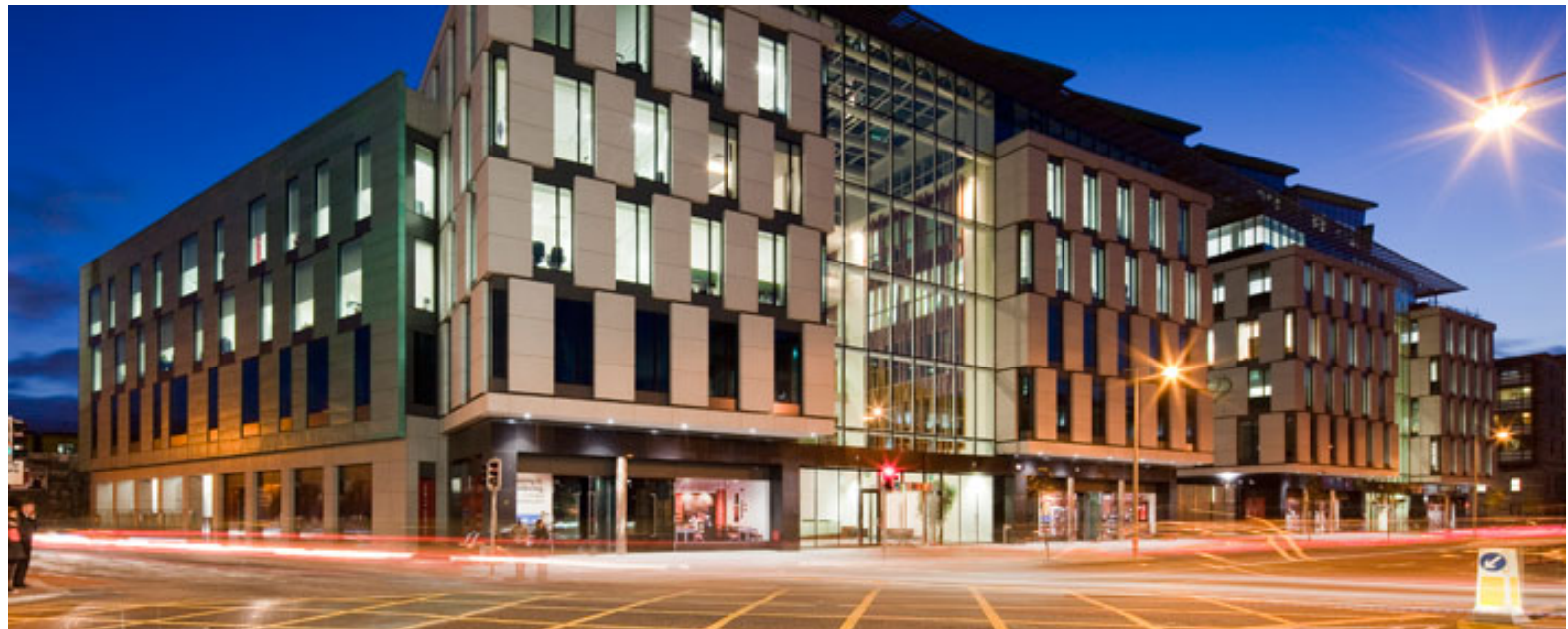
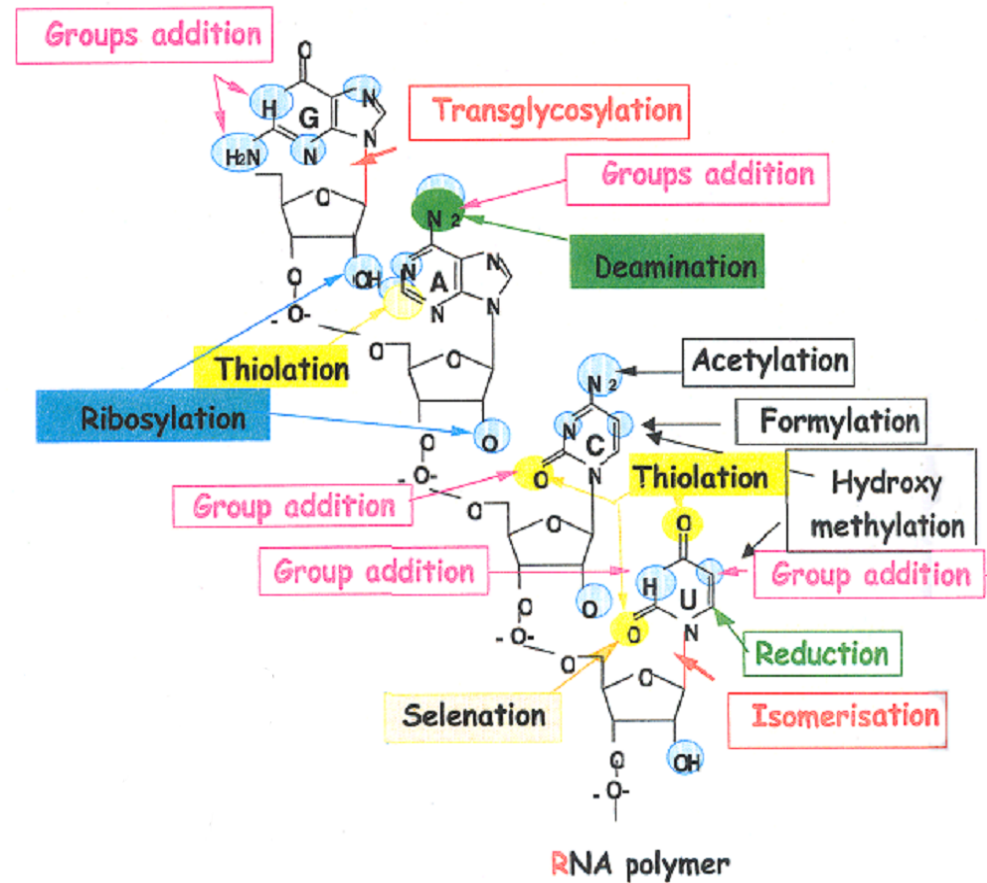
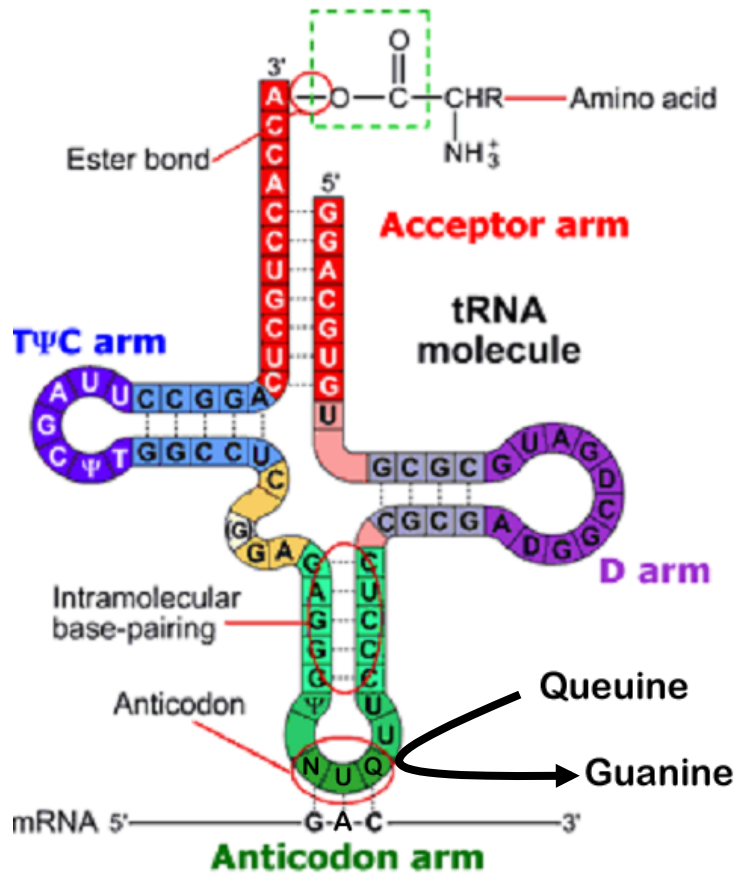


