Morphogen Control of Wing Growth through the Fat Signaling Pathway

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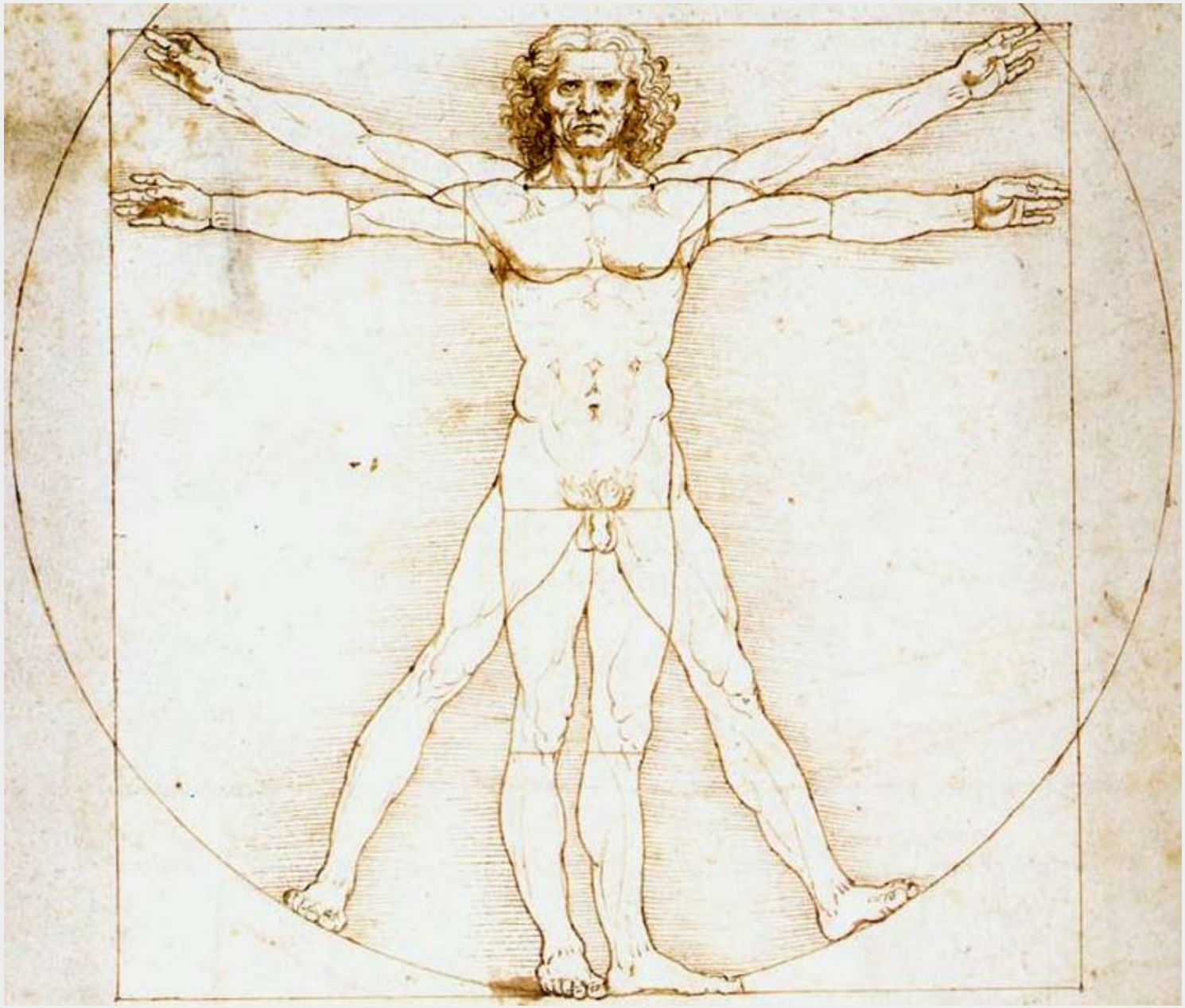
KITP Workshop: Physics and Biology of Morphogenesis

March 7, 2008

Morphogen Control of Wing Growth through the Fat Signaling Pathway

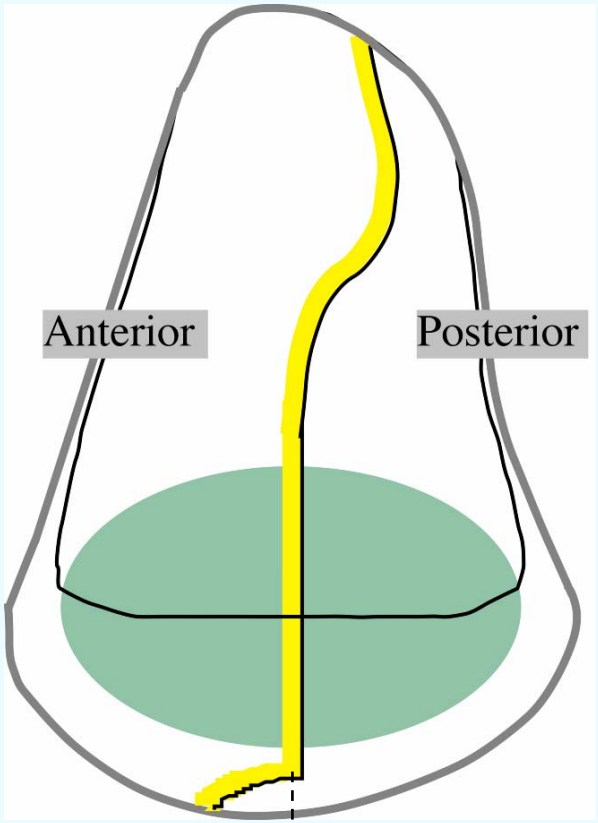
Yaopan Mao **Eunjoo Cho** **Dragana Rogulja** **Cordelia Rauskolb**

Patterning and Growth

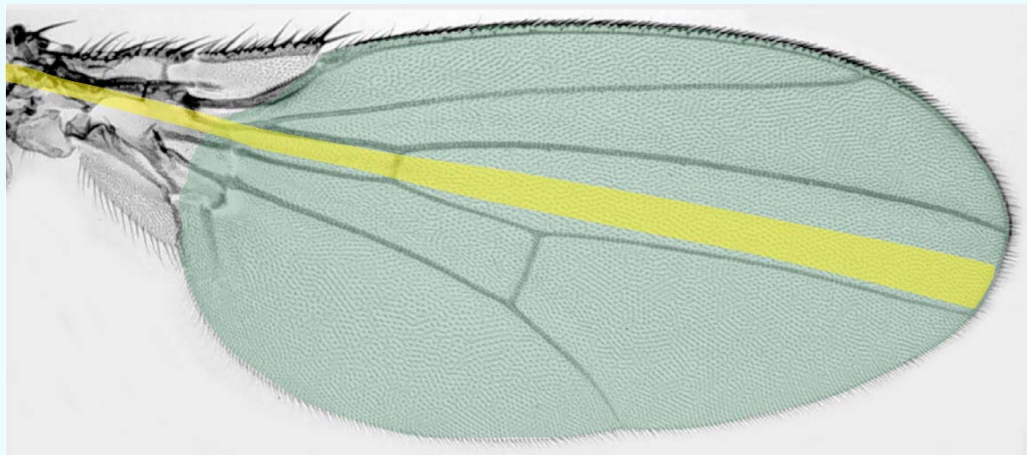


Anterior-Posterior Patterning of the *Drosophila* Wing

Wing imaginal disc

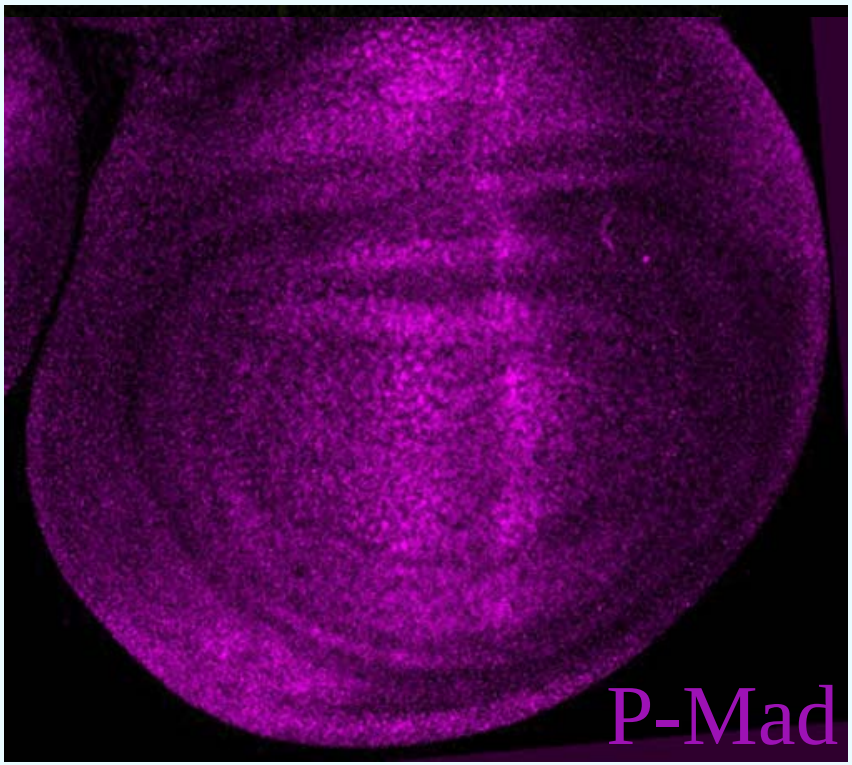


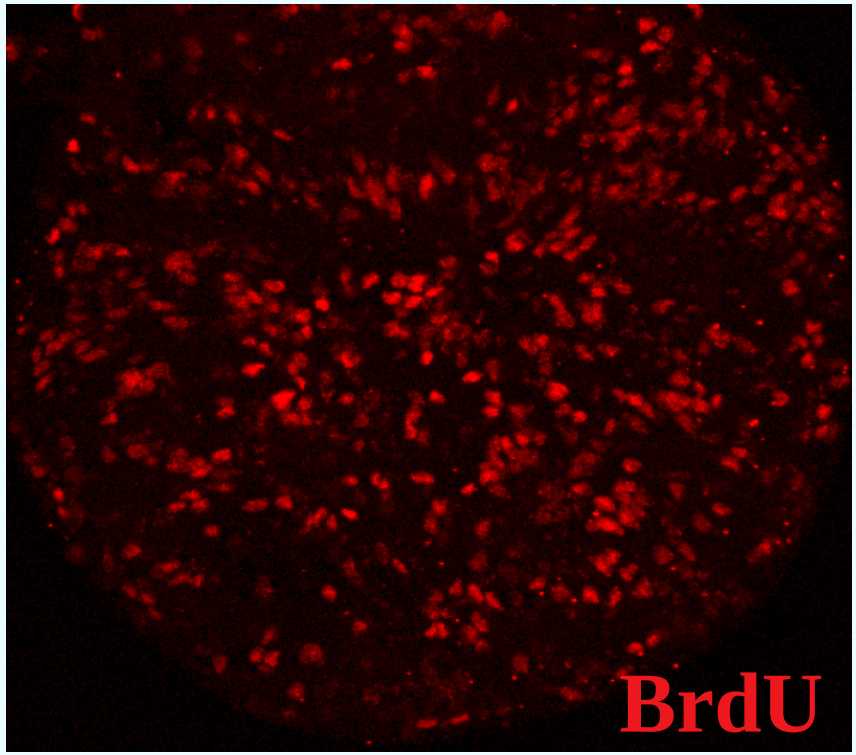
Adult wing



Decapentaplegic (DPP)

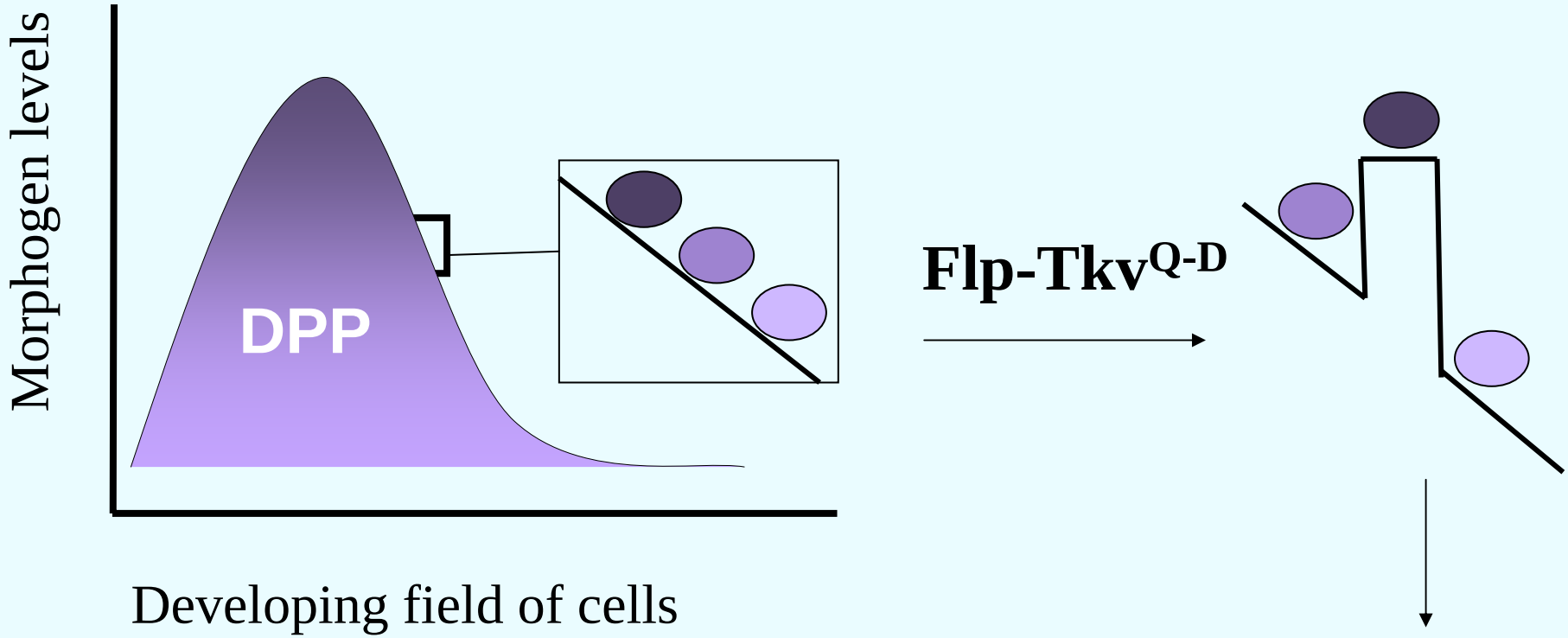
How is the gradient of DPP pathway activity converted into even growth?





Tests of the gradient model:

1. Create ectopic, sharp juxtaposition in Dpp signaling values

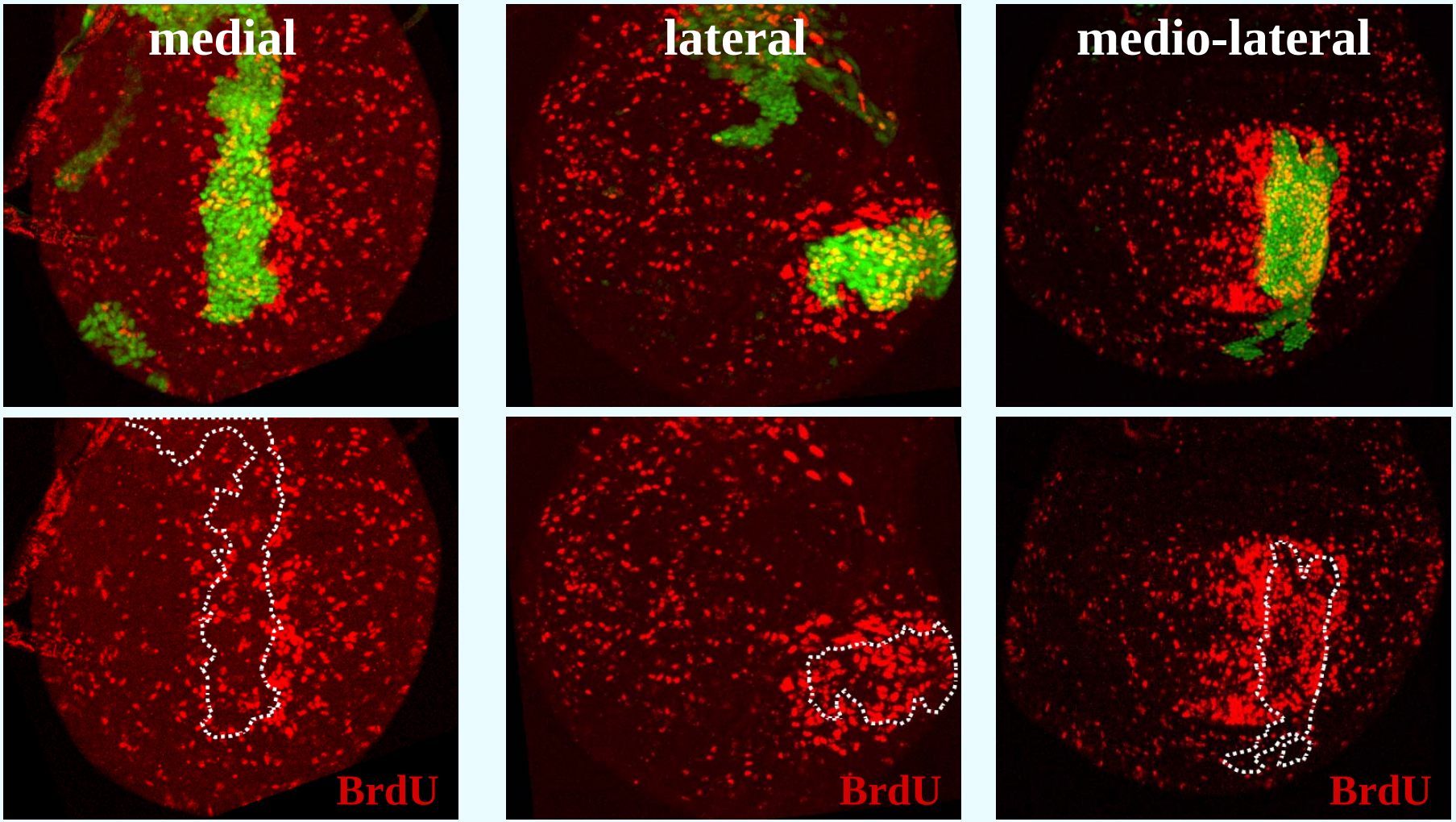


Dragana Rogulja

Clones of cells expressing an activated form of a DPP receptor (Tkv^{Q-D}) exert non-autonomous effects on cell proliferation:

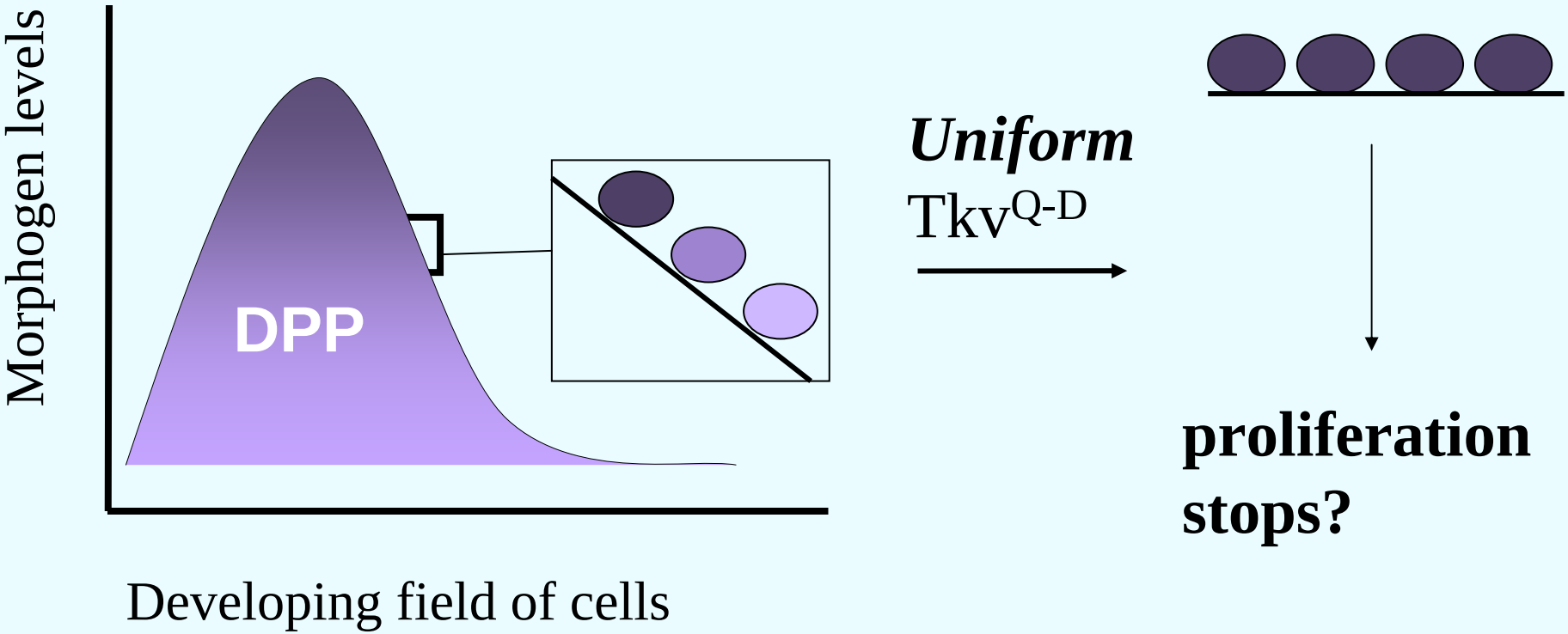
UAS-tkv^{Q-D}

8-24^{h} after induction



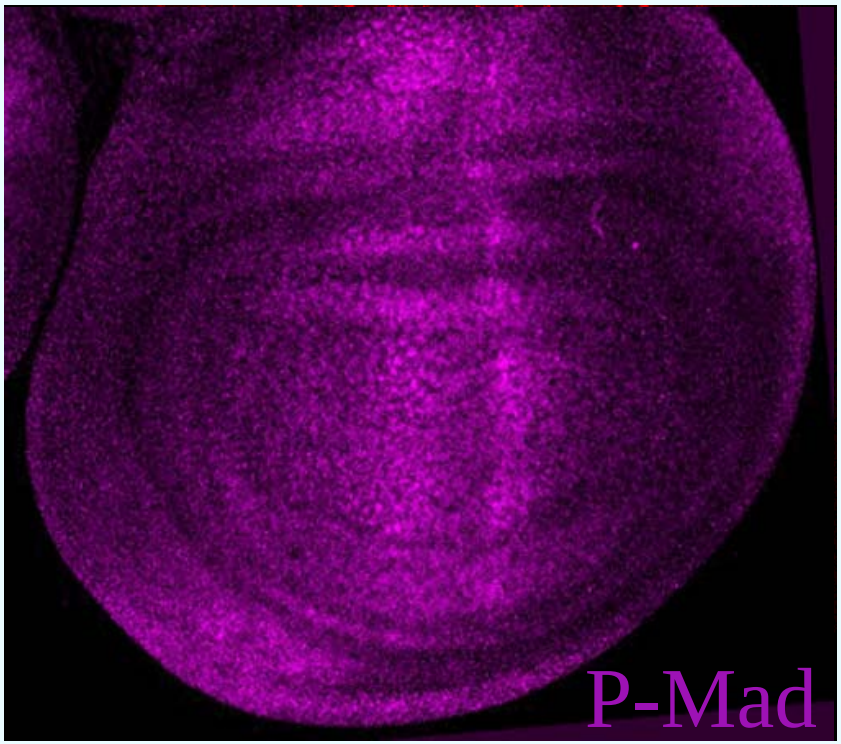
Tests of the gradient model:

2. Is the gradient of DPP *necessary* in the wing?

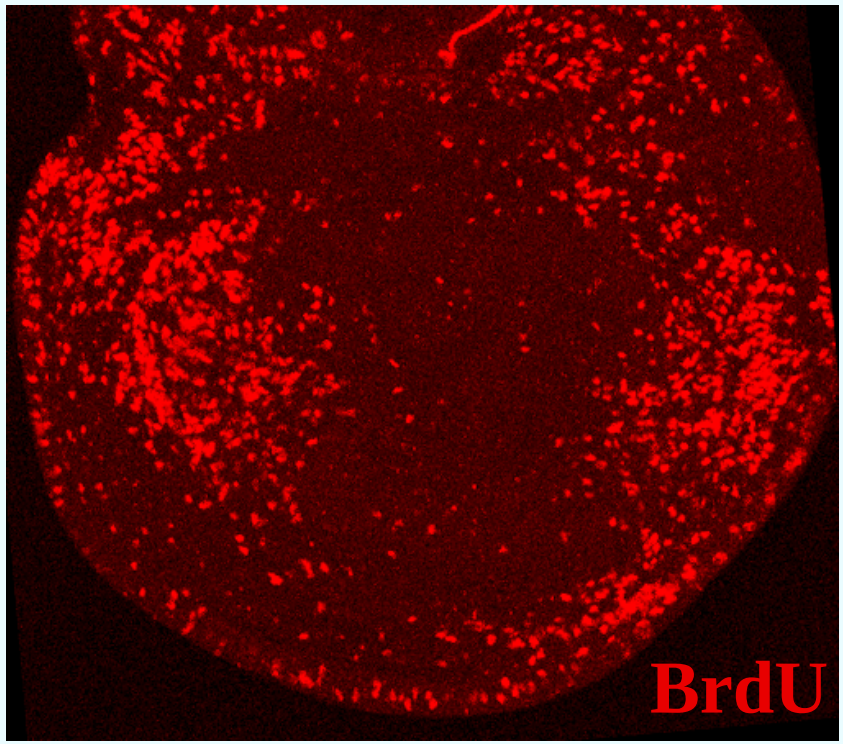


Uniform Tkv^{Q-D}: <u>medial</u> wing cells <u>stop</u> proliferating

0^h



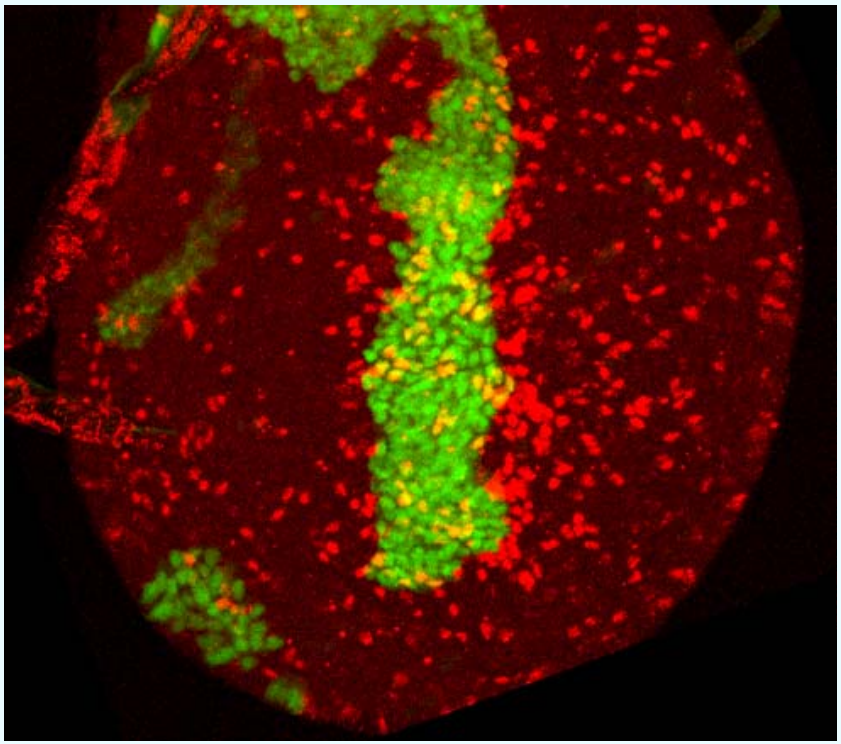
18^h RU486



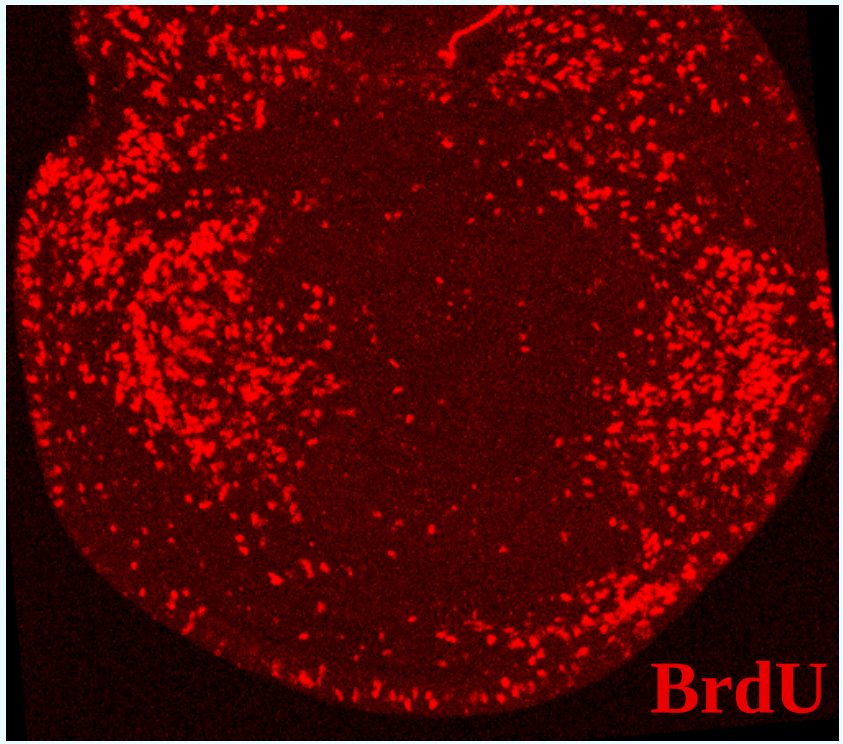
A Gradient of DPP is *necessary* for medial proliferation

Uniform versus clonal activation of Tkv

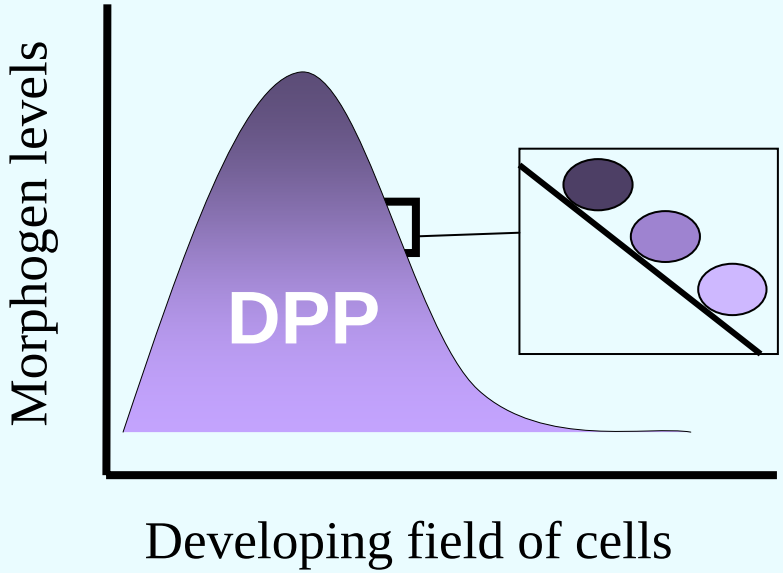
Clone



Uniform



Juxtaposition of cells that perceive different levels of DPP signaling is essential for medial cell proliferation



Converting morphogen gradients into growth

Requires a signaling pathway that:

-Is regulated by graded signals

-Involves cell surface molecules that could be used to compare "positional values"

