Classic Phenylketonuria (PKU)

Erin Syverson

What is PKU?

Permanent brain damage, cognitive disabilities

Seizures

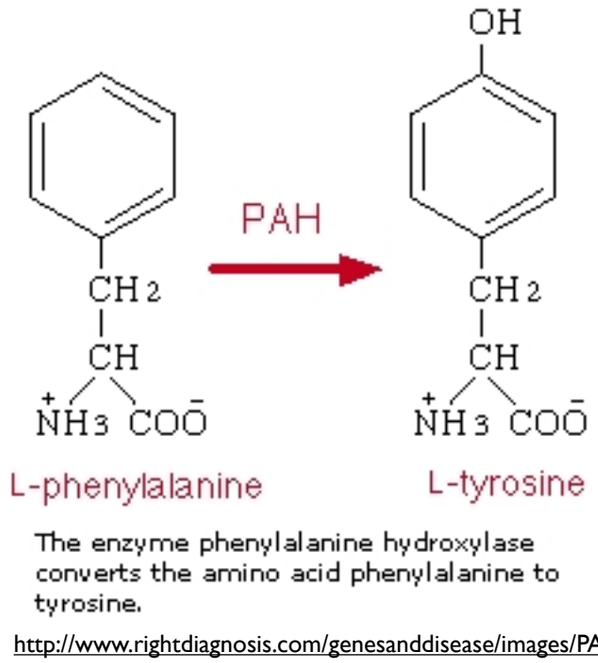
Reduced melanin

Microcephaly

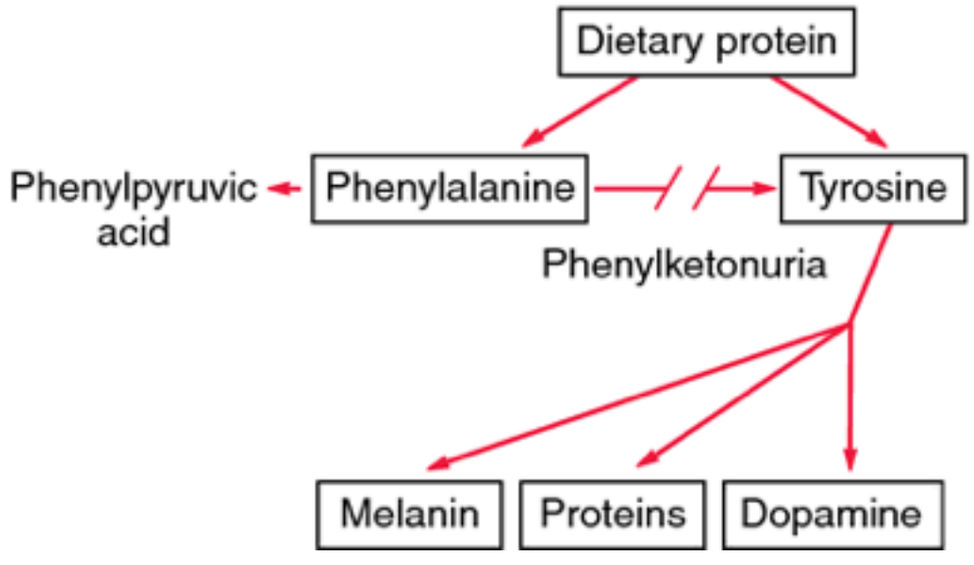
Behavioral problems

Musty odor

Tyrosine starvation



http://www.rightdiagnosis.com/genesanddisease/images/PAH.gif



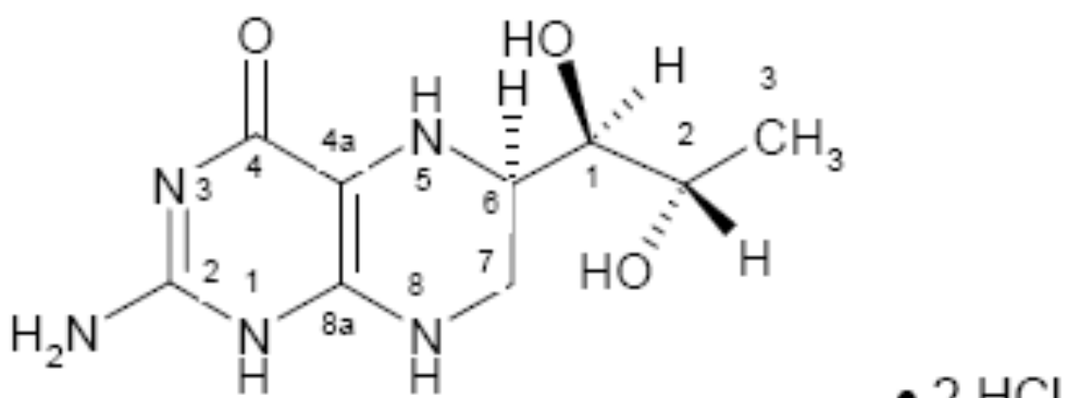
Miller-Keane Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health, Seventh Edition.

Treatments

Kuvan:

Supplement of BH4

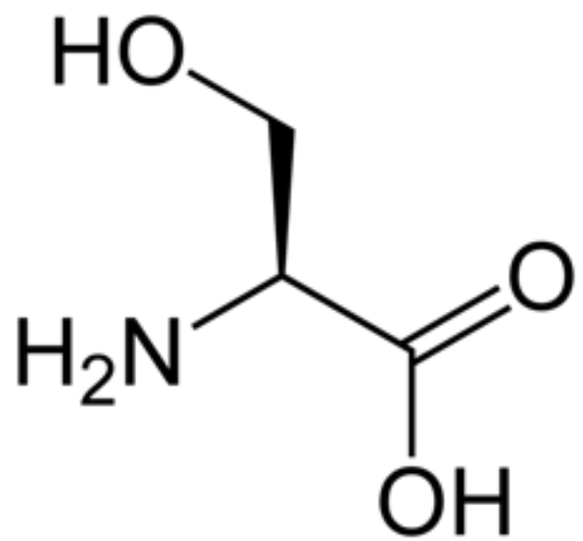
Successful in 10% of classic PKU cases



http://images.rxlist.com/images/rxlist/kuvan1.gif

LNAA Supplementation:

Balances Phe levels with other LNAA



http://upload.wikimedia.org/wikipedia/commons/5/57/L-serine-2D-skeletal.png

The Diet

http://4.bp.blogspot.com/-GEClzTQ1DYs/T6f2IIdbg9I/AAAAAAAAAJM/cjQC_gjleLk/s1600/Meat58.jpg

