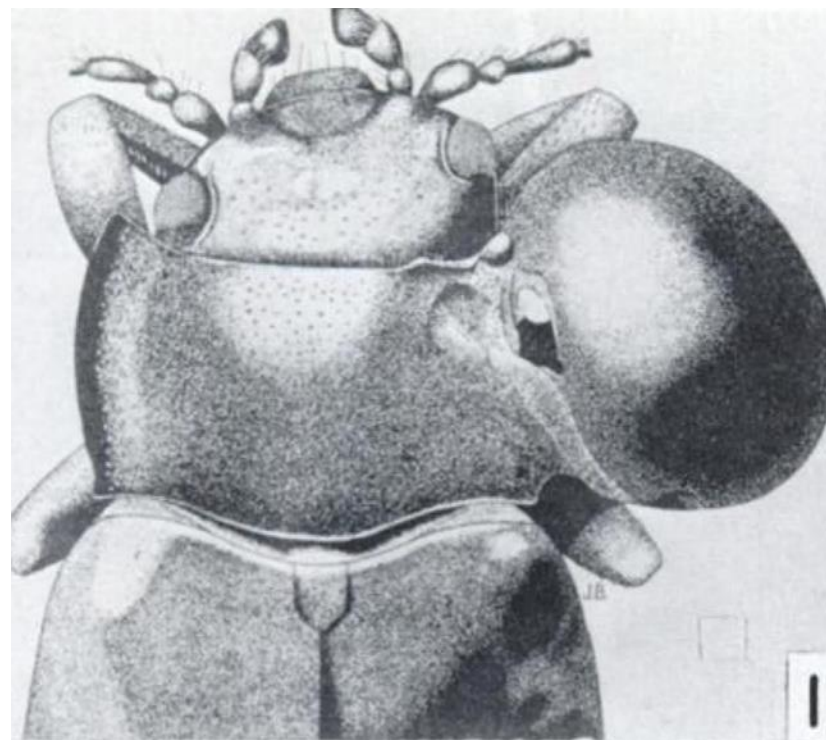




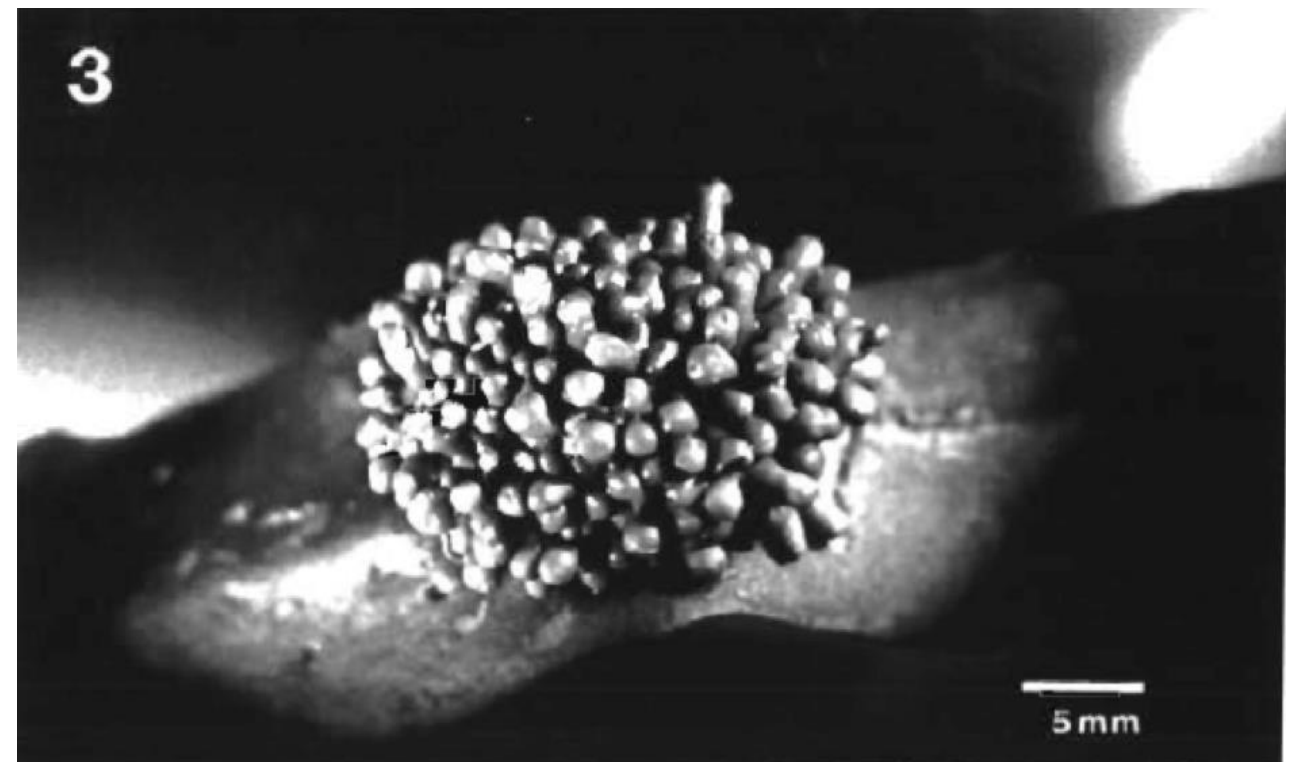
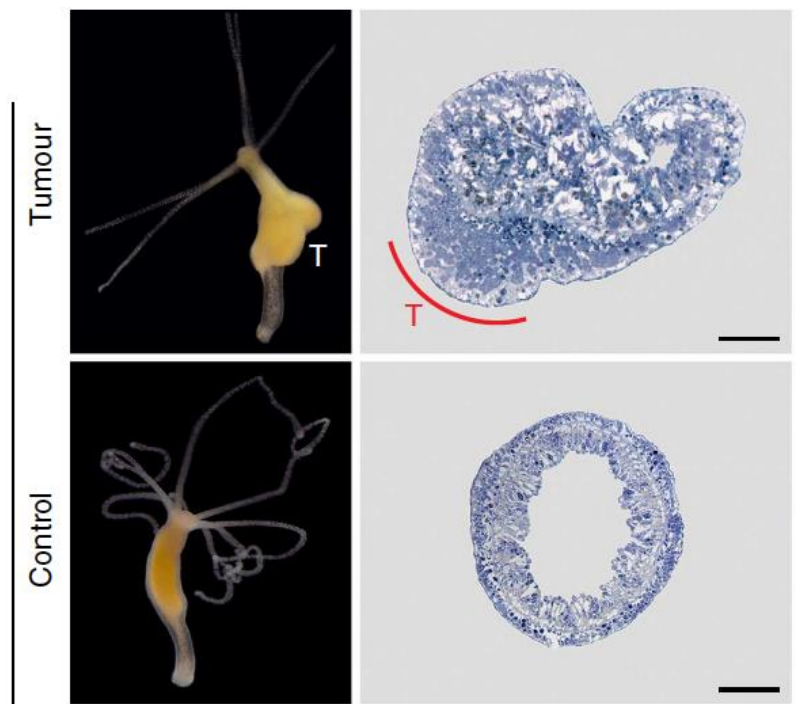
The Evolution of Cancer Suppression Across Life

Carlo C. Maley

 @cmaley



H. oligactis



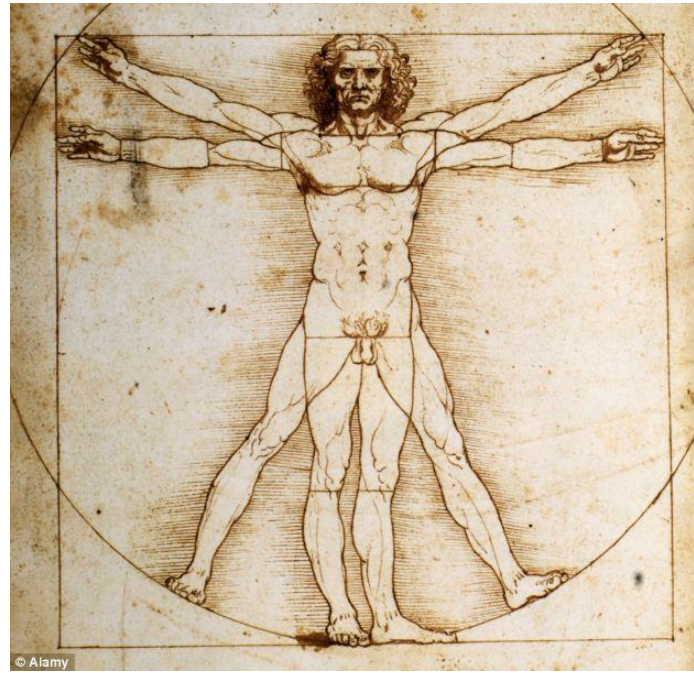
All multicellular organisms
have the problem of cancer

Aktipis et al. *Phil Trans B*, 2015
Domazet-Lošo et al. *Nat Comms* 2014



There have been 2 billion years
of natural selection on cancer
suppression mechanisms

Can we learn from nature how to
prevent cancer?



