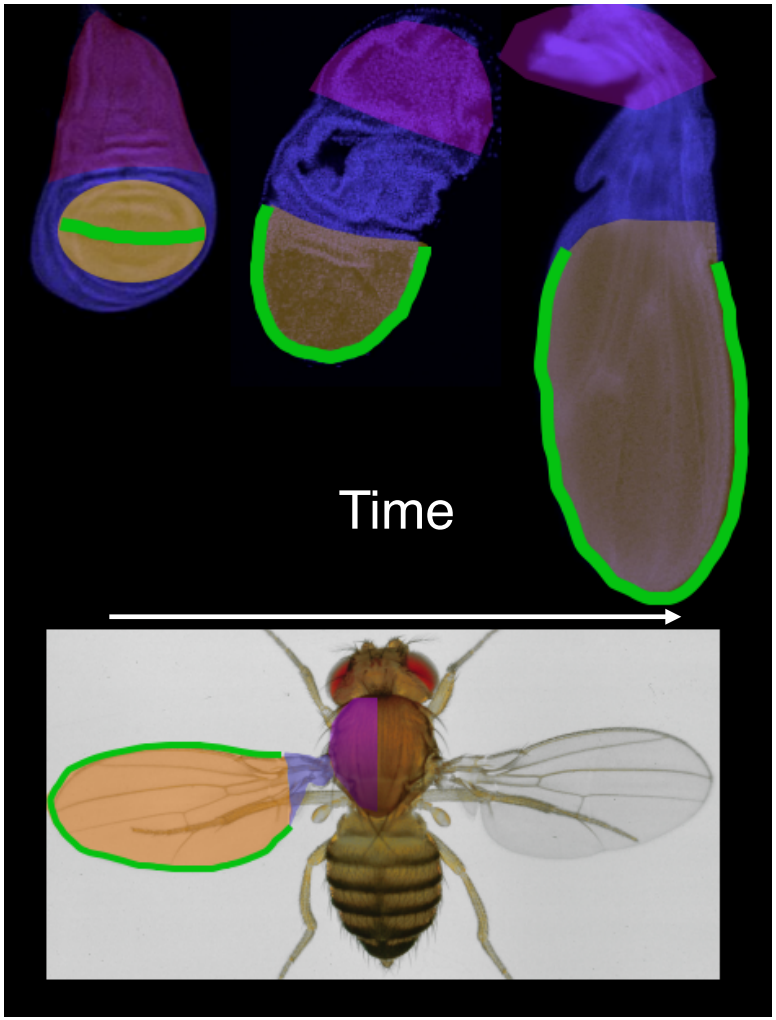
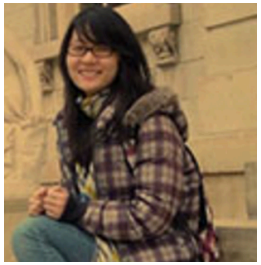
Temporal regulation of the cell cycle in the Drosophila wing during metamorphosis

Buttitta Lab, University of Michigan



Distinct states of cell cycle exit:

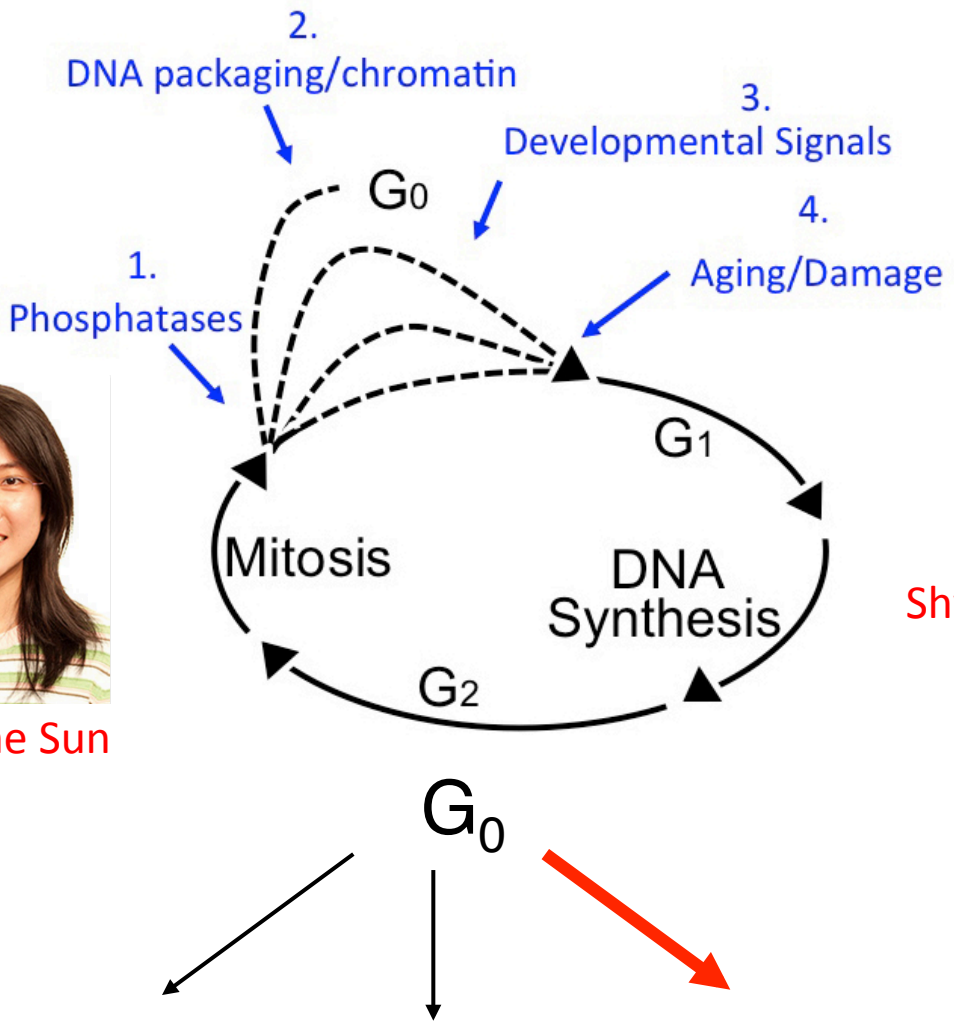


Yiqin Ma

Kerry Flegel

Rosaline Sun

Shyama Nandakumar

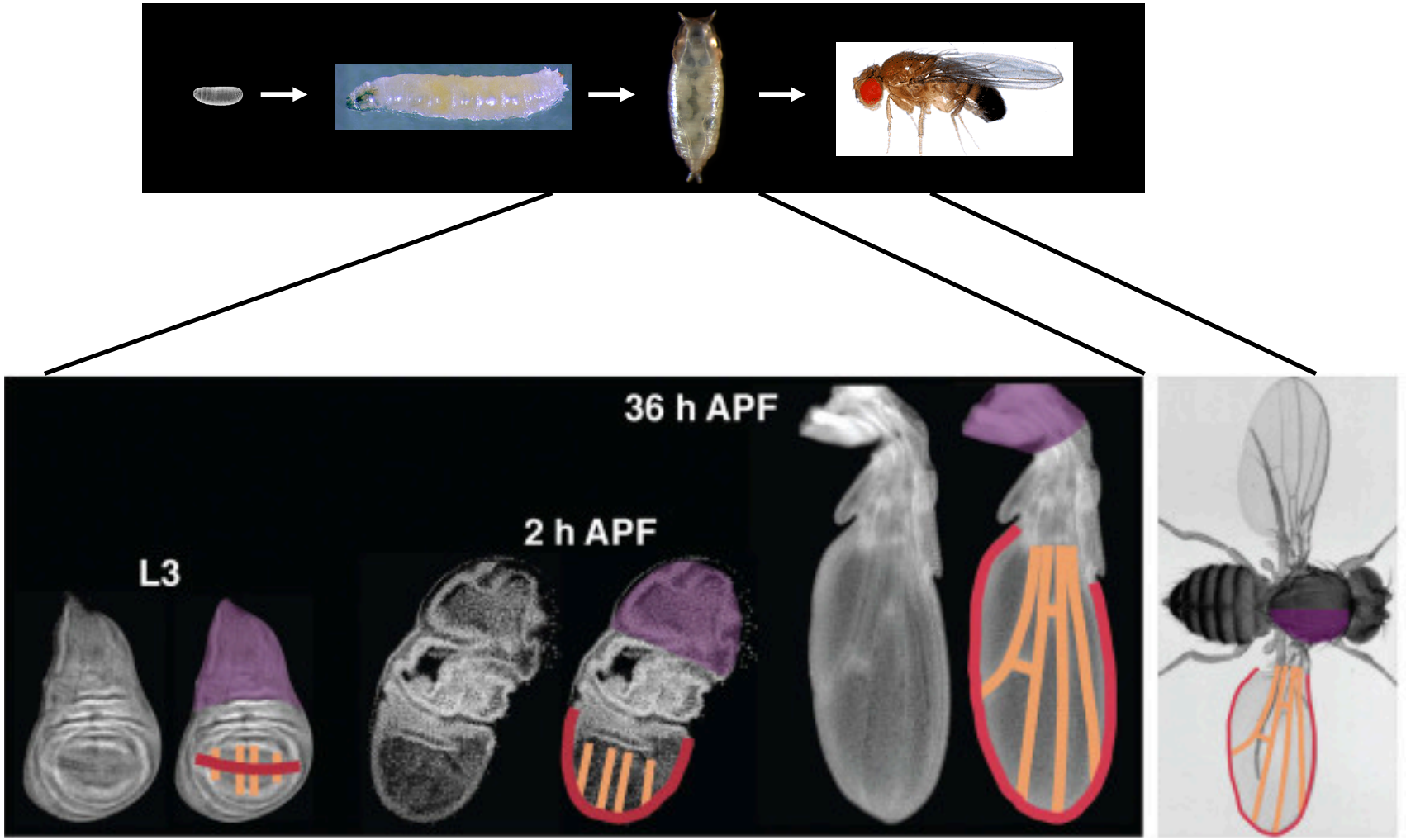


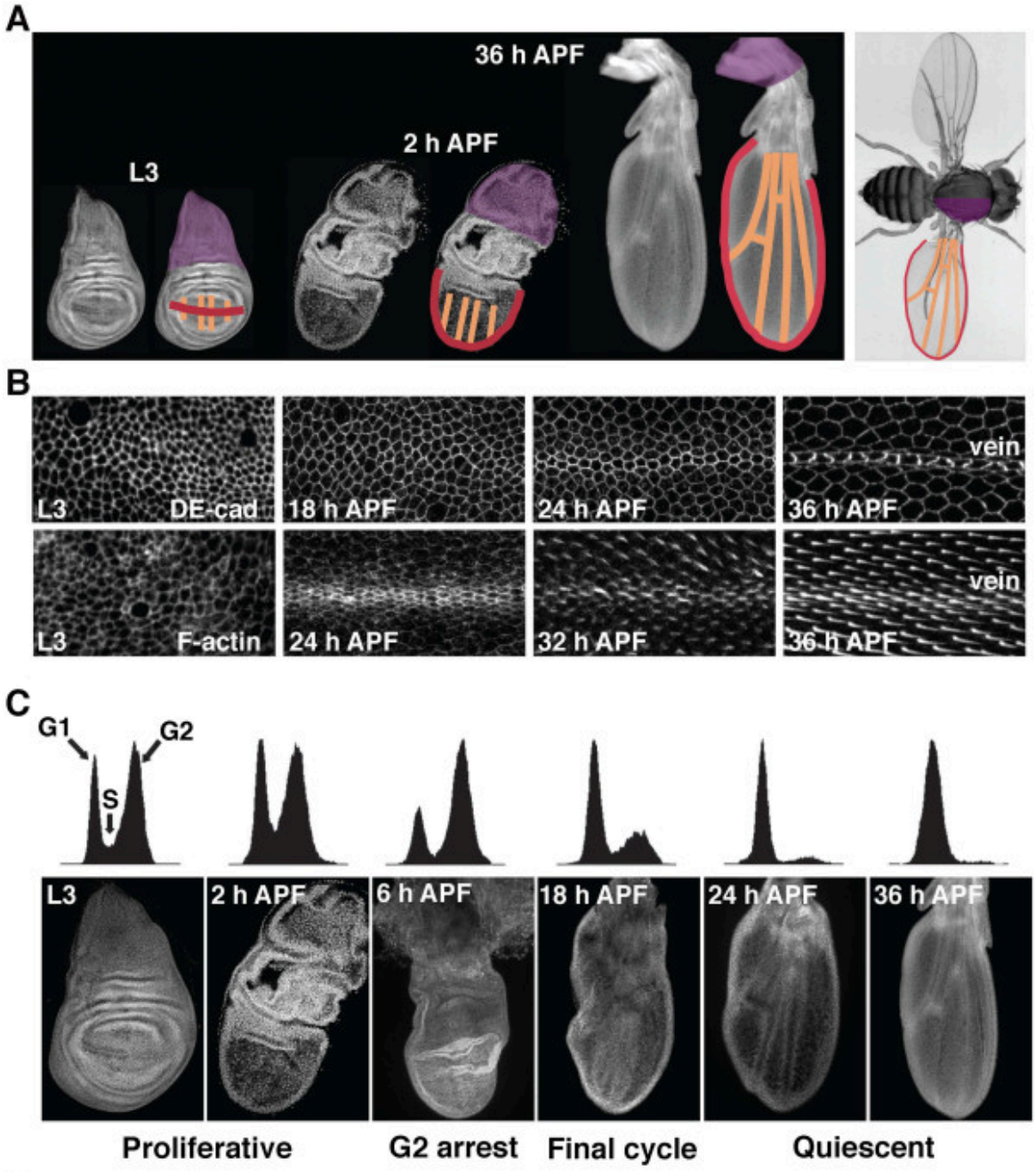
Reversible Quiescence

Senescence

Terminal differentiation

Drosophila metamorphosis – remarkably cool, and complicated





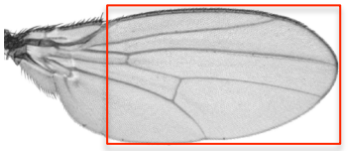
Cell shape/identity

Hair differentiation

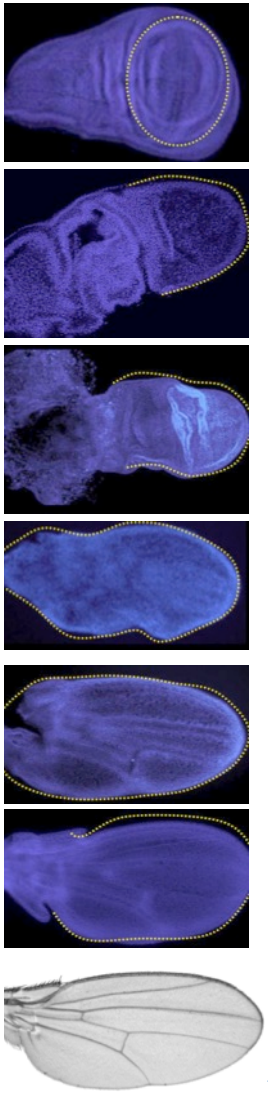
Cell cycle changes

Morphological changes

The transition to G0 in the fly wing



DNA



0h APF
(After Puparium Formation)

2h APF

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Adult

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Mitosis

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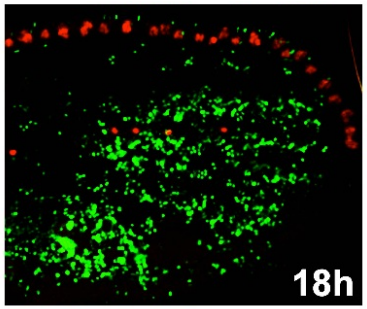
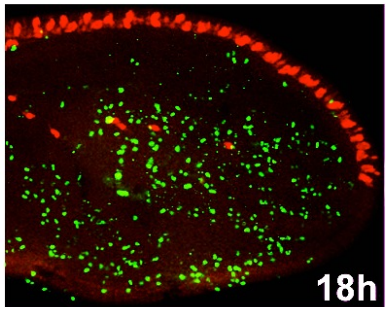
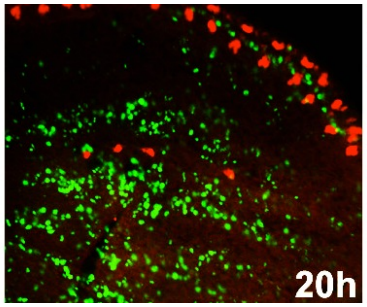
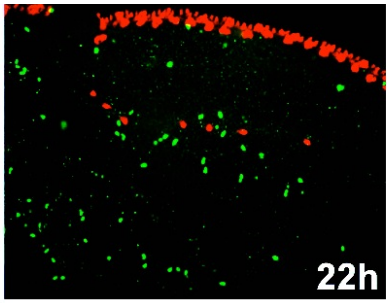
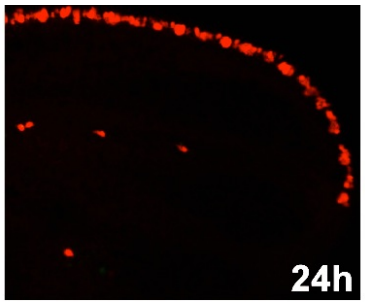
Differentiation