http://fillyourplate.org/blog/wp-content/uploads/2012/06/guide-dairy.jpg

http://www.artfertilityblog.com/wp-content/uploads/2013/01/carbs.jpg

http://www.stirlingfoods.com.au/images/beans_legumes.jpg

http://www.infiniteunknown.net/wp-content/uploads/2010/10/Aspartame.jpg

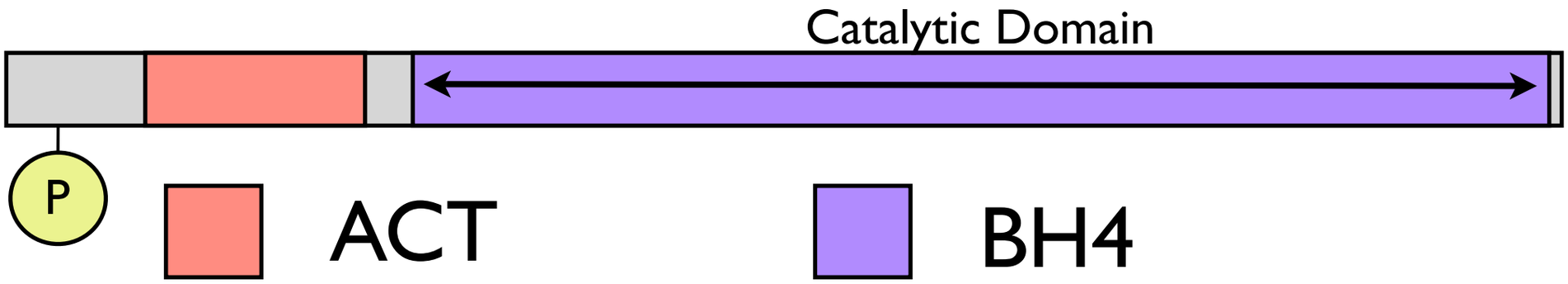
The Diet

http://eng.balviten.com/temp/cache/images/bulki_jaski_pku_kw_700x1200_noncropped_1540304608_thumb.jpg

http://images.mudfooted.com/fruit-and-vegetables.jpg

http://stores.pkuperspectives.com/catalog/PhenylAde-Essential.jpg

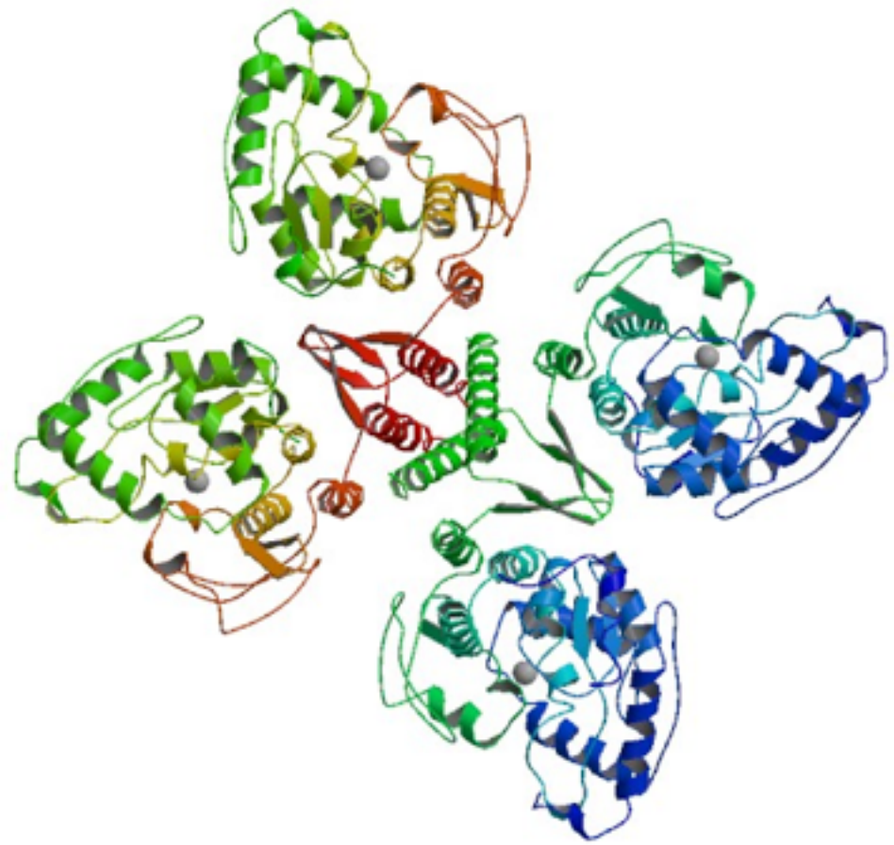
The PAH gene



Regulated by Phe, phosphorylation, and BH4

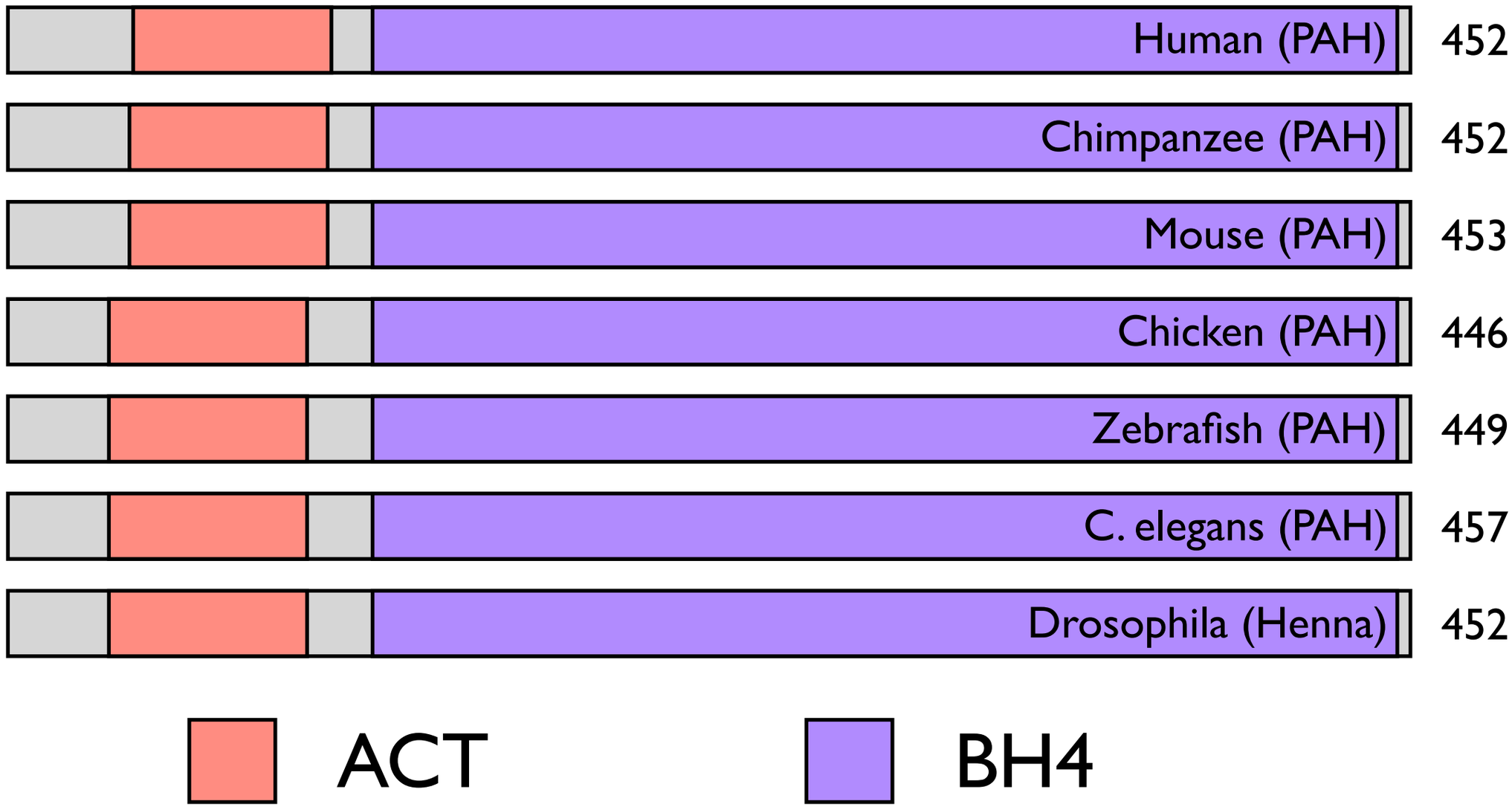
Most null mutations occur in catalytic or tetramer-forming sites.

