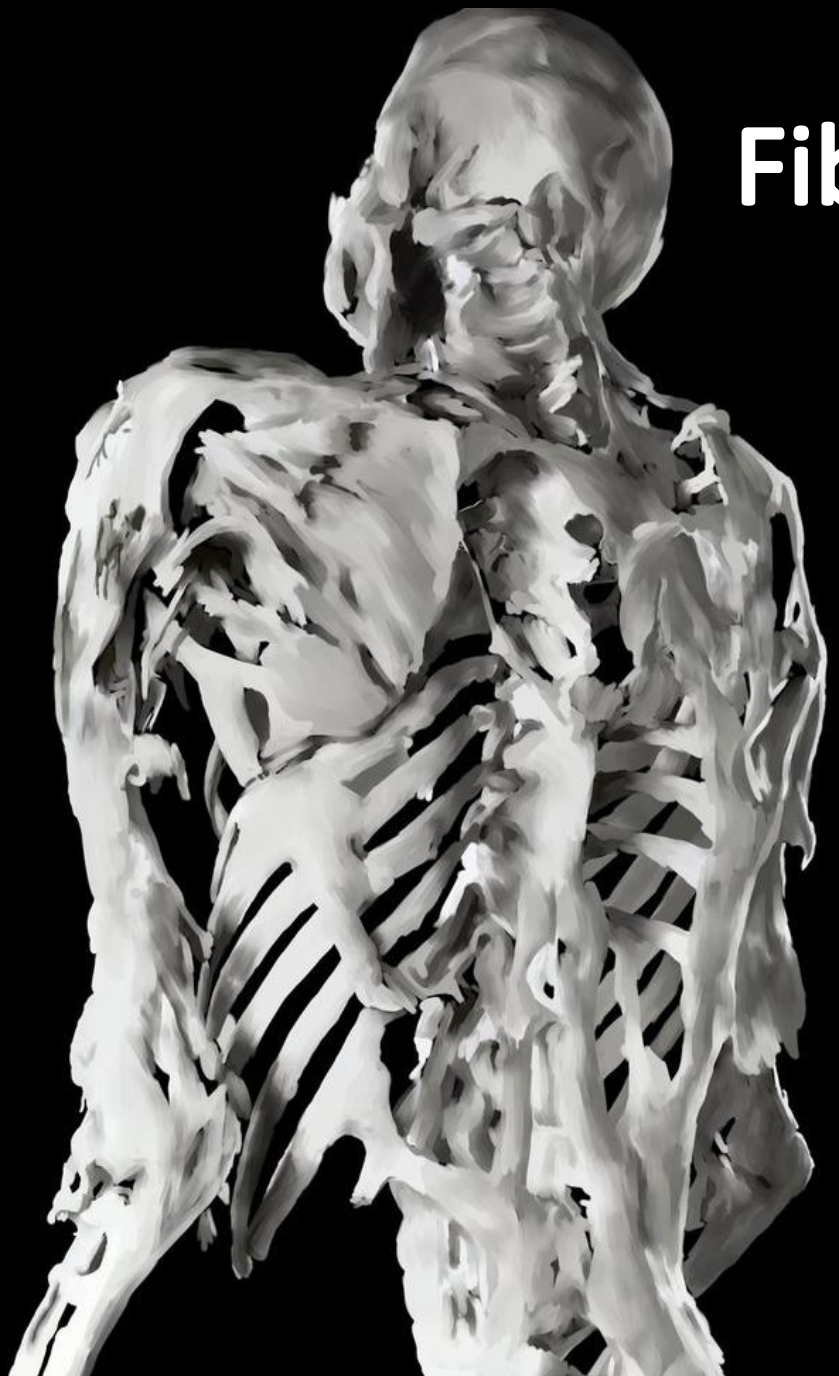
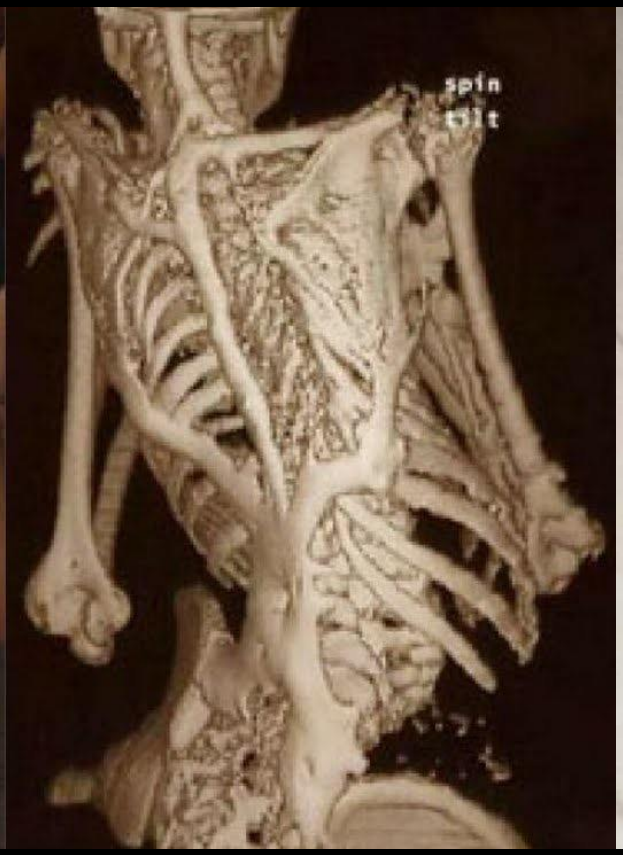
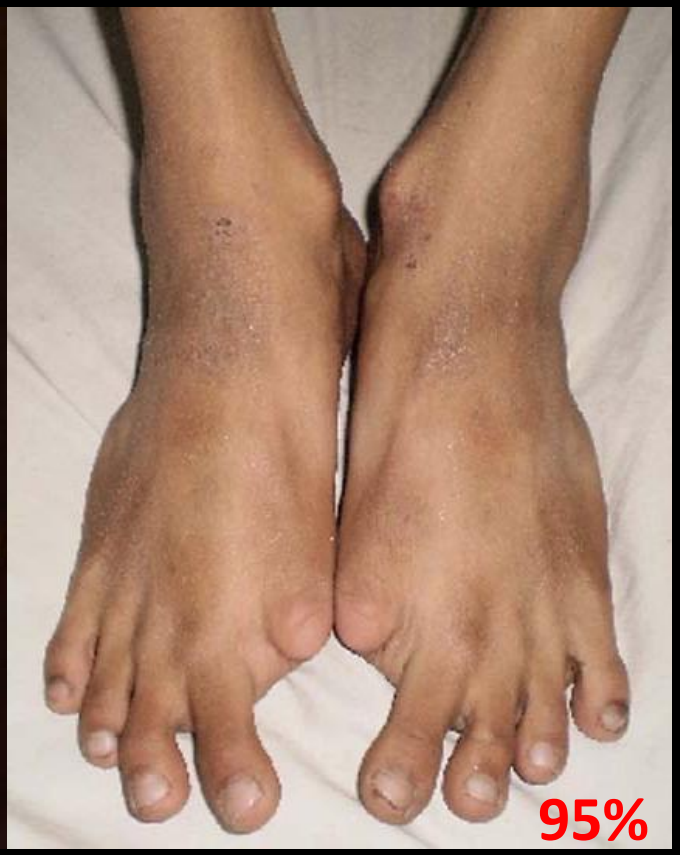


Fibrodysplasia Ossificans Progressivia (FOP) & ACVR1

By: Cassie Heilingoetter

What is FOP?

