



Larsen Syndrome

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Genetics 564

Spring 2014

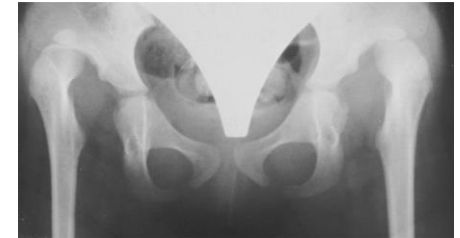
What is Larsen Syndrome?



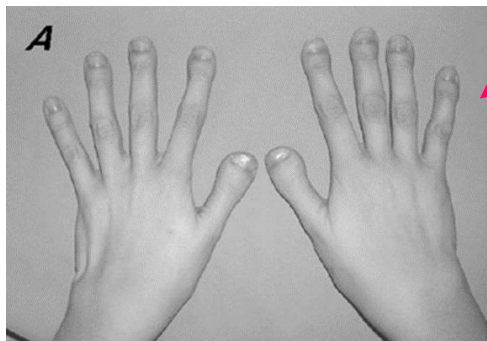
Dobbs, Matthew B. et al., 2008



Bicknell, L. S., et al., 2006



Hosoe, Hideo et al., 2006



Bicknell, L. S., et al., 2006



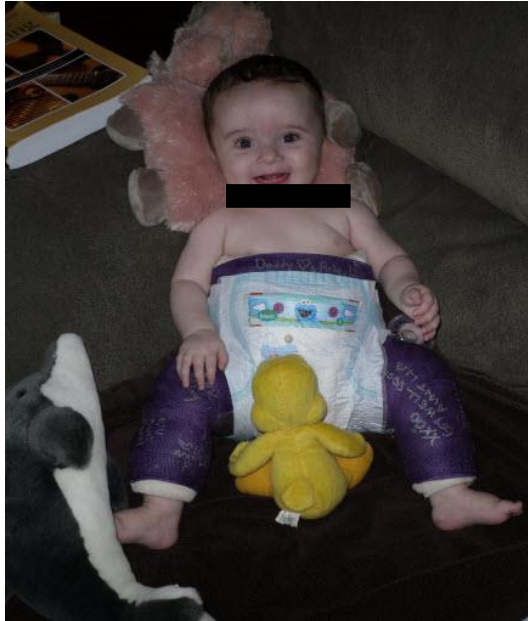
Krakow, D. et al., 2004

<https://www.youtube.com/watch?v=poc6TBCNez8>

Management after orthopedic surgery:



Hironobu, Sakaura et al., 2007



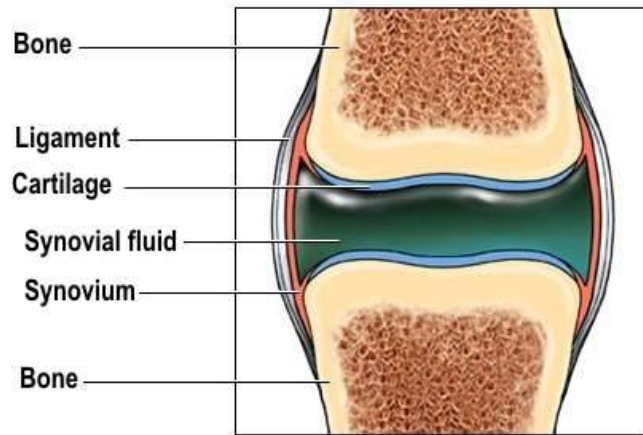
Kaissi, Ali Al et al., 2011

A result from **severe bone defects**

The FLNB gene is affected in Larsen Syndrome patients



Bone Development



Actin/ filamin binding

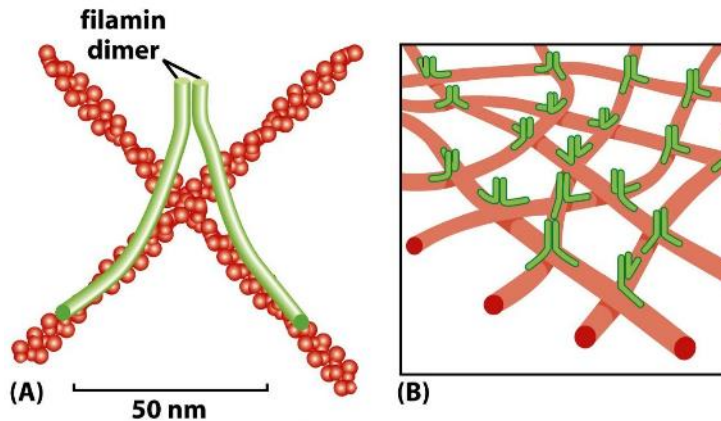
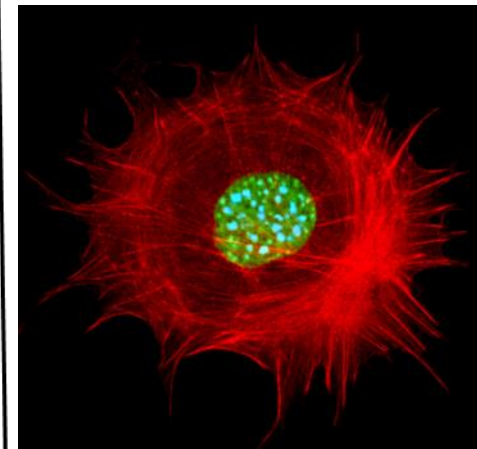