Cytosolic - in the liver and minimally in kidneys and pancreas



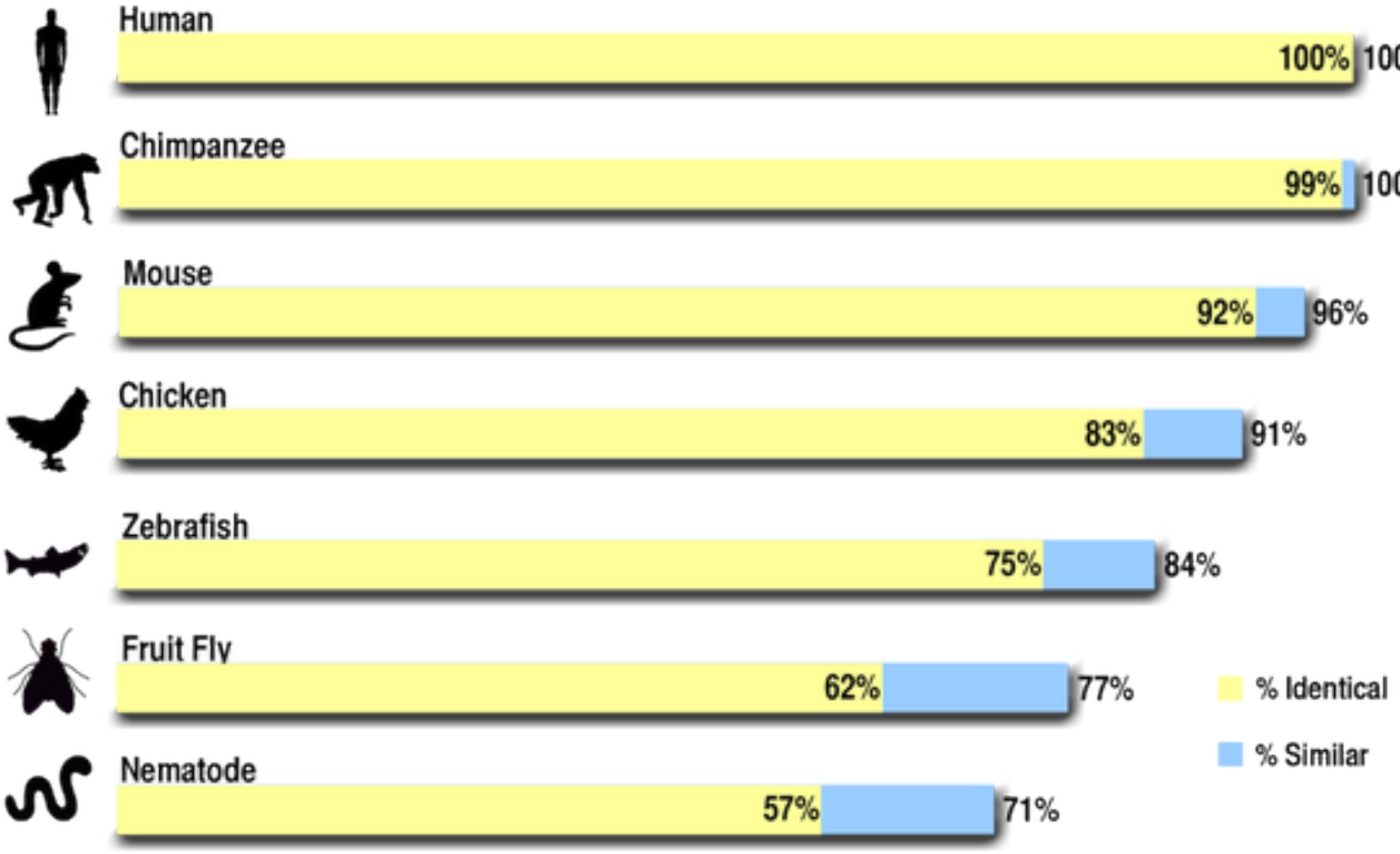
Fusetti F, Erlandsen H, Flatmark T, Stevens RC. Structure of tetrameric human phenylalanine hydroxylase and its implications for phenylketonuria. J Biol Chem. 1998 Jul 3;273(27):16962-7. PubMed PMID: 9642259.

