Kindler Syndrome

Skin blistering and cancer development

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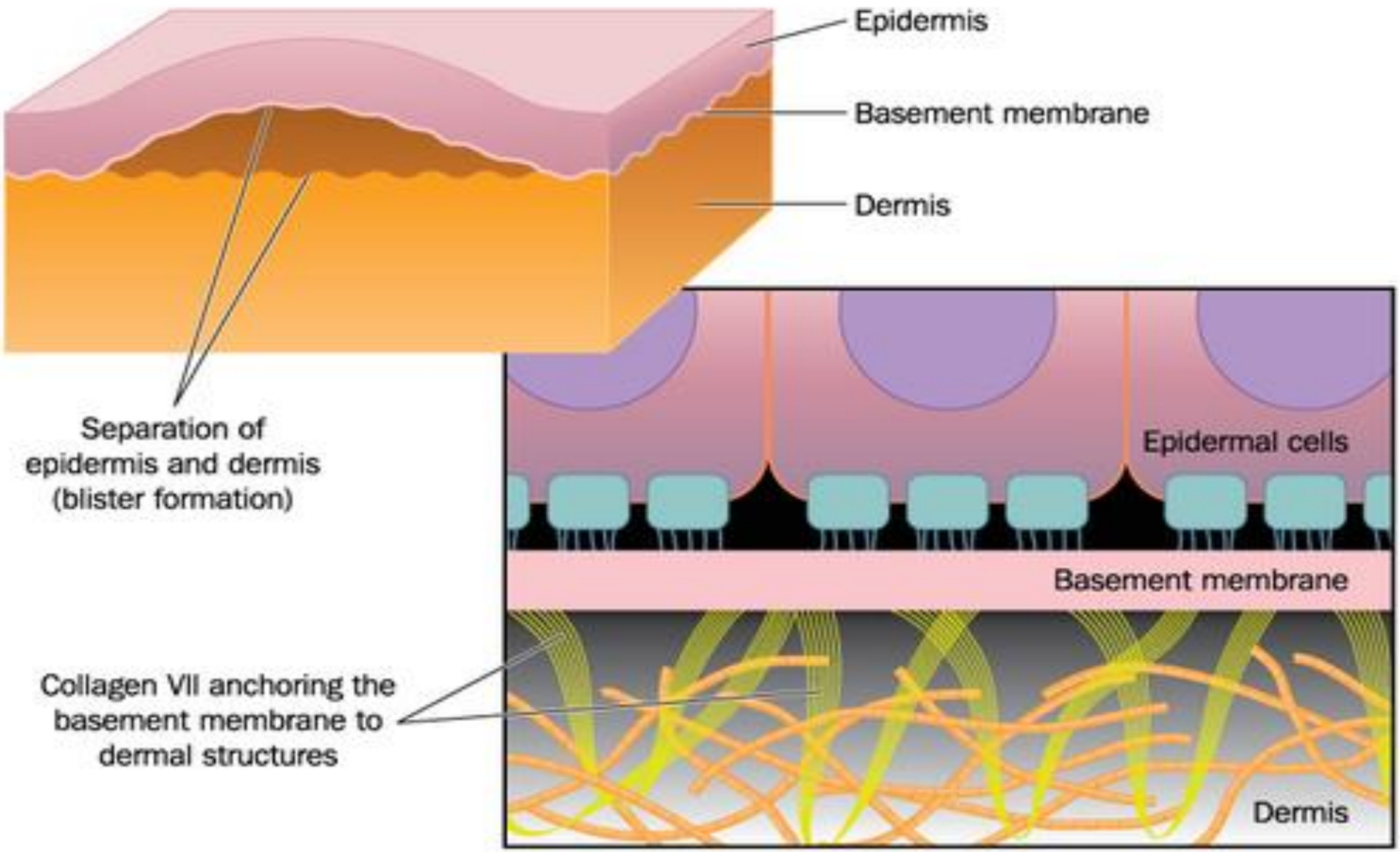
Kindler syndrome is a skin condition with some severe phenotypes. Some of the following images may be graphic.

What is Kindler Syndrome?

Skin blistering

Squamous-cell carcinoma

How do these blisters form in Kindler Syndrome?



Older Kindler syndrome patients develop skin cancer

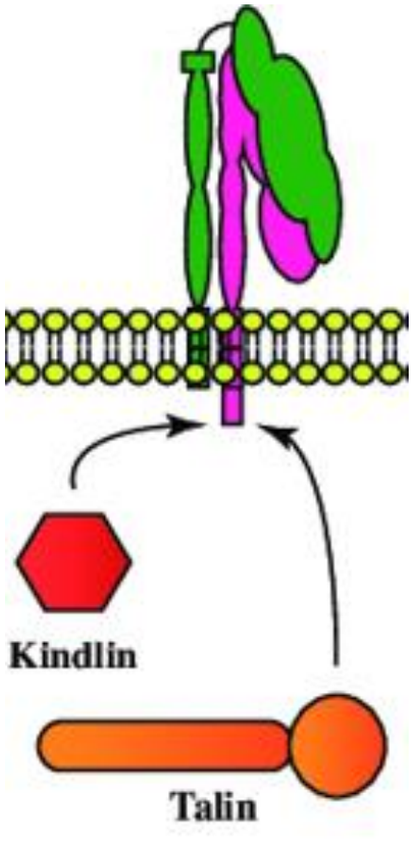
Youth

Adult

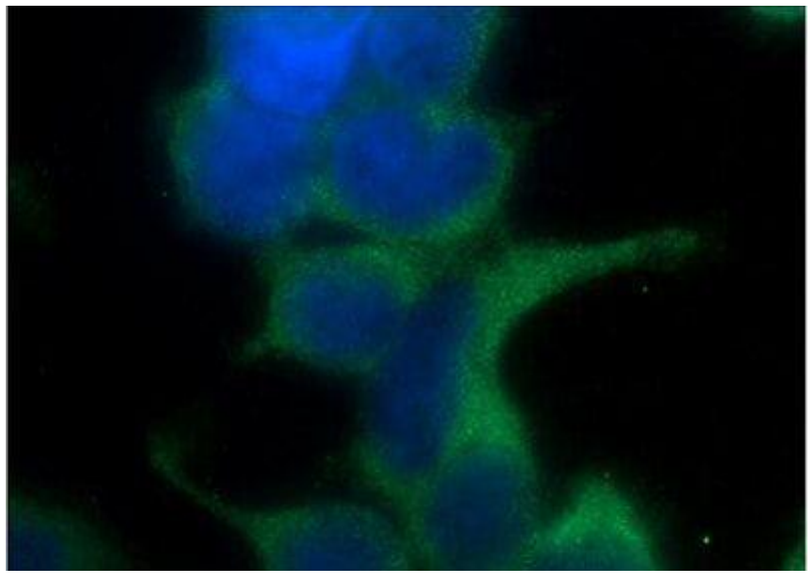
Skin blistering

Squamous cell carcinoma

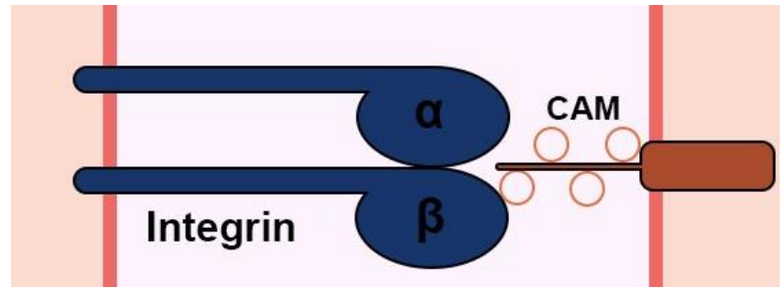
What gene causes Kindler Syndrome?

