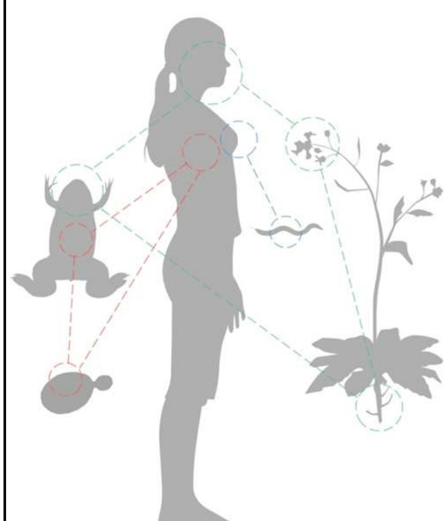
Phenologs

An example of using bioinformatics to find new genes for genetic traits

BCH364C/391L Systems Biology / Bioinformatics – Spring 2015

Edward Marcotte, Univ of Texas at Austin

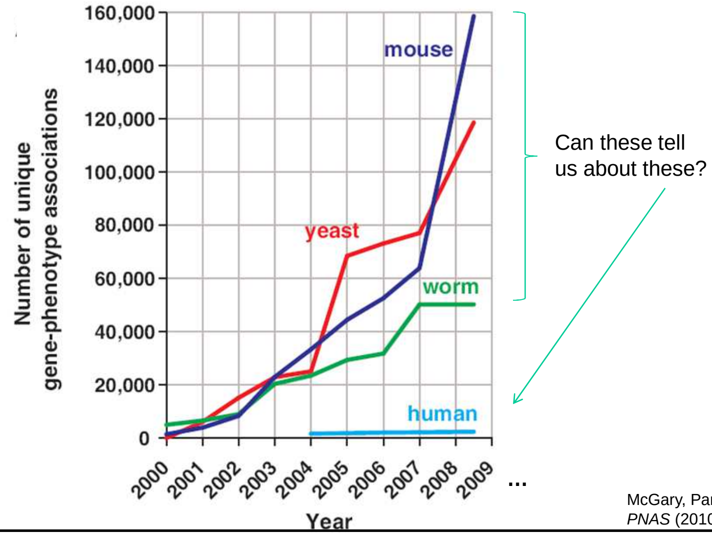


Virtually all genetic traits and diseases affect molecular structures that are evolutionarily conserved.

Consequently, human traits and diseases often have equivalents in other species, even distant ones.

We know far more about genes & traits in lower organisms than in us.

How do deeply conserved gene networks relate to traits, structures, and diseases in different organisms?



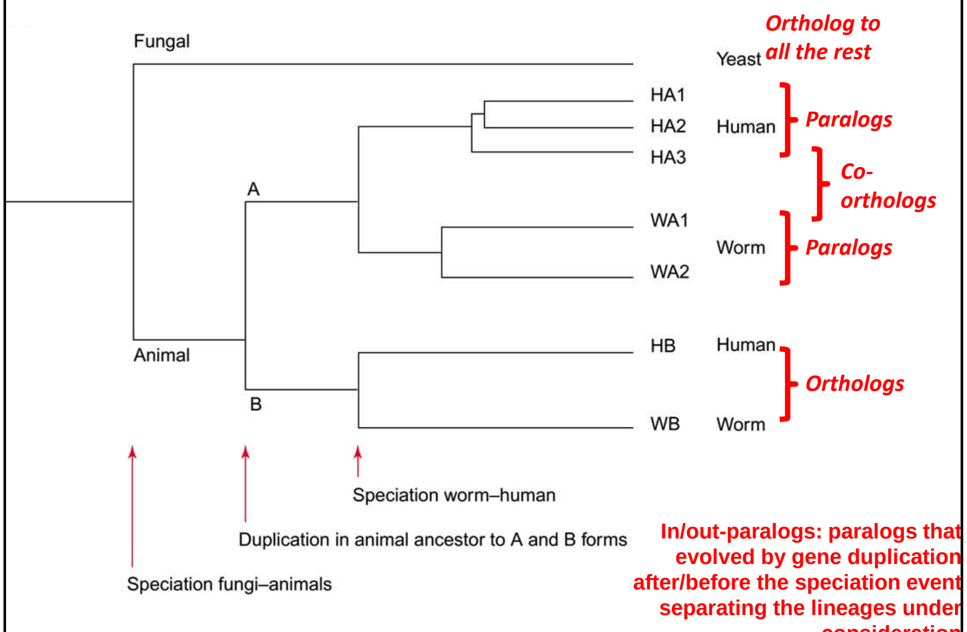
McGary, Park *et al.* *PNAS* (2010)