The PAH protein is very well conserved



Data generated from PFAM

PAH has high similarity across the animal kingdom

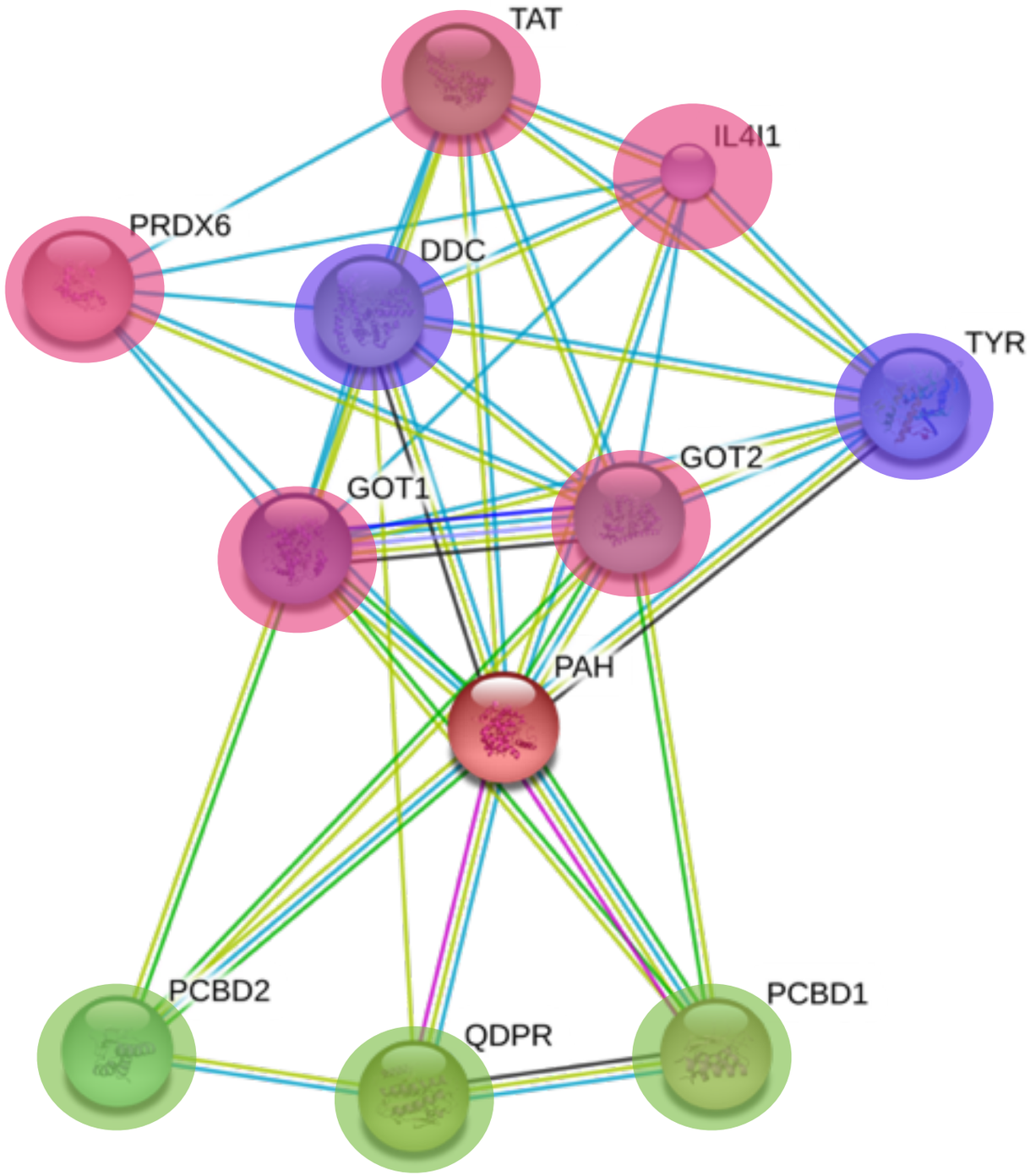


How does PAH function in the body?

Tyrosine metabolism

BH4 synthesis

L-amino acid catabolism/
carboxylation/
monooxygenation



Generated from the String Database

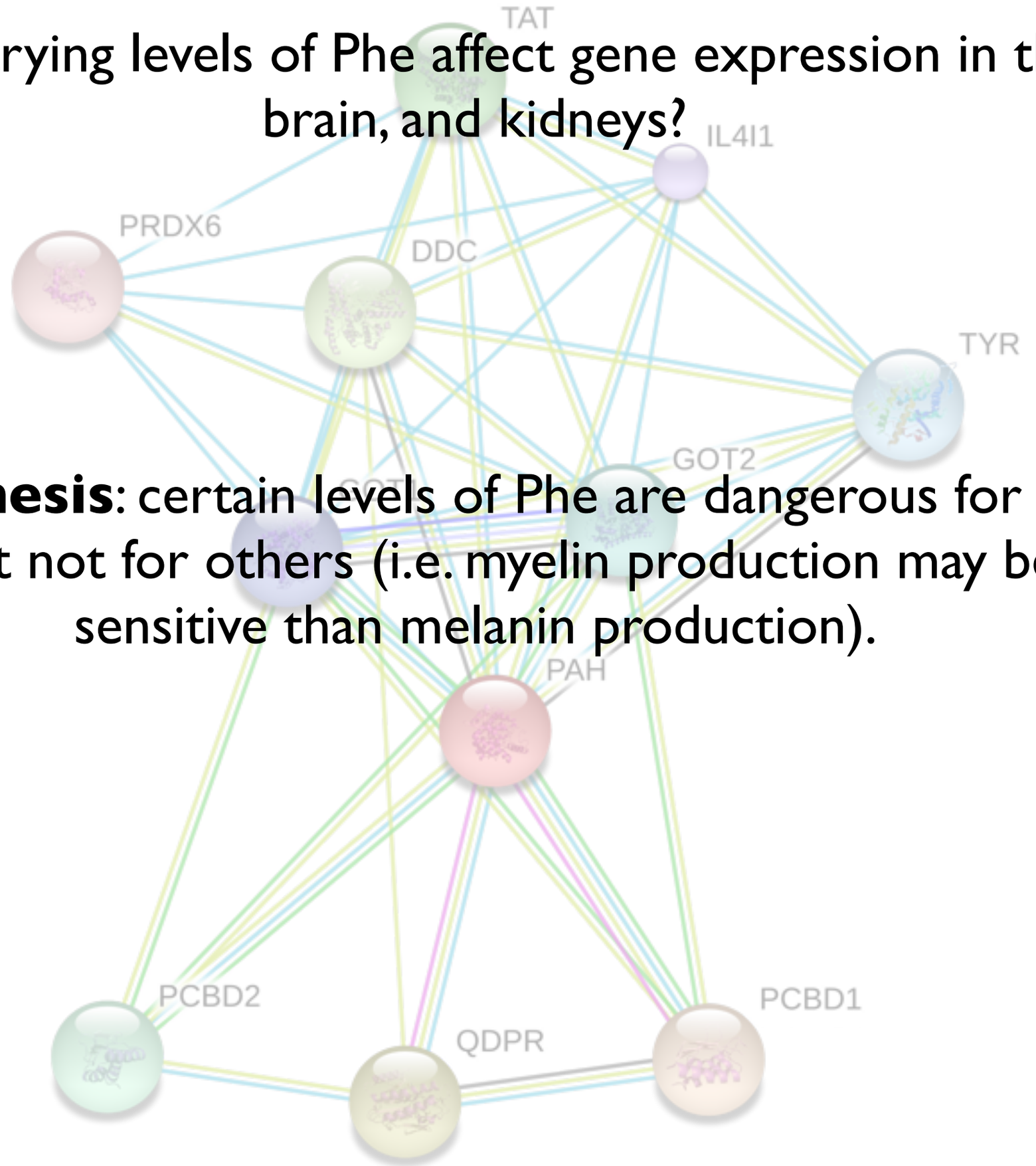
What is the state of current research?

Research has mostly focused on finding new mutations

Most knowledge comes from trial and error/ correlation observations

Not much concrete or whole-body evidence

How do varying levels of Phe affect gene expression in the liver, brain, and kidneys?



Hypothesis: certain levels of Phe are dangerous for some traits, but not for others (i.e. myelin production may be less sensitive than melanin production).

Why is this relevant?

Be able to define causes behind problems in treated patients

Patients will be informed of effects of certain Phe levels at specific ages

Make more informed dietary choices

http://www.tdalfredos.com/Ice-CreamSundae.jpg

When, if ever, is it ok to stop the diet?

http://www.forevergeek.com/wp-content/media/2012/11/thing_drseuss_thing1andthing2.jpg