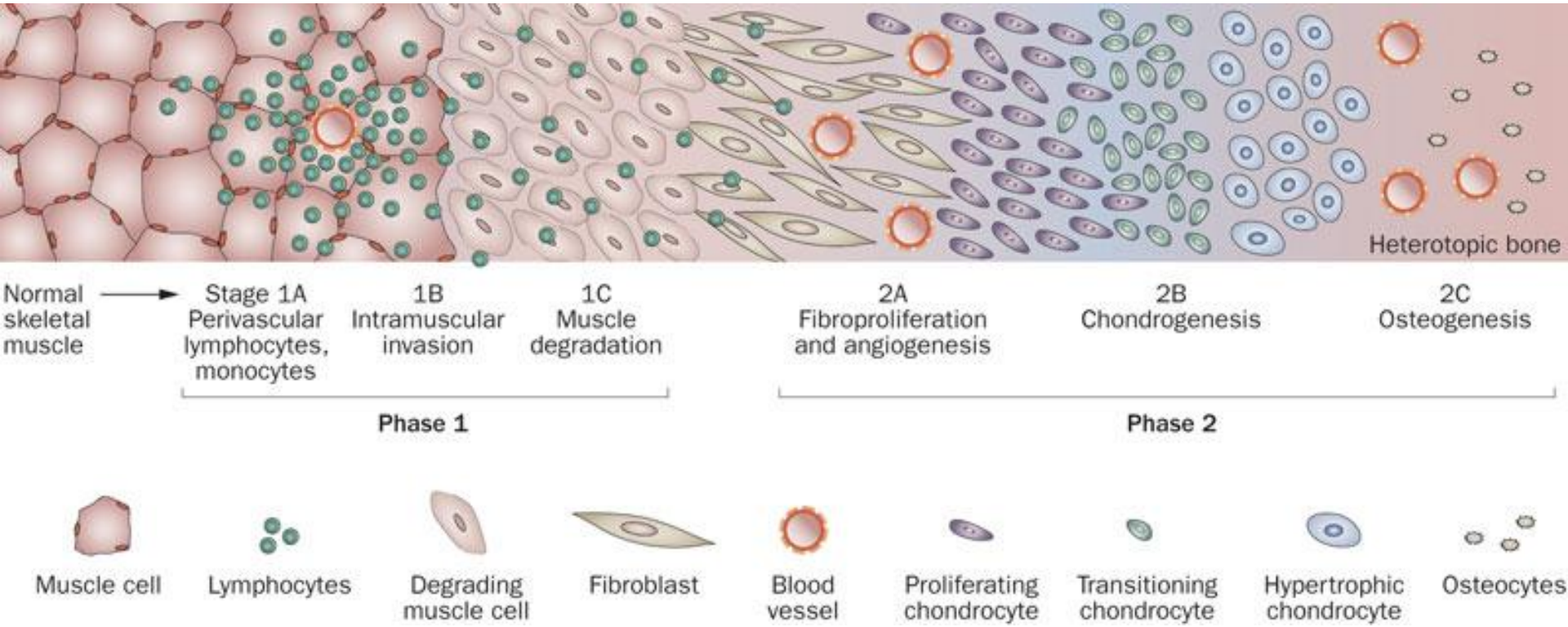




Abnormal bone growth

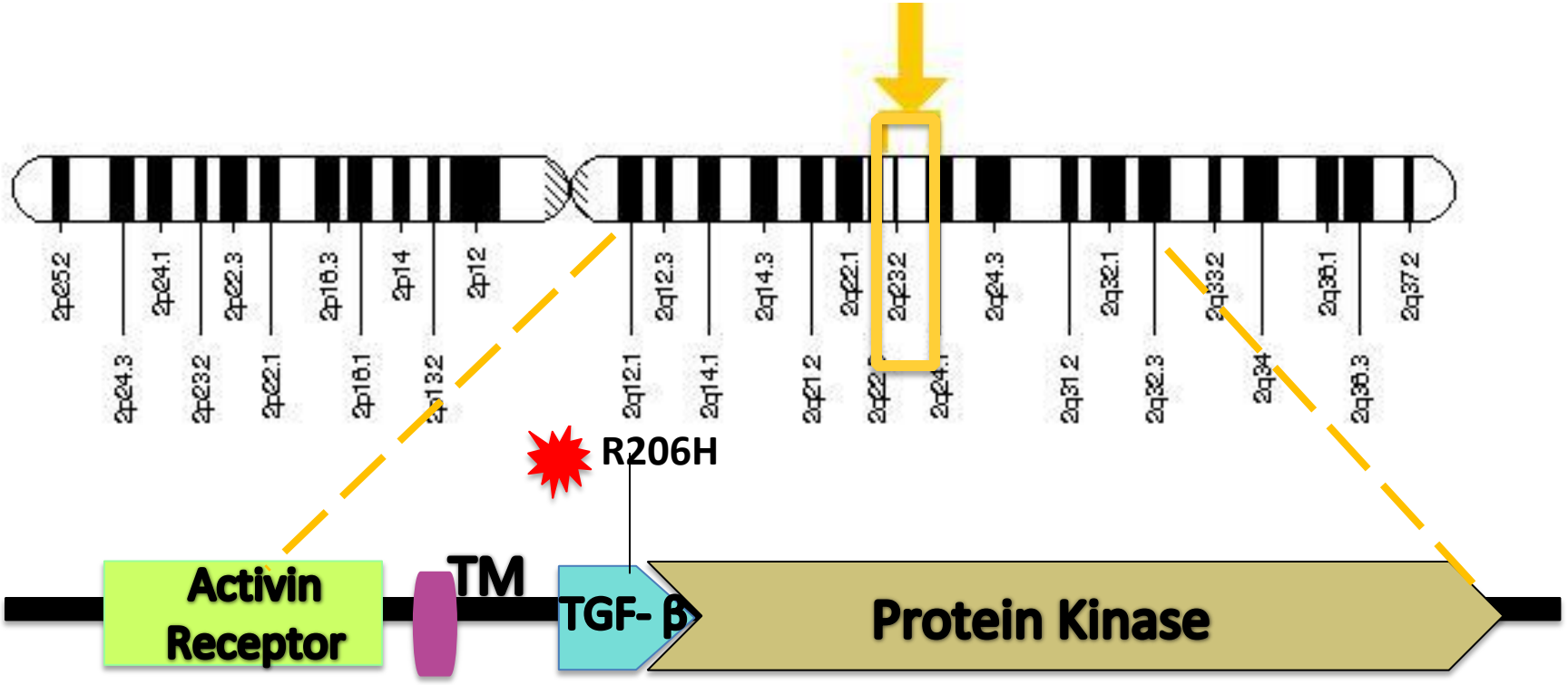
Malformations in first metatarsal

Muscle cells turn into bone cells in FOP patients

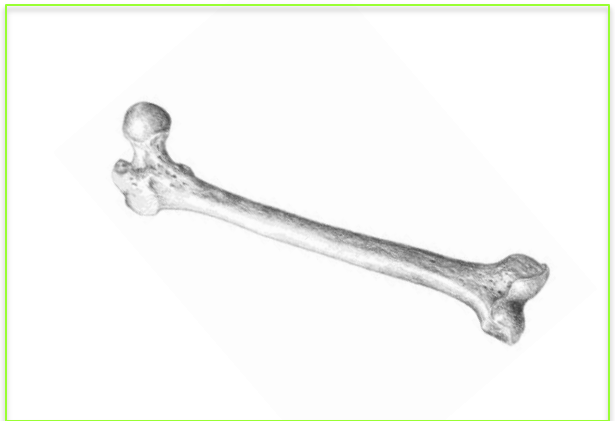


Muscle ????? **Bone**