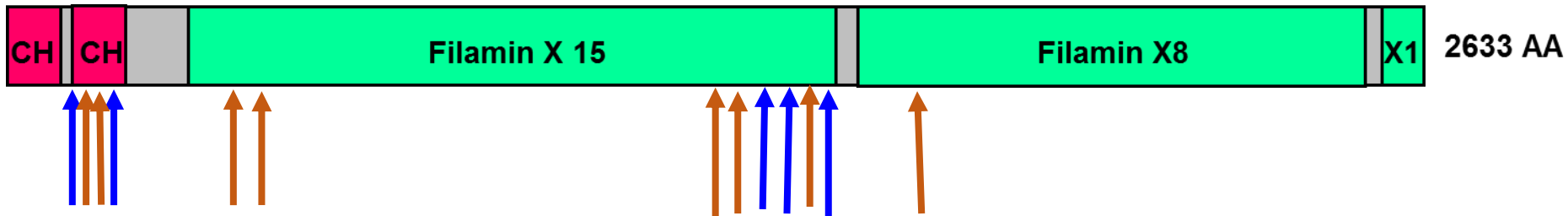
Figure 16-51 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Actin Cytoskeleton organization



What are the mutations of FLNB that result in Larsen Syndrome?

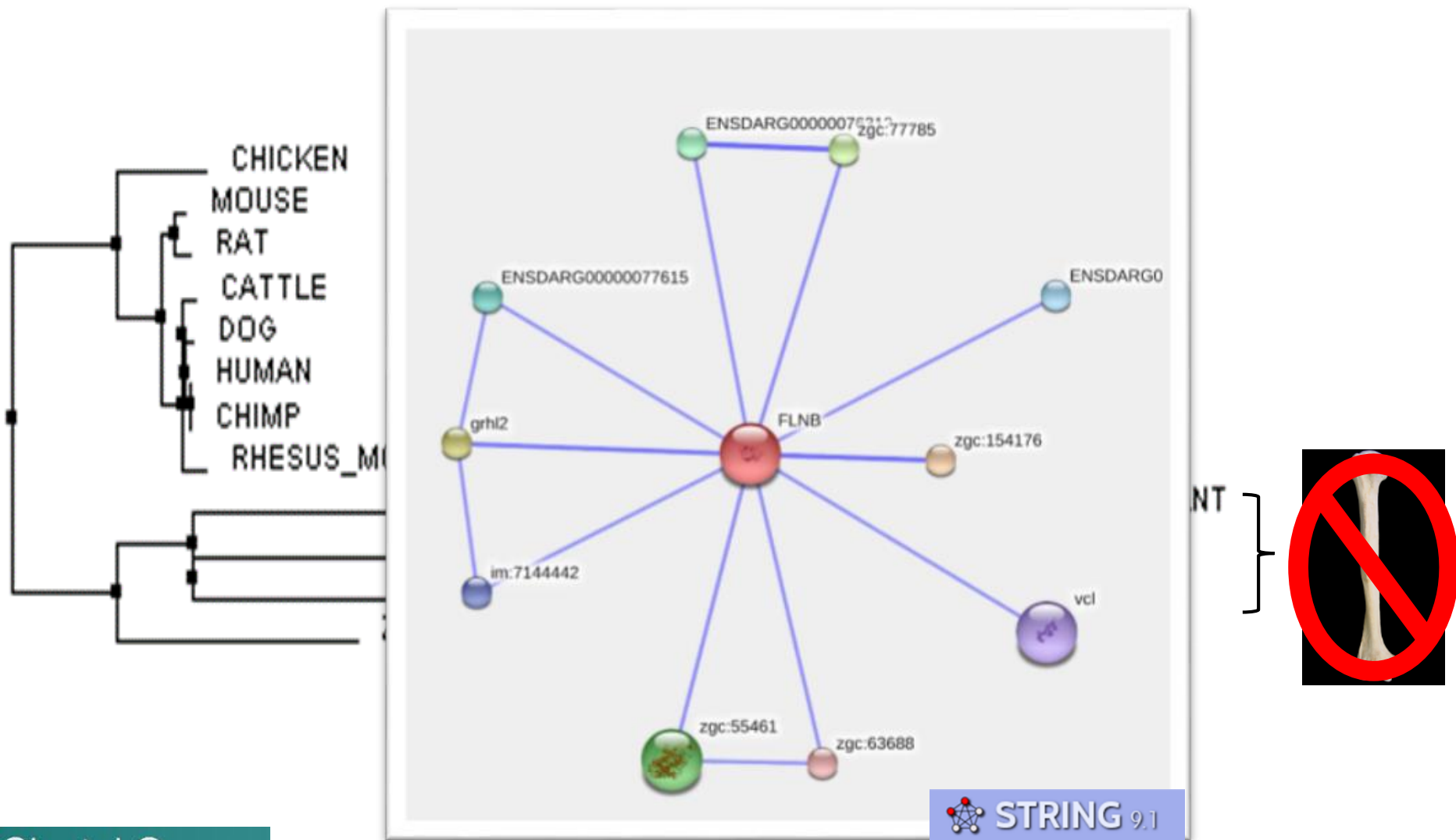
13 missense mutations and counting...