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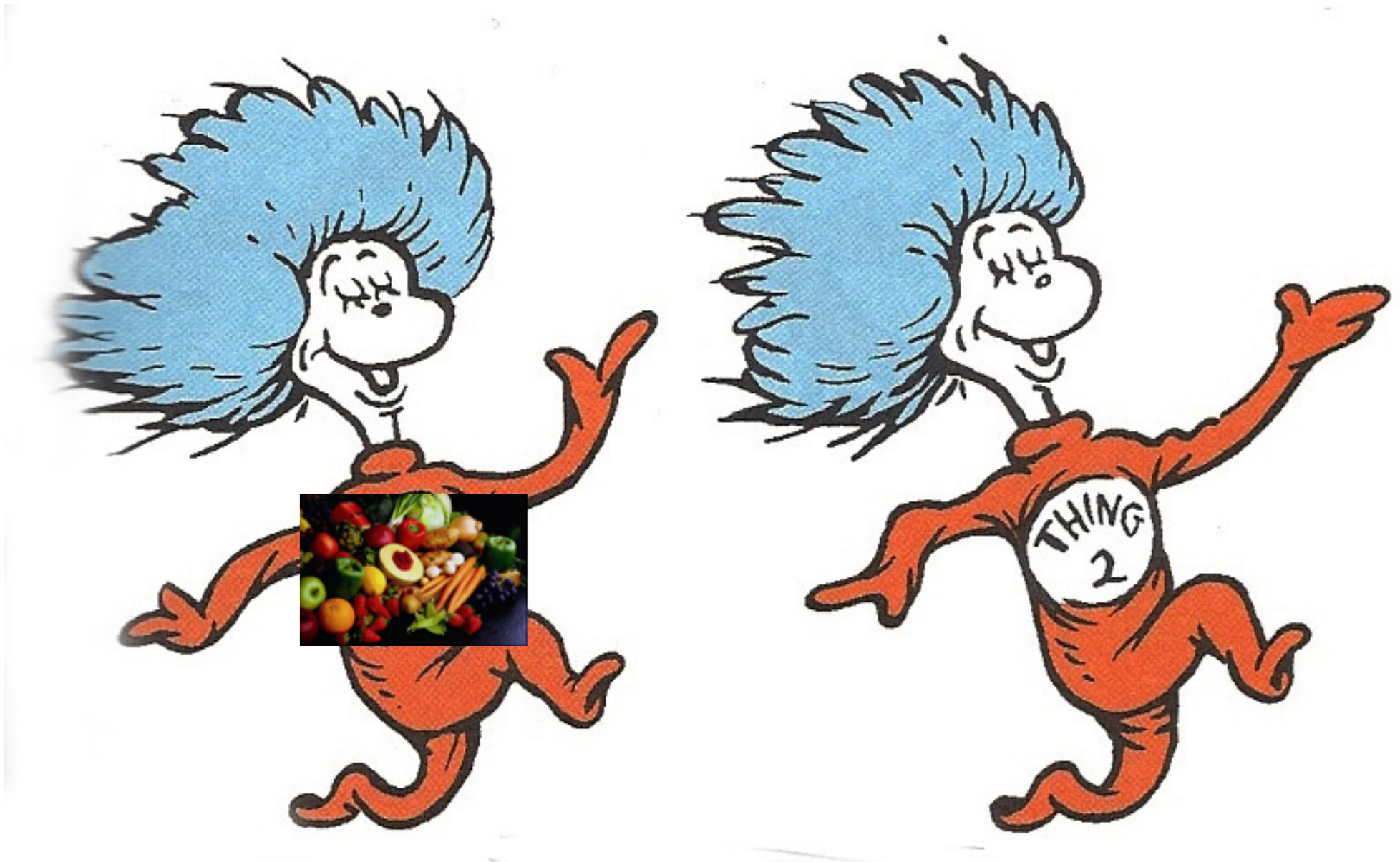

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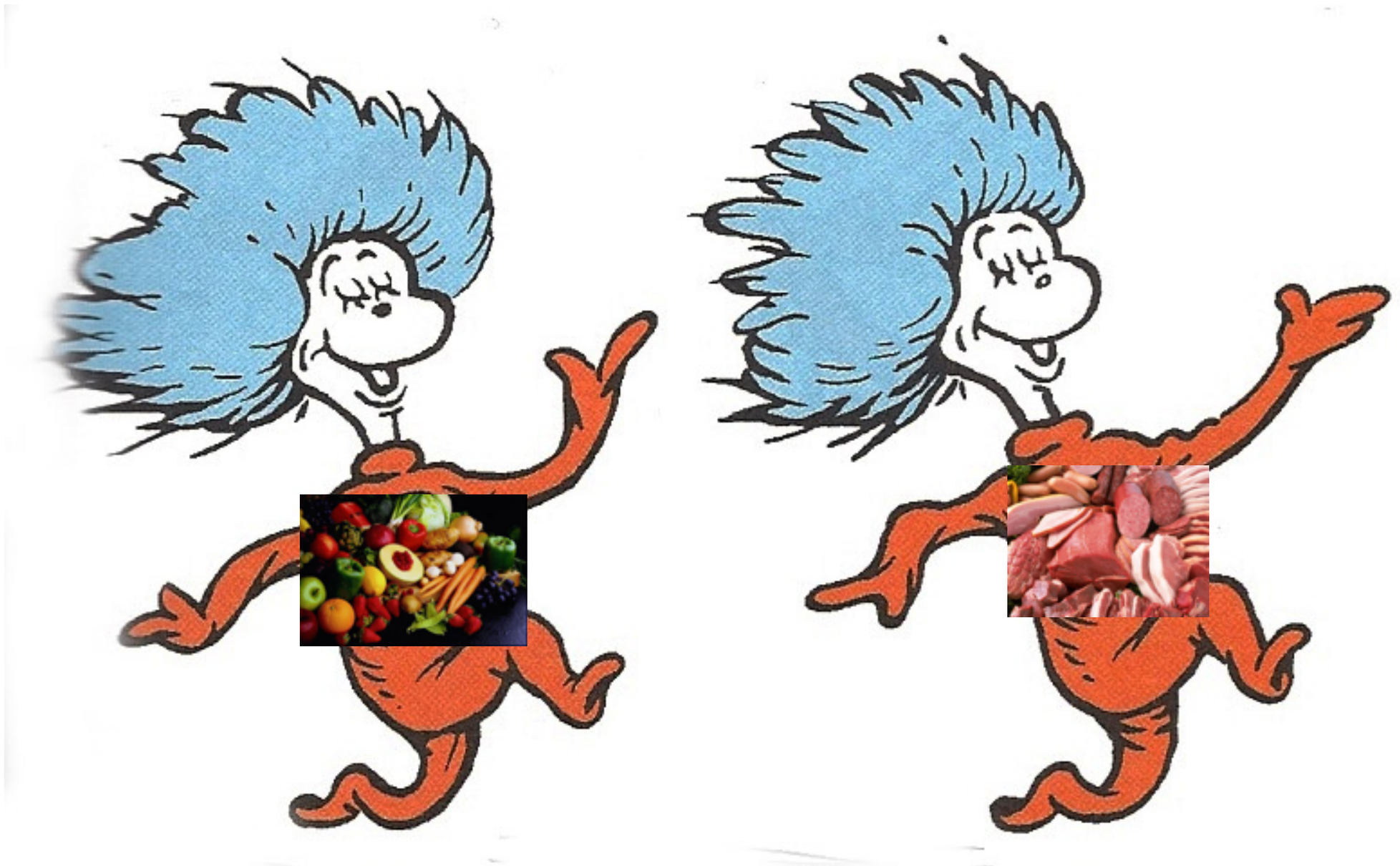