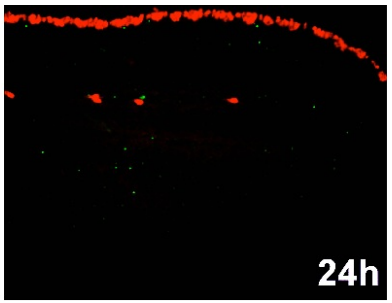








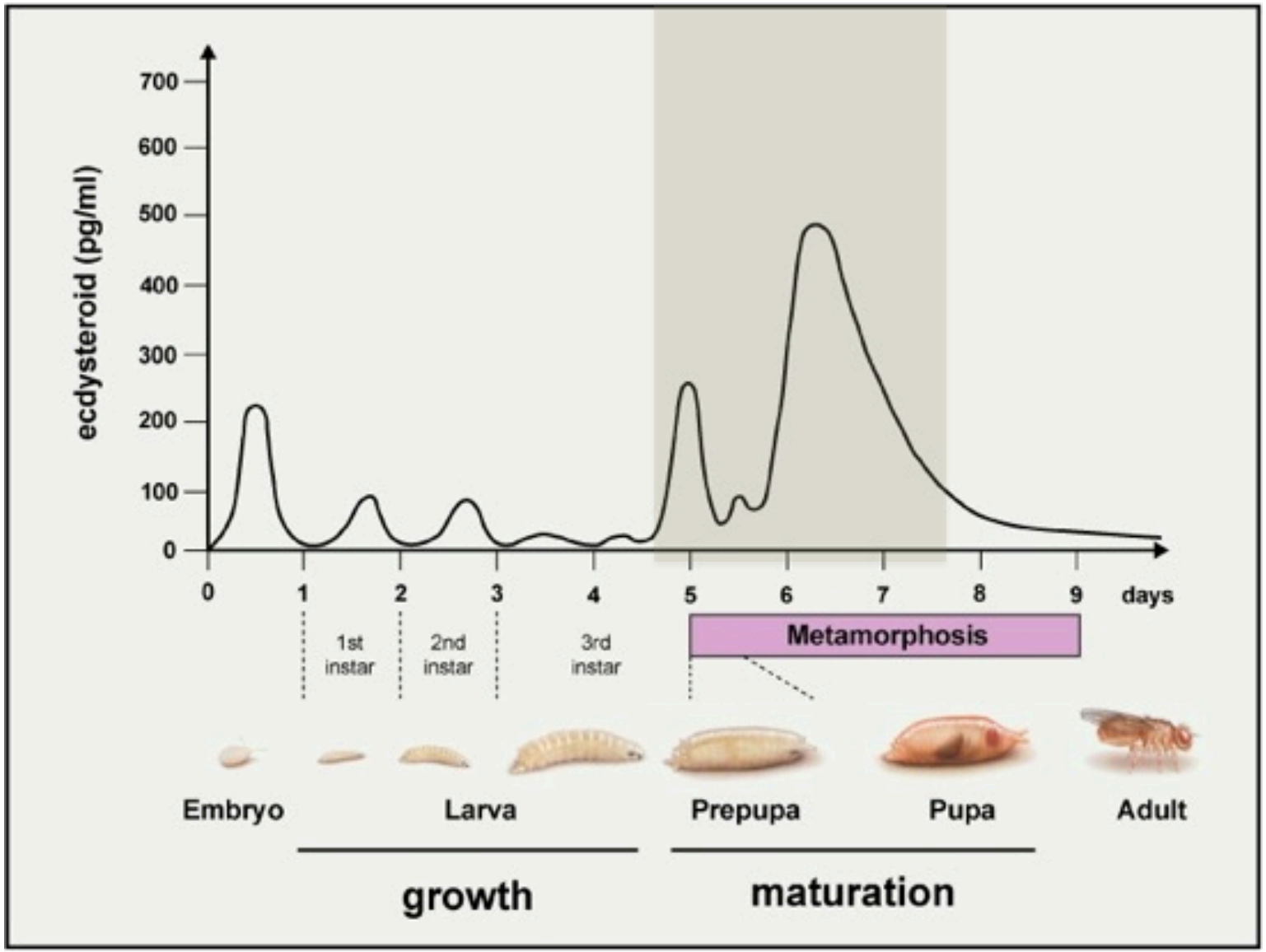




S-pase /neurons

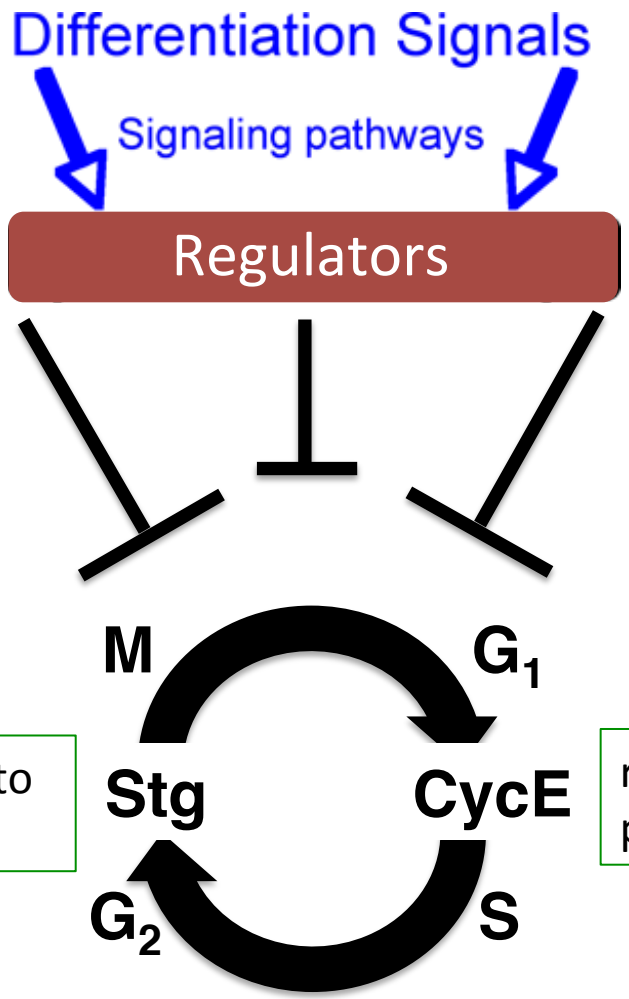
mitoses / neurons

Temporal events are regulated by the hormone Ecdysone



Ashburner 1989

How is ecdysone signaling connected to the cell cycle?



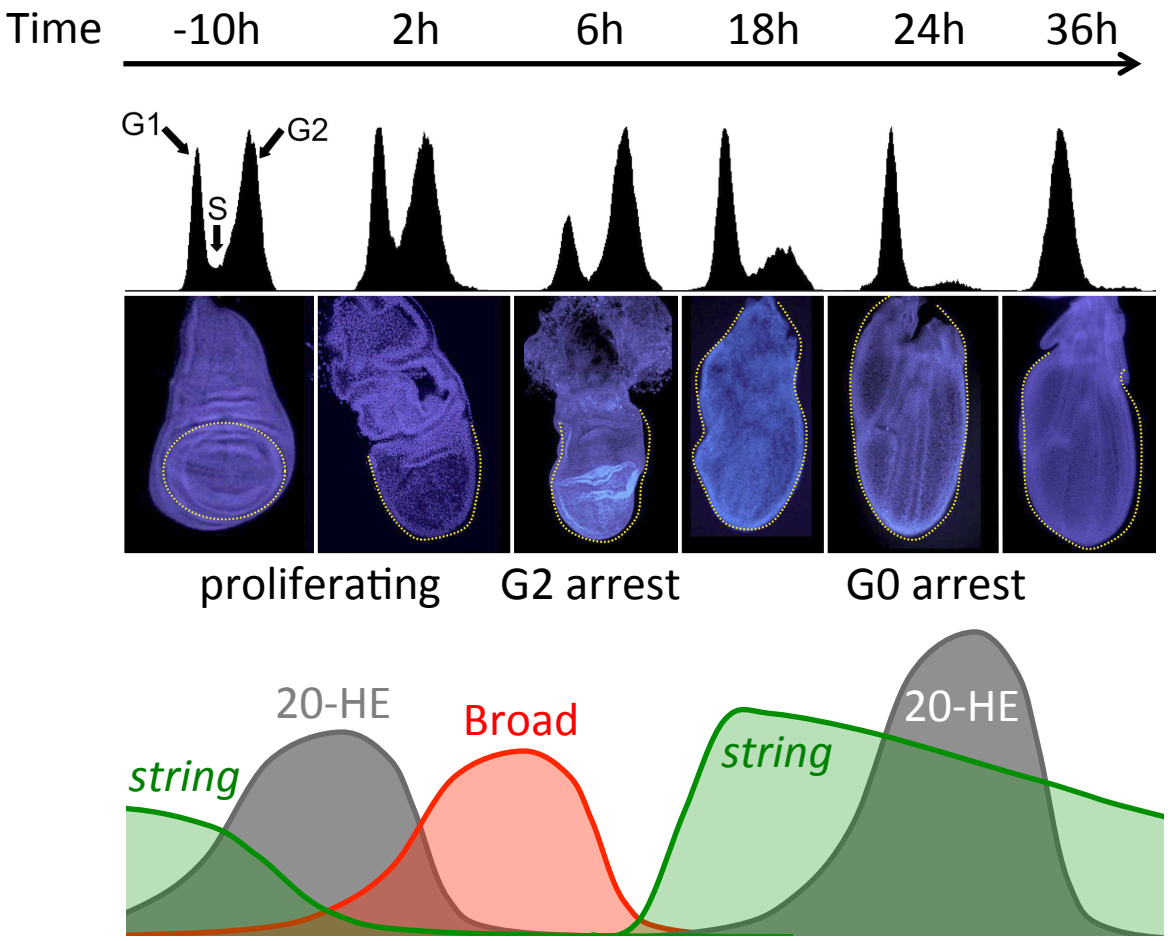
rate limiting for entry to mitosis

rate limiting for S phase entry

Stg (cdc25c) ⟶ CycB/Cdk1 ⊣ Wee/Myt1

Y. Guo, K. Flegel

How is ecdysone signaling connected to the cell cycle?