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)

Comparative evolution studies rely on finding orthologs

OMA: http://omabrowser.org/oma/home/
InParanoid: http://inparanoid.sbc.su.se/cgi-bin/index.cgi
PhylomeDB: http://phylomedb.org/
MOSAIC: http://pythonhosted.org/bio-MOSAIC/

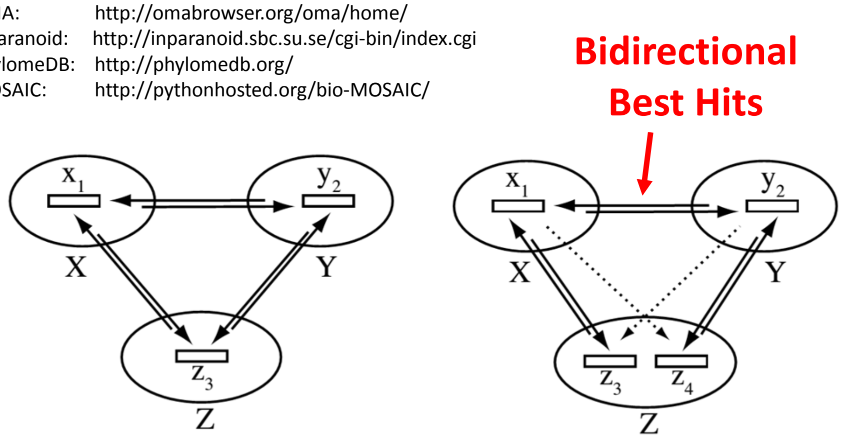
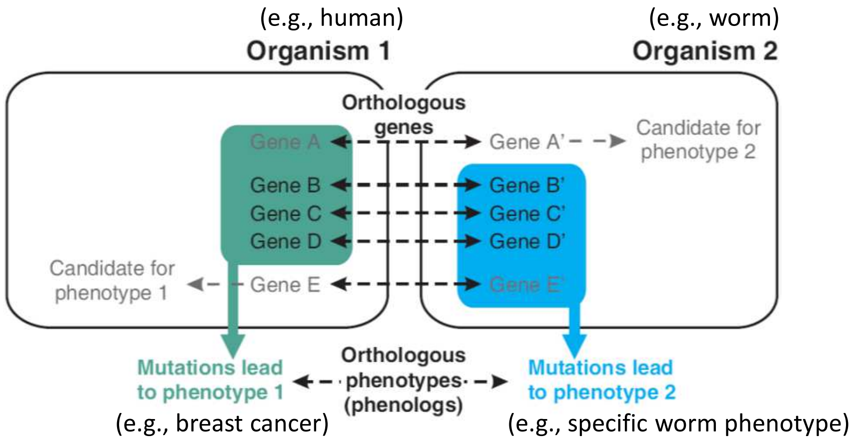


Fig. 1. Orthologous relationship between x_1 and y_2

Fig. 2. Paralogous relationship between x_1 and y_2, demonstrated by presence of z_3 and z_4 in Z

A. McLysaght et al. (Eds.): RECOMB 2005 Ws on Comparative Genomics, LNBI 3678, pp. 61–72, 2005.

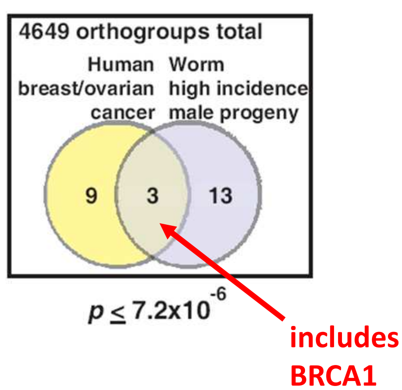
Phenologs = significantly overlapping sets of orthologous genes, such that each gene in a given set gives rise to the same phenotype in that organism



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

An example phenolog: a high incidence of male *C. elegans* maps to human breast/ovarian cancers