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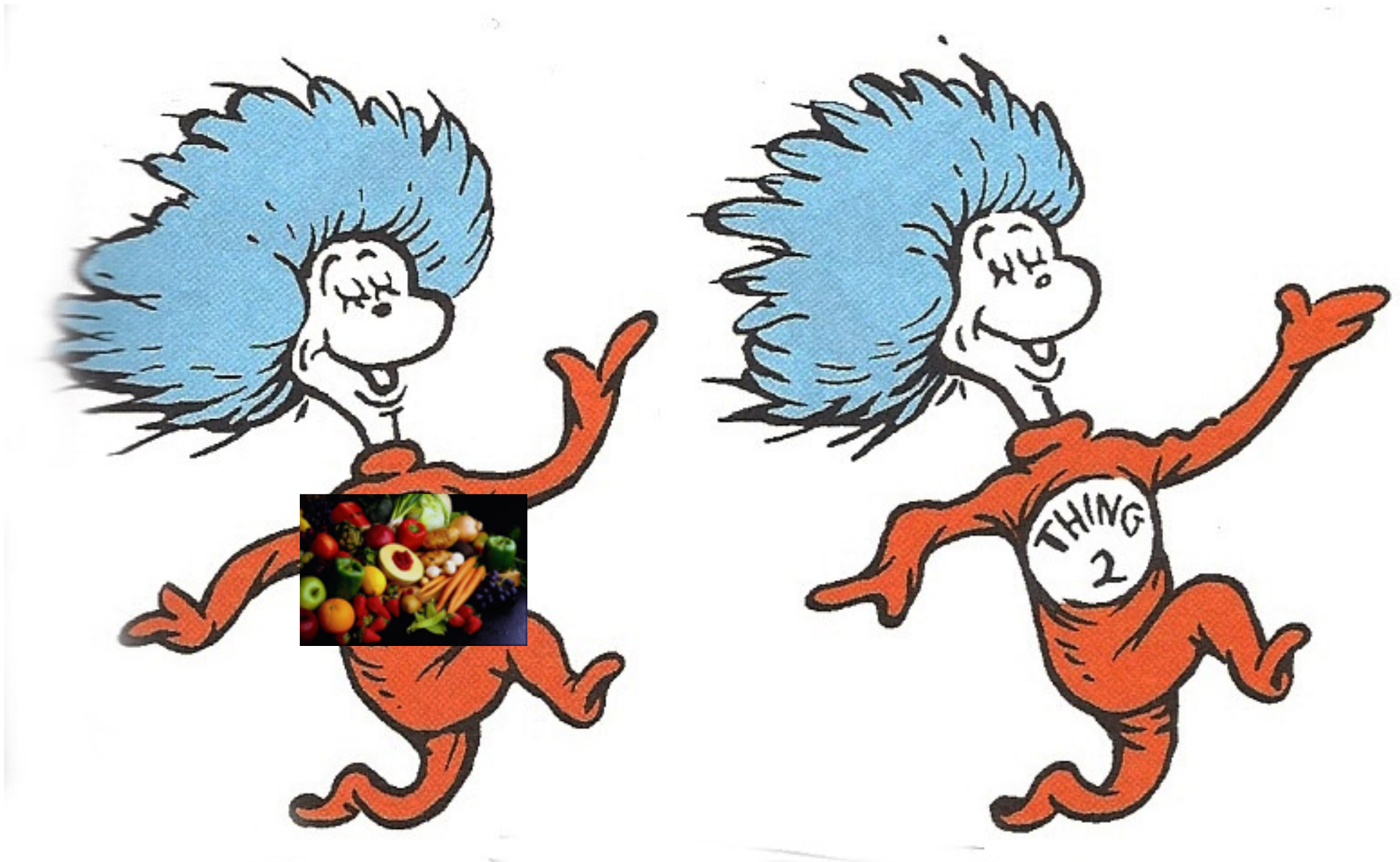

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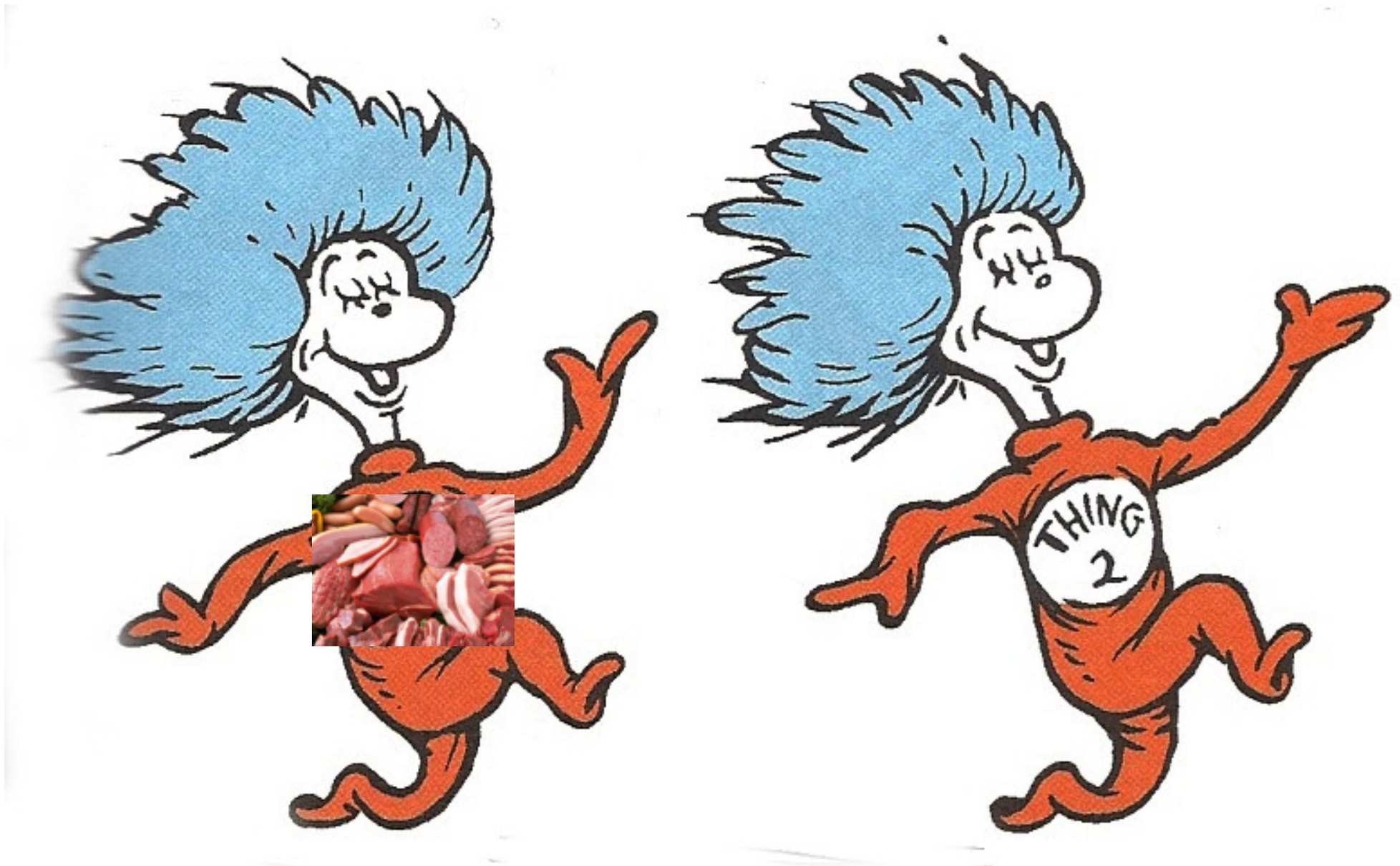

