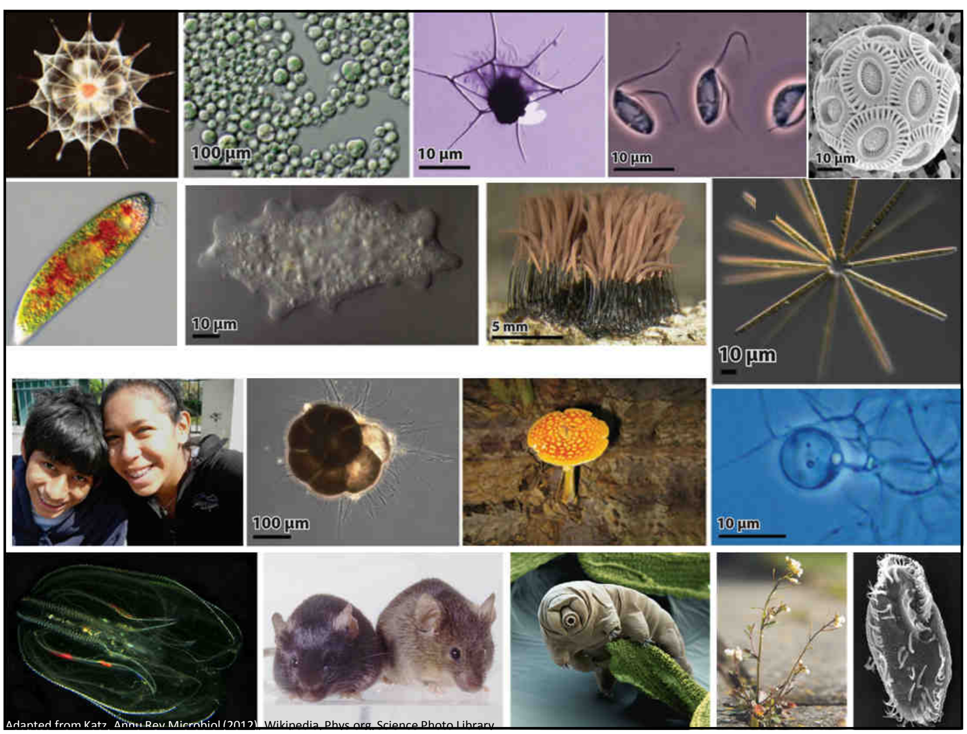
Phenologs

A case study of using bioinformatics to find new genes for genetic traits

BCH339N Systems Biology / Bioinformatics – Spring 2016

Edward Marcotte, Univ of Texas at Austin



Adapted from Katz, Annu Rev Microbiol (2012), Wikipedia, Phys.org, Science Photo Library

