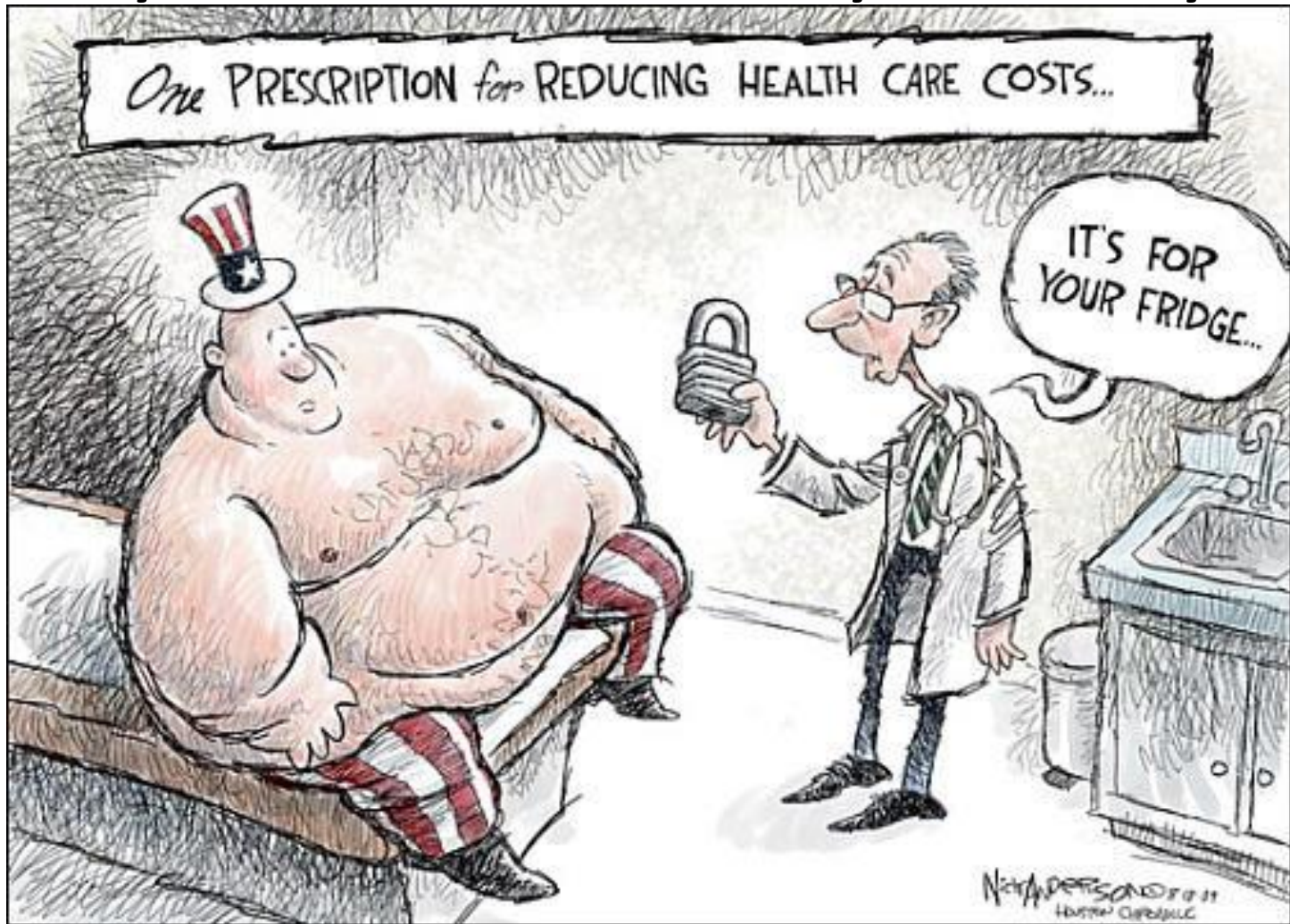


Are your jeans too tight because
of your genes?



Tubby (HsTUB) and Obesity

Why should we study obesity?



<http://www.weird-strange-facts.com/adolescent-obesity.html>

<http://fauzil.blogspot.com/2013/04/obesity-health-risk.html>

What gene is associated with obesity?