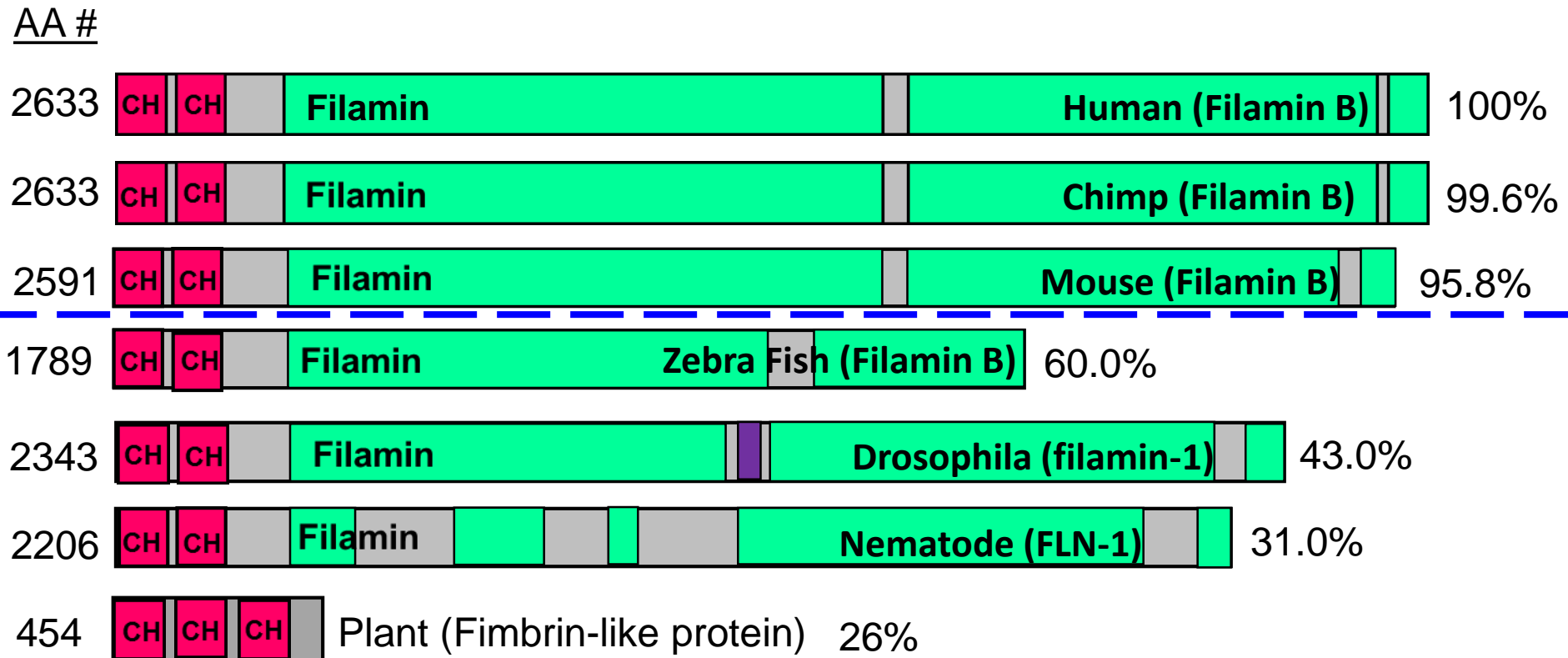
→ Bicknell et al., 2007

→ Karakow et al., 2004

How well conserved is FLNB?

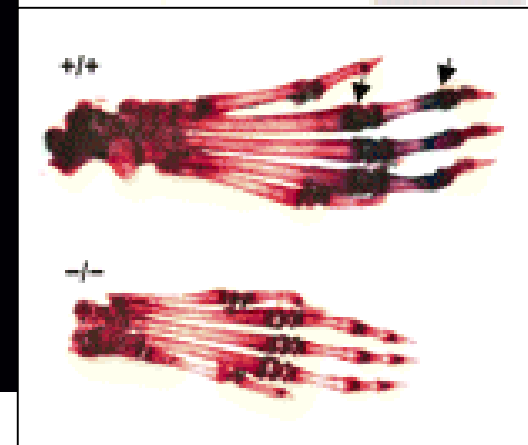
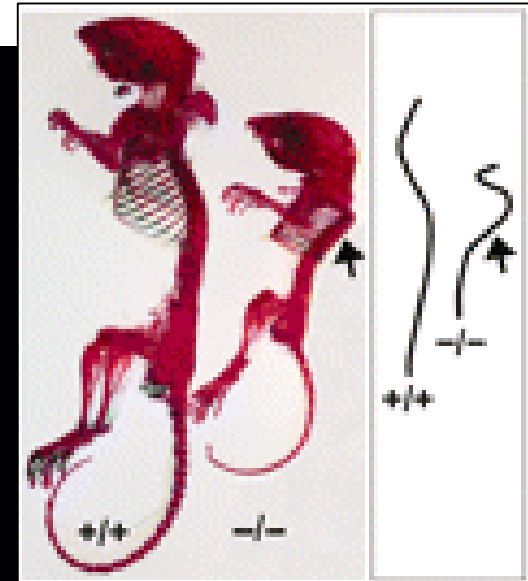
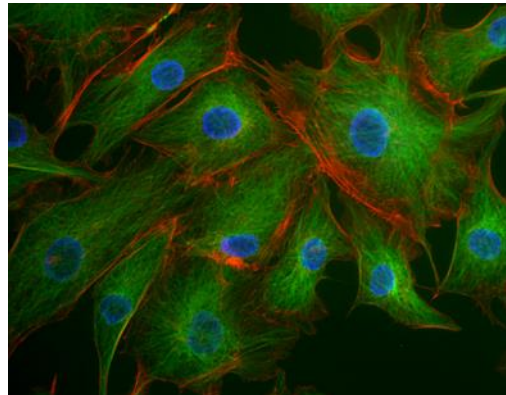
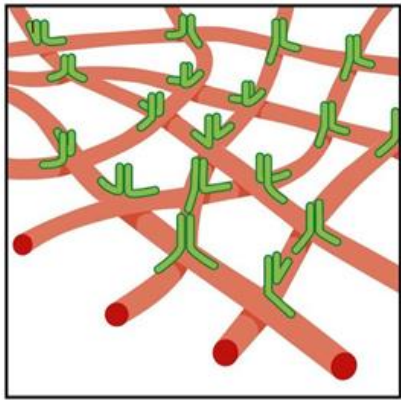
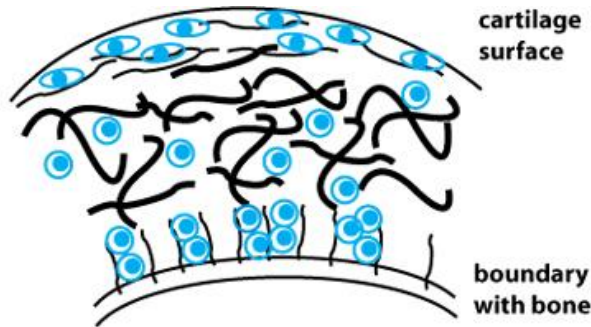