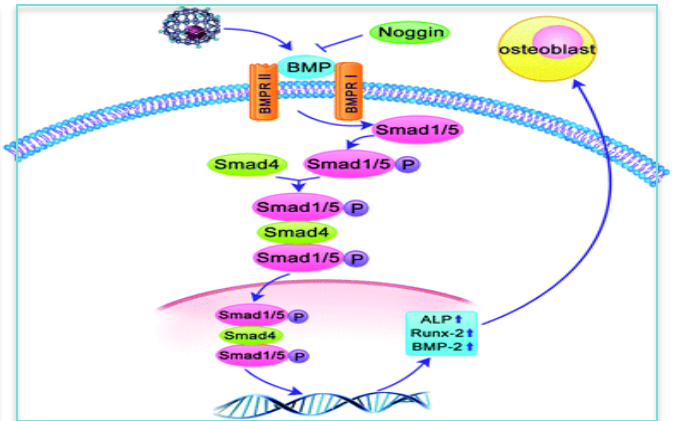
ACVR1 is mutated in FOP



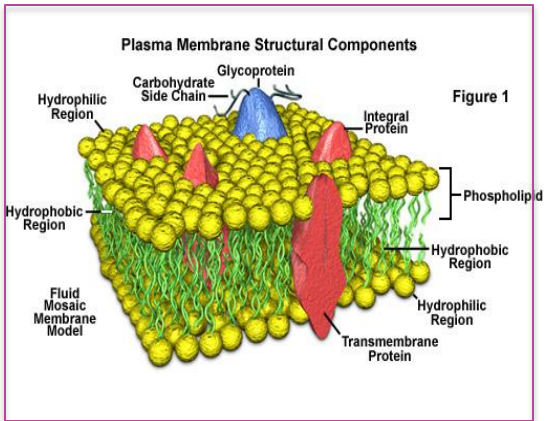
Biological Process



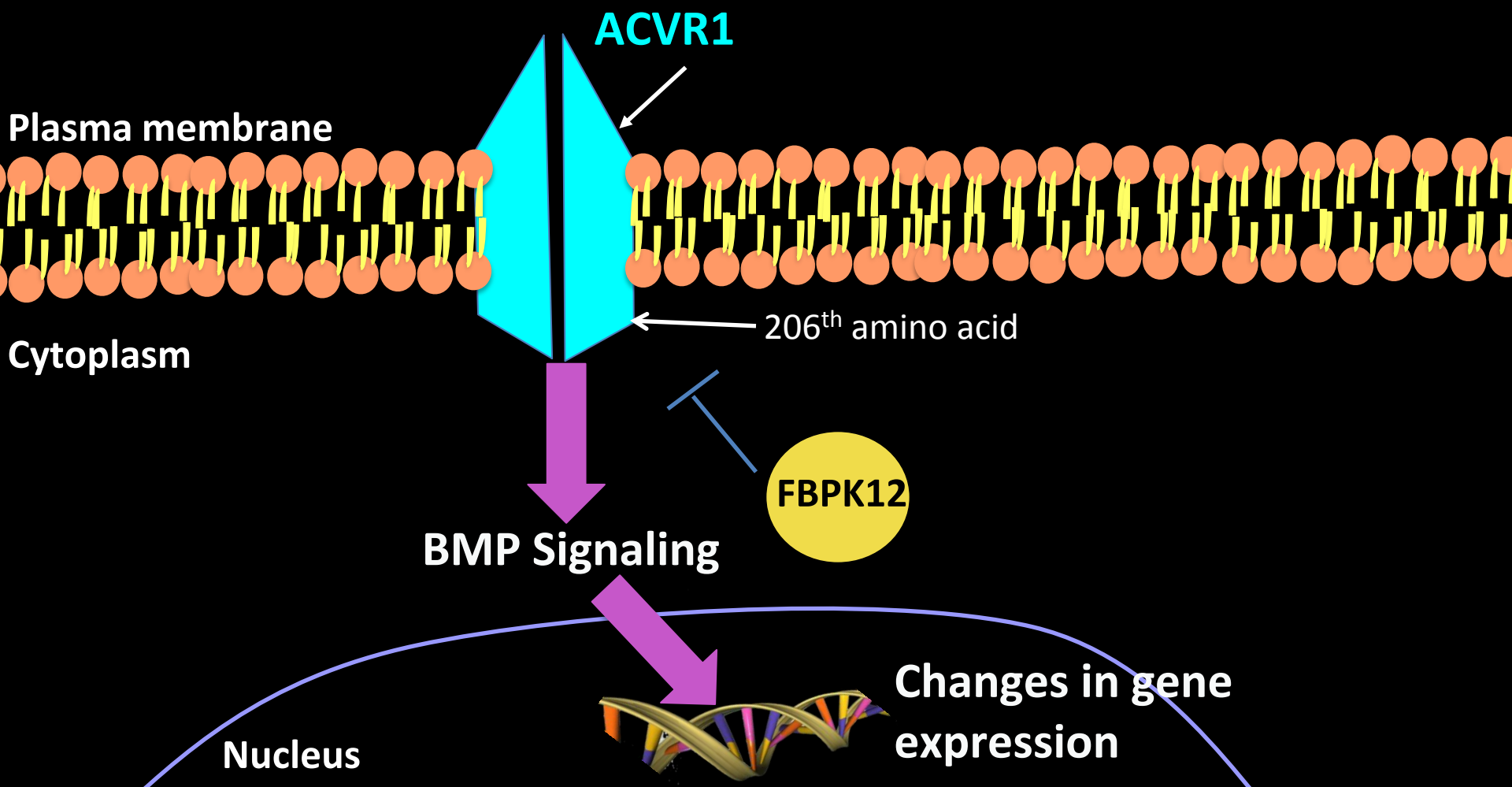
Molecular Function



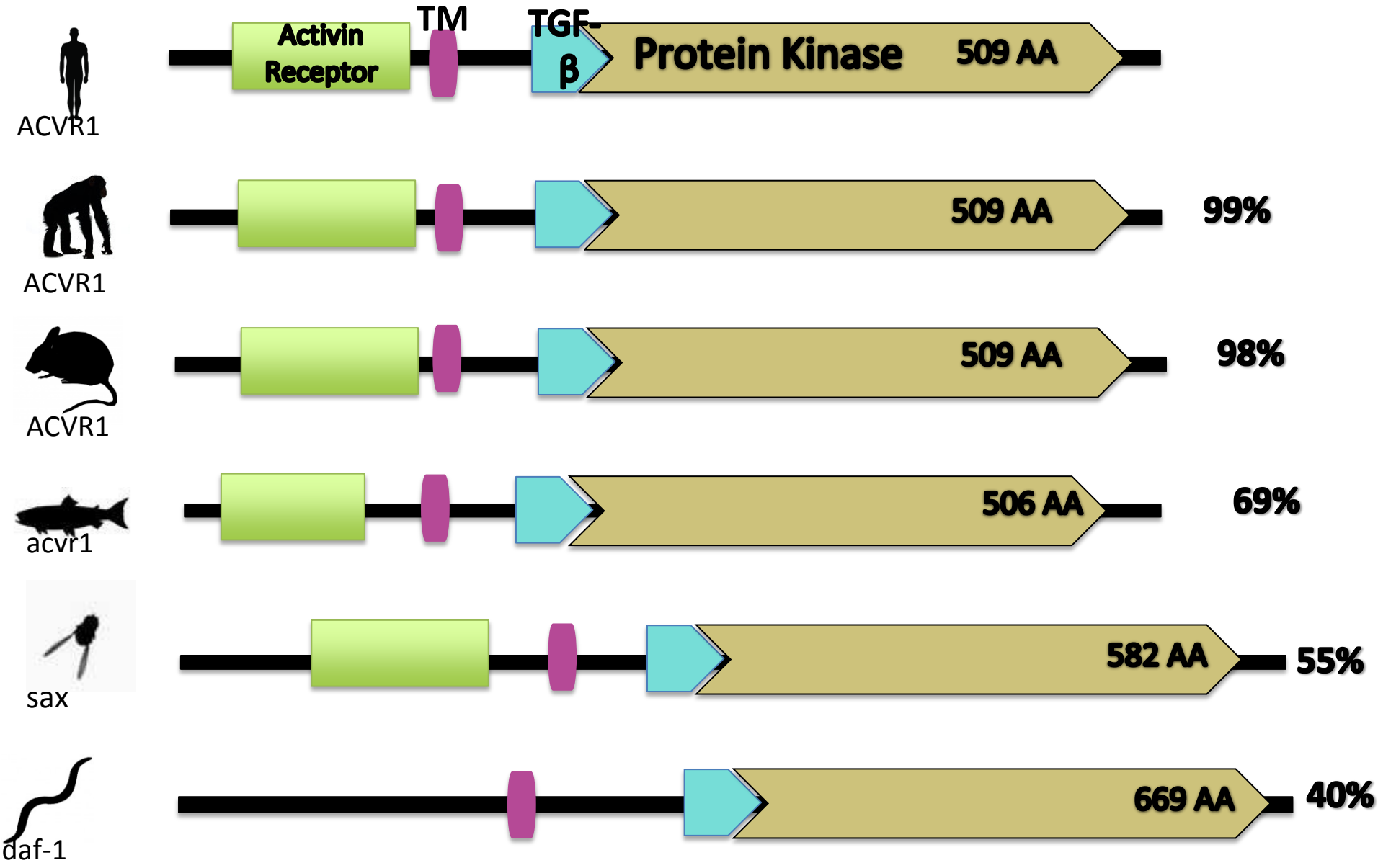
Cellular Component



How does ACVR1 function in the cell?