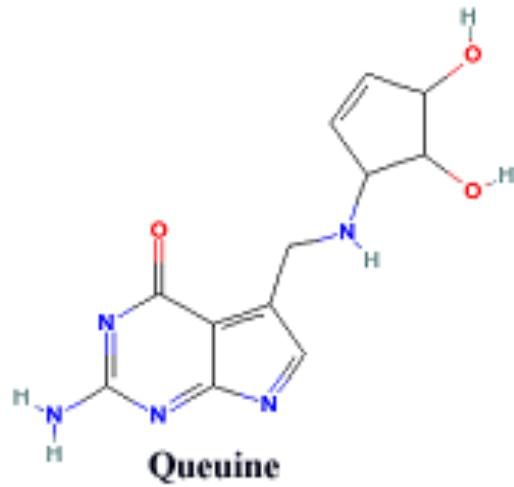
Queuine's influence on tetrahydrobiopterin and tyrosine metabolism



A wide range of tRNA modifications exist



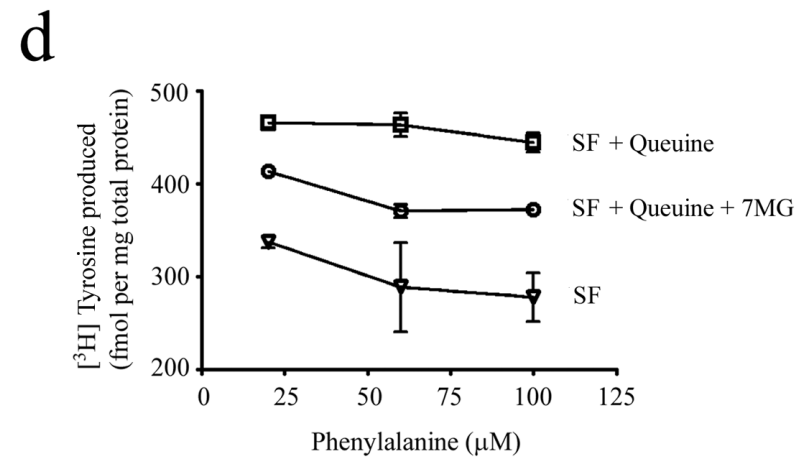
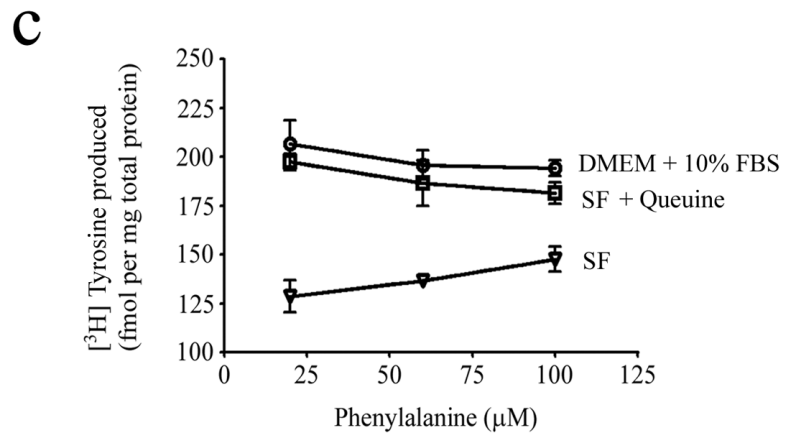
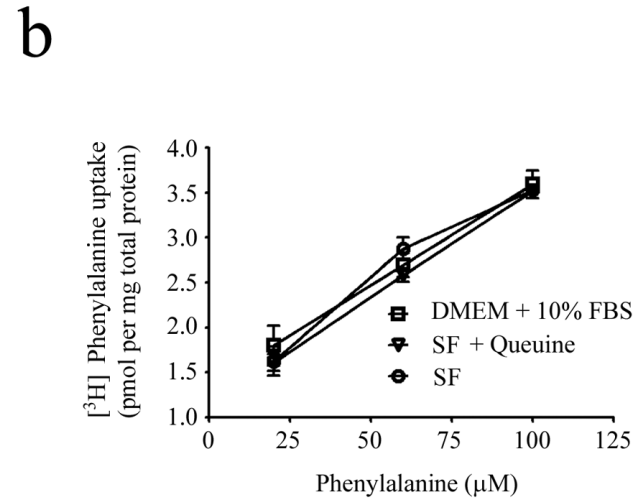
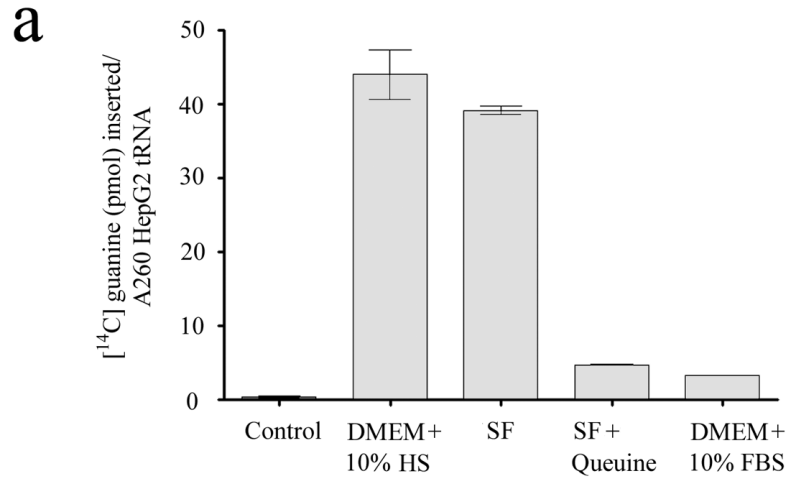
Queuine deficiency makes animals non-autotrophic for tyrosine