Wing

20HE

↓

EcR/USP

↓

Broad

⊣

Stg

G2 arrest

Abdominal histoblasts

20HE

↓

EcR/USP

⊣

miR-965

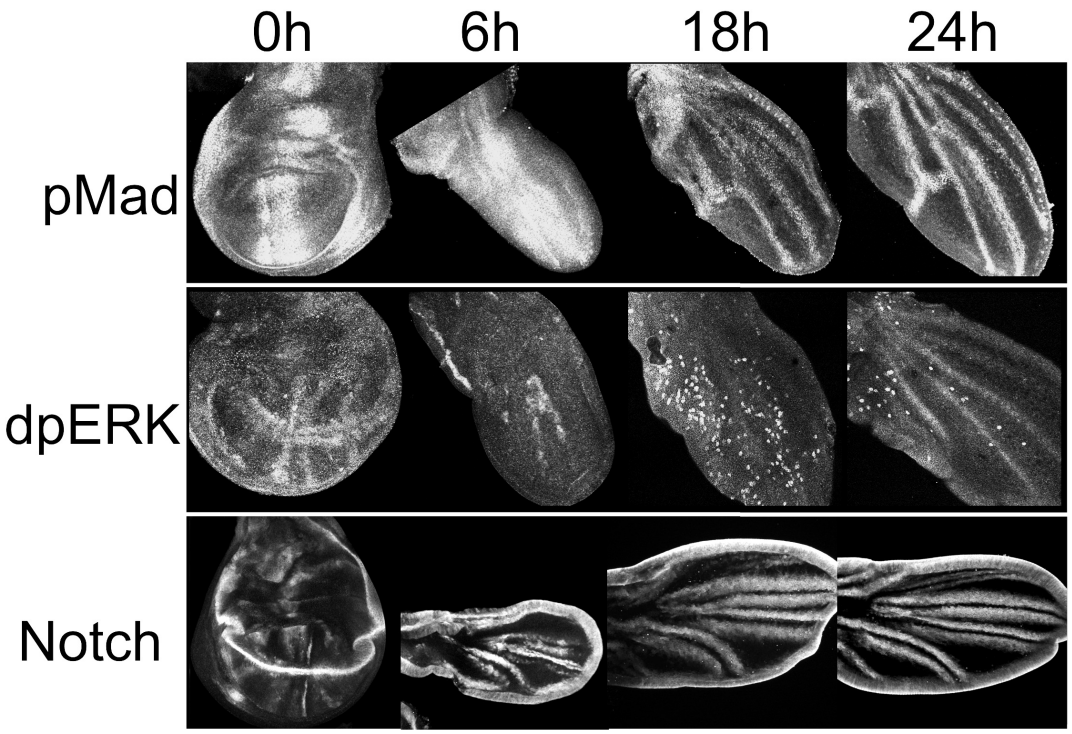
⊣

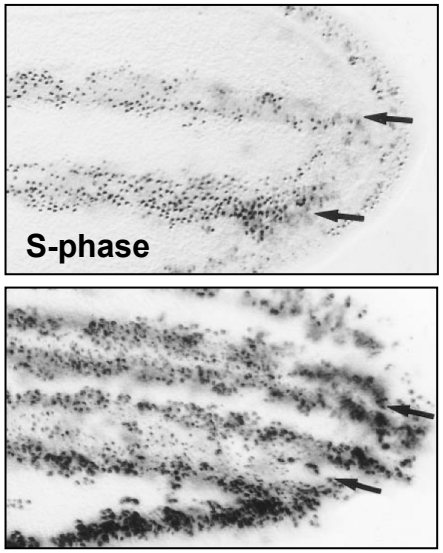
Stg

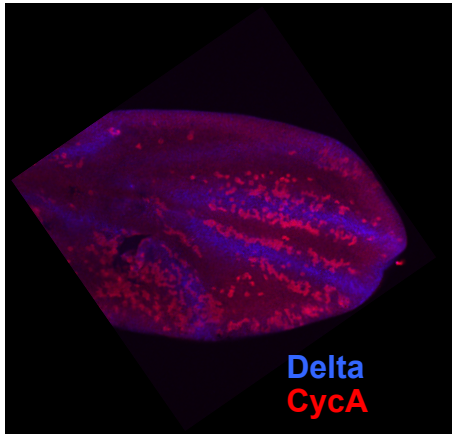
M entry

Verma & Cohen

Y. Guo, K. Flegel





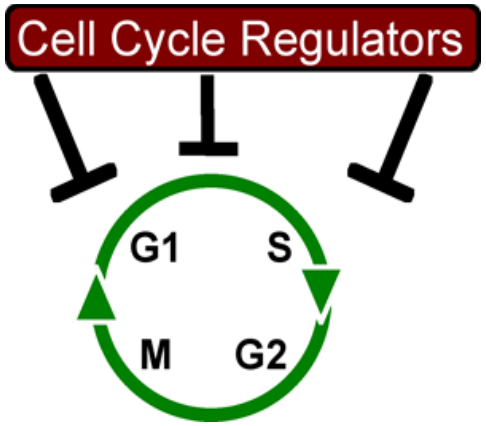


Schubiger and Palka

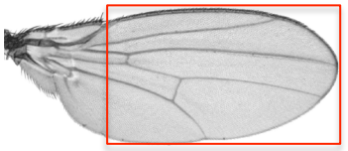
temporal patterning

Hormone signaling

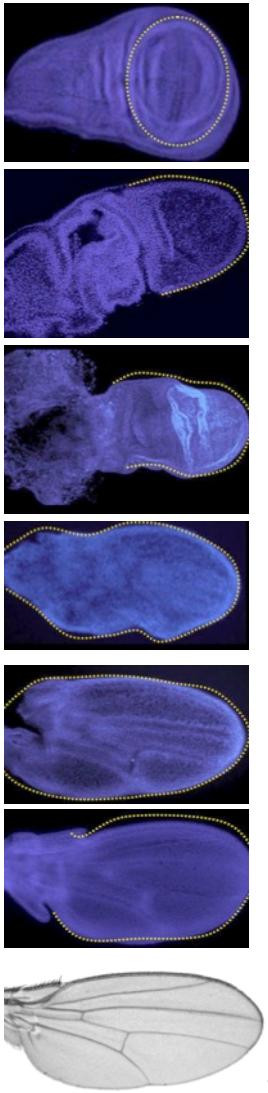
Vein/intervein



The transition to G0 in the fly wing



DNA



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Adult

S-phase

Mitosis

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time

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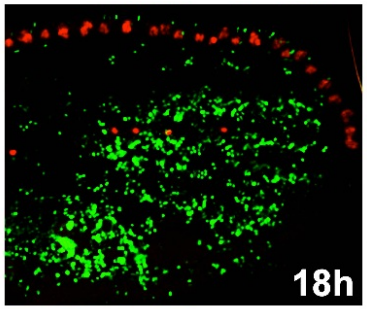
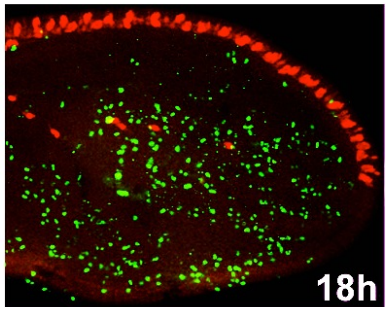
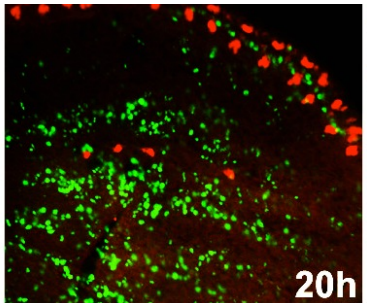
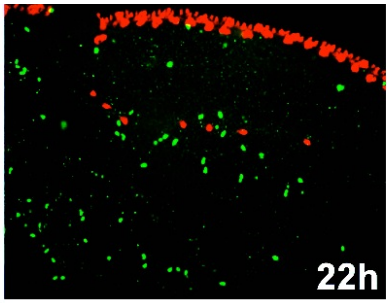
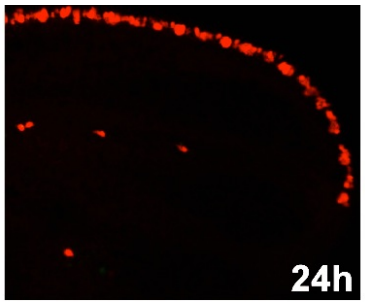
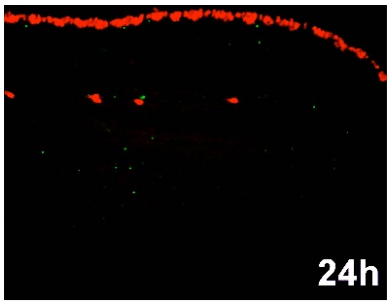