We share genes with almost every known organism

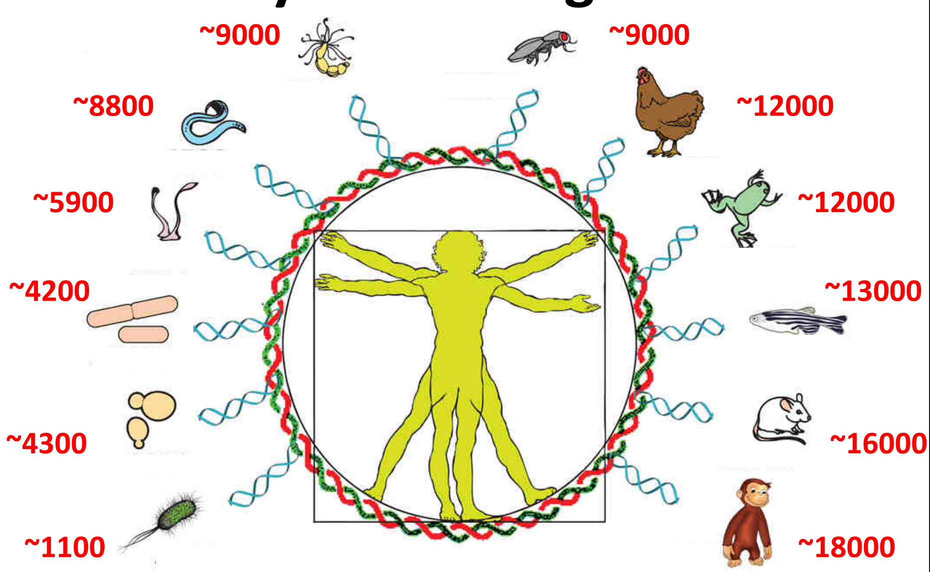


Image: Aashiq Kachroo, #'s from InParanoid

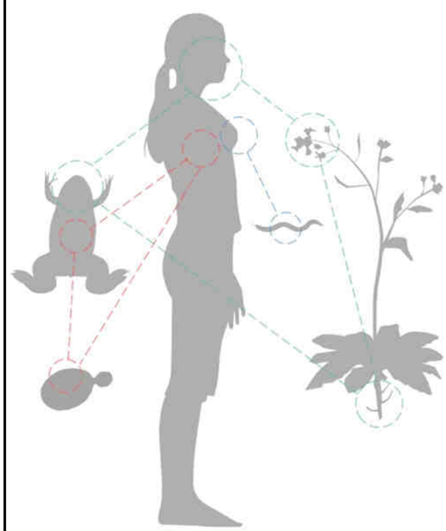
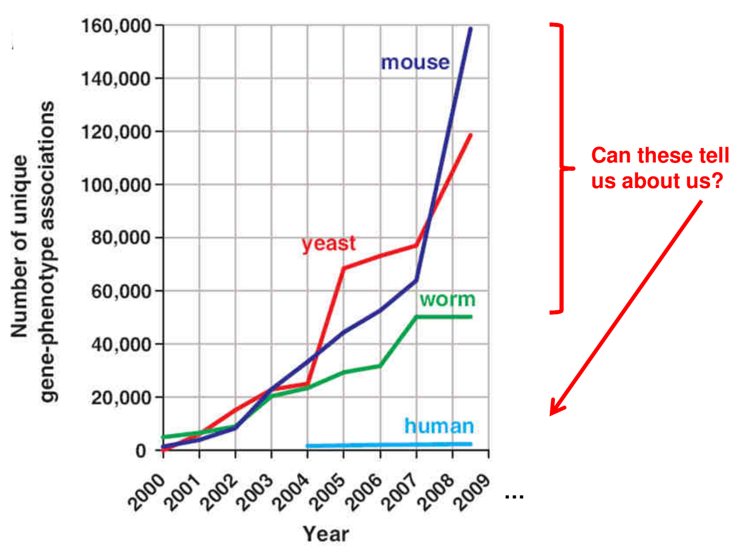


Illustration by Kathryn Weir

All genetic traits and diseases affect molecular structures that are evolutionarily conserved.

We know far more about genes & traits in lower organisms than in us. Can we transfer that knowledge to us?



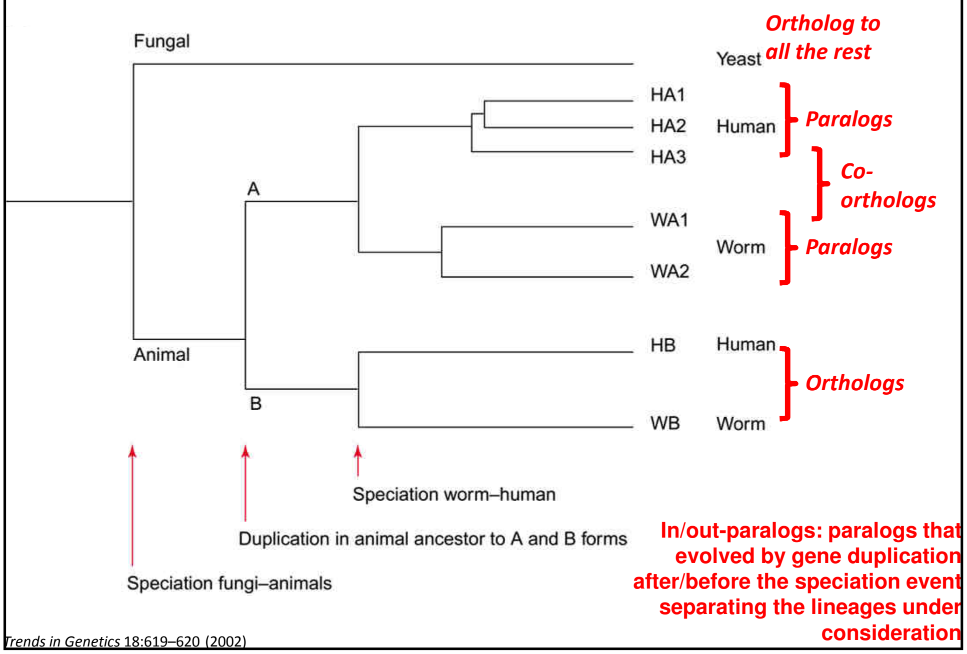
McGary, Park *et al. PNAS* 107:6544-9 (2010)