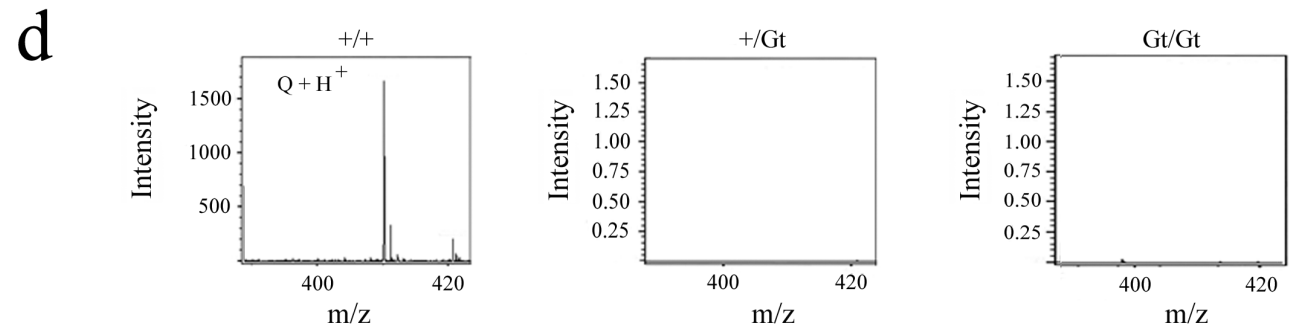
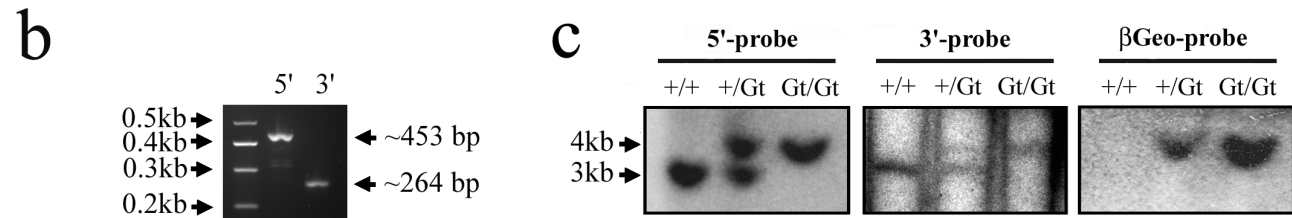
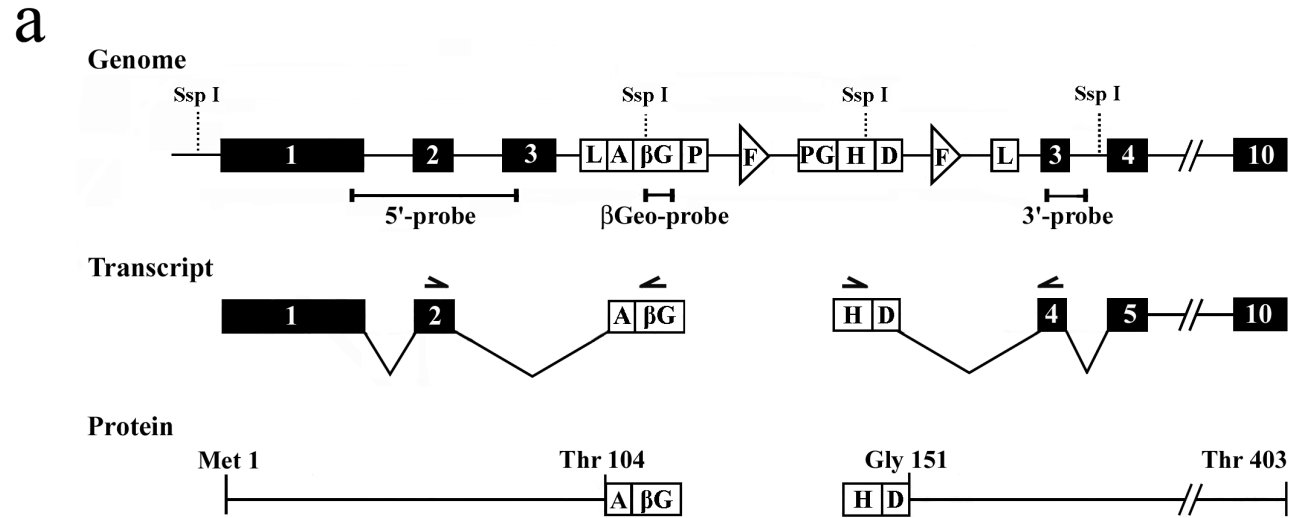
Symptoms of germfree mice – tyrosine/ - queuine

- Squinting
 - Rough coat
 - Stiffness of neck and forelimbs
 - Lethary
 - Staggered walk
 - Huddling
 - Labored breathing
 - Seizures
 - Death
-