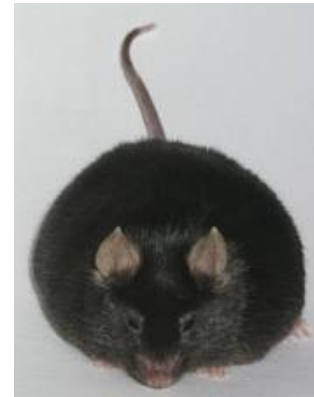
Mouse
TUB

TUB

505aa

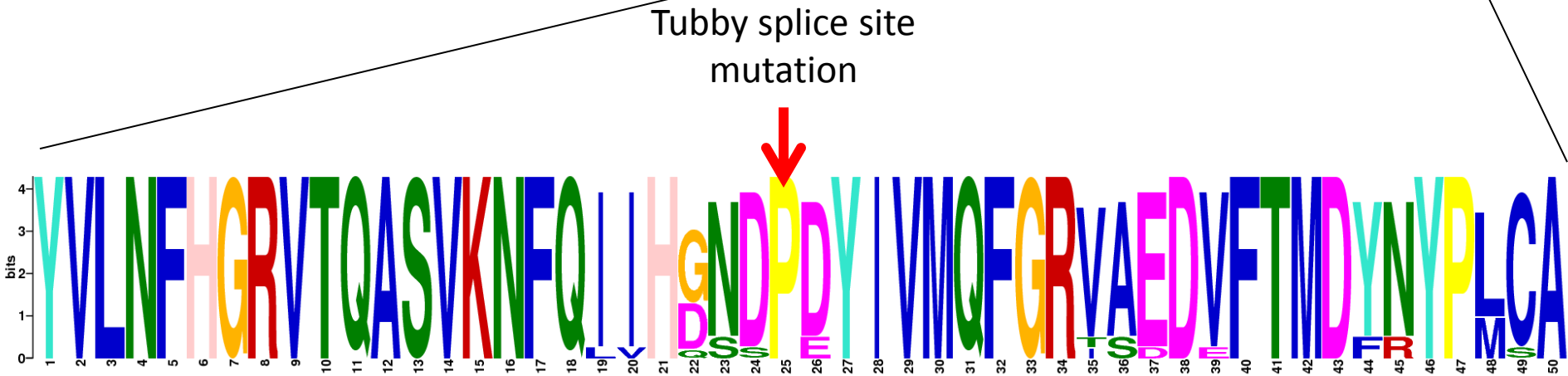


vs.