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



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

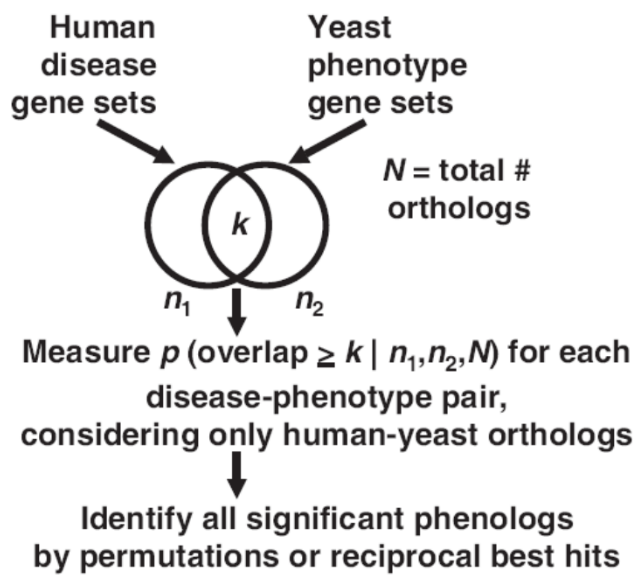
Spanning ~300 human diseases,
>7,000 model organism mutational phenotypes

↓

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

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

Discovering phenologs



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

There are 1,000's of phenologs between human diseases and mouse, yeast, worm, and even plant traits

Some cases we knew about already, serving as positive controls…

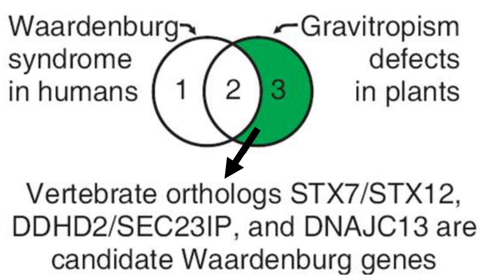
For example, genes for mouse cataracts suggest genes for human cataracts...

But many cases were surprising!

A defect in...	suggests genes for ...
yeast lovastatin sensitivity →	**angiogenesis defects**
worm abnormal body wall muscle cell polarization →	**gastrointestinal hemorrhage**
yeast hydroxyurea sensitivity →	**hemolytic anemia**
plant cotyledon development defects →	**mental retardation**
***E. coli* chemical sensitivies** →	**chemically-induced seizures**

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

Example #2: plant *negative gravitropism* defects predict *Waardenburg syndrome*, a congenital disease with characteristic craniofacial, hearing, and pigmentation alterations

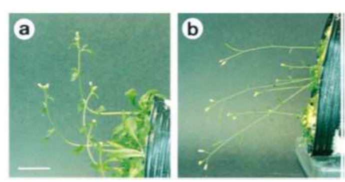


Michael Murphy, M.D.

Assorted websites

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

≈

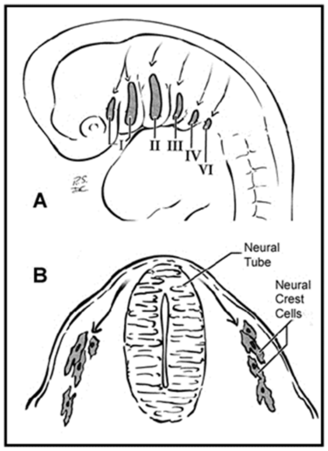


Plants failing to grow upwards

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

Waardenburg syndrome is a defect of neural crest cells

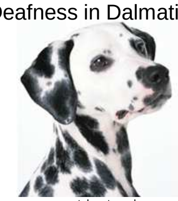
Neural crest cells migrate during embryonic development



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 of Cavalier King Charles Spaniels

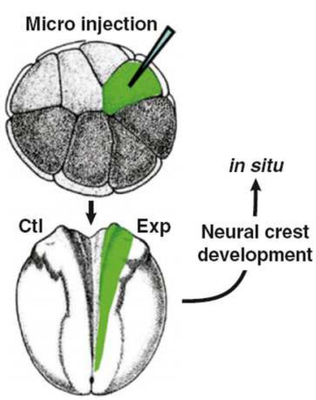
www.silvarcea.co.uk

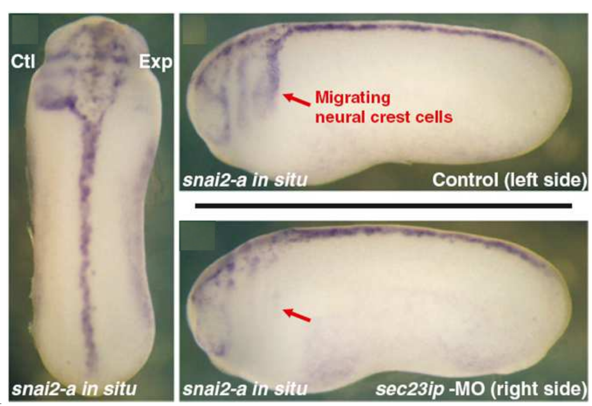
Association between white blue-eyed cats and deafness (noted by Darwin in 1859)

White forelock and deafness/bowel bowel blockage in foals

& many more...

