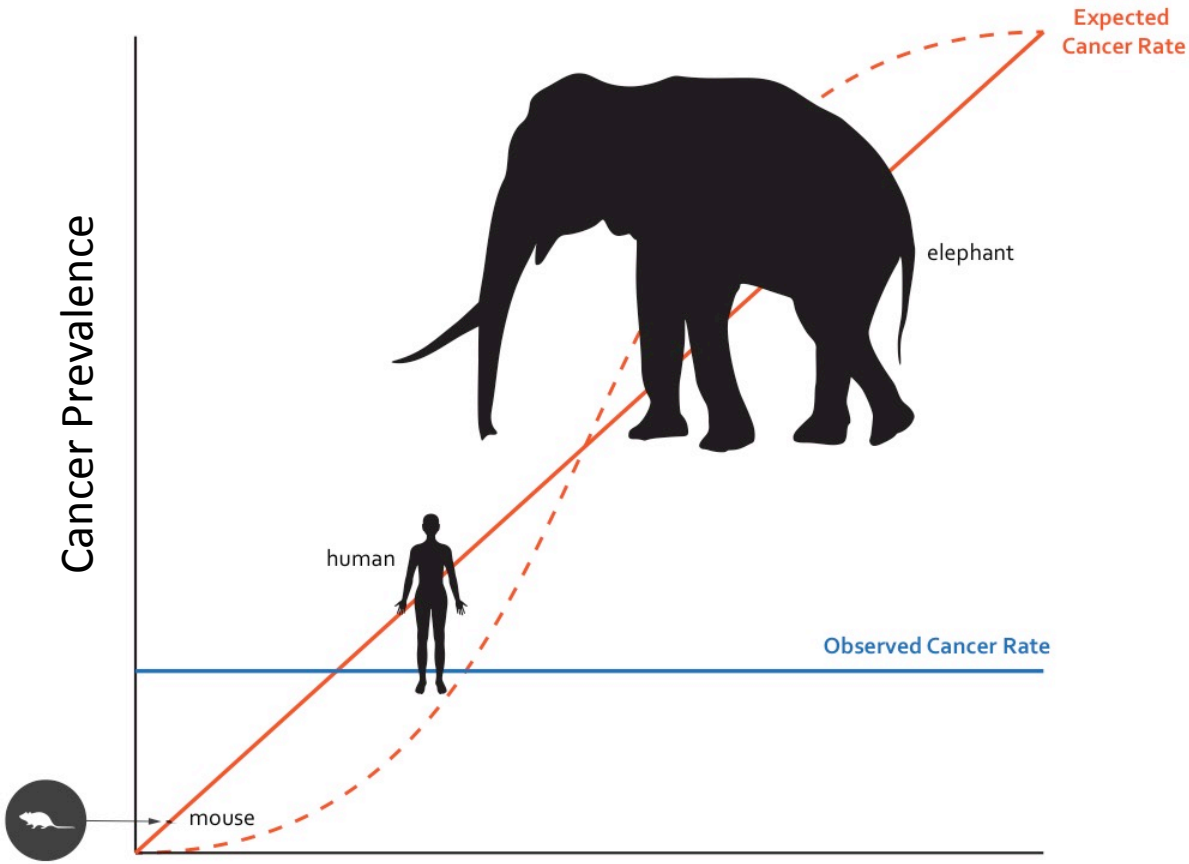
Batty et al. (2006) Adult height in relation to mortality from 14 cancer sites in men in London (UK): evidence from the original Whitehall study.

We expect large long-lived animals to have more cancer…



Tollis et al. (2017) *BMC Biology*

…but they do not.



Tollis et al. (2017) *BMC Biology*

Peto's Paradox

"A man has 1000 times as many cells as a mouse... and we usually live at least 30 times as long as mice… However… the probabilities of carcinoma induction in mice and in men are not vastly different."

--Richard Peto (1977)

Cancer risk ~ number of cell divisions

yet

Cancer is not a major form of mortality for large and long-lived wild animals

Peto's Paradox

"A man has 1000 times as many cells as a mouse... and we usually live at least 30 times as long as mice… However… the probabilities of carcinoma induction in mice and in men are not vastly different."

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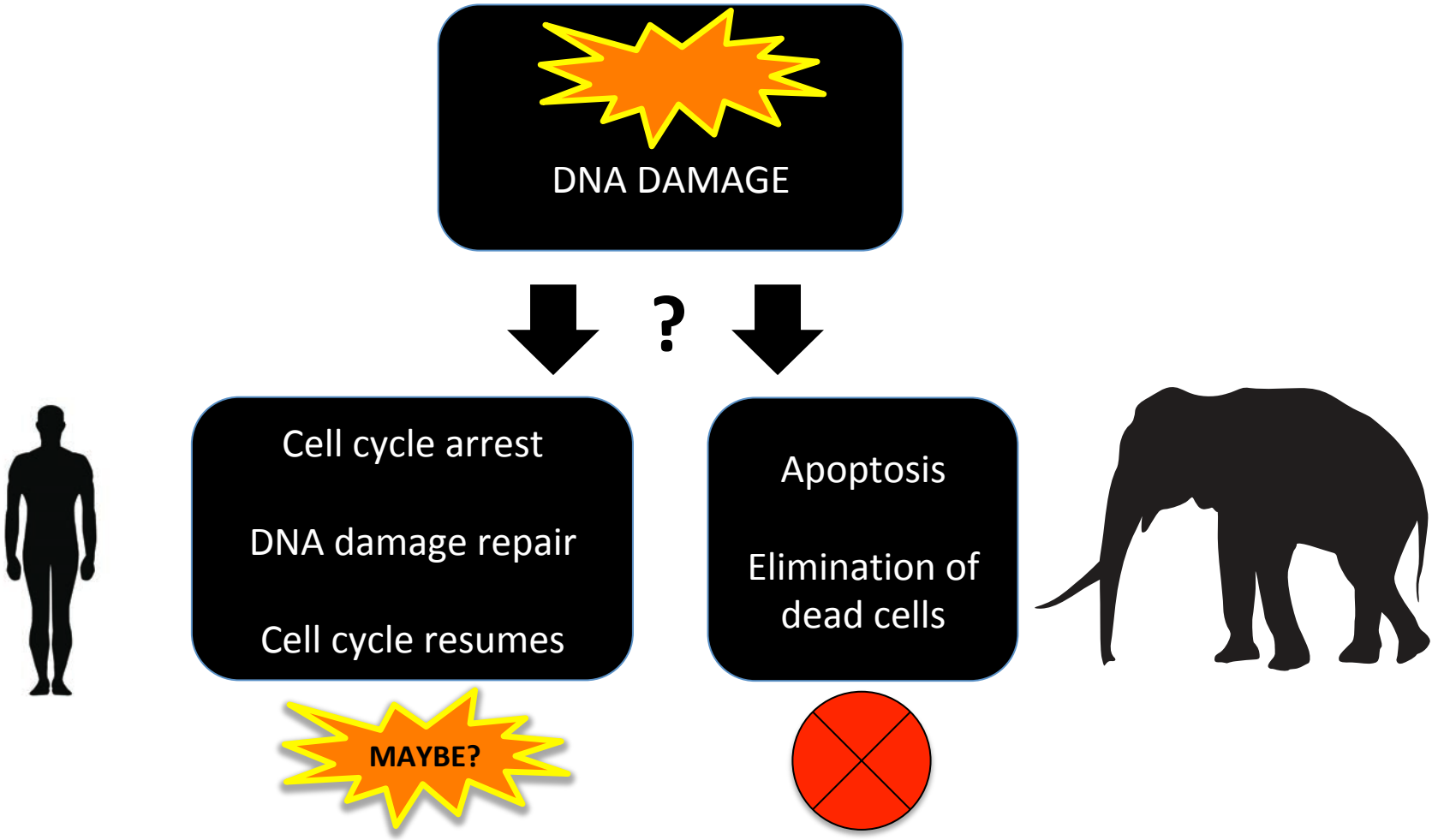
Cancer risk ~ number of cell divisions

yet

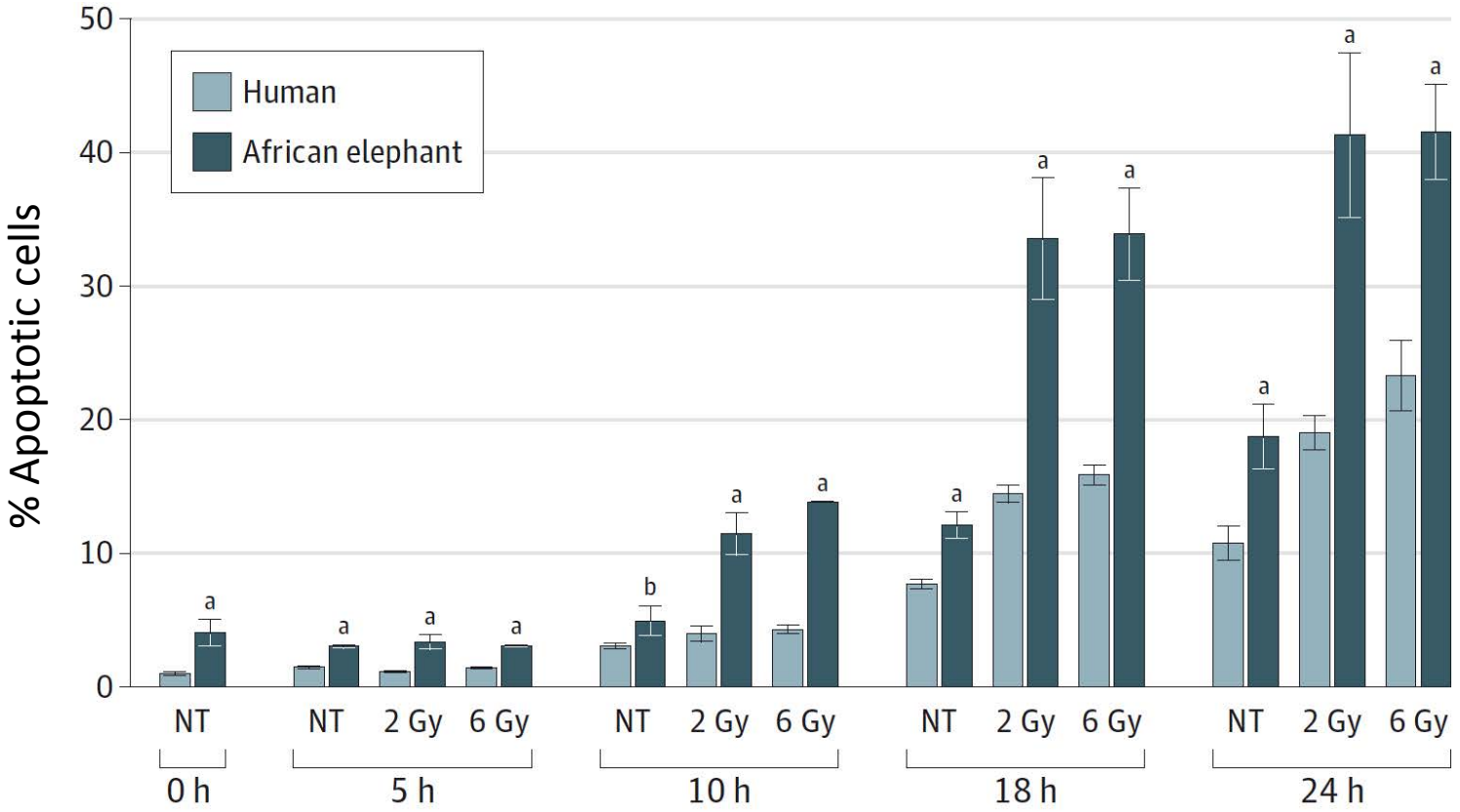
Cancer is not a major form of mortality for large and long-lived wild animals