How well conserved is FLNB across species?

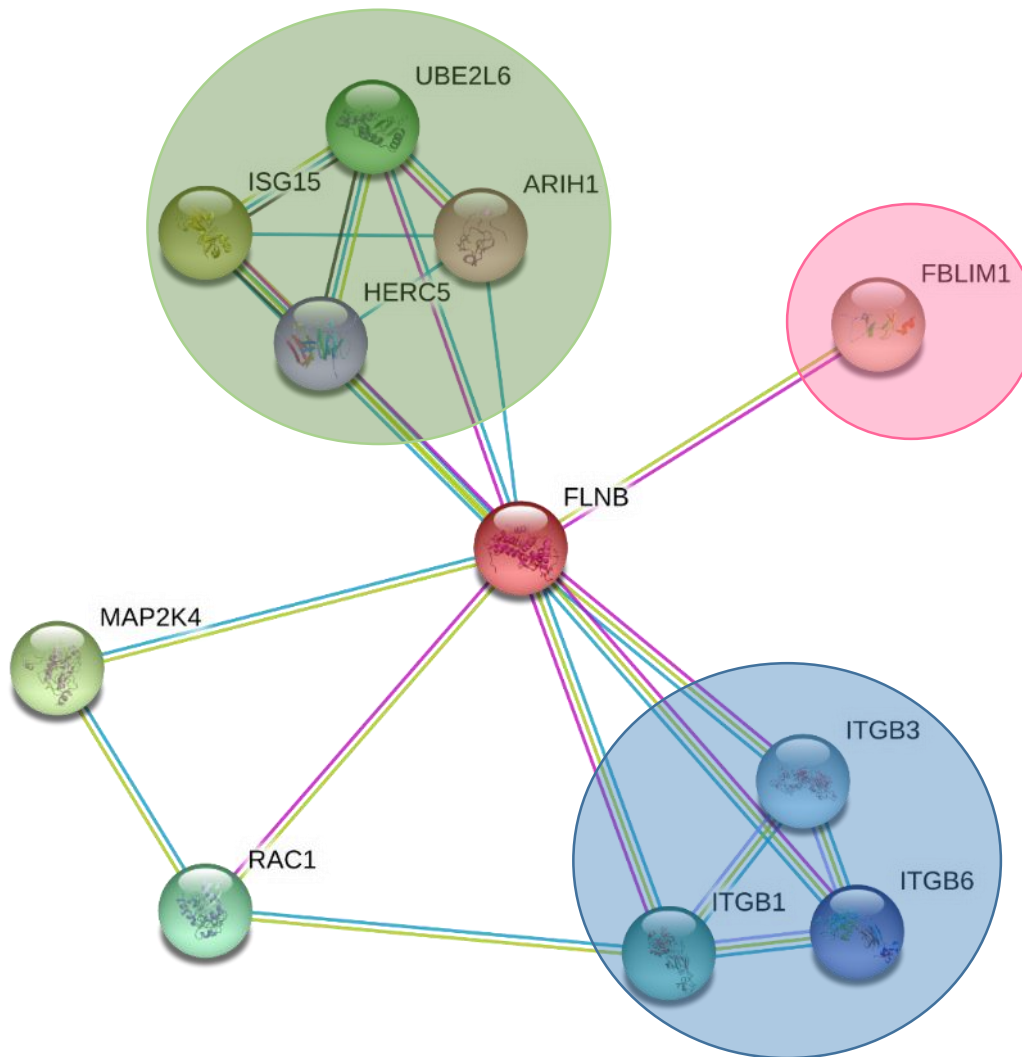


 Filamin-like

The role of FLNB in bone development is unclear



What proteins interact with FLNB?