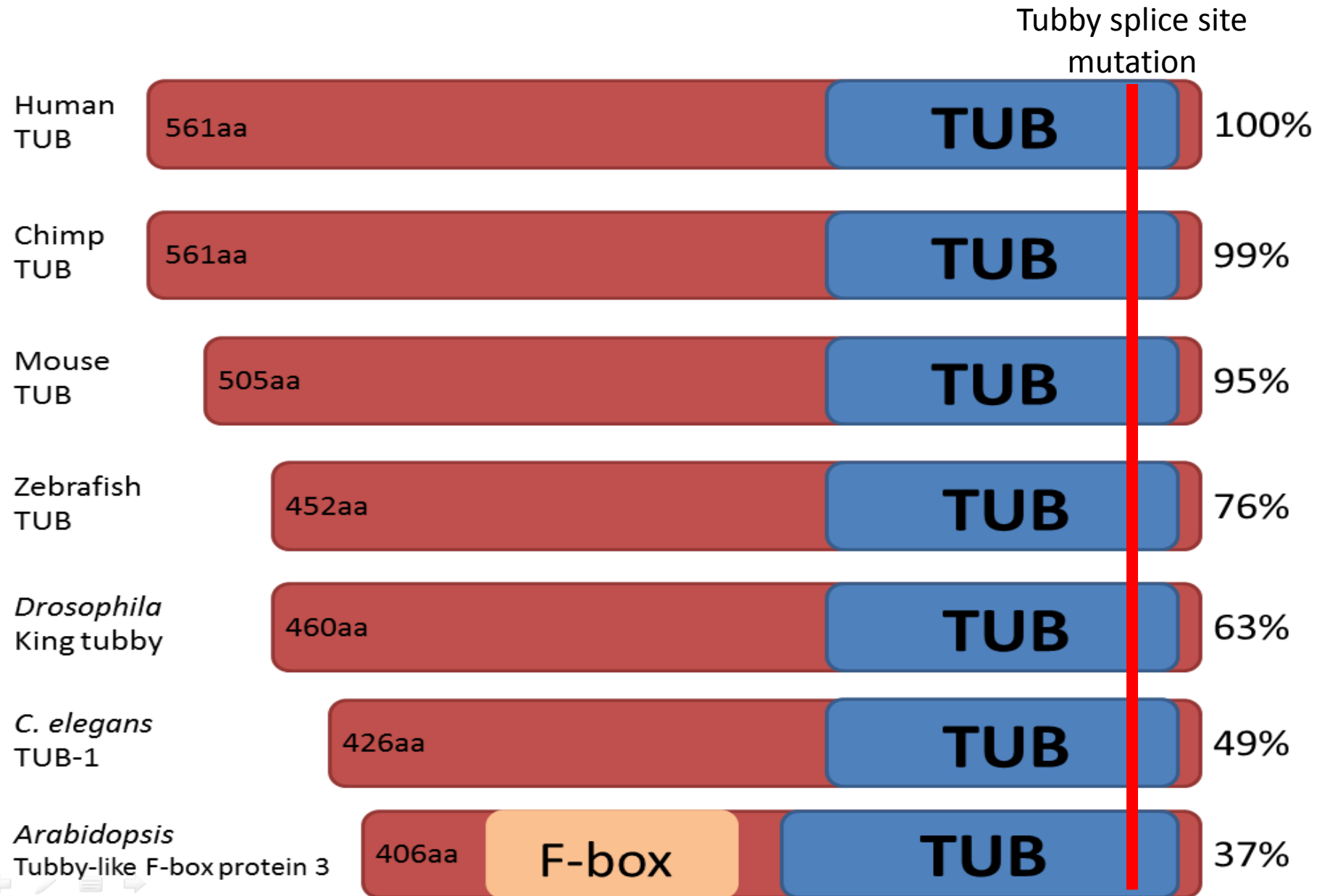


Tubby mutant

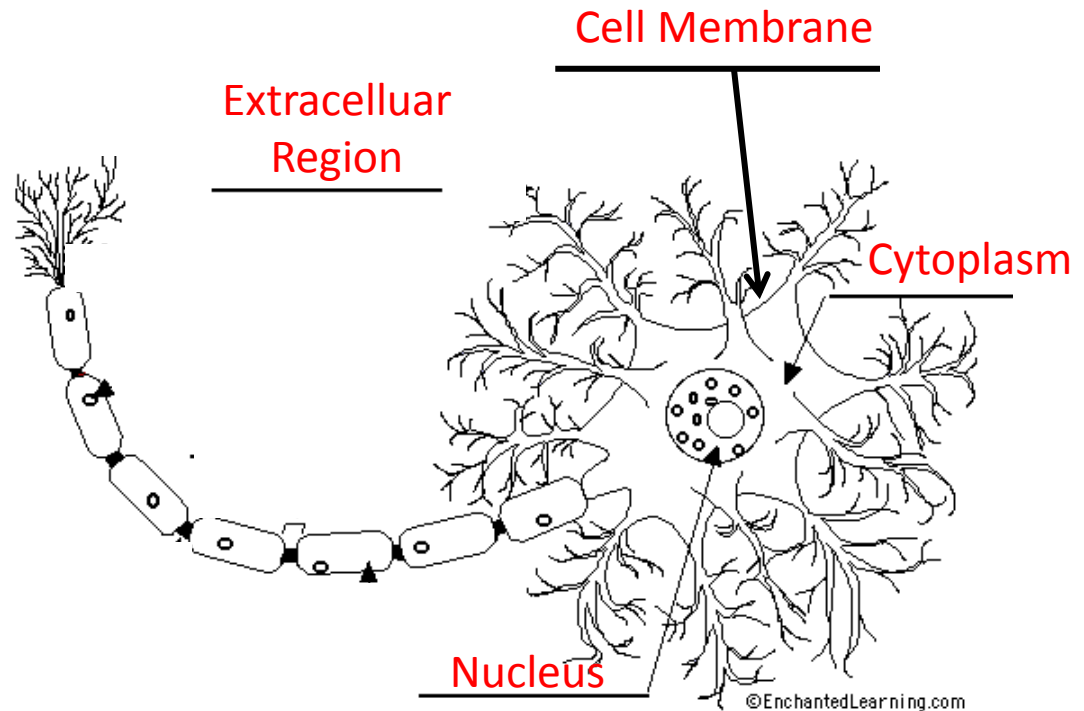
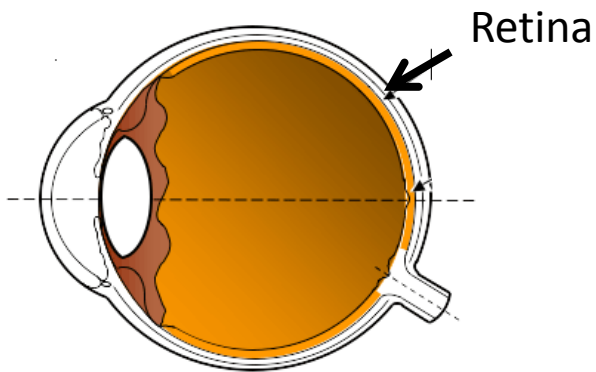
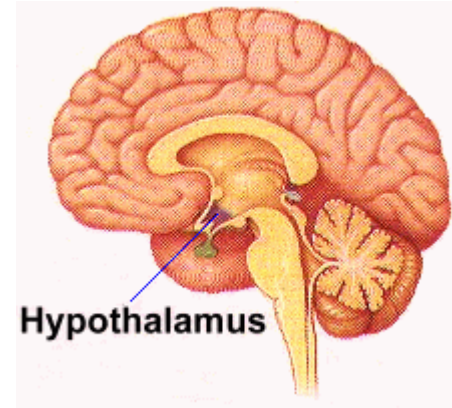
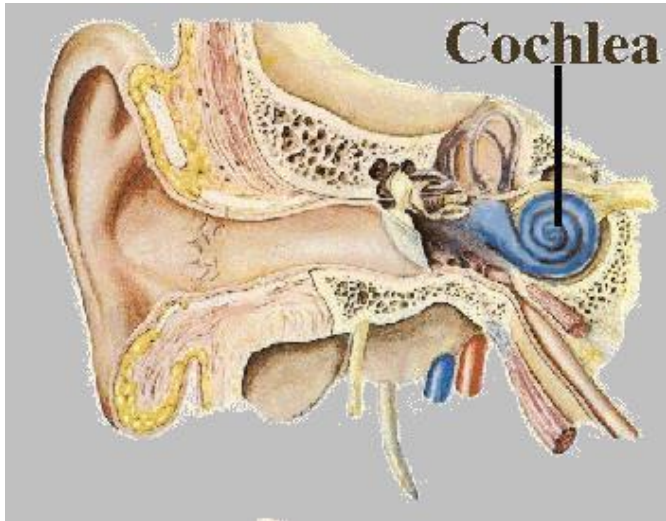
What causes the tubby phenotype?



How well conserved is tubby?



Where is Tubby found (GO)?



What are the tubby mutant phenotypes?