Queuine deficiency in HepG2 cells compromises tyrosine production

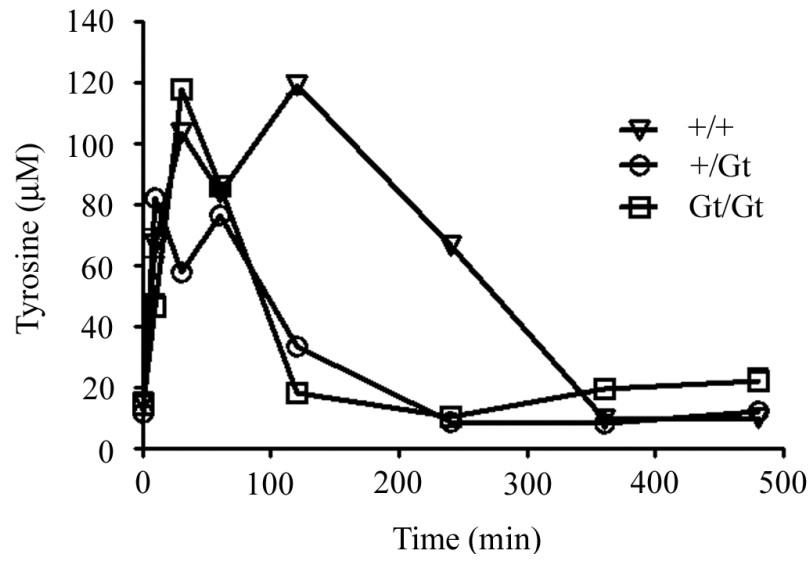


Queuine tRNA ribosyltransferase gene-trap mice are deficient in QtRNA

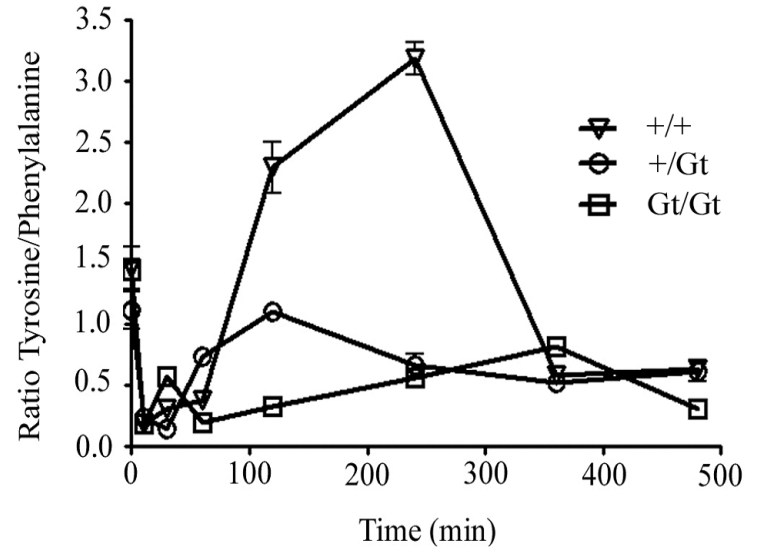


TGT gene-trap mice have compromised tyrosine production