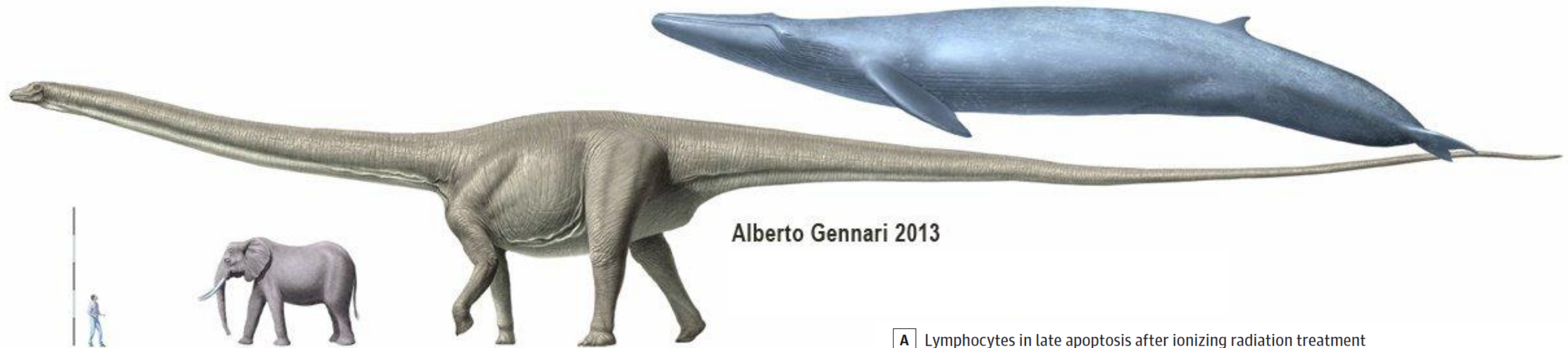
1000X

100X

Peto's Paradox

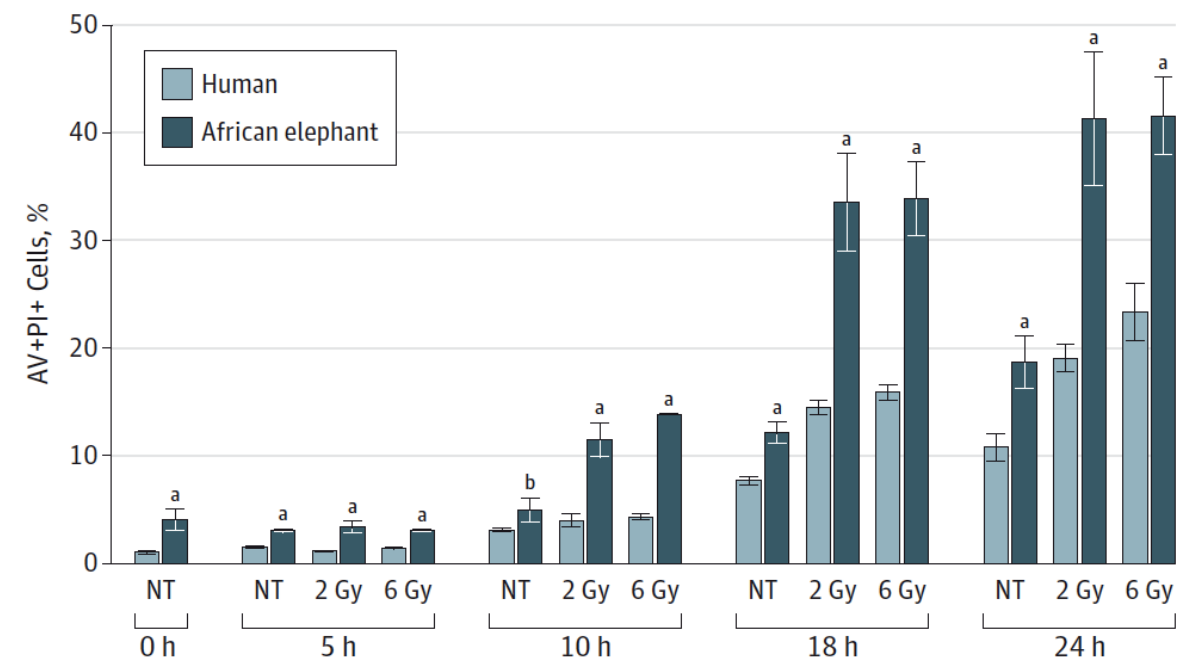
Humpback Genome and cancer gene evolution across cetaceans

Tollis et al. MBE 2019



Elephants get tumors but only 5% mortality rate, 20 copies of TP53
Abegglen et al. JAMA 2015

A Lymphocytes in late apoptosis after ionizing radiation treatment

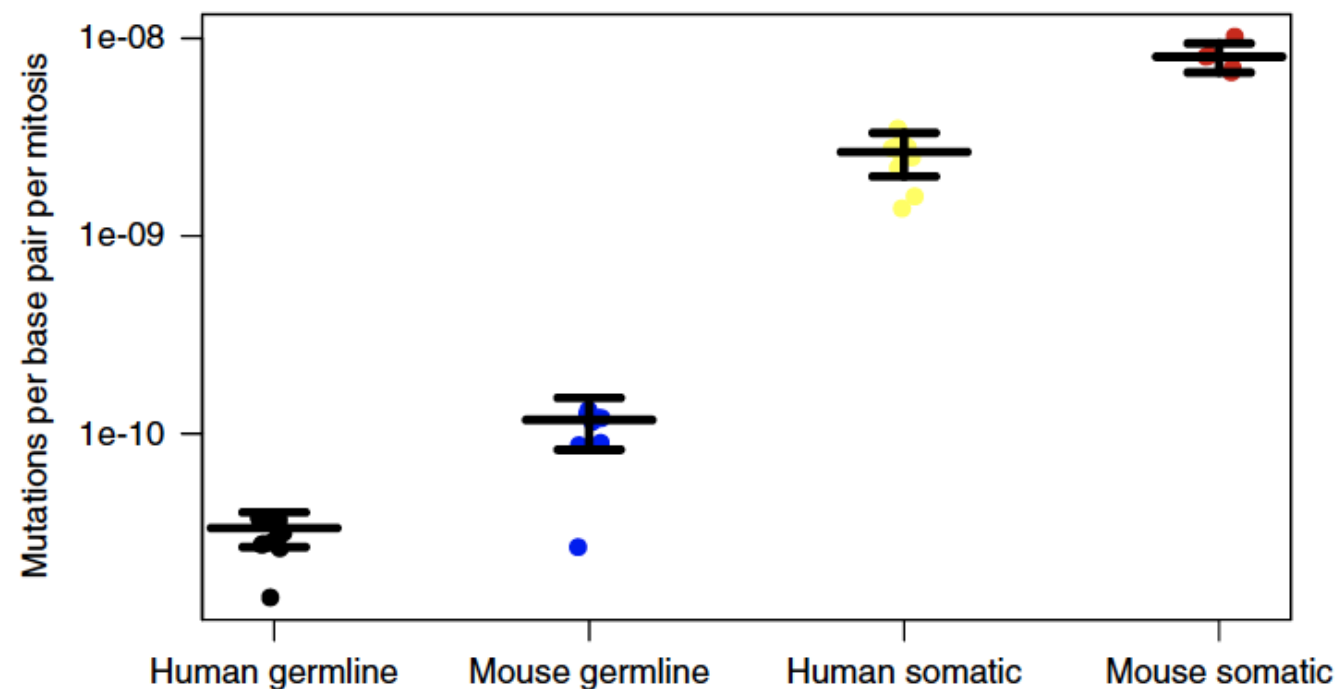


Cancer prevention: What can we learn from these exceptional organisms?