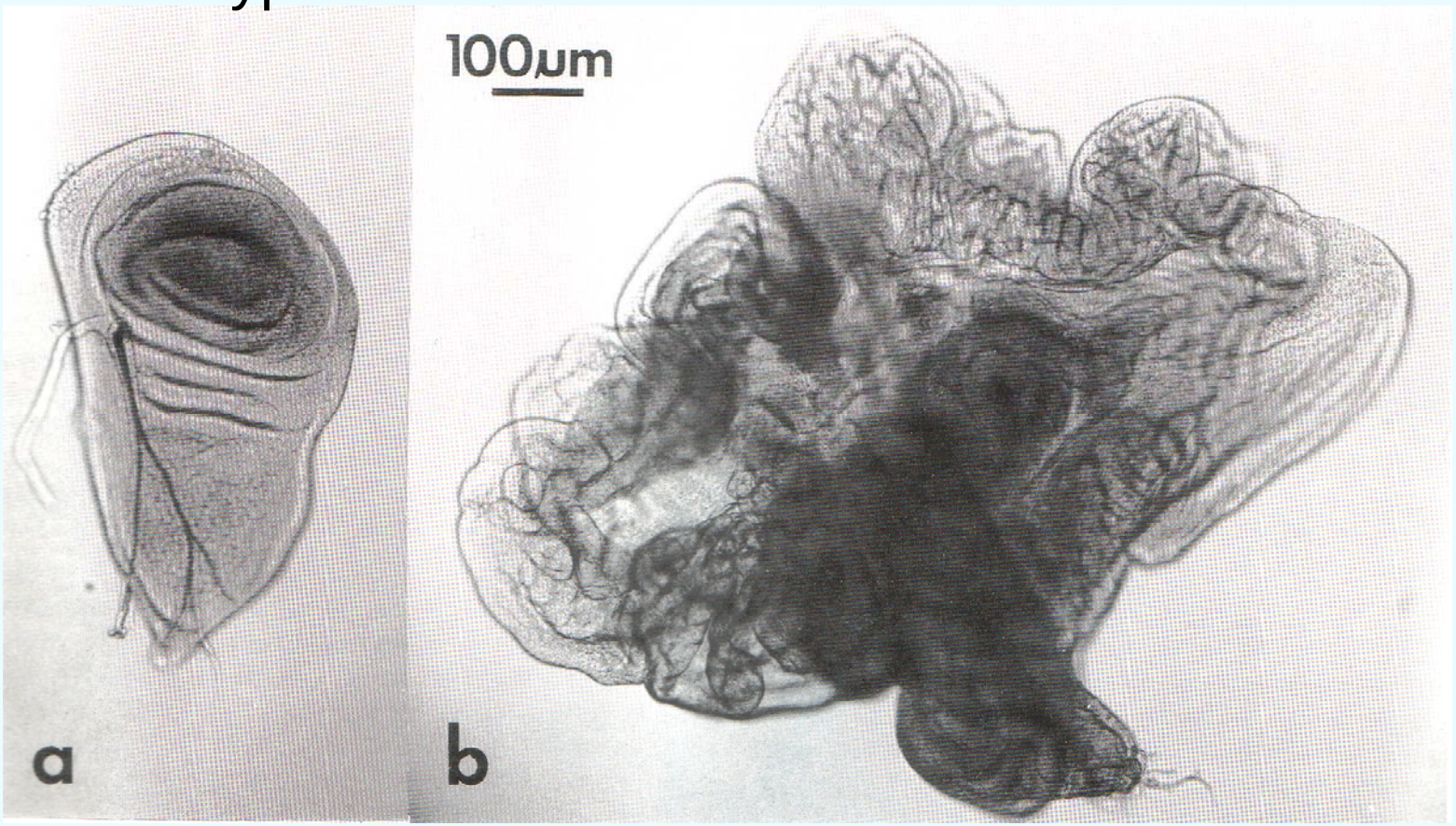
-Controls Growth

The Fat signaling pathway fulfills these criteria

fat, a *Drosophila* tumor suppressor

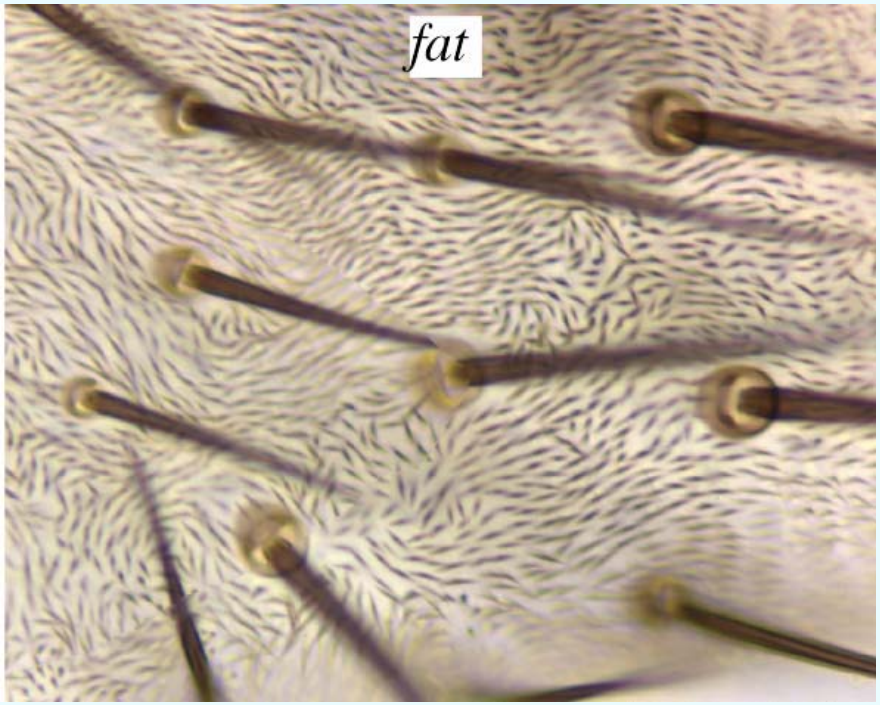
Wild type

fat^{fd}



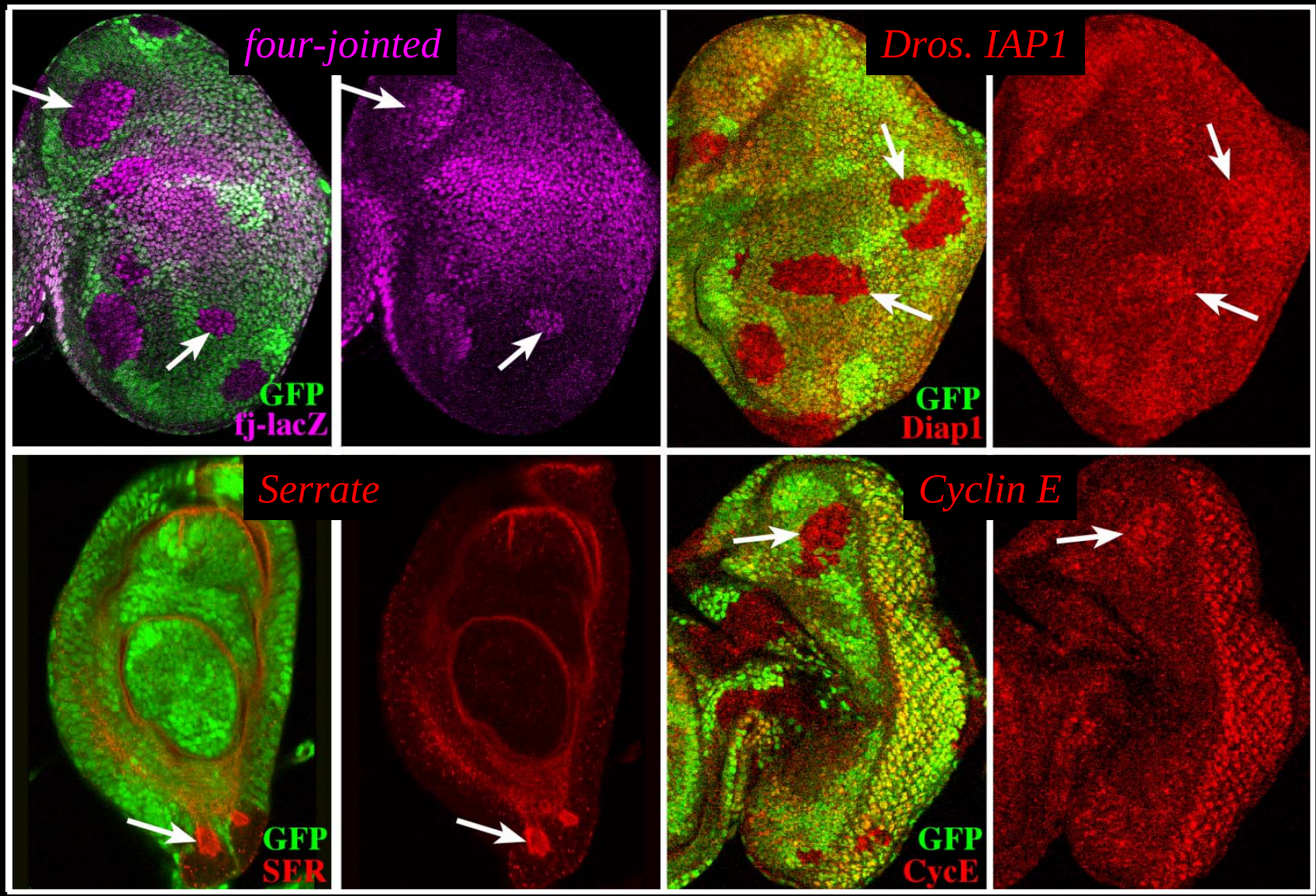
Mahoney *et al*, 1991. Cell *(5)*

fat, a regulator of PCP



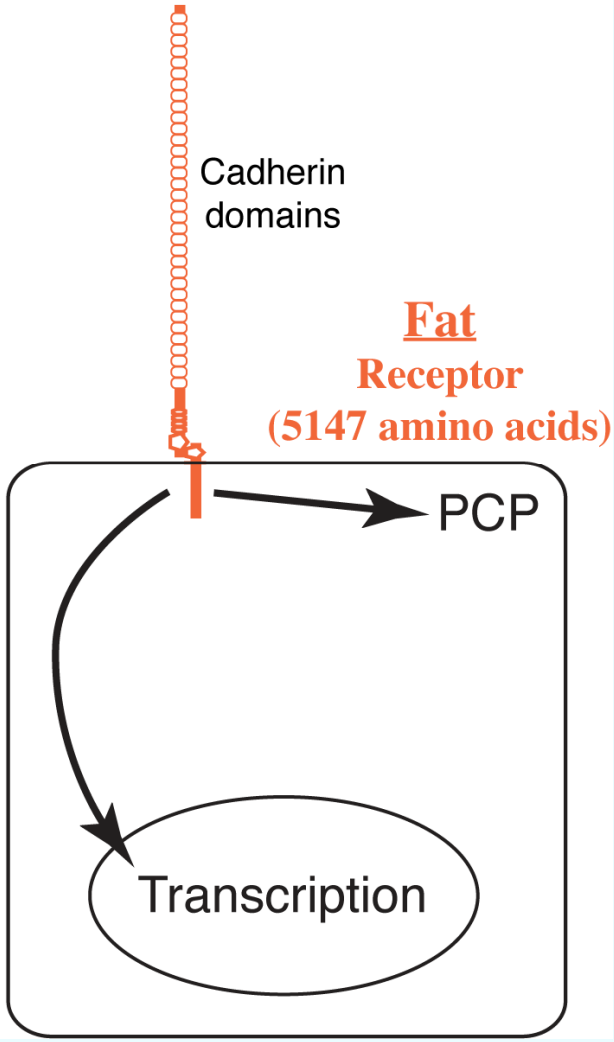
Fat, a regulator of gene expression

fat⁻ clones

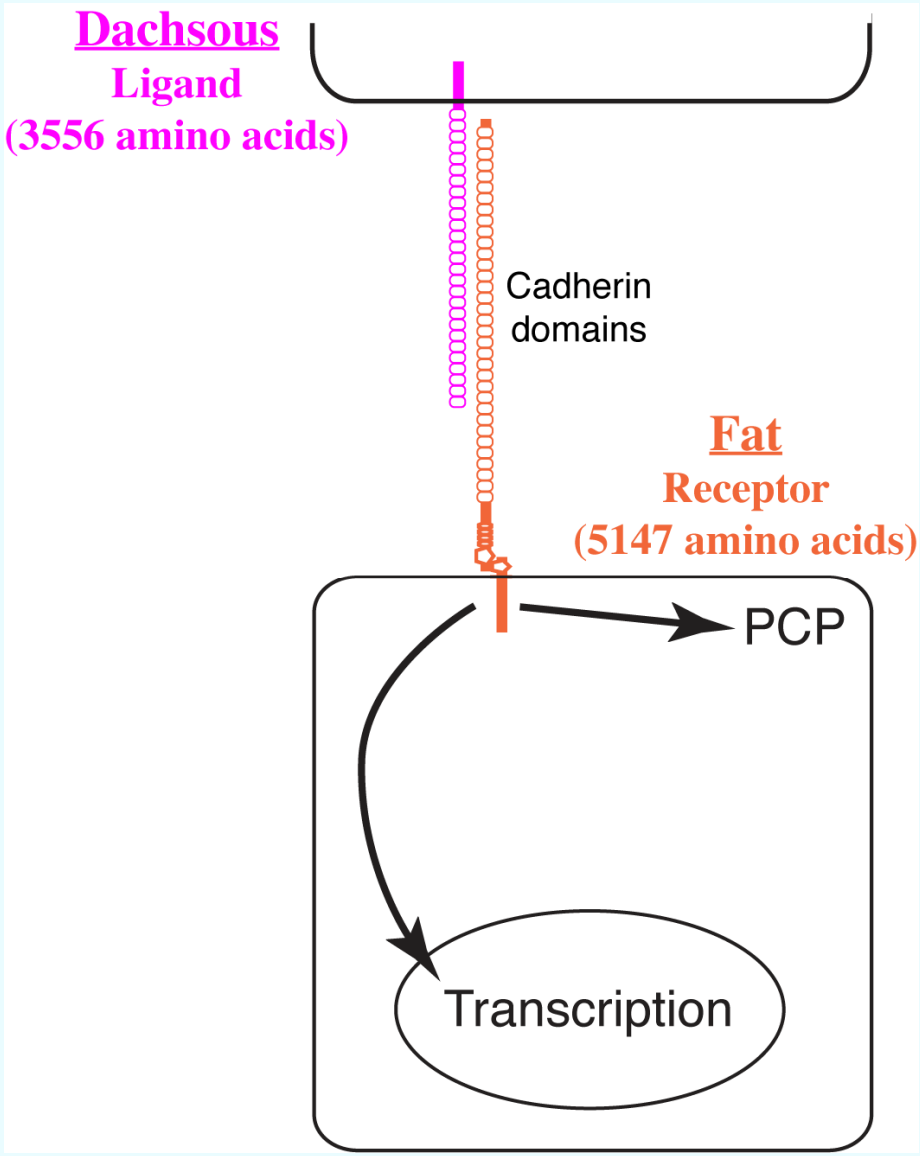


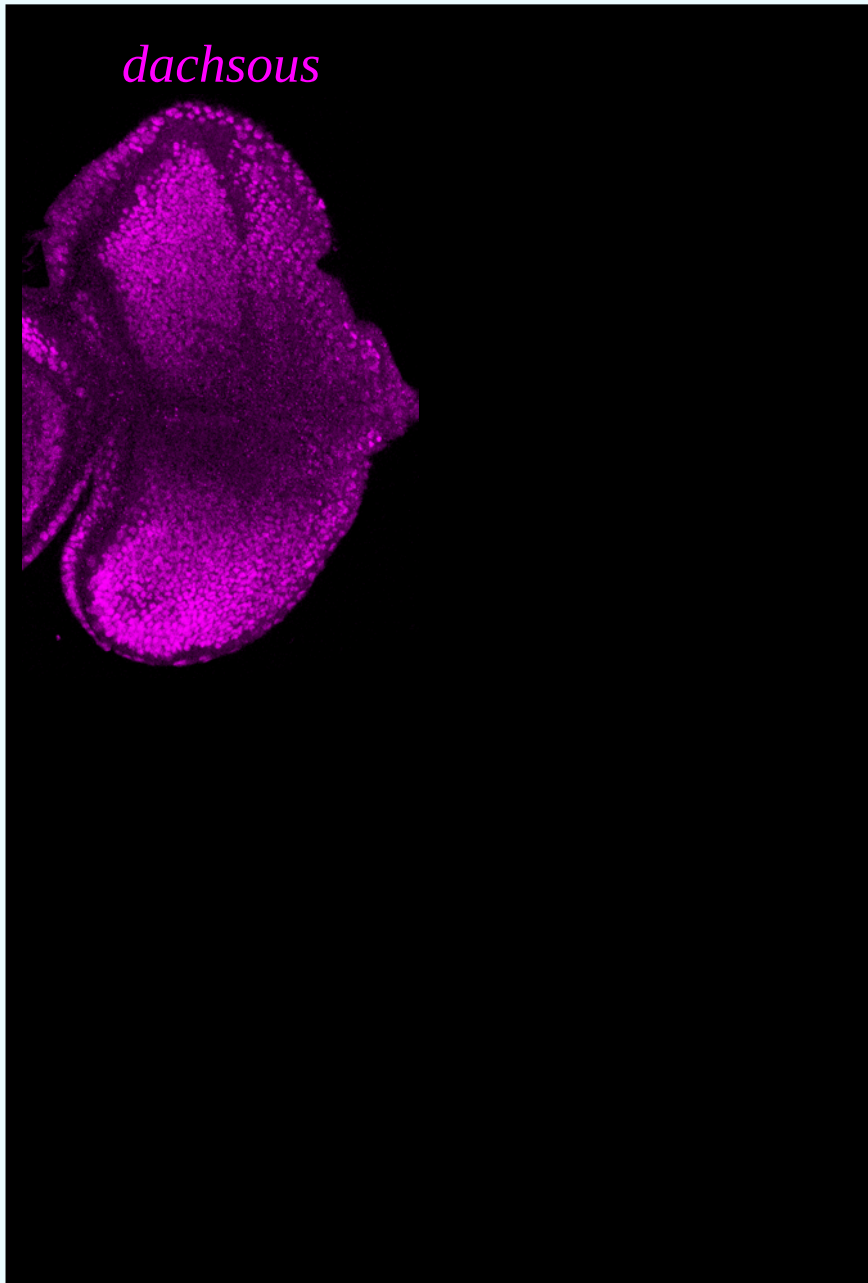
Eunjoo Cho

Fat, a large cadherin

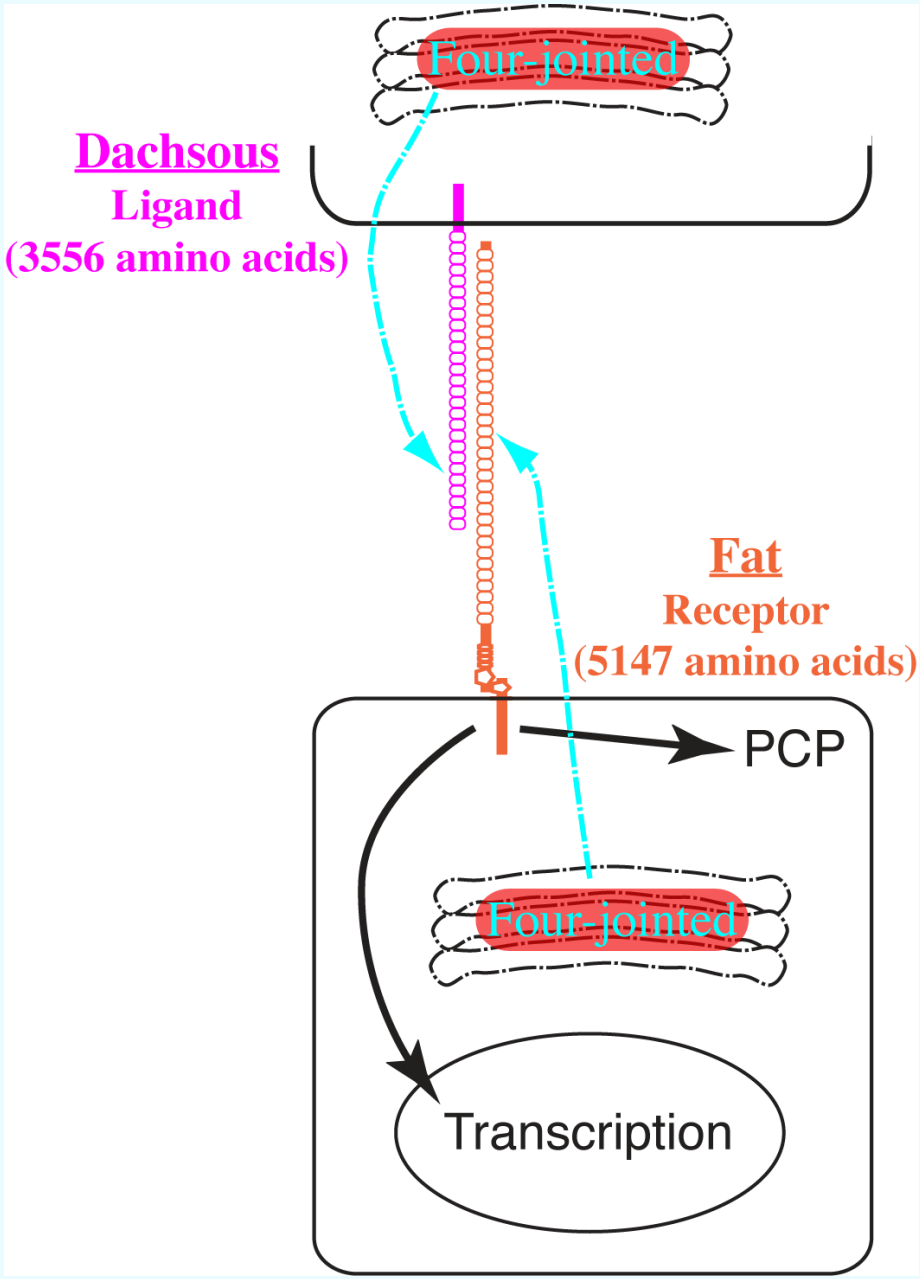