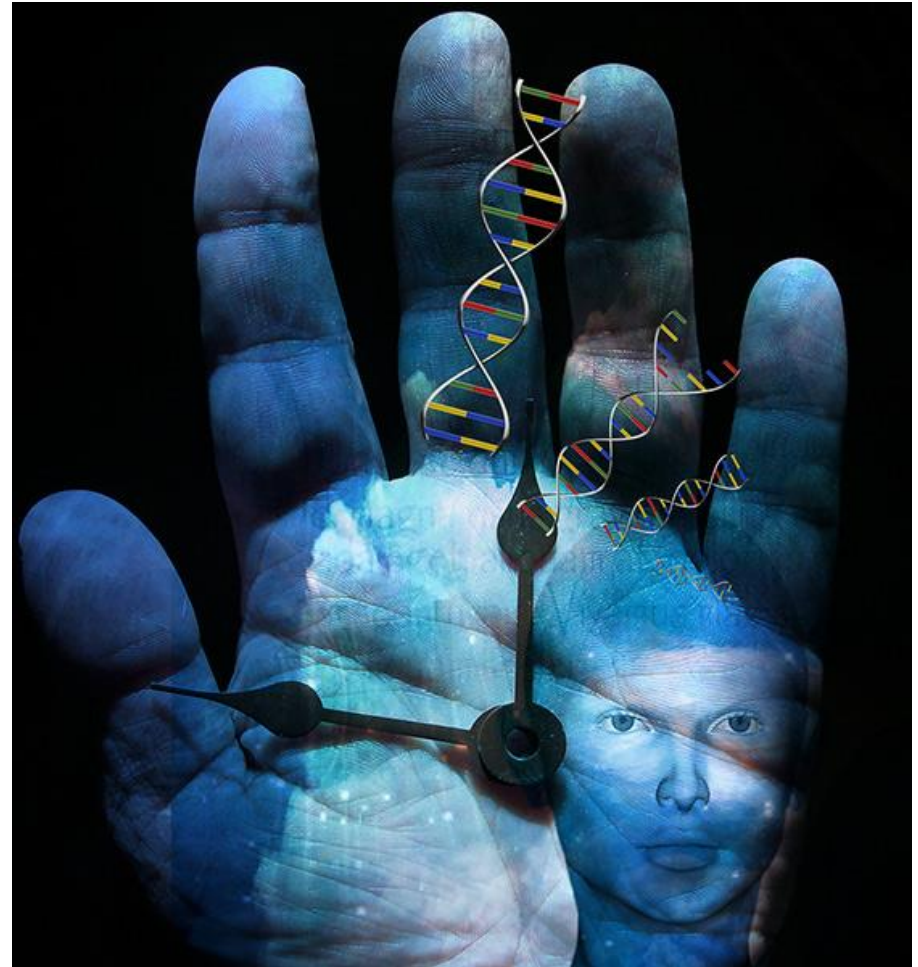
Ubiquitin proteins

Adhesion to cell ECM

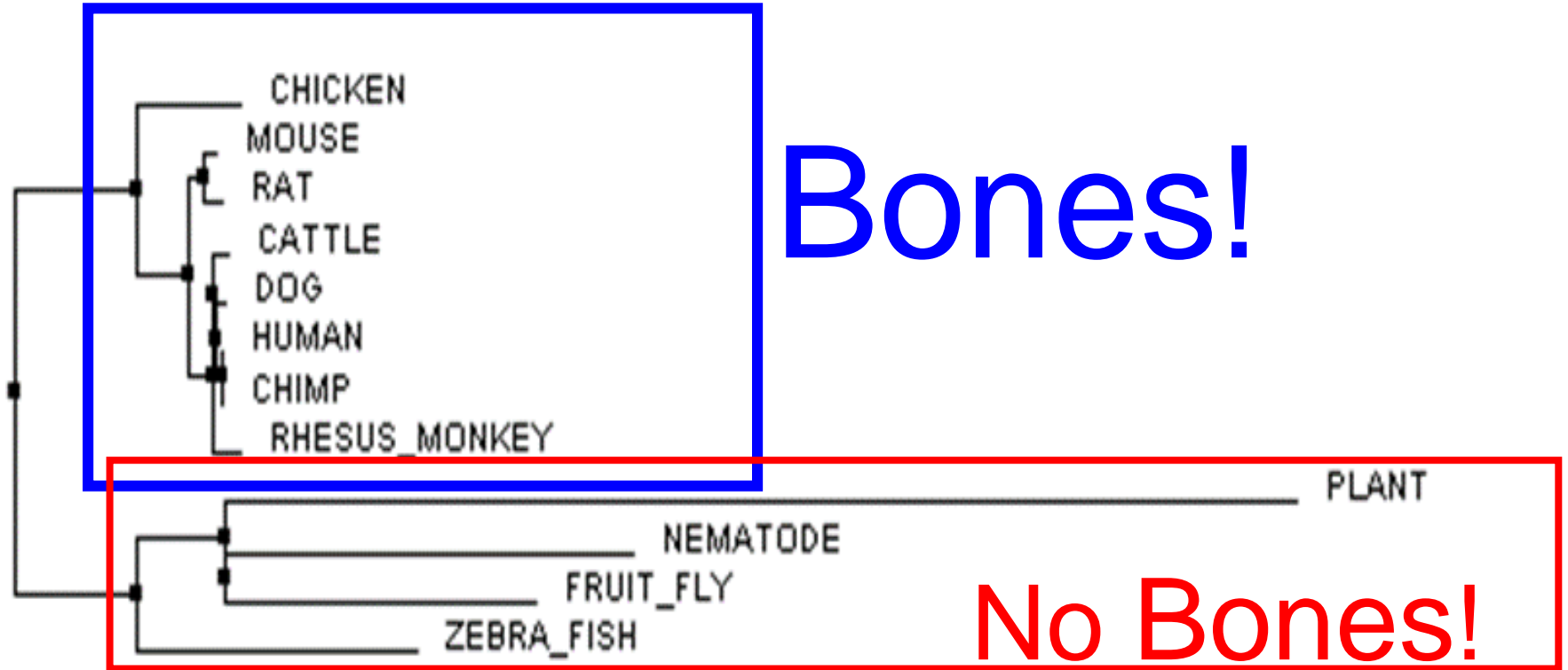
Fibronectin receptors

Primary goal

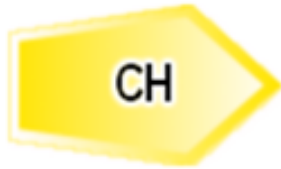
To understand FLNB's
function across species
and time to lead to
future medical
advances



Aim 1: To determine the difference in FLNB between species with and without bones



Aim 1: How well conserved is the CH domain in species with and without bones?