Obesity



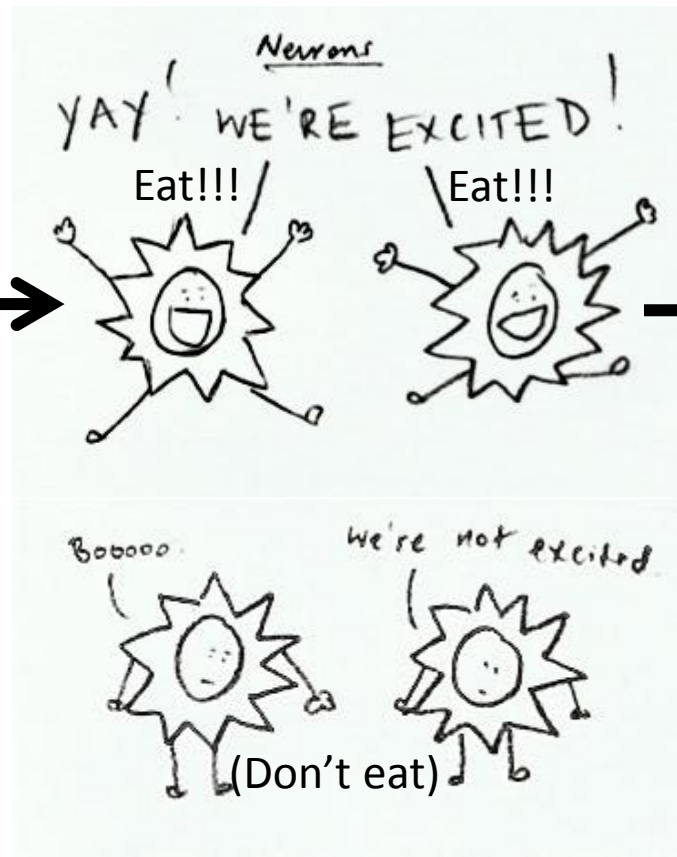
Increased food intake



Altered neuropeptide expression

Hypothesis

Tubby regulates the expression of hunger neuropeptides to control feeding behavior



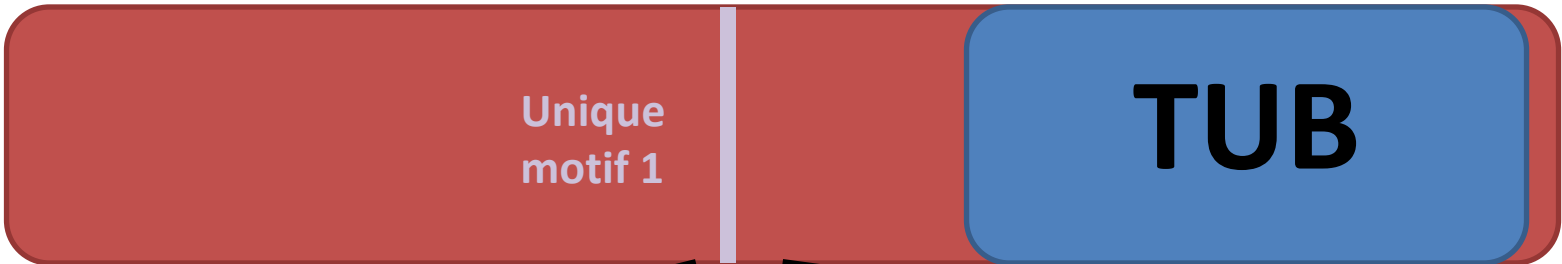
SPECIFIC AIM 1: Determine why mutations in TUB, but not other TULPs, result in increased food intake.

Why? Regions unique to TUB could be responsible for obesity phenotype.

How? Alignments and MEME



AIM1: What regions of the TUB protein are unique?

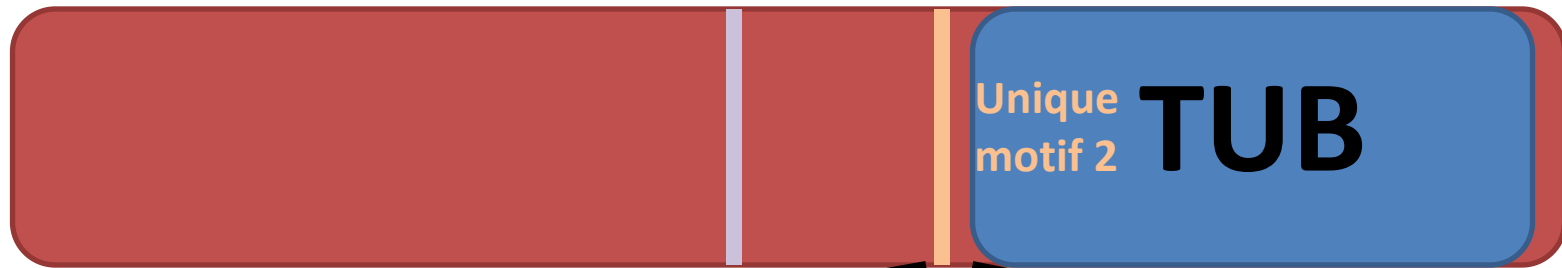


Tulp4_Human	QERT-----AQTSGPNPLKLSLMLSQGQHLDVSRLPFISPKSPASP--TATFQTG	1184
Tulp4_Mouse	QERT-----AQPTVPNPLKLSPLMLGQGQHLVDARVPFVPPKSPSSP--TATFPTG	1188
Tulp2_Human	DNSDAELEEVSVENGSVSPPPFKQSPRIRRKGW---Q---AHQRPGTIRAEGESDSQD---	183
Tulp2_Mouse	DSSSDVVEEVTMEDIPVISRPPQTNLANLRGW---L---ASPGPGISQEEKEEEVGSTD	204
Tulp1_Human	GEAD-----KDPS-----GSPASARK-SPAAM---FLVGEKSPDK-----	233
Tulp1_Mouse	GETD-----KDPA-----GSPAALRKEFPAAM---FLVGEKGAEE-----	228
TUB_Human	HKGT-----SGPA---ALAE-DKSEAQGPVQI---LTVGQSDHAQD---AGETA	224
TUB_Mouse	HKGT-----SGPA---TLAE-DKSEAQGPVQI---LTVGQSDHDKD---AGETA	169
Tulp3_Human	---I-----DGPA---AVLKPDEVHAPSVS-----SSV-----VEEDA	112
Tulp3_Mouse	---I-----DGPA---AFLKPEAQDLESKPQV---LSVGSPAPEEG--TEGSADG	124



AIM1: What regions of the TUB protein are unique?