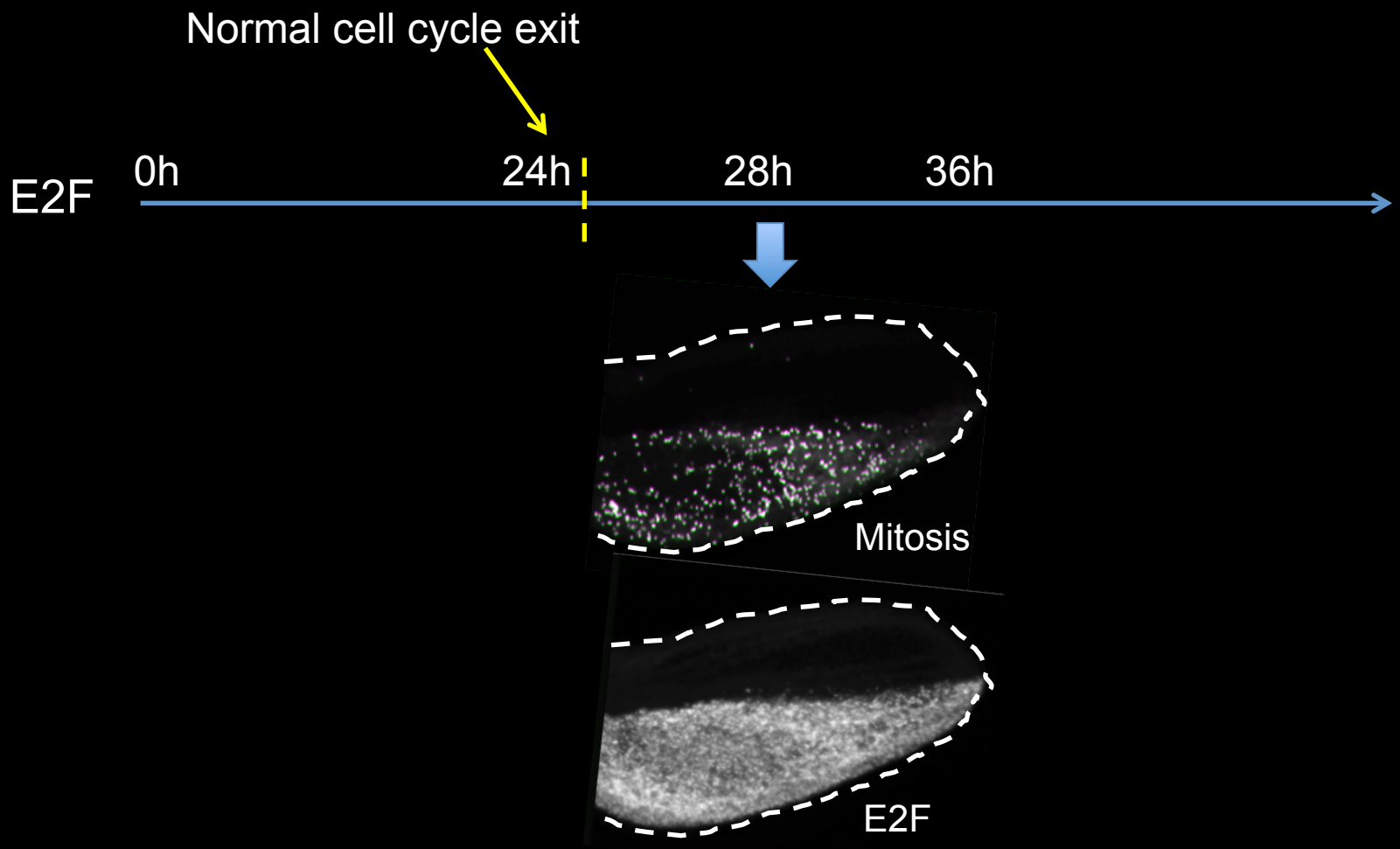




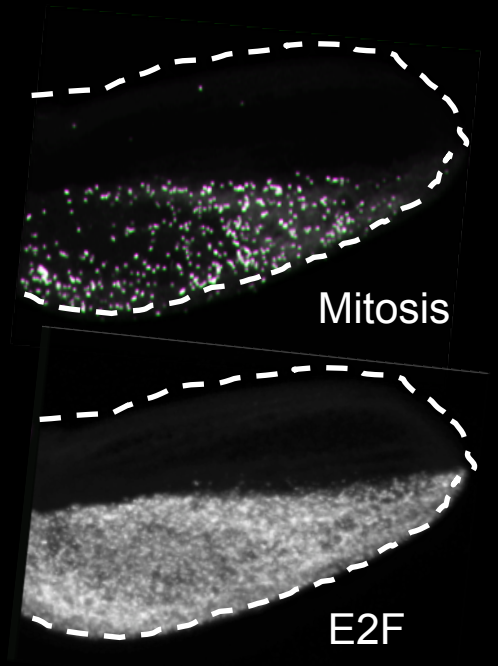
S-pase /neurons

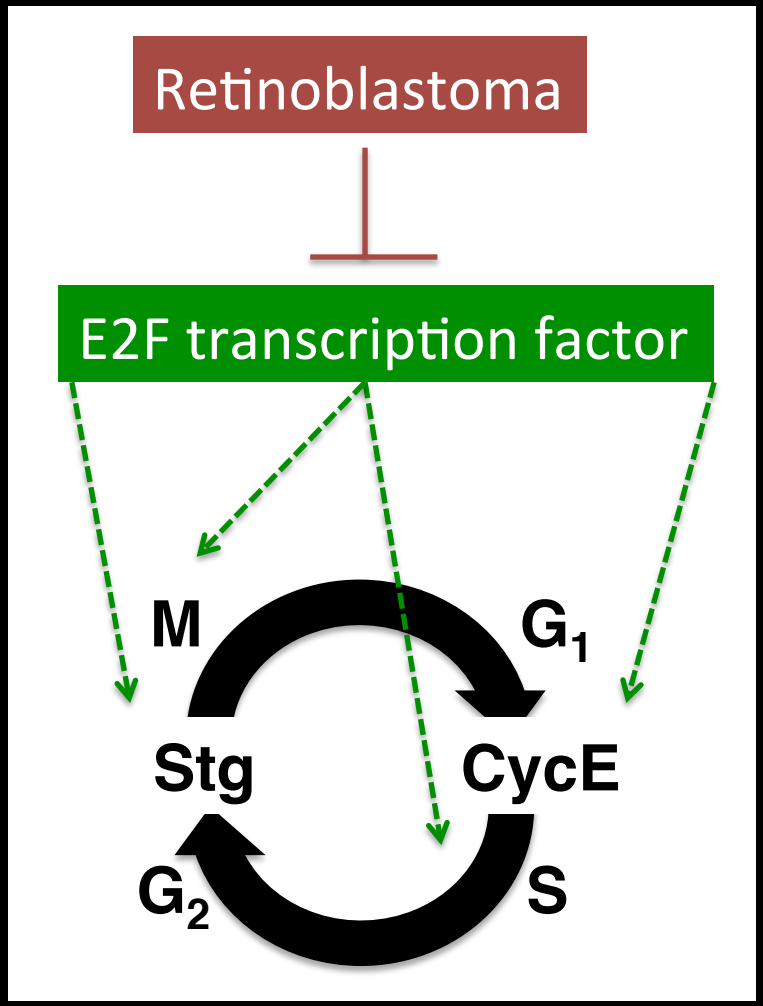
mitoses / neurons

Two stages of G_0 imply multiple levels of cell cycle shut down

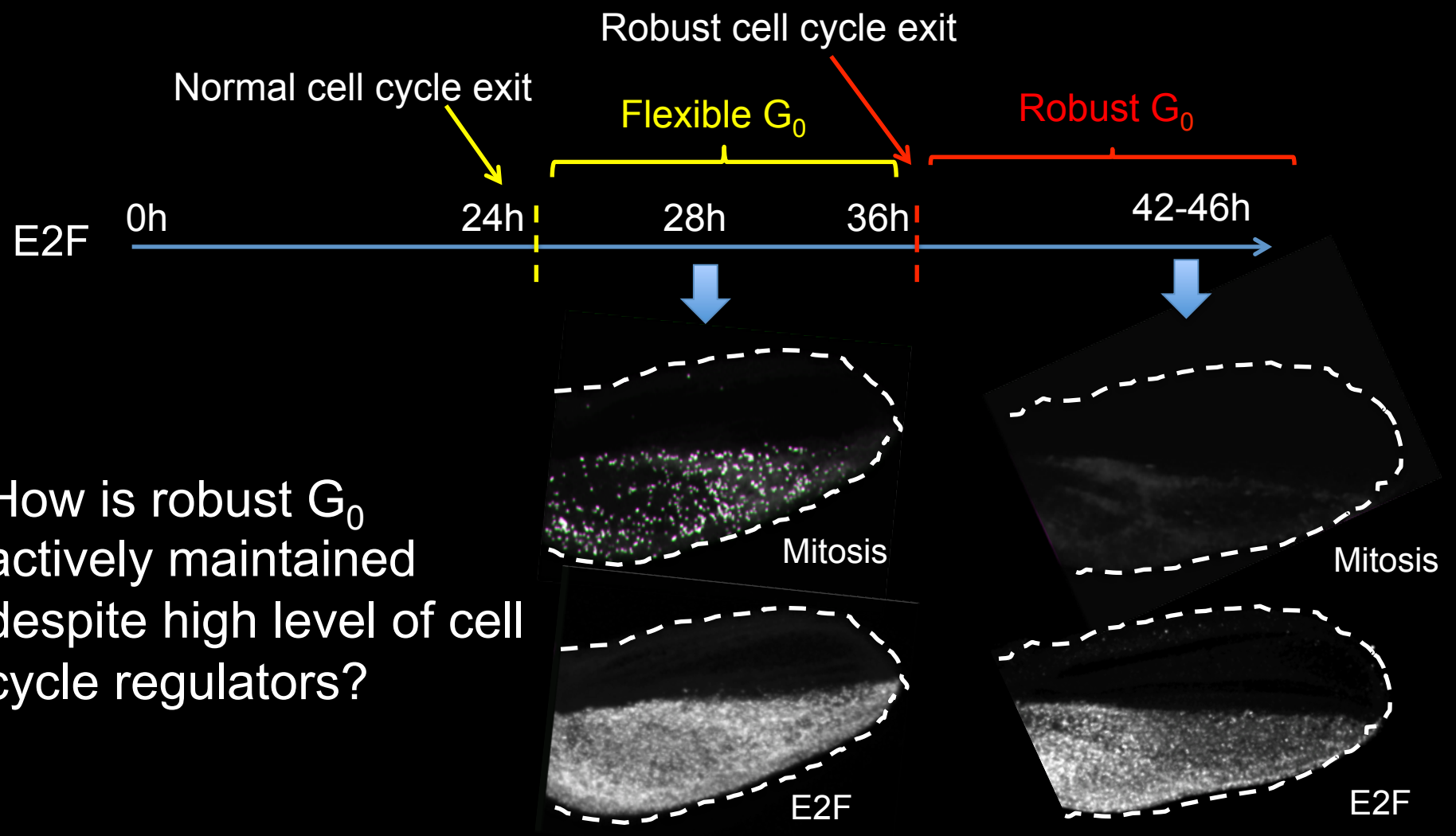


How do we manipulate cell cycle exit?





Two stages of G_0 imply multiple levels of cell cycle shut down



How is robust G_0 actively maintained despite high level of cell cycle regulators?

Yiqin Ma

