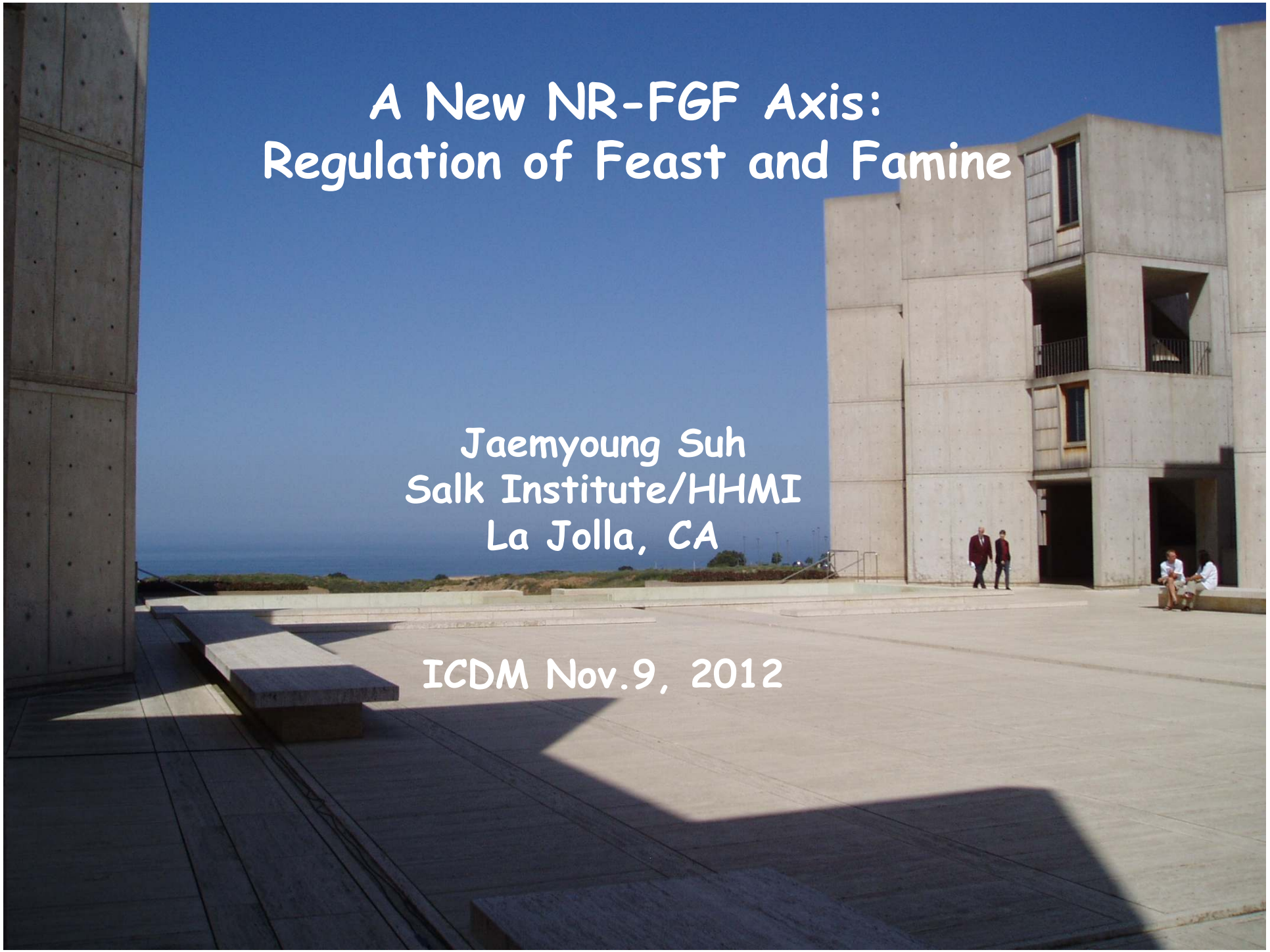


A New NR-FGF Axis: Regulation of Feast and Famine

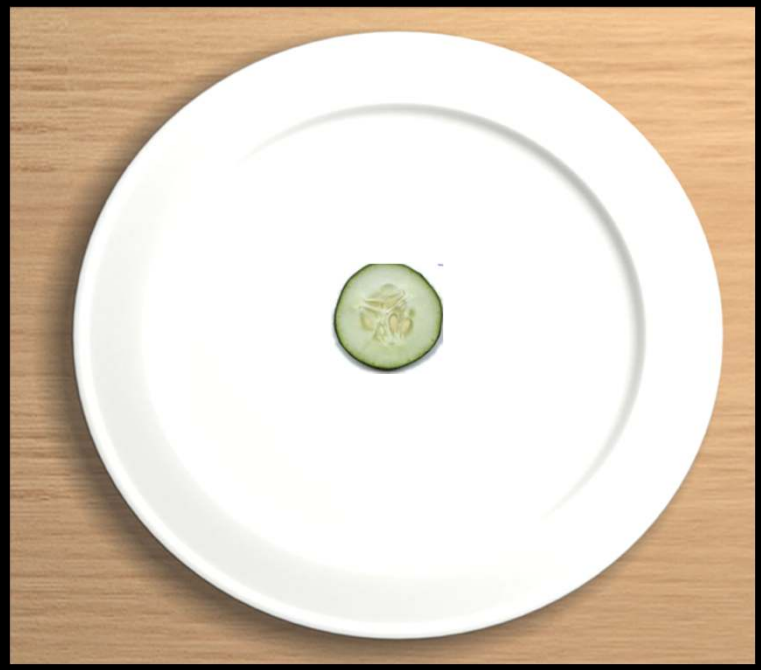
Jaemyoung Suh
Salk Institute/HHMI
La Jolla, CA

ICDM Nov.9, 2012

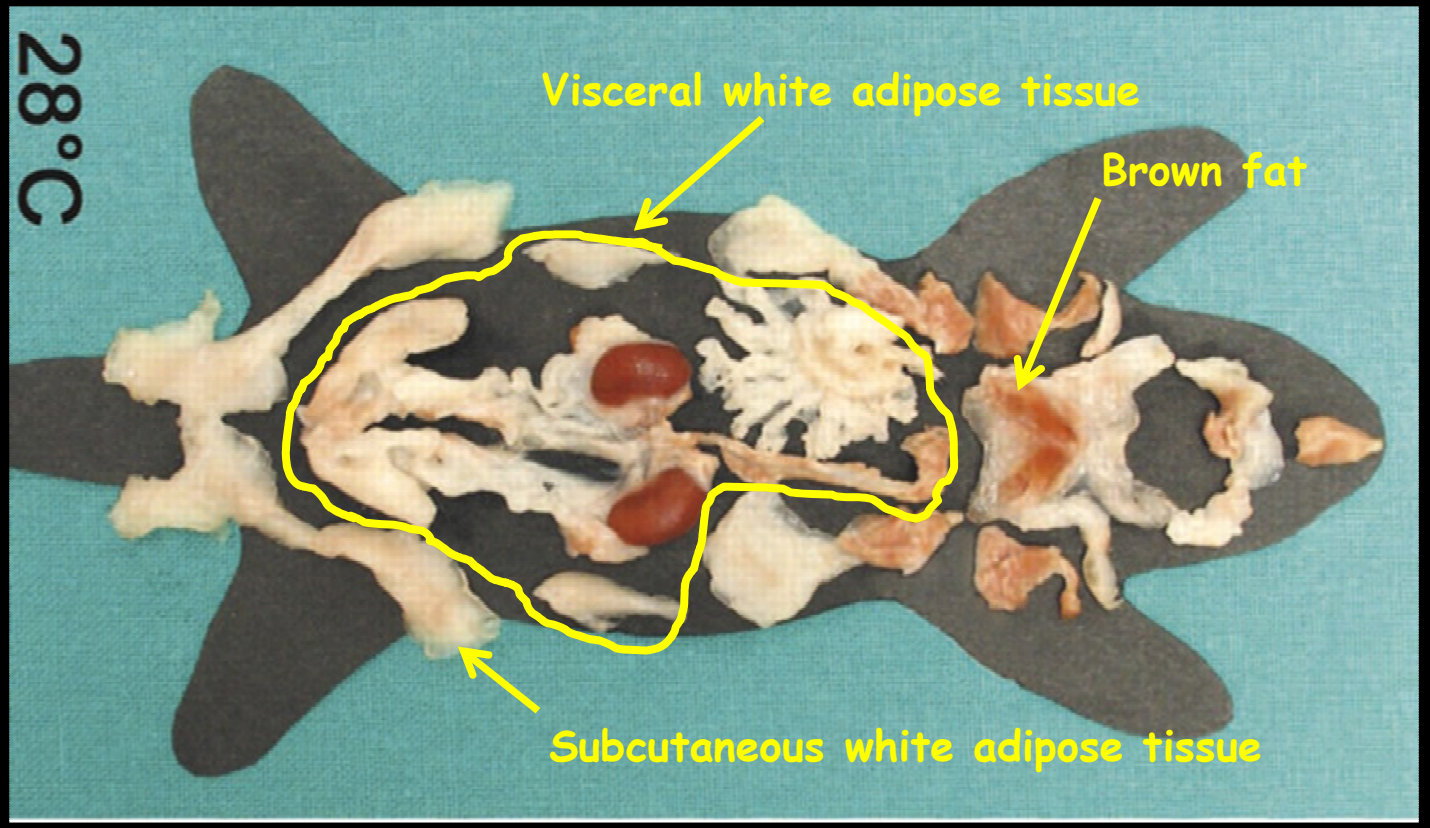
Feast and Famine

- Feast/famine cycles are a recurrent environmental stressor

- The ability to withstand periods of limited/excess nutrient availability is critical to animal survival