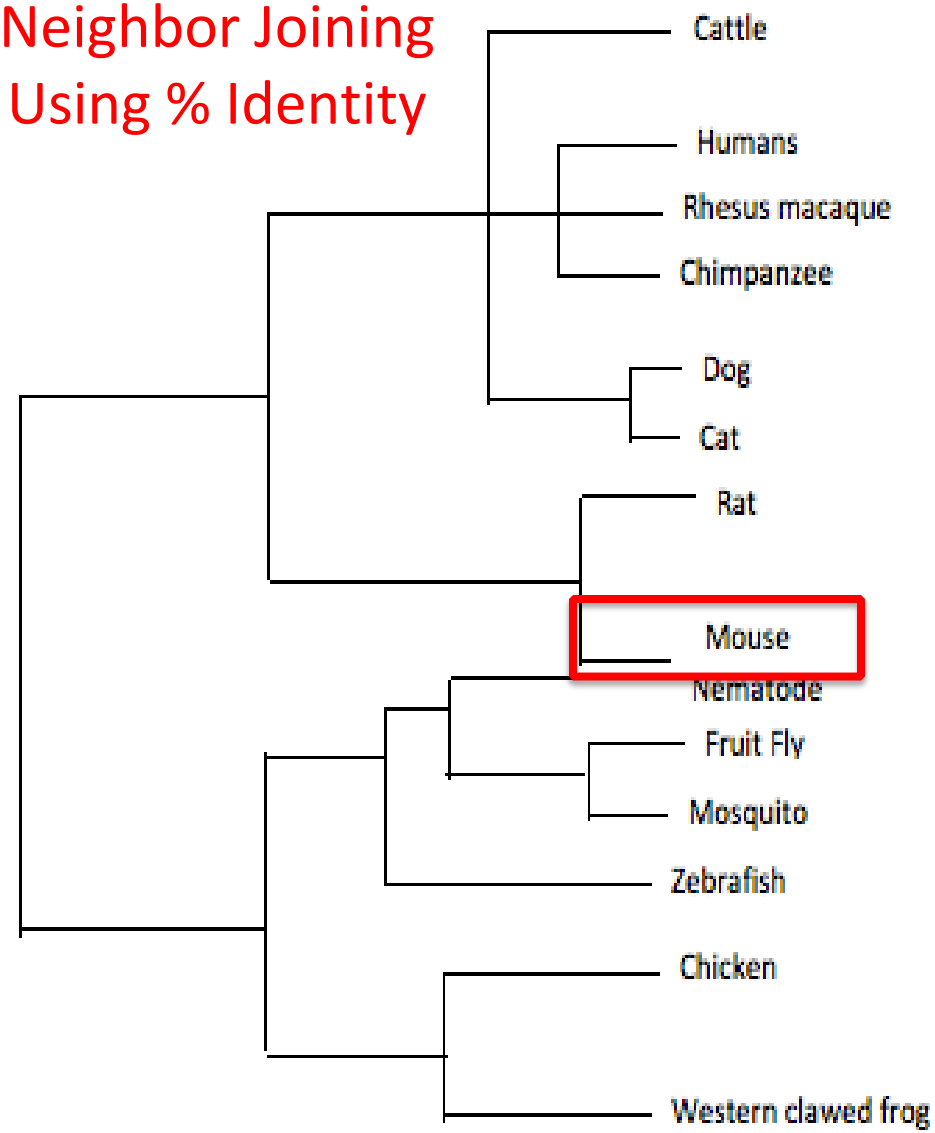


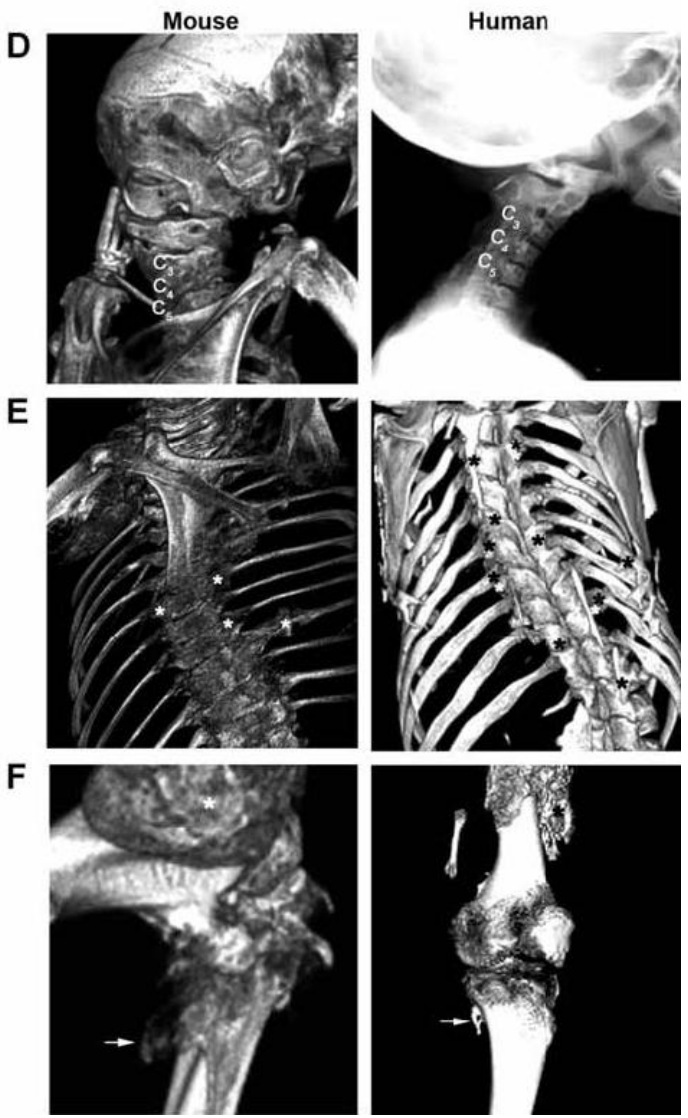
How well conserved is ACVR1 in vertebrates and invertebrates?