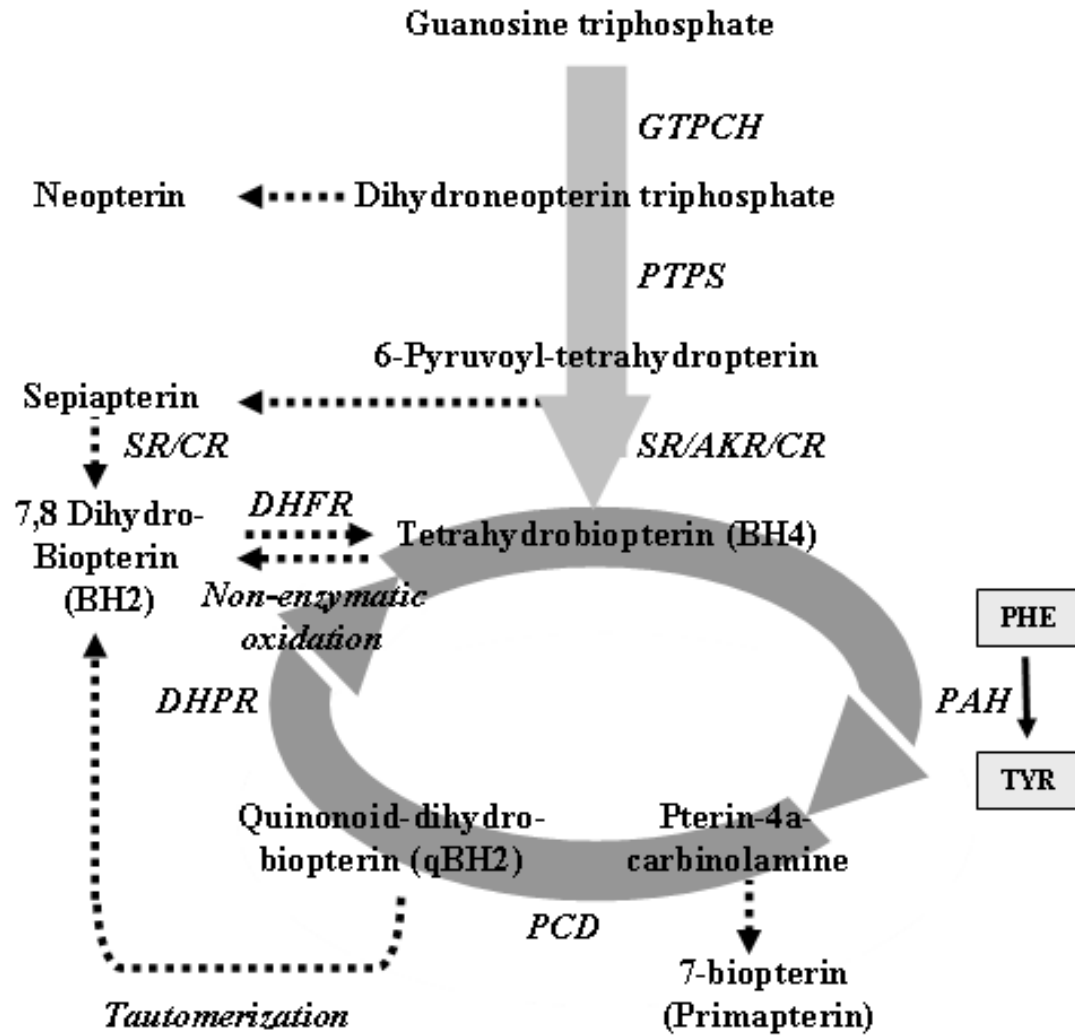
a



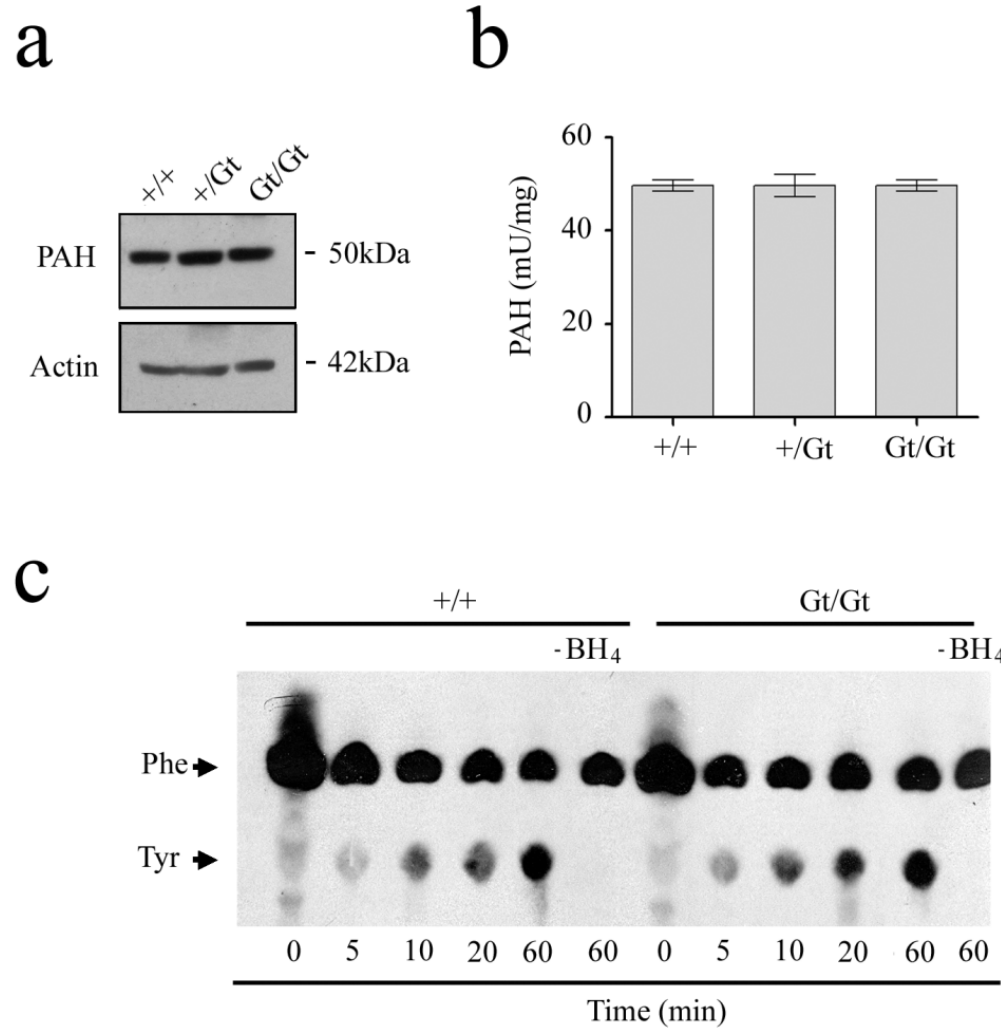
b



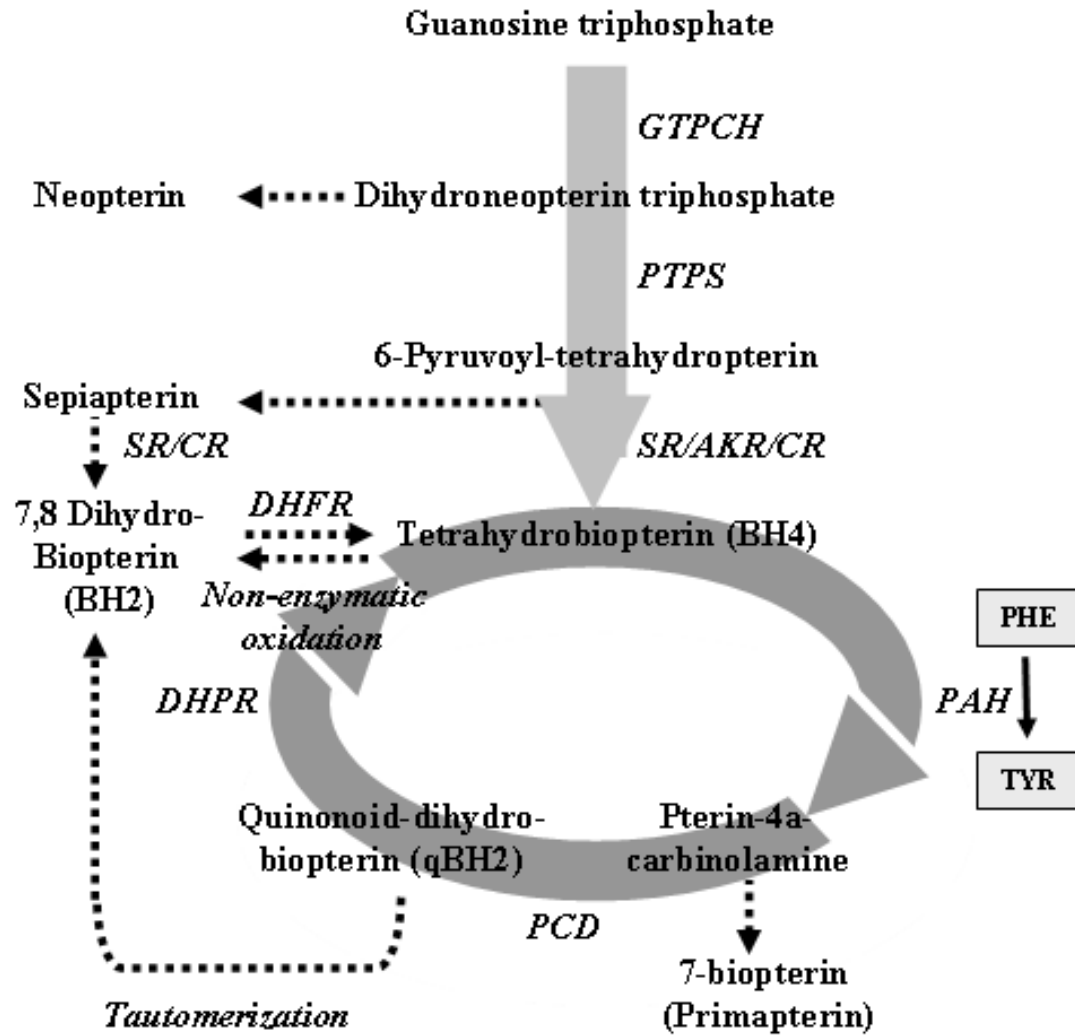
Tyrosine production from phenylalanine



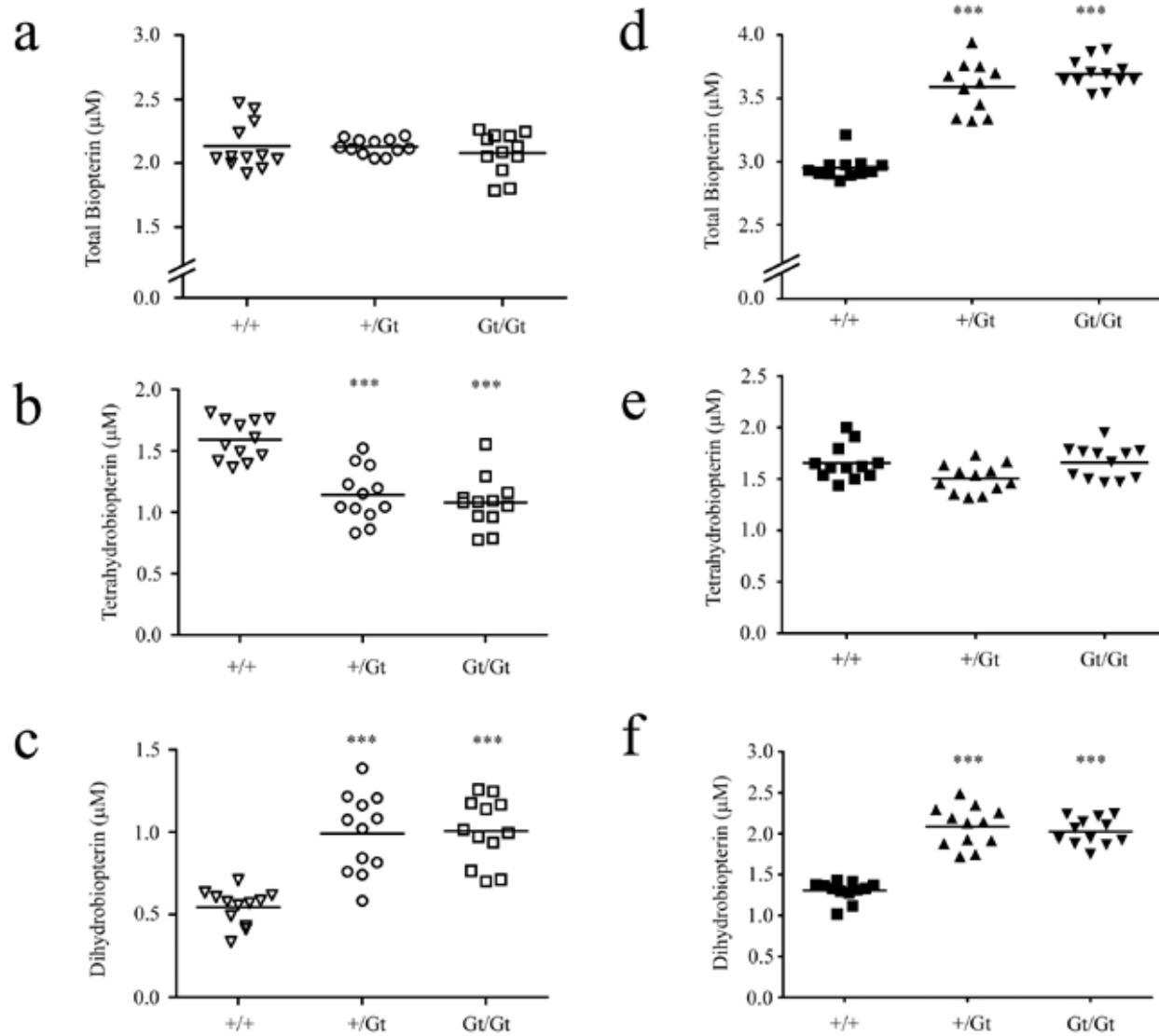
TGT gene-trap mice show no change in PAH protein levels or activity