Common “lockdown” models

Key cell cycle genes recruited to periphery/constitutive heterochromatin

VanSteensel Lab

Key cell cycle genes silenced by PRC or HP1 heterochromatin formation

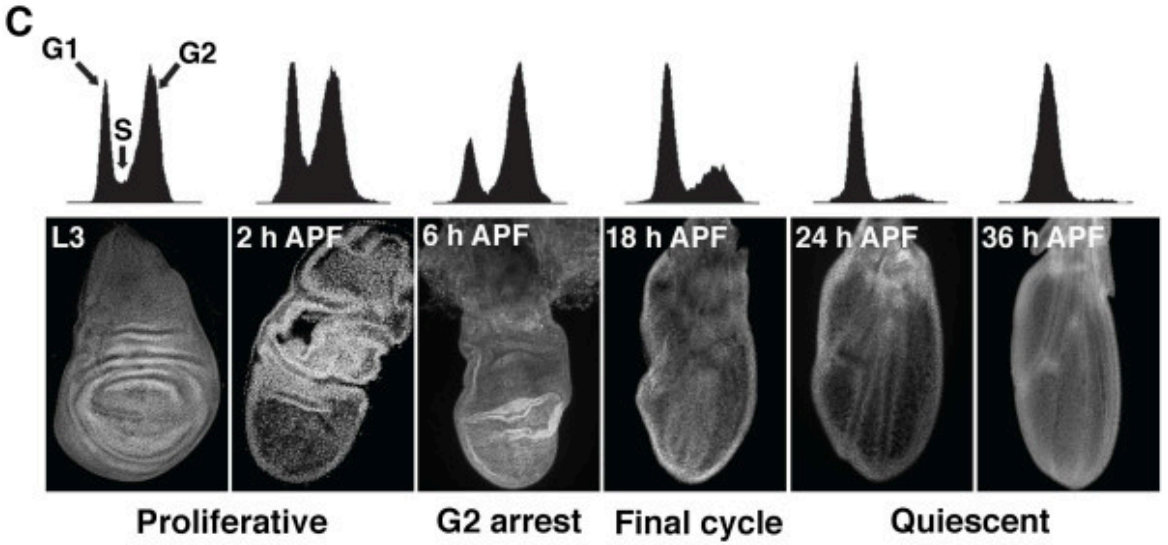
Dynlacht, MacLellan Labs

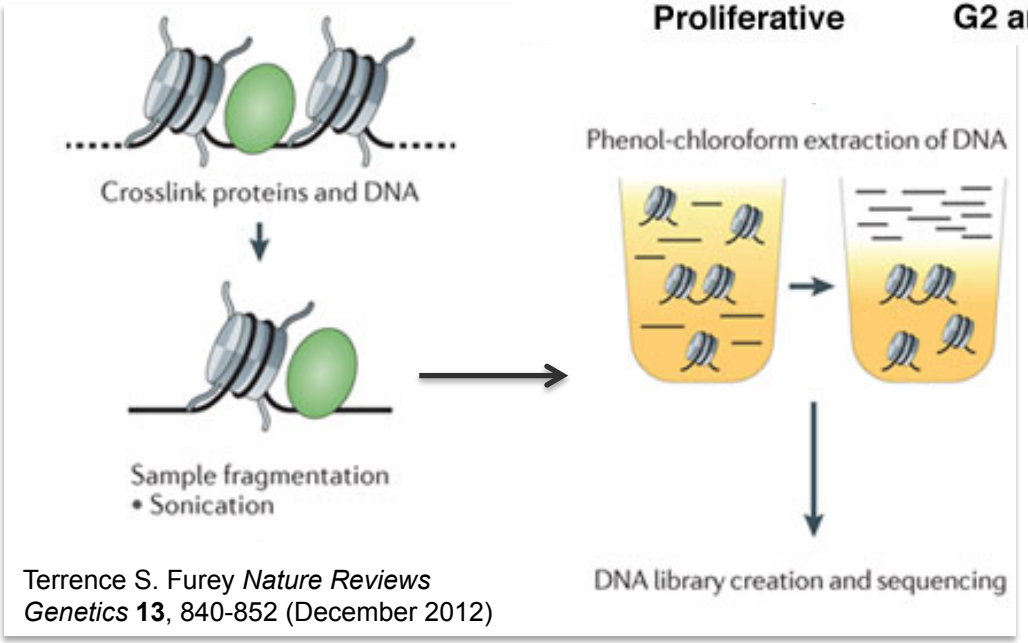
Origins become inaccessible

Crescenzi Lab

Regulatory element accessibility + RNAseq during metamorphosis

FAIRE-seq (Formaldehyde-Assisted Isolation of Regulatory Elements)