Solving Peto's Paradox can show us how *NATURAL SELECTION* has beat cancer

Apoptosis as a Means of Cancer Suppression

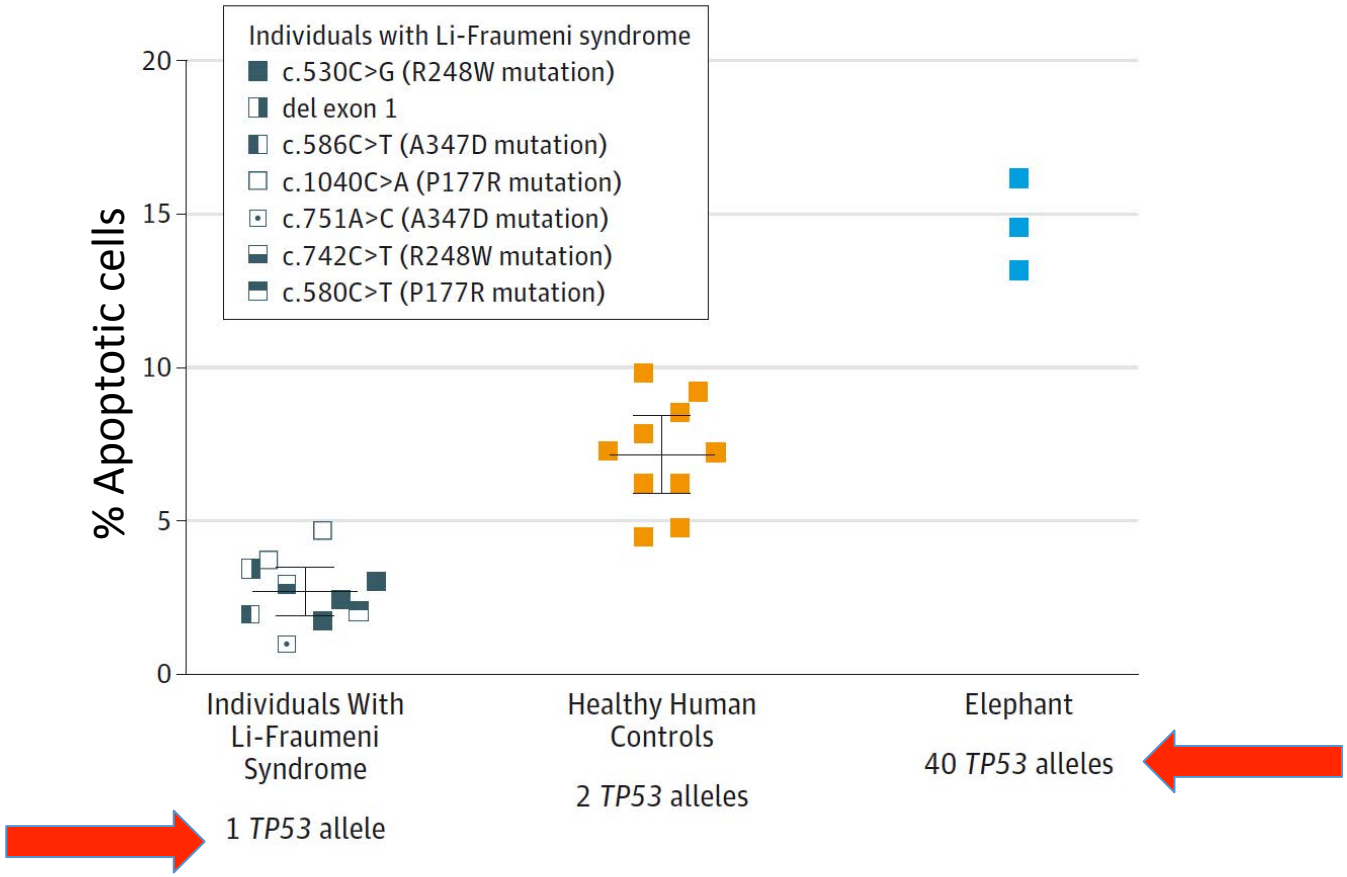


DNA-Damaged Elephant Cells undergo More Apoptosis



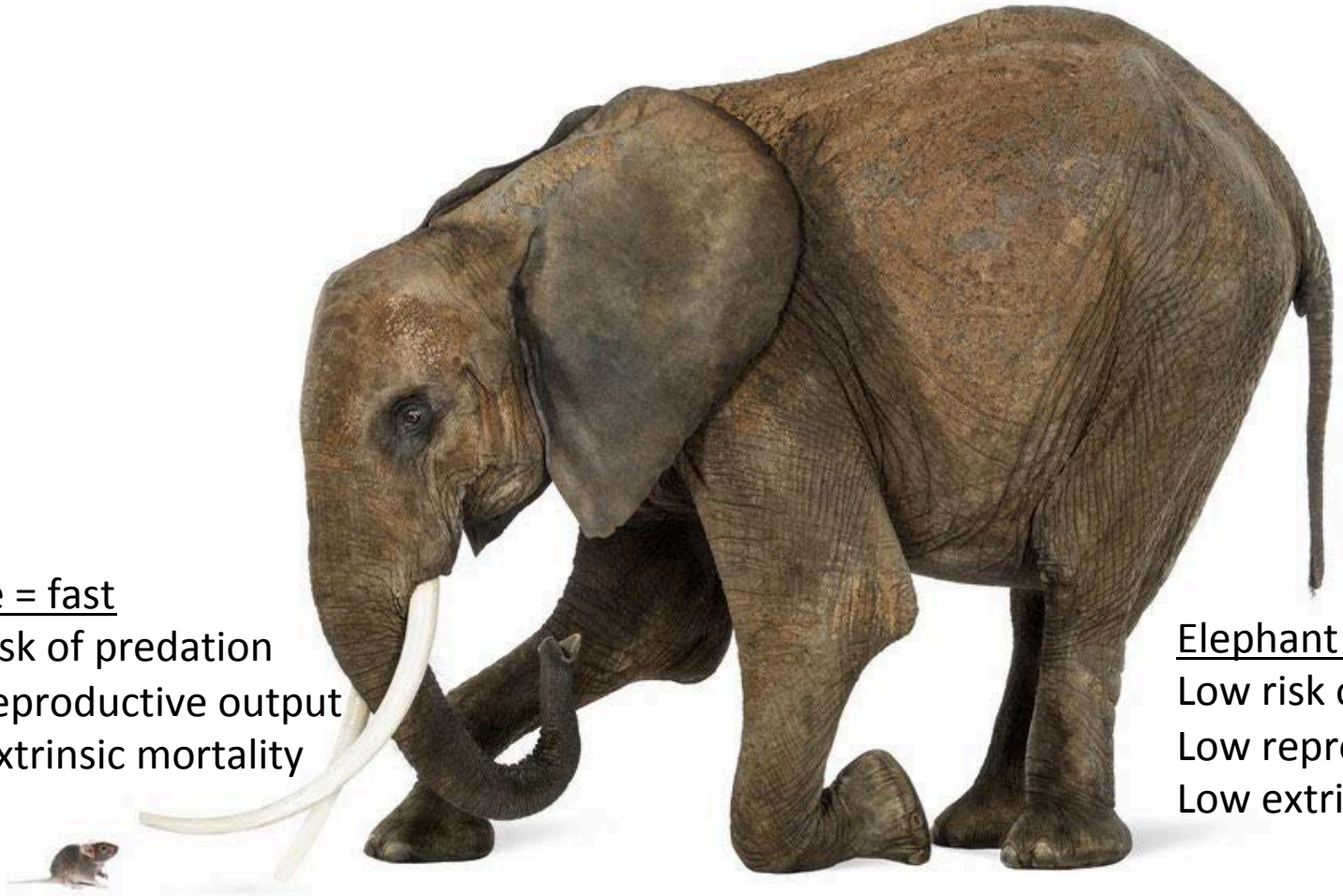
Abegglen et al. (2015) *JAMA*

Apoptotic Response is Related to the Number of TP53 Alleles



Abegglen et al. (2015) *JAMA*

Life Histories and Cancer Suppression as an Adaptation



Mouse = fast
High risk of predation
High reproductive output
High extrinsic mortality

Elephant = slow
Low risk of predation
Low reproductive output
Low extrinsic mortality