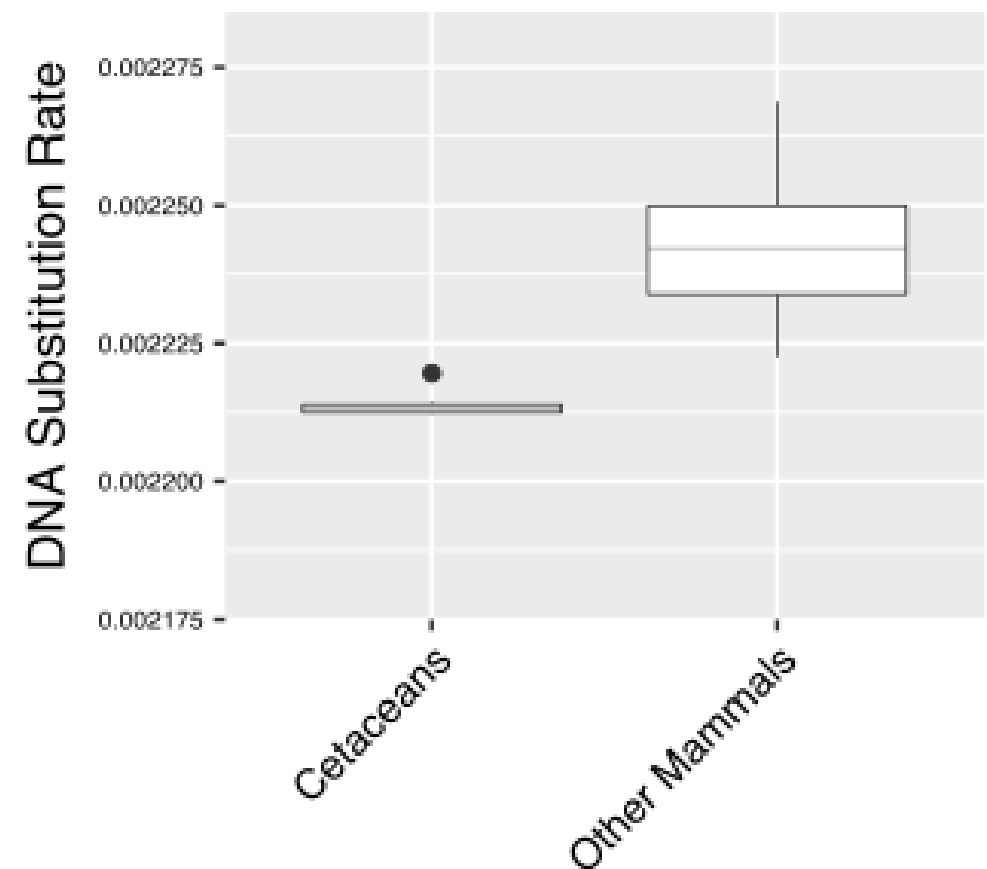
Sensitive DNA damage response

Slower somatic mutation rates?

Germline and somatic mutation rates are correlated
Whales have low germline mutation rates



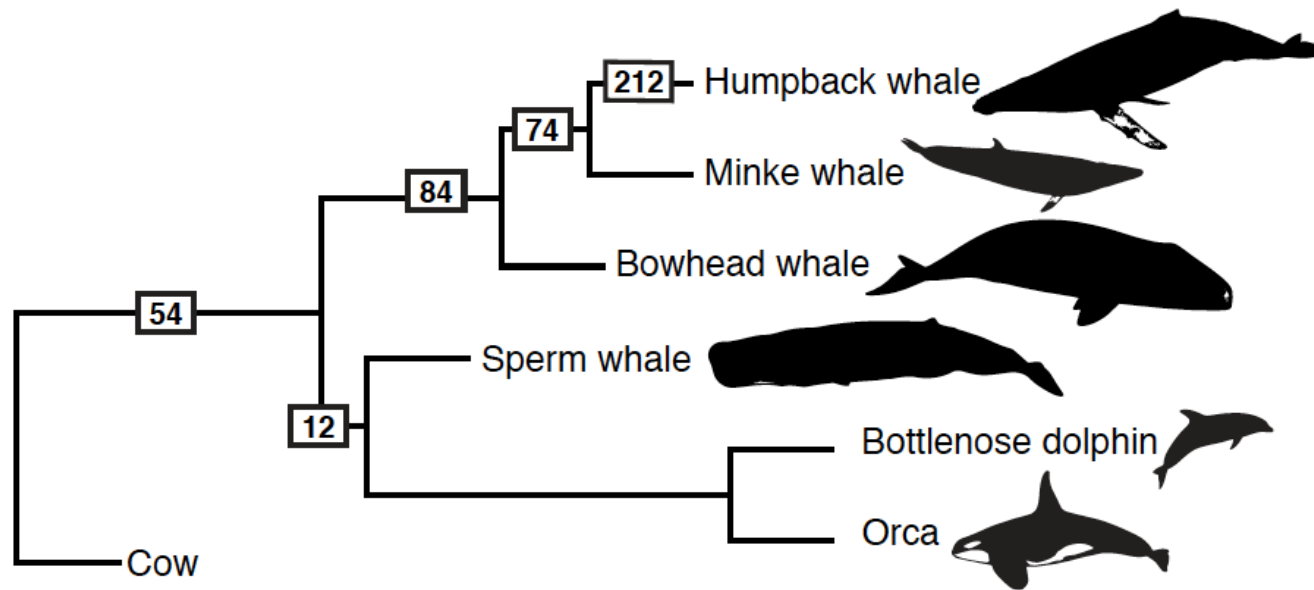
Milholland et al. (2017) Nat Comm



Tollis et al. (2019) Mol Biol Evol

Somatic mutation rates in cetaceans haven't been measured yet

Many genes evolving under positive selection in cetaceans are directly linked to human cancers



Mysticeti ancestor:

ERCC5*	Excision repair, DNA double-strand break repair following UV damage
PRDM1*	Regulation of TP53 expression and degradation

Minke and humpback whale ancestor:

MUC1°	Overexpressed in epithelial tumors
RET†	Plays a role in cell differentiation and growth

Humpback whale:

ATR*	Suppression of growth, escaping programmed cell death, change of cellular energetics
BCORL1*†	Invasion and metastasis
PICALM*	Change of cellular energetics
PRDM2*	Regulation of TP53 expression and degradation
TPR°	Involved in the activation of oncogenic kinases

Cetacea ancestor:

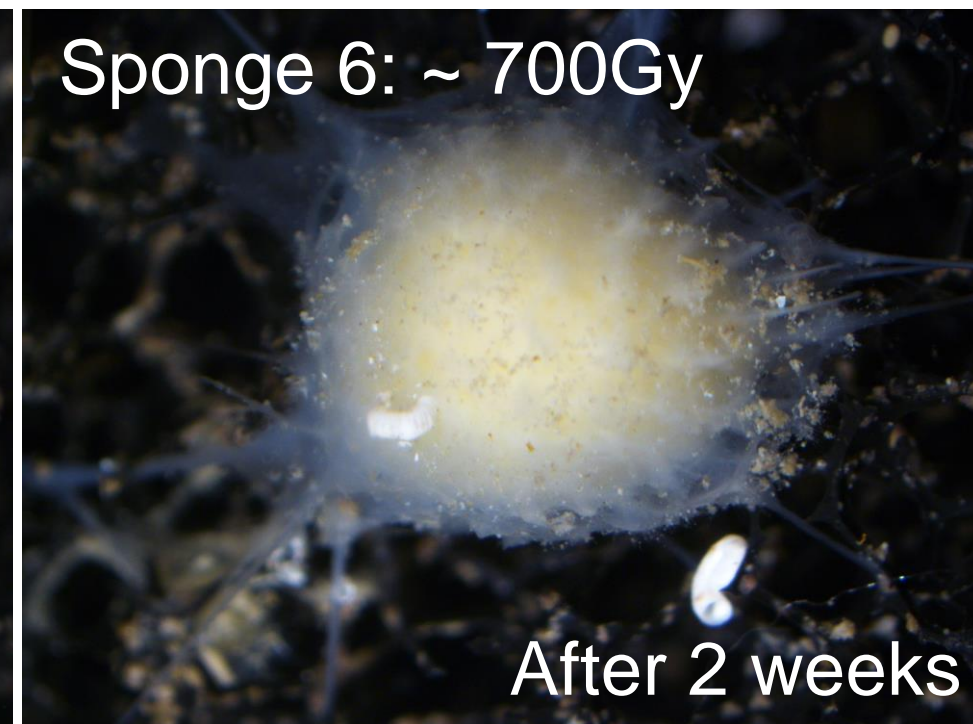
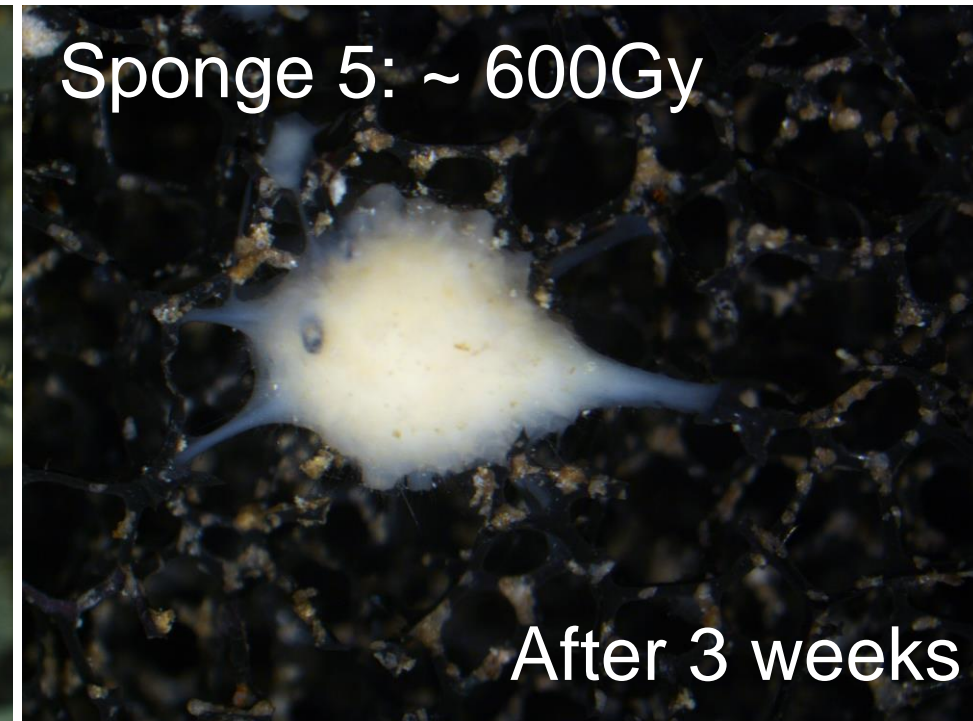
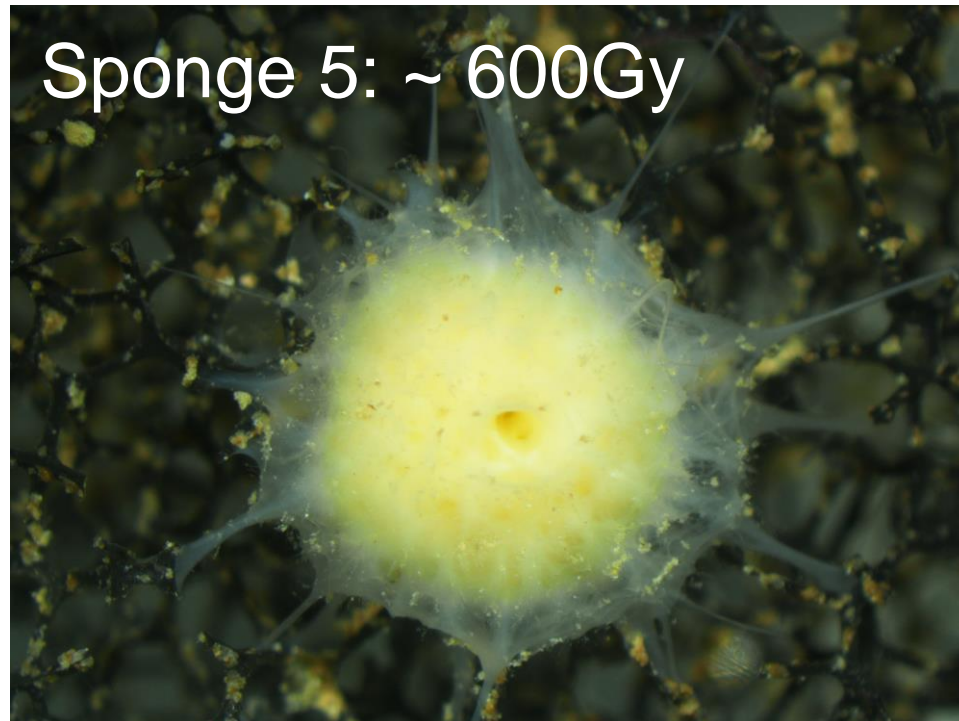
AMER1*	Promotes suppression of growth
CCNB1IP1*	Suppresses invasion and metastasis
KMT2C*	Methylates 'Lys-4' of histone H3.
POLE*	Participates in DNA repair and DNA replication
POU2AF1†	Promotes proliferative signaling

Odontoceti ancestor:

PML*	Positively regulates TP53; by inhibiting MDM2-dependent degradation
------	---

Catalogue Of Somatic Mutations In Cancer
<https://www.sanger.ac.uk/science/tools/cosmic>

Tethya wilhelma



3-5 Gy X-rays are lethal for humans
600 Gy of X-rays are not for sponges

We don't yet know why...
Fortunato, unpublished



What species have exceptionally low cancer rates?



Data:

Veterinary necropsy & pathology records

72,938 individuals
247 species with >50 individuals each

In Abegglen et al. JAMA 2015
We only had 850 individuals and
36 species with >10 individuals each



Amy Boddy



Athena Aktipis



Valerie Harris



Northwest ZooPath



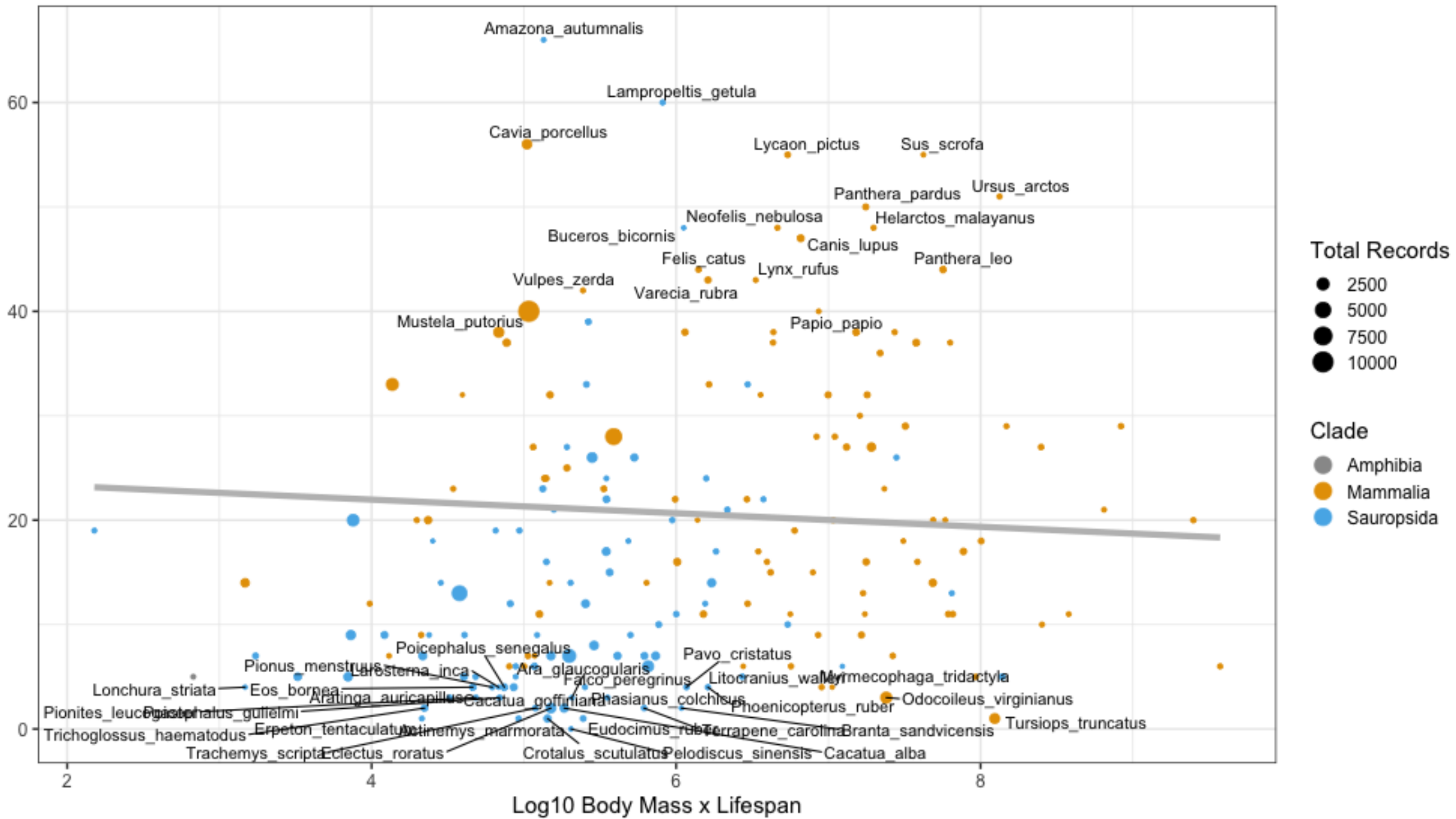
Shawn Rupp



Zach Compton

Log10 Body Mass x Lifespan Neoplasia %
Adjusted R²: 0.001645 p-value: 0.2527 lambda: 0.602

Neoplasia Prevalence



Peto's Paradox



Unpublished. Please don't share!