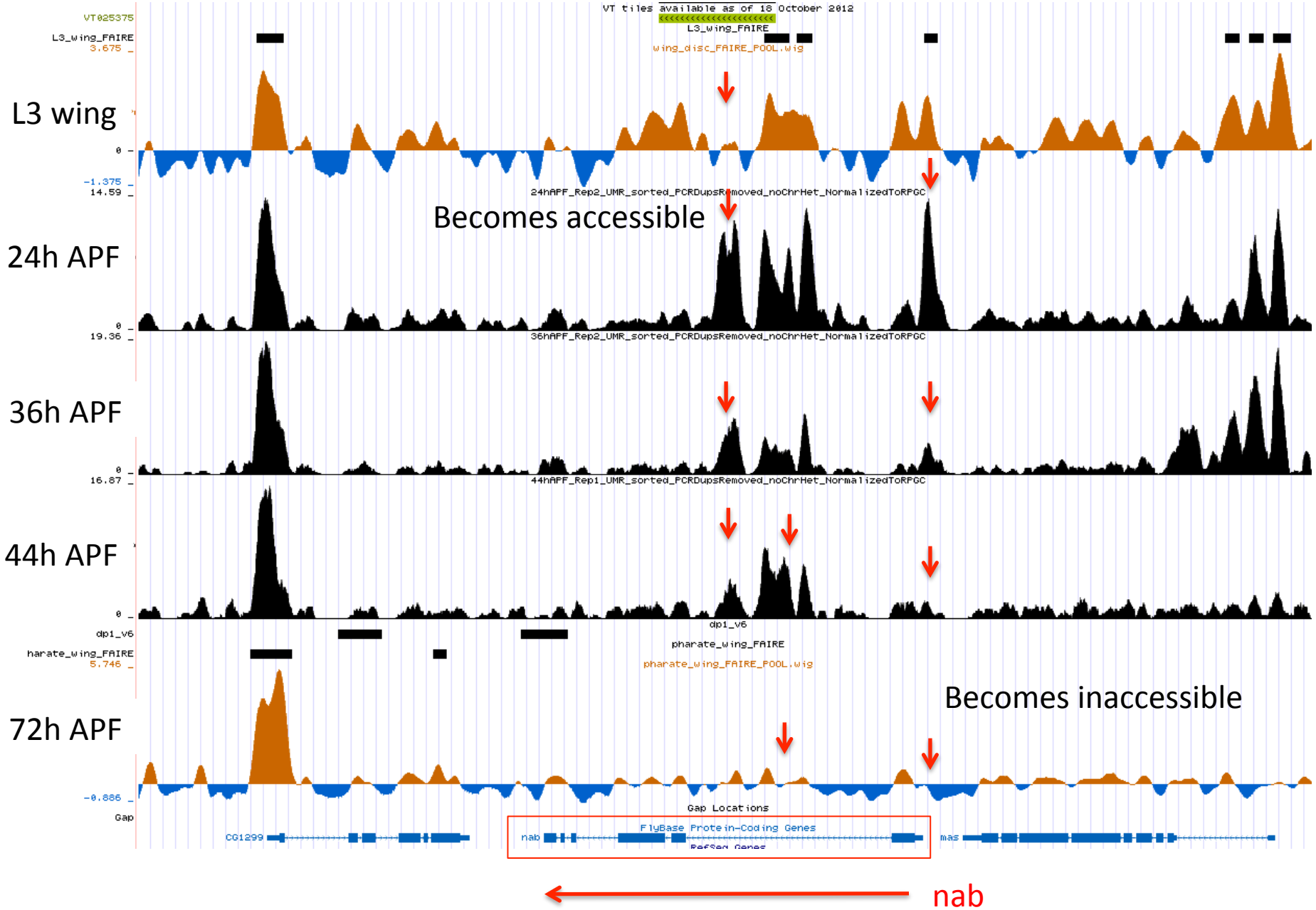




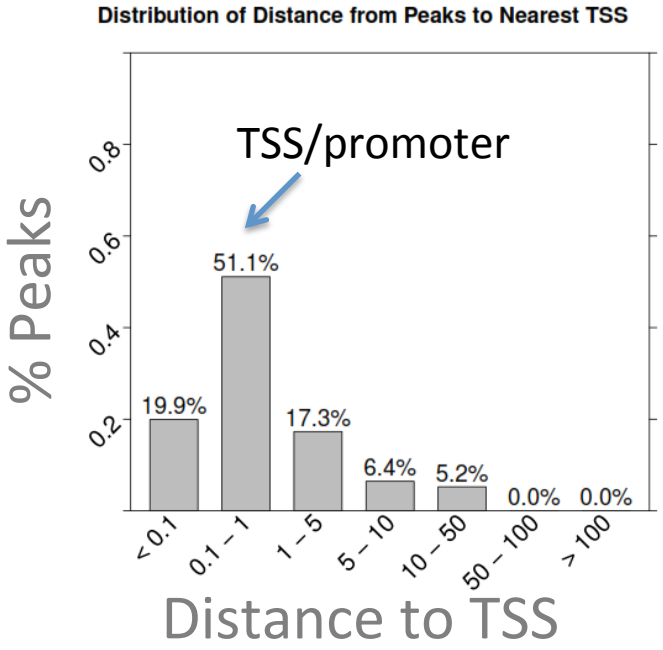
Terrence S. Furey *Nature Reviews Genetics* **13**, 840-852 (December 2012)

Dan McKay
UNC Chapel Hill

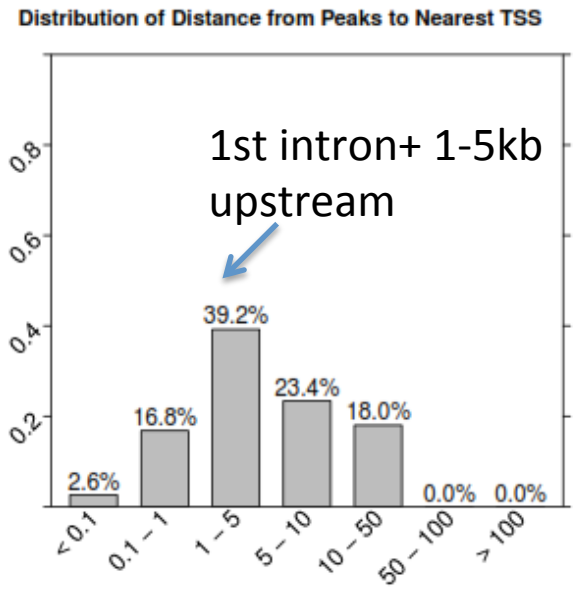
Chromatin accessibility changes at the nab locus during larval->pupal stages