Comparative evolution studies rely on finding orthologs

<u>Orthologs</u> = genes from different species that derive from a single gene in the last common ancestor of the species

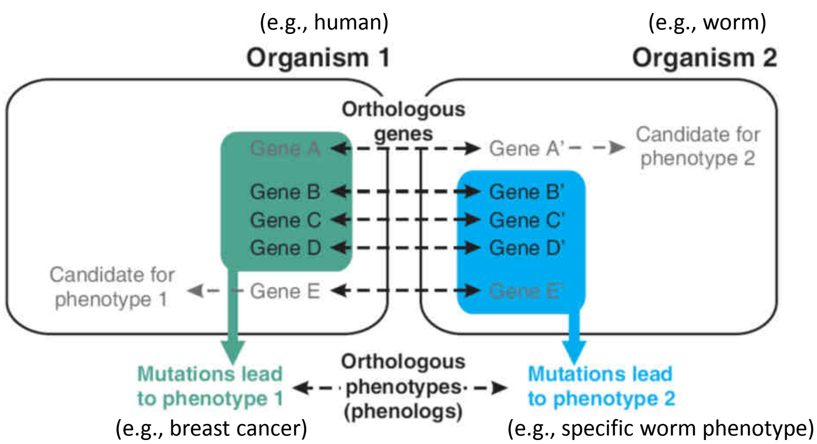
<u>Paralogs</u> = genes that derive from a single gene that was duplicated within a genome

Comparative evolution studies rely on finding orthologs



Trends in Genetics 18:619–620 (2002)

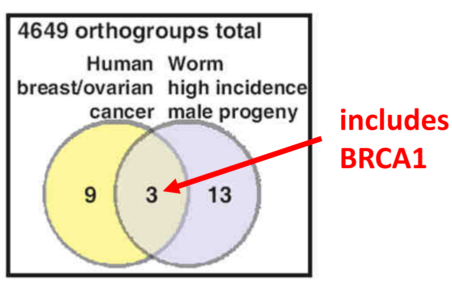
Phenologs = significantly overlapping sets of orthologous genes, such that each gene in a given set gives rise to the same phenotype in that organism



McGary, Park *et al.* *PNAS* 107:6544-9 (2010)

E.g., 'high incidence of male' *C. elegans* genes predict human breast/ovarian cancer genes

Human/Worm Ortholog	Linked to breast cancer in humans	Linked to more males in worms
ATM/atm-1	X	
BRIP1/dog-1	X	
KRAS/let-60	X	
PHB/phb-1	X	
PIK3CA/age-1	X	
RAD51/rad-51	X	
RAD54L/rad-54	X	
SLC22A18/C53B4.3	X	
TSG101/tsg-1010	X	
BARD1/brd-1	X	X
BRCA1/brc-1	X	X
CHEK2/chk-2	X	X
FAM82B/F33H2.6		X
GCC2/hcp-1,hcp-2		X
HMG20A,B/W02D9.3		X
HORMAD2,1/him-3,htp-1,2		X
KIF15/klp-10,18		X
MRE11A/mre-11		X
PIGA/D2085.6		X
RAD1/mrt-2		X
RAD21/coh-1		X
SEH1L/npp-18		X
SVIL/viln-1		X
TSPO,BZRPL1/C41G7.3		X
WDHD1/F17C11.10		X



$p \leq 7.2 \times 10^{-6}$

McGary, Park *et al.* *PNAS* 107:6544-9 (2010)

Building & searching a collection of phenotypes

Mining available databases +
manual collection from the primary literature

↓

Organism	# gene-phenotype associations
human	1,923
mouse	74,250
worm	27,065
yeast	86,383
Arabidopsis	22,921

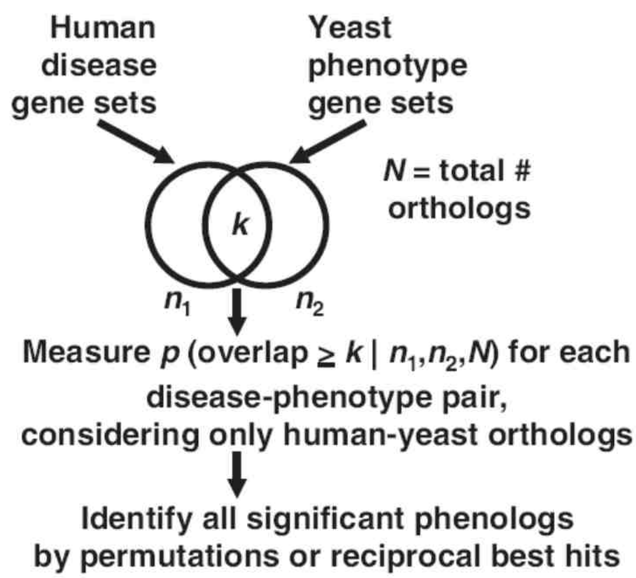
Spanning ~300 human diseases,
>7,000 model organism mutational phenotypes