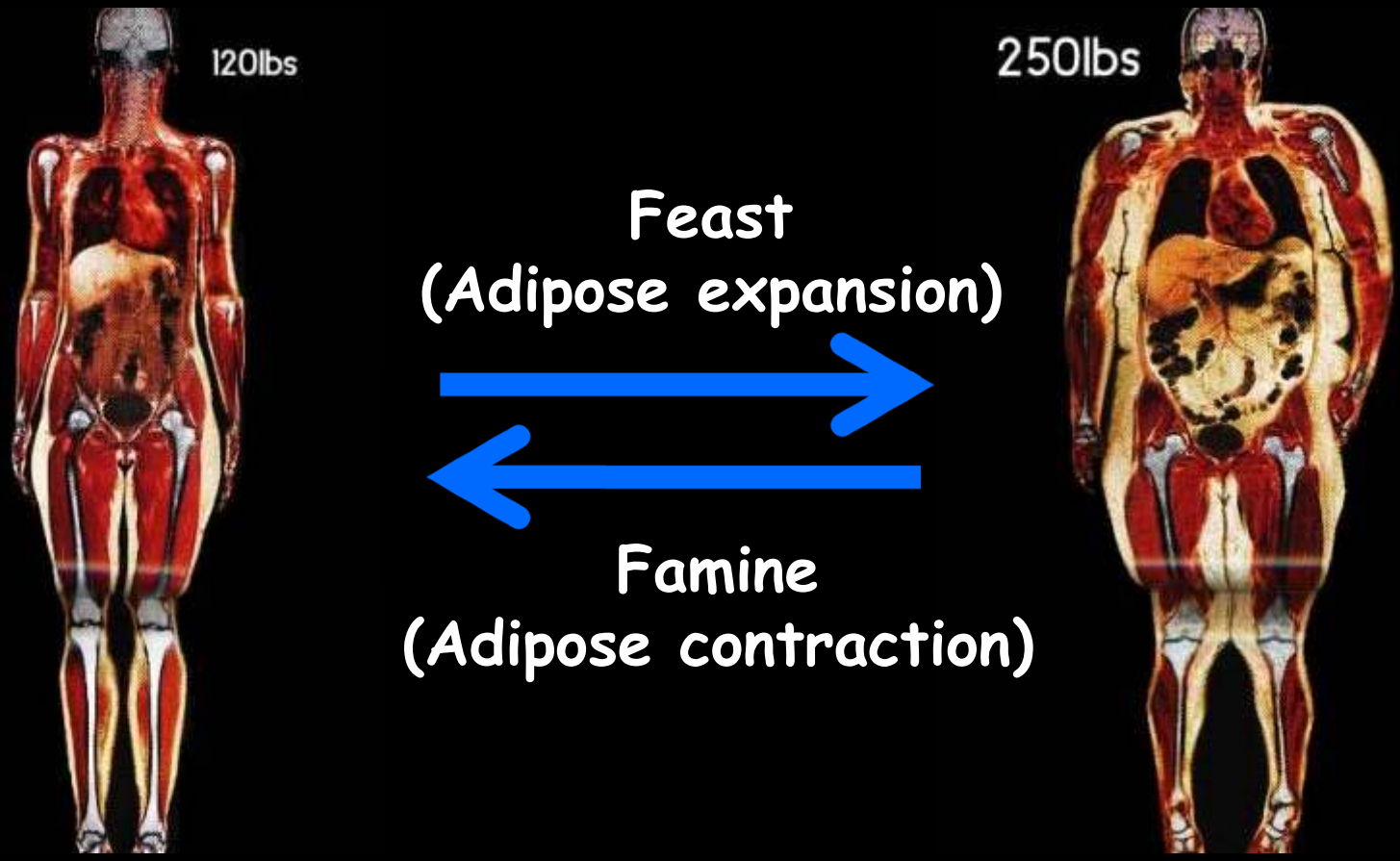


Adipose tissues: Central to the feast/famine response

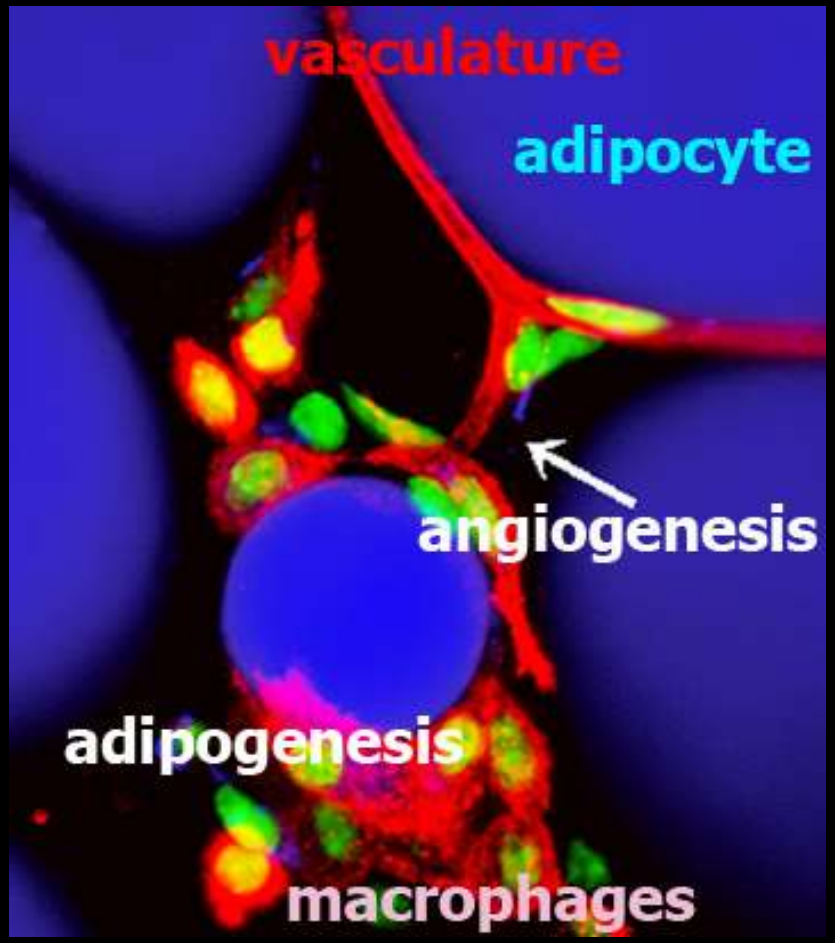


Cinti S Am J Physiol Endocrinol Metab 2009;297:E977-E986

Adipose tissues are dynamic and possess wide developmental potential



Adipose development and remodeling– coordination of multiple cell types



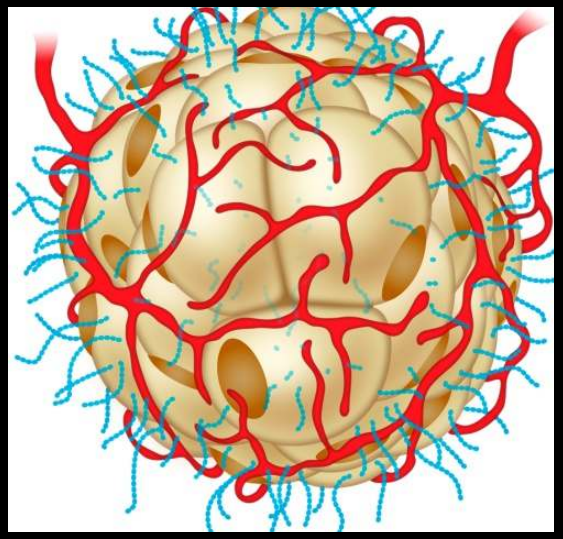
Adipose tissue remodeling - adaptive response to energy stress

- Adipose tissues expand and contract during feast/famine cycles
  → a process called “remodeling”

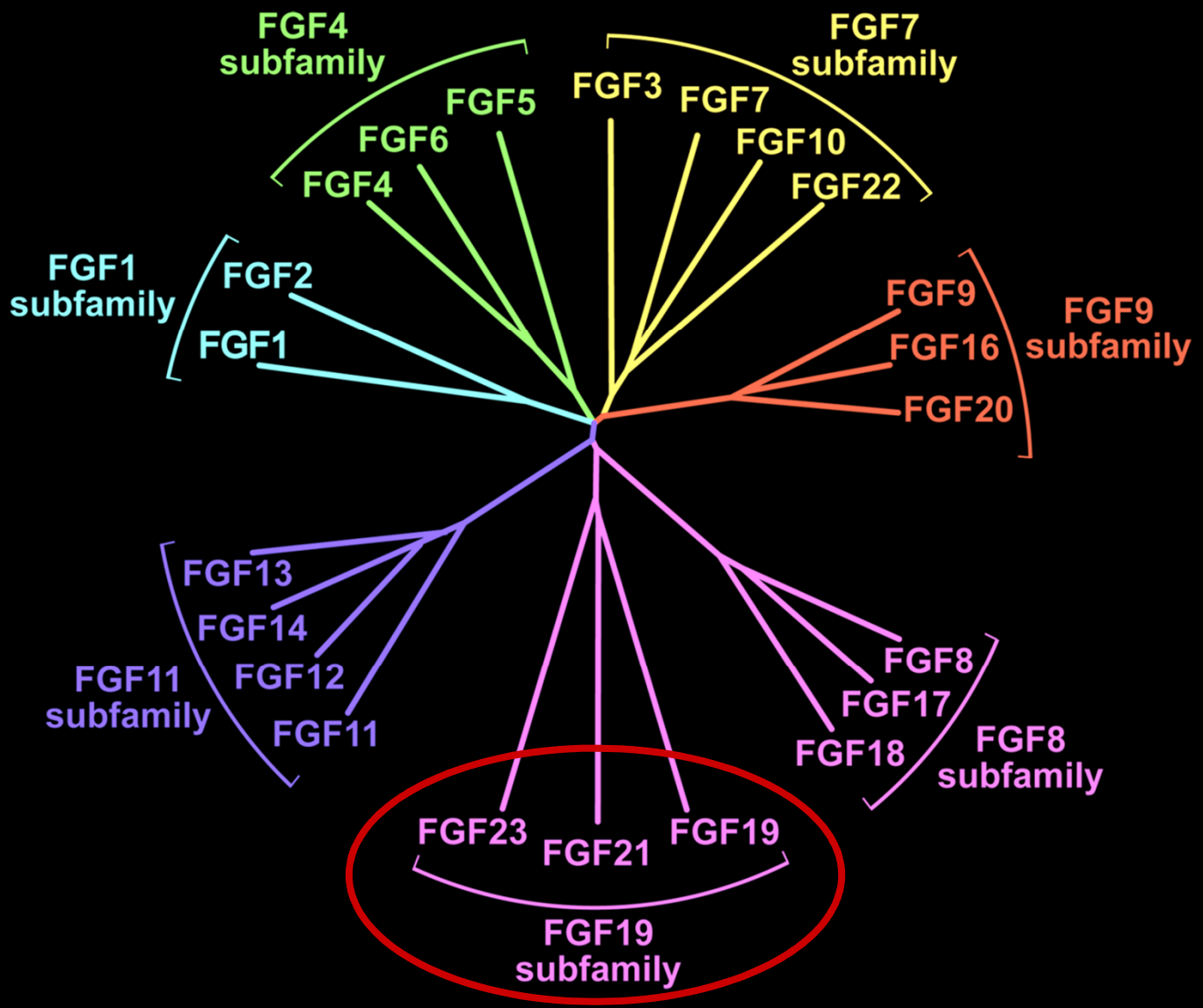
- Remodeling is a complex process that requires coordinated changes within adipocytes, immune cells, surrounding vasculature, and the extracellular matrix

- Adaptive remodeling is dynamic and critical for maintaining metabolic homeostasis

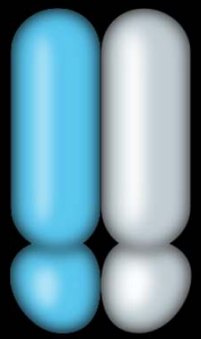
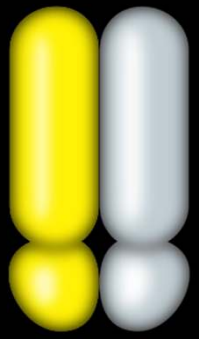
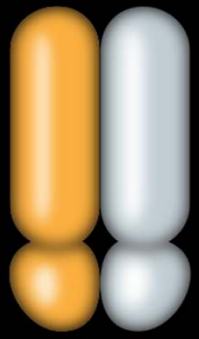
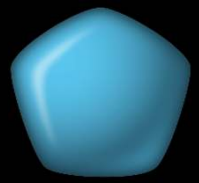
- The mechanisms underlying remodeling are poorly understood



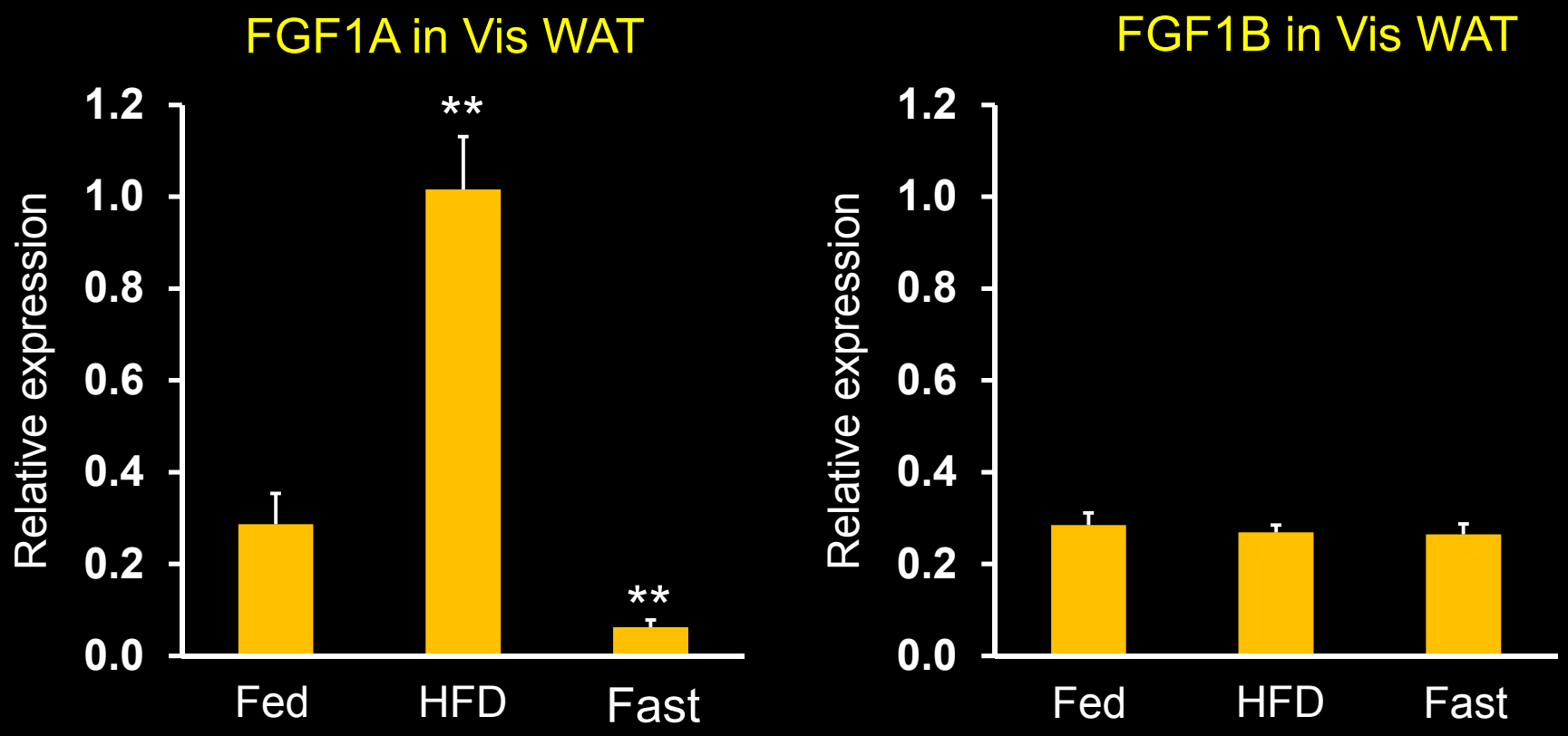
Fibroblast growth factors



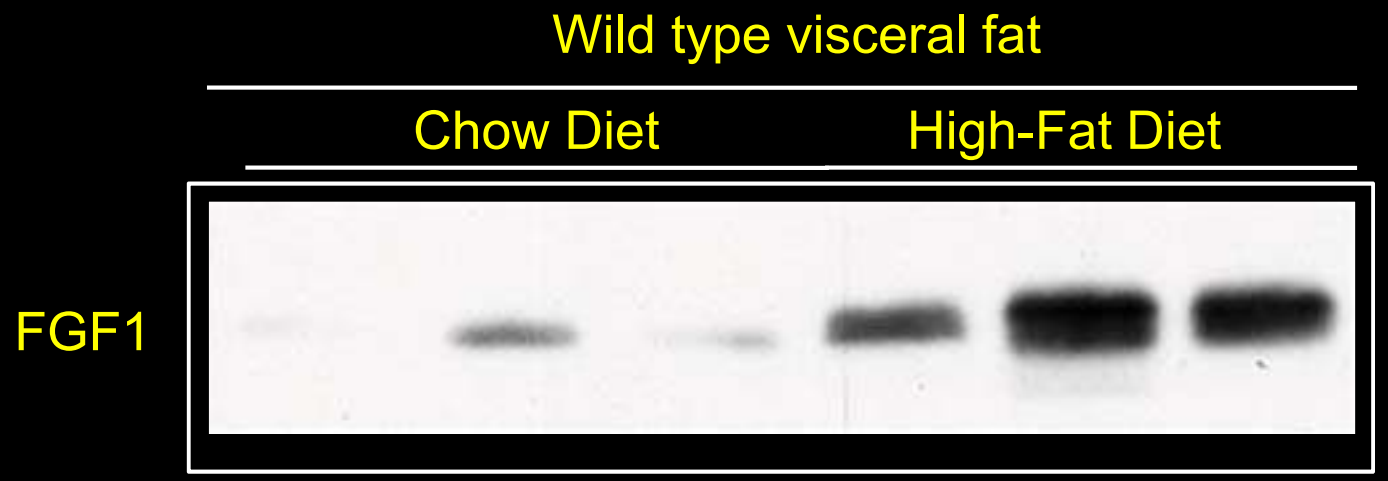
The NR-FGF axis

Ligands	**Fatty acids**	**Bile acids**	**Vitamin D**
	PPARα/RXR	**FXR/RXR**	**VDR/RXR**
Nuclear receptor			
	FGF21	**FGF15/19**	**FGF23**
Growth factor expression			
Physiological response	**Energy homeostasis**	**Bile acid homeostasis**	**Phosphate / Ca^{+} homeostasis**