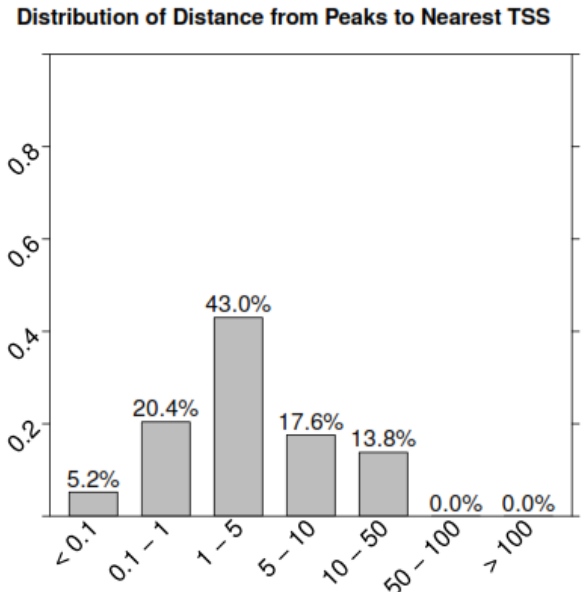
UNCHANGED



DYNAMIC AT 24H

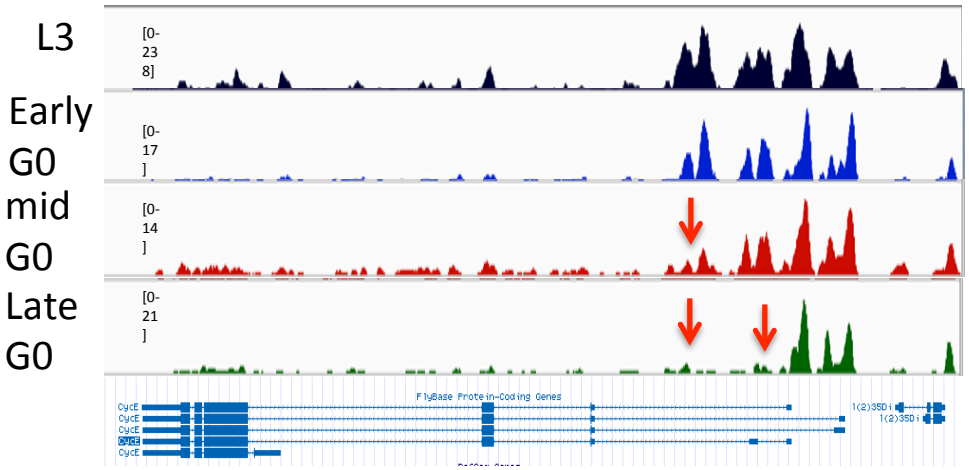


DYNAMIC AT 44H

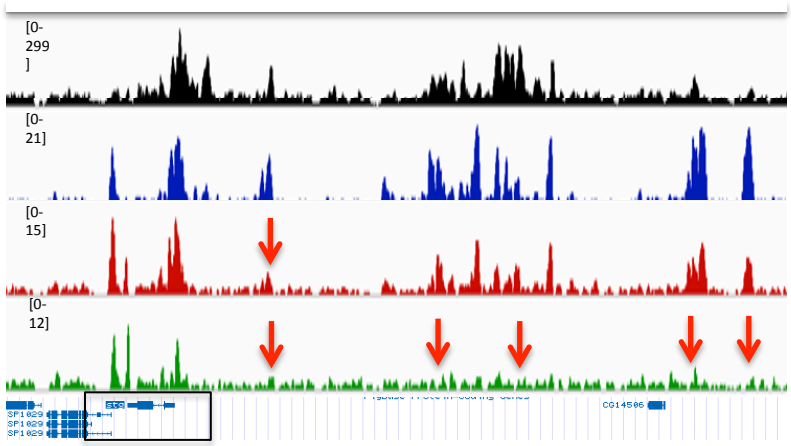


Chromatin accessibility changes at cell cycle genes after cell cycle exit

CycE gene locus



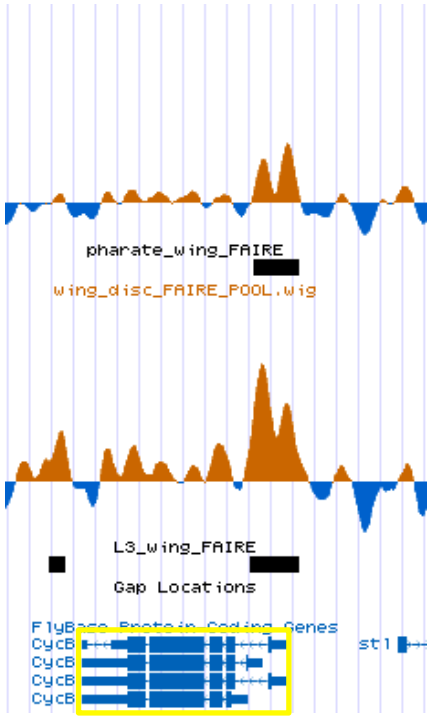
Stg gene locus

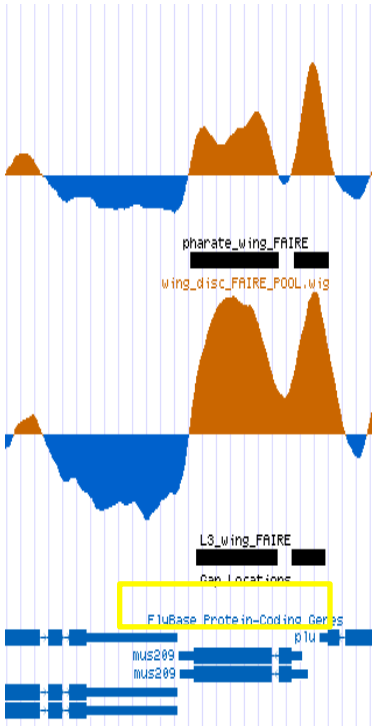


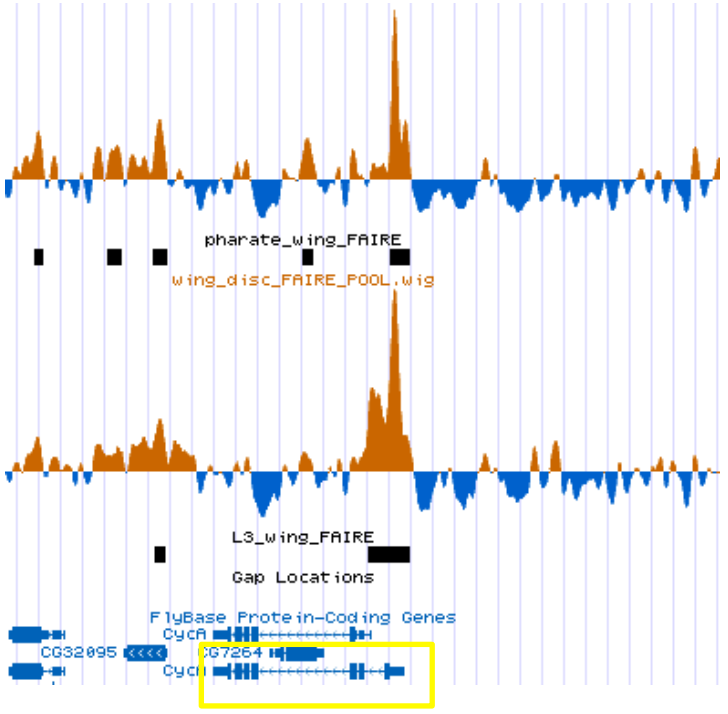
Enhancer E2.2 E2.3 E5.3 E6.7

…but few chromatin accessibility changes at most other cell cycle genes

Proliferating Postmitotic

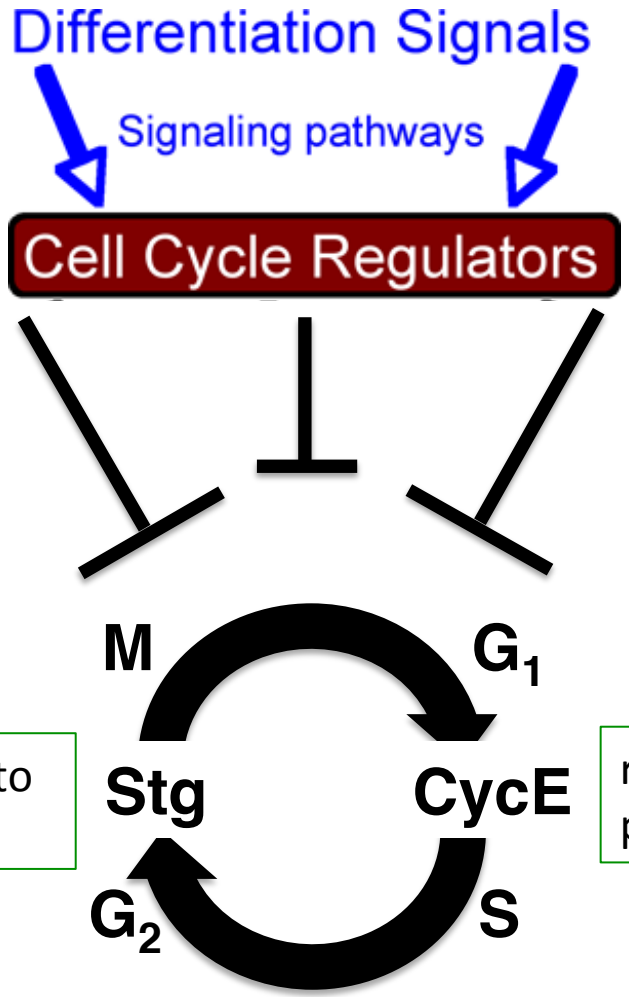






Cyclin B PCNA CycA

Chromatin accessibility changes at the few "Generals", not the many "Soldiers"

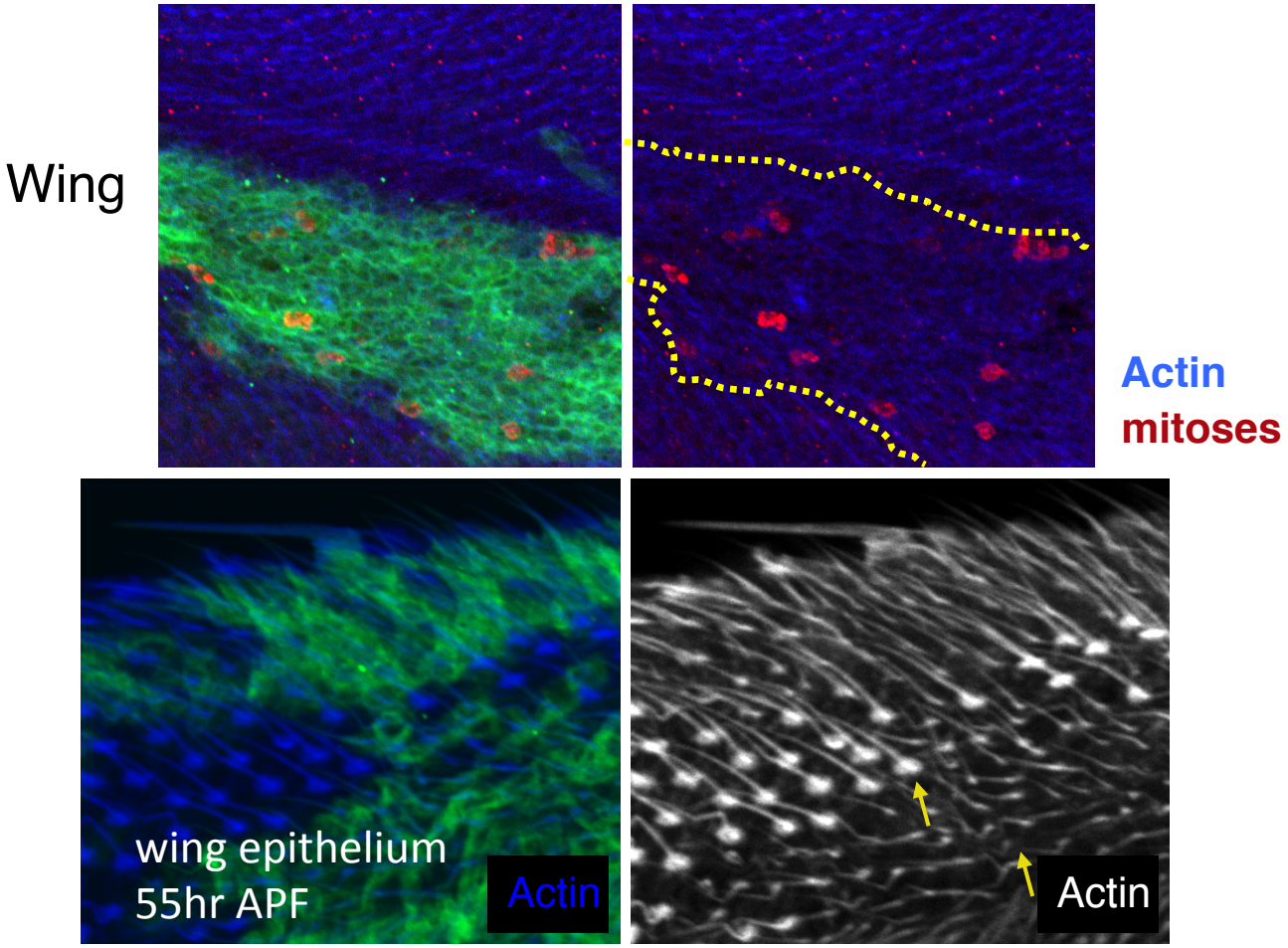


rate limiting for entry to mitosis

rate limiting for S phase entry

Adding exogenous CycE+Stg to E2F bypasses G_0

Bypassing G0 in the fly wing using E2F+CycE+Stg > 44 hr APF



What drives the changes in accessibility at cell cycle genes in G0?

Many questions remain:

- What happens to accessibility when we bypass G0? (cause or consequence?)
- How does Mi-2 impact chromatin accessibility at cell cycle genes?
- Does preventing changes in accessibility lead to a more flexible G0 state?
- Can we reverse an established G0 state and re-open the inaccessible spots?

Acknowledgements

Buttitta Lab
Kerry Flegel
Rosaline Sun
Yiqin Ma
Olga Grushko
Shyama Nandakumar

Reagents:
Bloomington Stock Center
Bob Duronio

Collaborators:
Dan McKay (FAIRE-seq)

Funding:
American Cancer Society
NIH NIA
U. Michigan BSSP Award