↓

Computational scan phenotypes for novel models of a disease of interest, identify significant phenologs using permutation tests

McGary, Park *et al.* *PNAS* 107:6544-9 (2010)

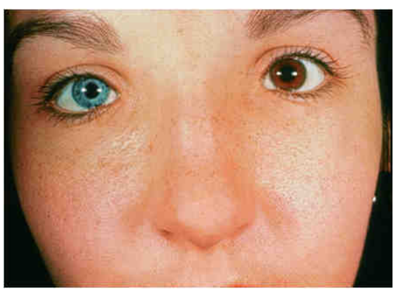
Discovering phenologs



McGary, Park *et al.* *PNAS* 107:6544-9 (2010)

Computationally, we find many genes shared between human diseases and mouse, yeast, worm, and even plant traits

McGary, Park *et al. PNAS* 107:6544-9 (2010)
Woods, Blom *et al. BMC Bioinformatics*, 14:203 (2013)

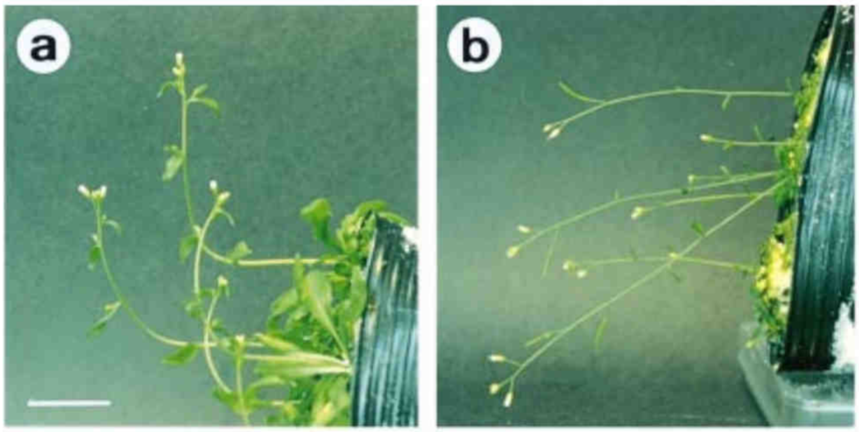


Michael Murphy, M.D.

Waardenburg syndrome accounts for ~2-5% of cases of deafness

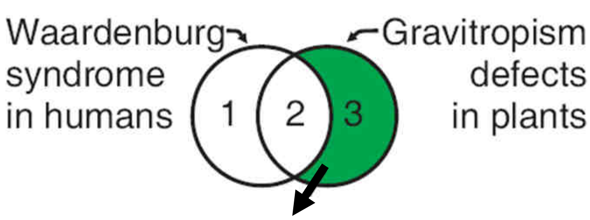
Assorted websites, incl. www.verywell.com/waardenburg-syndrome-1048692, http://stephaniemariesanchez.blogspot.com/

Plants sense and respond to gravity → gravitropism



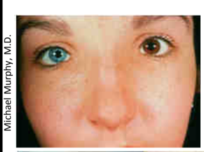
Fukaki *et al.*, *The Plant Journal* 14, 425–430 (1998)

Plant gravitropism predicts genes for Waardenburg syndrome, a human congenital deafness syndrome



The human versions of these plant genes are <u>candidate Waardenburg genes</u>

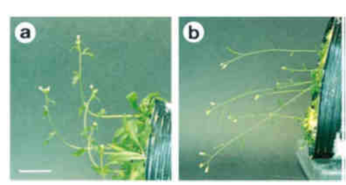
Michael Murphy, M.D.