FGF1 in adipose tissue is regulated by nutritional cues

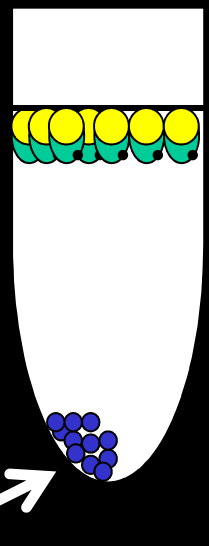


FGF1 protein is induced by high fat diet in adipose tissue



Adipose tissue subcompartments – adipocytes and stromal cells

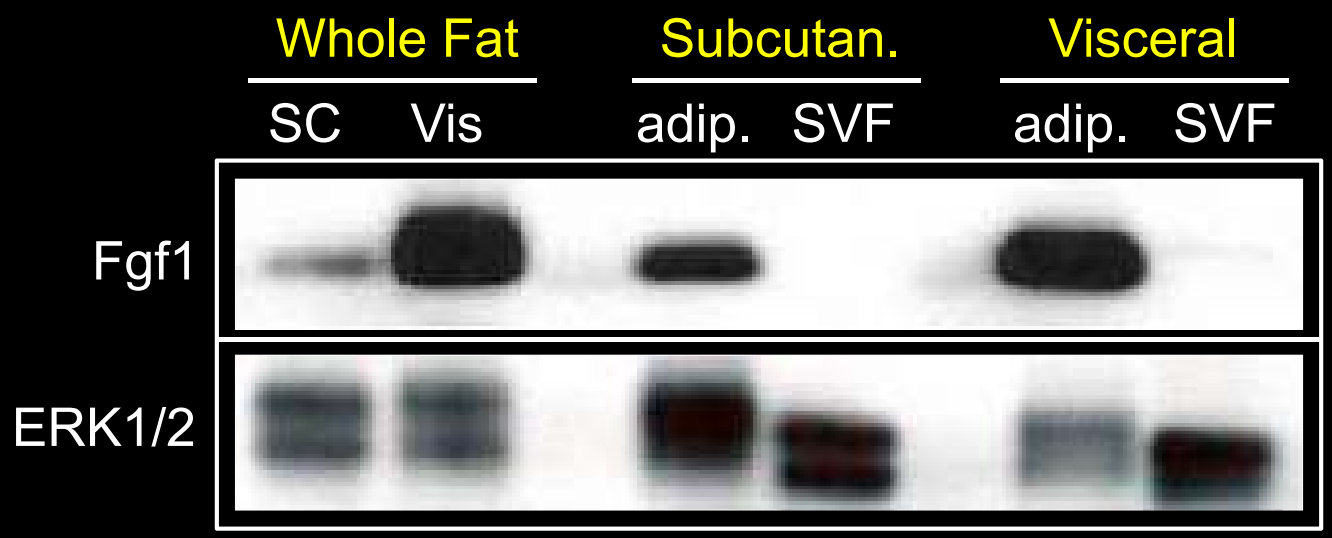
Collagenase



Adipocytes (float)

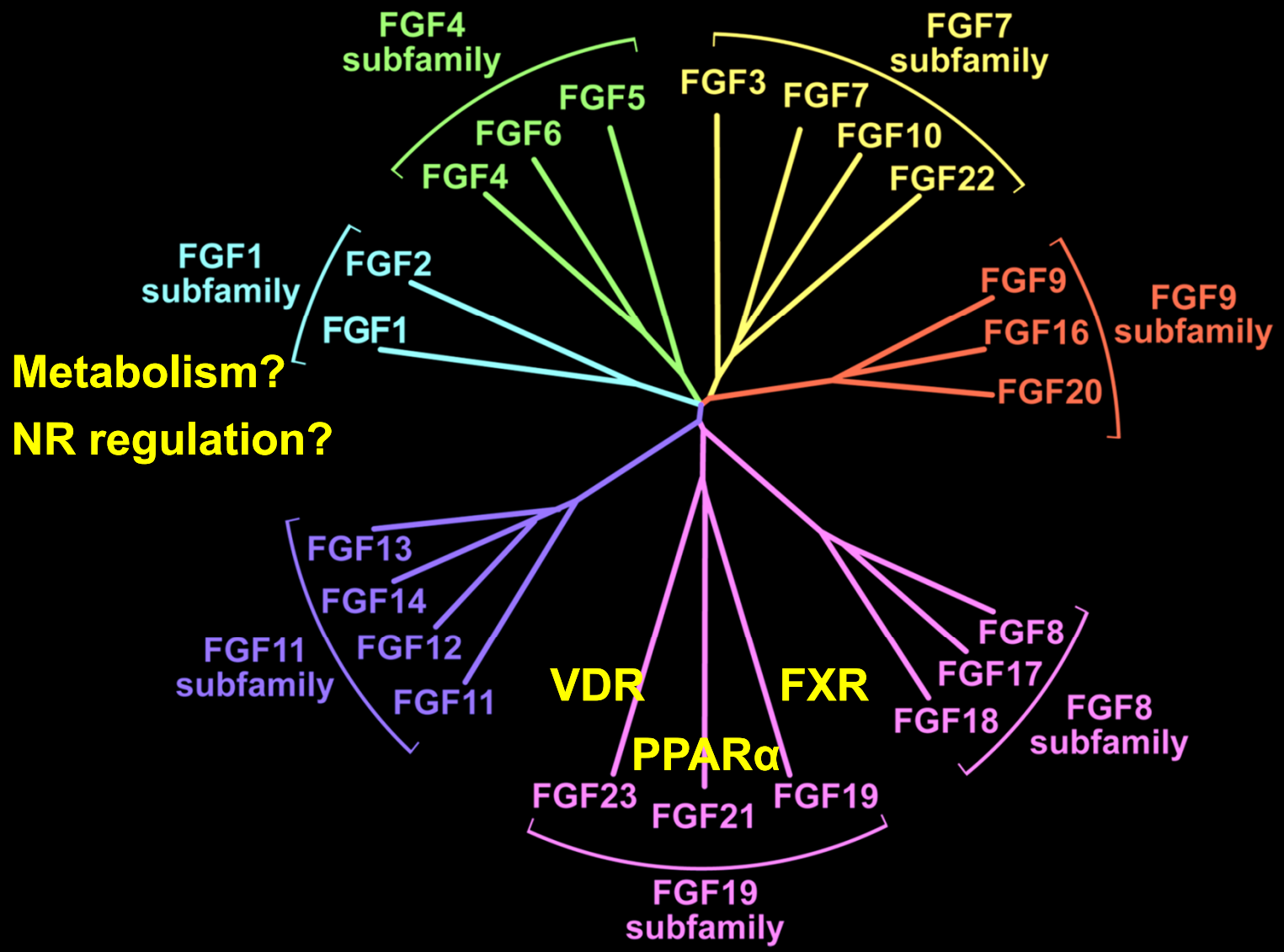
Stromal –Vascular-Fraction (sink)

FGF1 is expressed predominantly in visceral adipocytes



Visceral fat depots are linked to metabolic disease and has more active remodeling capacity than subcutaneous fat

Fibroblast growth factors



Fibroblast growth factor (FGF)	Phenotype of knockout mouse	Physiological role
FGF1	Normal	Not established
FGF2	Loss of vascular tone Slight loss of cortex neurons[72–73]	Not established
FGF3	Inner ear agenesis in humans[9]	Inner ear development[9]
FGF4	Embryonic lethal[128]	Cardiac valve leaflet formation Limb development[126–128]
FGF5	Abnormally long hair[129]	Hair growth cycle regulation[129–131]
FGF6	Defective muscle regeneration[133]	Myogenesis[132,133]
FGF7	Matted hair Reduced nephron branching in kidney[137,138]	Branching morphogenesis[138]
FGF8	Embryonic lethal[162]	Brain, eye, ear and limb development[160,161]
FGF9	Postnatal death Gender reversal Lung hypoplasia[170]	Gonadal development Organogenesis[170,171]
FGF10	Failed limb and lung development[142]	Branching morphogenesis[142]
FGF16	Embryonic lethal[172]	Heart development[172]
FGF17	Abnormal brain development[163]	Cerebral and cerebellar development[163]
FGF18	Delayed long-bone ossification[164,165]	Bone development[164,165]
FGF19	Increased bile acid pool[189]	Bile acid homeostasis Lipolysis Gall bladder filling[3,6,197–201]
FGF20	No knockout model	Neurotrophic factor[175]
FGF21	No knockout model	Fasting response Glucose homeostasis Lipolysis and lipogenesis[4,208–225]
FGF22	No knockout model	Presynaptic neural organizer[143]
FGF23	Hyperphosphataemia Hypoglycaemia Immature sexual organs[185,235]	Phosphate homeostasis Vitamin D homeostasis[226–261]

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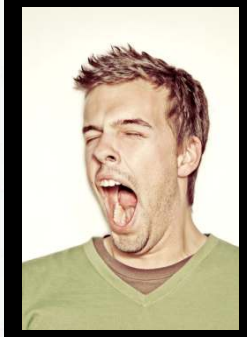
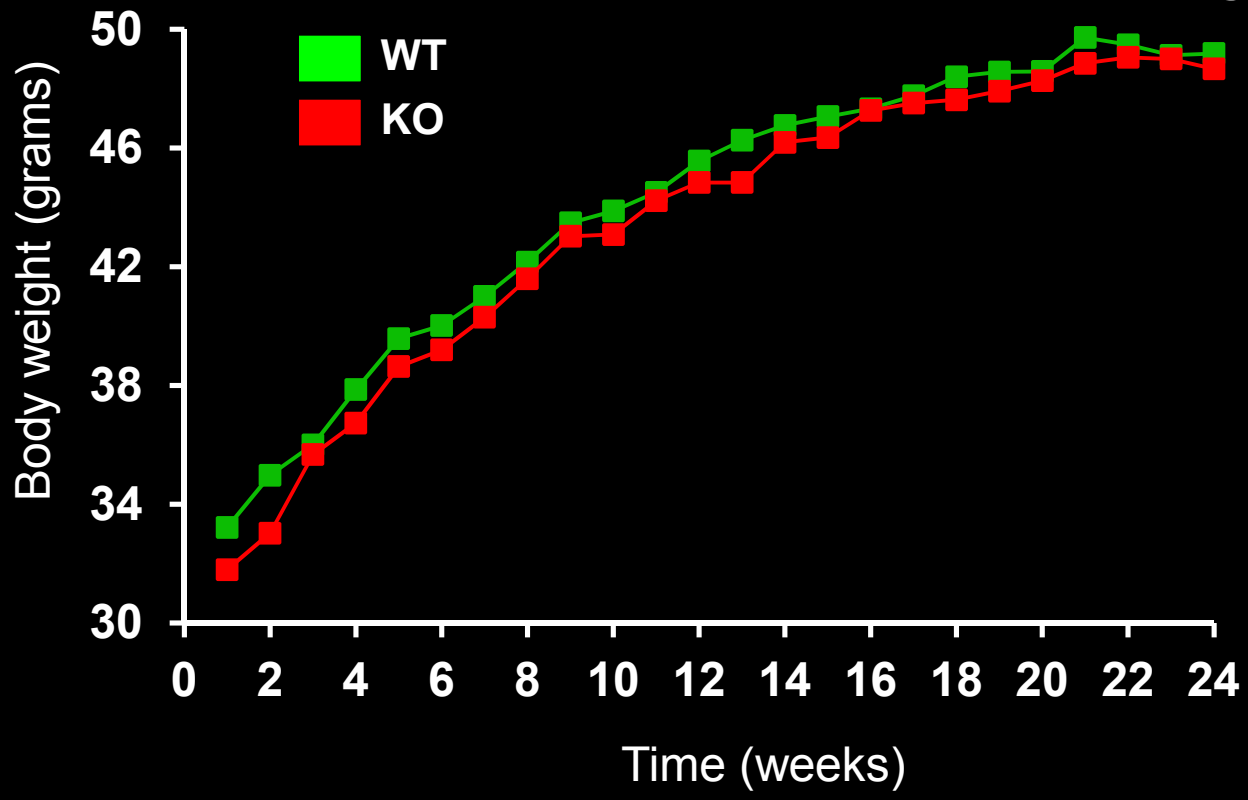
FGF23	Hyperphosphataemia Hypoglycaemia Immature sexual organs[185,235]	Phosphate homeostasis Vitamin D homeostasis[226–261]

FGF1:
a “boring” FGF

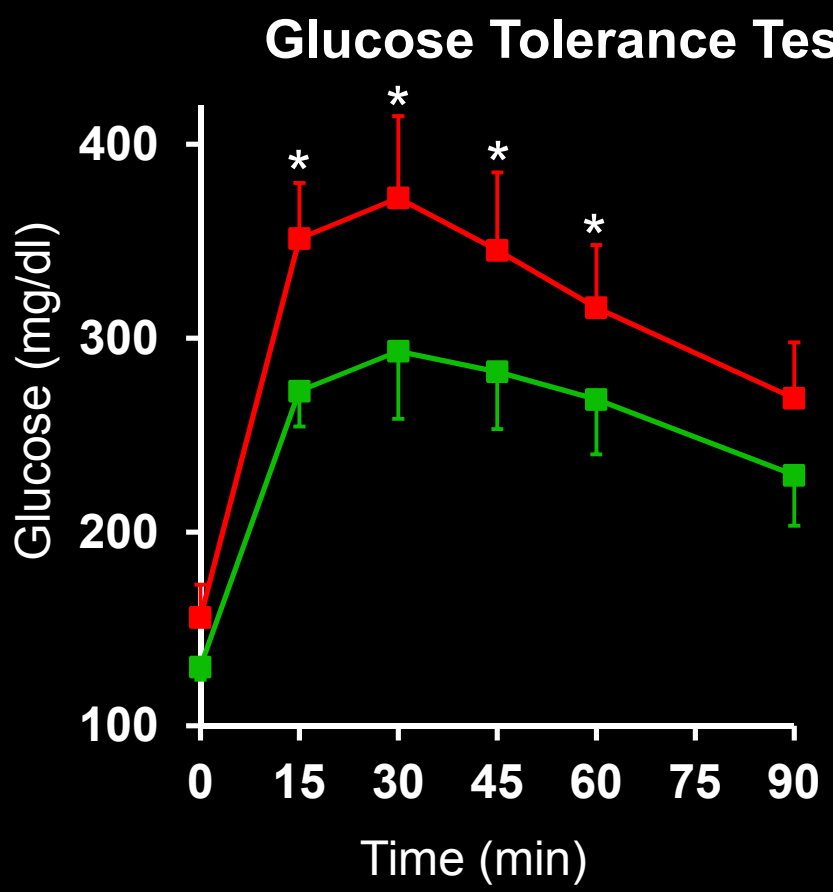


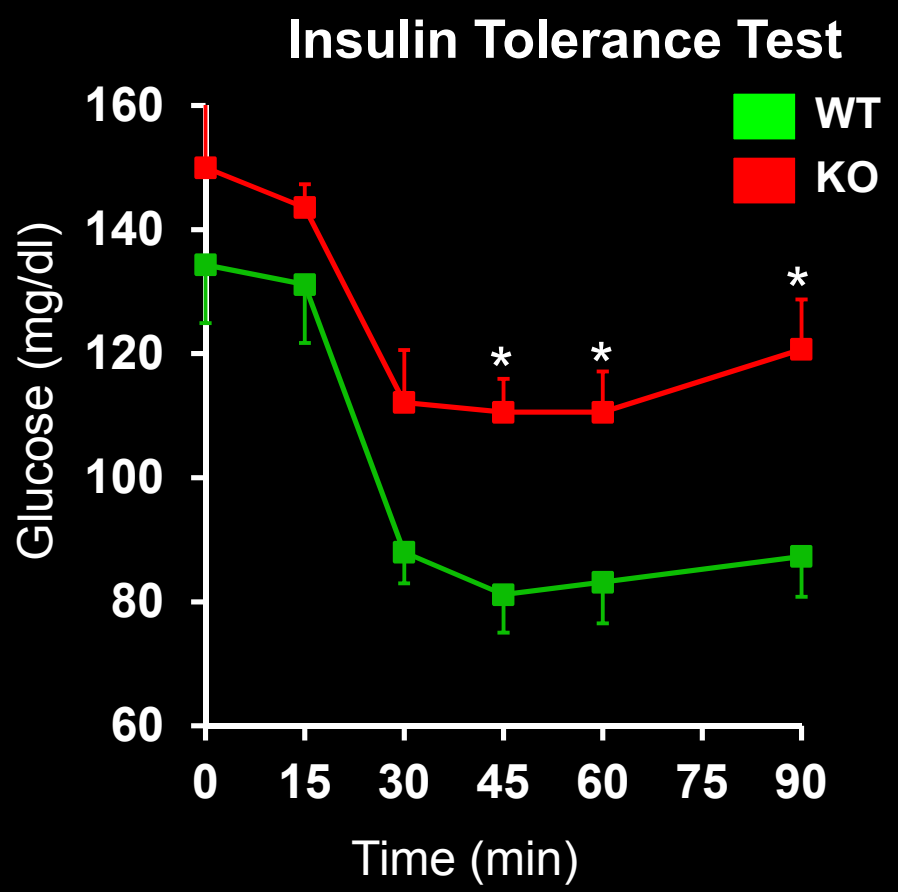
No change in body weight gain in FGF1 KO mice on a HFD