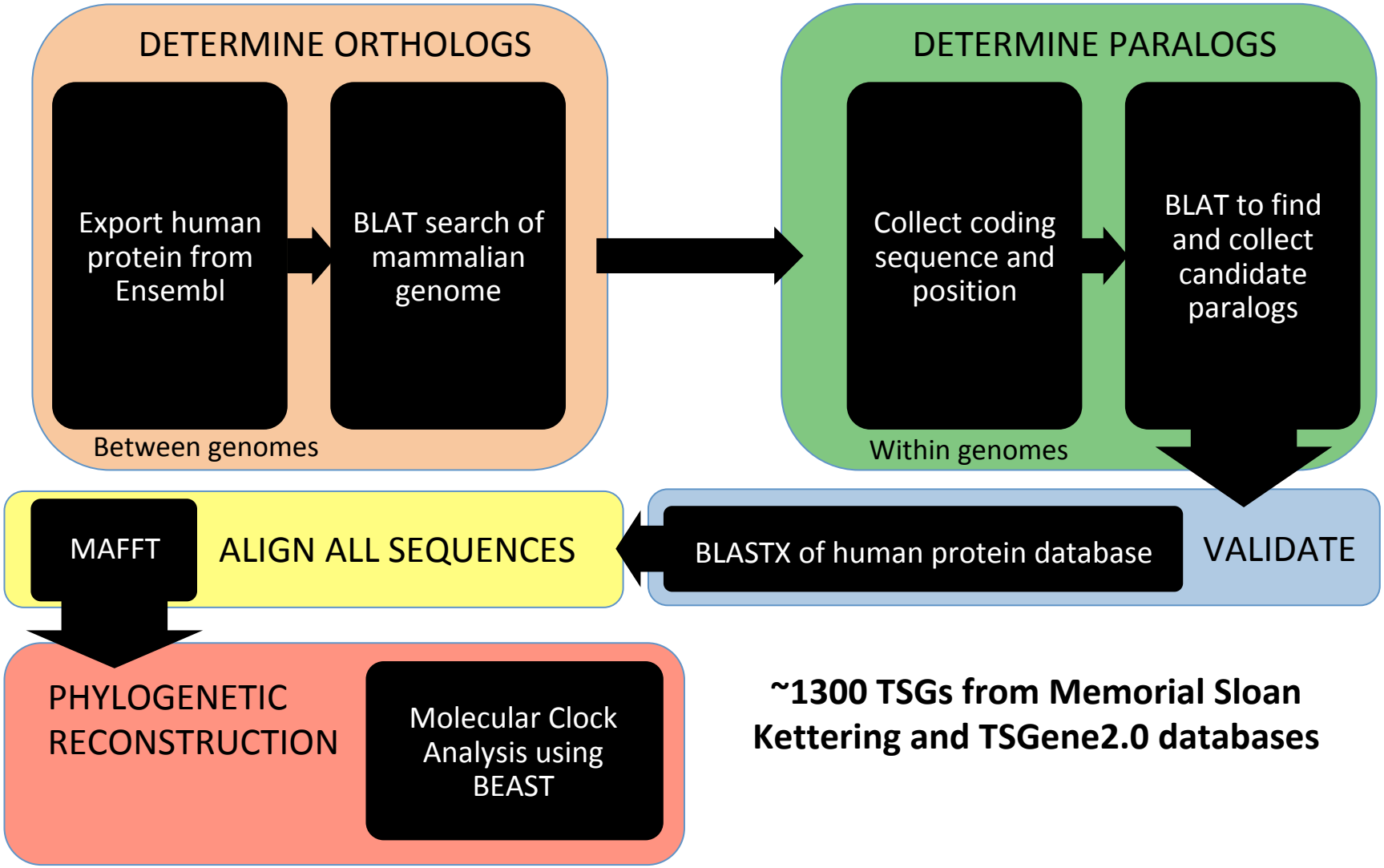
Are there TSG duplications in other giant and long-lived mammals?

Evolution of cancer suppression as revealed by mammalian comparative genomics

Marc Tollis[1,2], Joshua D Schiffman[3] and Amy M Boddy[1]

Tollis et al. (2017) *Current Opinion in Genetics and Development*

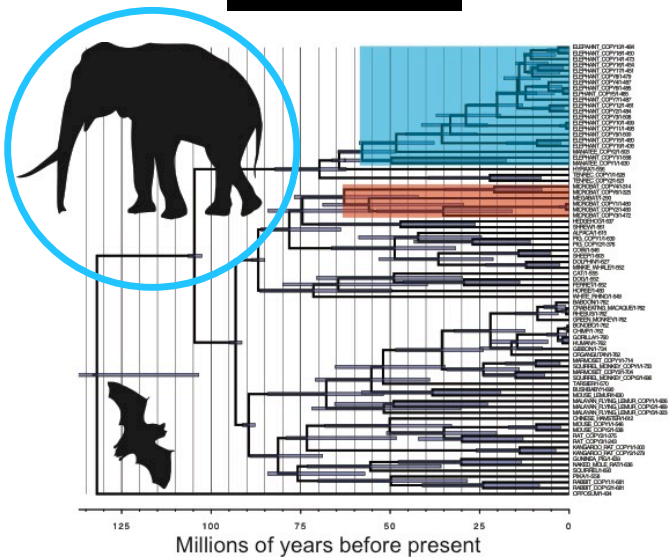
Discovering Gene Duplications:
Bioinformatics Pipeline



~1300 TSGs from Memorial Sloan Kettering and TSGene2.0 databases

TSG Duplications in Mammalian Genomes

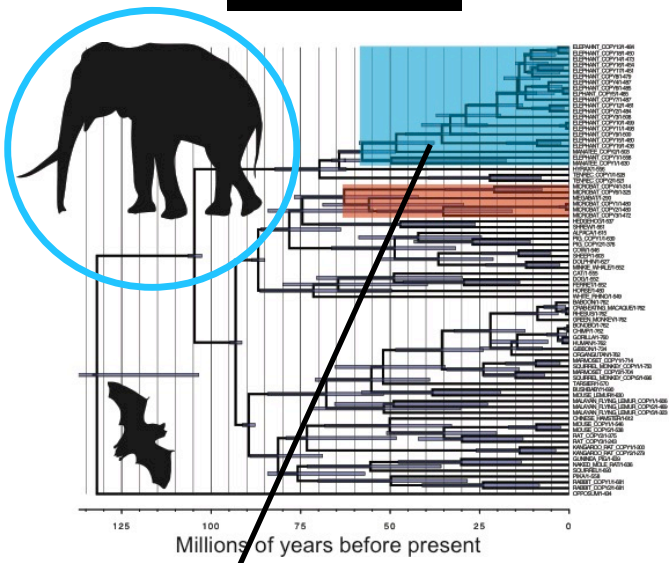
TP53



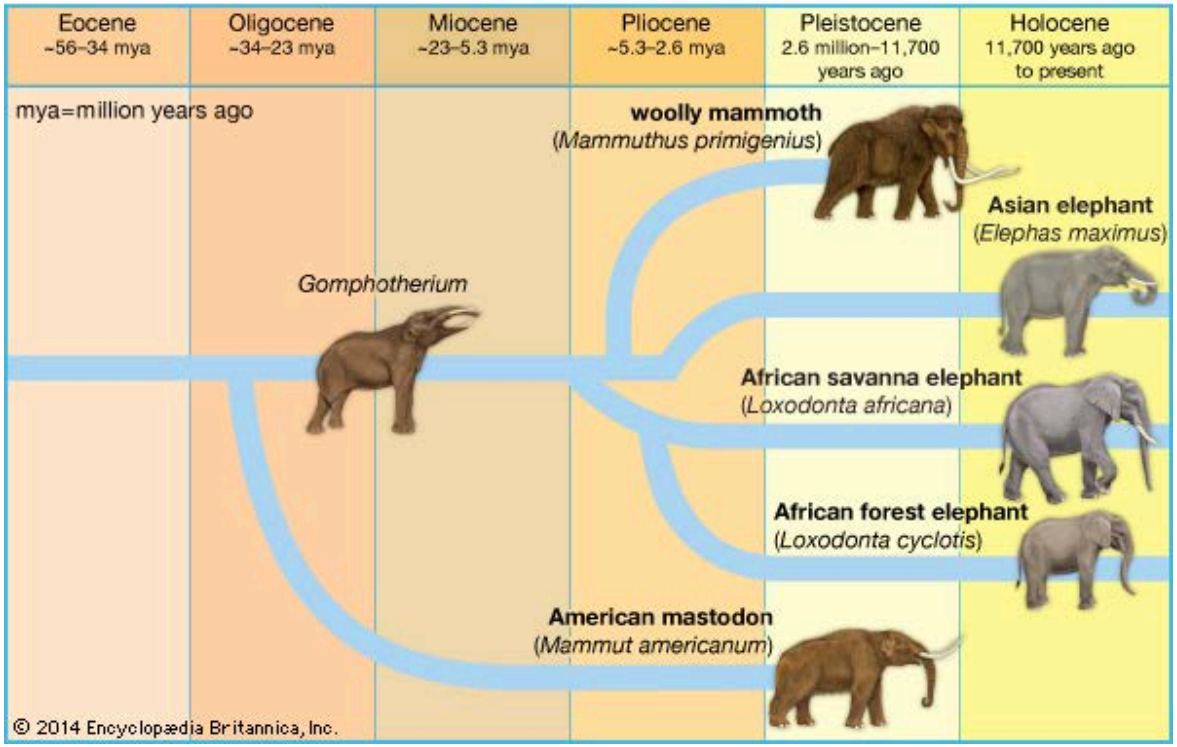
Tollis, Schneider-Utaka et al. in prep

TSG Duplications in Mammalian Genomes

TP53



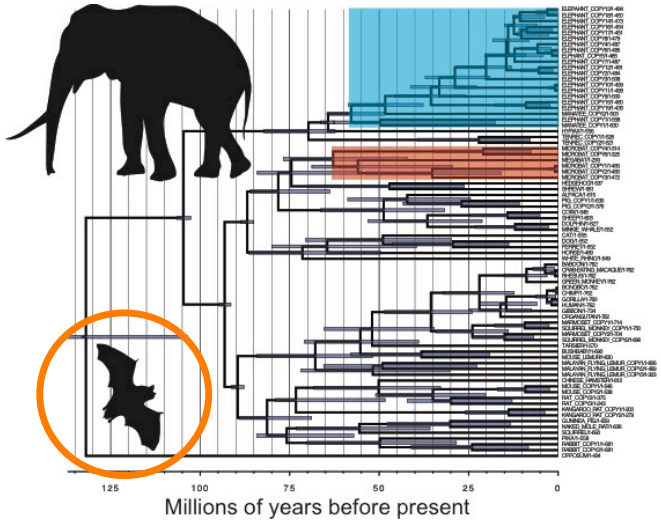
~40my of elephant family evolution



Tollis, Schneider-Utaka et al. in prep

Do bats suppress cancer?