: actin binding domain

PLANT	PEKILIRWANNPQLRKTEYKKTVTNFS\$DVFDAEAYTNLMLVLAPEHKNP\$H\$LA\$VK\$SS\$F\$--
FRUIT_FLY	QQNTFTRWANEHLKTI--DRSINNLETDLSDGLRLIALLEVL\$SQKRM-PKY-NKRPTFRS
ZEBRA_FISH	QQNTFTRWANEHLKSA--NKR\$VADLQODLSDGLRLIALLEVL\$SQK\$KMERKY-HSRPTFRQ
HUMAN	QQNTFTRWANEHLKCV--NKRIGNLQTDLSDGLRLIALLEVL\$SQKRM\$YRKY-HQRPTFRQ
CHIMP	QQNTFTRWANEHLKCV--NKRIGNLQTDLSDGLRLIALLEVL\$SQKRM\$YRKY-HQRPTFRQ
MOUSE	QQNTFTRWANEHLKCV--NKRIGNLQTDLSDGLRLIALLEVL\$SQKRM\$H\$HKY-HQRPTFRQ
	:: : ** * :: : : : : * . * . * : : : : : * : *

PLANT	---ERAKLVLEHADKMGCR-RYLTAKTIVEGSPNLLLAFVAHIFQH
FRUIT_FLY	QKLENVSVALKFLQDEGIKIVNIDSSDIVDCKLKLGLIWTLILH
ZEBRA_FISH	MKLENVSVALEFLDRENIKLV\$IDS\$KAI\$VDGNLKLGLVWTLILH
HUMAN	MQLENVSVALEFLDRESIKLV\$IDS\$KAI\$VDGNLKLGLVWTLILH
CHIMP	MQLENVSVALEFLDRESIKLV\$IDS\$KAI\$VDGNLKLGLVWTLILH
MOUSE	MKLENVSVALEFLDRESIKLV\$IDS\$KAI\$VDGNLKLGLVWTLILH
	* * : : : : : * : * * : : : *

Aim 1: How well conserved is the Filamin domain in species with and without bones?



: actin binding cytoskeletal protein ie. latice

NEMATODE	MKPKVQ-ATISNLDK-ILQVNDPREFDLKLSDG-FKPKVSIRDEDGQDIHLSLKKVEDK
FRUIT FLY	-NPNRVRAYGPGIEPIGVPVVGAPANFTVETFSAGKGSVDVDIQGPNGEIEKADVRFNNDK
HUMAN	-NPKKARAYGRGIEPTIGNMVKQPAKFTVDTISAGQGDMVVFVEDPEGNKEEAQVTPDSDK
CHIMP	-NPKKARAYGRGIEPTIGNMVKQPAKFTVDTISAGQGDMVVFVEDPEGNKEEAQVTPDSDK
MOUSE	-NPKKARAYGRGIEPTIGNMVKQPAKFTVDTISAGQGDMVVFVEDPEGNKEEARVTPDSDK
ZEBRA_FISH	-NPKKARAYGPGIEPTIGNRVMRPAVFTVDTFSAGQGQVMVYVEDPEGRREEVKPVL-NEG

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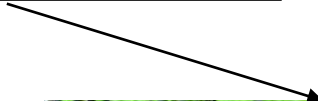
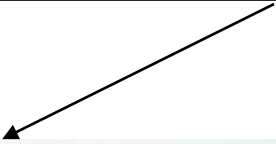
NEMATODE	ENAYKVKFTPTKIGFIHVDVAANDVHTFETQTIPASVICQVVP-
FRUIT_FLY	NLTYTVSYIPKSEGSCHKVAVK-----FSGRDIPISSPFFVKVEGH
HUMAN	NKTYSVEYLPKVTGLHKVTVL-----FAGQHISPSPFVSVDKA
CHIMP	NKTYSVEYLPKVTGLHKVTVL-----FAGQHISPSPFVSVDKA
MOUSE	NKTYSVEYLPKVTGLHKVIVL-----FAGQHISPSPFVNVDKA
ZEBRA_FISH	KKTYSVTIYVPOVMGTHKVTVL-----FAGQOIPISPFVNVDKA