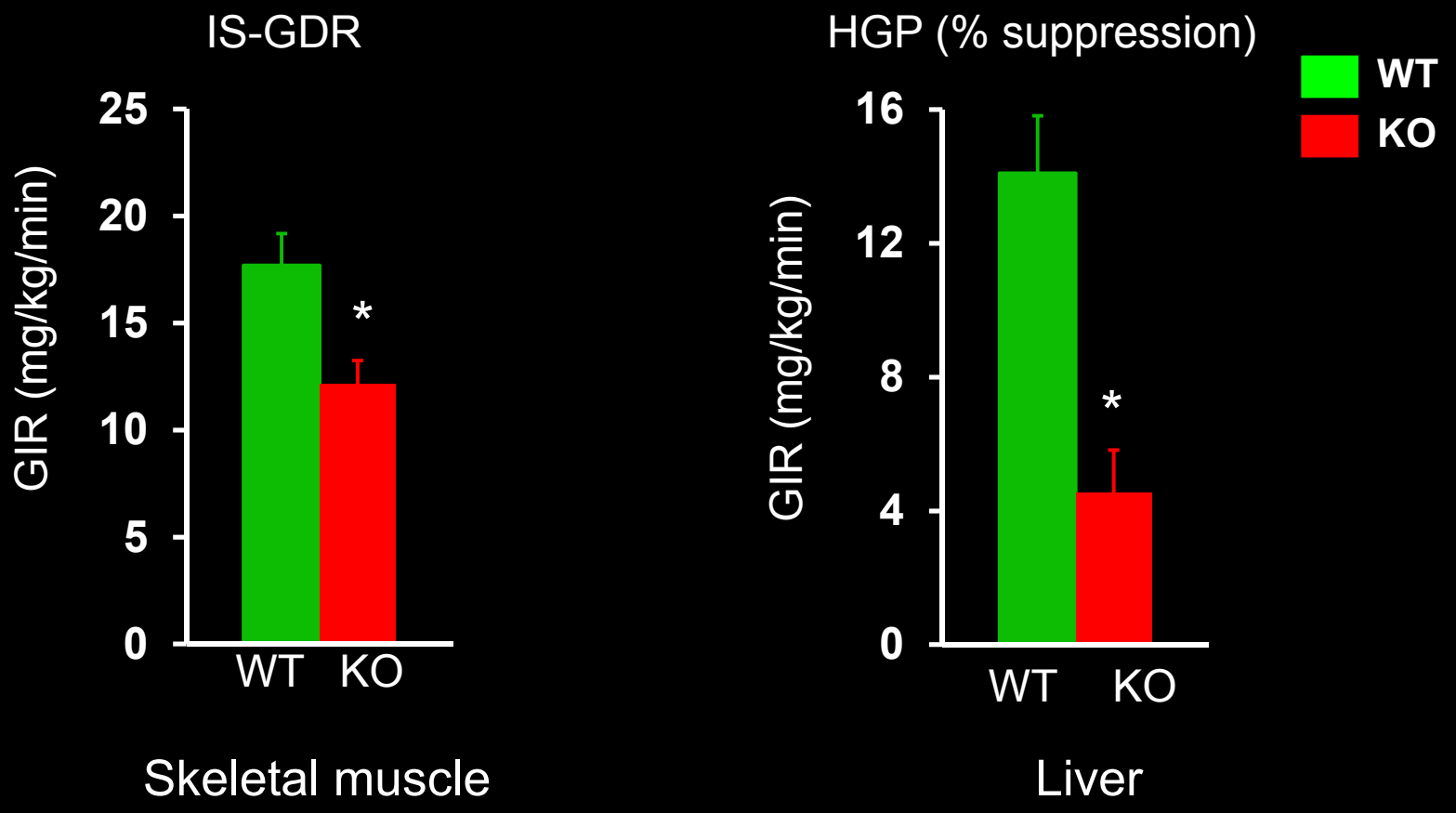
Still boring…….?

Increased insulin resistance in FGF1 KO mice on HFD

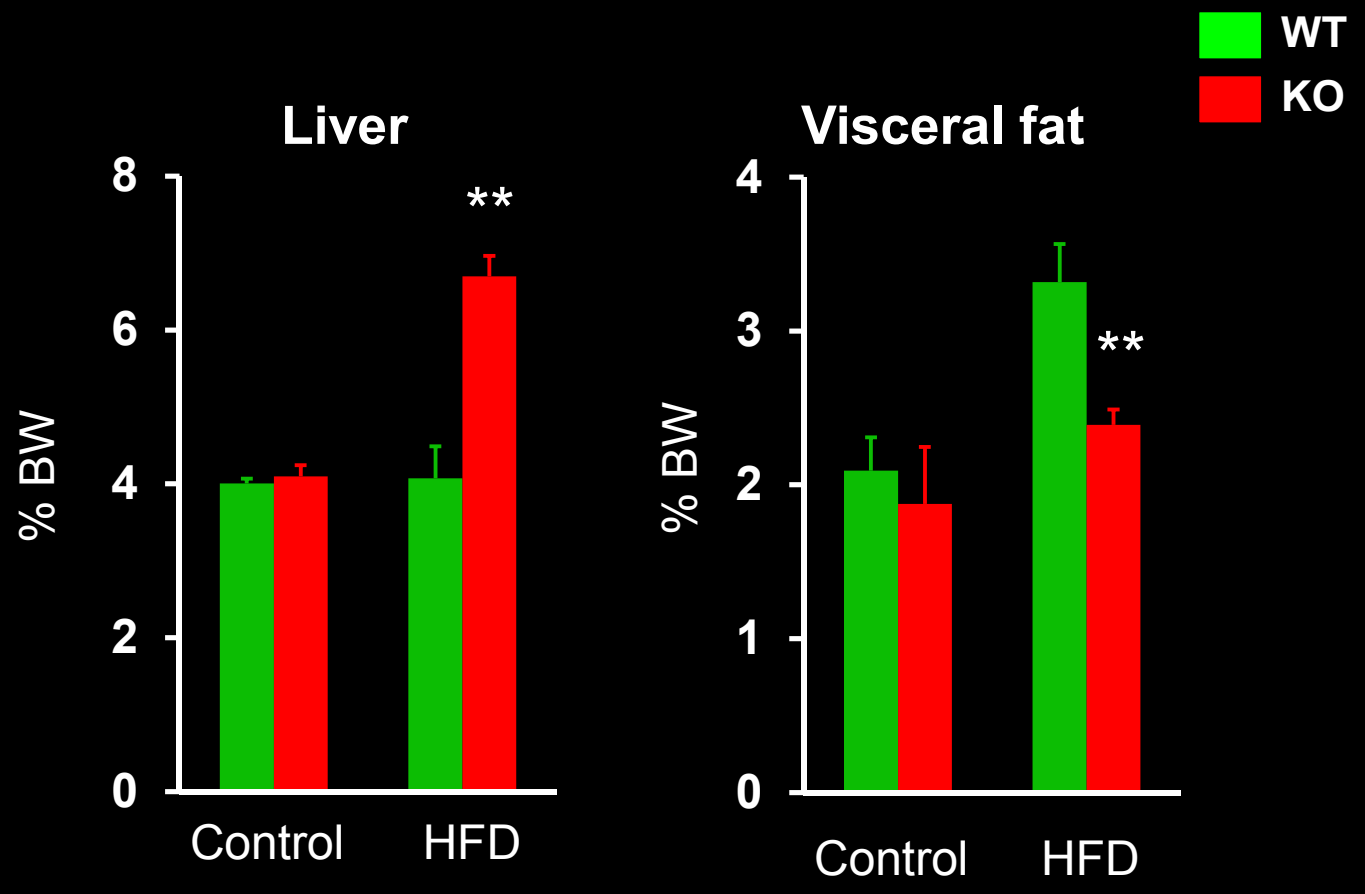




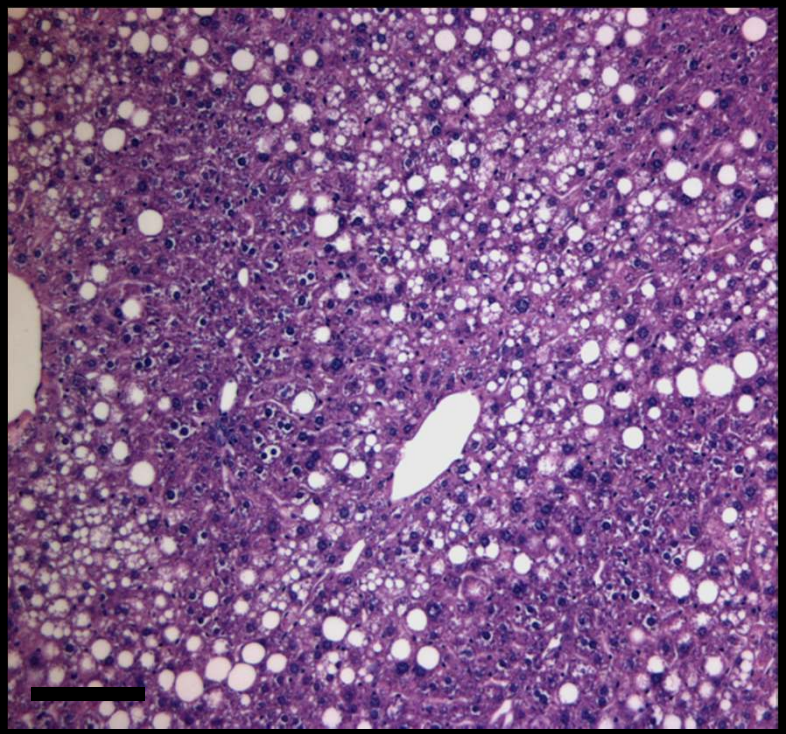
Increased peripheral and hepatic insulin resistance in FGF1 KO mice on a HFD



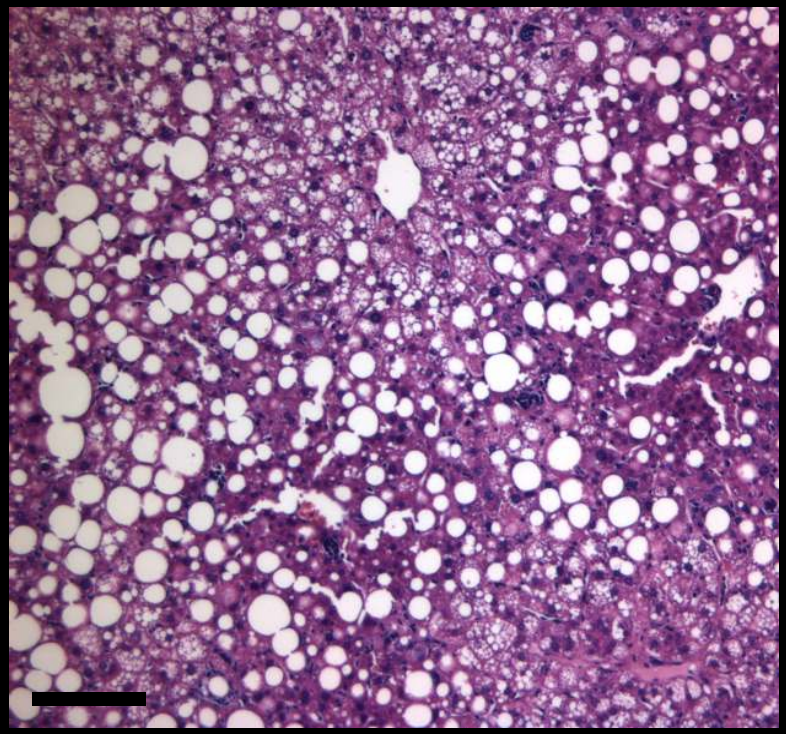
Visceral adipose tissue fails to expand in FGF1 KO mice on a HFD