Inactivating SEC23IP—predicted from *Arabidopsis*—in a tadpole disrupts neural crest cells, consistent with Waardenburg syndrome

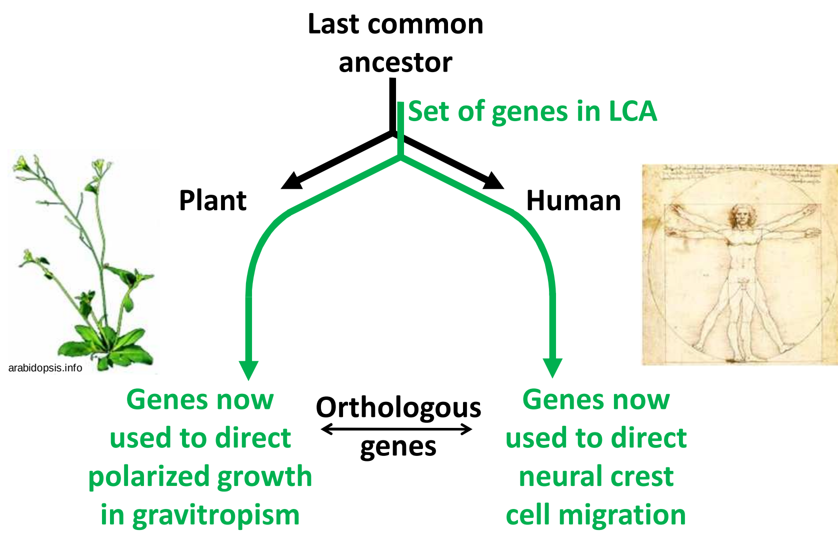




SEC23IP localizes to the neural crest cells & induces neural crest defects upon knockdown

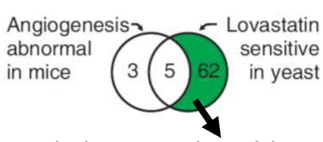
McGary, Park *et al*. *PNAS* 107:6544-9 (2010)

Phenologs identify evolutionarily conserved systems of proteins relevant to particular traits/diseases.



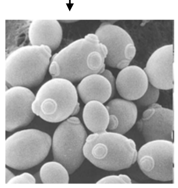
McGary, Park *et al.* *PNAS* (2010)

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

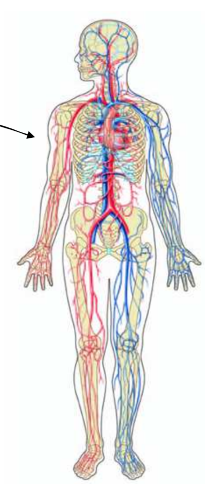


The human versions of these yeast genes are <u>candidate angiogenesis genes</u>

Can these really tell us about these?



www.chemistryland.com



Dorling Kindersley

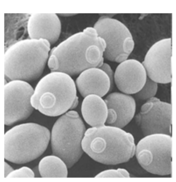
McGary, Park *et al.* *PNAS* (2010)