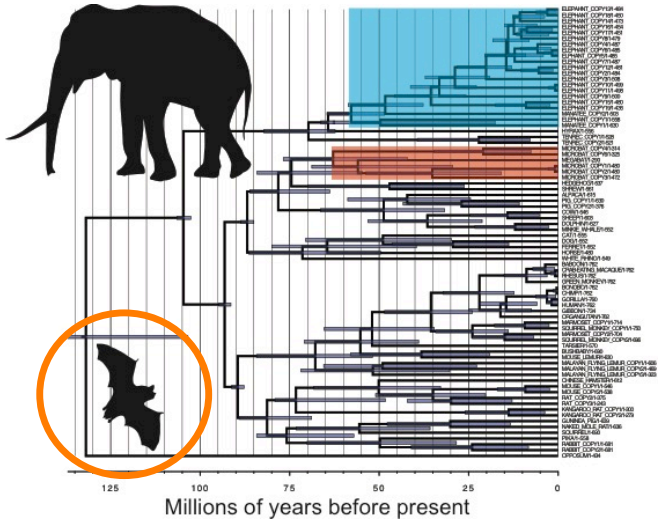
TP53

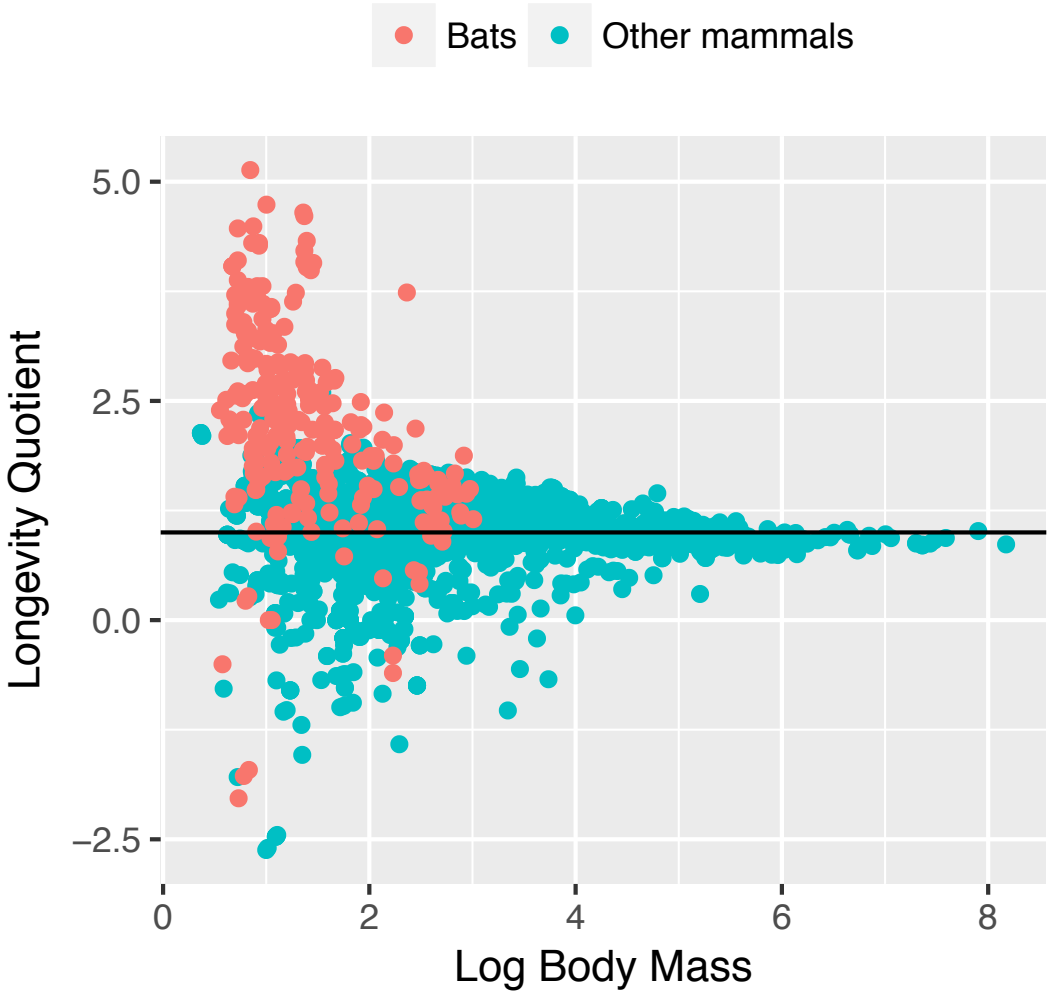


Tollis, Schneider-Utaka et al. in prep

Do bats suppress cancer?

TP53

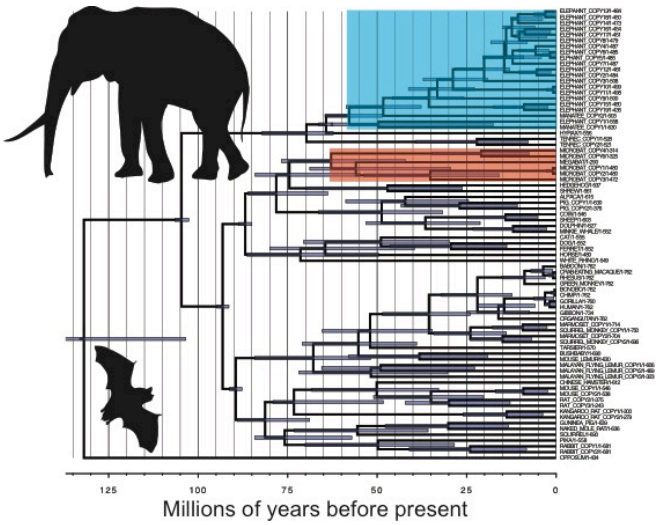




Tollis, Schneider-Utaka et al. in prep

TSG Duplications in Mammalian Genomes

TP53



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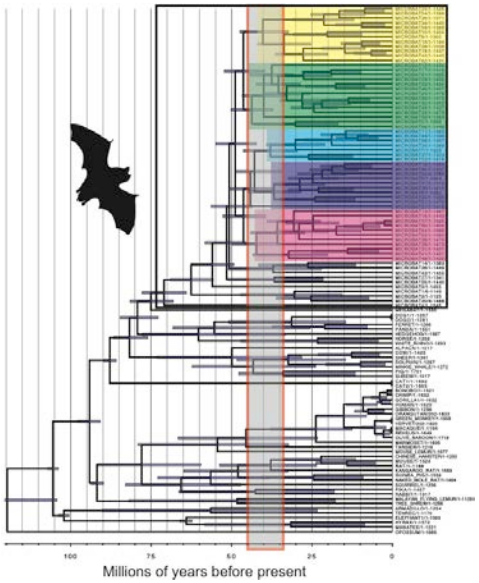
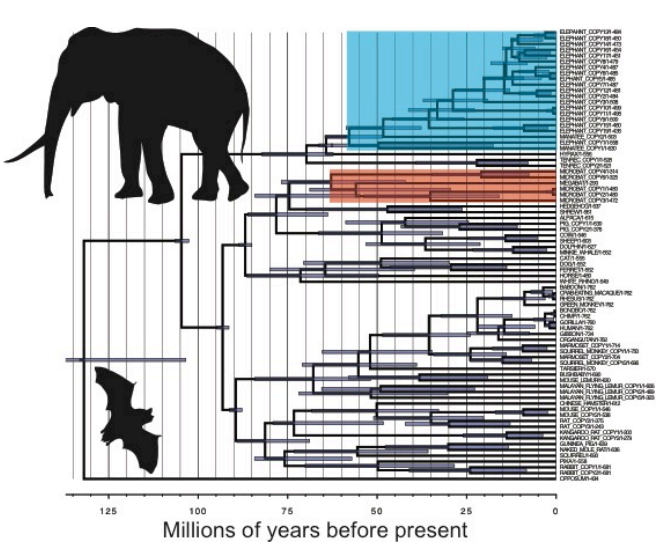


Tollis, Schneider-Utaka et al. in prep

TSG Duplications in Mammalian Genomes

TP53



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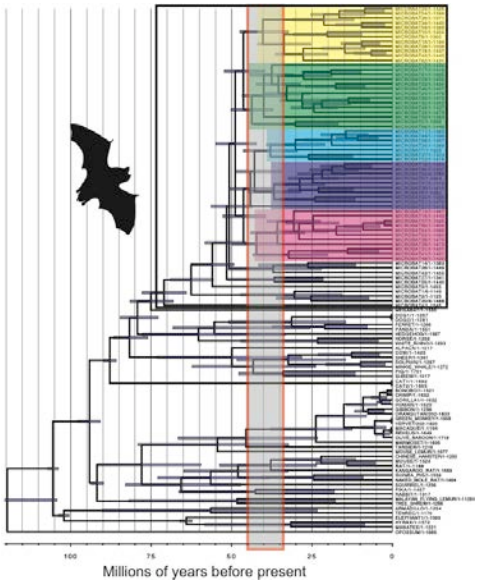
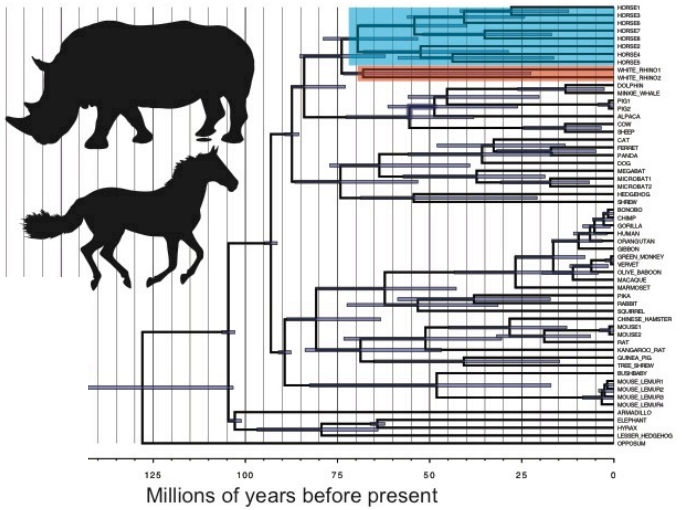