Increased liver fat accumulation in FGF1 KO mice on a HFD

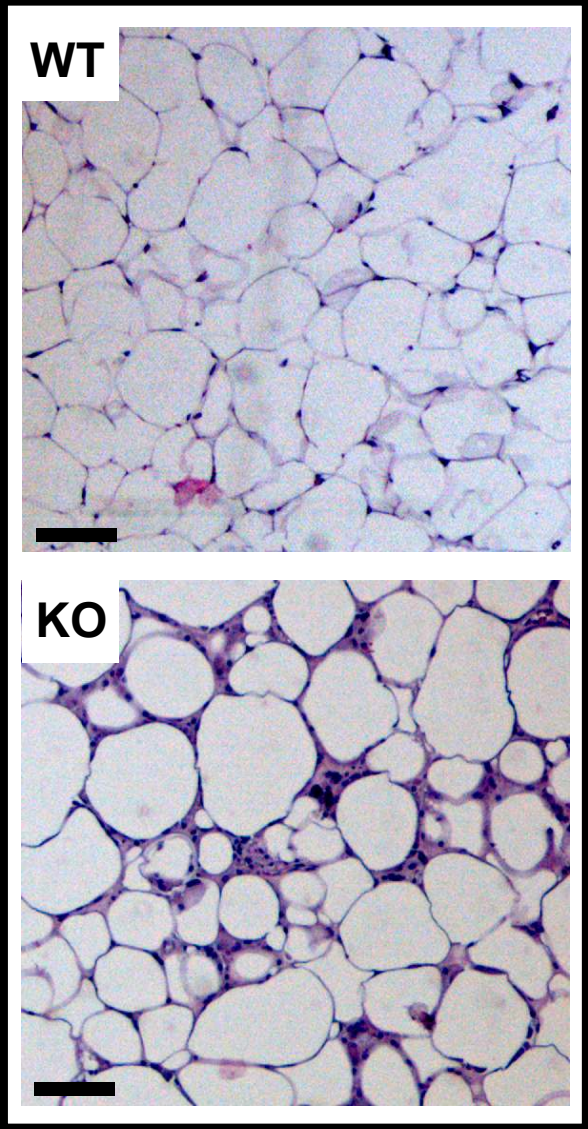


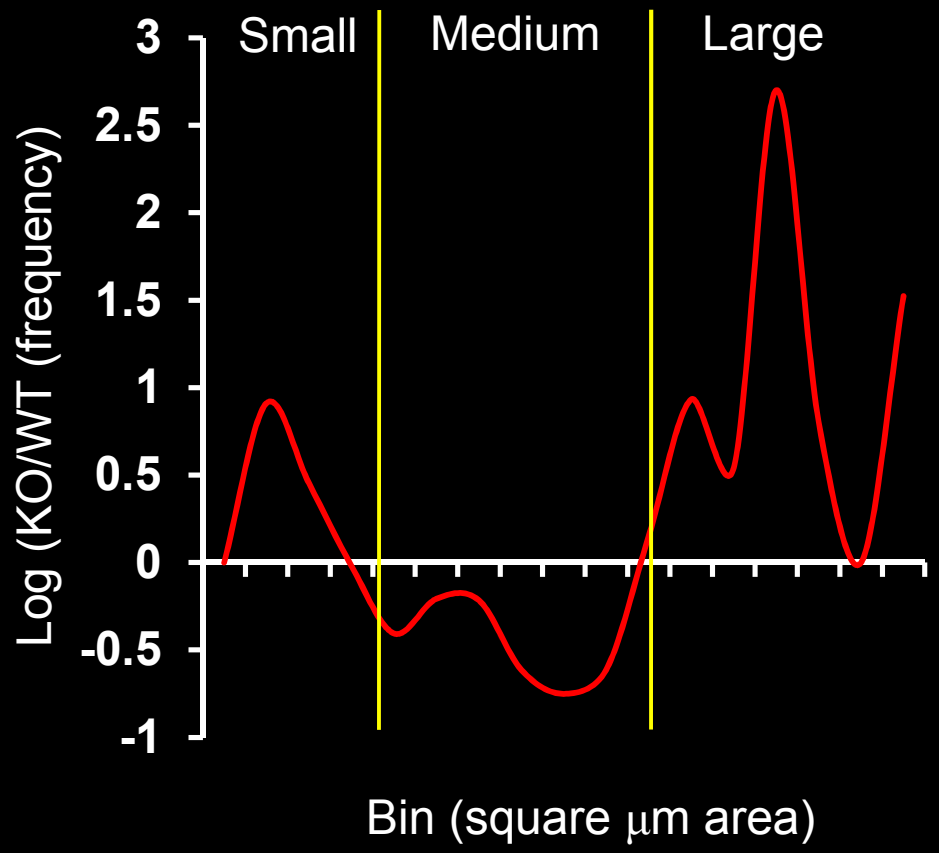
WT



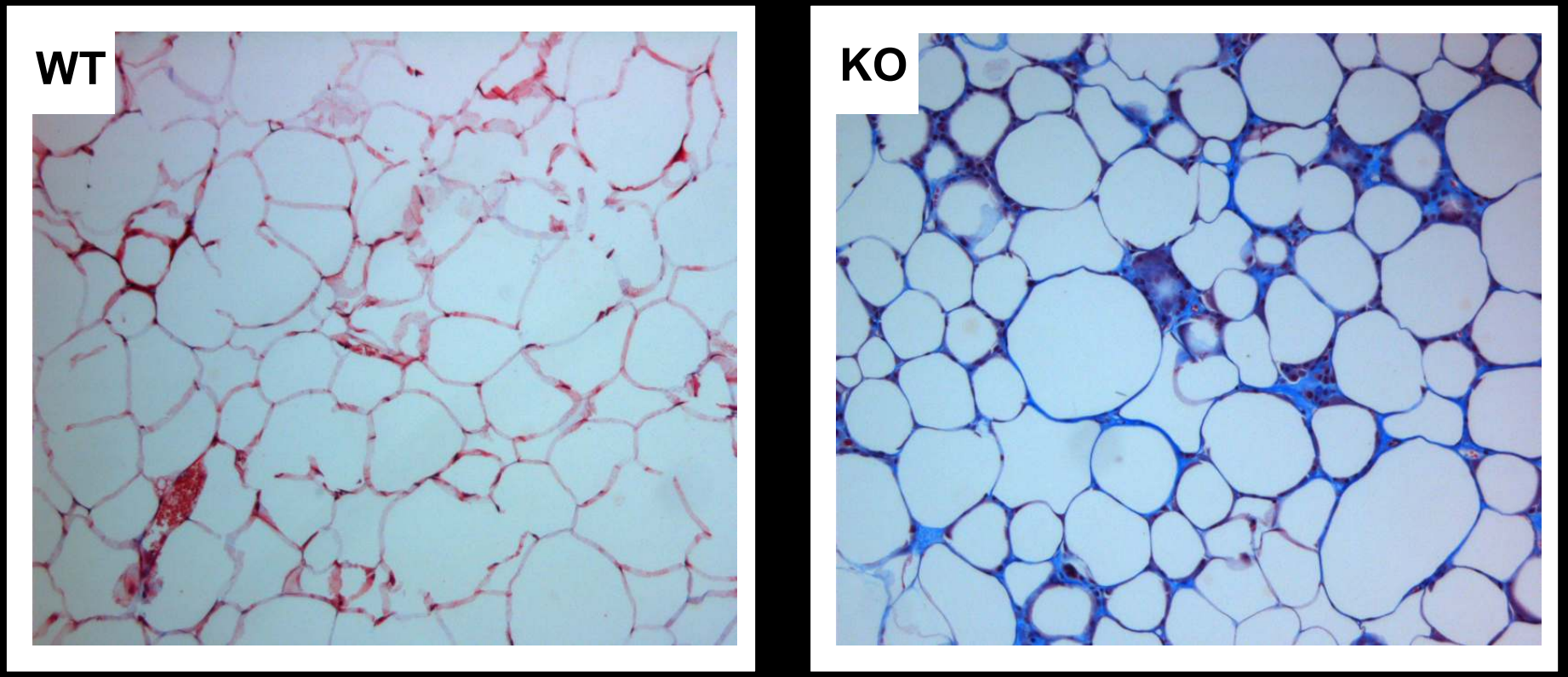
KO

Non-uniform size distribution in FGF1 KO visceral adipocytes



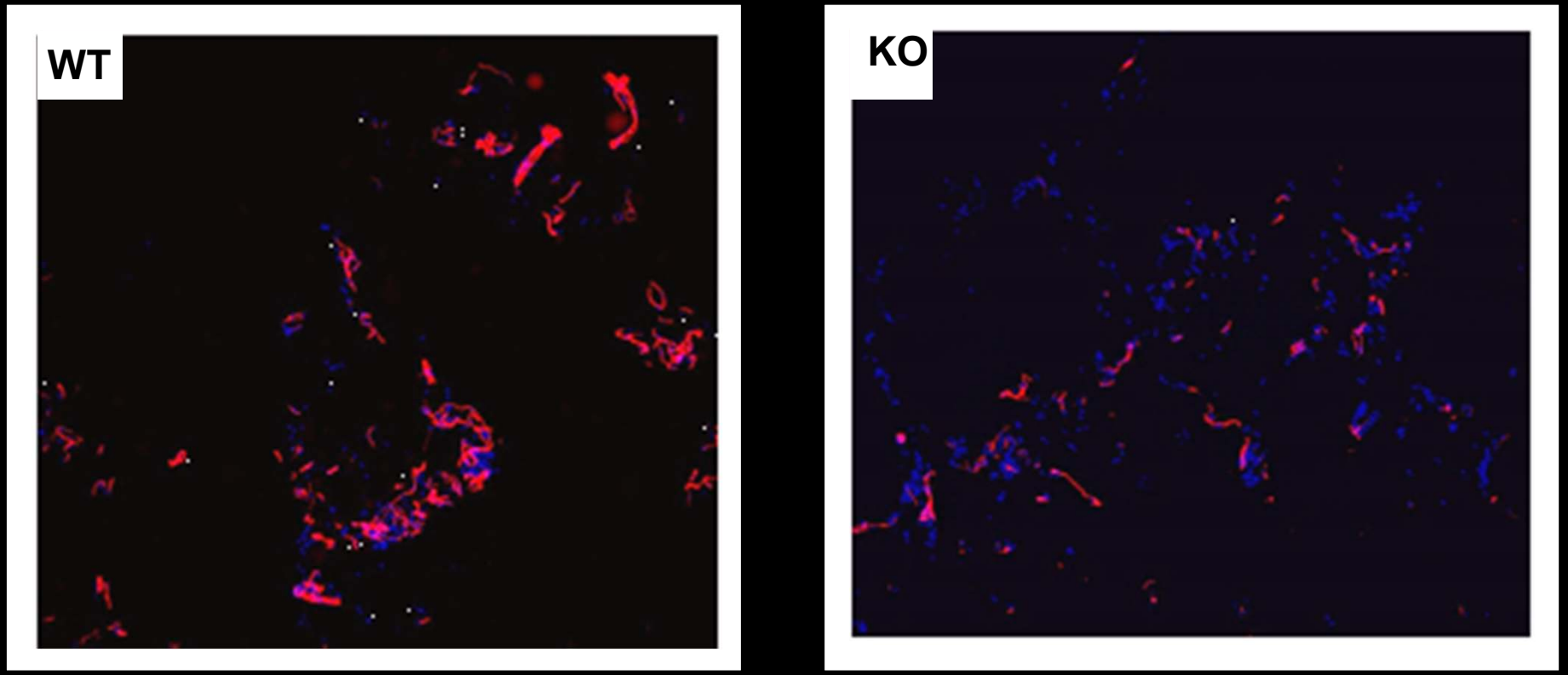


Increased fibrosis in visceral adipose tissue of FGF1 KO mice on a HFD



Masson's trichrome stain – collagen stains blue

Impaired vascularity in visceral adipose of FGF1 KO mice on a HFD



Heart perfusion of fluorescent spheres – vascular space in red, nuclei in blue

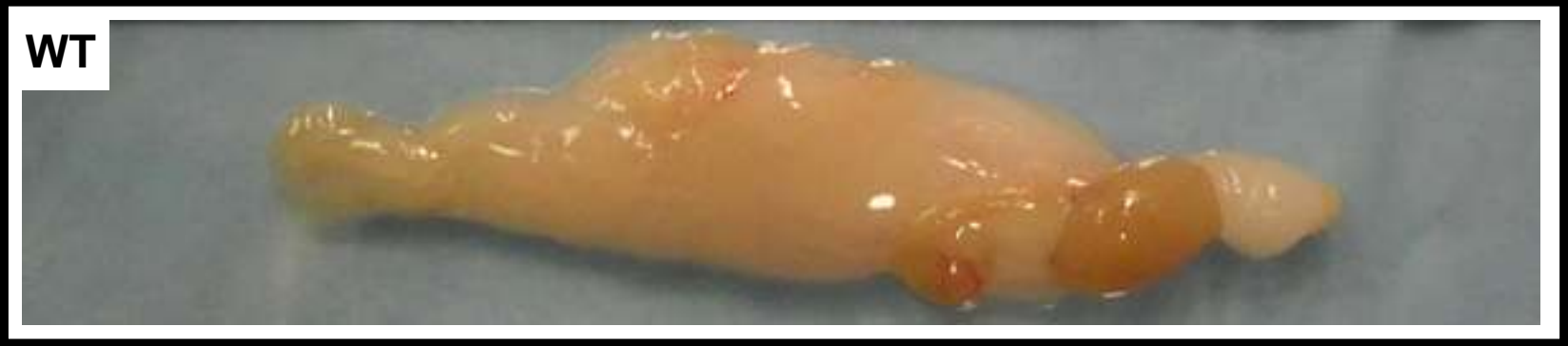
Visceral adipose tissue can't properly expand in response to HFD in FGF1 KO mice……. But, can it contract?