Assorted websites

Waardenburg syndrome

≈

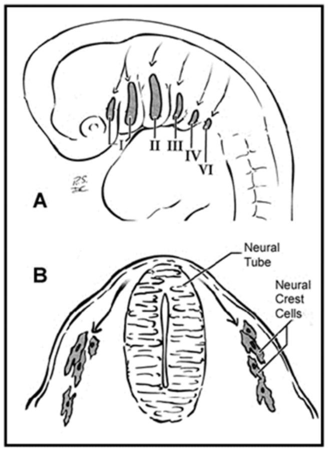


Fukaki *et al.*, *The Plant Journal* 14, 425–430 (1998)

Gravitropism defects

Waardenburg syndrome is a defect of neural crest cells

Neural crest cells migrate during embryonic development

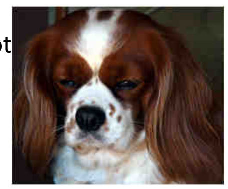


Heike & Hing, *Gene Reviews* (2009)

Some WS correlates in other animals:
Deafness in Dalmatian dogs (22% unilaterally deaf)

www.petplanet.co.uk

Variations in the Blenheim spot Cavalier King Charles Spaniels

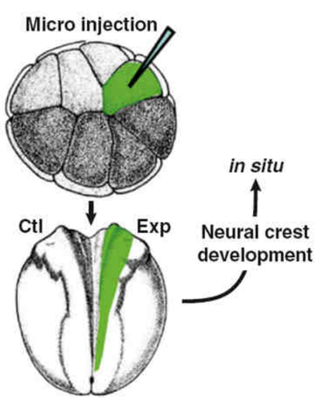


www.silvarcea.co.uk

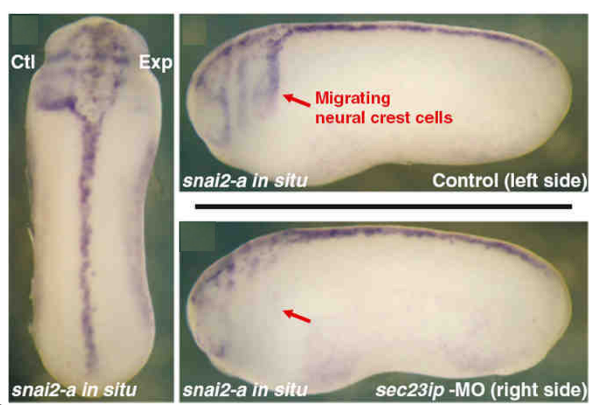
Association between white blue-eyed cats and deafness (noted by Darwin in 1859)

White forelock and deafness/bowel blockage in foals & many more...

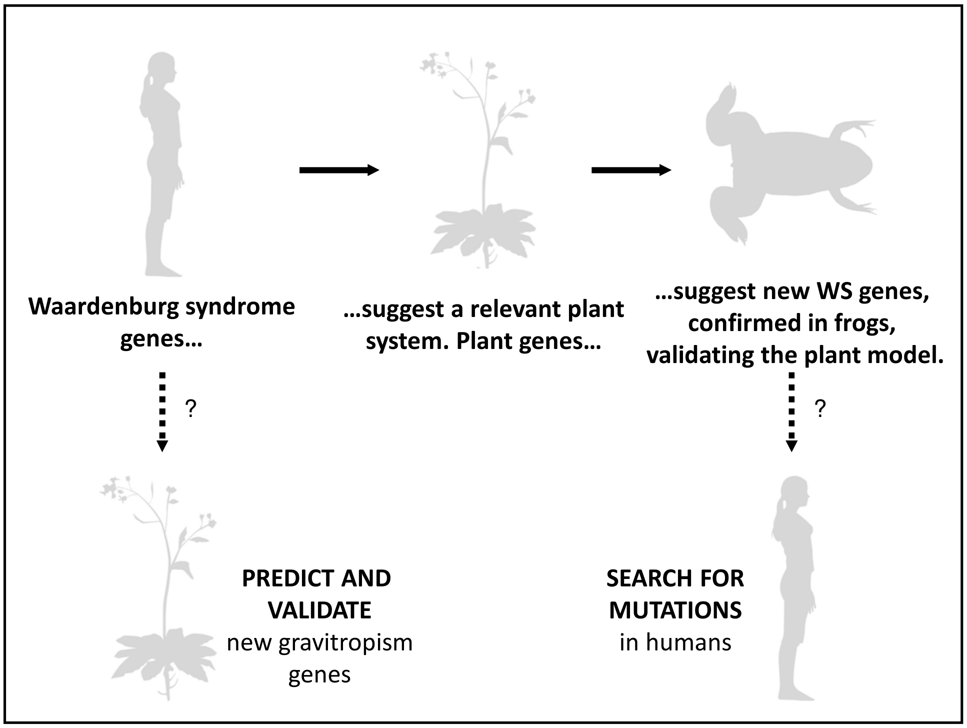
Sure enough, inactivating one of the genes—predicted from plants—in a tadpole disrupts neural crest cells, consistent with Waardenburg syndrome