: : * . * : * * : * * * : : : . *

Bones → Phosphorylated Serine
 No Bones → Proline

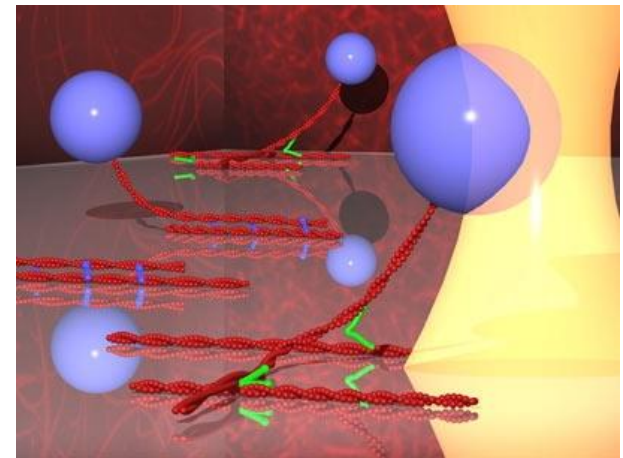
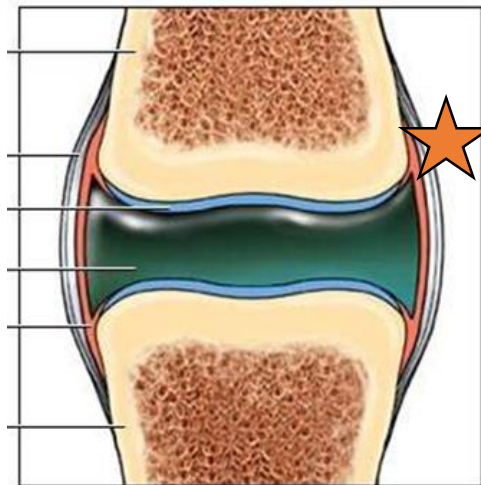
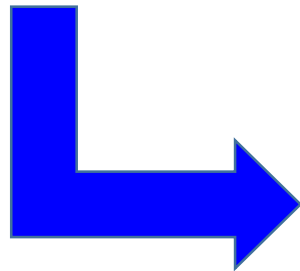
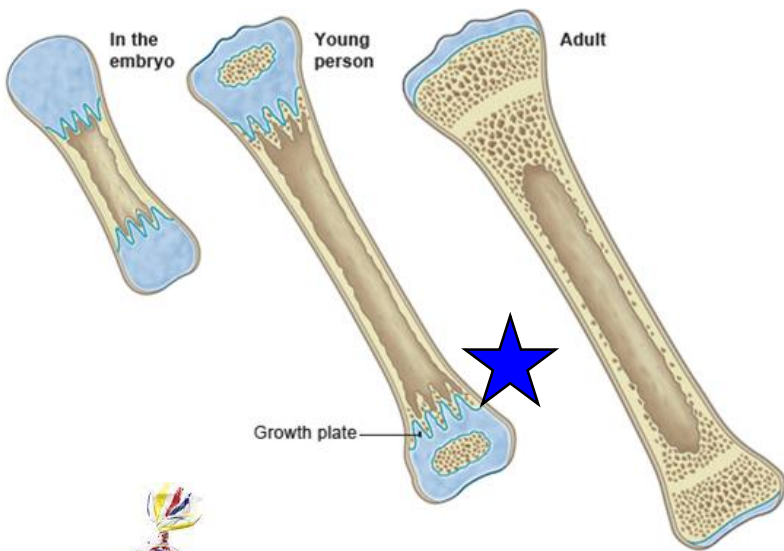
What's going on with FLNB across species?

GFP + protein

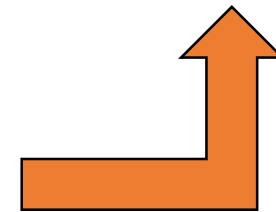


Hypothesis:
new functions of FLNB

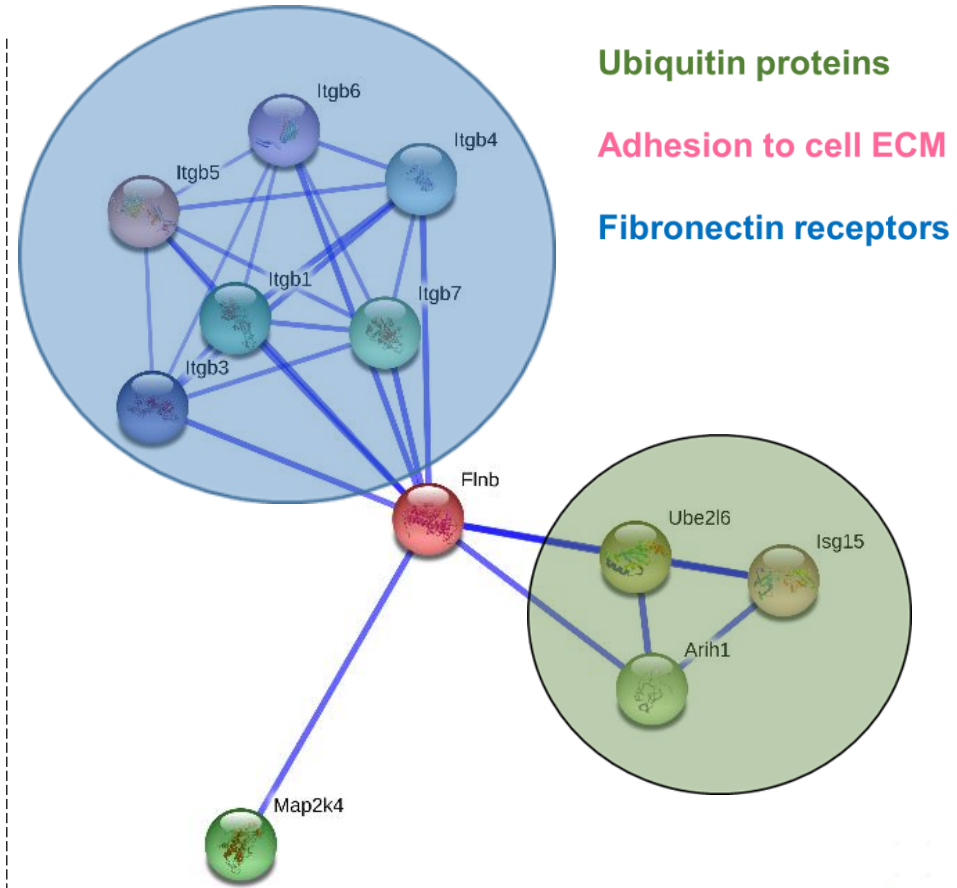
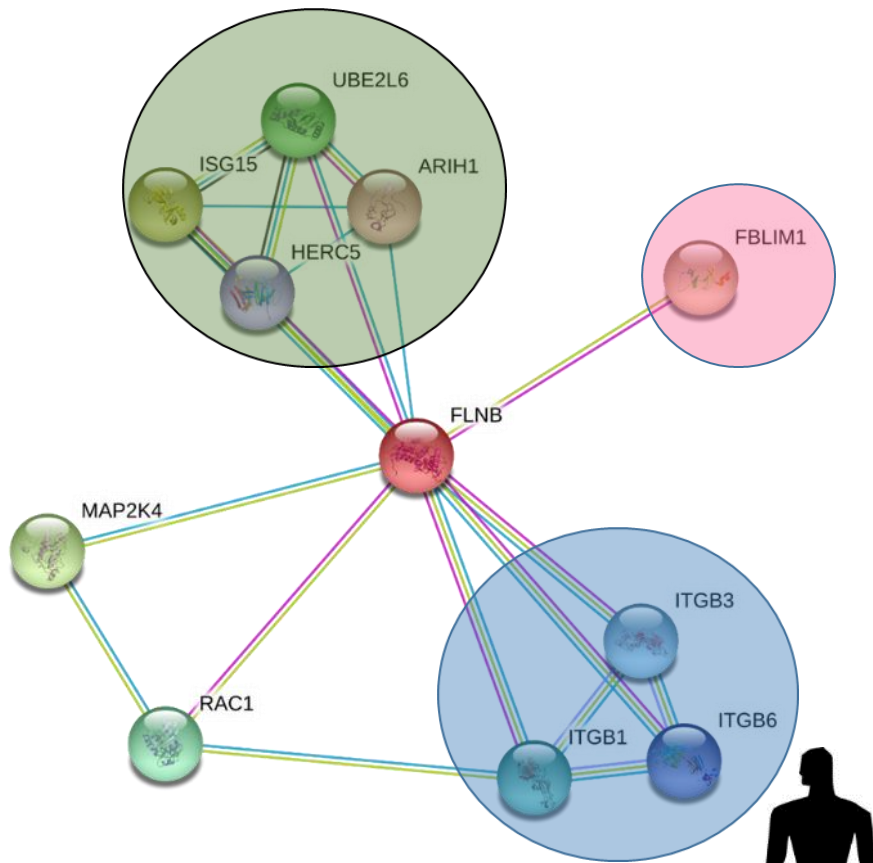
Aim 2: To determine the role of FLNB in bone development with age