Disrupting the SOX13 gene causes strong blood vessel defects

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

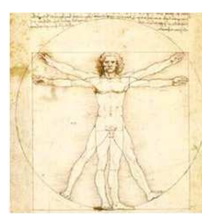
Last common ancestor

Set of genes in LCA



Yeast

Human

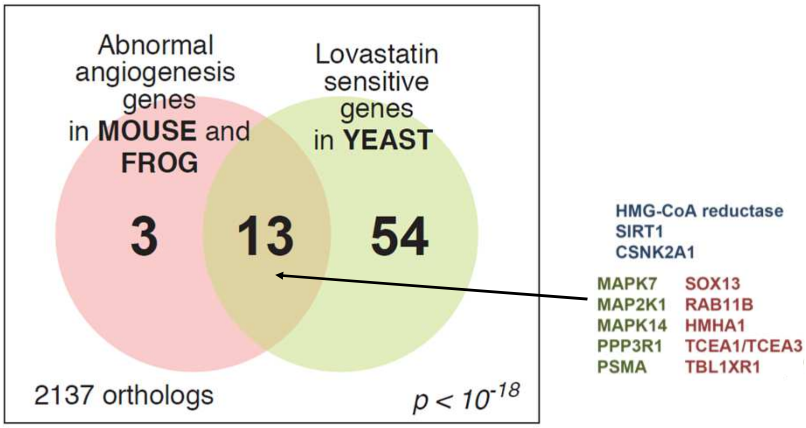


Genes now used to maintain cell walls

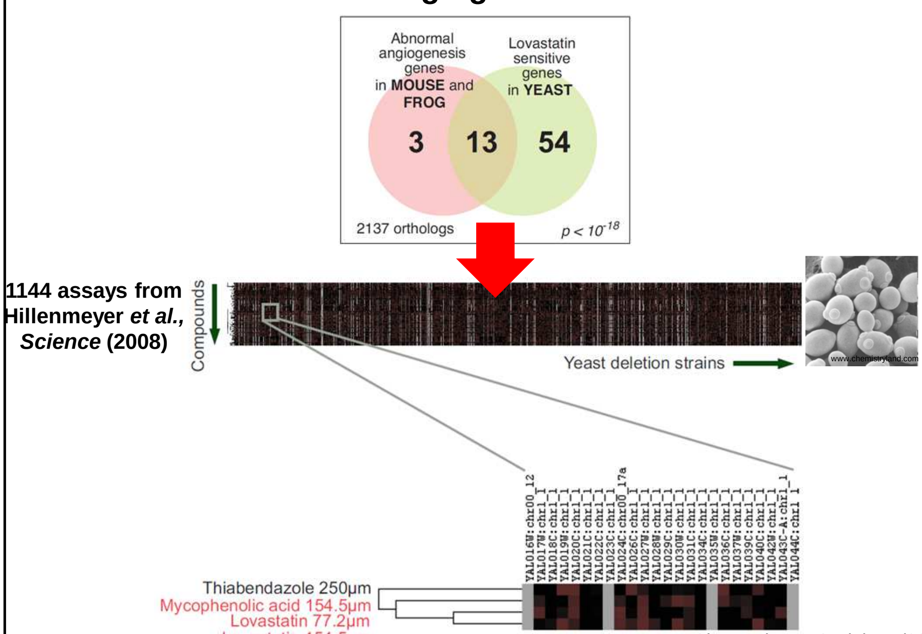
Orthologous genes

Genes now used to form blood vessels

The yeast/angiogenesis gene module



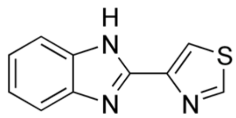
Chemicals that interact genetically with this module are candidate angiogenesis inhibitors



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

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

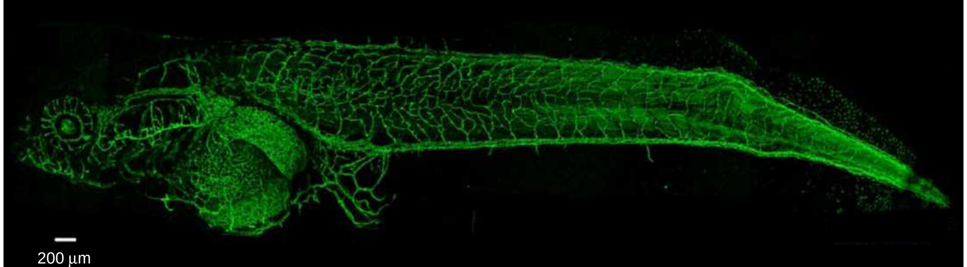
TBZ = thiabendazole
An FDA-approved antifungal drug with 40 years of safety data



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

- fungicide and parasiticide
- No mutagenic or carcinogenic effects
  2 year safety trials in animals
- Off-patent, now marketed as a generic drug

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



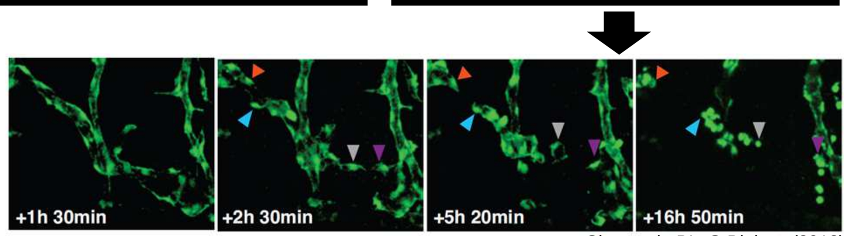
kdr:GFP transgenic *Xenopus laevis*

Image: Hye Ji Cha

Thiabendazole disrupts vascular integrity, causing retraction and rounding of vascular endothelial cells