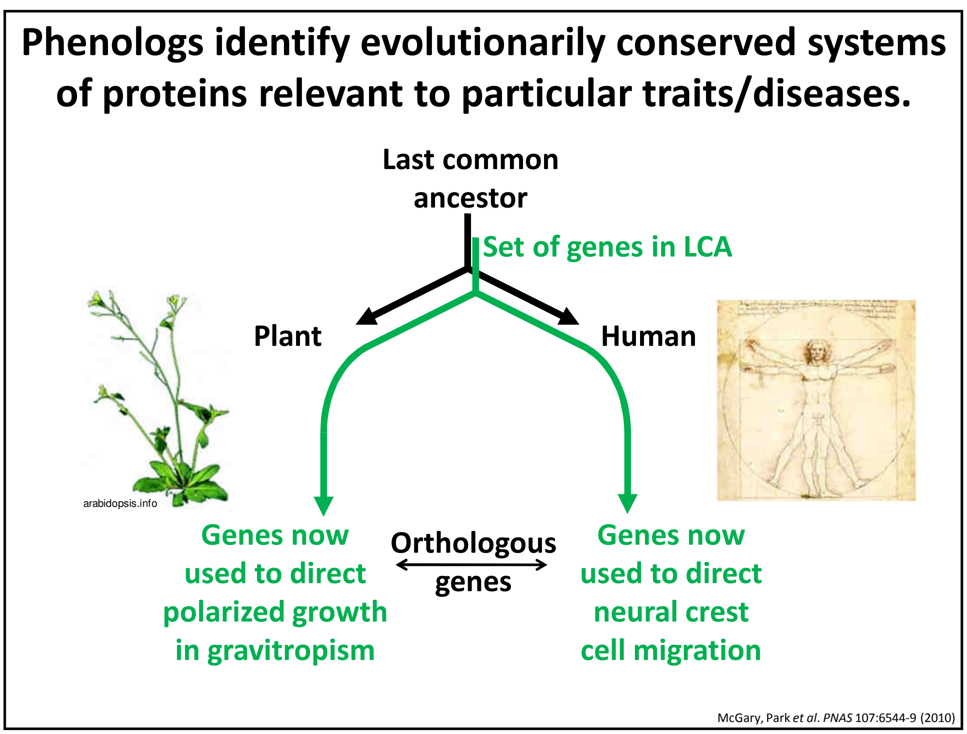


Frog embryo

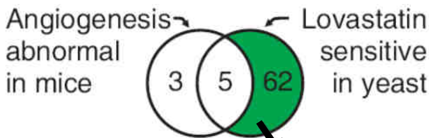


McGary, Park *et al.* *PNAS* 107:6544-9 (2010)


Waardenburg syndrome genes…
…suggest a relevant plant system. Plant genes…
…suggest new WS genes, confirmed in frogs, validating the plant model.
?
?
PREDICT AND VALIDATE new gravitropism genes
SEARCH FOR MUTATIONS in humans

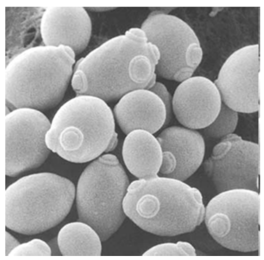

Phenologs identify evolutionarily conserved systems of proteins relevant to particular traits/diseases.
Last common ancestor
Set of genes in LCA
Plant
Human
arabidopsis.info
Genes now used to direct polarized growth in gravitropism
Orthologous genes
Genes now used to direct neural crest cell migration
McGary, Park et al. PNAS 107:6544-9 (2010)

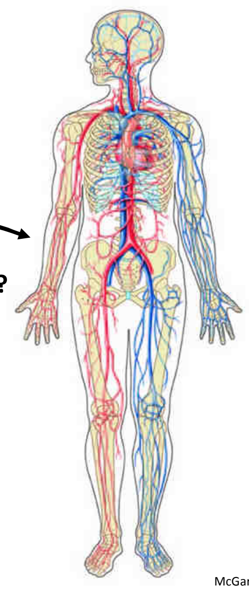
Example #3: Yeast genes linked to statin sensitivity predict blood vessel defects



The human versions of these yeast genes are <u>candidate angiogenesis genes</u>

Can these really tell us about these?