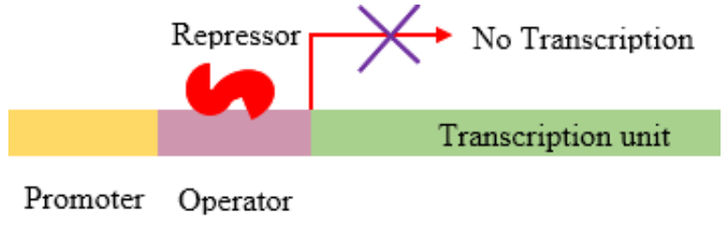


Molecular Function



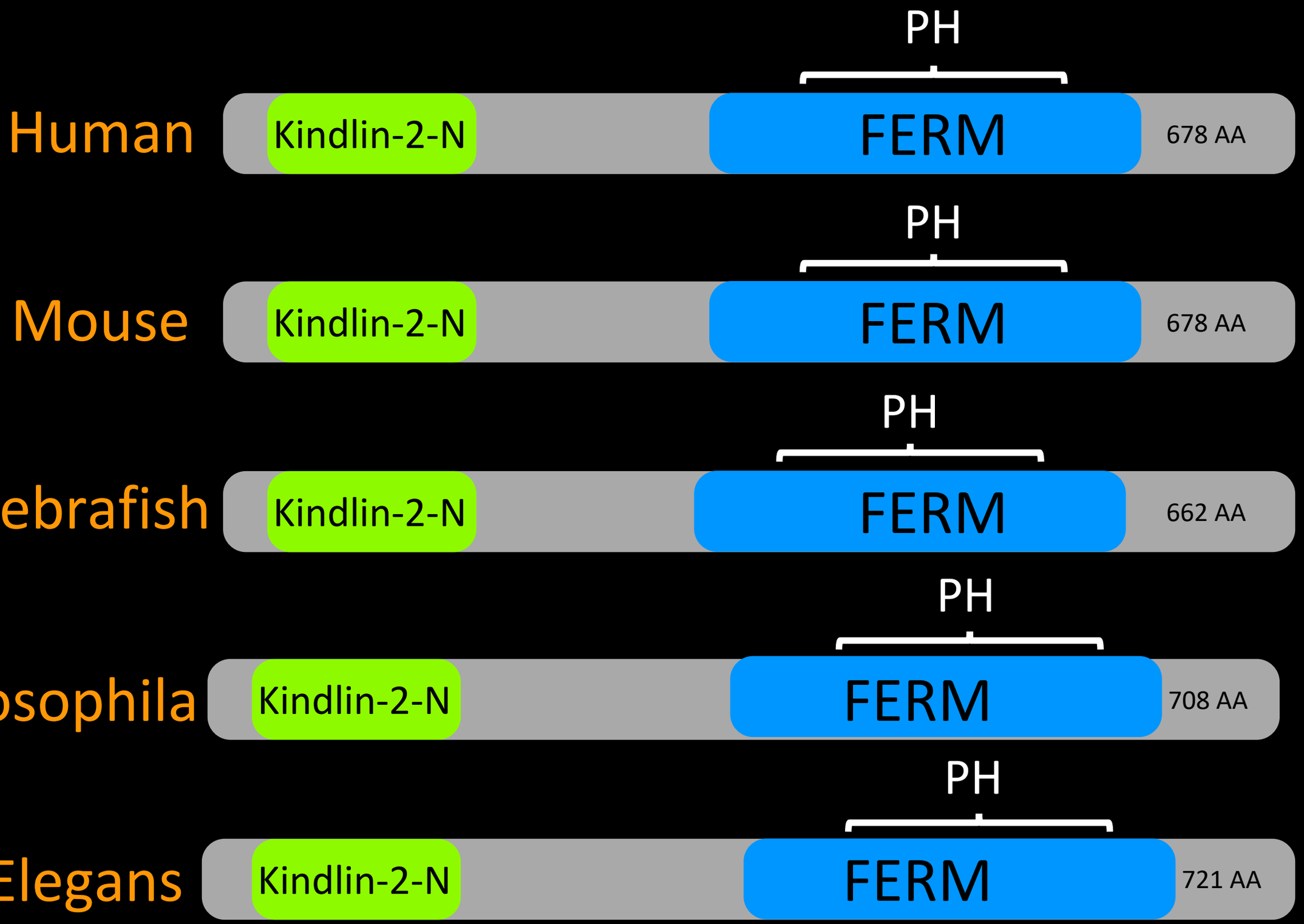
Cellular Component



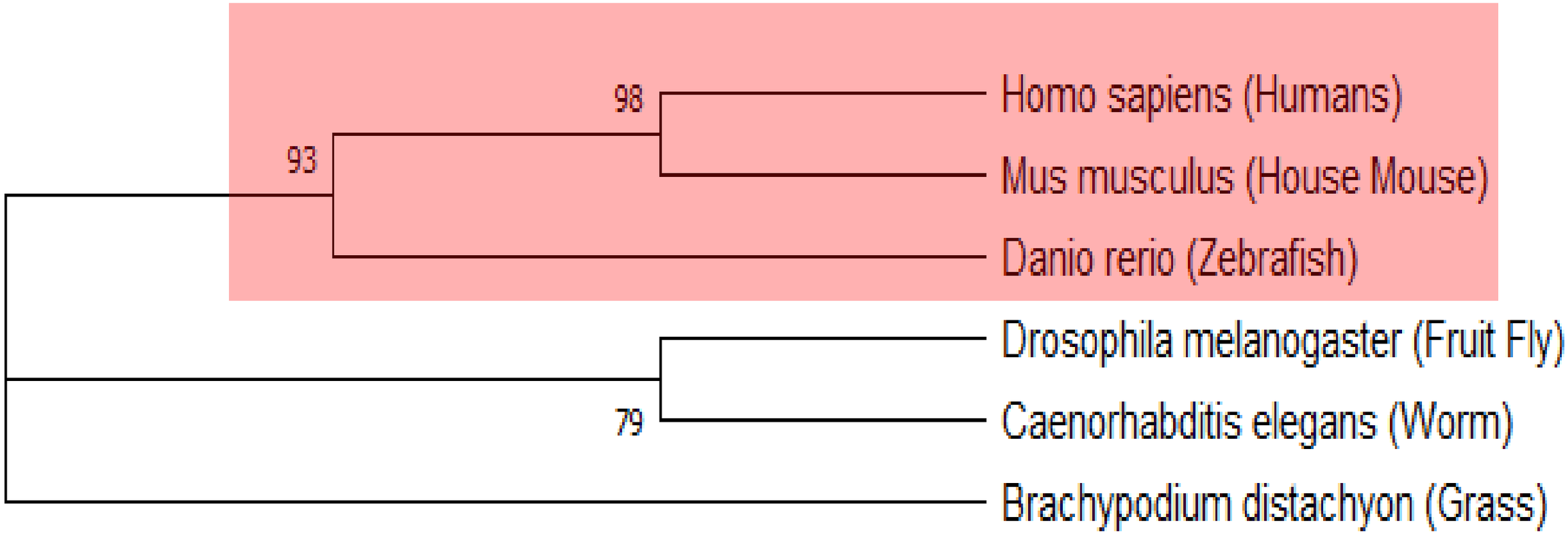


Biological Function

FERMT1 is highly conserved across model organisms

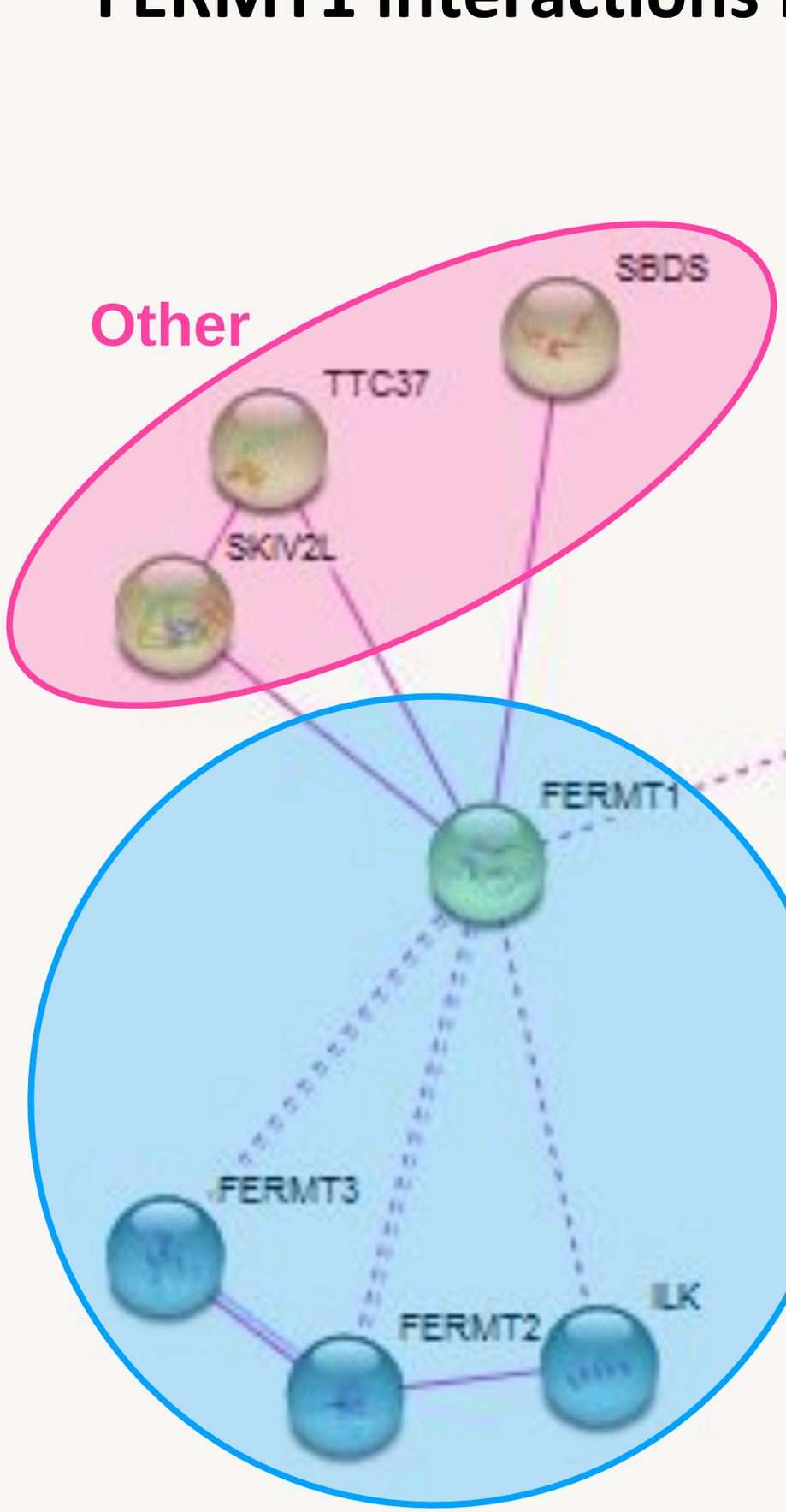


FERMT1 in mice and zebrafish is most closely related to humans

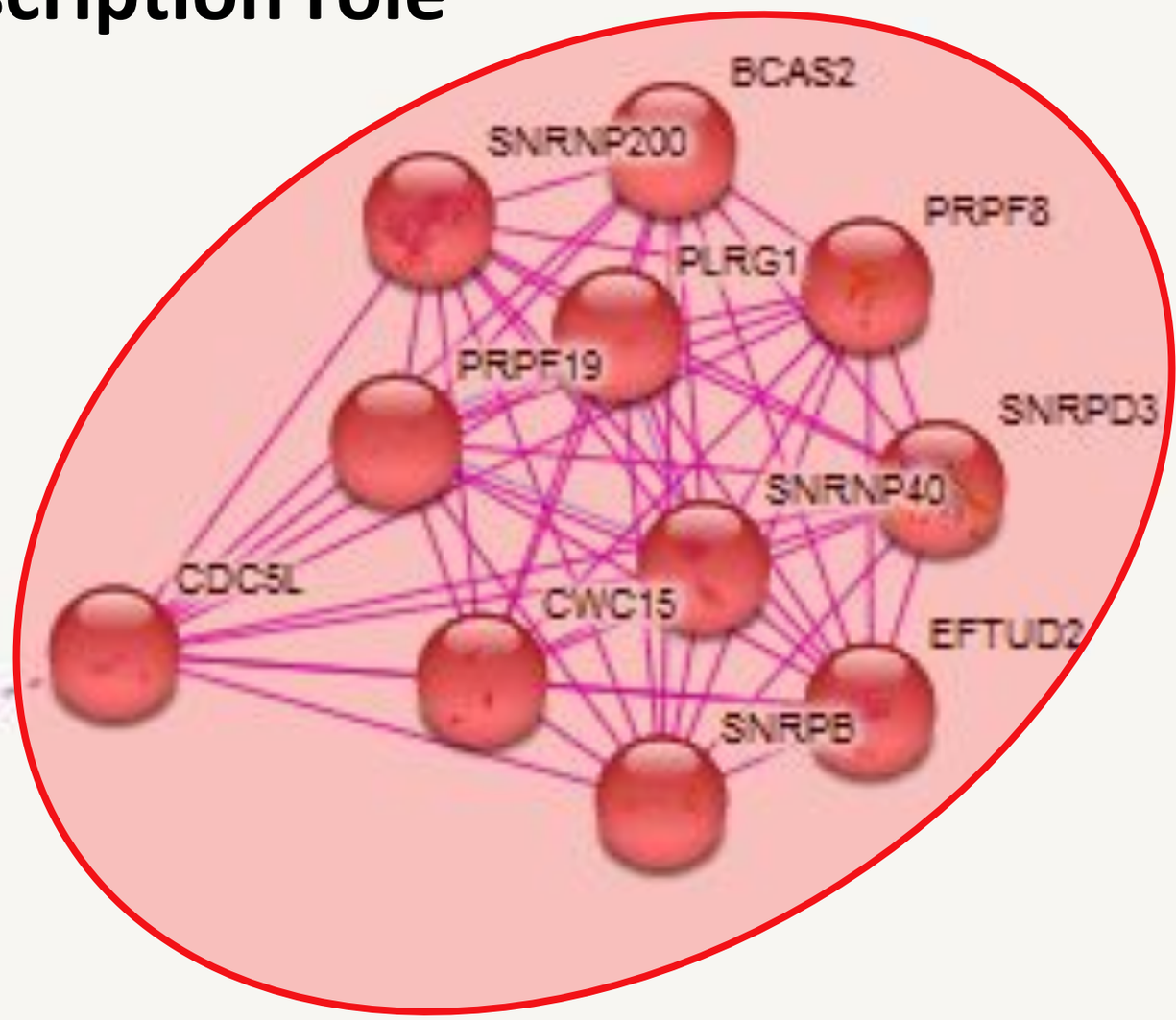