Modern-day yoyo diet

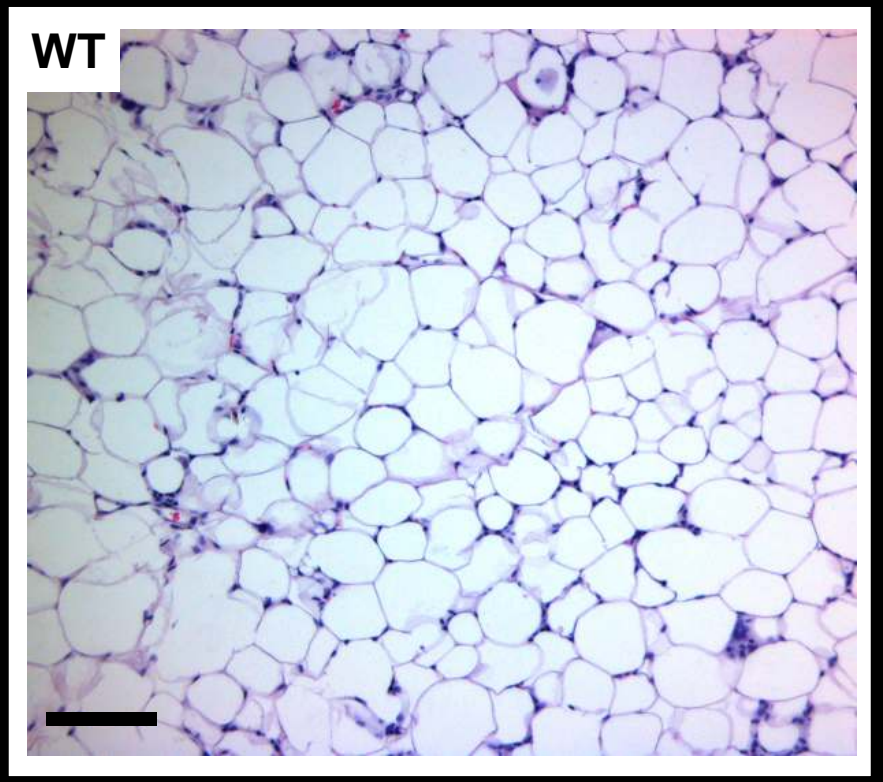
36 weeks high fat diet

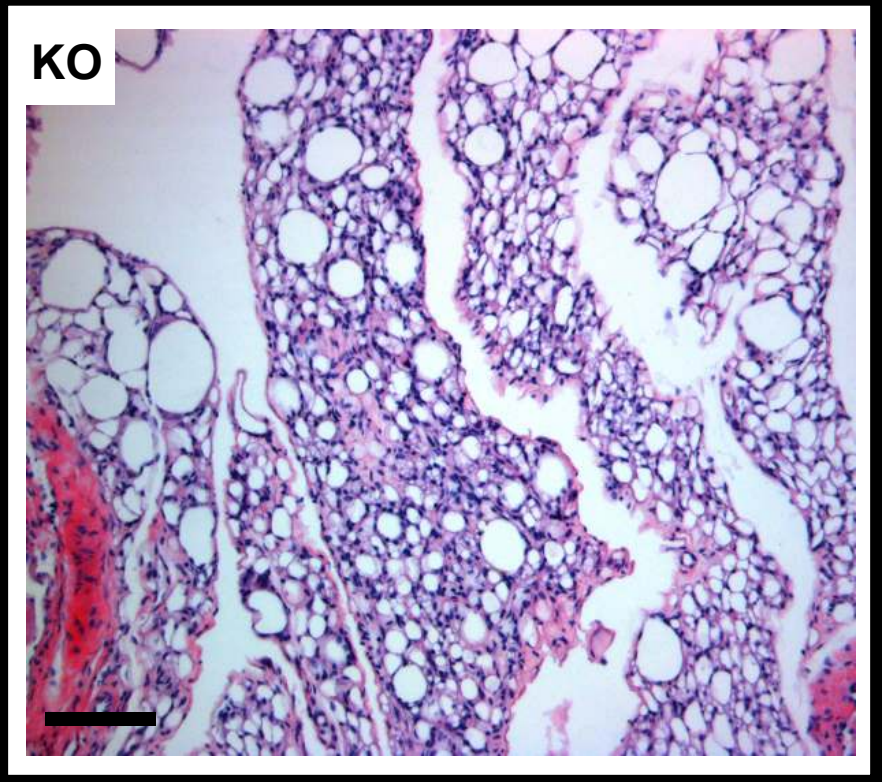
6 weeks chow diet

Further impairment of FGF KO visceral adipose tissue upon HFD withdrawal

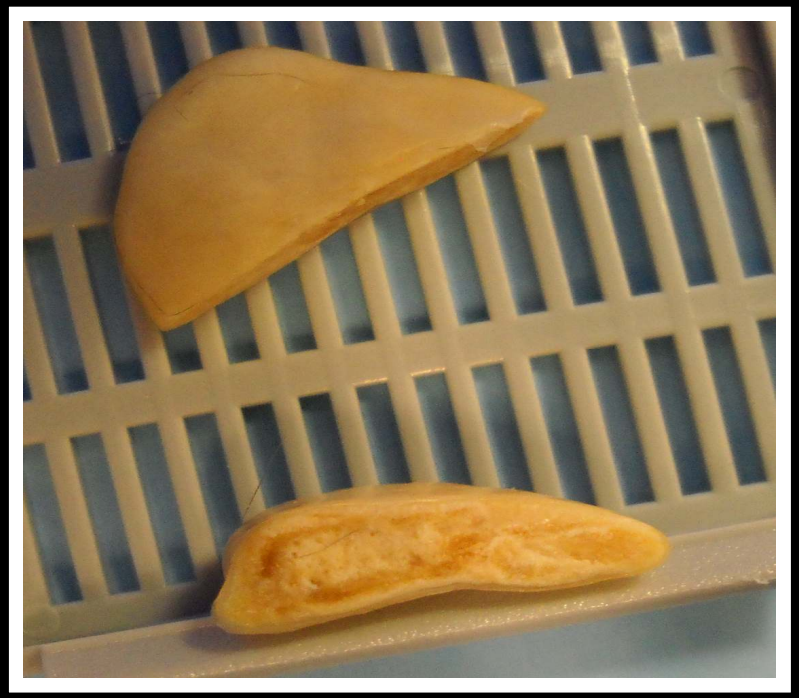


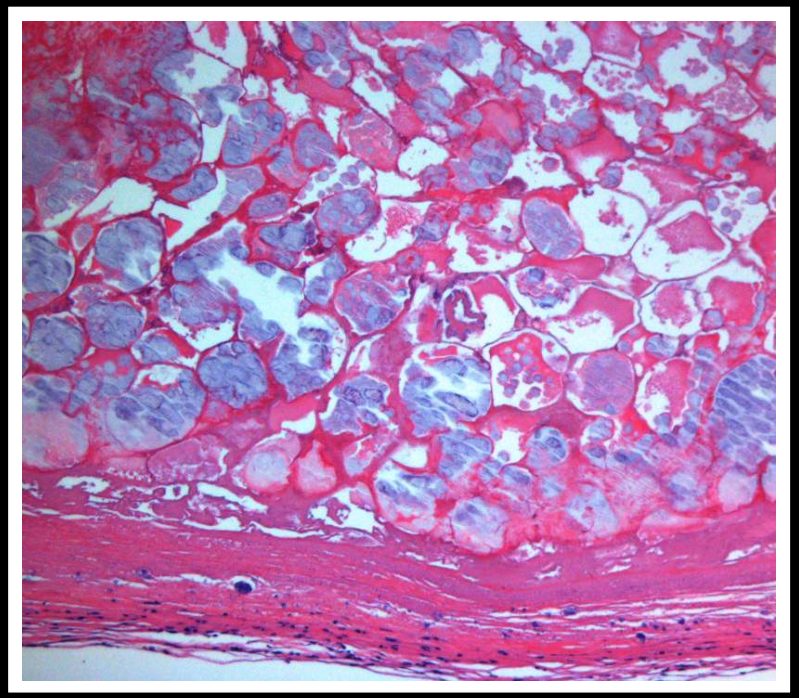
Failure of FGF1 KO visceral WAT to properly contract upon HFD withdrawal

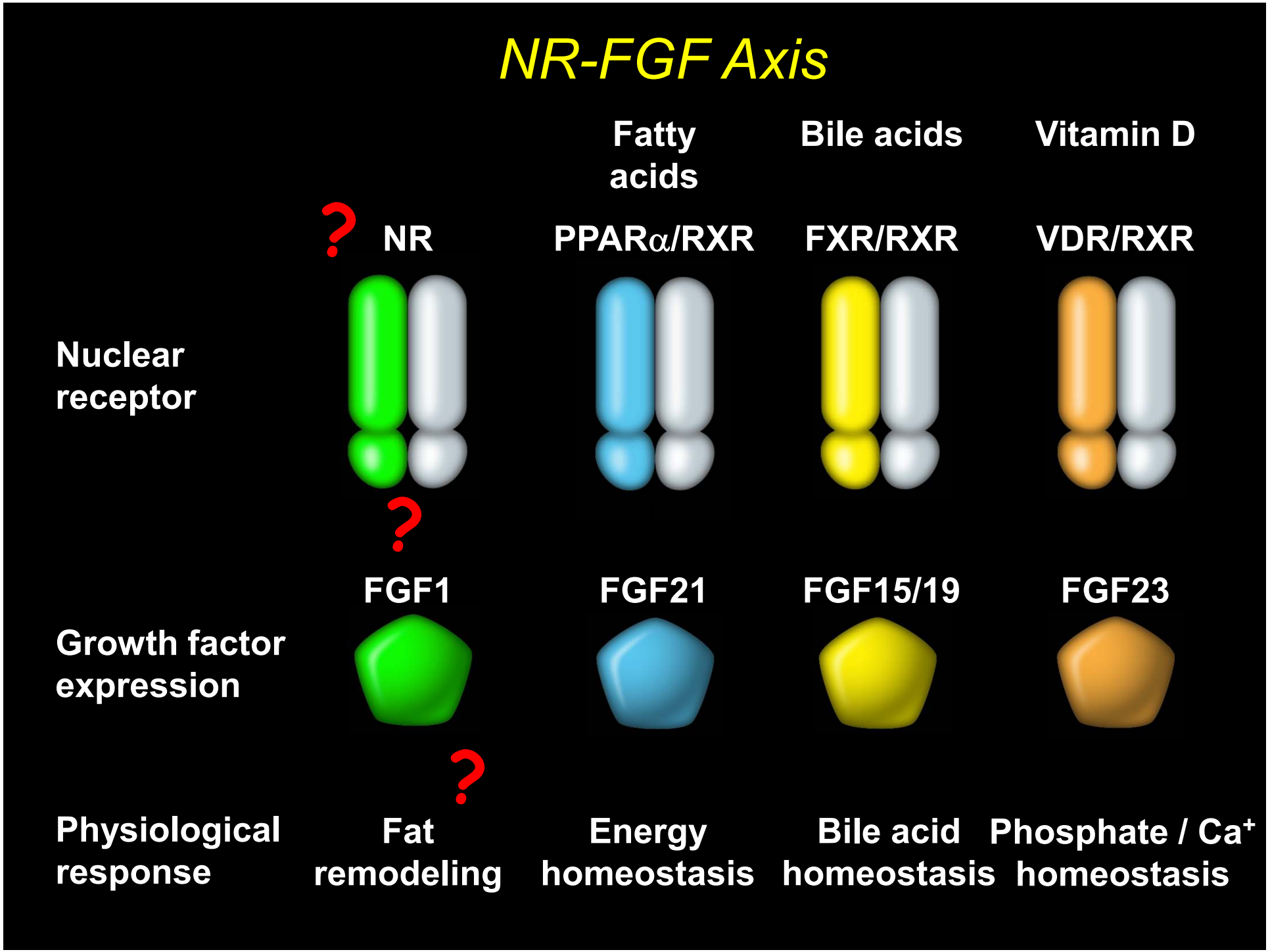




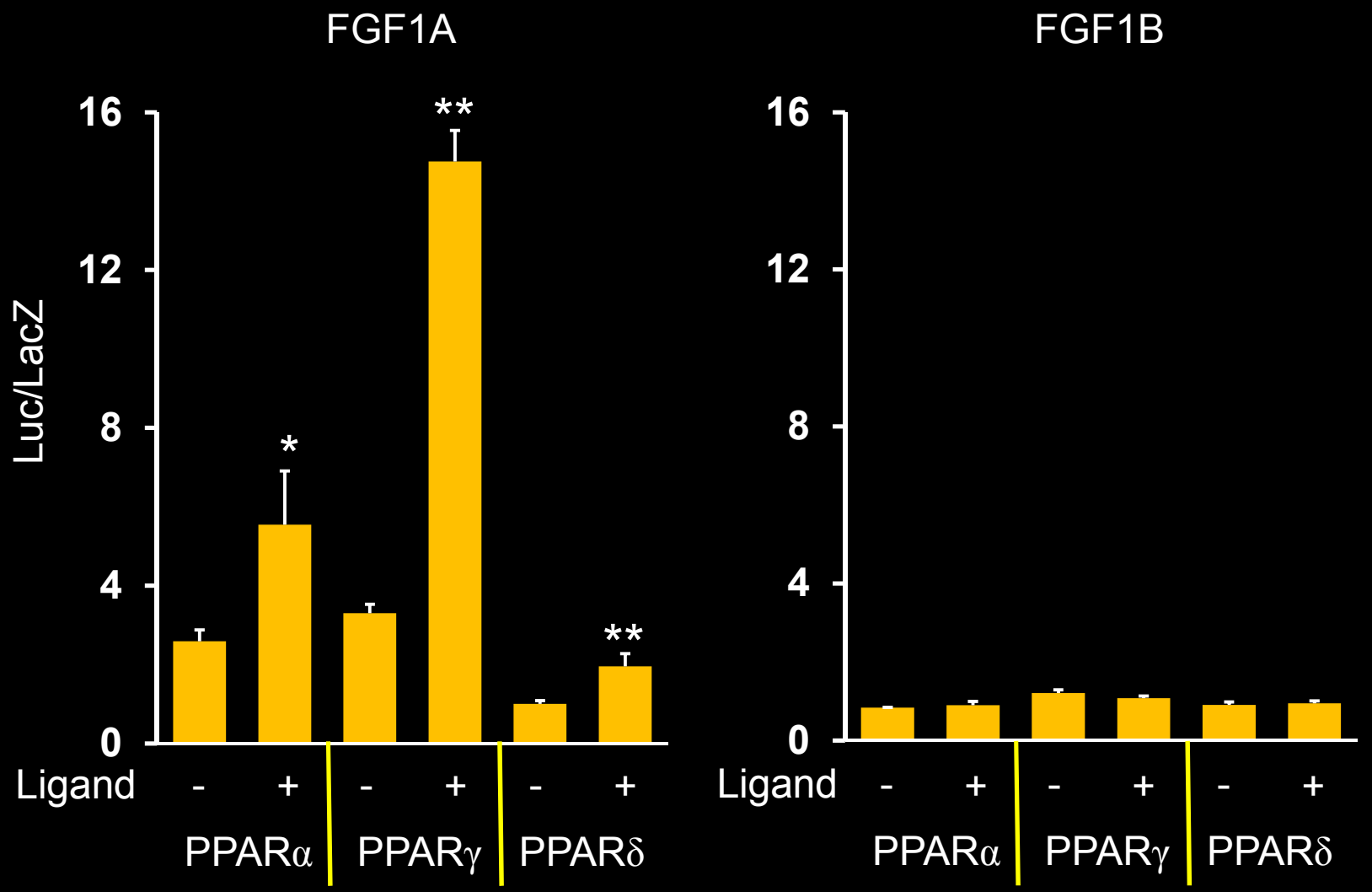
Fat necrosis in FGF1 KO mice after removal of HFD