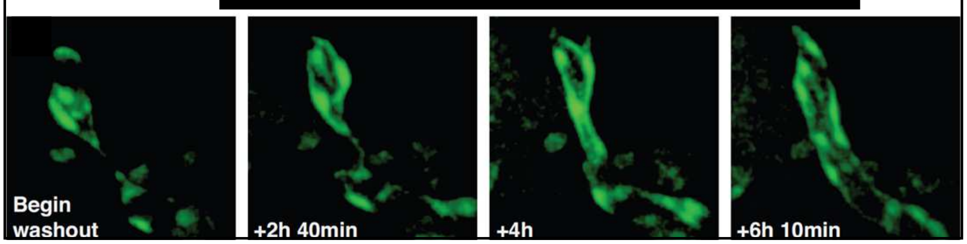
Control (DMSO carrier)

+ TBZ

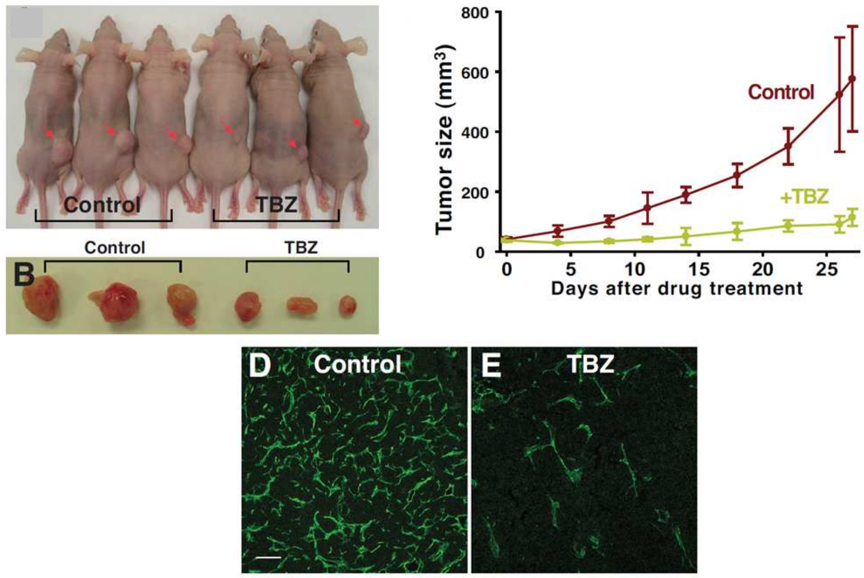


Cha *et al.*, *PLoS Biology* (2012)

reversibly…



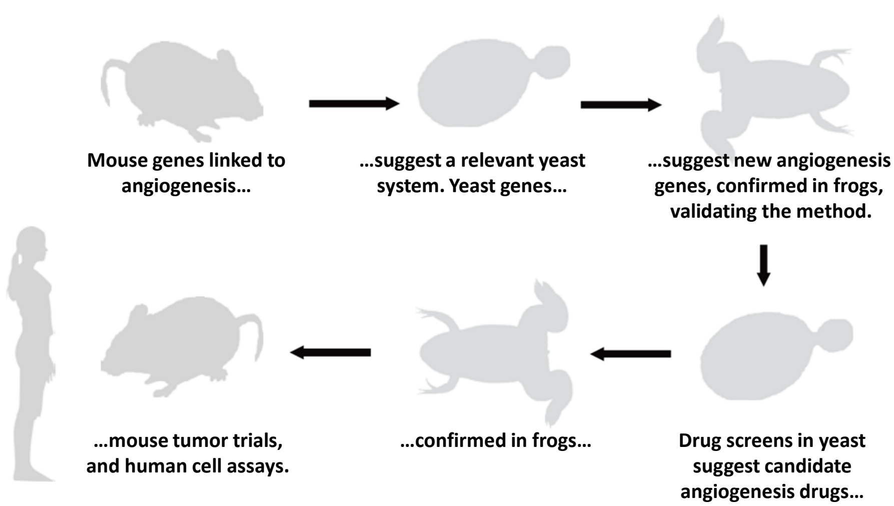
TBZ slows the growth of human fibrosarcoma tumors transplanted into immune-compromised mice



Vasculature in tumor sections

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

Summarizing the "road map" to a new vascular disrupting agent



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