www.chemistryland.com

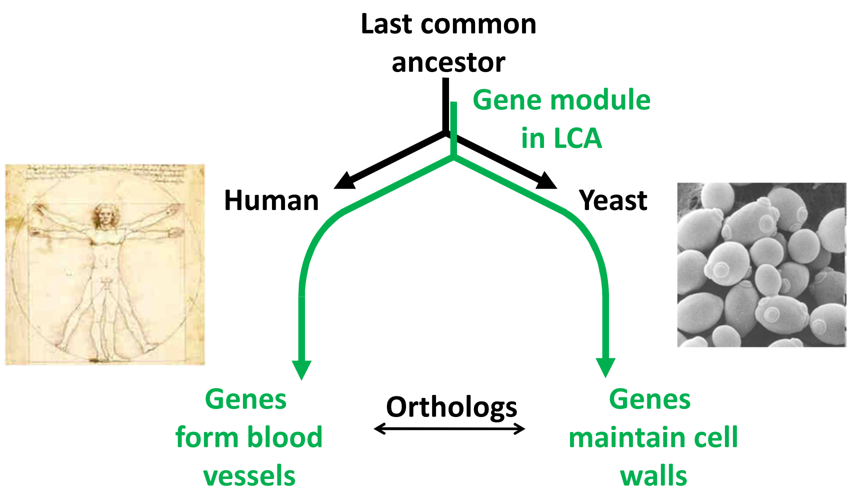
Dorling Kindersley

McGary, Park *et al.* *PNAS* 107:6544-9 (2010)

Disrupting the SOX13 gene causes strong blood vessel defects

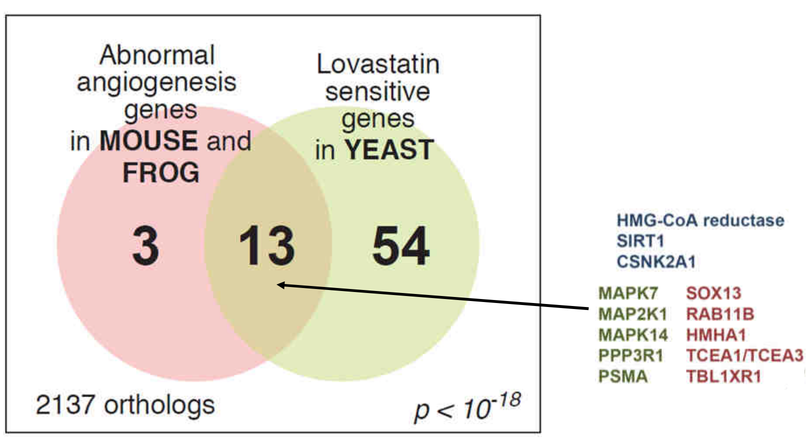
McGary, Park *et al.* *PNAS* 107:6544-9 (2010)

A yeast model of angiogenesis = example of a deeply conserved, but "repurposed" gene module



McGary, Park *et al. PNAS* (2010)

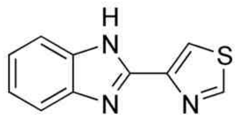
The yeast/angiogenesis gene module



Screening for drugs that interact genetically with this yeast module led us to identify a new angiogenesis inhibitor

TBZ = thiabendazole

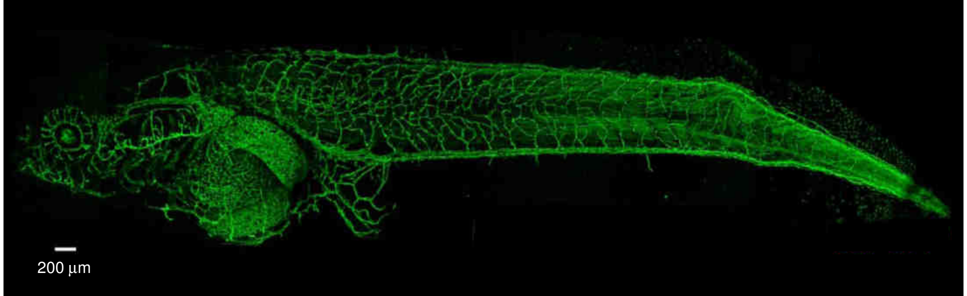
FDA-approved antifungal drug with 40 years of safety data



- **Approved by U.S. Food and Drug Administration in 1967**

- Fungicide and parasiticide
- Not mutagenic or carcinogenic; 2 year dog safety trials
- Off-patent, marketed as a generic