filamin actin









Aim 2: Mouse Flnb protein network conserved



Aim 2: How does Flnb interacting proteins change with time in mouse model?

Hypothesis:

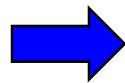
- Ubiquitin protein function increases with age
- Fibronectin receptor function decreases with age

	Ubiquitin	Fibronectin receptors
Embyonic		
Young		
Adult		

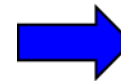
Low



High



tap tag
proteins and
sort



Mass Spectrometry

Future directions



Illumina Hi Seq 2000



Options

Questions?

References:

- Hip surgery: <http://hipdysplasia.org/patient-stories/infant-child/rileys-story/>
- Bone and cartilage: <http://performanceequinevs.com/client-education/lameness/osteoarthritis.html>
- Filamin/ actin binding: <http://classconnection.s3.amazonaws.com/264/flashcards/1854264/jpg/filamin1347637952868.jpg>
- Actin cell: <http://mterasaki.us/lomakin/artgallery.html>
- Bone: <http://www.cea1.com/anatomy-systems/humerus-bone-2/>
- Cartilage diagram: <http://ocw.mit.edu/courses/biological-engineering/20-109-laboratory-fundamentals-in-biological-engineering-spring-2010/labs/module-3-day-4-preparing-cells-for-analysis/>
- Actin/ microtubule staining: <http://www.photometrics.com/applications/imaging/fluorescenceimaging.php>
- Bone “?”: <http://cdn.songshuhui.net/wp-content/uploads/2011/10/osteoporosis-awareness-question-mark-.jpg>
- Hand: http://news.stanford.edu/pr/2012/images/evolution_illustration.jpg
- Zebra fish: <http://www.mpg.de/640043/zoom.jpeg>
- Fruit fly: <http://www.thewhirlingblog.com/wp-content/uploads/2012/05/fruit-fly1.jpg>
- Arabidopsis: <http://www.ulb.ac.be/sciences/lpgmp/labora8.jpg>
- Large group: <http://www.gograph.com/illustration/diverse-population-of-symbol-people-form-large-group-gg5126108.html>
- Illumina HiSeq 2000: <http://www.ige3.unige.ch/genomics-technologies.php>
- Tri-State: <http://www.crwoodturner.com/location.shtml>
- GO: <http://www.galter.northwestern.edu/news/index.cfm/2010/12/3/GeneGo-MetaCore-Pathway-Analysis-Software>
- Mouse image: <http://www.warrenphotographic.co.uk/photography/big/26017-Wood-mouse-white-background.jpg>
- Mass Spec: <http://www.medicalexpo.com/prod/thermo-scientific/liquid-chromatography-systems-coupled-mass-spectrometers-ic-ms-78678-507460.html>
- Blood sample: <http://www.behavioral.net/blogs/nick-zubko/depression-diagnosed-simple-blood-test>
- “Questions?” Image: <http://www.unmemorabletitle.co.uk/wp-content/uploads/2013/01/questions.jpg>