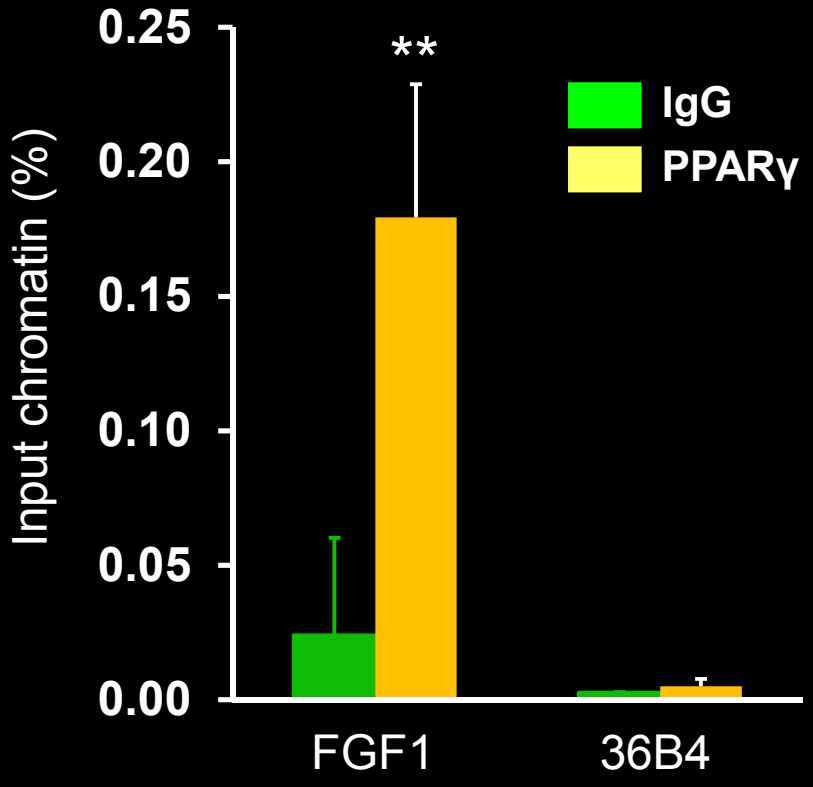


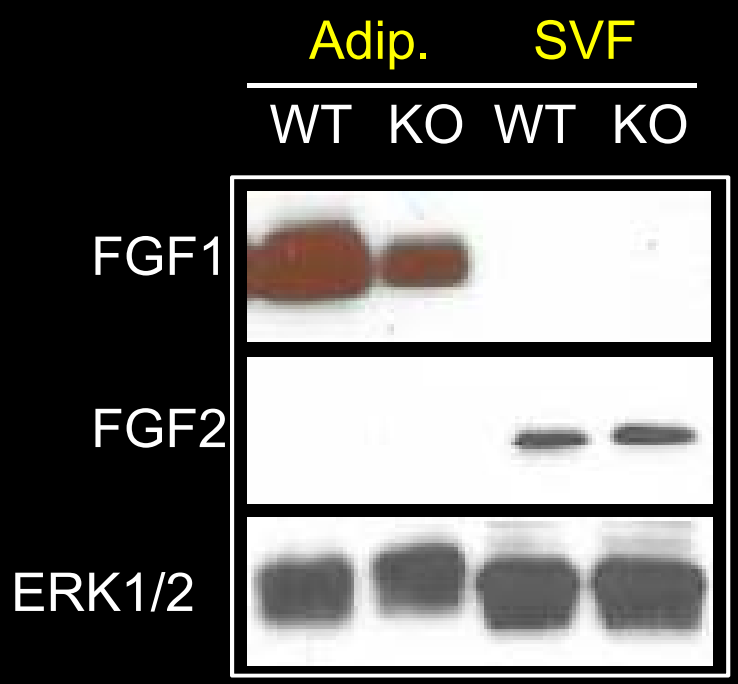

NR-FGF Axis
Fatty acids
Bile acids
Vitamin D
?
NR
PPARα/RXR
FXR/RXR
VDR/RXR
Nuclear receptor
?
FGF1
FGF21
FGF15/19
FGF23
Growth factor expression
?
Physiological response
Fat remodeling
Energy homeostasis
Bile acid homeostasis
Phosphate / Ca+ homeostasis

Regulation of FGF1 by PPARγ and TZDs



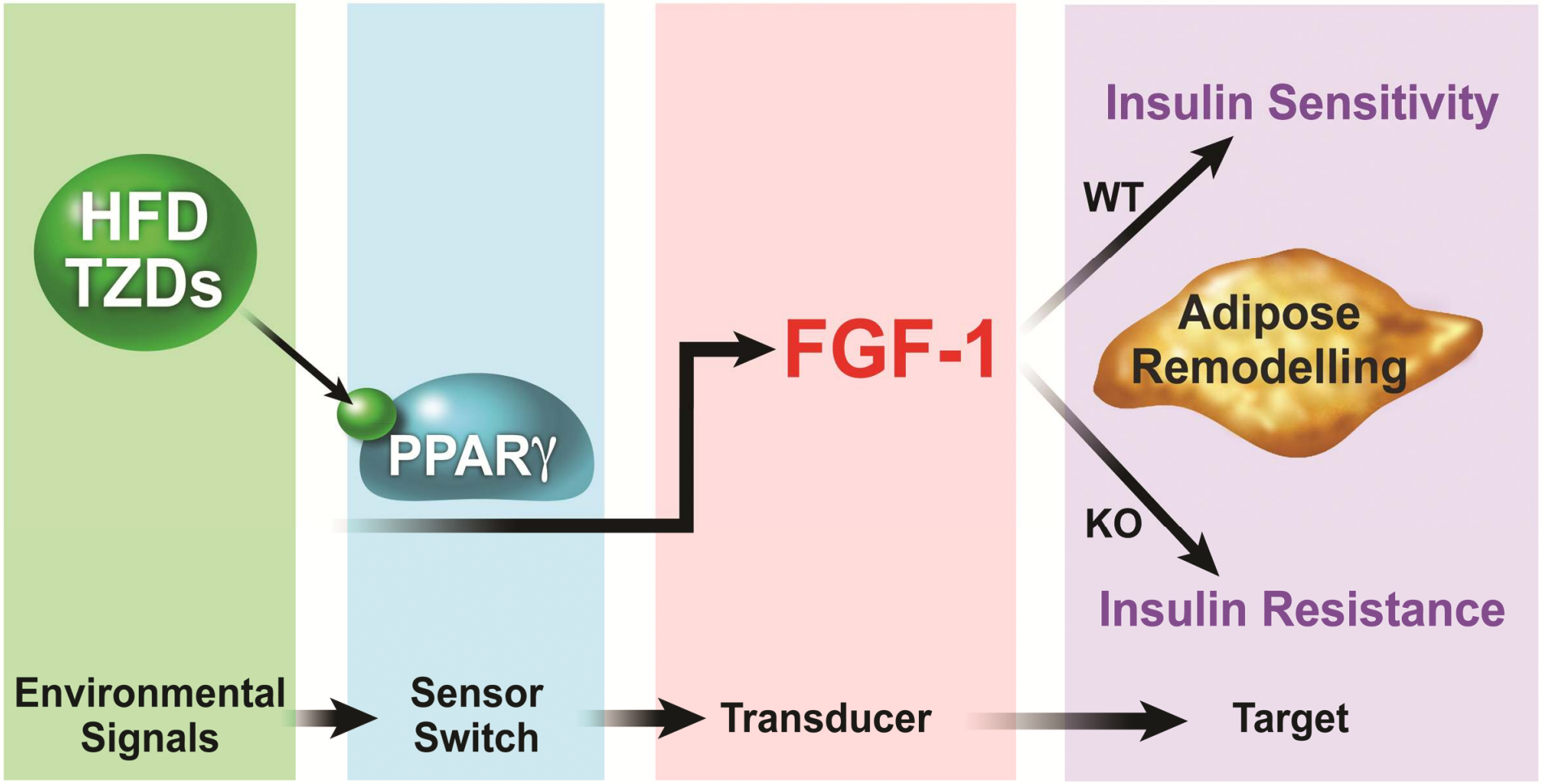
PPARγ binds to the FGF1 promoter





FGF1 levels reduced in PPARγ adipose KO mice

A new NR-FGF axis



Acknowledgements

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Pingping Li

HHMI
HOWARD HUGHES
MEDICAL INSTITUTE

THE LEONA M. AND HARRY B.
HELMSLEY
CHARITABLE TRUST

60 years 1950 2010
NIDDK
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

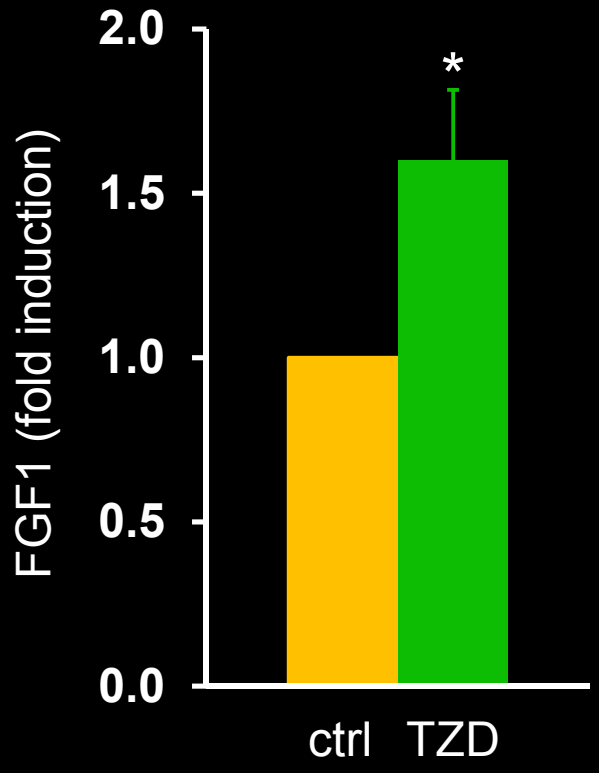
Future directions

- Some major questions …

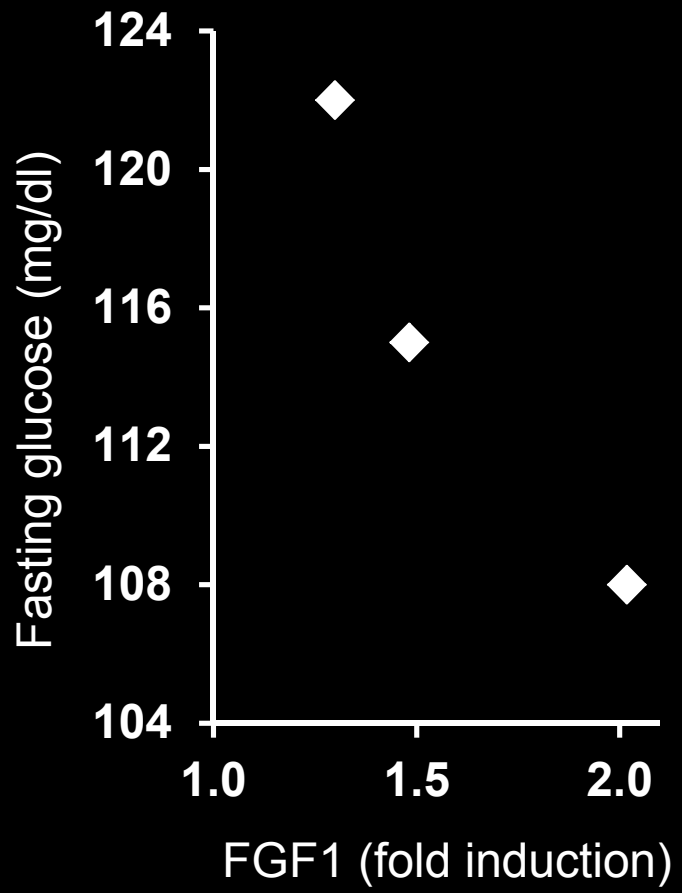
- Why is only visceral fat affected by loss of FGF1?
- Are adipocytes solely responsible for the whole body KO phenotype?
- What are the target cells of FGF1 action?
- Is there any therapeutic relevance for FGF1 in treating metabolic disease?

FGF1 link to insulin sensitization - Is there a human connection?

Induction of FGF1 by TZD



Fasting blood glucose



FGF1 gain-of-function studies
- exploring therapeutic possibilities

Experimental approaches

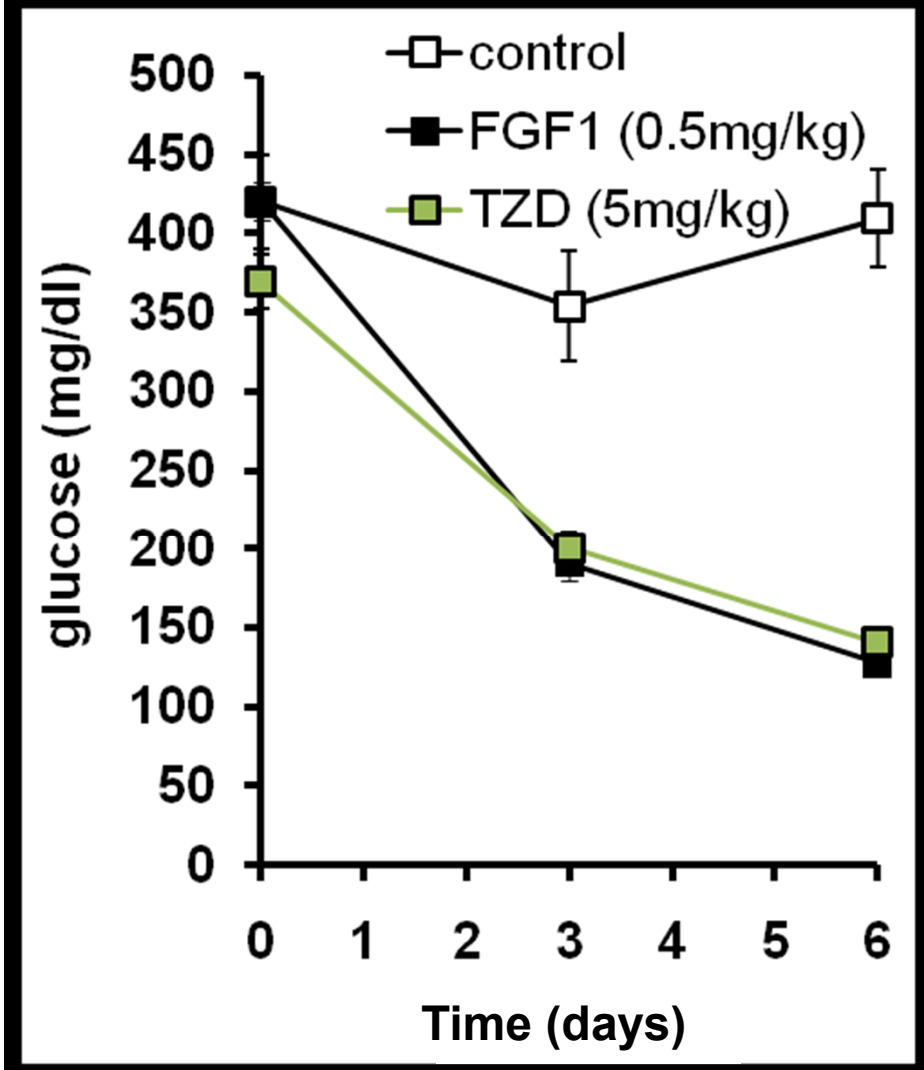
- Pharmacological

  - Parental delivery of recombinant FGF1 protein into animal models of obesity/diabetes.

- Genetic

  - Tissue-specific transgenic overexpression of FGF1
  - Viral overexpression of FGF1

FGF1 : therapeutic possiblities ?



Recombinant FGF1 has potent glucose lowering effects in diabetic ob/ob mice

TZD

Actos
Avandia

$ 4 bn

PPARγ (master regulator)

>100 target genes

FGF1

?

Anti-diabetic
Insulin sensitization

Cardiovascular toxicity
Weight gain
Edema
Liver toxicity
Bone loss

?