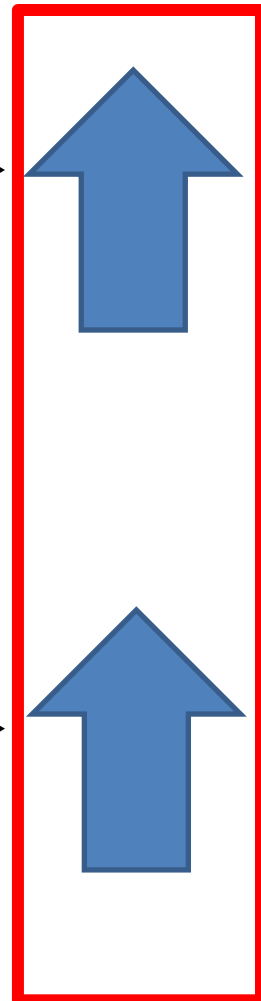
TUB



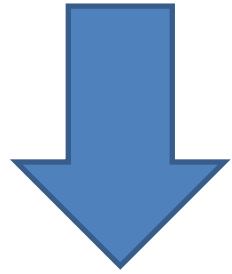
Tulp4_Human	-----TQFAQQEPAVVLQPLYPP	1233
Tulp4_Mouse	-----AQFAQQESAVVLQPAYPP	1237
Tulp2_Human	STGTNSSAAHNEELSKALKGEGGTDSDHMRHE-ASLAIRSPCPGLEEDMEAYVLRPALPG	283
Tulp2_Mouse	STETN----YAPVASKVLQGGDASNHNAWNMTCQPRIQPRIGEDMEAYVLLPAPRD	319
Tulp1_Human	TVIKKSNQ-----K GKAKGKG-----K KKAKEERAPSPFVEVDEPREFVLRPAPQG	302
Tulp1_Mouse	AVMKNSNQ-----K GRAKKG-----K KKVKEERASSPFVEVGEPREFVLQPAPQG	303
TUB_Human	SSQLNSNTRPSSATS RKSVREAAASA-----P SP TAP E Q PVDVEVQDLEEFALRPAPQG	317
TUB_Mouse	SSQLNSNTRPSSATS RKSI REAAASA-----P SPAAP E PVDIEVQDLEEFALRPAPQG	261
Tulp3_Human	LERPN-----S ASSQNSTDTGTS-----G SATAAQPADNLLGDIDDLEDFVYSPAPQG	199
Tulp3_Mouse	LSSPSARSEESAAASQKAASETG-----A SGVTAQQGDAQLGEVENLEDFAYSAPPRG	217



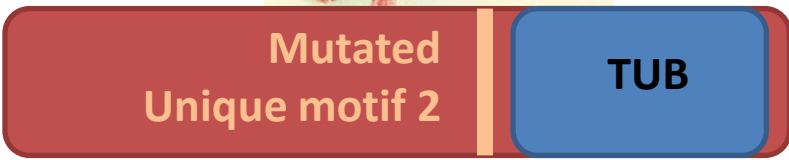
AIM1: Do mutations in unique protein motifs affect feeding behavior?