Adjusted R²: -0.004937 p-value:0.8121 lambda: 0.423



Top Ten Neoplasia Prevalence

Common Name	Total Records	Neoplasia Rate
Red-Lored Amazon	59	66%
Eastern Kingsnake	85	60%
Guinea Pig	1134	56%
African Wild Dog	136	55%
Wild Boar	56	55%
Brown Bear	80	51%
Leopard	170	50%
Clouded Leopard	83	48%
Sun Bear	82	48%
Great Hornbill	52	48%



Unpublished. Please don't share!

Bottom Ten Neoplasia Prevalence

Common Name	Total Records	Neoplasia Rate
Chinese Softshell Turtle	55	0%
Rainbow Lorikeet	244	1%
Tentacled Snake	67	1%
Mohave Rattlesnake	440	1%
Western Pond Turtle	100	1%
Scarlet Ibis	144	1%
Bottlenose Dolphin	1338	1%
Hawaiian Goose	52	2%
Coconut Lorikeet	260	2%
Common Box Turtle	113	2%



Unpublished. Please don't share!

Top Ten Malignancy Prevalence

Common Name	Total Records	Malignancy Rate
Eastern Kingsnake	85	49%
Great Hornbill	52	48%
Red-Lored Amazon	59	47%
Sun Bear	82	44%
African Wild Dog	136	32%
Fennec Fox	74	31%
Four-Toed Hedgehog	1446	28%
Leopard	170	27%
Pacific Gophersnake	100	26%
Common House Cat	121	26%



Unpublished. Please don't share!

Bottom Ten Malignancy Prevalence

Common Name	Total Records	Malignancy Rate
American Alligator	170	0%
Chinese Softshell Turtle	55	0%
African Elephant	82	0%
Scarlet Ibis	144	0%
Rainbow Lorikeet	244	1%
American Mink	287	1%
Coconut Lorikeet	260	1%
Tentacled Snake	67	1%
Red Lory	275	1%
Blue-Headed Parrot	90	1%



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Highest Proportion of Malignancies / Neoplasia

Common Name	Total Records	Neoplasia Prev.	Malignancy Prev.	Proportion
Great Hornbill	52	48%	48%	1
Eastern Diamondback Rattlesnake	69	12%	12%	1
Bali Myna	63	14%	13%	0.92
Sun Bear	82	48%	44%	0.91
Savannah Monitor	85	10%	09%	0.9
Wild Turkey	101	20%	17%	0.85
Red Junglefowl	1275	26%	22%	0.84
Bali Myna	242	14%	13%	0.92
Carpet Python	66	60%	18%	0.81
Eastern Kingsnake	85	21%	49%	0.81



Unpublished. Please don't share!

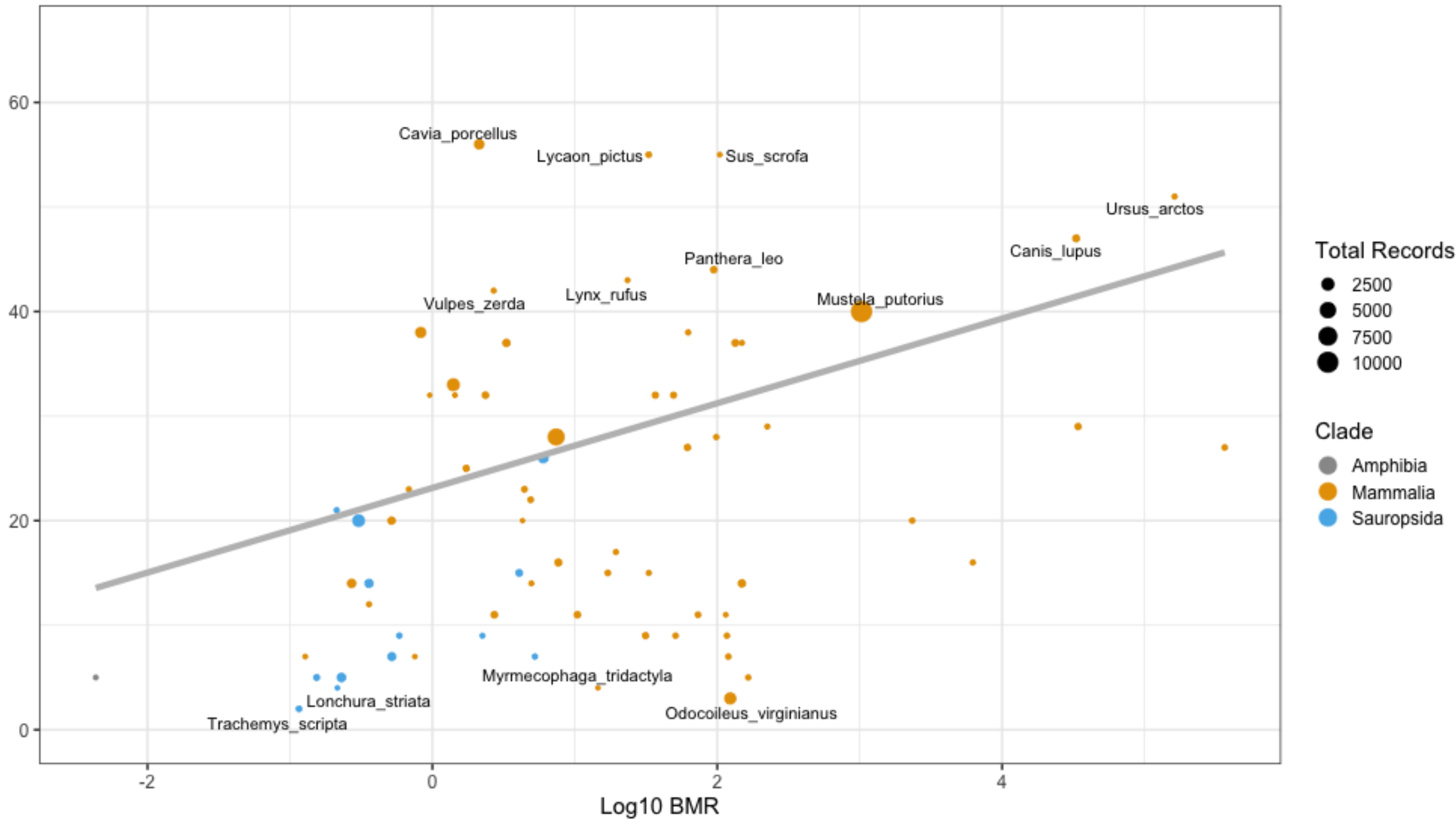
Lowest Proportion of Malignancies / Neoplasia

Common Name	Total Records	Neoplasia Prev.	Malignancy Prev.	Proportion
Greater Kudu	134	11%	1%	0.09
American Mink	287	11%	1%	0.09
Common Squirrel				
Monkey	154	23%	3%	0.13
Swamp Wallaby	124	12%	2%	0.16
Chimpanzee	221	29%	5%	0.17
Bighorn Sheep	55	11%	2%	0.18
Red Panda	139	22%	4%	0.18
Southeast African				
Cheetah	227	27%	5%	0.18
Asian Elephant	103	20%	4%	0.2
Kinkajou	50	20%	4%	0.2