FERMT1 phylogeny

FERMT1 interactions reveal transcription role



Integrin Mediated Signaling Pathway



Transcription regulation

Zebrafish will be used to address my goals

Danio rerio

Inexpensive

Inexpensive

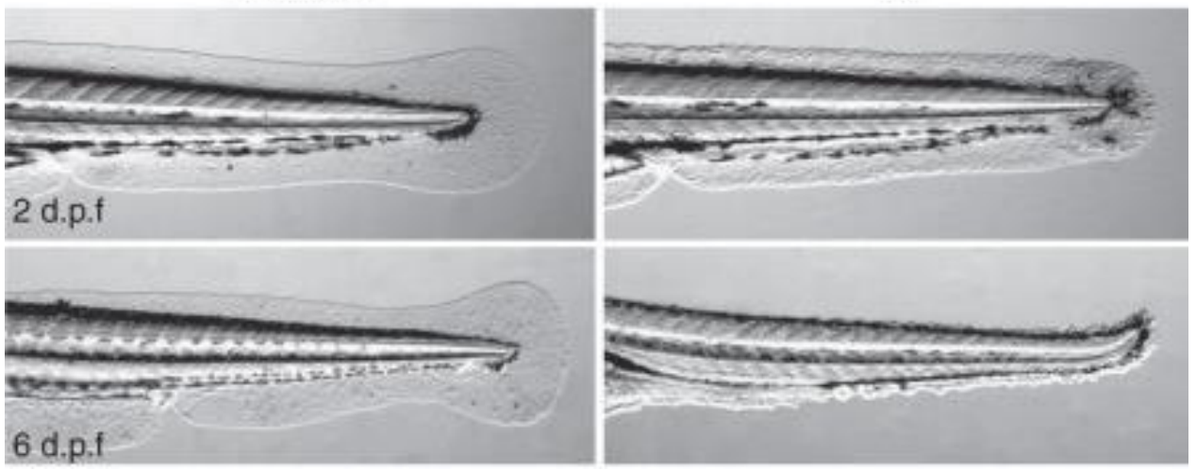
Shows BLISTERING phenotype

Visualize cell division easily

Tumor development

Wild Type

kindlin mutant

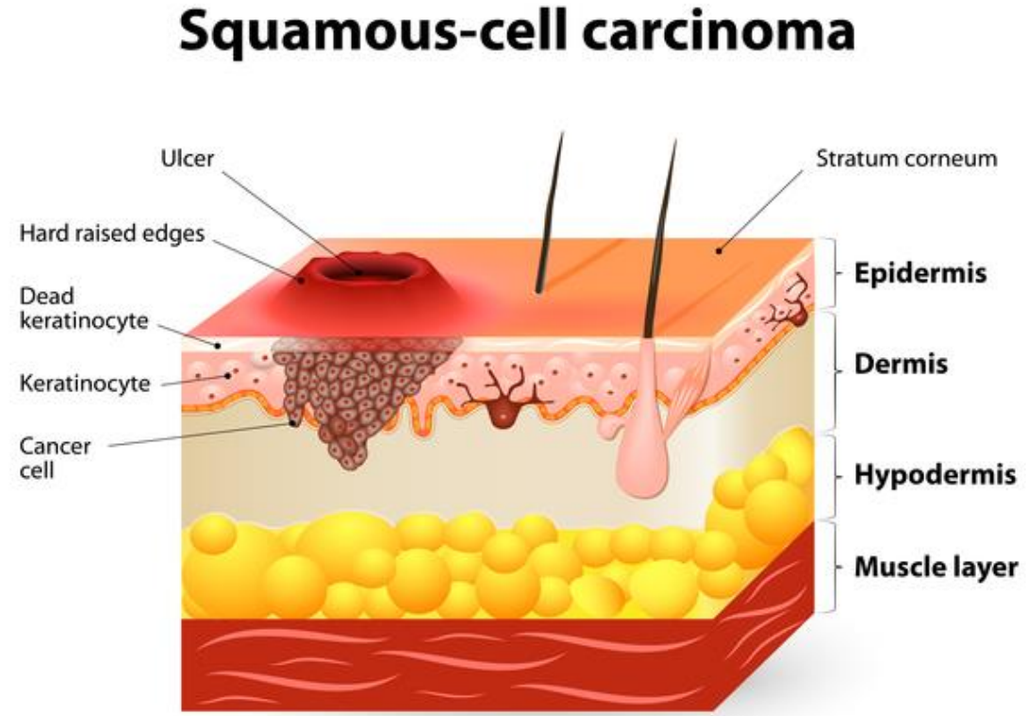