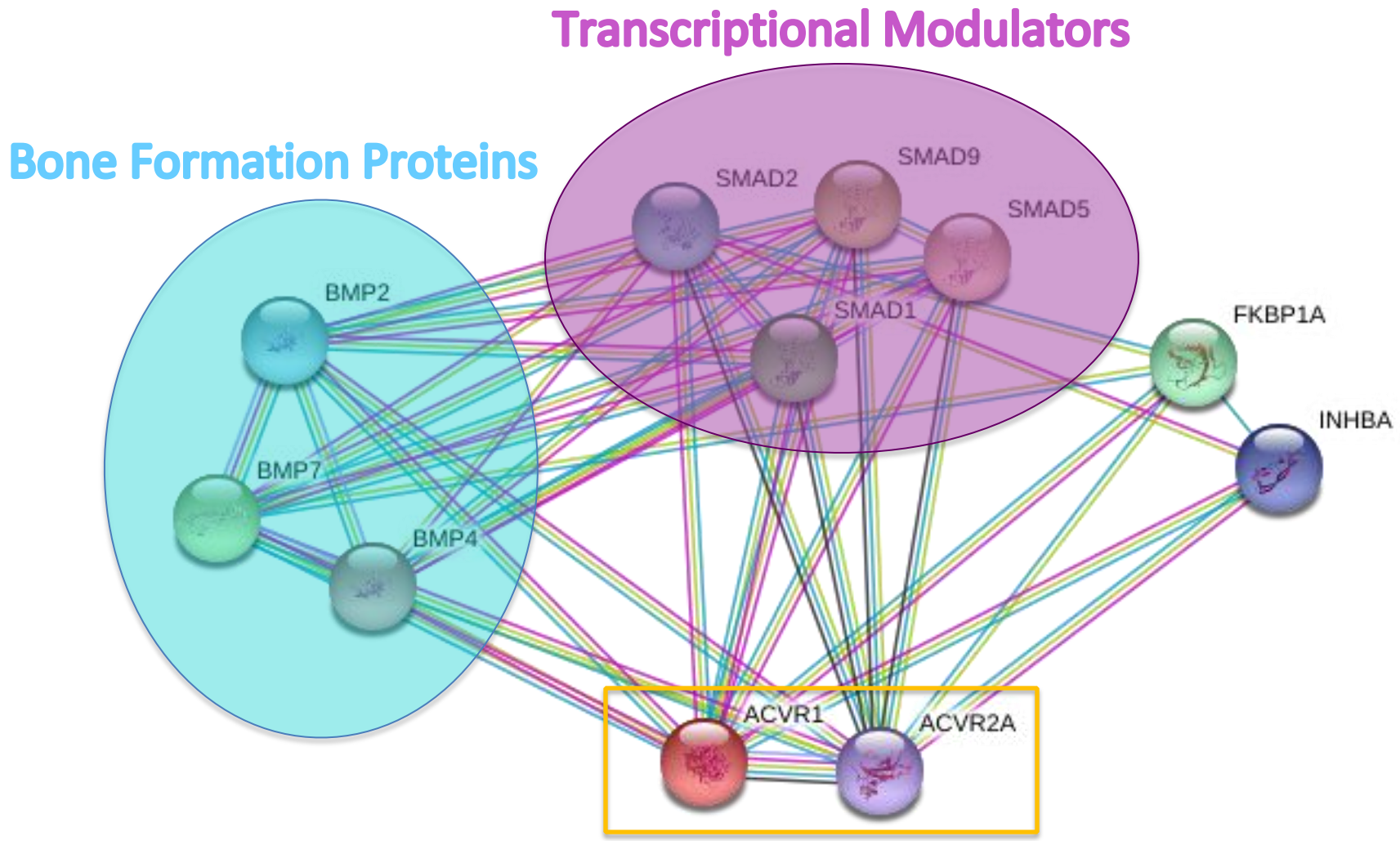
Phylogeny: What is the relationship of ACVR1 between species

Neighbor Joining
Using % Identity

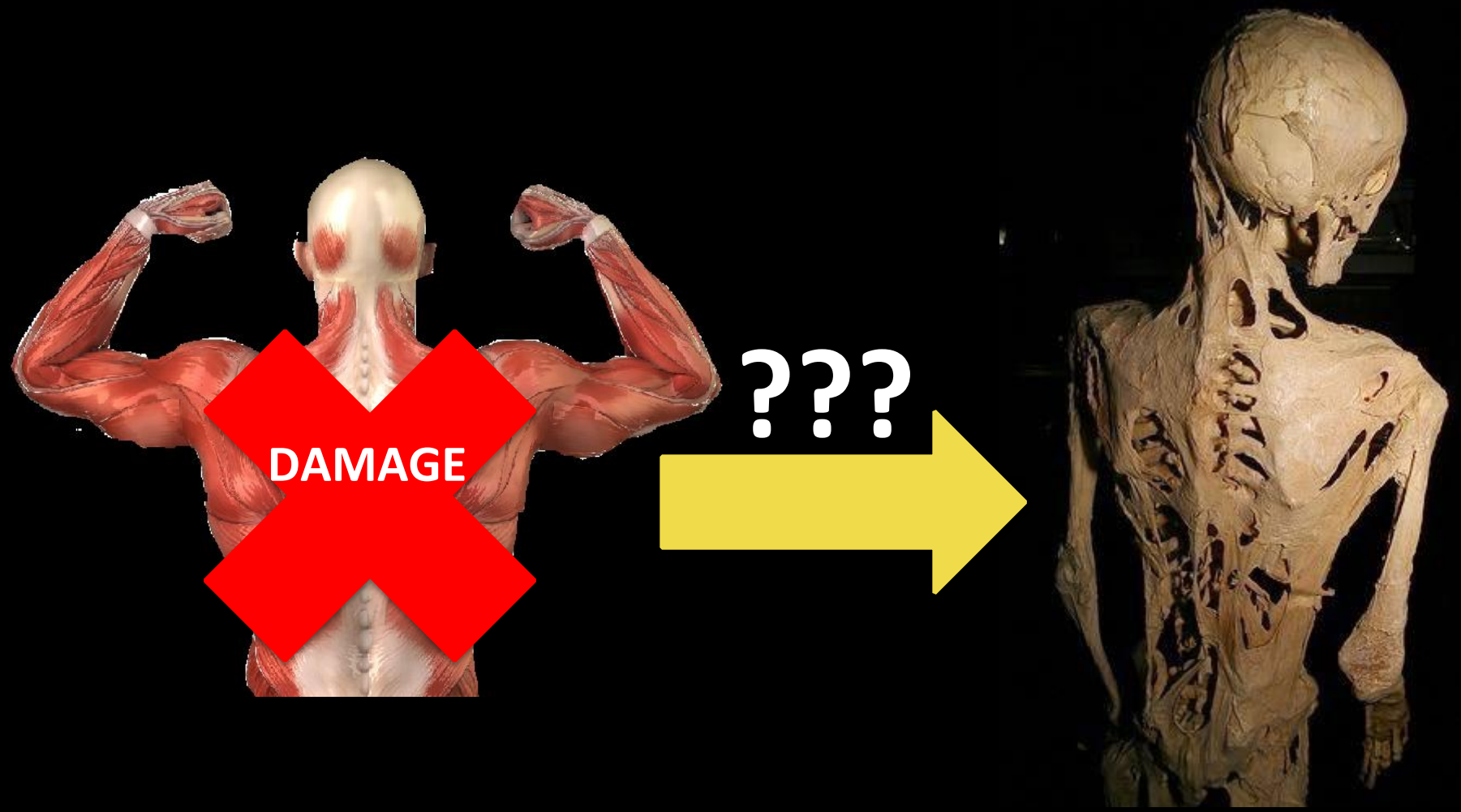




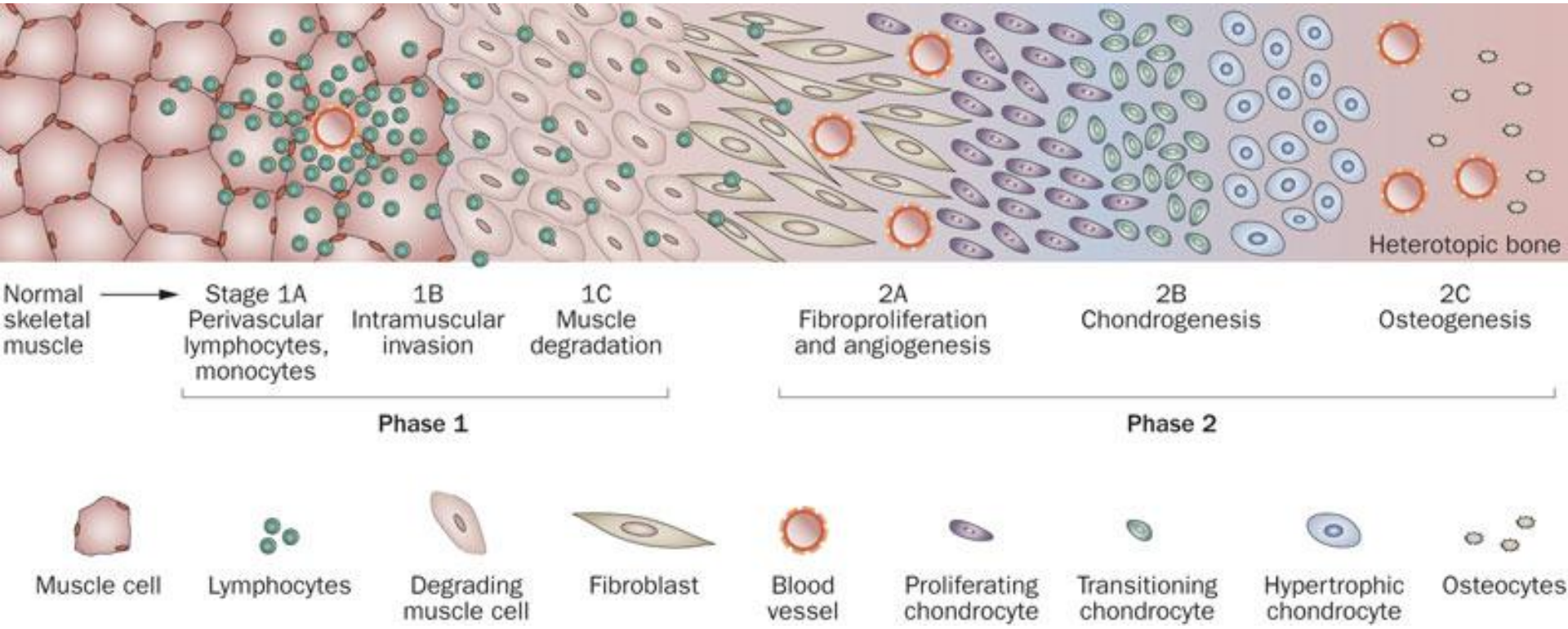
Protein Interactions: What types of proteins does ACVR1 interact with?