Log10 BMR Neoplasia %

Adjusted R²: 0.05221 p-value: 0.03289 lambda: 0.314

Neoplasia Prevalence



Metabolic Rate

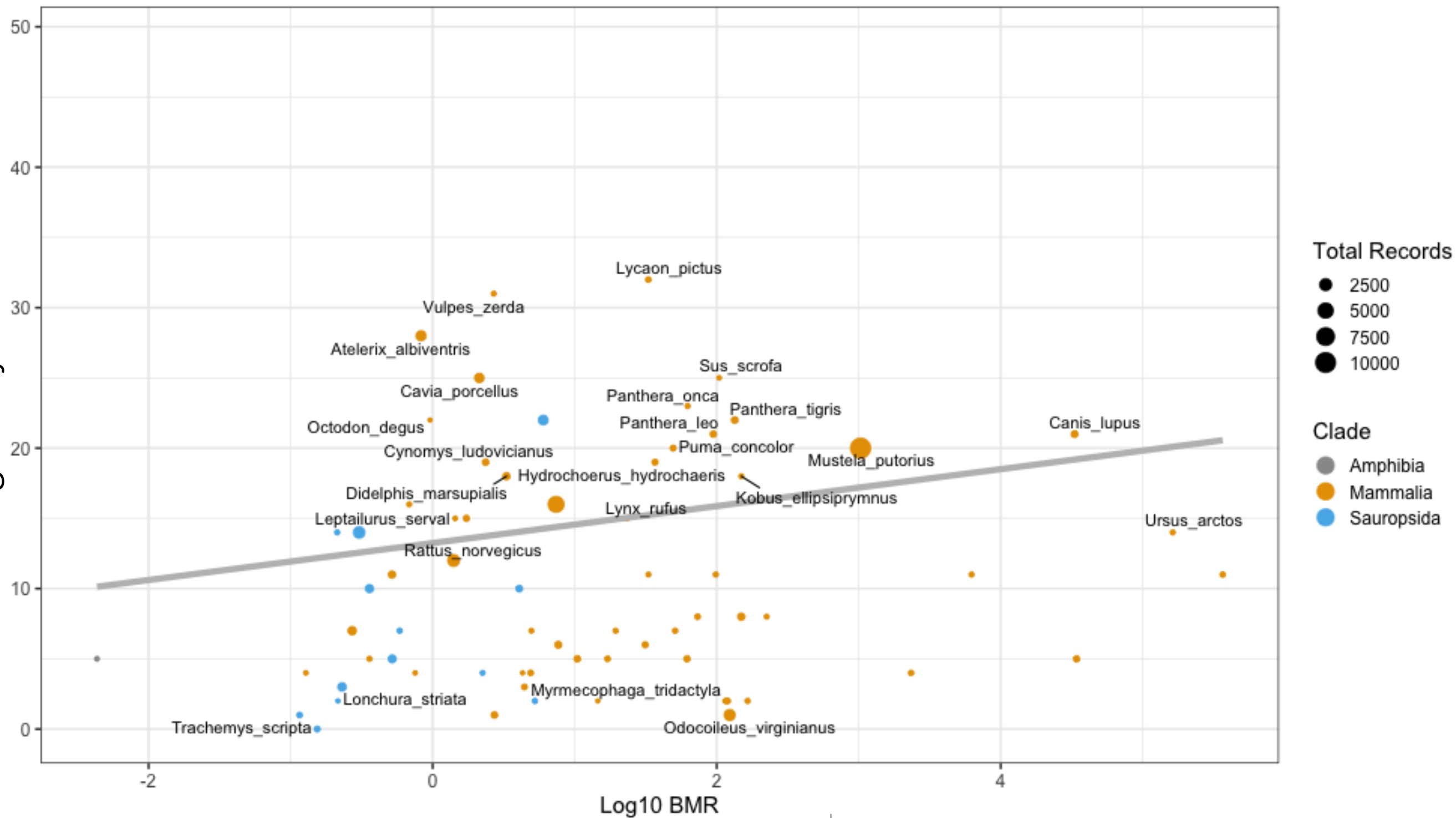


Unpublished. Please don't share!

Log10 BMR Malignancy %

Adjusted R²: 0.00183 p-value: 0.2927 lambda: 0.000

Malignancy Prevalence



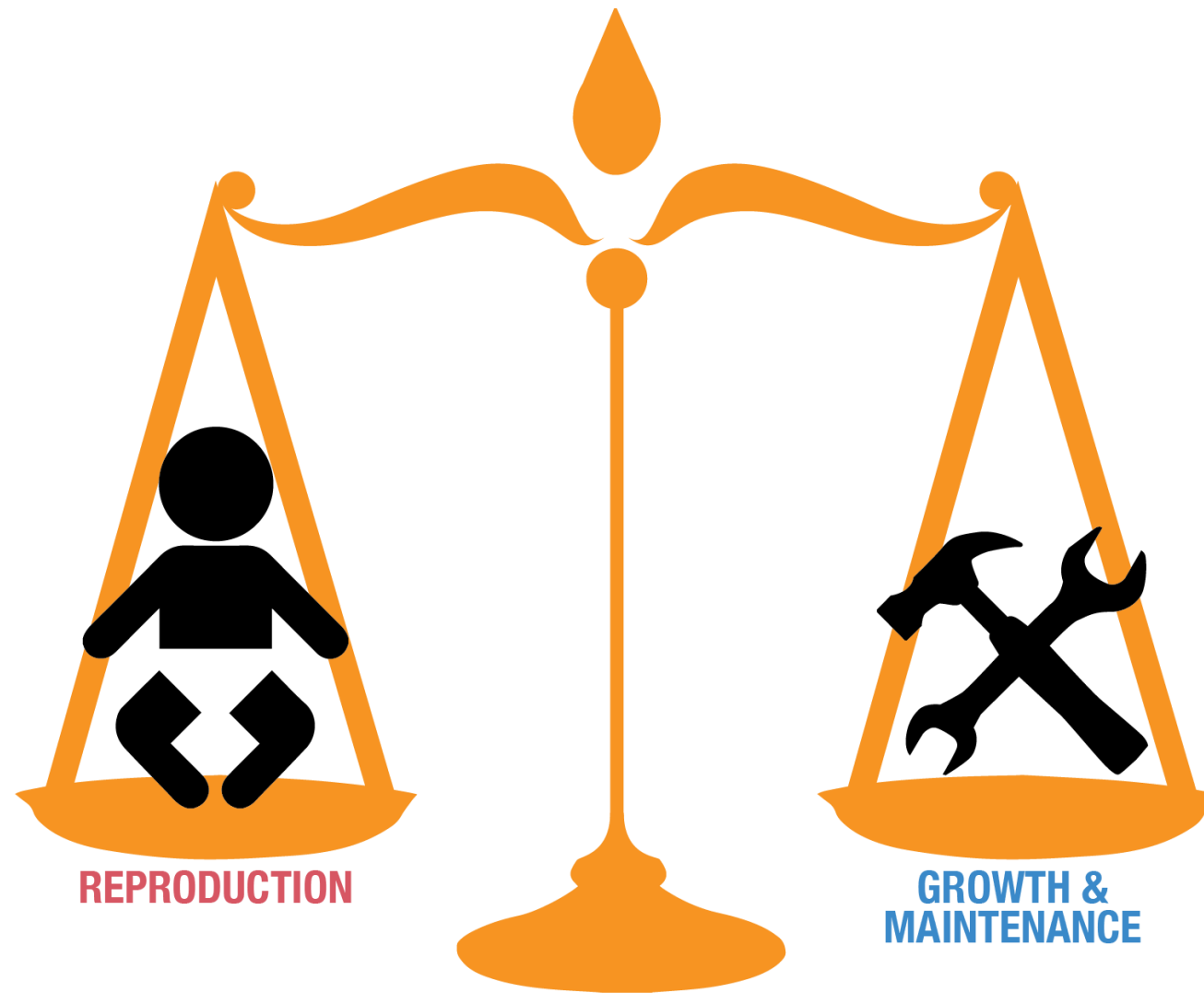
Metabolic Rate

Yes!



Unpublished. Please don't share!