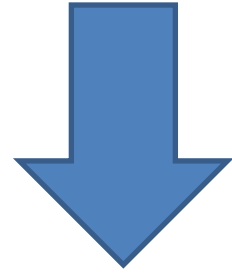
or



Food Intake



or

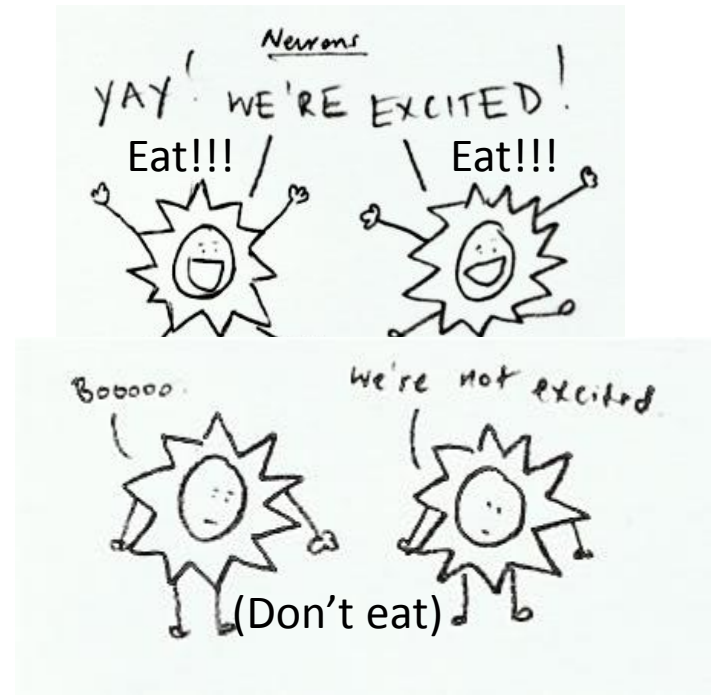


Food Intake

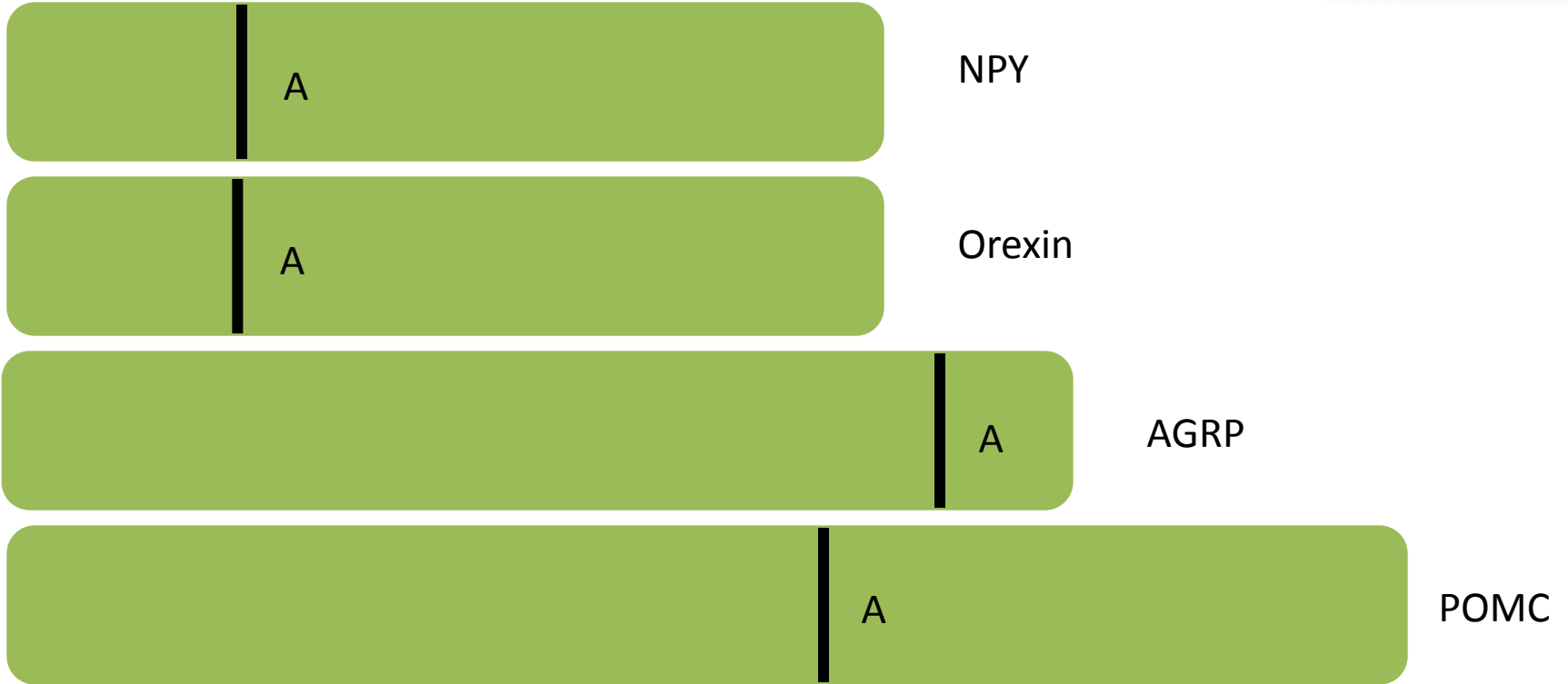
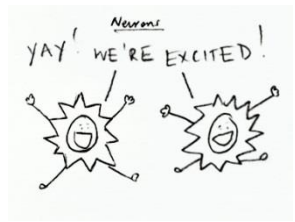
SPECIFIC AIM 2: Identify DNA motifs in the differentially expressed hunger neuropeptides that are important for regulating food intake.