Postel, et. Al 2013

GAP: Why does loss of Kindlin-1 lead to development of squamous-cell carcinomas in older patients?

Human

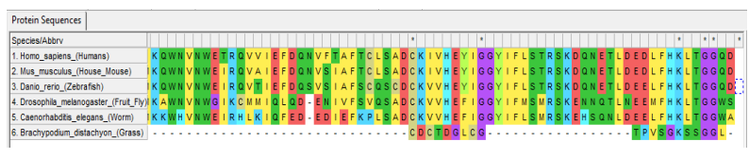
vs.



GOAL: Determine the role of FERMT1 in mediating cell proliferation

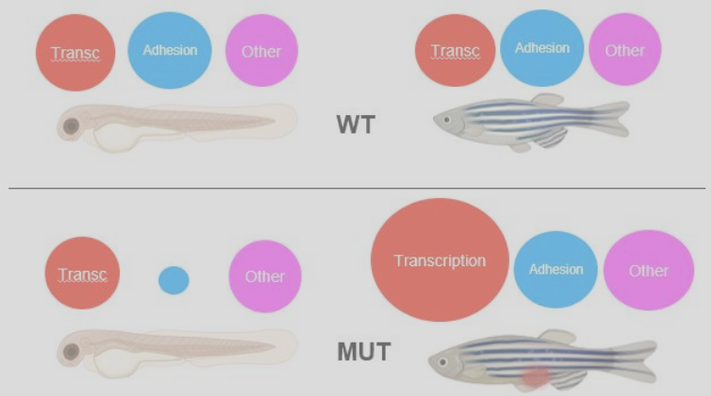
Human

AIM 1



Identify highly conserved residues of FERMT1 that maintain cell proliferation in skin in older patients