The adipocyte life cycle

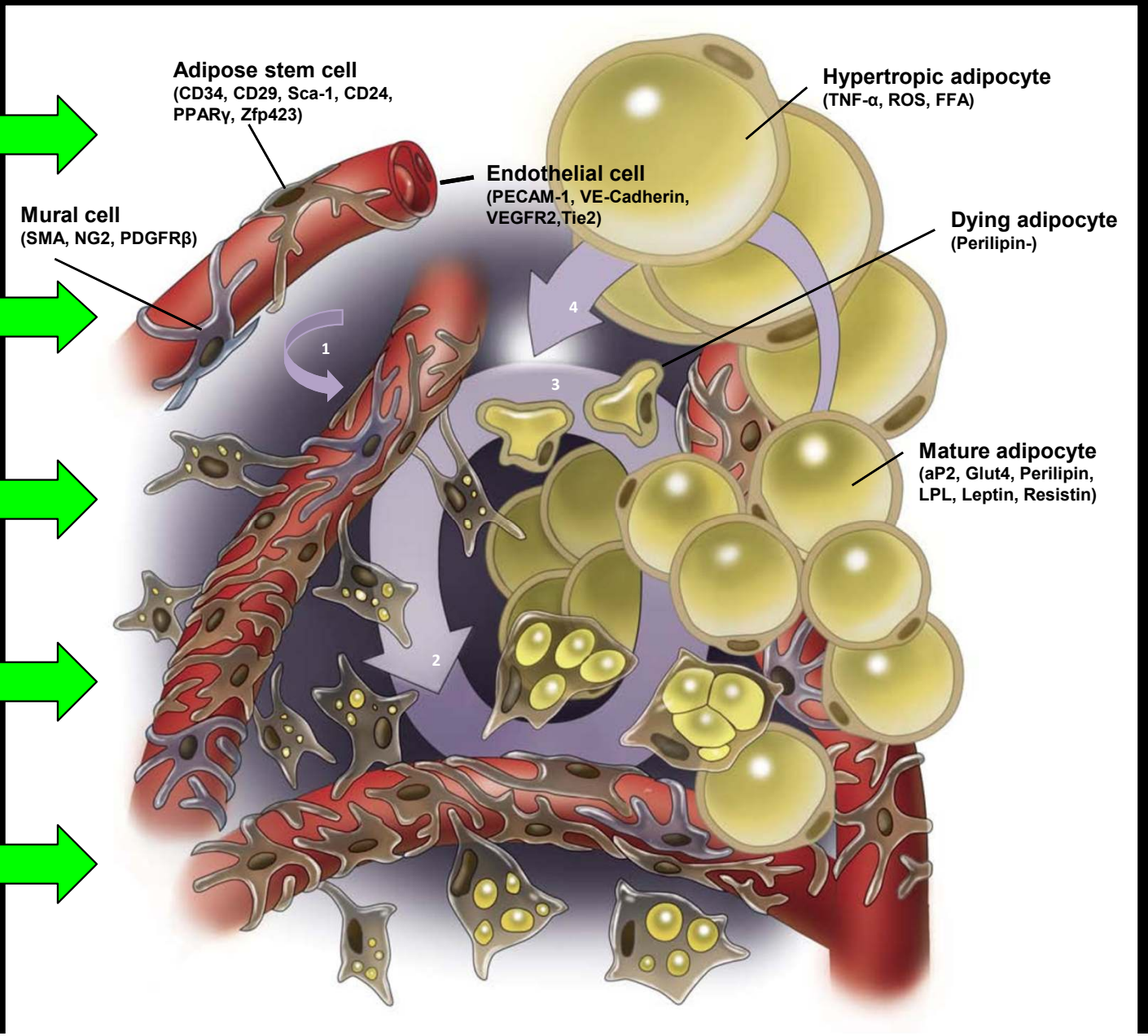
DEVELOPMENT

DIET & NUTRITION

DRUGS

AGING

DISEASE

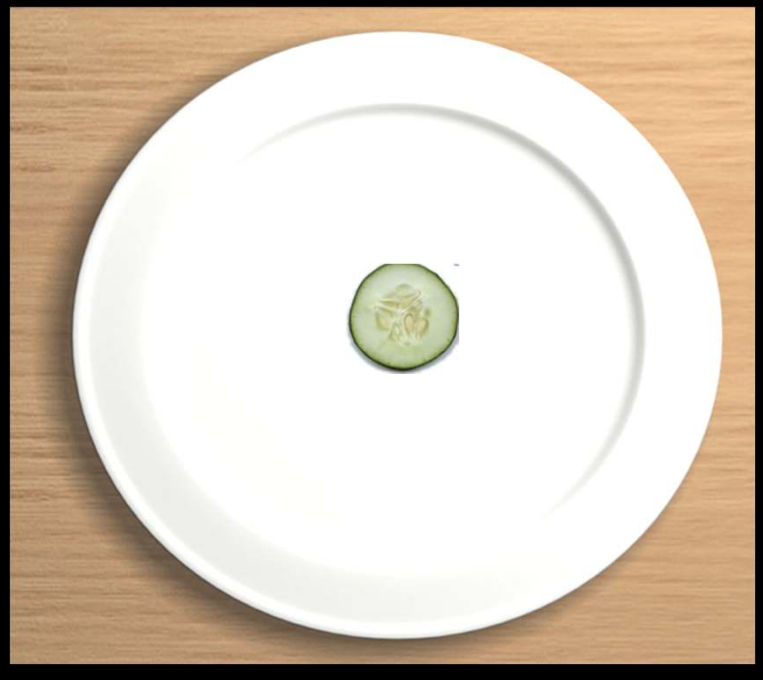


Biology of adipose tissues

Feast and Famine

-Feast/famine cycles have occurred throughout time

-The ability to withstand periods of limited/excess nutrient availability is a critical aspect of survival



Why would alleles predisposing to obesity exist in natural populations?

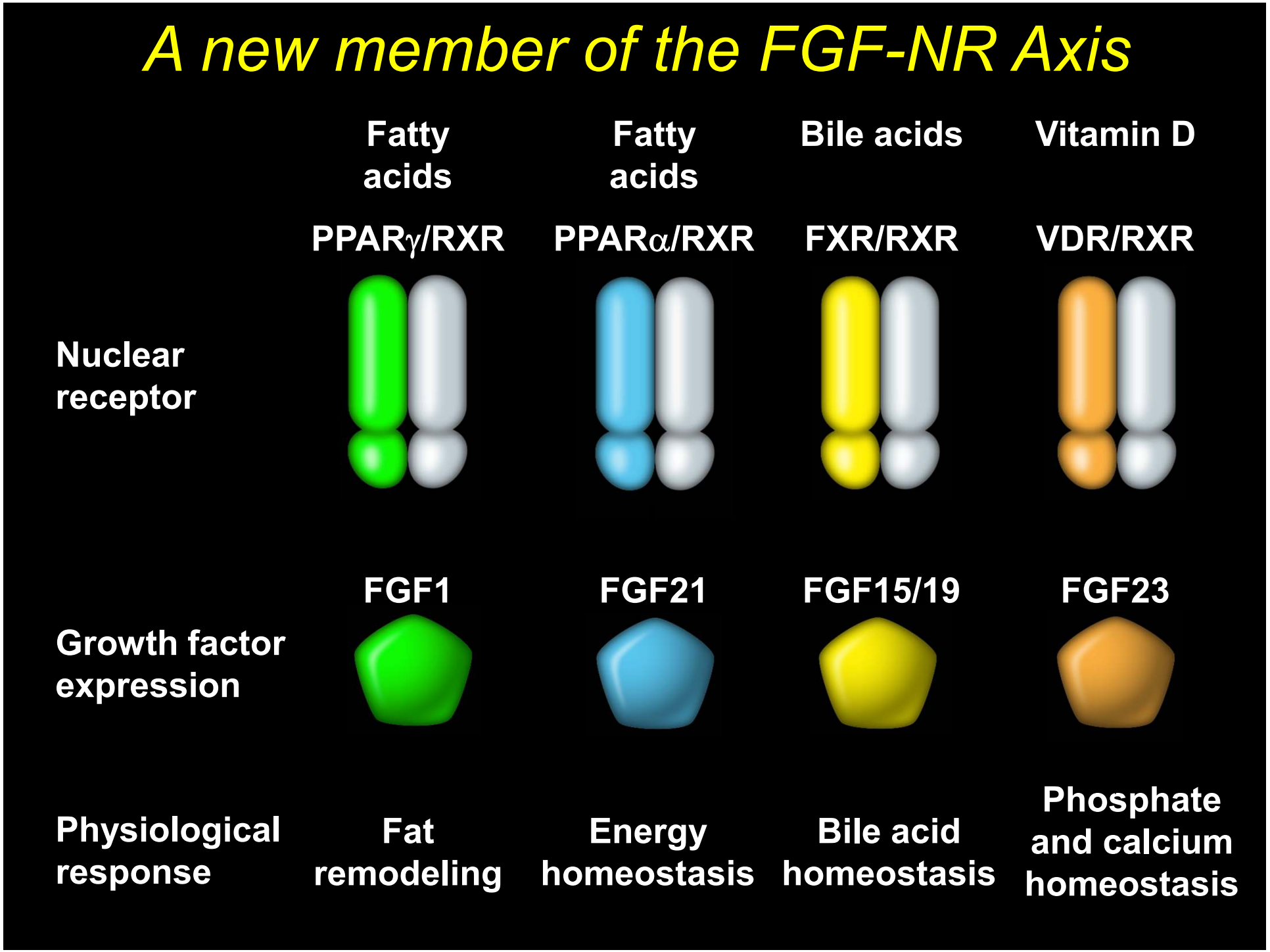
"Thrifty allele hypothesis"

James V. Neel, M.D.,Ph.D.

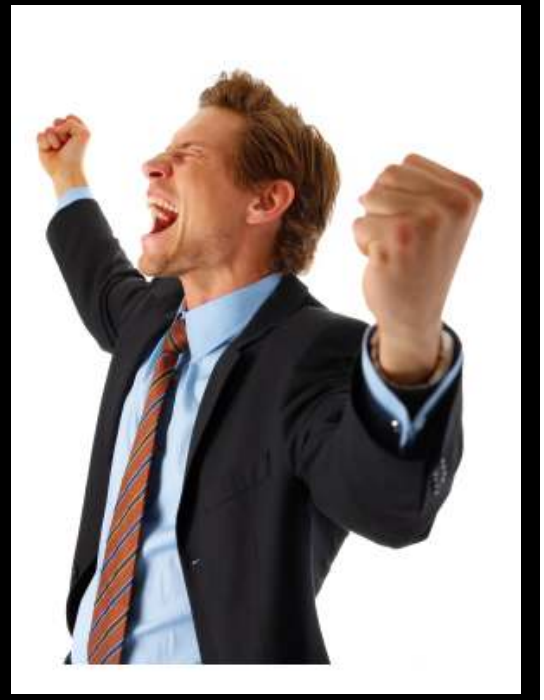
(1960s)

"Genes associated with common modern diseases like diabetes, hypertension and obesity are part of the human gene pool, because they helped our early ancestors survive when calories and salt were less abundant."

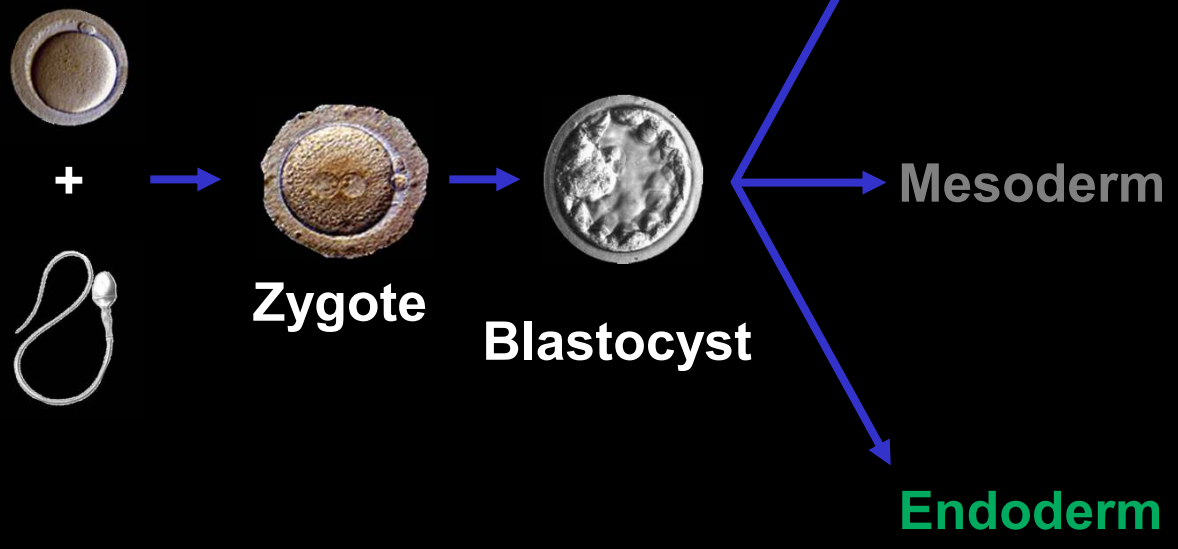
A new member of the FGF-NR Axis

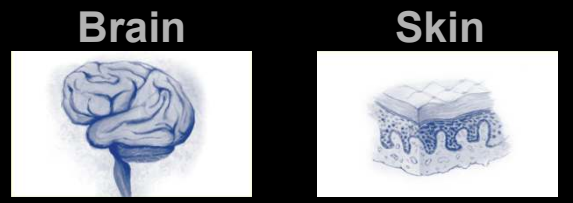


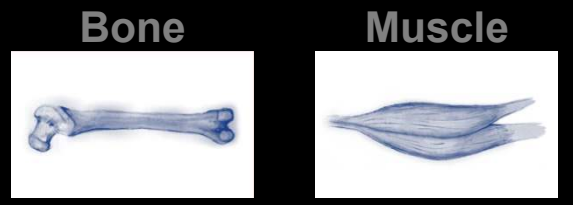
FGF1 is NOT boring!

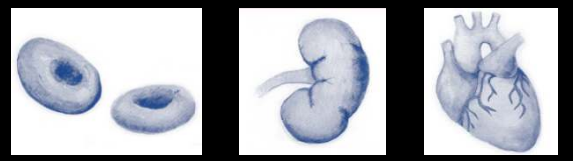


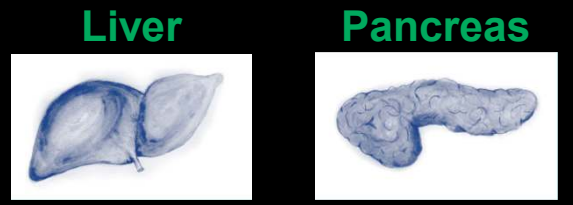
Development: Lineage Restriction











Topological distribution of adipose organs – developmentally regulated