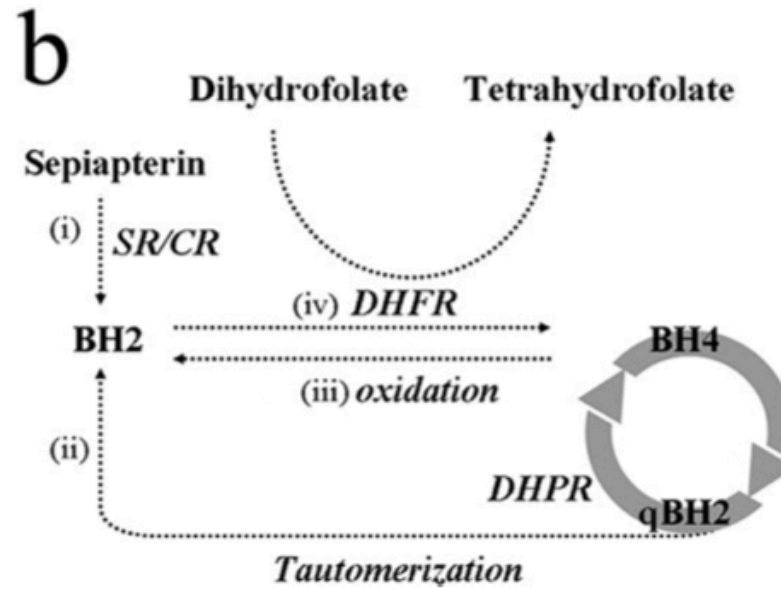
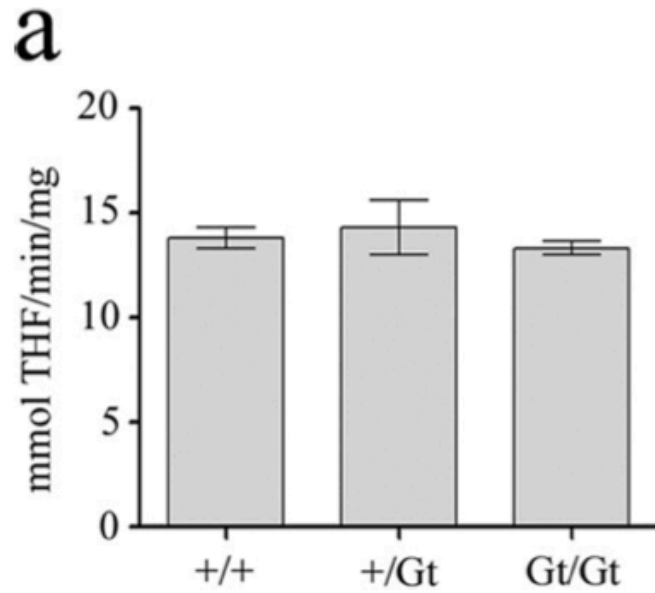
Tyrosine production from phenylalanine



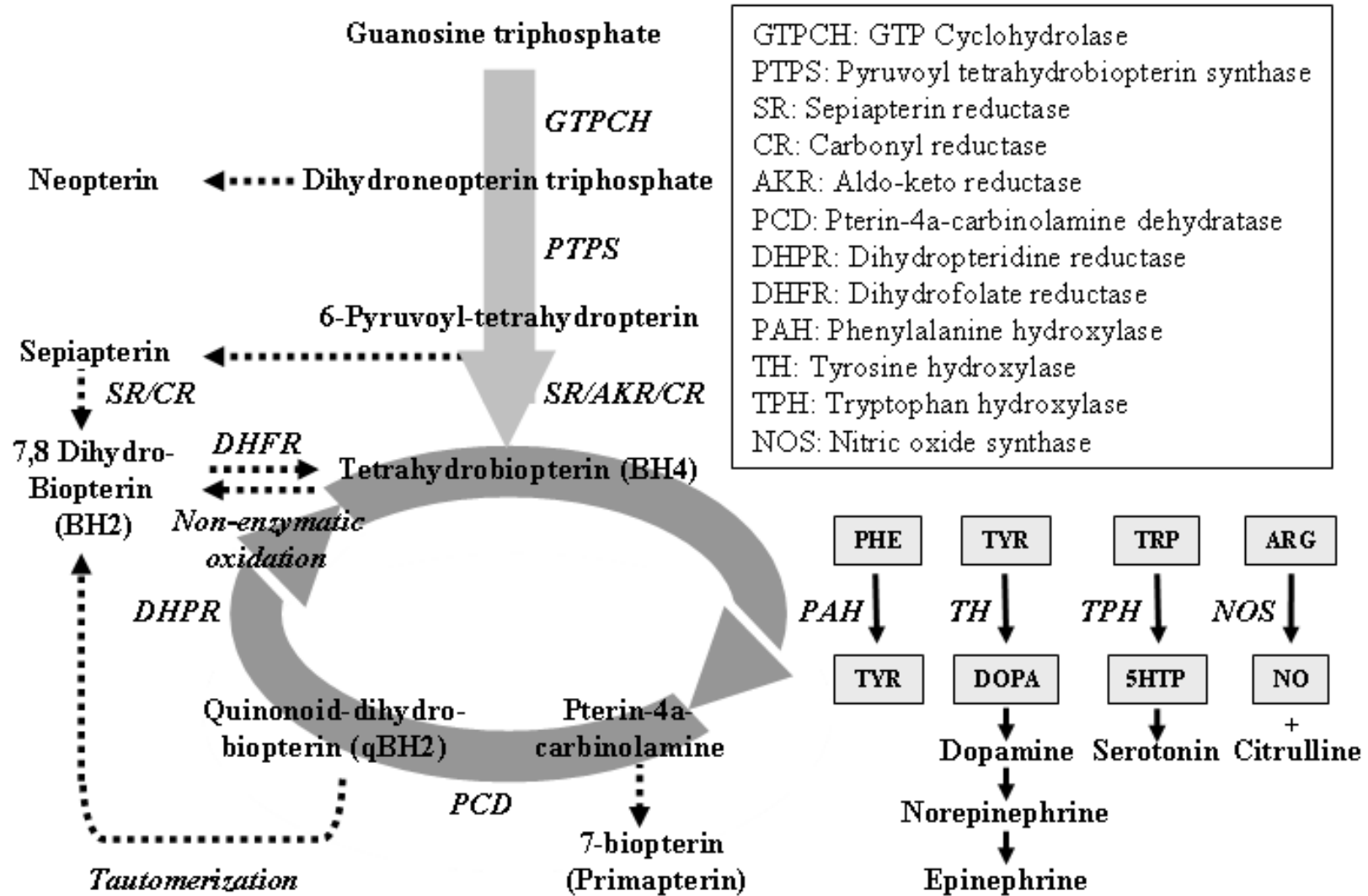
TGT gene-trap mice have elevated 7,8-dihydrobiopterin and decreased BH4 levels in plasma



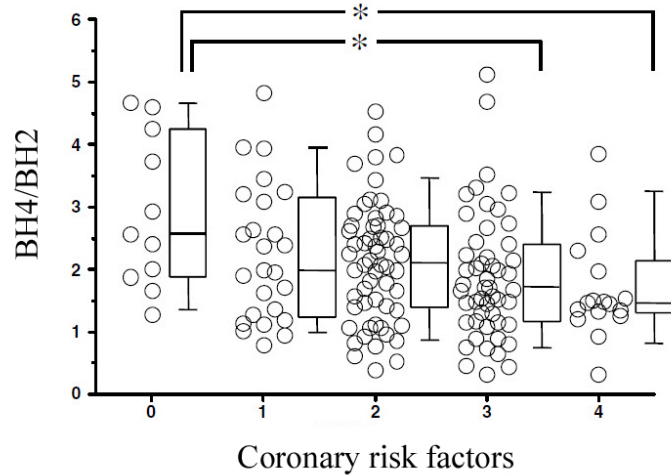
DHFR activity in liver is not affected by TGT status



Amino acid hydroxylase enzymes & nitric oxide synthase rely on tetrahydrobiopterin for activity



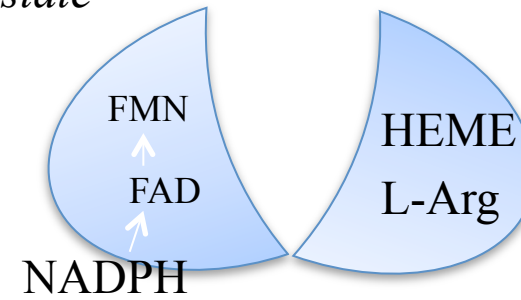
Elevated 7,8-dihydrobiopterin is a coronary risk factor & linked to endothelial dysfunction