Why? Tubby may bind to conserved motifs to regulate expression

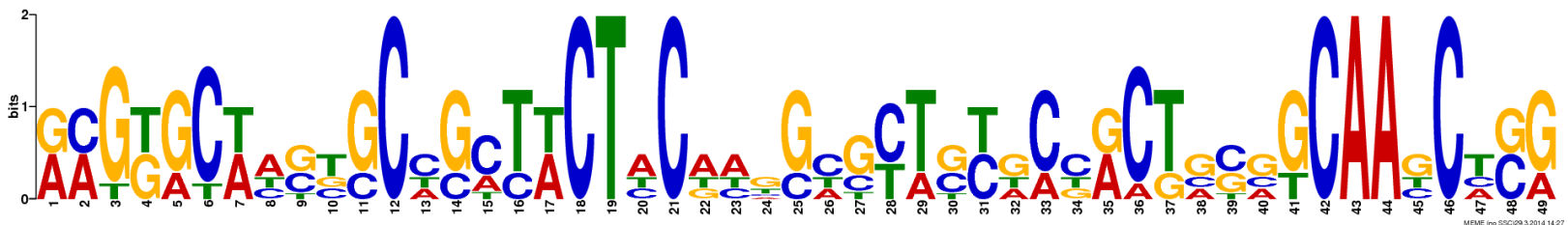
How? DREME



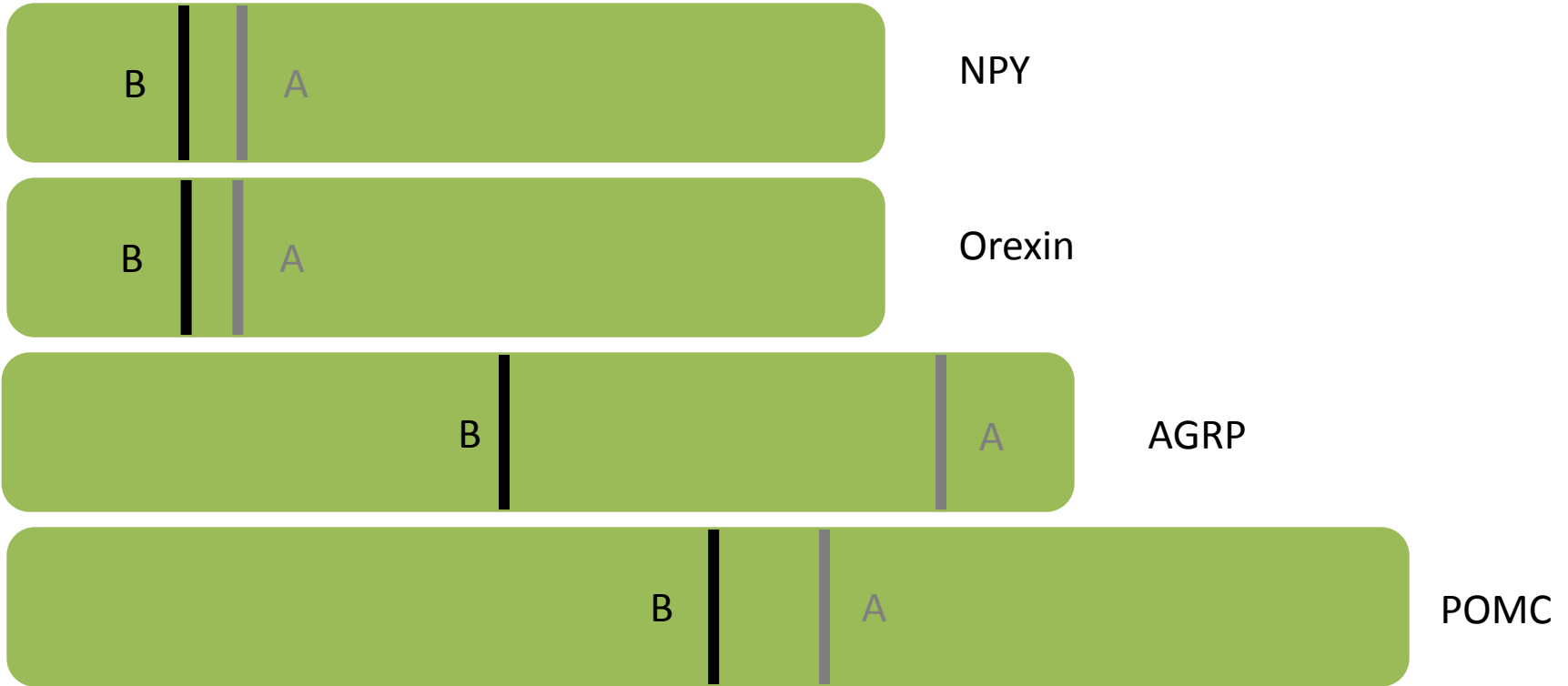
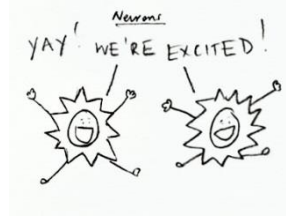
AIM2: Are there conserved DNA motifs in hunger neuropeptides?



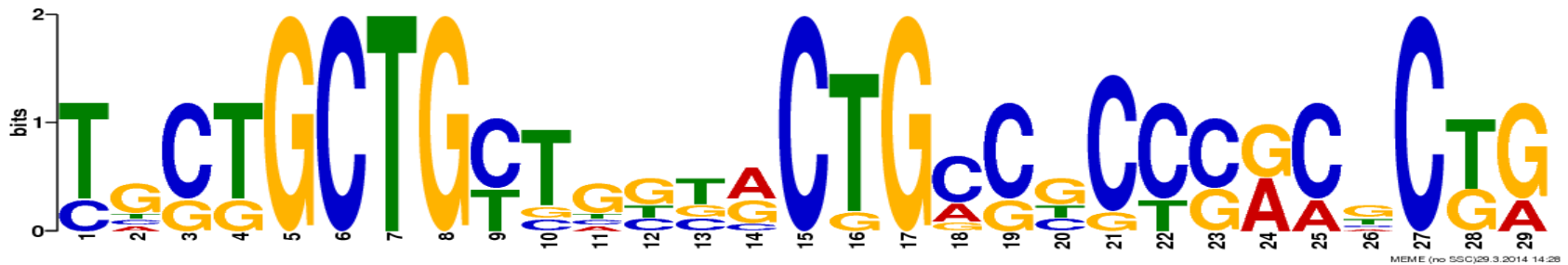
Hunger Motif A



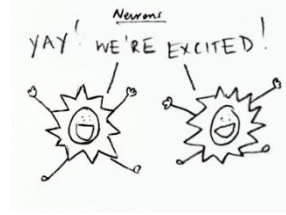
AIM2: Are there conserved DNA motifs in hunger neuropeptides?



Hunger Motif B



AIM2: Are there conserved DNA motifs in hunger neuropeptides?



NPY



Orexin



AGRP

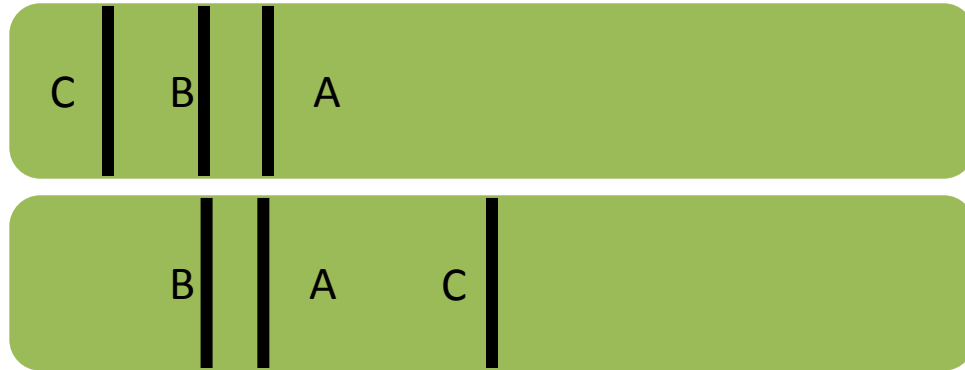
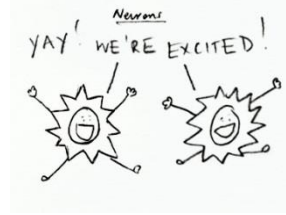