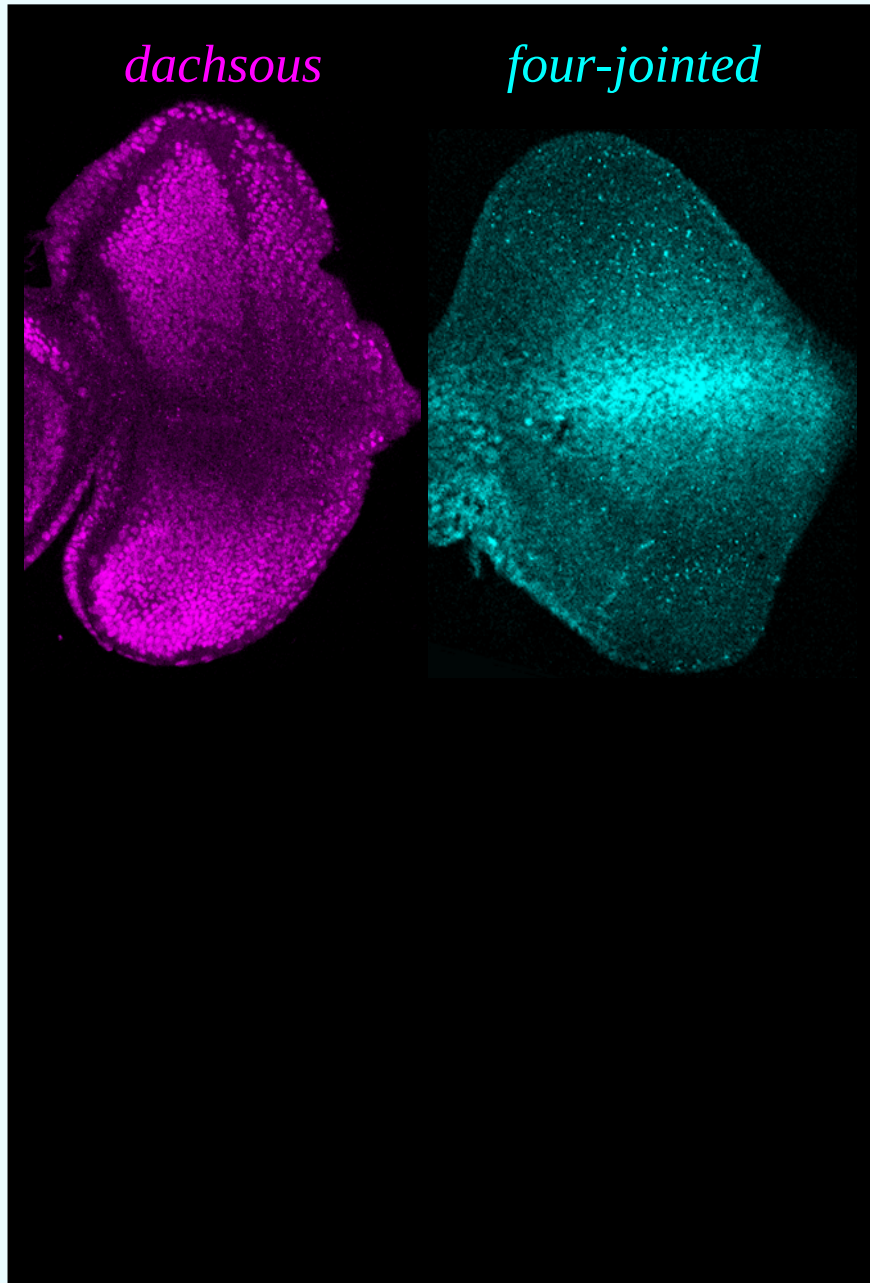
Regulation of Fat signaling: Dachsous



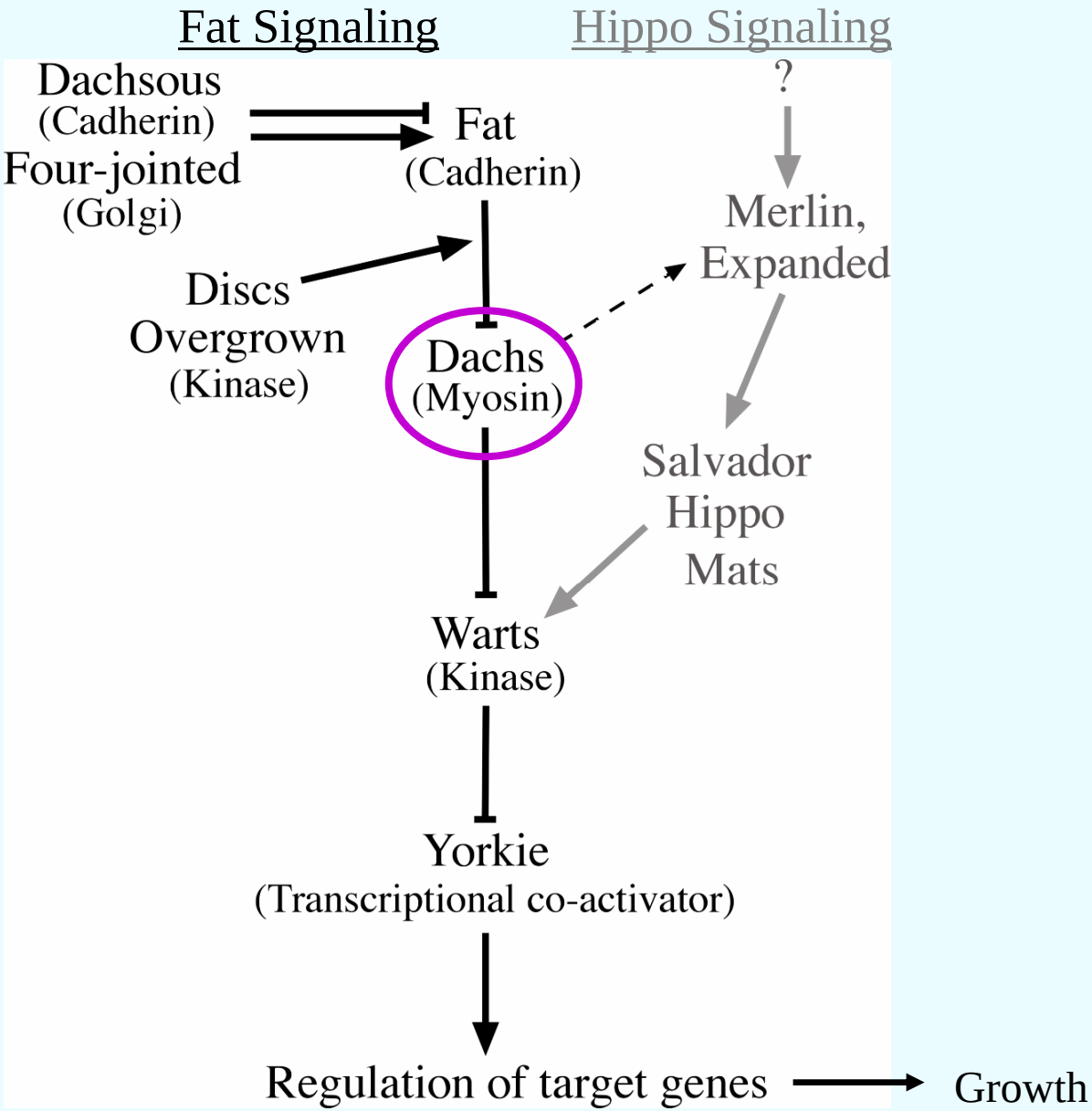


Regulation of Fat signaling: Four-jointed

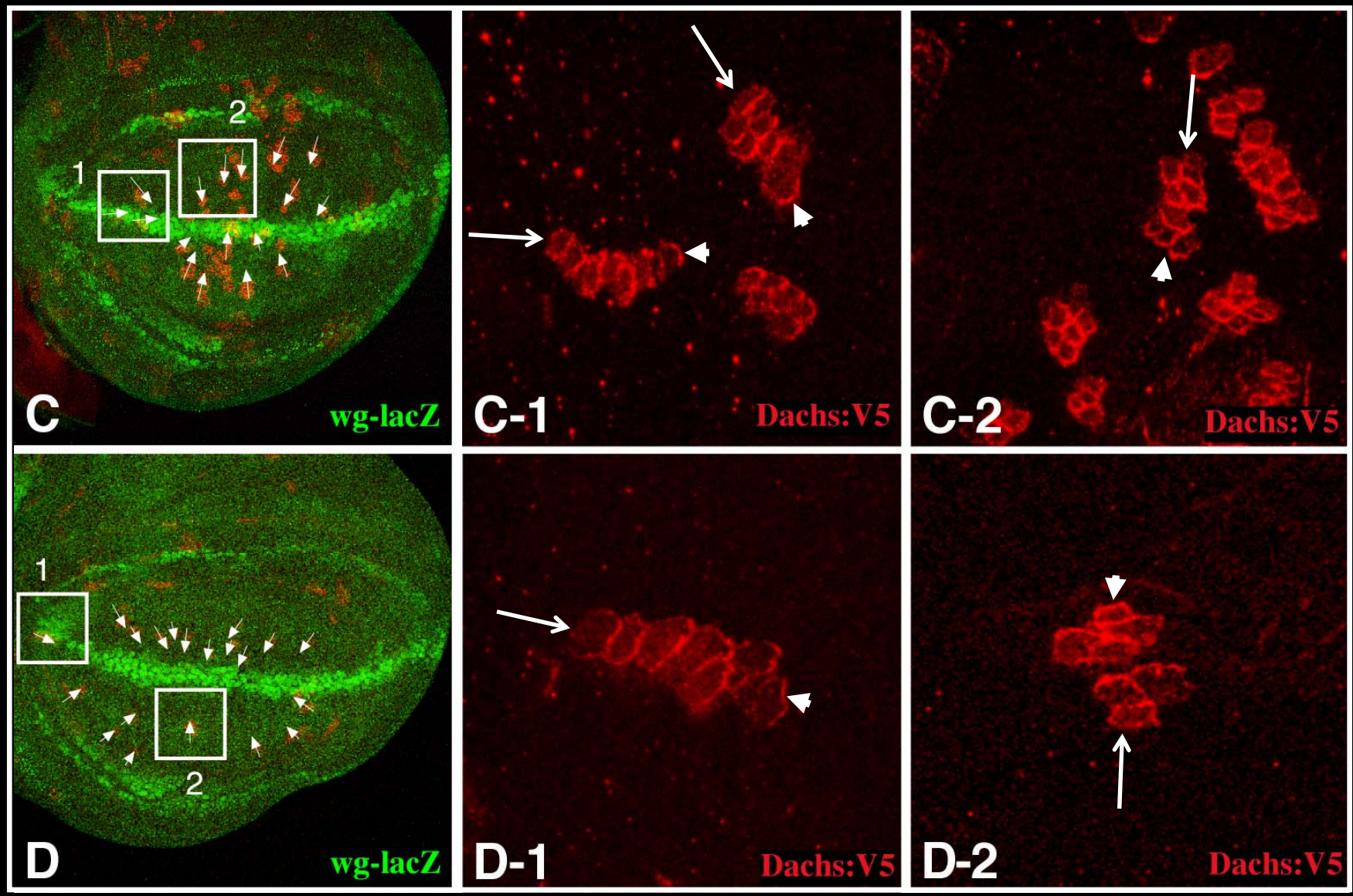




The Fat-Hippo Signaling network

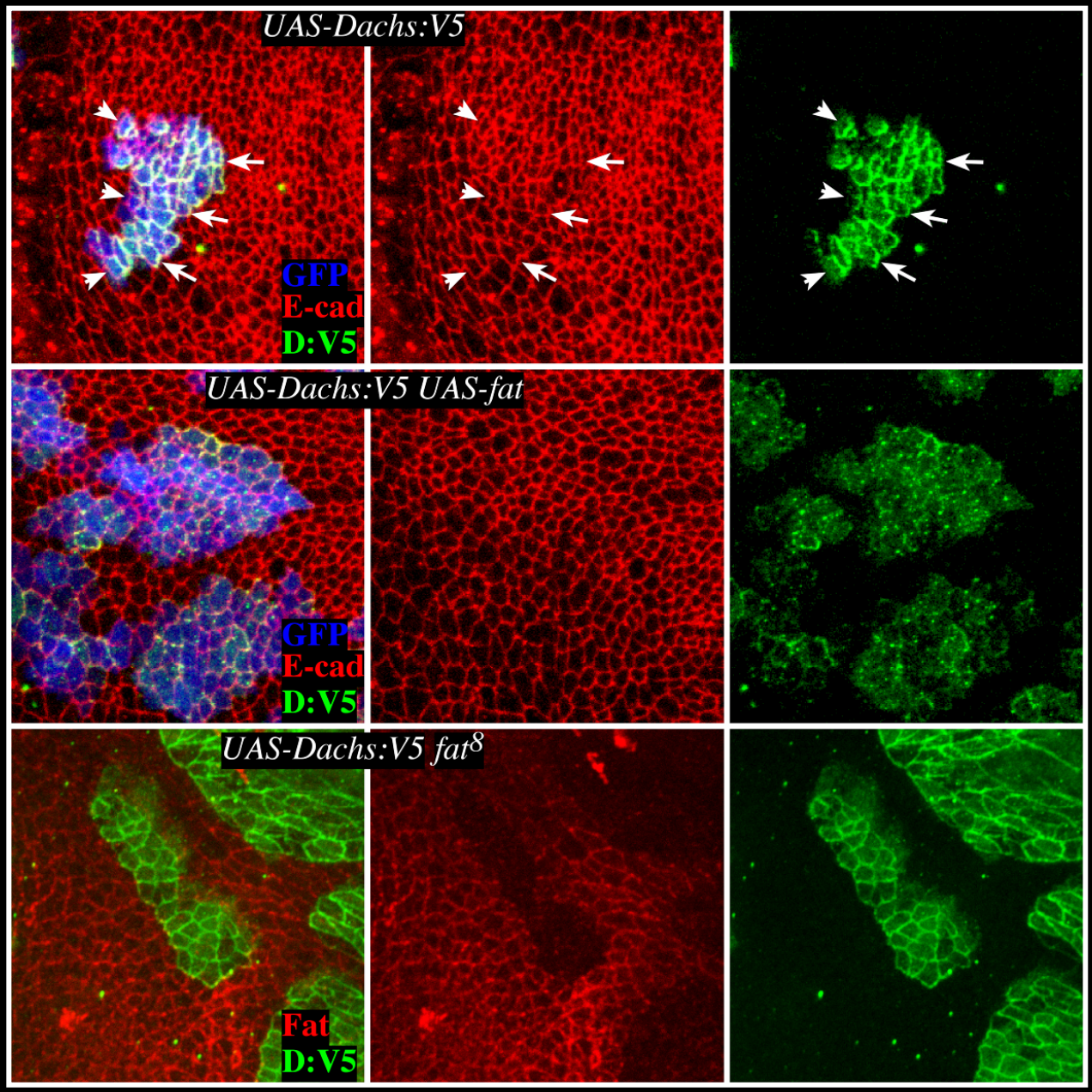


A Dachs polarity map



Cordelia Rauskolb

Dachs protein localization is modulated by Fat

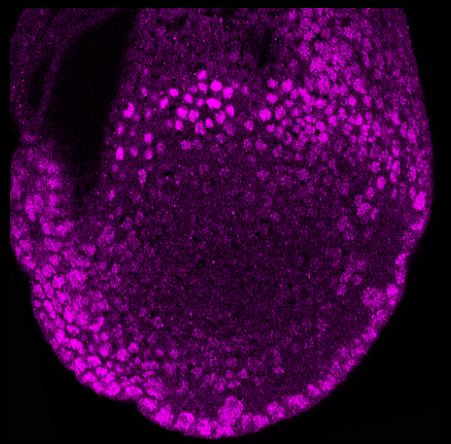


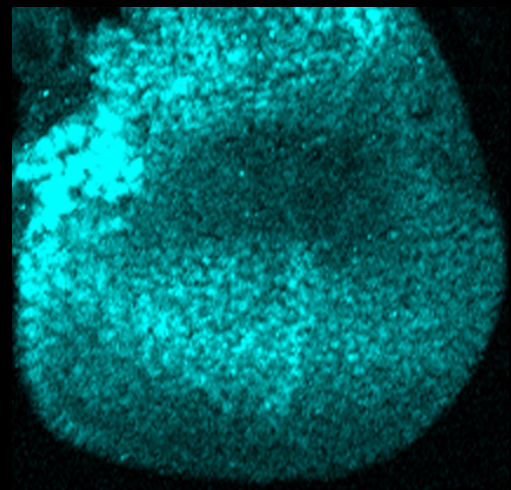
Yaopan Mao

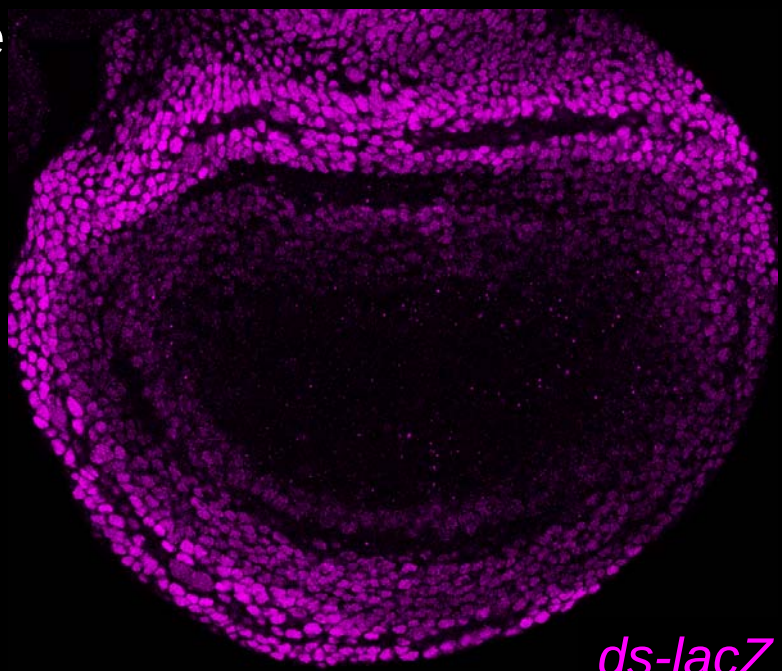
Dachsous and Four-jointed gradients in the wing