Gap in knowledge: What are the molecular mechanism that cause muscle damage to transform into bone?



Hypothesis: Mutations in acvr1 lead to the conversion of muscle to bone because of altered BMP signaling pathways



wild type → BMP levels are normal in muscle

acvr1 +/- → ↑ altered BMP signalling in muscle

Goals

Long–term goal: is to understand the molecular mechanisms involved in muscle turning into bone

Aim 1
Compare gene expression in the normal and pathological state

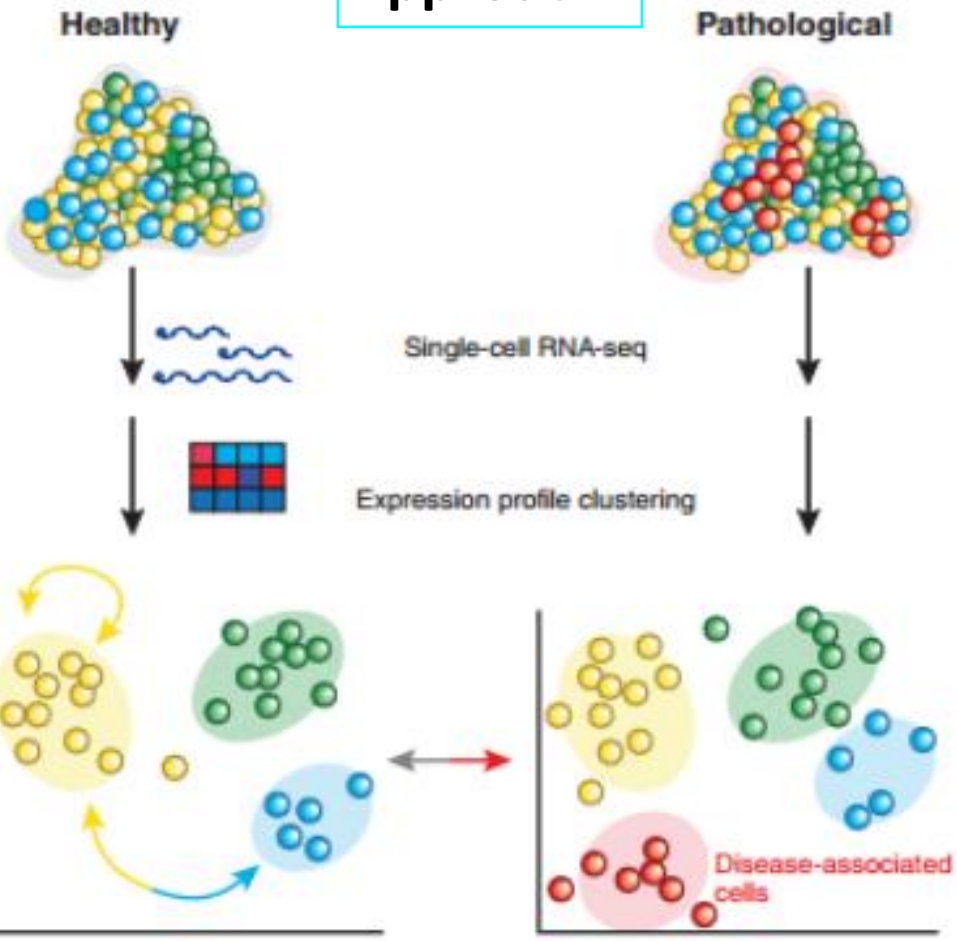
Aim 2 use chemical genetics to see if any drugs rescue the abberant signaling and phenotype

Aim 3 Determine if a new phosphorylation site is responsible for decreased FKBP12 affinity

Specific Aim 1: Identify genes that are differentially expressed in wild type and ACVR1 mutant mouse muscle using RNA Seq

WT

Approach:



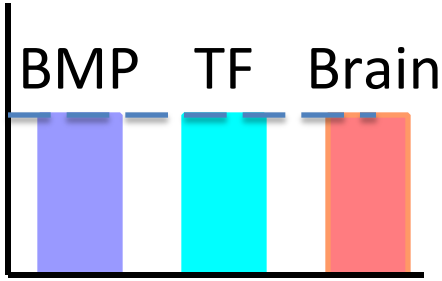
+/-

Specific Aims 1: Identify the types of genes differentially expressed

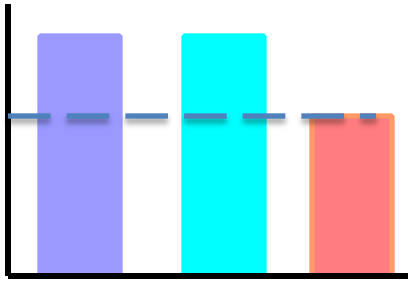
Hypothesis

Protein expression level

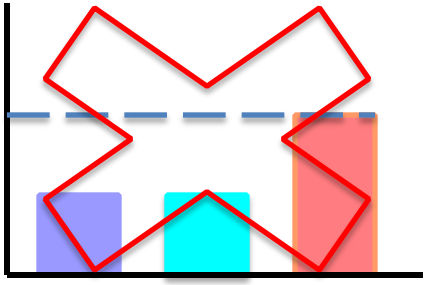
ACVR1 WT



ACVR1 +/-

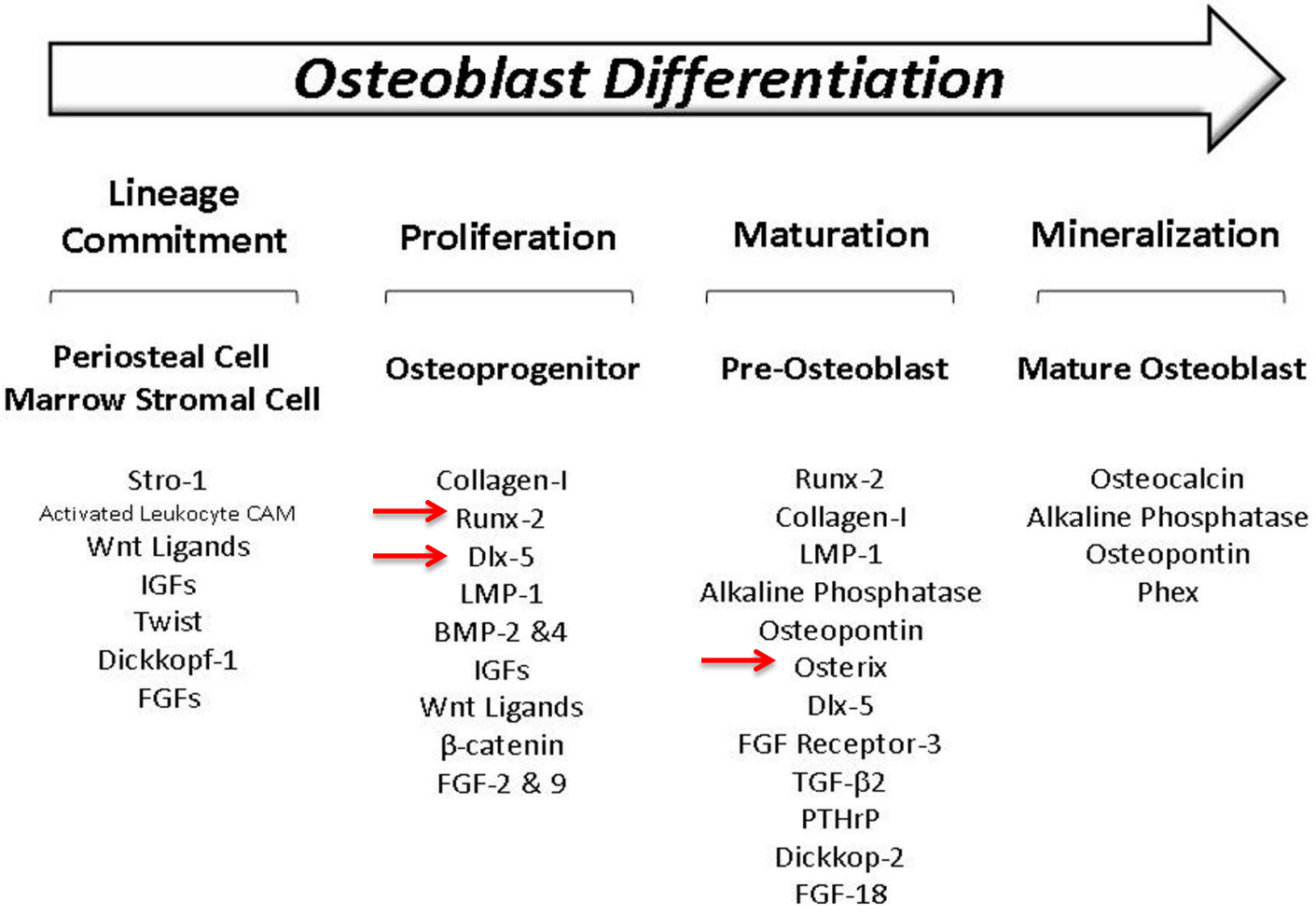


ACVR1 -/-



Rationale: Find differentially expressed gene and proteins to better understand the molecular mechanisms of FOP

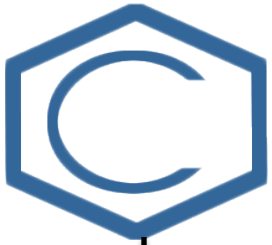
Specific Aims 1: Additional proteins that may have increased expression in RNA seq

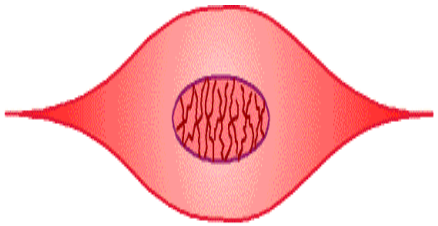


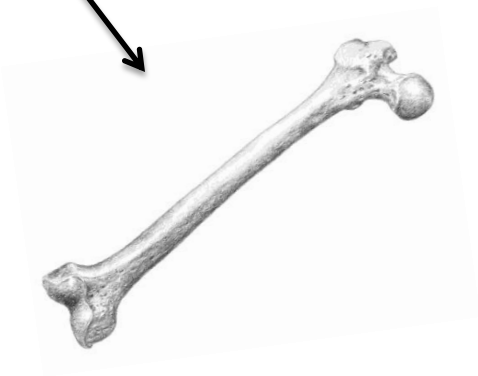
Strohbach, 2011

Specific Aim 2: Identify compounds using PubChem that interact with ACVR1

Approach



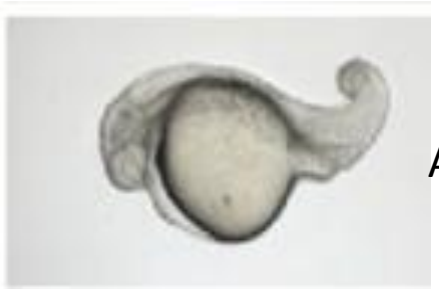




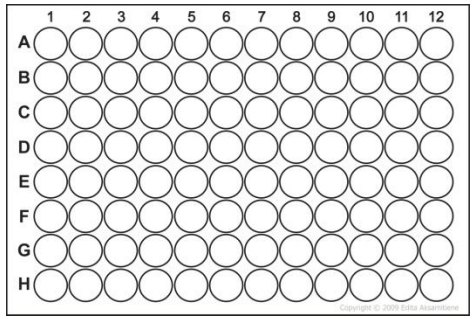
Specific Aim 2: Identify compounds using PubChem that interact with ACVR1

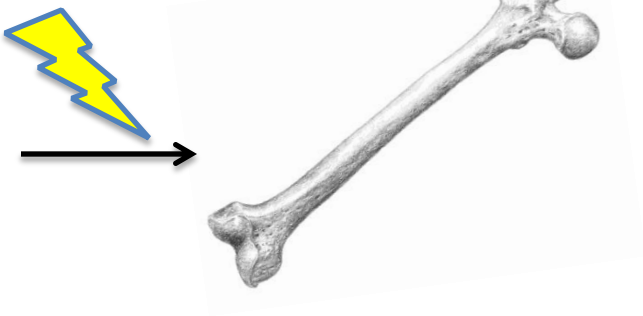
Hypothesis:

WT



ACVR1
ACTIVATORS

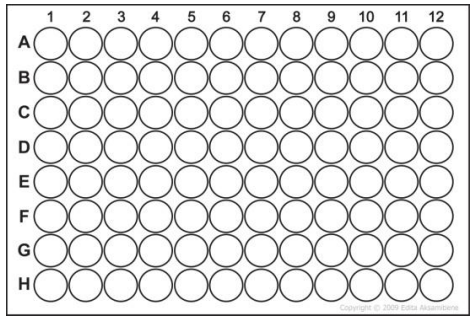


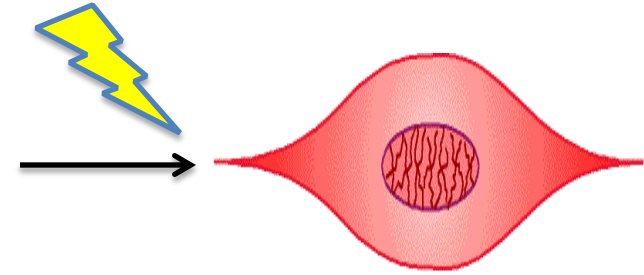


Acvr1 +/-

R206H

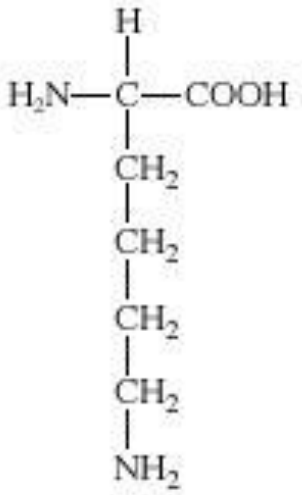
ACVR1
INHIBITORS

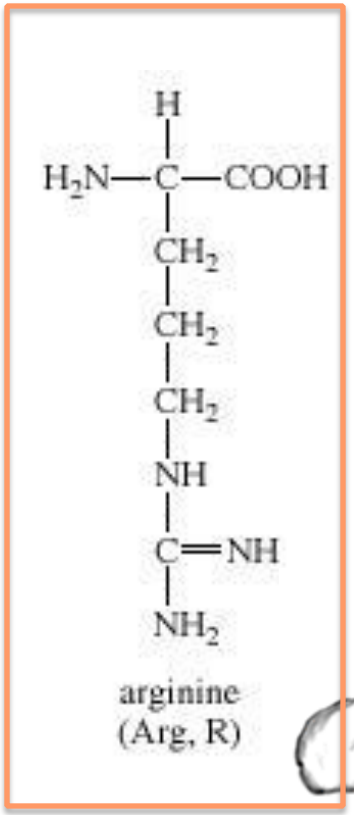


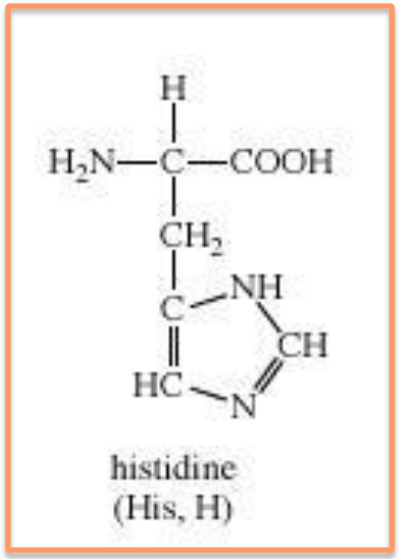


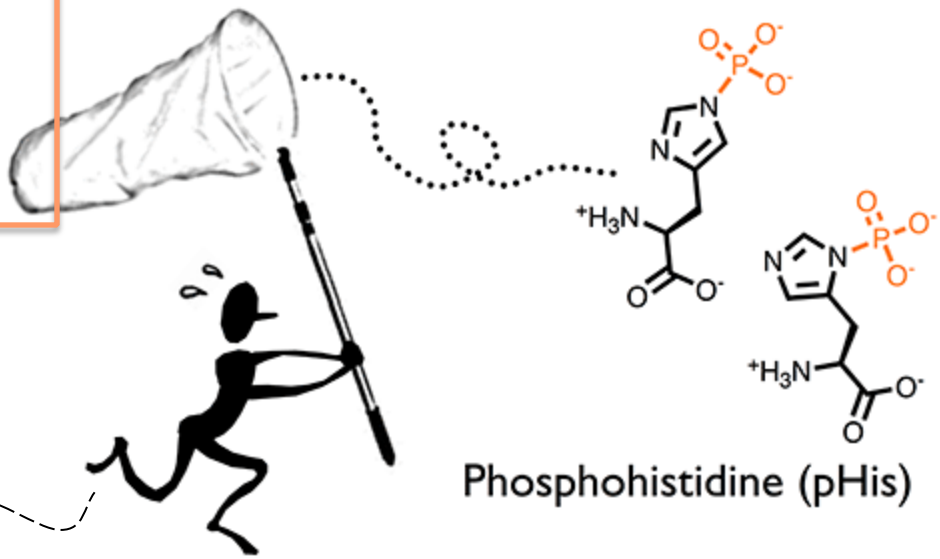
Rationale: Try to find drugs that will rescue abberant ACVR1 signaling

Specific Aim 3: Determine if the muation in ACVR1 creates a new phosphorylation site and if it is responsible for the decreased FKBP12 affinity for ACVR1





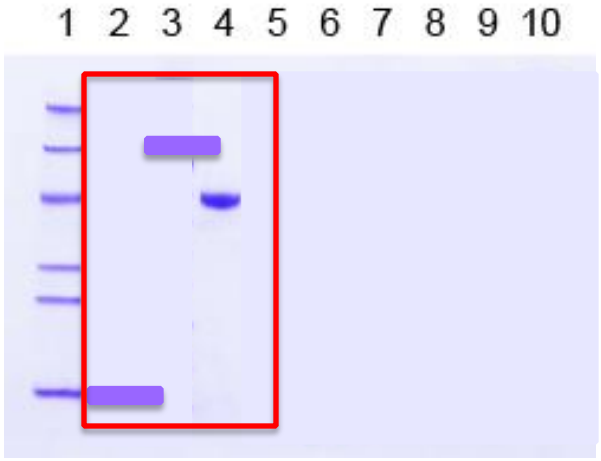




Specific Aims 3 Approach & Hypothesis

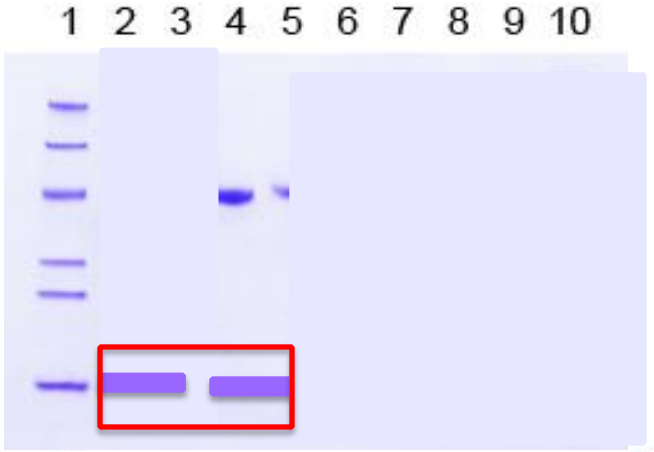
WT Column 2

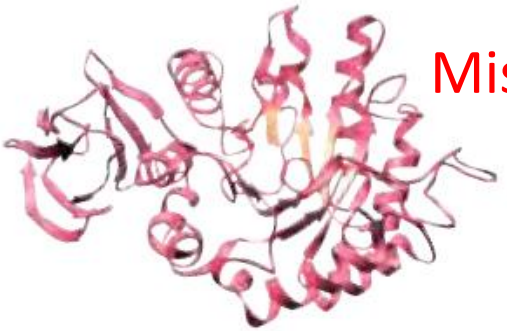
+ Shift



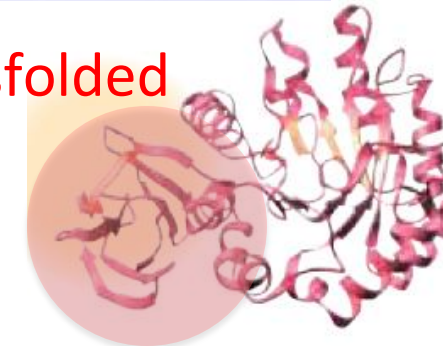
Mutant ACVR1 +/-
Column 3

- Shift





Misfolded



Rationale: To understand why the inhibitor has decreased binding affintity to ACVR1

Future Directions

Block activity of mutant FOP receptor

Inhibit inflammatory trigger

Diverting mesenchymal stem cells to soft tissue fate

Reference

http://th08.deviantart.net/fs70/PRE/i/2014/033/7/5/fibrodysplasia_ossificans_progressiva_by_atirum-d74wcd4.png

http://i.imgur.com/QujYXfL.jpg
http://jpma.org.pk/images/April2011/FibrodysplasiaOssificansProgressivafigure2.jpg
Rigueur, Diana ; Brugger, Sean ; Anbarchian, Teni ; Kim, Jong Kil ; Lee, Yoojin ; Lyons, Karen M The Type I BMP Receptor ACVR1/ALK2 is Required for Chondrogenesis During Development
Journal of Bone and Mineral Research, 2015, Vol.30(4), pp.733-741

http://ghr.nlm.nih.gov/gene/ACVR1
http://www.ncbi.nlm.nih.gov/pubmed/16795049

http://posterng.netkey.at/ranzcr/viewing/index.php?module=viewimage&task=&mediafile_id=590601&201407160703.gif

http://4.bp.blogspot.com/-zW4fosG1V3A/U-fuwaW7HjI/AAAAAAAABbE/guMRjfzCzwk/s1600/FOP+(1).jpg

http://www.nlm.nih.gov/medlineplus/images/needlehand.jpg

https://kinasepro.files.wordpress.com/2009/05/sgc_2.gif?w=500&h=659

http://upload.wikimedia.org/wikipedia/en/thumb/c/c8/Microarray-schema.jpg/220px-Microarray-schema.jpg

http://www.extremetech.com/wp-content/uploads/2014/01/dnahead.jpg

http://www.skullsunlimited.com/userfiles/image/variants_7281.jpg

Gene Therapy Applications for Fracture Repair
Cassandra A. Strohbach[1], Donna D. Strong[2] and Charles H. Rundle[3]

http://posterng.netkey.at/ranzcr/viewing/index.php?module=viewimage&task=&mediafile_id=590601&201407160703.gif
https://edc2.healthtap.com/ht-staging/user_answer/reference_image/4155/large/Bones.jpeg?1386670622

http://posterng.netkey.at/ranzcr/viewing/index.php?module=viewimage&task=&mediafile_id=590601&201407160703.gif
https://edc2.healthtap.com/ht-staging/user_answer/reference_image/4155/large/Bones.jpeg?1386670622

http://i.imgur.com/QujYXfL.jpg
http://jpma.org.pk/images/April2011/FibrodysplasiaOssificansProgressivafigure2.jpg
http://www.niams.nih.gov/health_info/kids/images/arm.jpg
http://www.skullsunlimited.com/userfiles/image/variants_7281.jpg