AIM 2

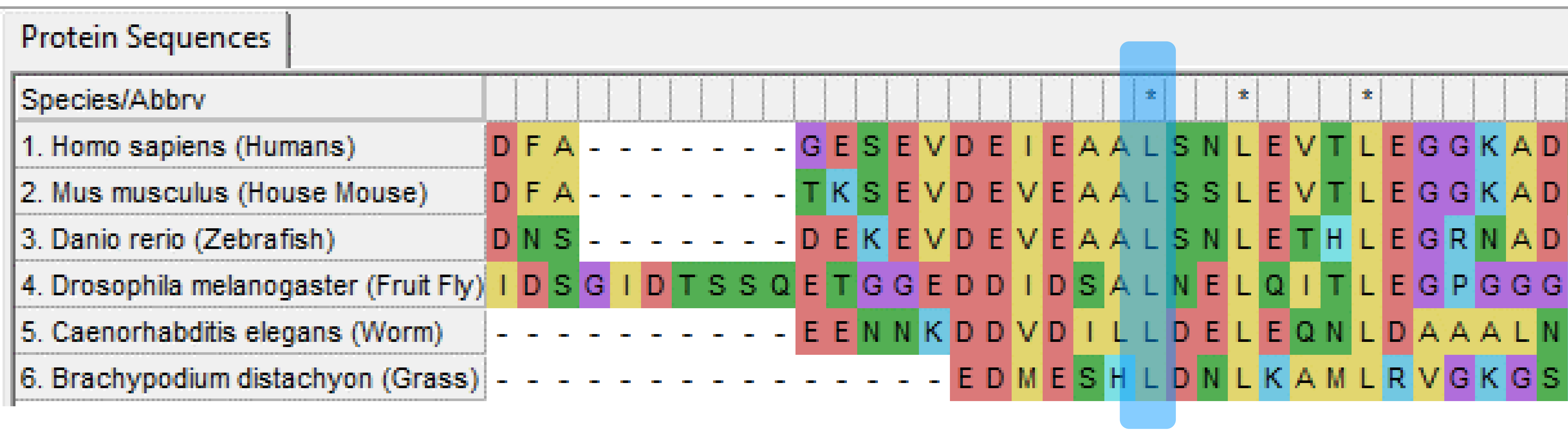


Identify differentially expressed genes in adult zebrafish mutants versus adolescent

AIM 3

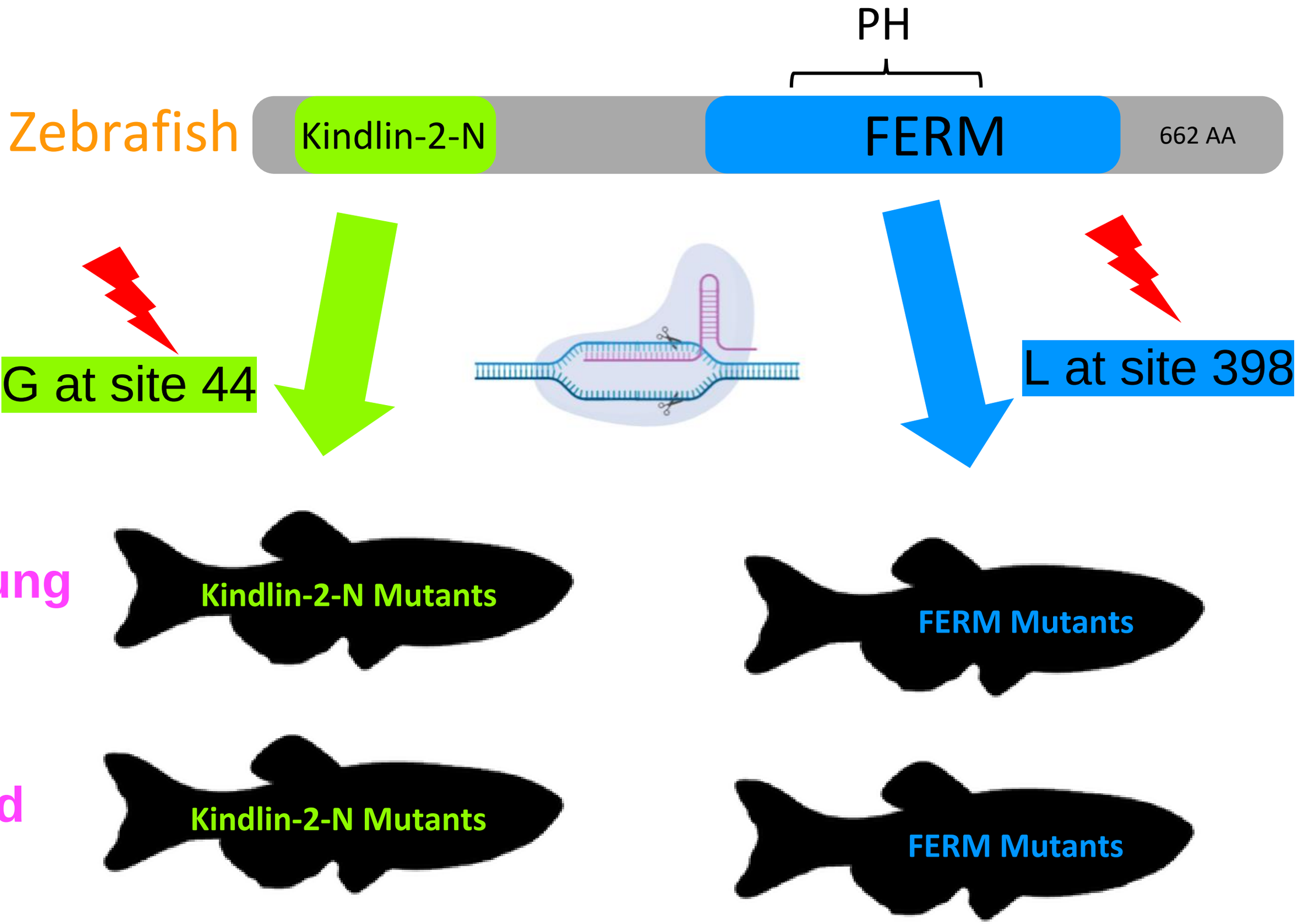
Identify protein interactions of FERMT1 in adult zebrafish mutants versus adolescent

AIM1: Determine which amino acids/domain are important for cell proliferation in the skin in older fish



The amino acids highly conserved in all species will be important for cell proliferation in older fish

AIM1: Truncation of kindlin-1 via CRISPR-Cas9 mutation



AIM1: Expected phenotypes in young and old FERMT1 mutants

Young

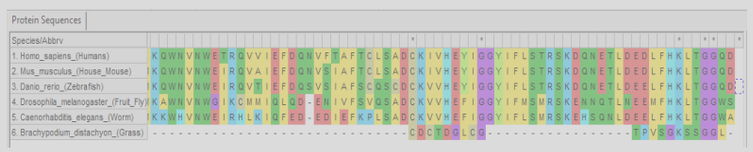
Old

Both **young** mutants will show **blistering** phenotype

Both **old** mutants will grow **tumors**

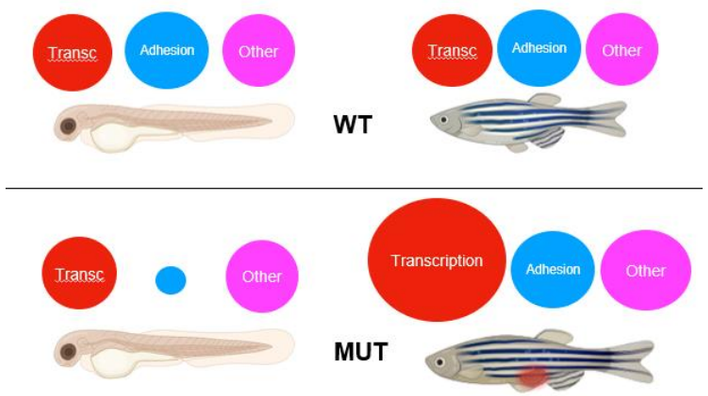
GOAL: Determine the role of FERMT1 in mediating cell proliferation

AIM 1



Identify highly conserved residues of FERMT1 that maintain cell proliferation in skin in older patients

AIM 2



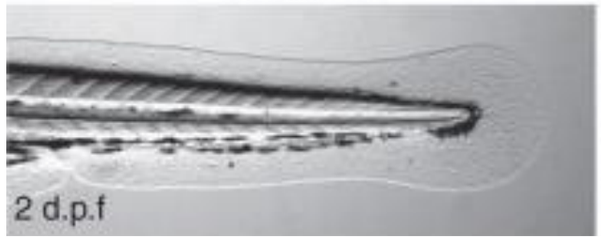
Identify differentially expressed genes in adult zebrafish mutants versus adolescent