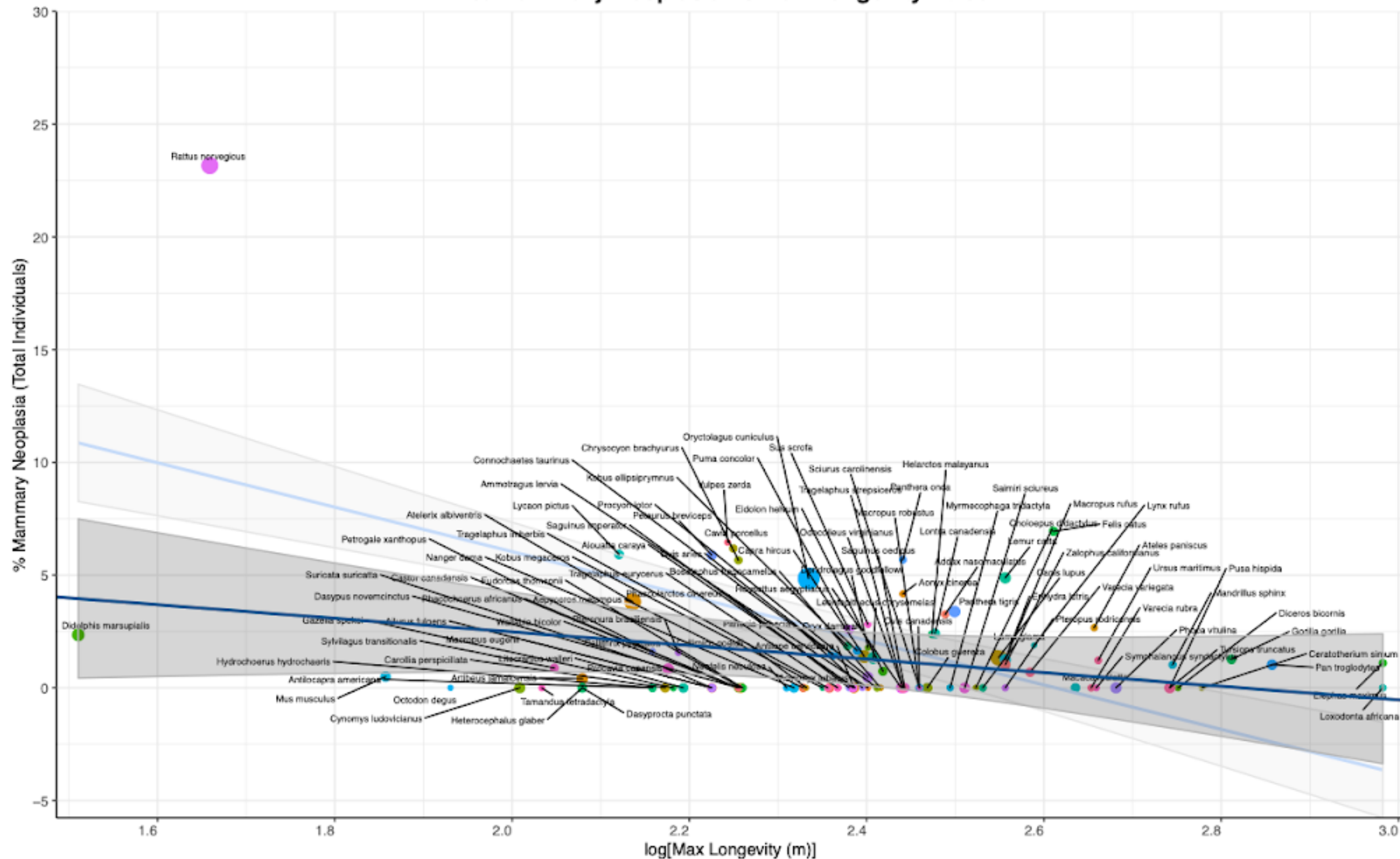
Life history theory suggests there should be tradeoffs between somatic maintenance and reproduction



Are reproductive cancers associated with life history traits?

Zachary Compton, Komal Majahil, Andrew Lovell

% Mammary Neoplasia vs Max Longevity n>50



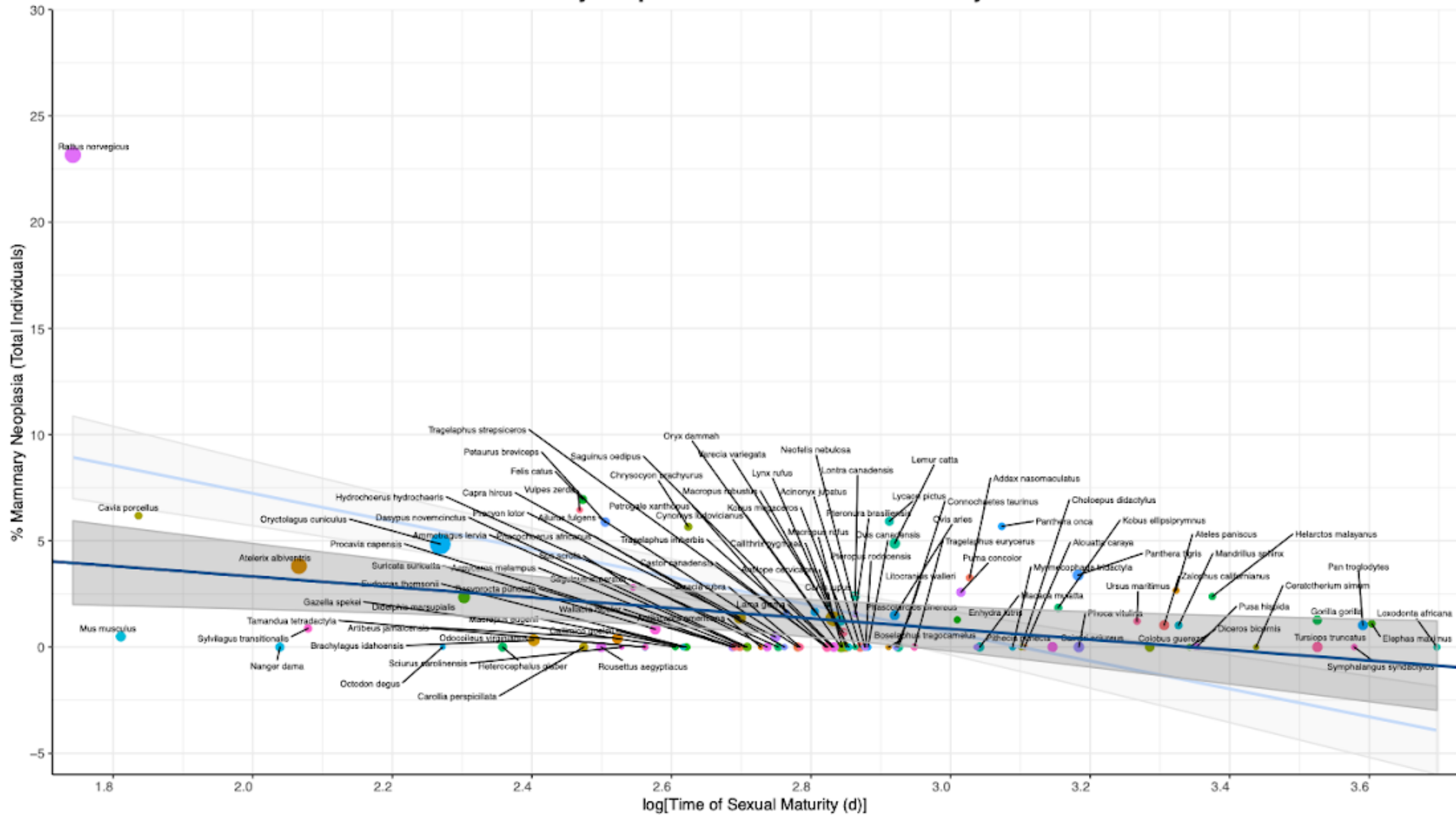
Breast Neoplasia Across Mammals

$p = 0.008$, adjusted $R^2 = 0.06$



Unpublished. Please don't share!