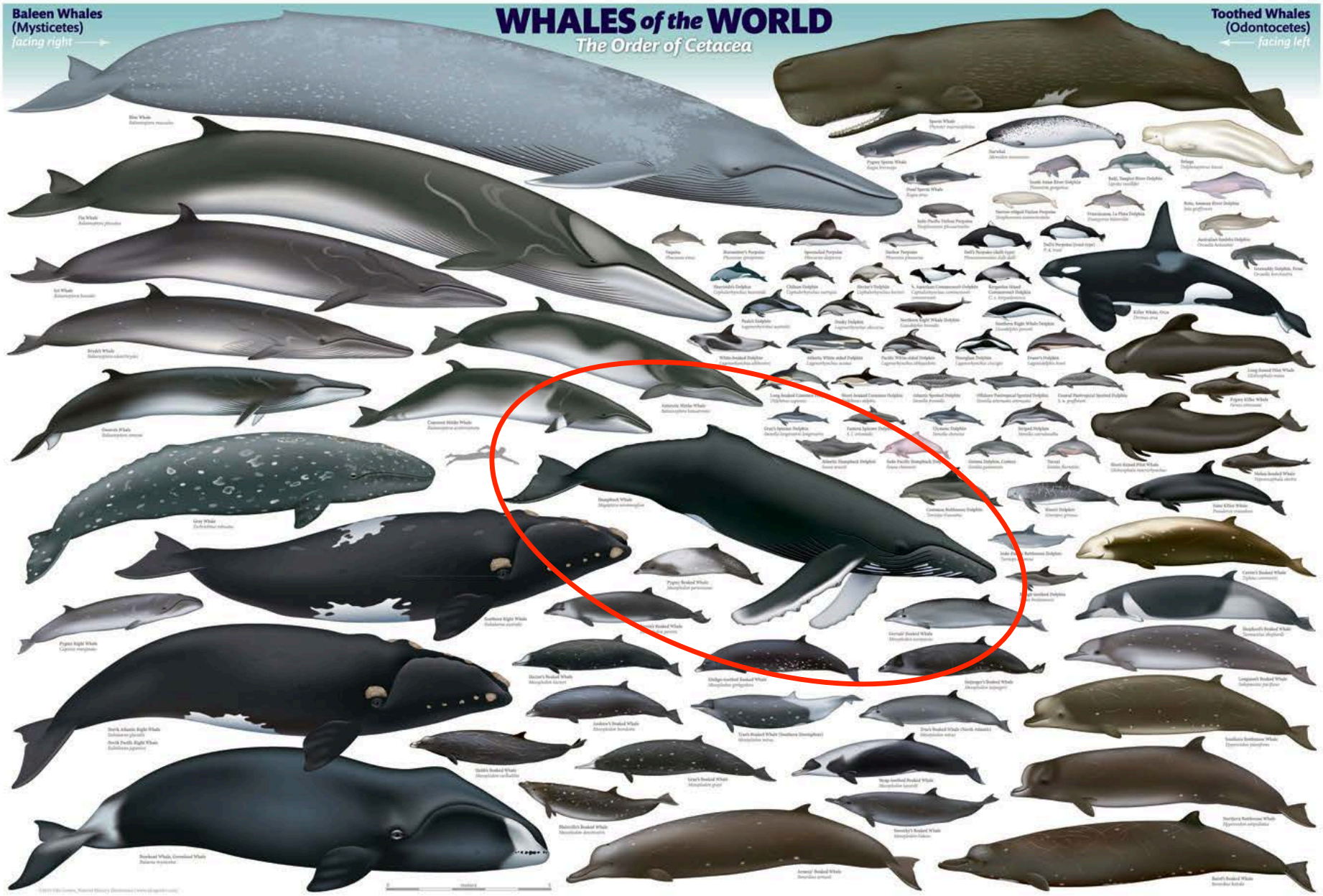
MAL



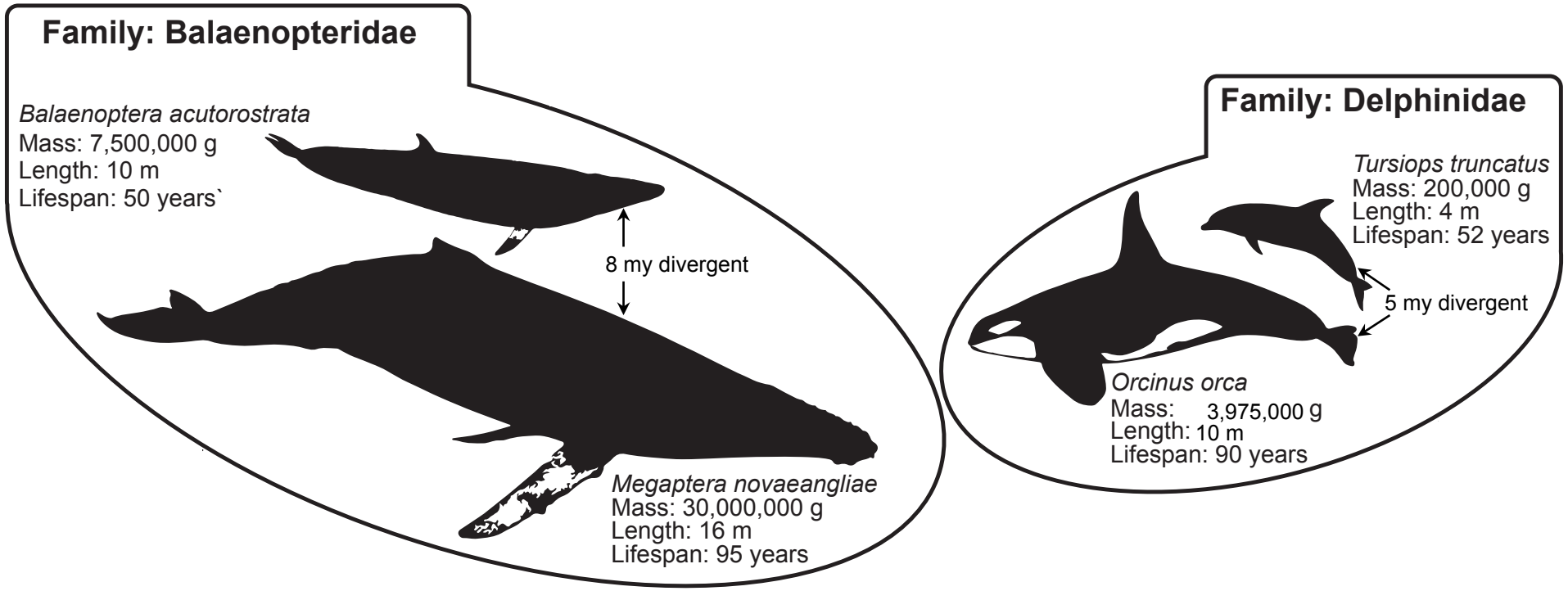
Tollis, Schneider-Utaka et al. in prep

Perissodactyls: Putting Elephants to Shame Since the Oligocene


Baleen Whales
(Mysticetes)
facing right
WHALES of the WORLD
The Order of Cetacea
Toothed Whales
(Odontocetes)
facing left
Blue Whale
Fin Whale
Sei Whale
Bryde's Whale
Omura's Whale
Common Minke Whale
Antarctic Minke Whale
Gray Whale
Humpback Whale
Southern Right Whale
Pygmy Right Whale
North Atlantic Right Whale
North Pacific Right Whale
Bowhead Whale, Greenland Whale
Pygmy Sperm Whale
Dwarf Sperm Whale
Sperm Whale
Narwhal
Beluga
Killer Whale, Orca
Long-finned Pilot Whale
Pygmy Killer Whale
Short-finned Pilot Whale
False Killer Whale
Melon-headed Whale
Risso's Dolphin
Rough-toothed Dolphin
Bottlenose Dolphin
Striped Dolphin
Common Dolphin
Pantropical Spotted Dolphin
Atlantic Spotted Dolphin
Spinner Dolphin
Clymene Dolphin
Fraser's Dolphin
Northern Right Whale Dolphin
Southern Right Whale Dolphin
Pygmy Sperm Whale
Dwarf Sperm Whale
Pygmy Beaked Whale
Sowerby's Beaked Whale
Blainville's Beaked Whale
Gervais' Beaked Whale
True's Beaked Whale
Gray's Beaked Whale
Hubbs' Beaked Whale
Andrews' Beaked Whale
Stejneger's Beaked Whale
Ginkgo-toothed Beaked Whale
Longman's Beaked Whale
Shepherd's Beaked Whale
Cuvier's Beaked Whale
Hector's Beaked Whale
Arnoux's Beaked Whale
Baird's Beaked Whale
Northern Bottlenose Whale
Southern Bottlenose Whale


Baleen Whales
(Mysticetes)
facing right
WHALES of the WORLD
The Order of Cetacea
Toothed Whales
(Odontocetes)
facing left