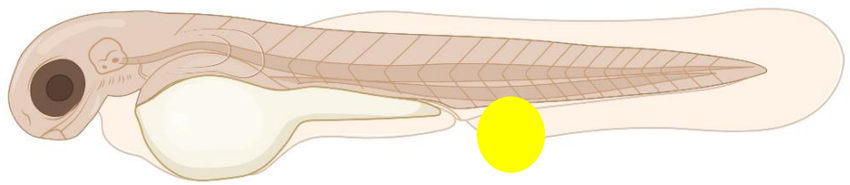
AIM 3

Identify protein interactions of FERMT1 in adult zebrafish mutants versus adolescent

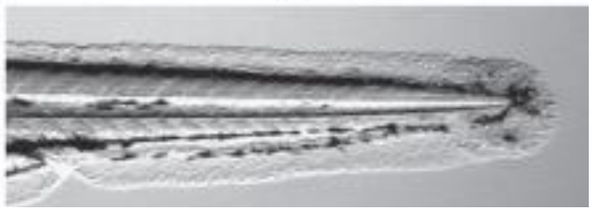
AIM2: Single-cell RNA Seq on young and old fish

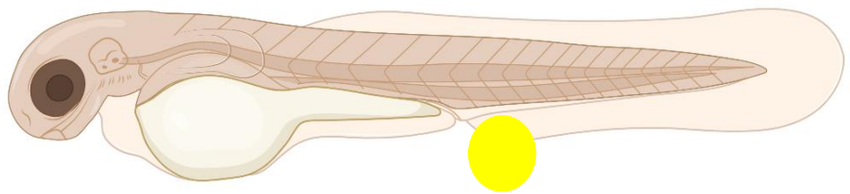
Wild Type

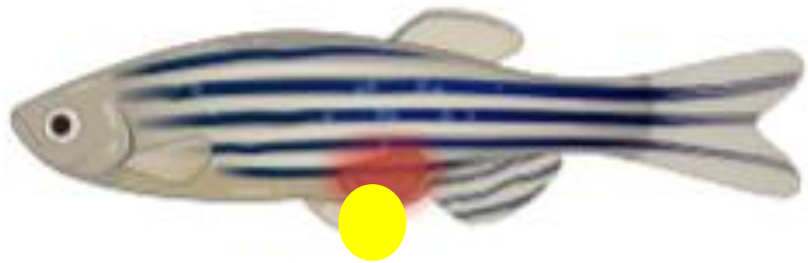




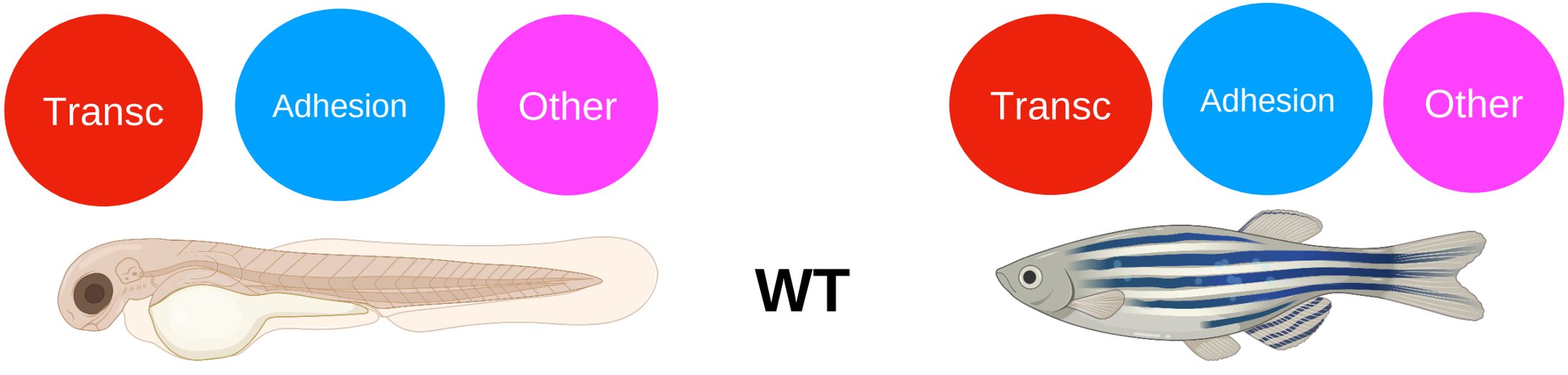
kindlin mutant







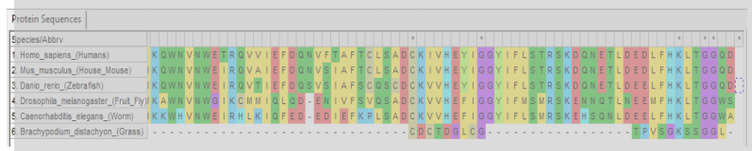
AIM2: Identify differentially expressed genes in adult mutants



Transcription related and adhesion related gene expression will **increase** significantly in **adult mutants**

GOAL: Determine the role of FERMT1 in mediating cell proliferation

AIM 1



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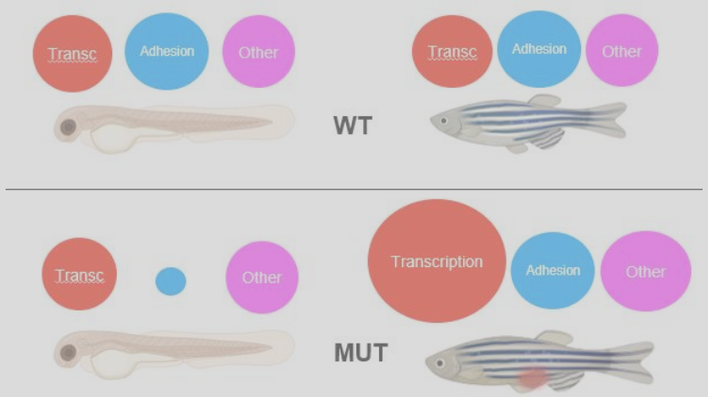
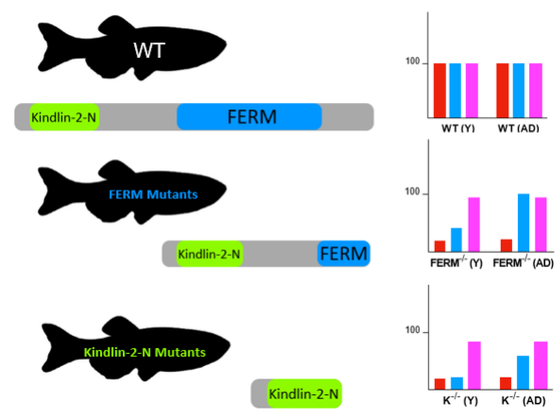
AIM 2



Identify differentially expressed genes in adult zebrafish mutants versus adolescent