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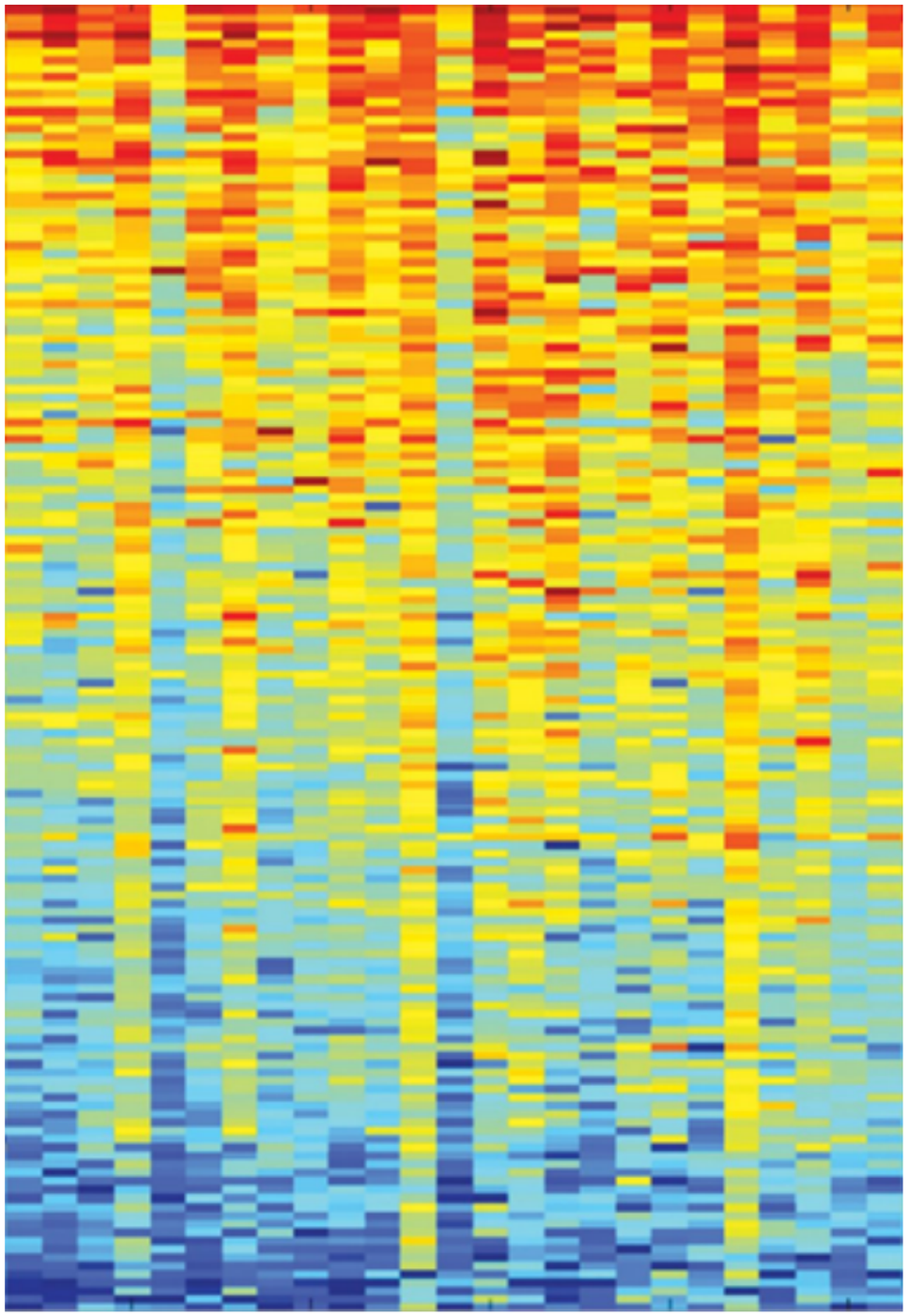
How can we study whole-body effects?

Different aged PKU mice (infancy, adolescence, maturity)

Liver, brain, and kidneys

Perform microarrays



http://www.popularmechanics.co.za/wp-content/uploads/resized/0000106921_resized_microarray687.jpg

How do varying levels of Phe affect gene expression in the liver, brain, and kidneys?

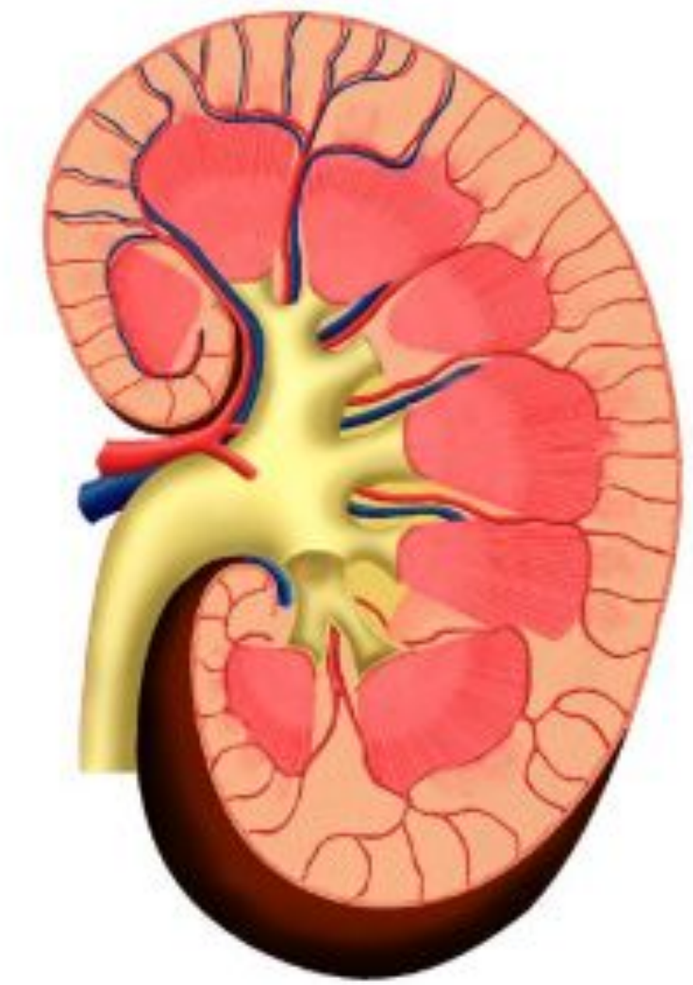
Serum Phe Levels/Diet	App. 0	100	450	750	1000
Brain - DOPA	Lowered	Lowered	Lowered	Lowered	Lowered
Liver - PAH	Lowered	Normal	Raised	Raised	Raised
Kidney - PAH	Lowered	Normal	Raised	Raised	Raised

Relative expression compared to healthy mice

How does PAH relate to kidney disease?