% Mammary Neoplasia vs Time of Sexual Maturity n>50



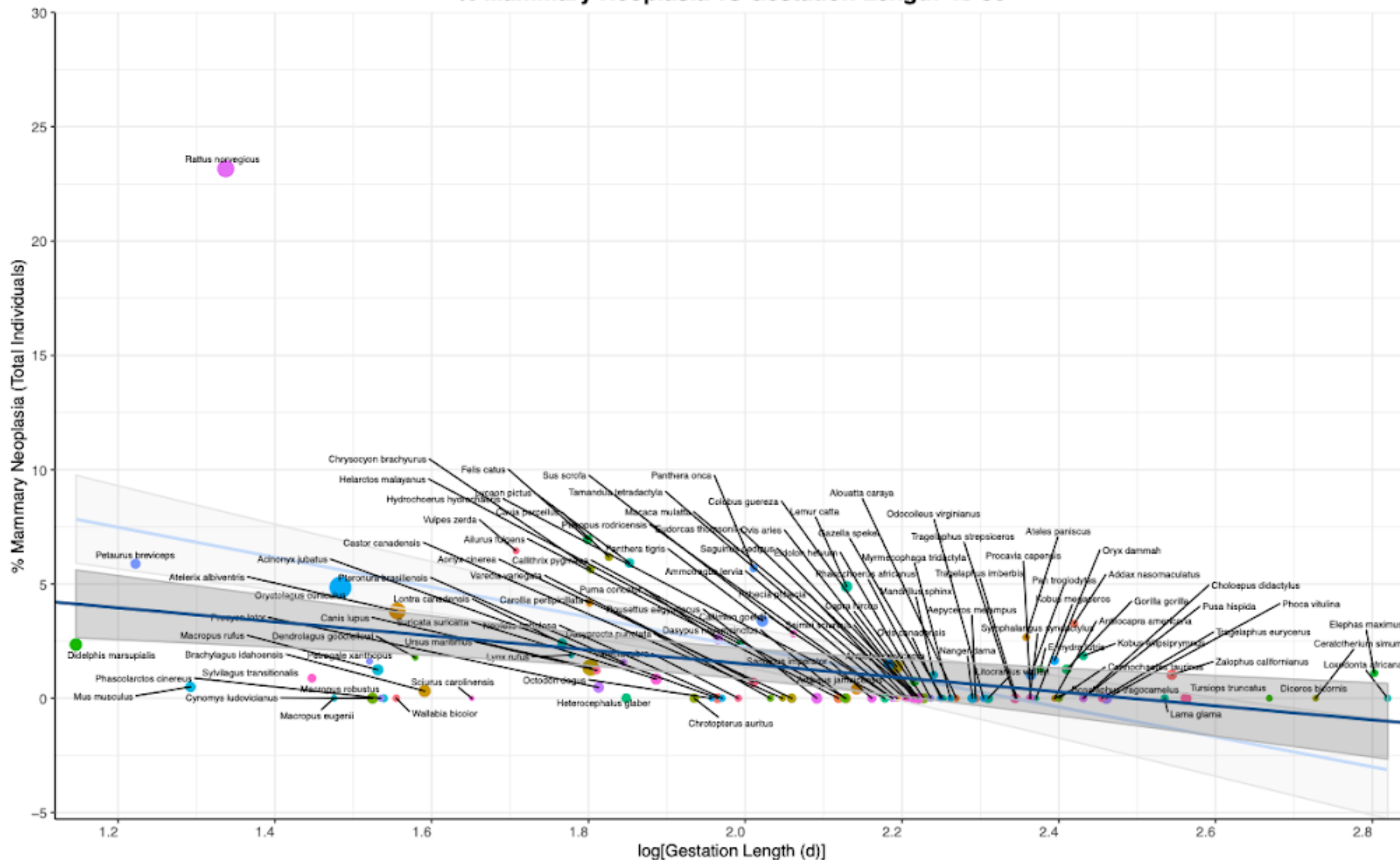
Time to sexual maturity

$p = 0.0007$, adjusted $R^2 = 0.10$



 Unpublished. Please don't share!

% Mammary Neoplasia vs Gestation Length n>50



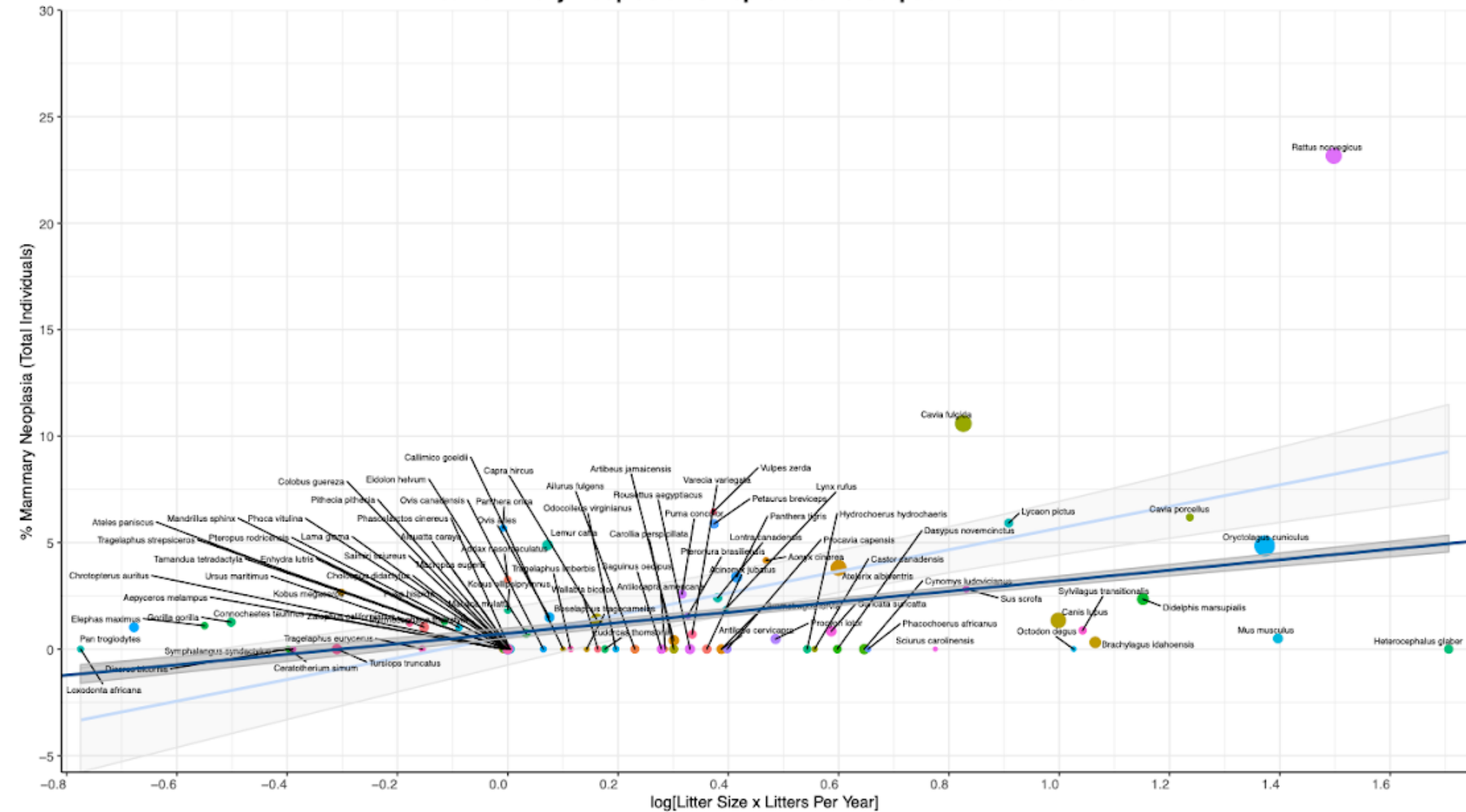
Gestation length

$p = 5.38 \times 10^{-5}$
adjusted $R^2 = 0.14$



 Unpublished. Please don't share!

% Mammary Neoplasia vs Reproductive Output Per Year n>50



Offspring per year

$p = 0.00018$, adjusted $R^2 = 0.14$



 Unpublished. Please don't share!

Caveats

- Animals in captivity (probably skews fast life history species)
- Includes both necropsies and illnesses
- Doesn't include healthy individuals



Conclusions

- Cancer is a problem for all multicellular organisms
- DNA damage response and mutation rates may explain some exceptional cancer defenses
- Life history variables aren't very predictive except in breast cancer (we are testing other reproductive cancers)
- Basal metabolic rate may explain some cancer prevalence
- Most of the variance in cancer prevalence remains unexplained
- Many cancer suppression mechanisms remain to be discovered
- Can we learn from exceptional species how to better prevent cancer in humans (and improve animal health)?



Acknowledgements

Grant Support

Maley-Shibata NIH U54 CA217376

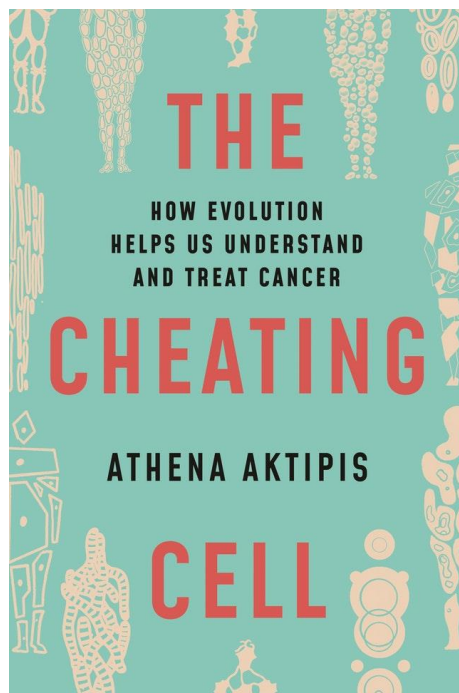
Maley NIH R01 CA140657

Maley-Hwang DoD BC132057

Maley-Hwang NIH R01 CA185138

Maley-Hwang-West NIH U2C CA233254

Reid NIH P01 CA91955



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