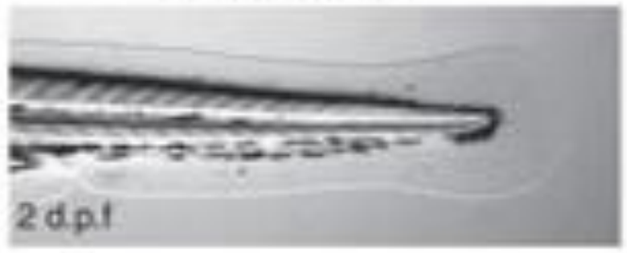
AIM 3



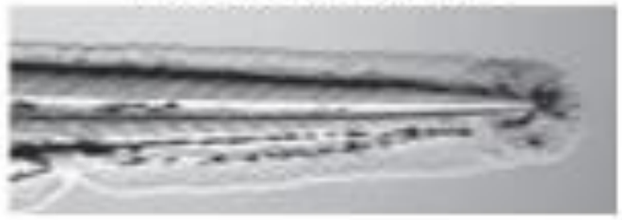
Identify protein interactions of FERMT1 in adult zebrafish mutants versus adolescent

AIM3: Sample protein interaction in fins of FERMT1 mutants *in vivo*

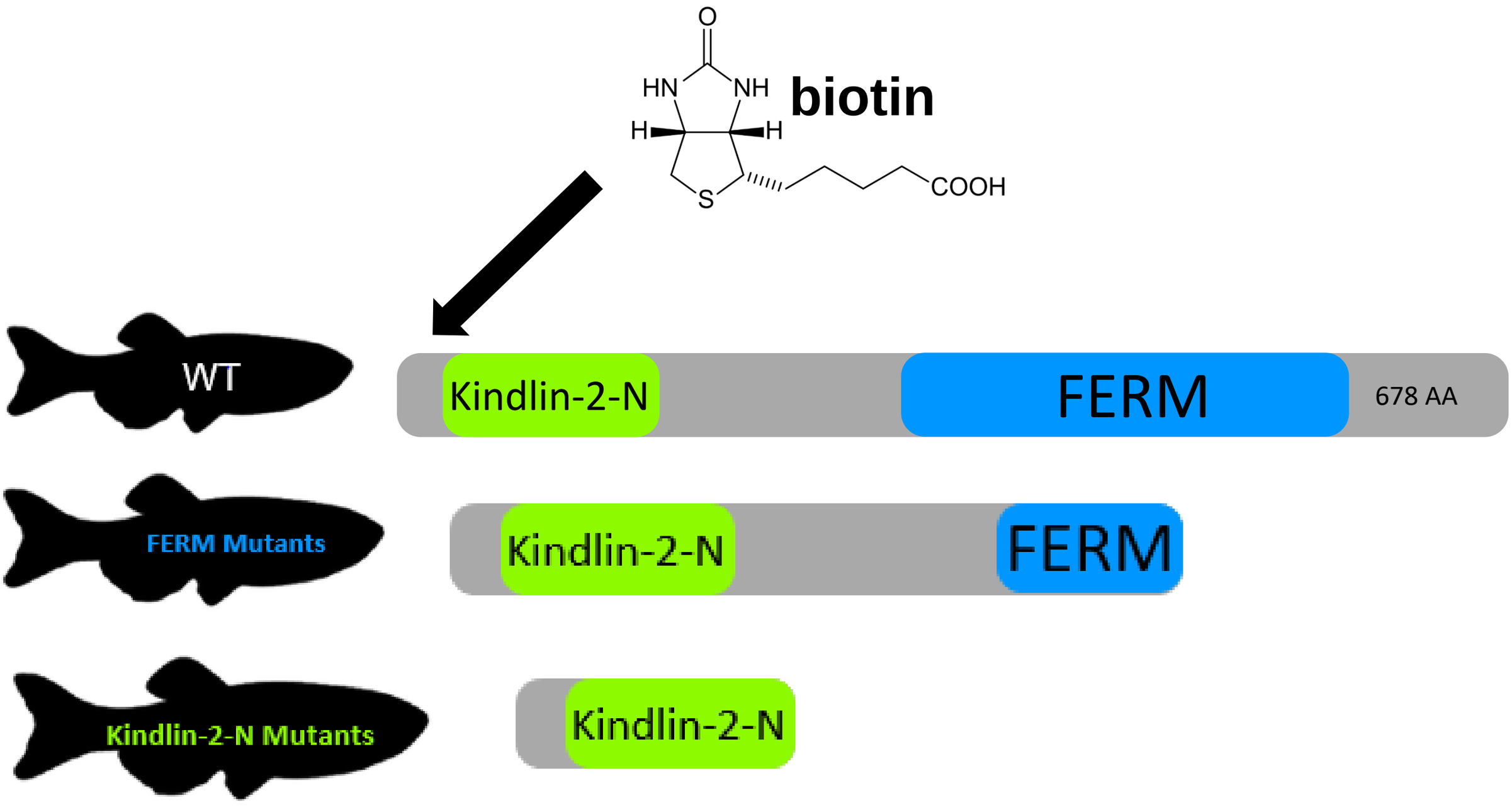
Wild Type



kindlin mutant

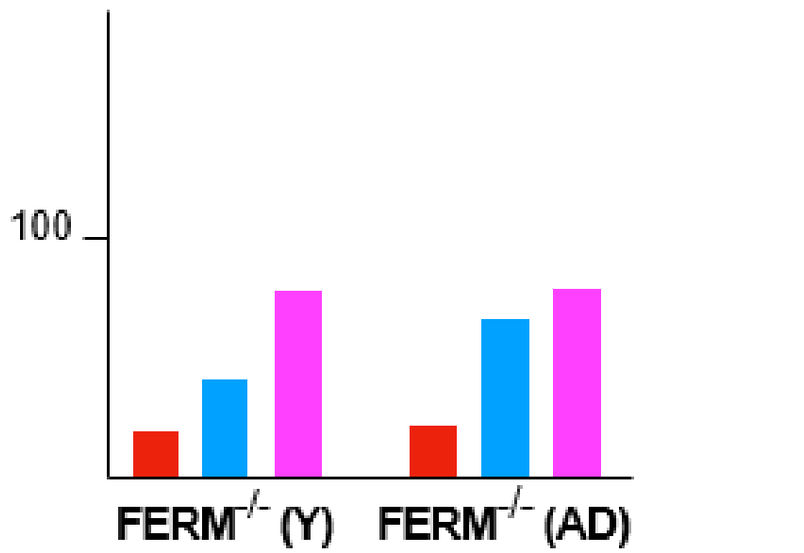


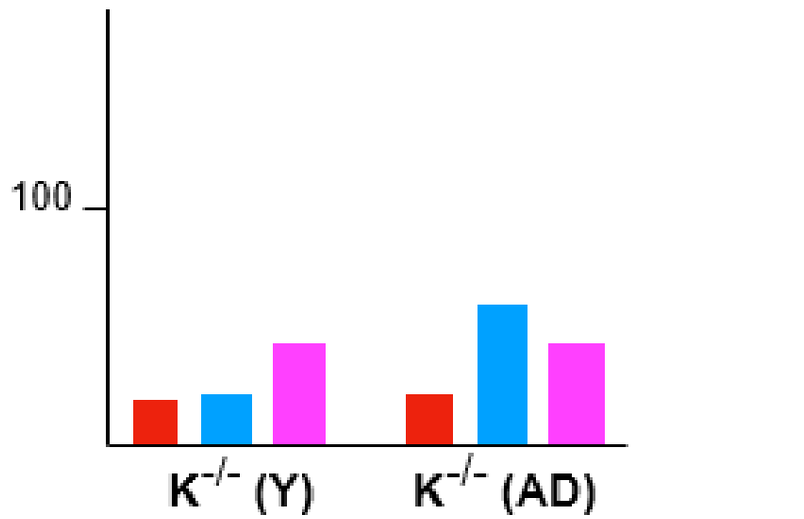
AIM3: Adding biotin to FERMT1



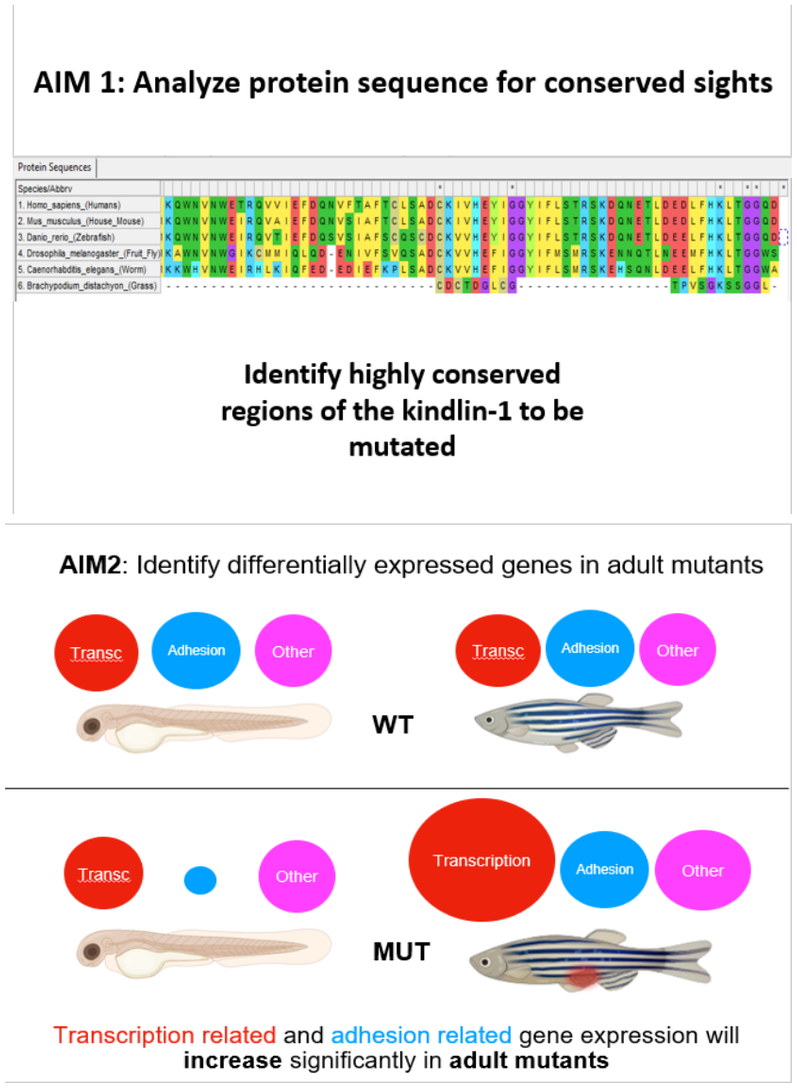
Add biotin near the N-terminus so it is in the same place for all mutants

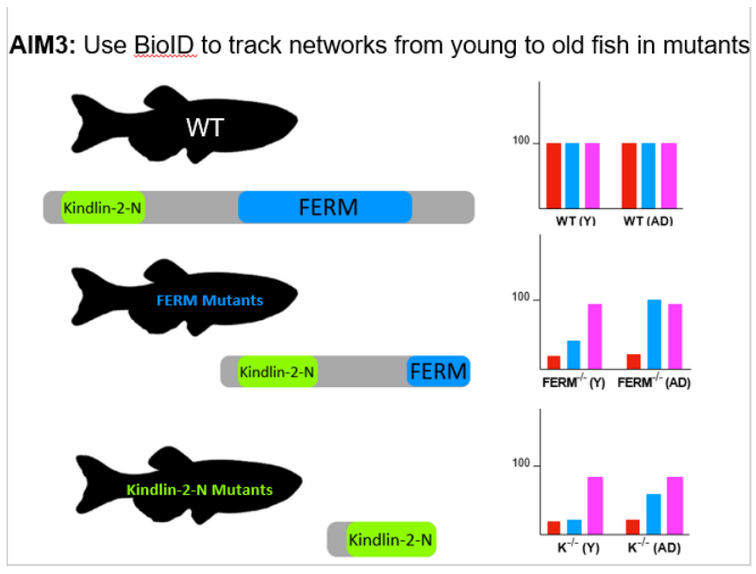
AIM3: Use BioID to track networks from young to old fish in mutants





Summary



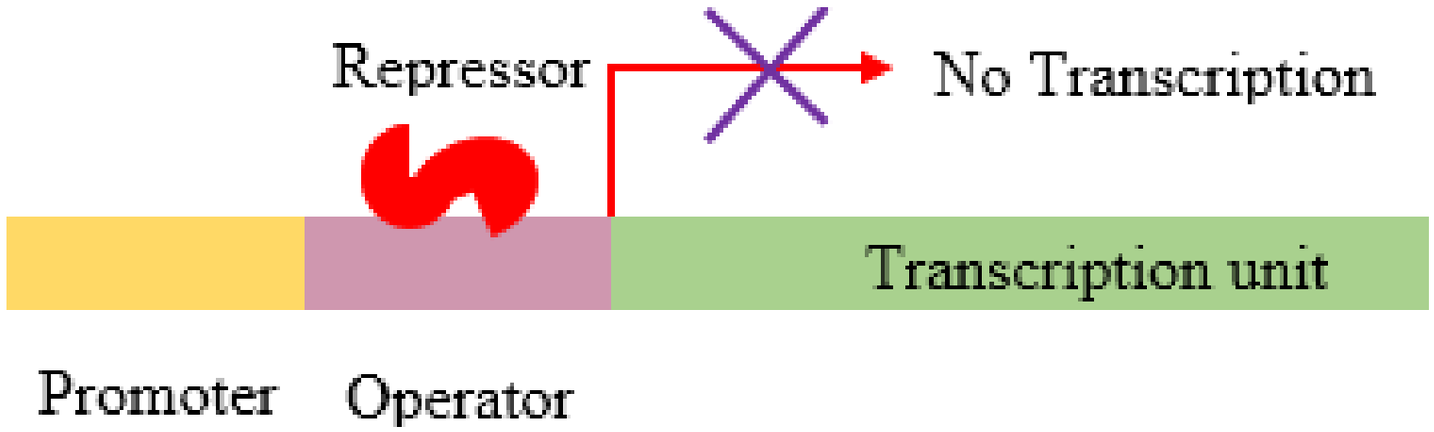


AIM1: Identify highly conserved residues of FERMT1 that maintain cell proliferation in skin in older patients

AIM2: Identify differentially expressed genes in adult zebrafish mutants versus adolescent

AIM1: Identify protein interactions of FERMT1 in adult zebrafish mutants versus adolescent

Future Directions



Does FERMT2 have a role in regulating cell proliferation?

FERMT2 rescues FERMT1 mutations

References

Epidermis Picture: https://ghr.nlm.nih.gov/condition/kindler-syndrome

Kindler Syndrome picture: https://www.debra.org.uk/uk-funded-projects/sonnenberg-kindler-syndrome
Kindler Knee: https://www.researchgate.net/figure/Clinical-features-of-Kindler-syndrome-a-b-Poikiloderma-with-hyperpigmentation-and_fig1_229161951
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Kindlin-1 function: https://www.researchgate.net/figure/Molecular-mechanisms-for-integrin-activation-Integrins-exist-in-two-activation-states-on_fig4_323191947
Zebrafish embryo: http://sitn.hms.harvard.edu/art/2014/zebrafish-embryo-development/
Zebrafish adult: http://www.sleepreviewmag.com/2019/10/zebrafish-study-sheds-light-sleep-regulated-brain/
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