Comparative Genomics of Cancer Suppression in Cetaceans

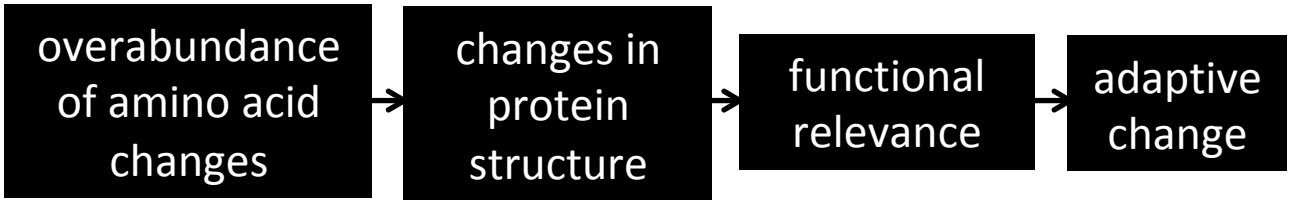


Tollis et al. in prep

Inferring Positive Selection on Protein Coding Genes

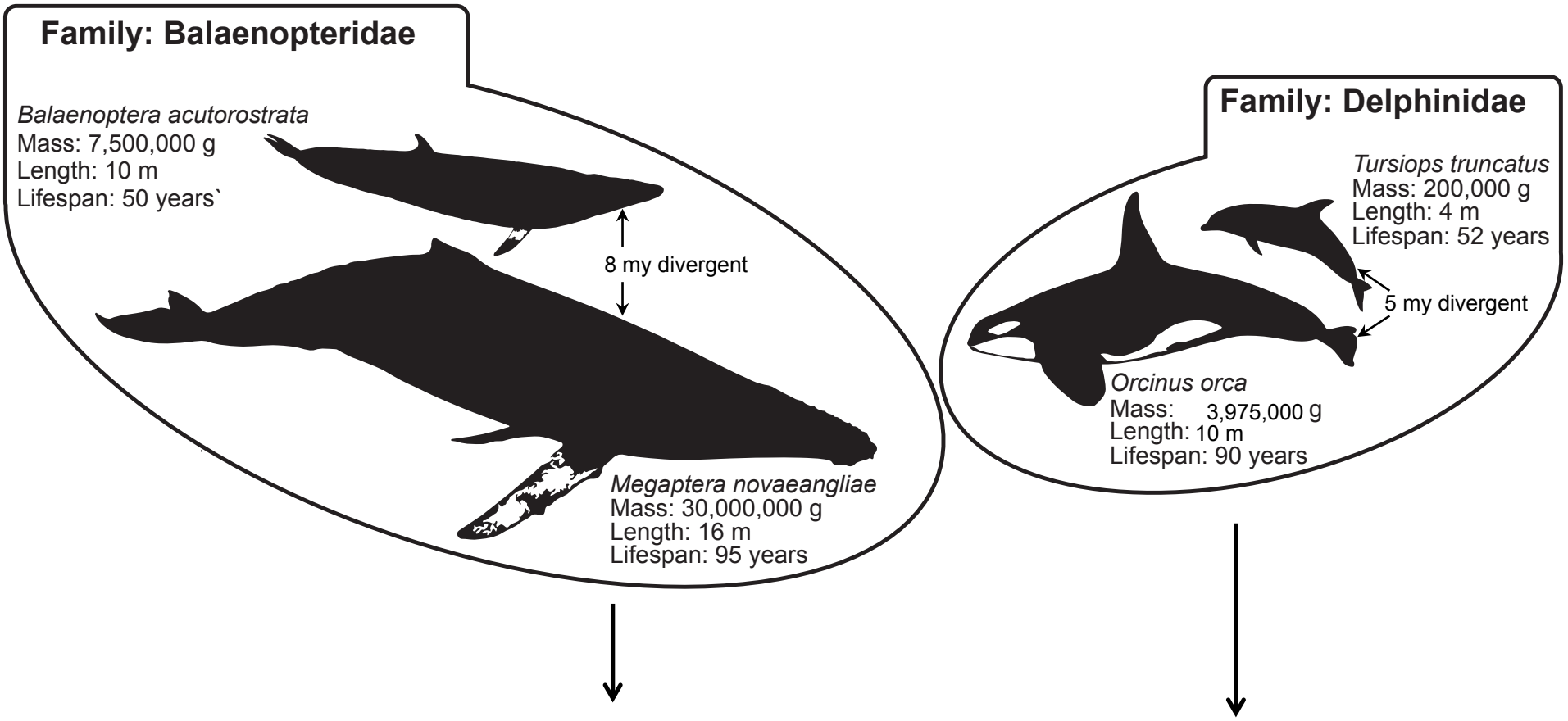
d_N	d_S
Nonsynonymous substitutions	Synonymous substitutions
Result in amino acid change	No amino acid change

If $d_N / d_S > 1$:



Positive selection.

Comparative Genomics of Cancer Suppression in Cetaceans

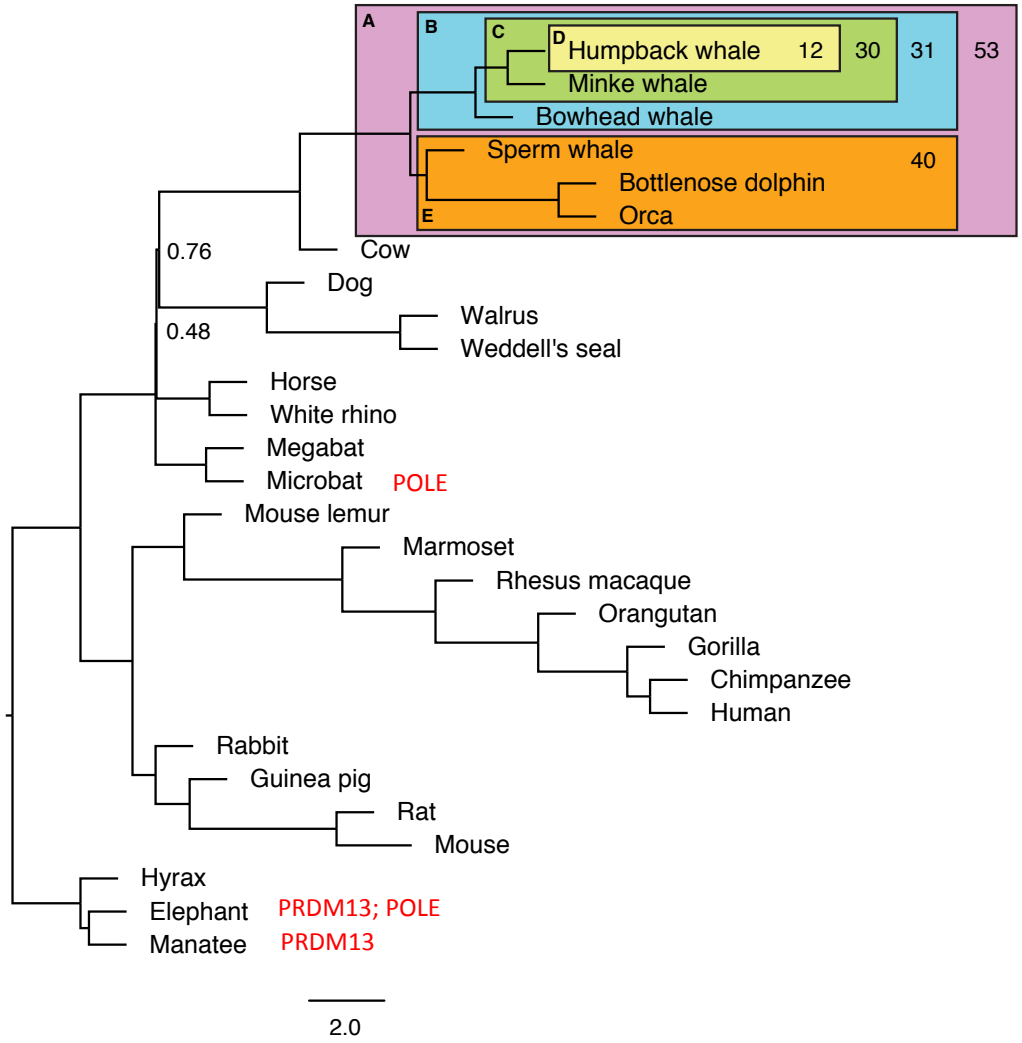


13 TSGs with $d_N/d_S>1$

36 TSGs with $d_N/d_S>1$

Tollis et al. in prep

How do you make a whale?



146 genes evolved under positive selection during cetacean evolution

Including cancer genes from COSMIC:

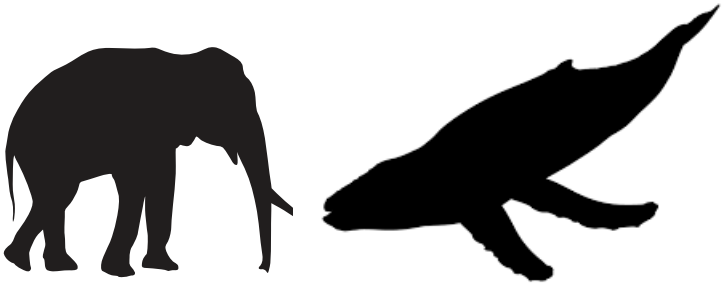
*tumor suppressor gene

AMER1*	Wnt signaling pathway; positive regulation of protein ubiquitination
KMT2C*	Methylates 'Lys-4' of histone H3.
POLE	Participates in DNA repair and DNA replication
PRDM13*	May be involved in transcriptional regulation
ERCC5*	Excision repair, DNA double-strand break repair following UV damage
KAT6A	Transcriptional repressor, acetylates p53
DOT1L*	Lysine methyltransferase, catalyzes the transfer of methyl groups from SAM to the lysine residues, particularly histones H3 and H4
PLCE1*	Activation of MAPK activity, regulation of cell growth
PRDM1*	Regulation of TP53 Expression and Degradation

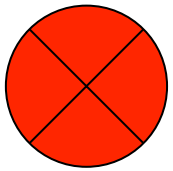
Tollis et al. in prep

The Evolution of Cancer Suppression

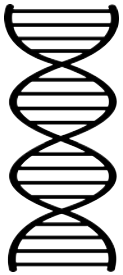
- Multiple species have converged on the cancer suppression phenotype



- Divergent molecular etiologies
  - In common: checks on neoplastic progression



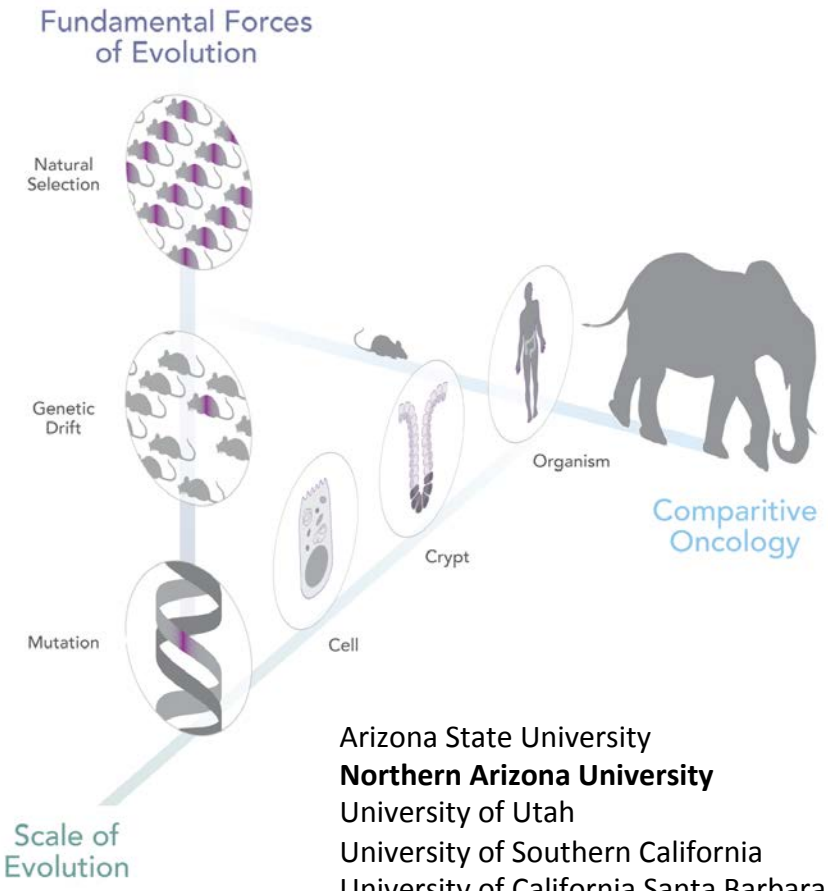
- Comparative genomics offers a promising template for finding genetic targets for cancer therapy



Arizona Cancer Evolution Center (ACE)

NCI CSBC U54 (2018 – 2023)

"The mission of the Arizona Cancer and Evolution Center (ACE) is to advance our **fundamental understanding of cancer** and its clinical management through the **development and application of evolutionary and ecological models to cancer biology**."