POMC

Hunger Motif C

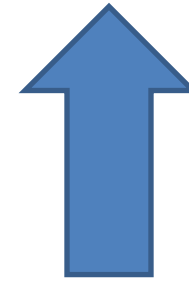


AIM2: Are there conserved DNA motifs in hunger neuropeptides?



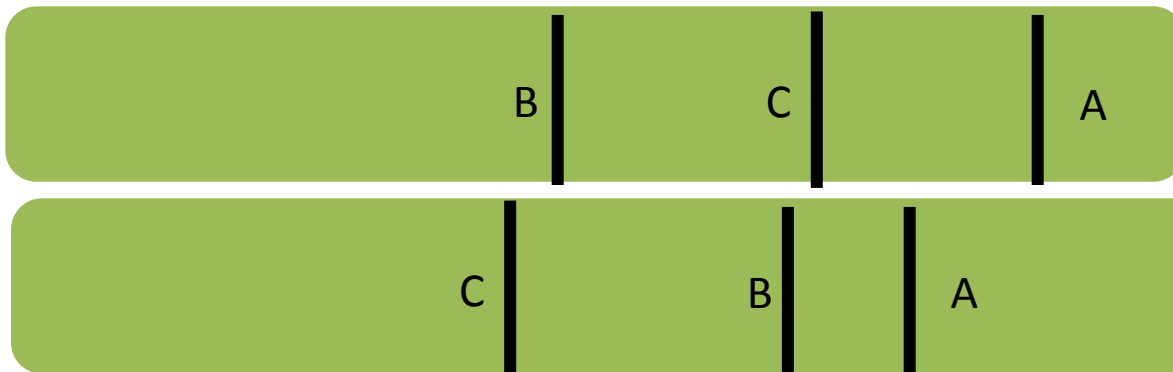
In Tubby mice

NPY



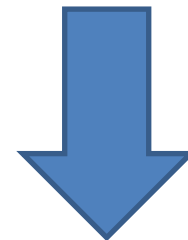
Orexin

Motifs all in first half of transcript



In Tubby mice

AGRP



Motifs later in transcript

POMC

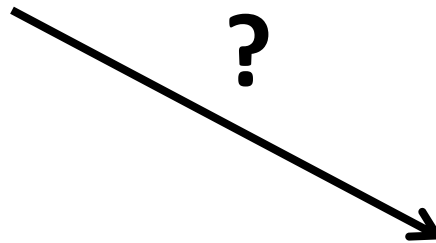
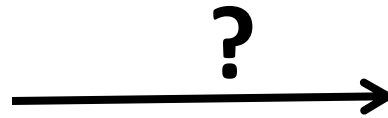
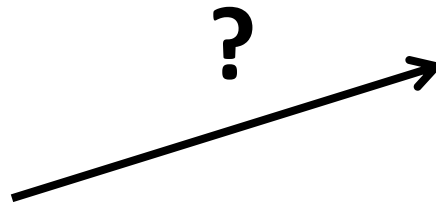
SPECIFIC AIM 3: Determine whether mutations in TUB affect food choice in addition to food intake.

Why? Food choice may affect gene expression.

How? Microarray



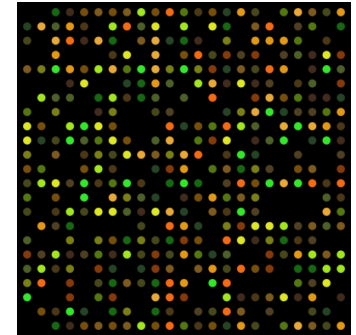
AIM3: Which food type will tubby mice choose?



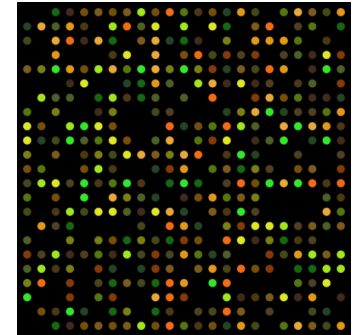
AIM3: Does food choice affect gene expression?



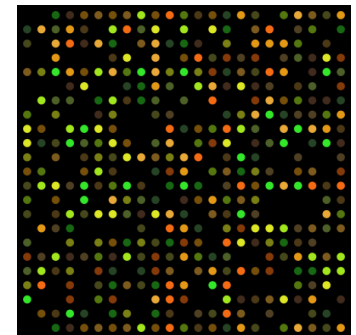
High Protein Diet



High Fat Diet

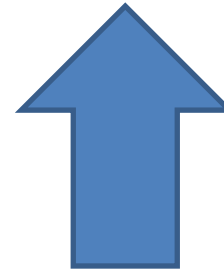


High Carb Diet

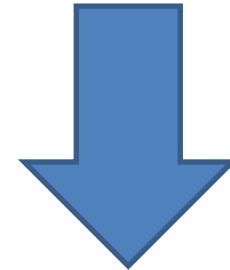


Future Directions

AIM1:



or



Food Intake

Mutated
Unique motif

TUB

AIM2:

TUB ?

C

B

A

NPY

Questions?