early

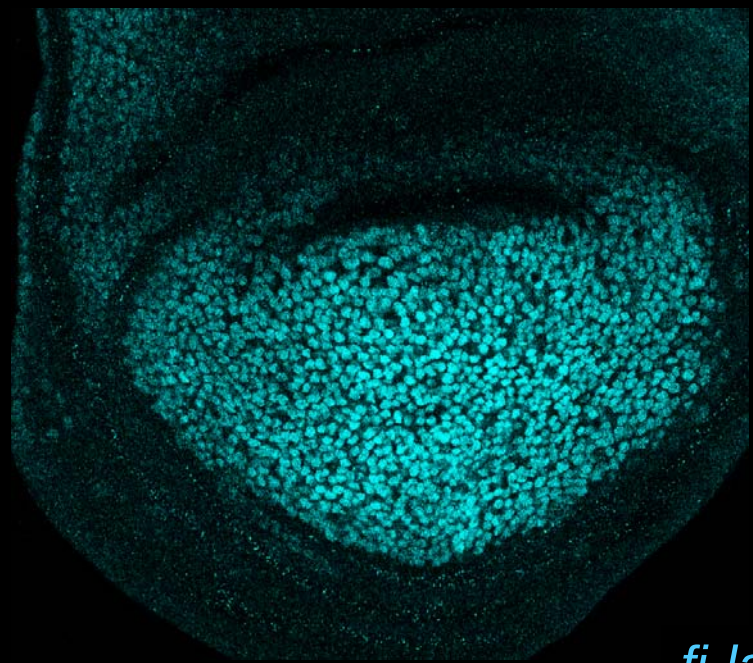
late





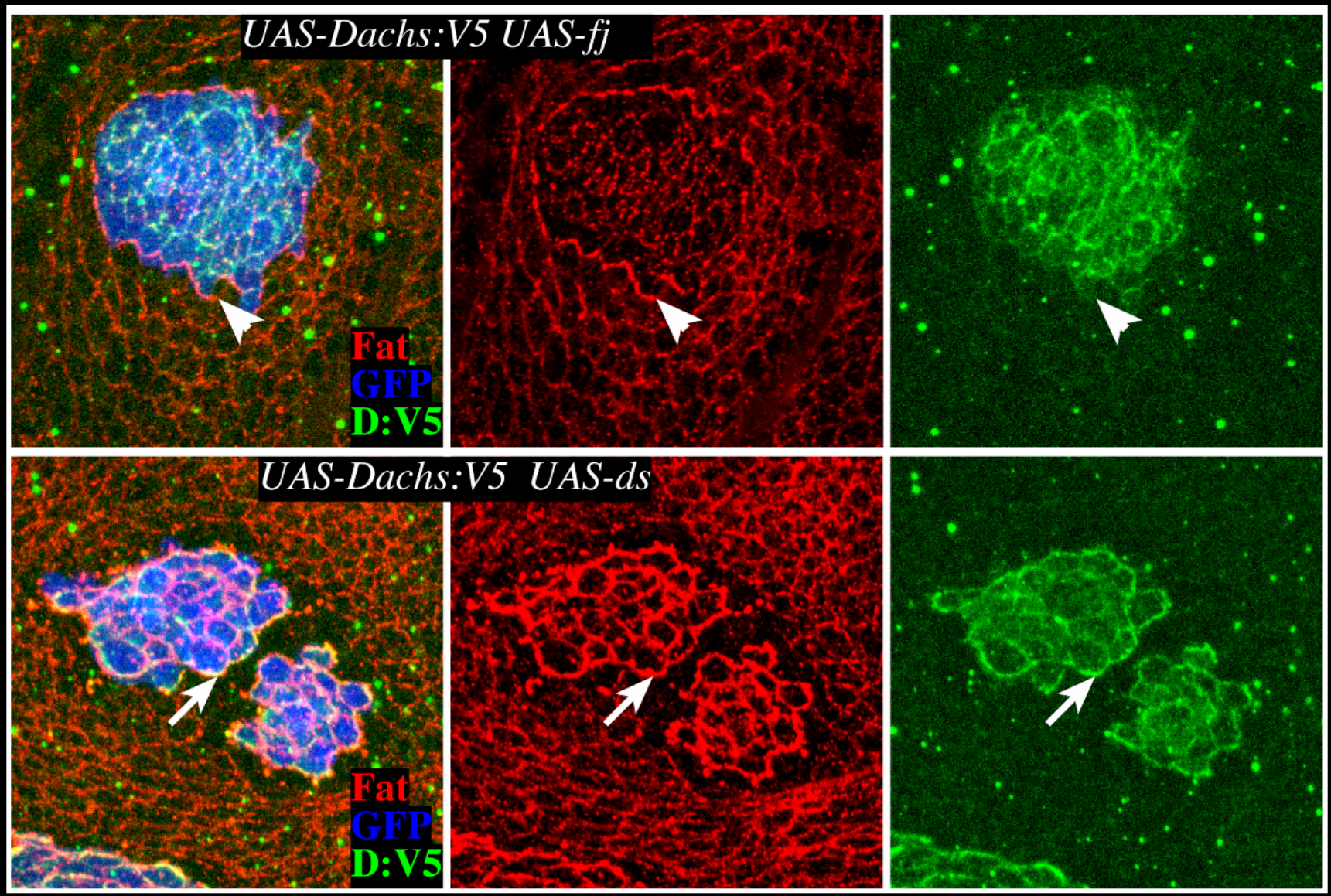


ds-lacZ

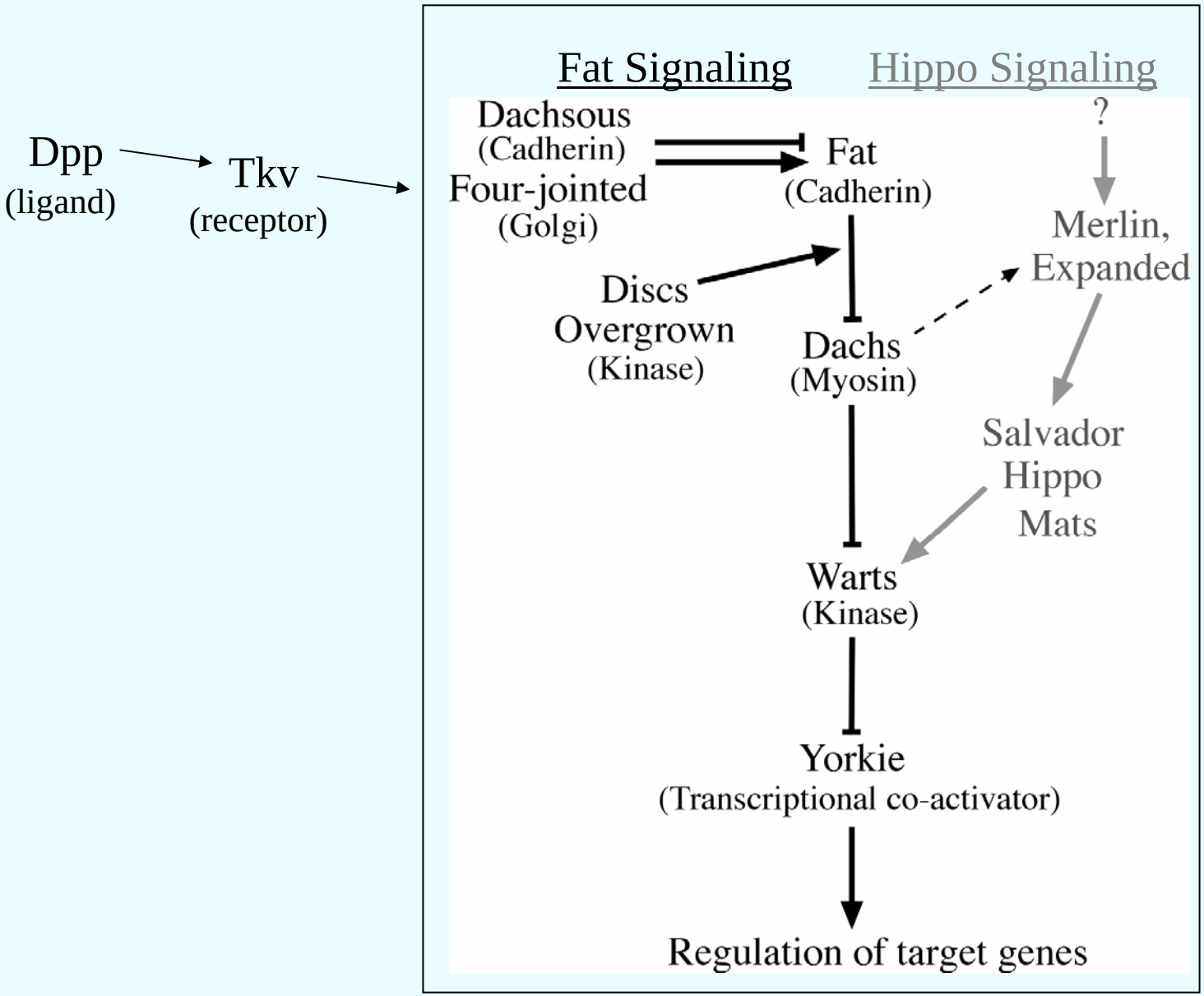


fj-lacZ

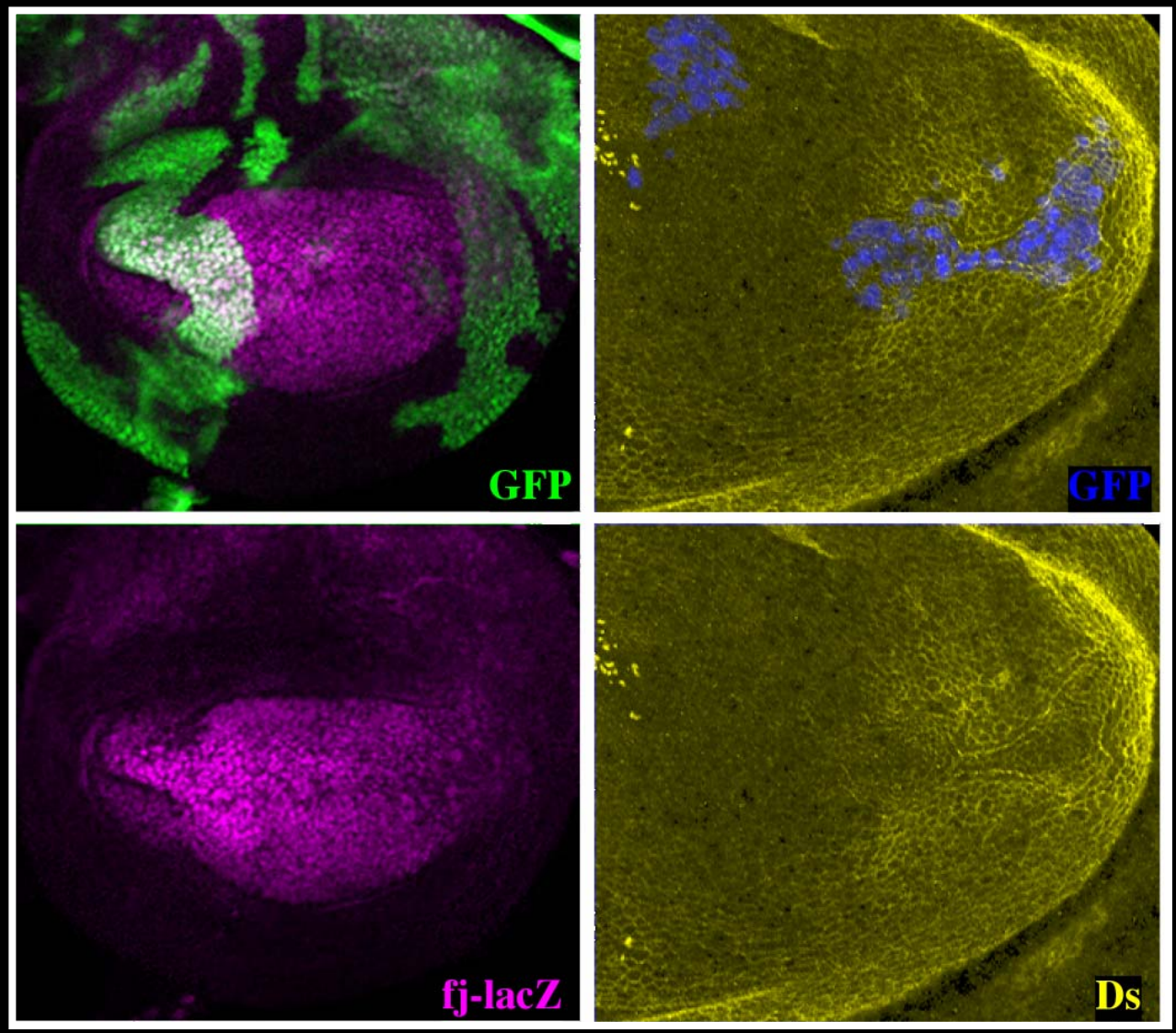
Dachs protein localization is modulated by Fj & Ds



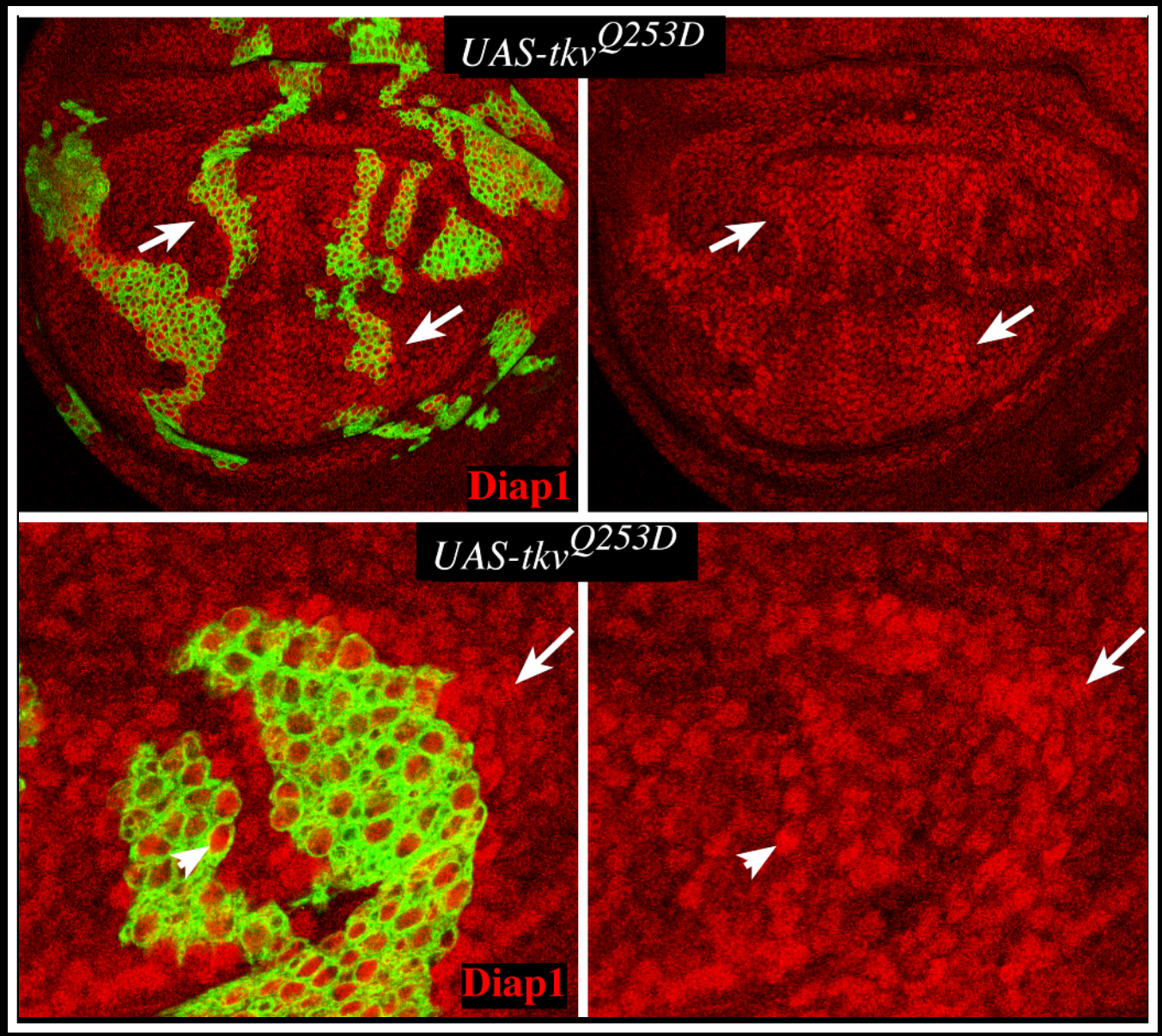
Does Dpp Signaling Influence Fat signaling?