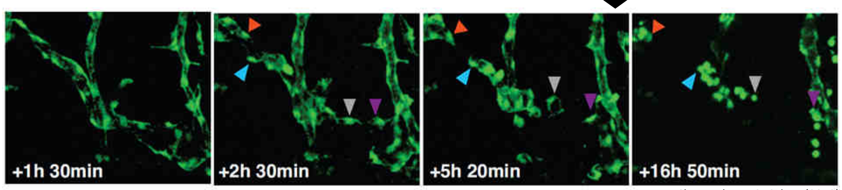
Imaging the blood vessels of a living, transgenic tadpole in a dish of water



kdr:GFP transgenic *Xenopus laevis*

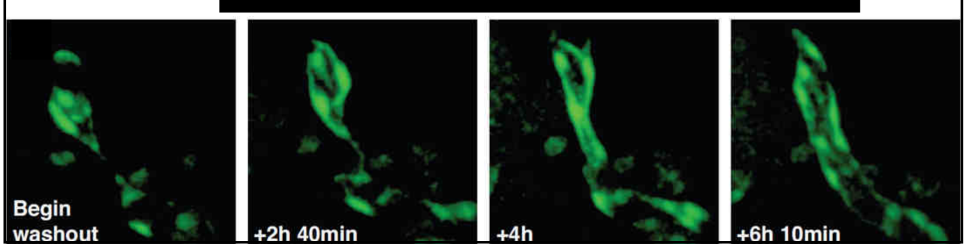
TBZ disrupts vascular integrity, making vascular endothelial cells retract & round up

Control (DMSO carrier) **+ TBZ**

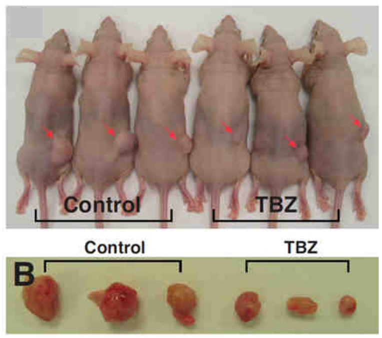


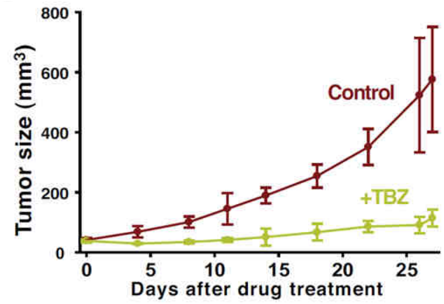
Cha *et al.*, *PLoS Biology* (2012)

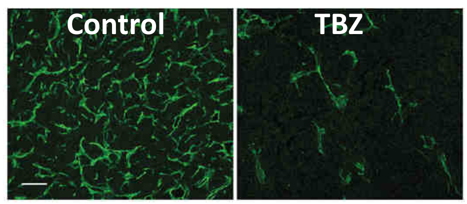
reversibly…



TBZ slows human fibrosarcoma tumors transplanted into immune-compromised mice



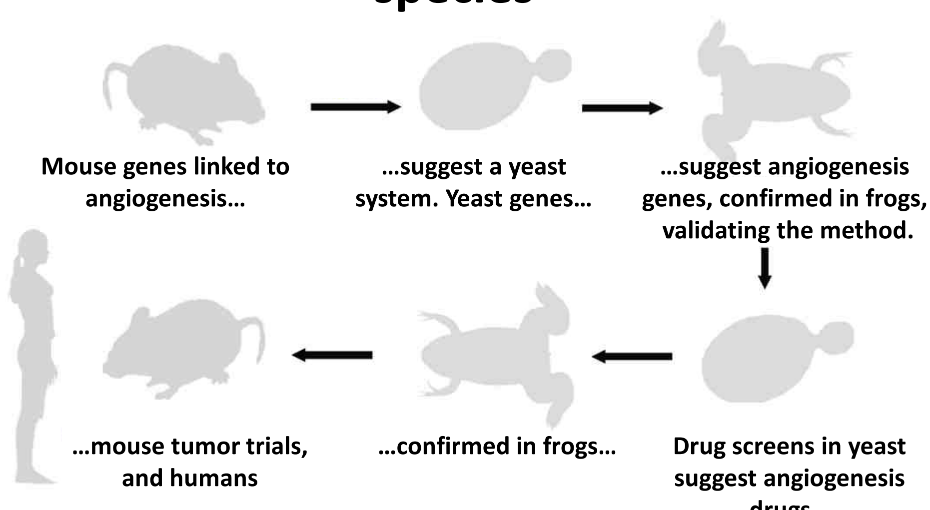




Vasculature in tumor sections

Cha *et al.*, *PLoS Biology* (2012)

"Road map" to a new vascular disrupting agent, by mapping phenotypes across species



Cha *et al.*, *PLoS Biology* (2012)