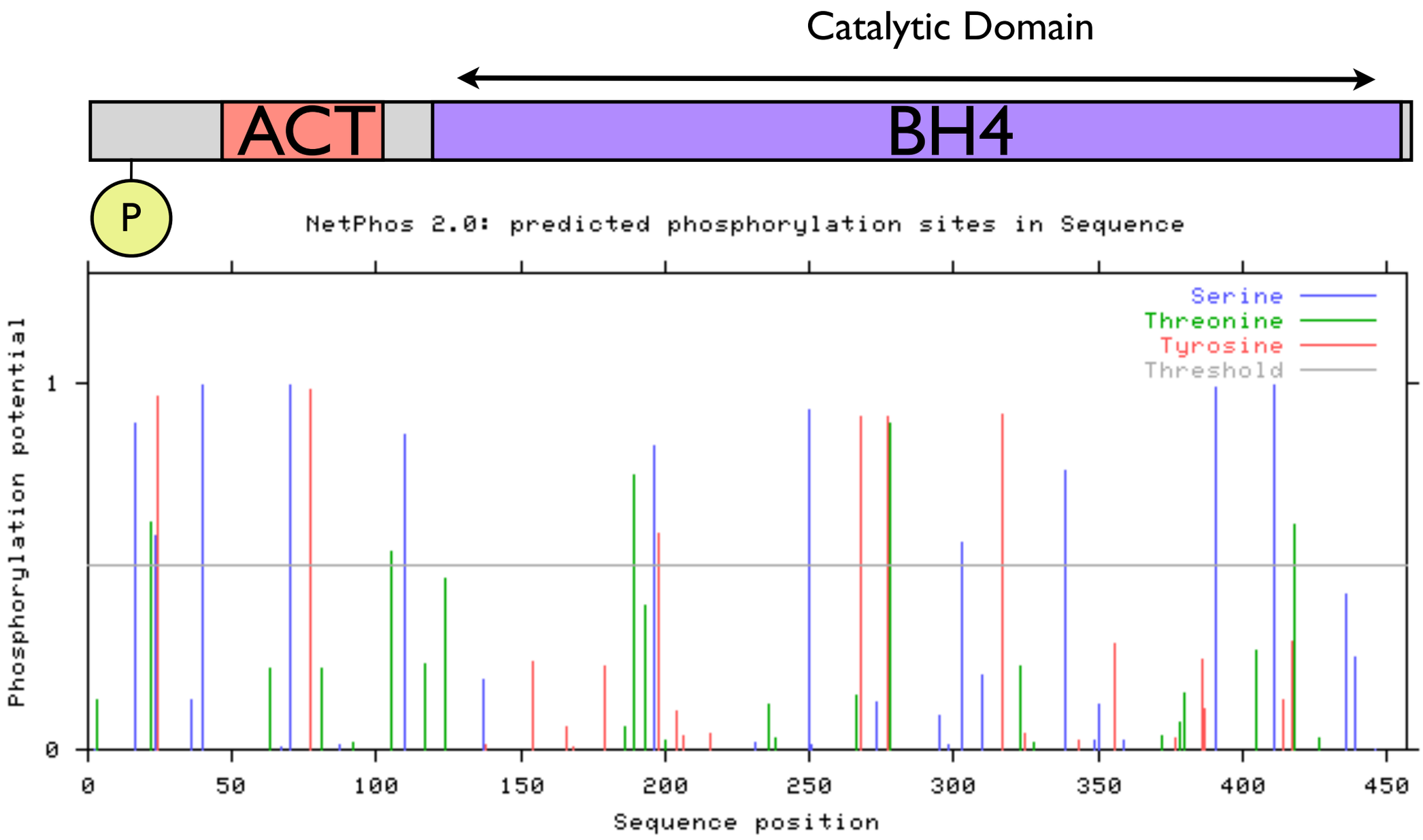
PAH activity is lowered in rats (and presumably humans) with Chronic Renal Failure (CRF), though hepatic expression remains normal.

Hypothesis: PAH in patients with Chronic Renal Failure is being over-phosphorylated at sites in the catalytic domain.



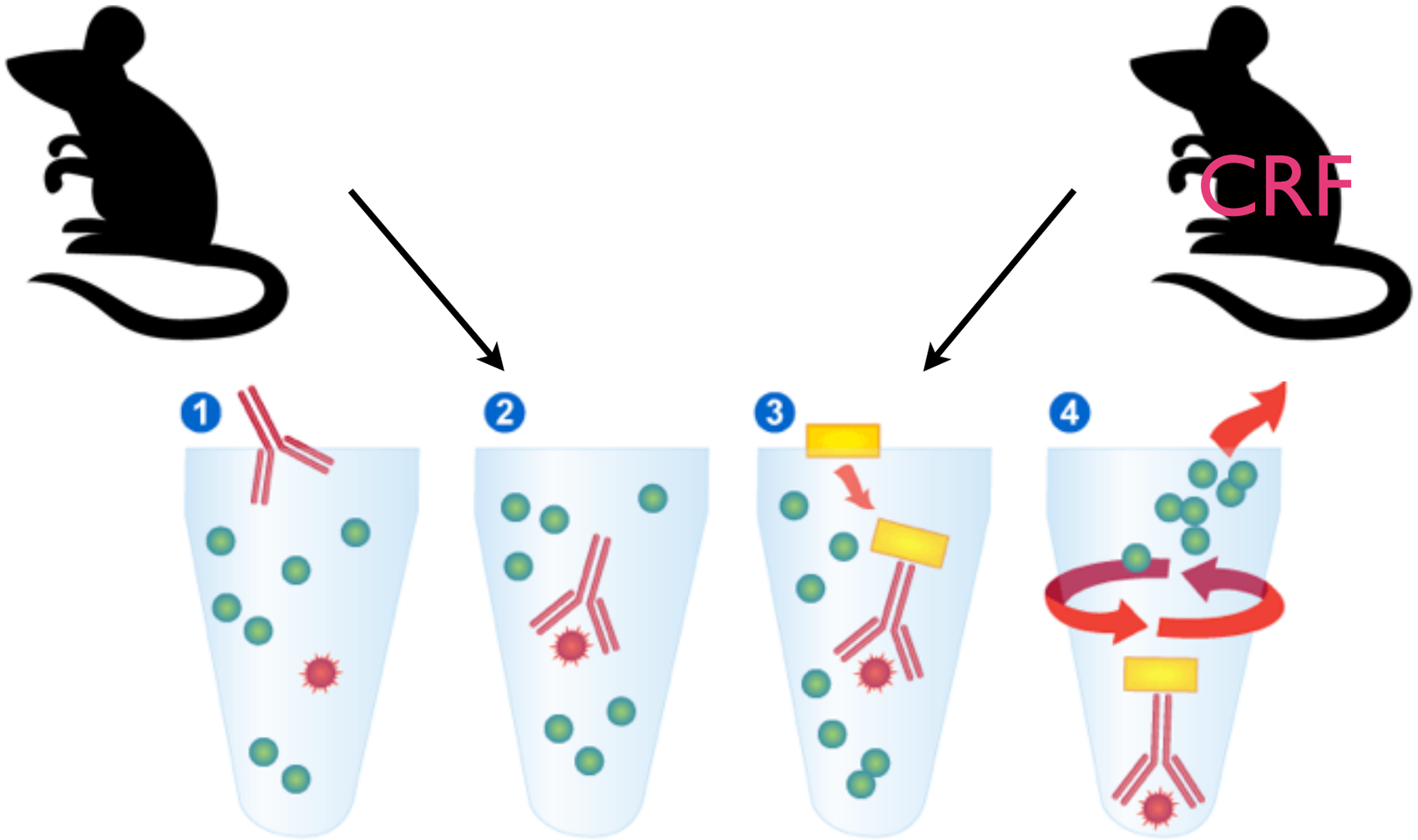
http://s1.hubimg.com/u/1039832_f260.jpg

Finding the phosphorylation sites of PAH



Sequence- and structure-based prediction of eukaryotic protein phosphorylation sites.
Blom, N., Gammeltoft, S., and Brunak, S.
Journal of Molecular Biology: 294(5): 1351-1362, **1999**.

Using immunoprecipitation and mass spectrometry to determine phosphorylation status



http://www.leinco.com/includes/templates/LeincoCustom/images/immunoprecipitation.gif

Normal Phosphorylation

Increased Phosphorylation

Where can we go from there?

Research phosphorylation of other important kidney proteins

BH4 supplementation

Specific role of PAH within the kidney

What are the implications?

PKU is tested for in all newborns

Phe is an important amino acid and should only be avoided if absolutely necessary.

Lack of biochemical and genetic evidence - how many unnecessary dieters?

http://www.healthy.arkansas.gov/programsServices/familyHealth/ChildAndAdolescentHealth/newBornScreening/PublishingImages/photo1.jpg

Questions?

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•and: http://www.ncbi.nlm.nih.gov/Structure/cdd/cddsrv.cgi?uid=207351 [3]

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