Activated Tkv influences Four-jointed and Dachsous

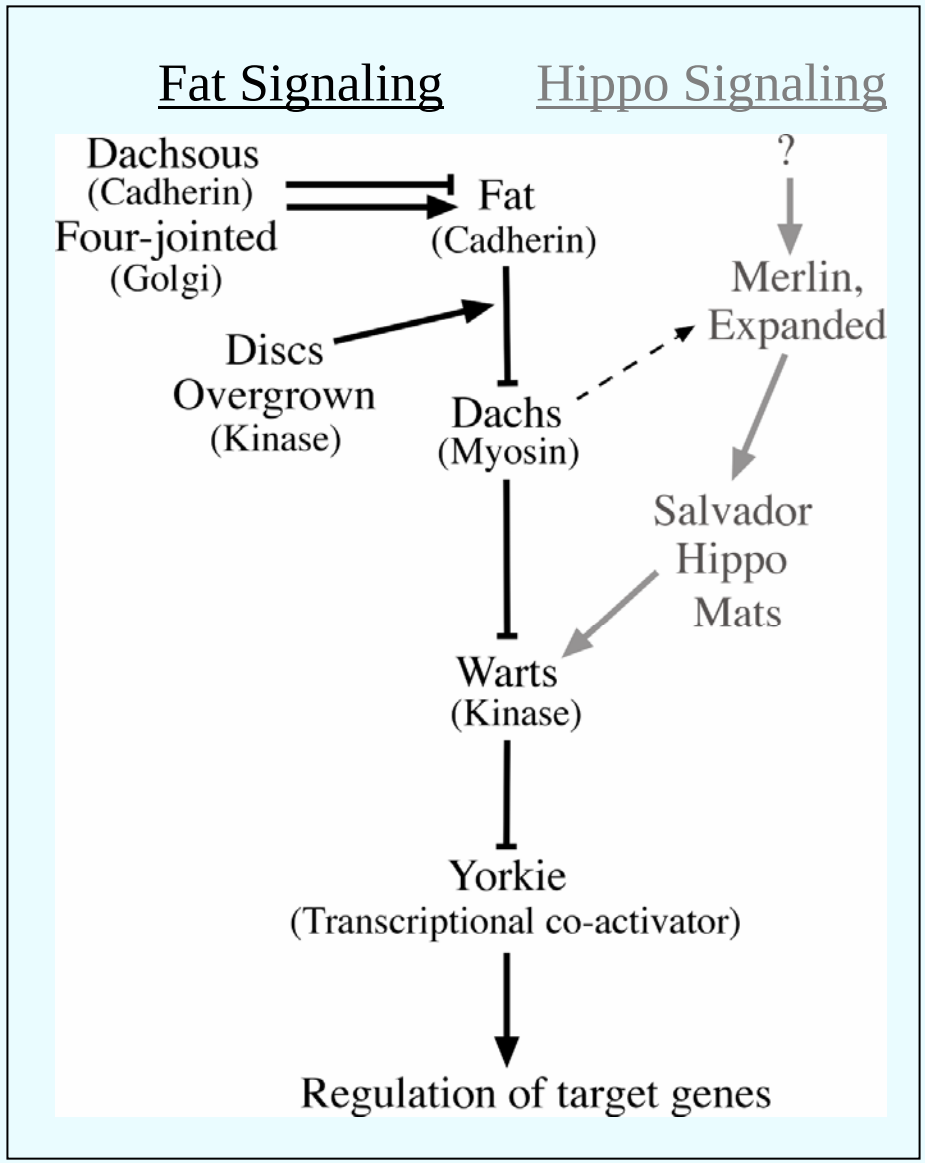


Activated Tkv influences Fat/Hippo targets

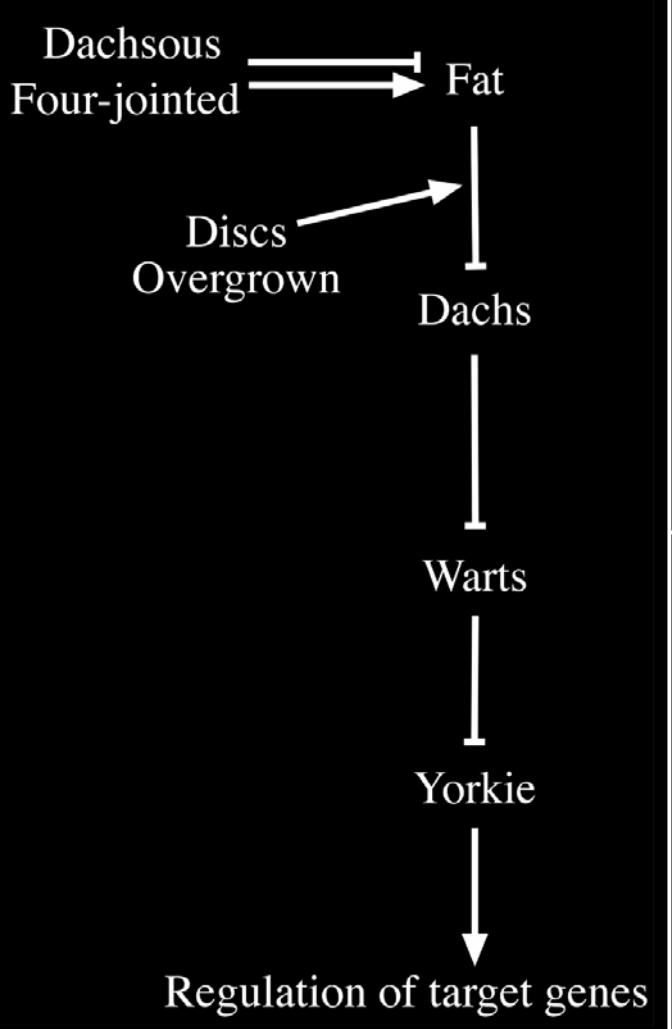


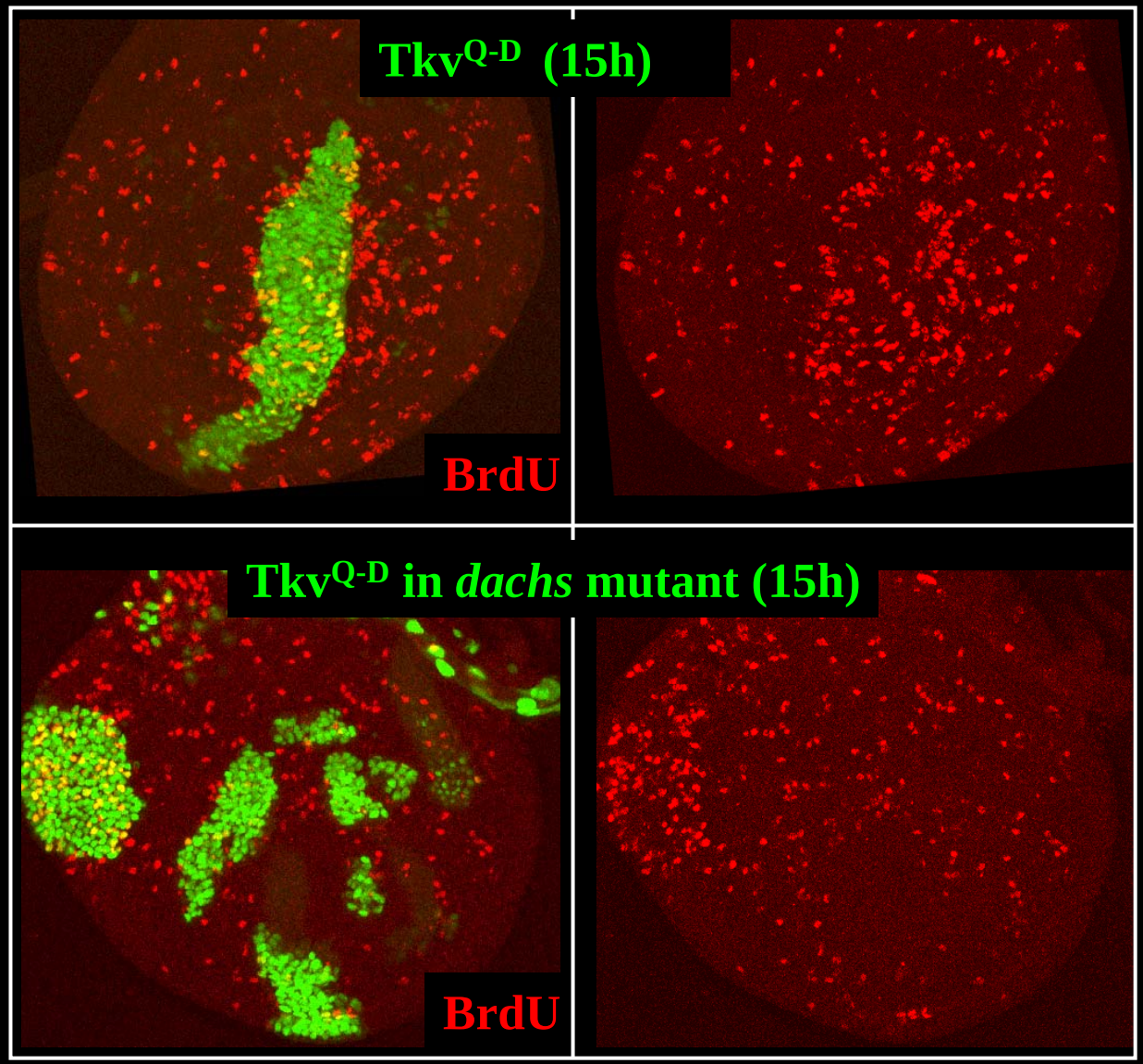
Does the Dpp gradient Influence growth through Fat signaling?

Dpp → Tkv →



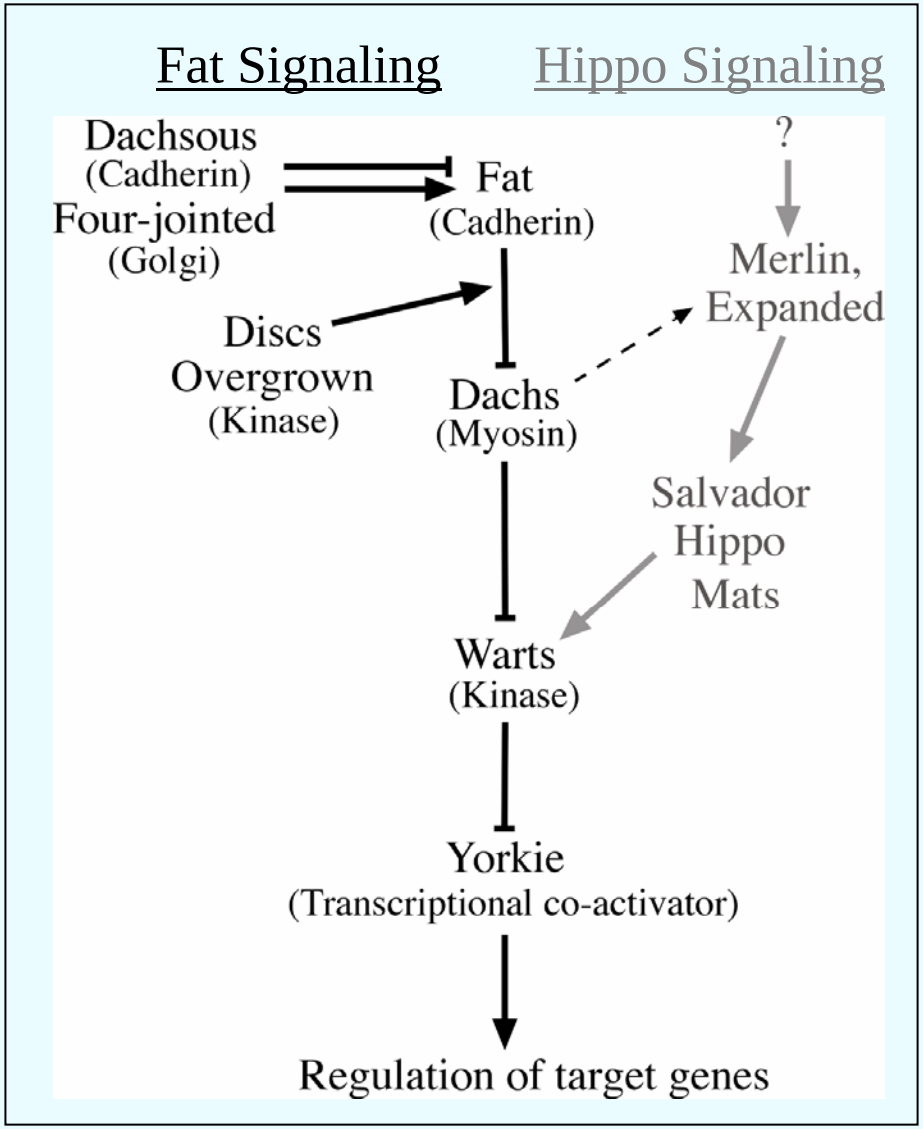
dachs is required for the non-autonomous influence of TKV on Cell proliferation





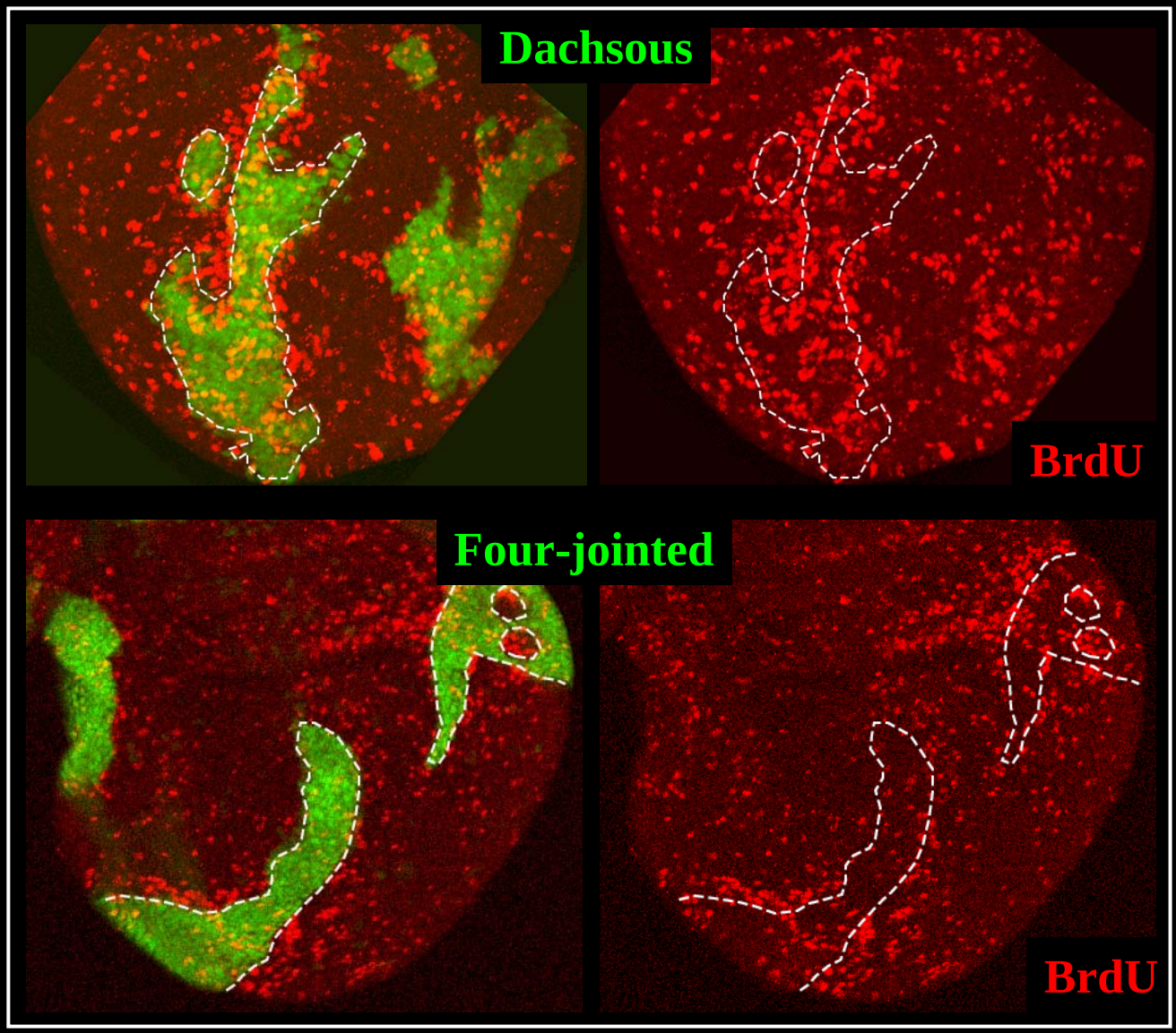
Dpp Signaling Influences growth through the Fat pathway

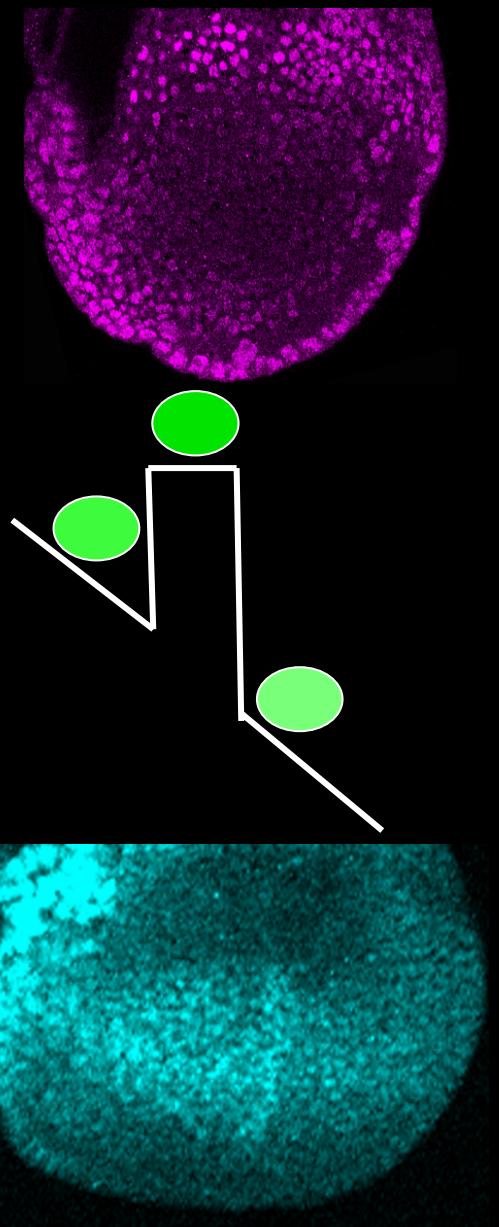
Dpp → Tkv →



Do the gradients Four-jointed and Dachsous regulate growth?

Juxtaposing cells that express different levels of Dachsous or Four-jointed stimulates cell proliferation.