Adapted from Takeda, M. *et al*, *Circ J* 2009; **73**: 955-962

- Hypertension
- Hypercholesterolemia
- Diabetes mellitus
- Cigarette smoking

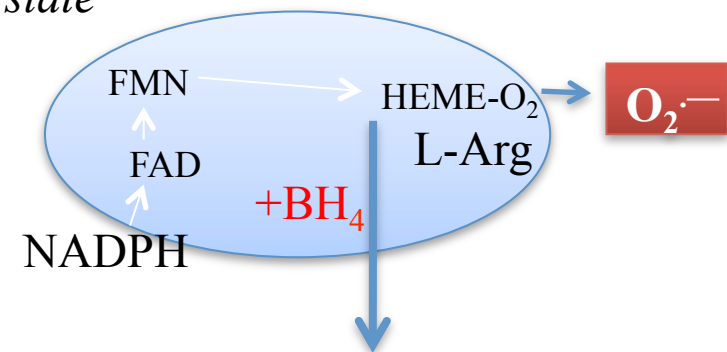
Resting state



Ca²⁺/CaM



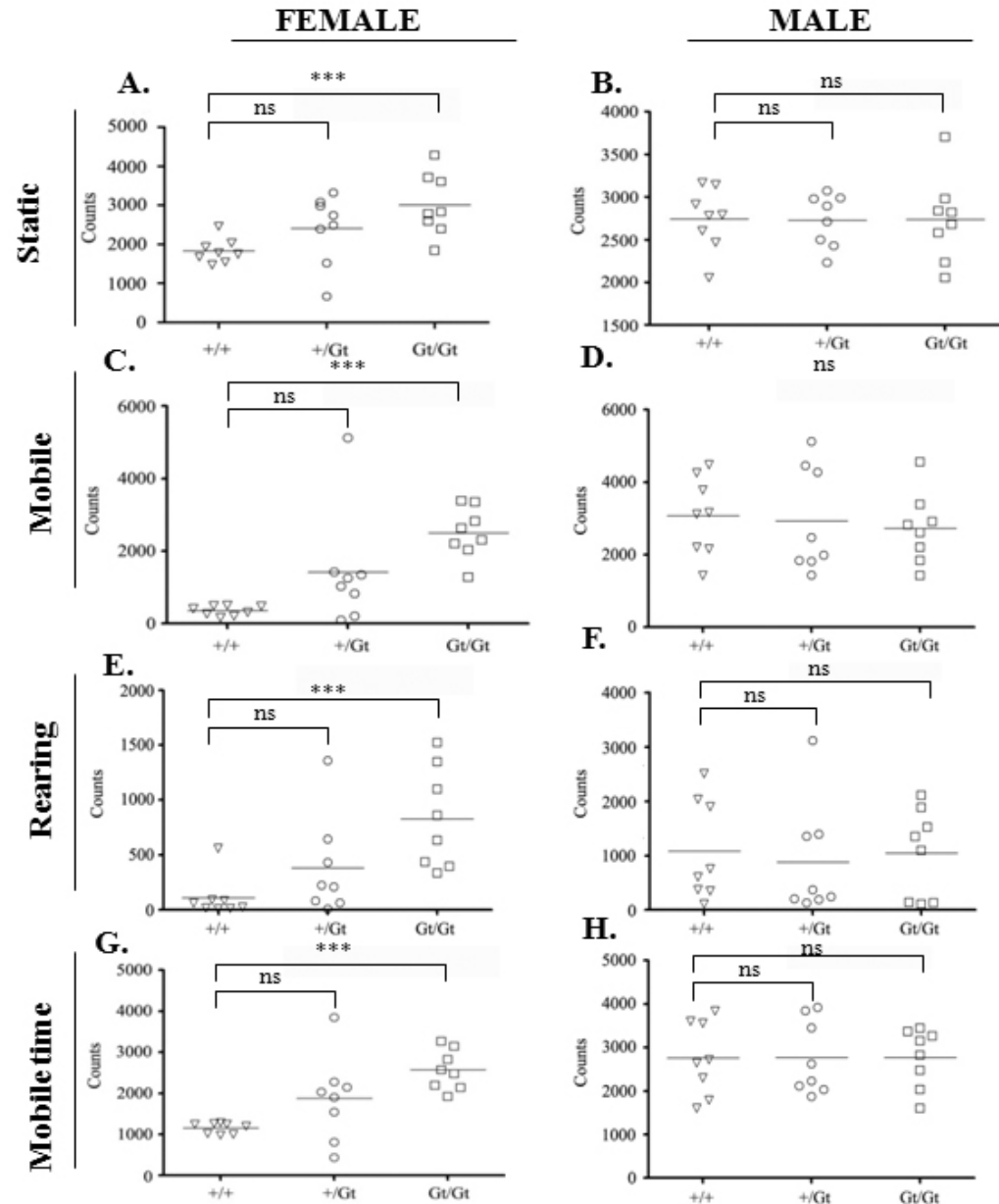
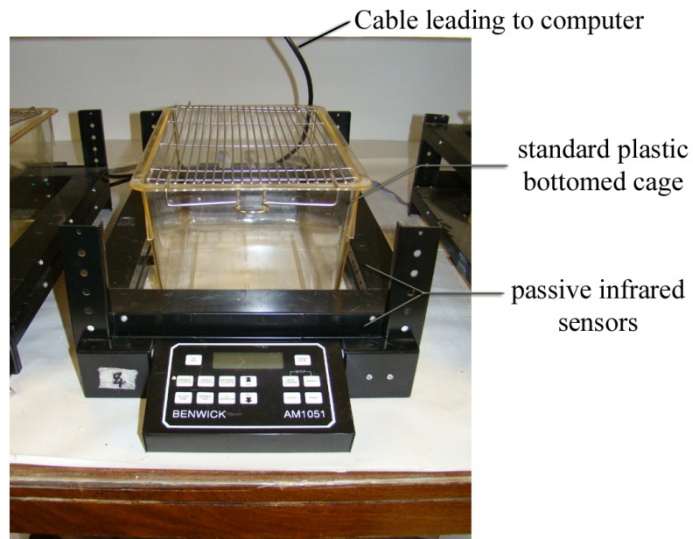
Active state