Arizona State University
Northern Arizona University
University of Utah
University of Southern California
University of California Santa Barbara
Stanford University
North Carolina State University
Institute of Cancer Research
Barts Cancer Institute
University of Zurich

Frontiers in Comparative Oncology



Birds get less cancer than mammals.

	Mammals	Birds
Total necropsies	3,127	5,957
Cancer Rate	2.75%	1.89%

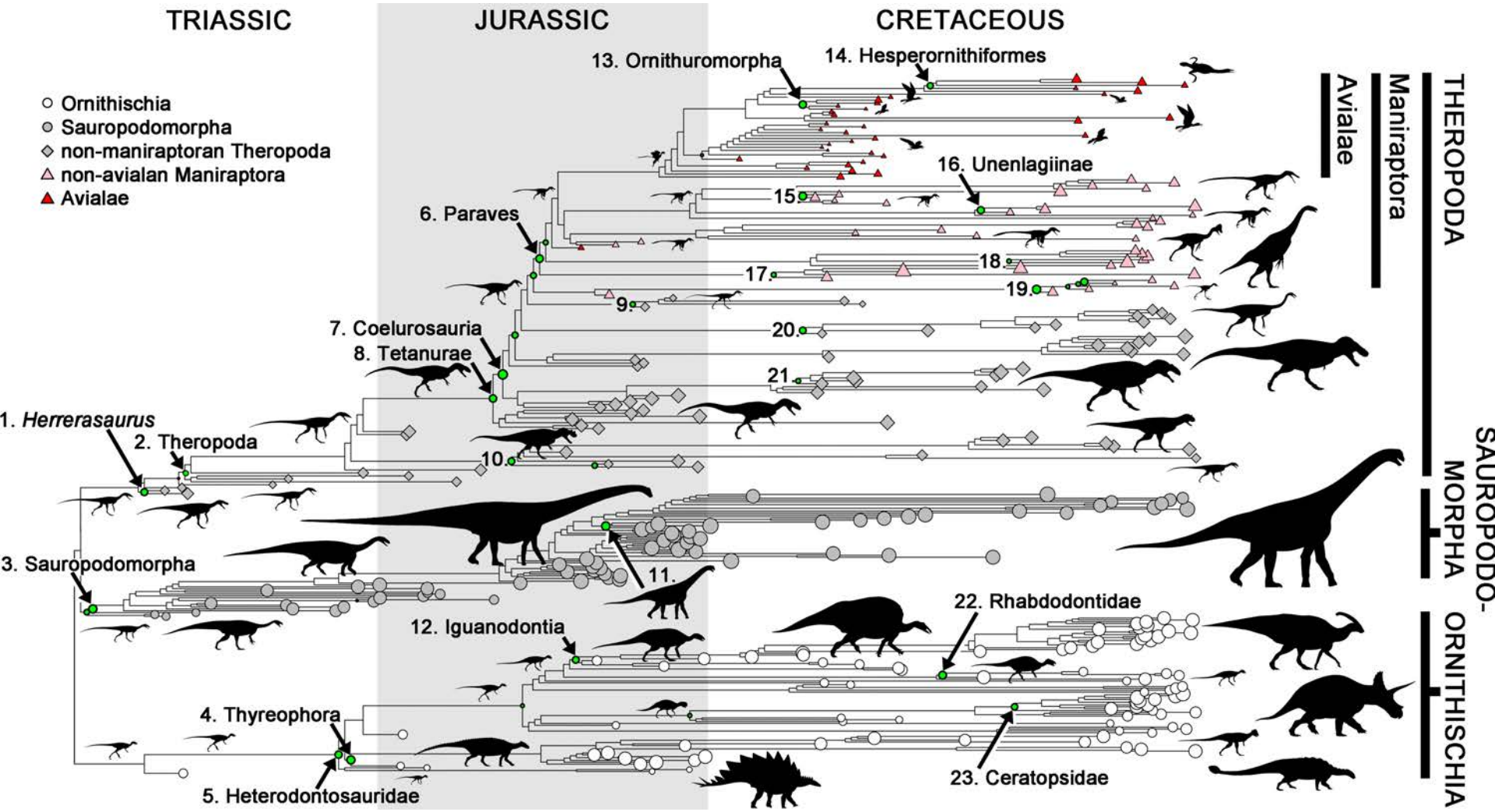
p = 0.0077

Effron et al. (1977) *Journal of the National Cancer Institute*

Northwest ZooPath

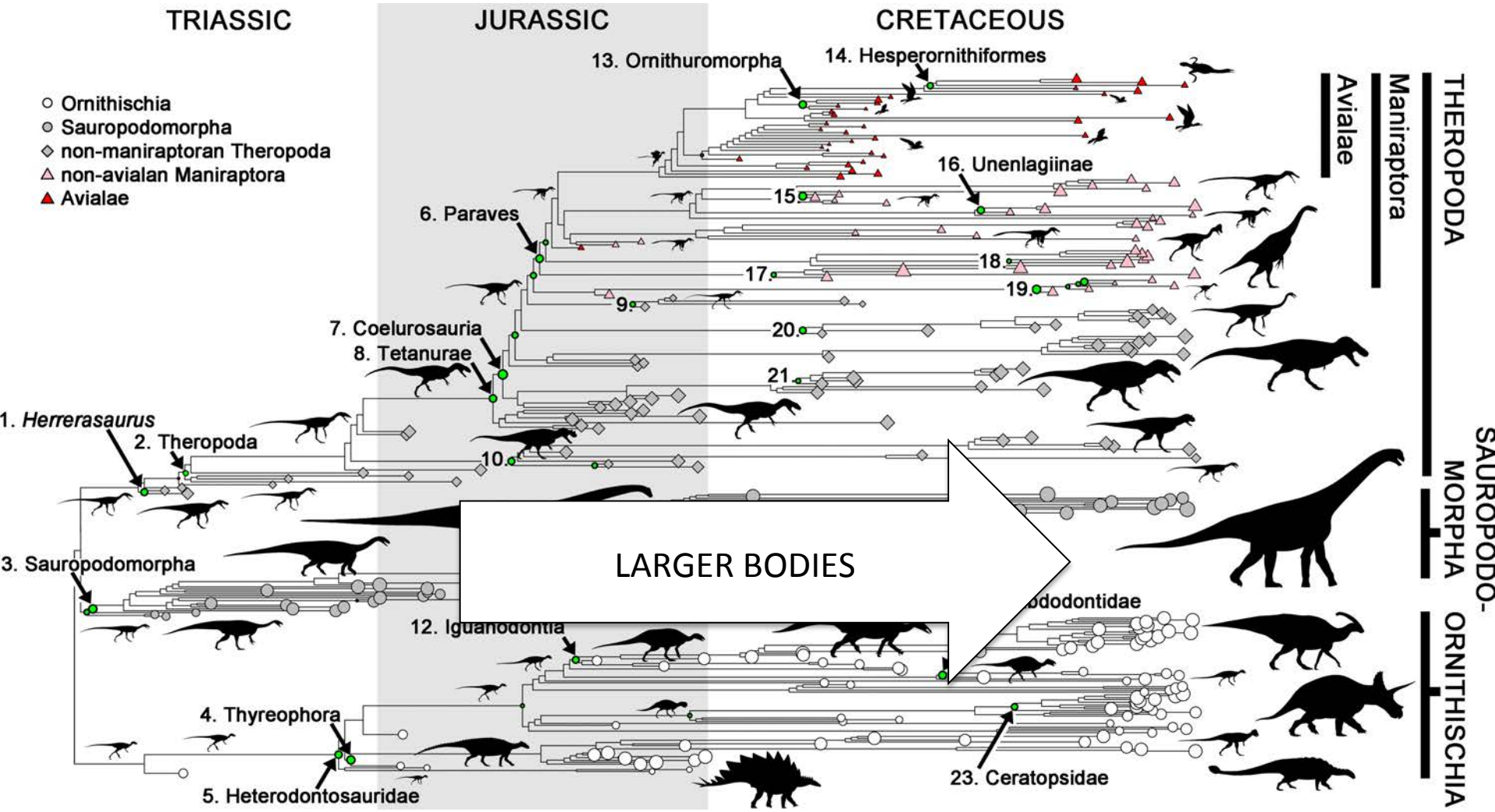
Specializing in the pathology of nondomestic species