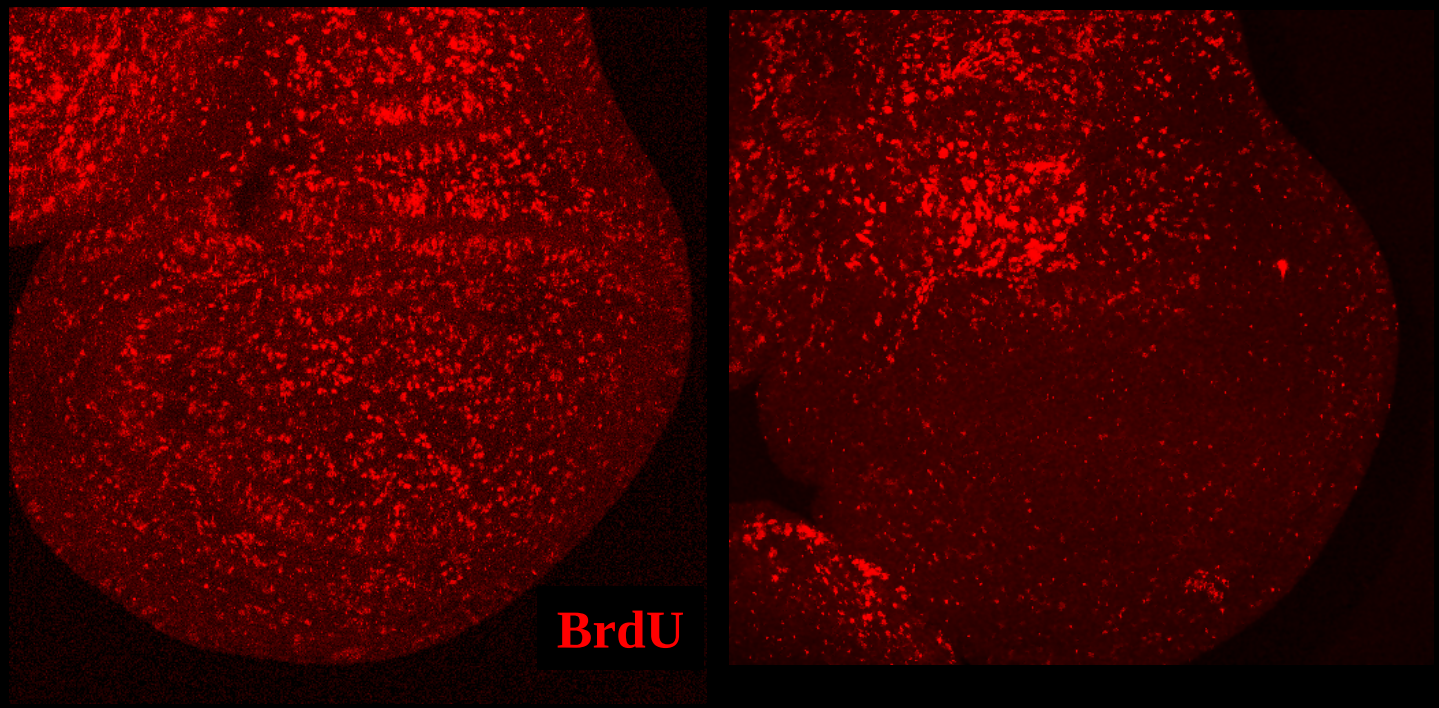


Uniform expression of Four-jointed and Dachsous inhibits proliferation

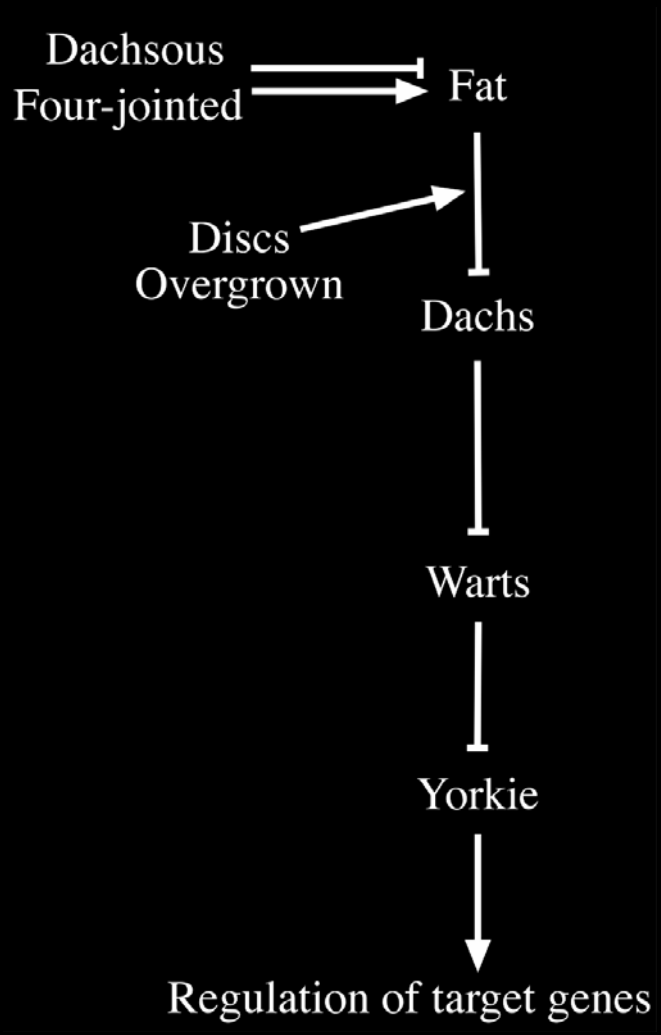
Actin-Gal4:PR UAS-Dachsous UAS-Four-jointed

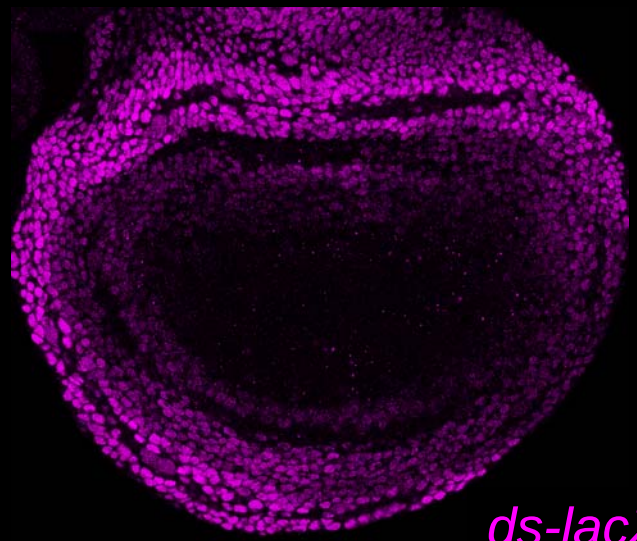
No RU486

19h on RU486

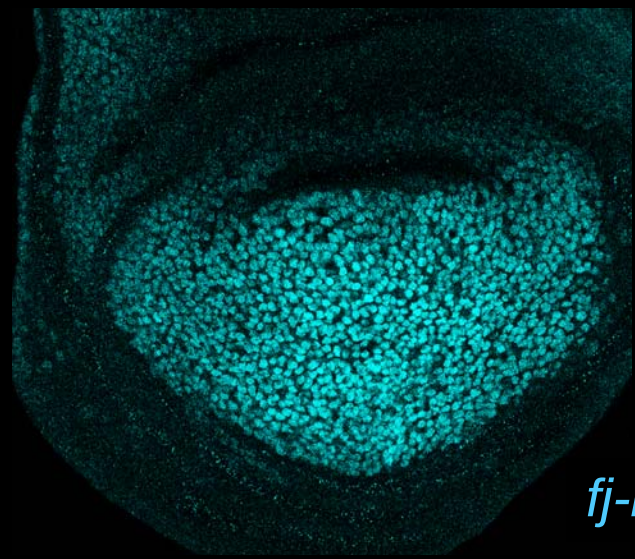


How might Fat signaling be regulated by Gradients?





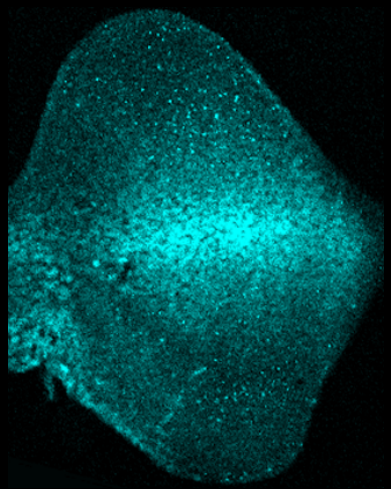
ds-lacZ

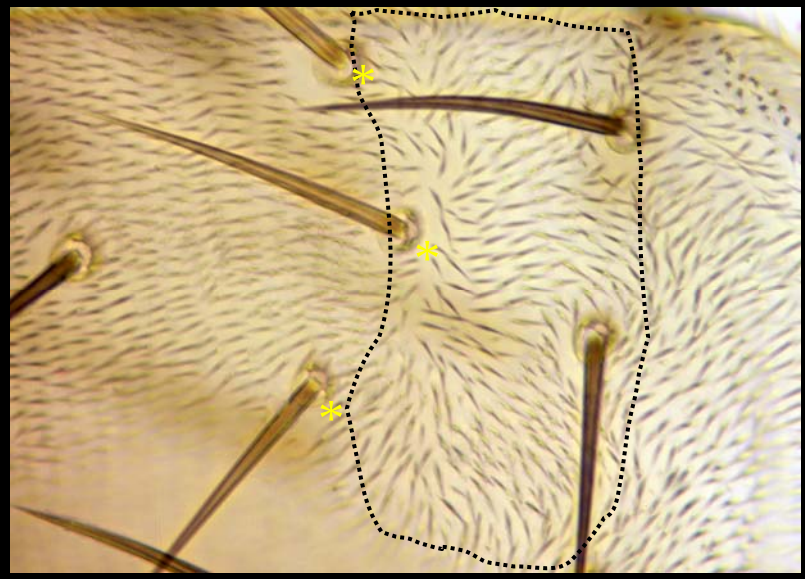


fj-lacZ

Dachsous and Four-jointed have opposite effects on polarity …

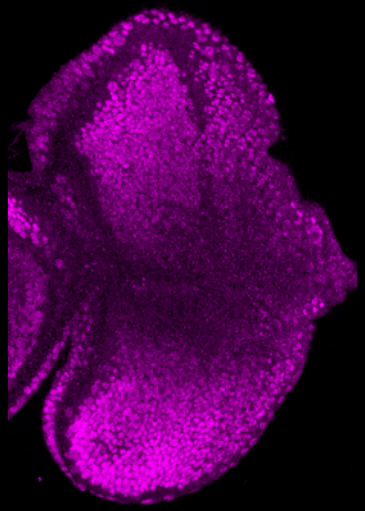
four-jointed

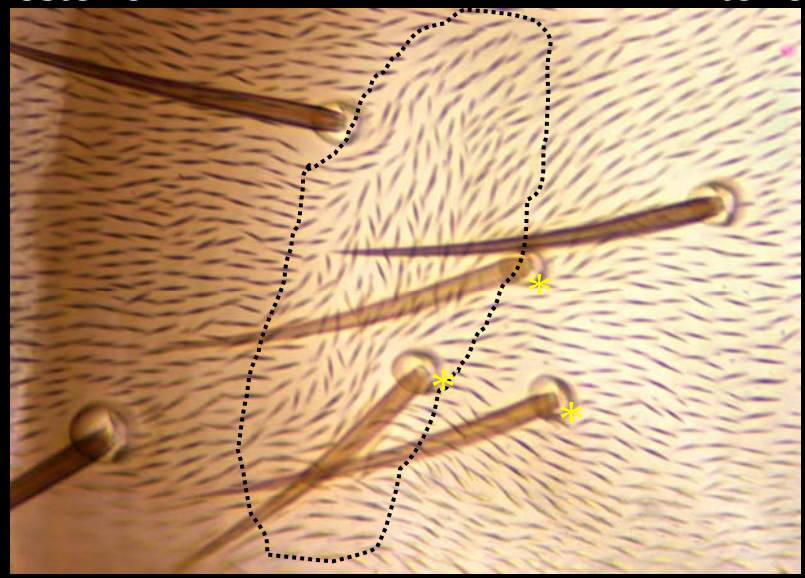


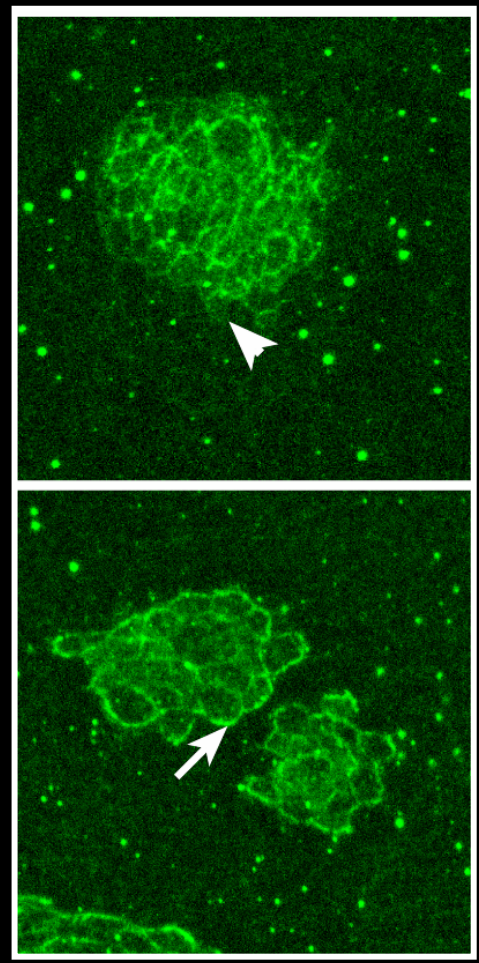


Posterior Anterior

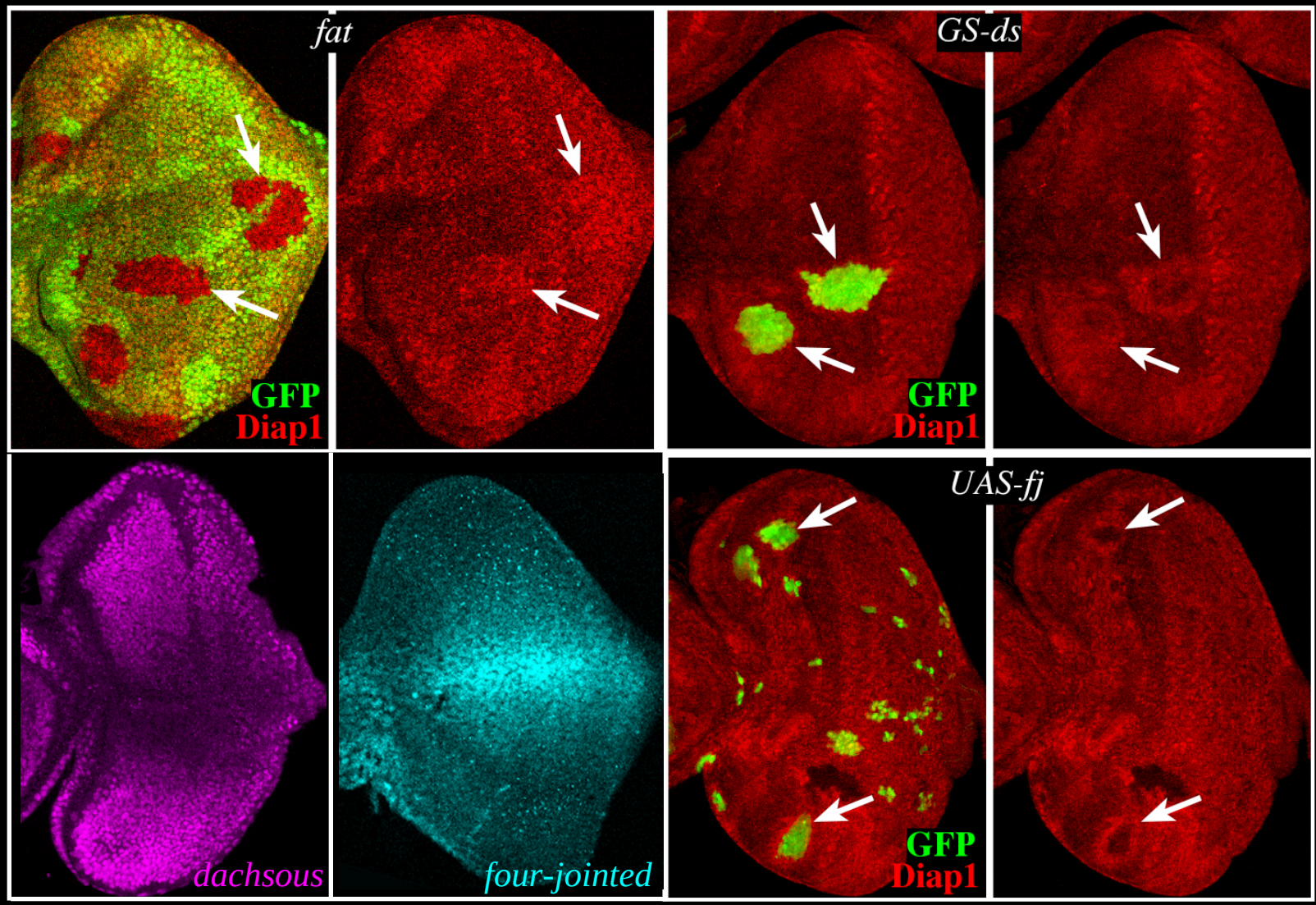
dachsous







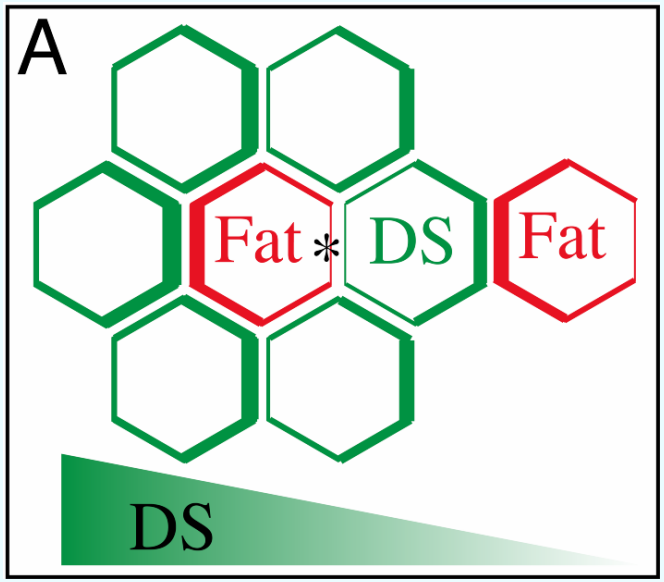
… but similar effects on target gene expression

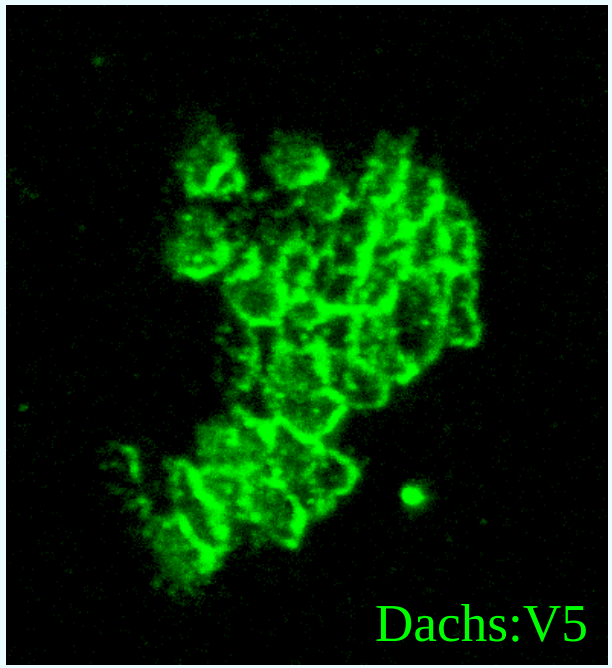


Fat activity is inhibited along the edges of fj- or ds-expressing clones
But, a dachsous mutant is similar to a fat mutant, and
uniform dachsous over-expression seems to activate Fat.