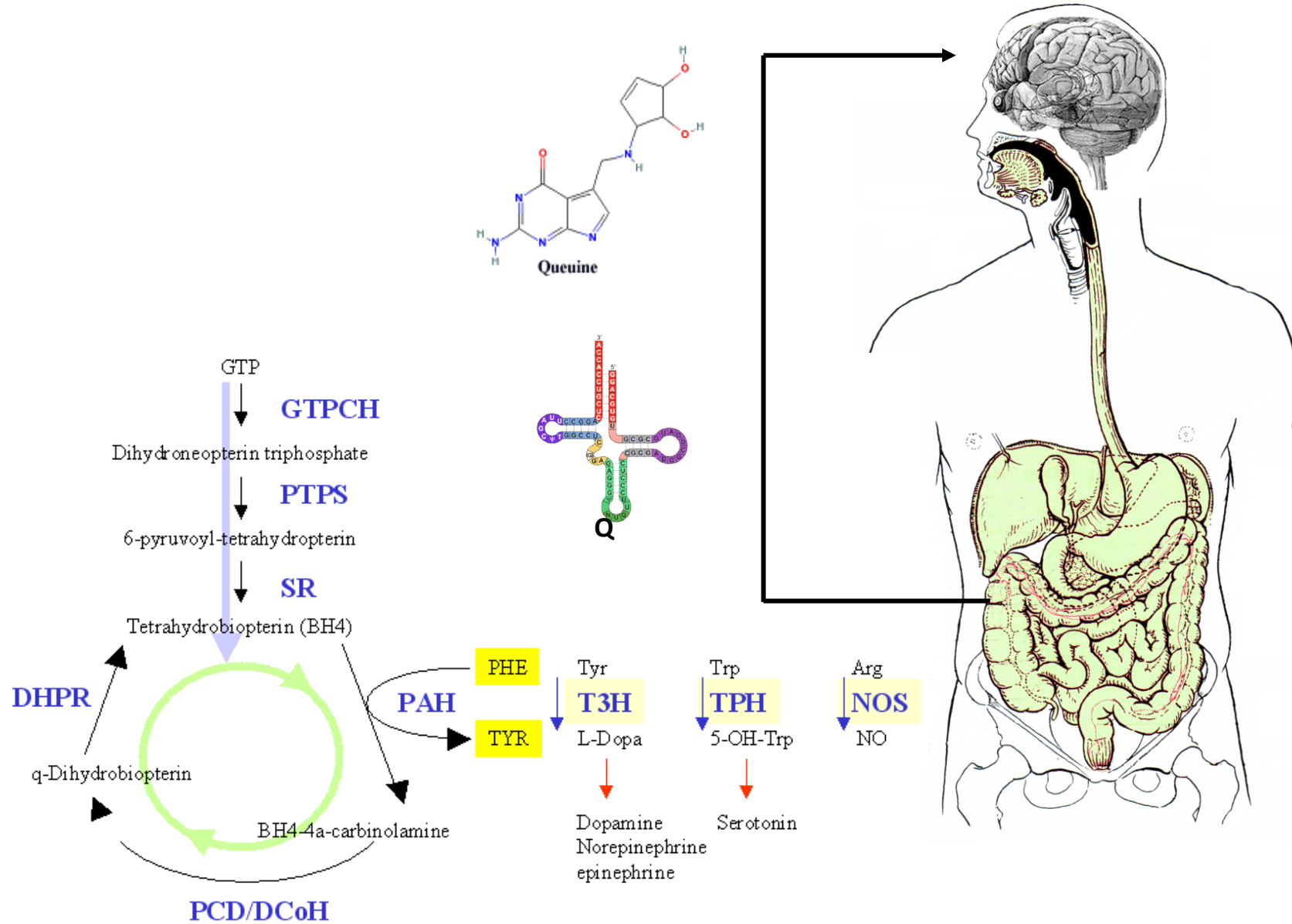
NO + Citrulline

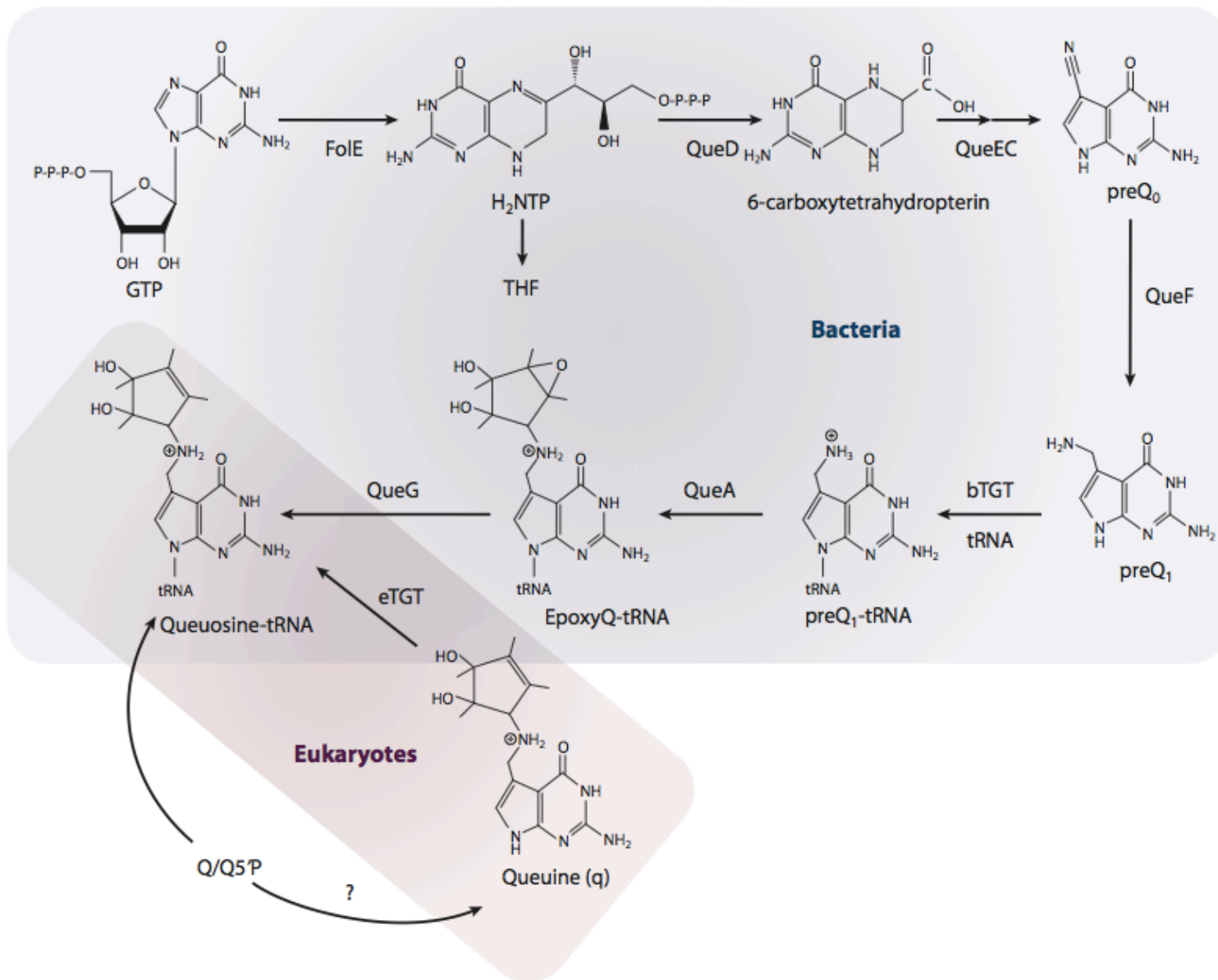
TGT gene-trap mice display stocastic movement and increased rearing

Home Cage Experiment



Queuine's link to metabolism & behaviour





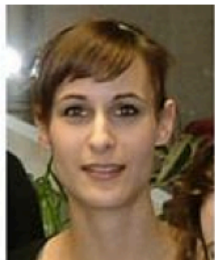


Collaborators:

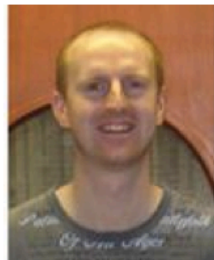
Prof. Brian McMurry, TCD, Ireland
 Prof. Stephen Connon, TCD, Ireland
 Dr. J. Mike Southern, TCD, Ireland
 Prof. George Garcia, University of Michigan, USA
 Prof. Dirk Iwata Reuyl, Portland State University
 Prof. Gerhard Klebe,
 Prof. Masayuki Yamamoto, Tohoku University, Japan
 Dr. Susumu Nishimura, University of Tsukuba, Japan



Graduates of the lab



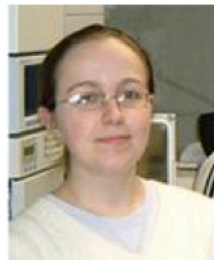
Ilana Bernstein
MSc, BA(mod)



Coilin Boland
PhD, B.Sc



Patti Hayes
PhD, BA(mod)



Tatsiana
Rakovich
PhD, BA(mod)



Sreeja Varghese
PhD, B.Sc