Cope's Rule in Dinosaurs



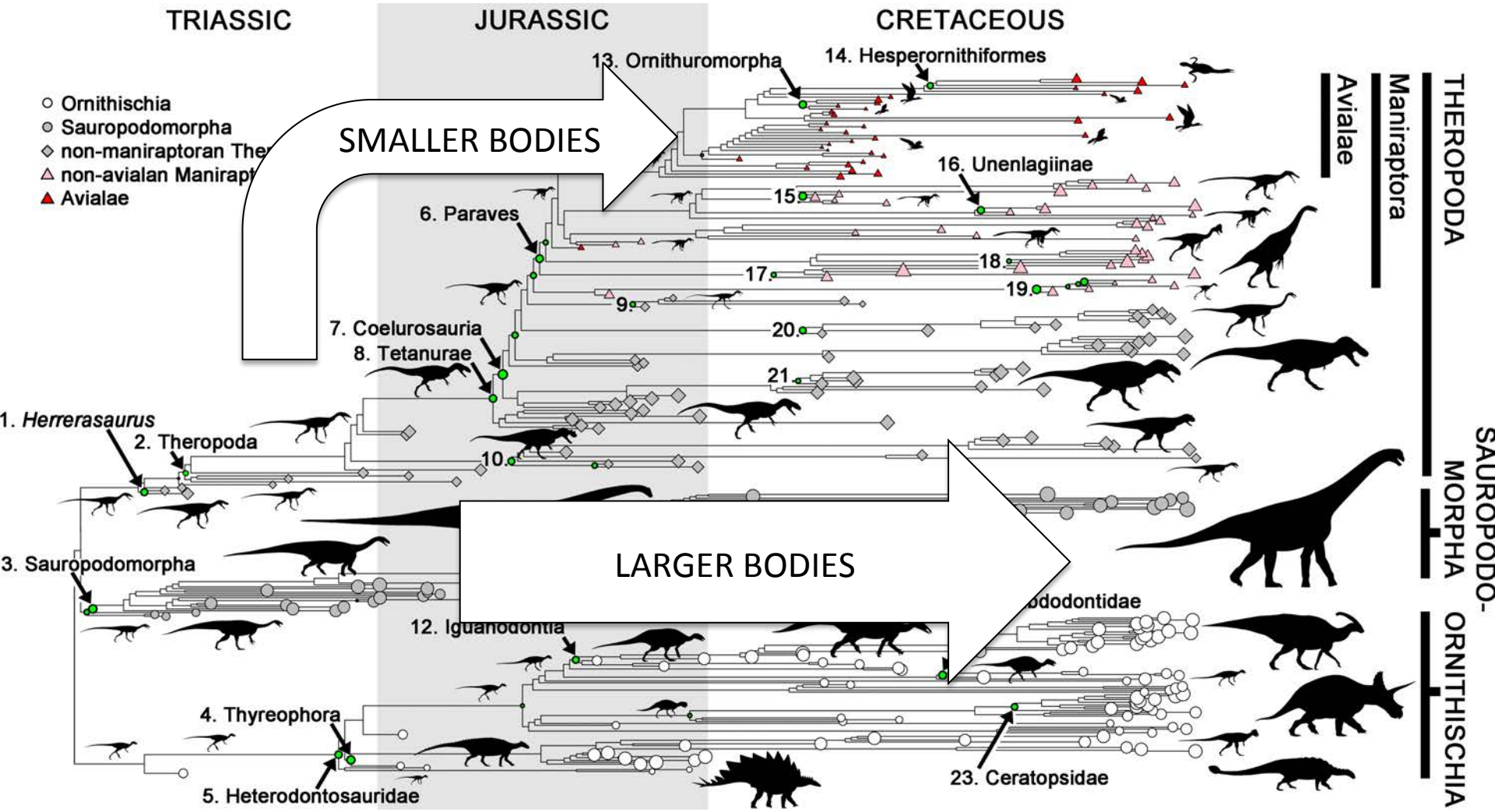
Benson et al. (2014) *PLoS Biology*

Cope's Rule in Dinosaurs



Benson et al. (2014) *PLoS Biology*

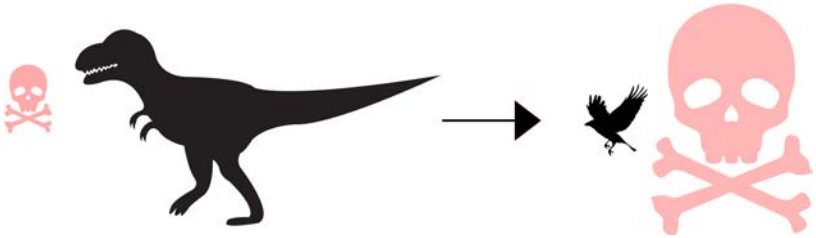
Birds reversed the body size evolutionary trend in dinosaurs



Benson et al. (2014) *PLoS Biology*

Did birds inherit cancer suppression from their giant dinosaurian ancestors?

Null hypothesis:



- Birds get smaller → higher extrinsic mortality

Null hypothesis:

- Birds g[illegible] higher extrinsic mortality

Null hypothesis:

LOSE CANCER SUPPRESSION

- Birds get smaller → higher extrinsic mortality

Alternate hypothesis:

- Birds fly → extrinsic mortality does not change

Hanna Kokko Yagmur Erten

University of Zurich

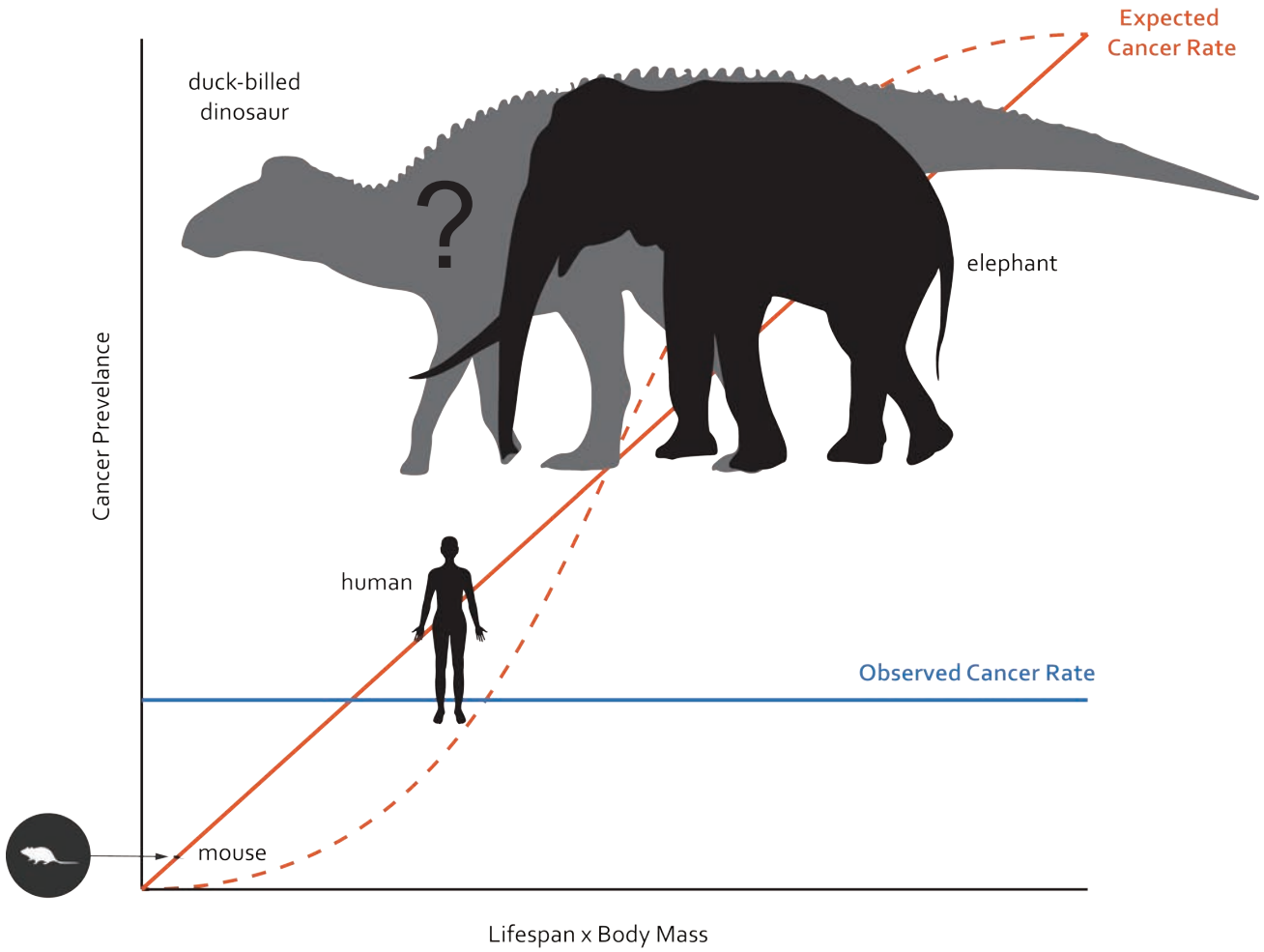
Null hypothesis:

- Birds g[illegible] → higher extrinsic mortality

Alternate hypothesis:

- Birds fly → extrinsic mortality does not change

Cancer is a Part of Life



Tollis et al. (2017) *BMC Biology*

Student Research Opportunities

Comparative Oncology

- Peto's Paradox – elephants, whales, bats, birds, dinosaurs
- Tortoises and crocodilians – reptiles in general are understudied
- Dinosaurs, mammoths (aDNA)

Vertebrate Genomics

- Transposable elements
- Highly conserved genomic regions
- Population genomics
  - Adaptation
  - Lizards, whales, etc

Pilot studies in CP biodiversity using museum collections

- CPBC – Tad Theimer
- MNA – Larry Stevens
- Field work opportunities

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Cassandra Balsley (ASU)
Aika Schneider-Utaka (ASU)
Yagmur Erten (University of Zurich)

Computing
City University of New York HPCC
ASU Research Computing
NAU Monsoon Cluster

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- Queens College

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Arizona State University School of Life Sciences
Smithsonian Tropical Research Institute
National Institutes of Health (R15, U54)
School of Informatics, Computing, and Cyber Systems (NAU)


Dinosaurs
Ancient Fossils
New Discoveries
AMERICAN MUSEUM & NATURAL HISTORY
MOVEABLE MUSEUM


AMERICAN MUSEUM & NATURAL HISTORY
Moveable Museum
Bloomberg


AMERICAN MUSEUM & NATURAL HISTORY
HAYDEN PLANETARIUM
DISCOVERING THE
UNIVERSE
WWW.AMNH.ORG

PHOENIX
COMICON
15

Sonoran mountain kingsnake
(*Lampropeltis pyromelana*)
Elden Lookout Trail

Greater short horned lizard
(*Phrynosoma hernandesi*)
Behind De Miguel Elementary