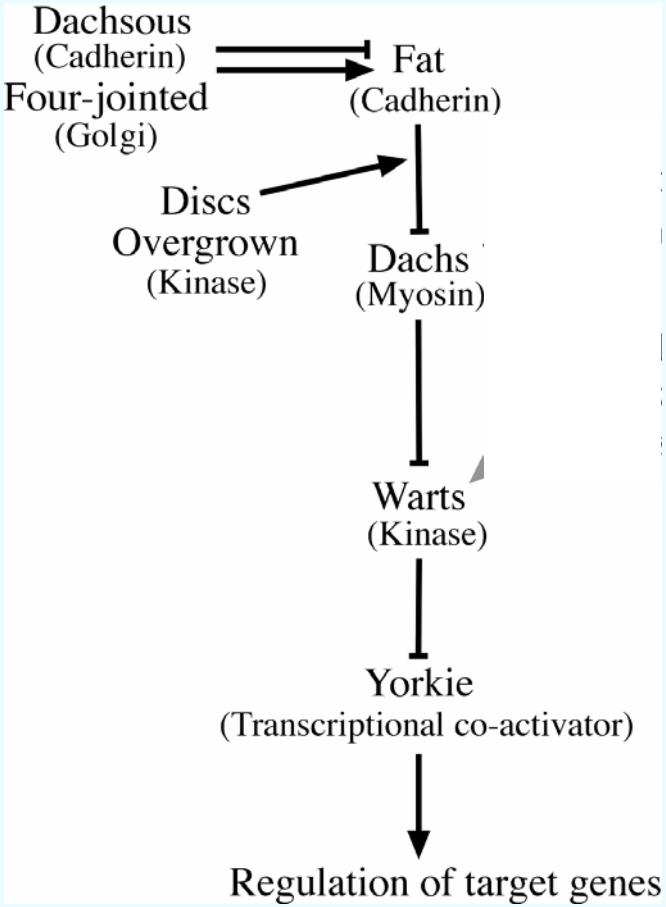
How might Dachsous and Four-jointed Gradients influence Fat Signaling?

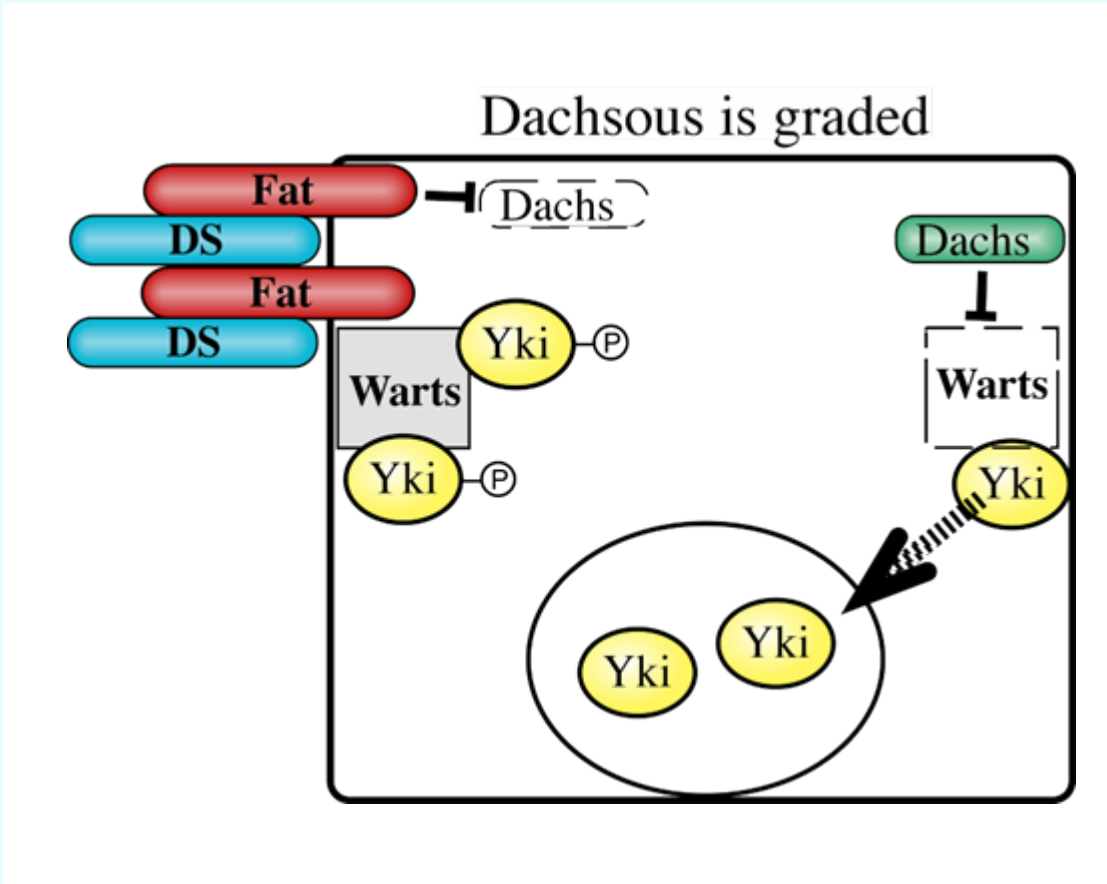
Observation: A gradient of Dachsous (&/or Four-jointed) is reflected in the asymmetric activity (localization?) of Fat.



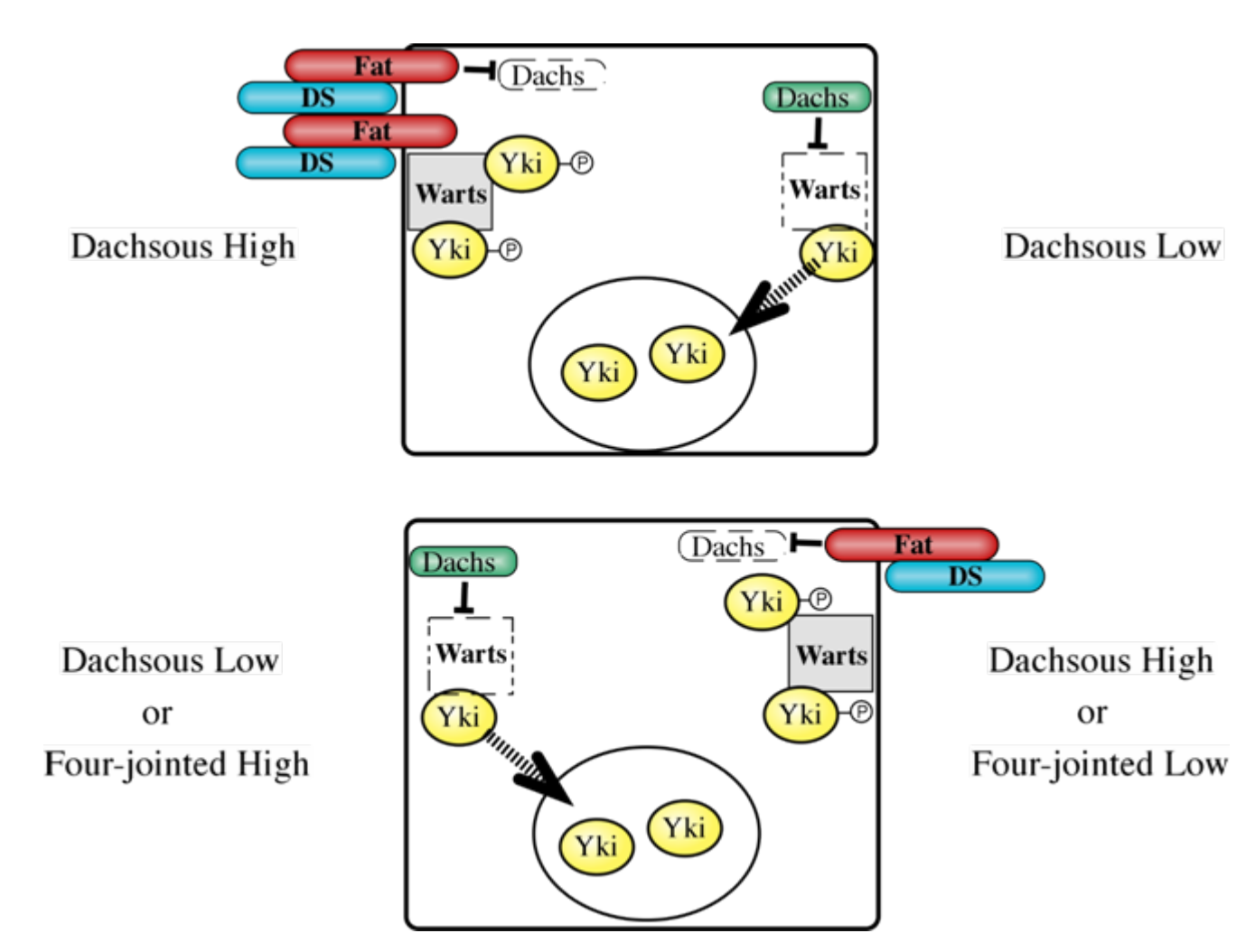


Hypothesis: Asymmetric activity/localization of Fat/Dachs allows local activation of Yorkie, and consequently activation of transcriptional responses.



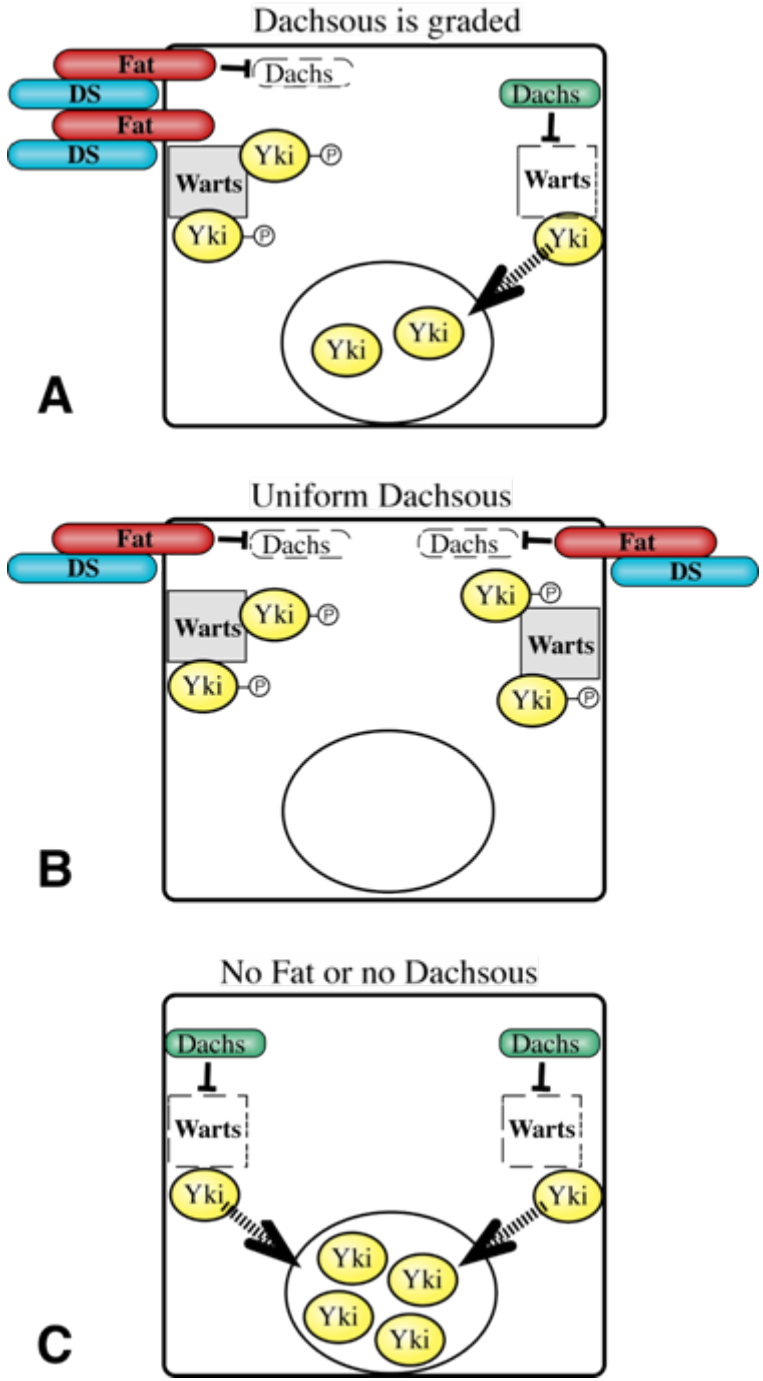


1) The influence of Fat on polarity depends on the direction of asymmetry, the influence on transcription (& growth) depends on the extent of asymmetry.

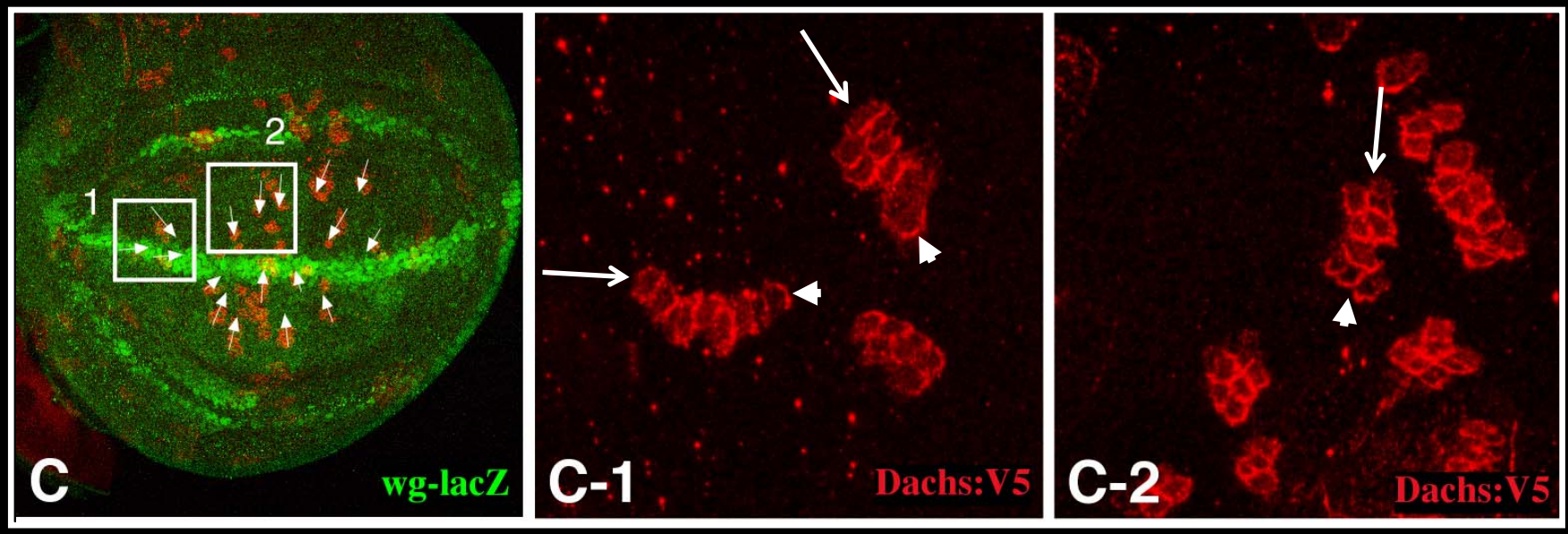


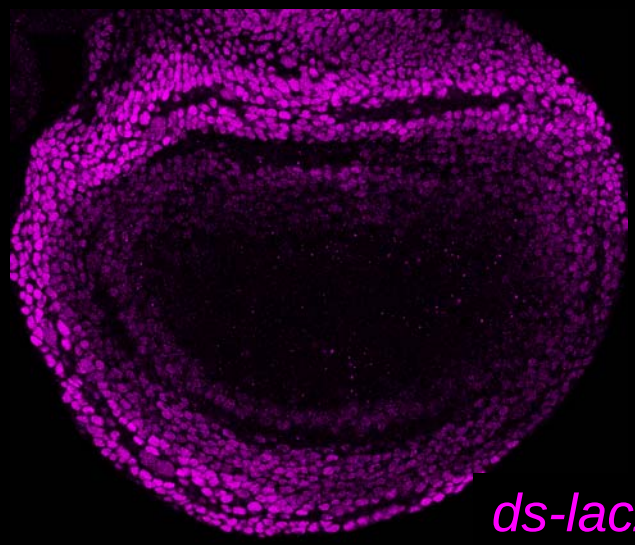
i.e., Polarity would be influenced by the vector of the DS & FJ gradients, whereas transcription would be influenced by their slope

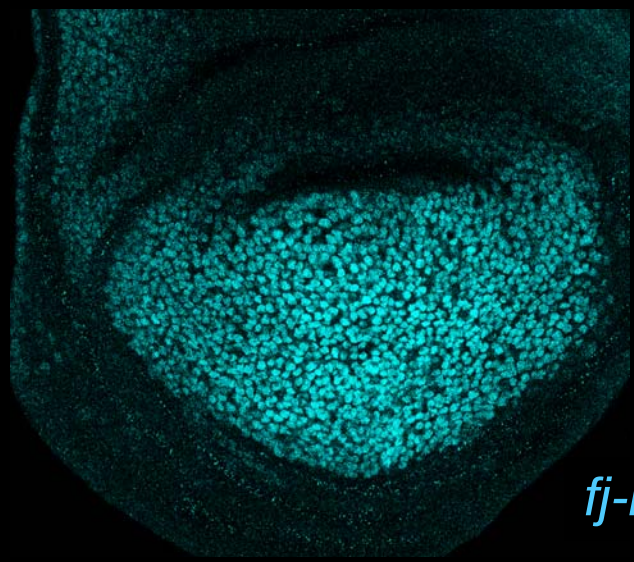
2) Fat pathway activity is a function of both the amount of Dachsous and the gradient of Dachsous



3) Transcriptional response need not be directly proportional to gradient slope







4) Fat signaling is required for ~60% of normal wing growth

Wild type

Wild type

tub-Gal4 UAS-dachsous UAS-four-jointed

dachs