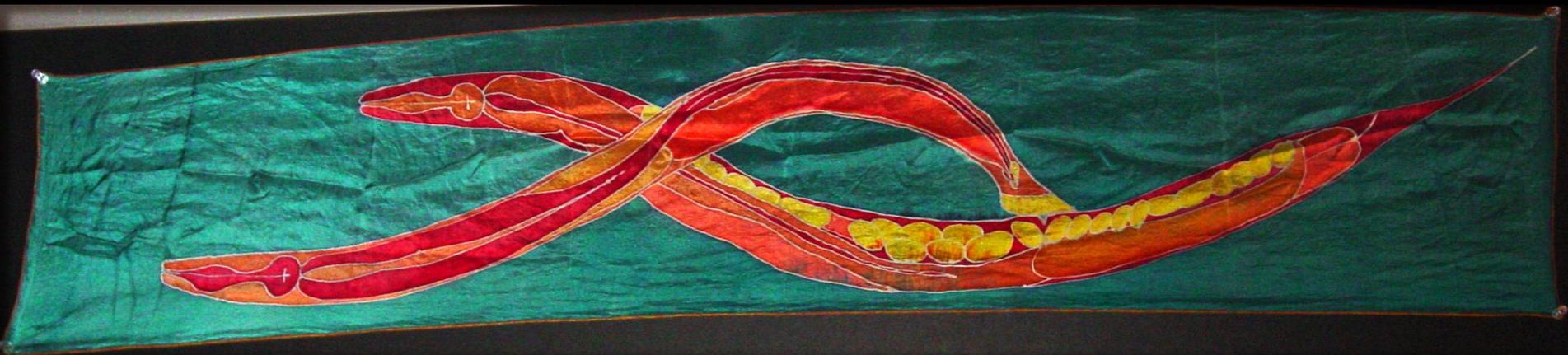


How cells sculpt organs



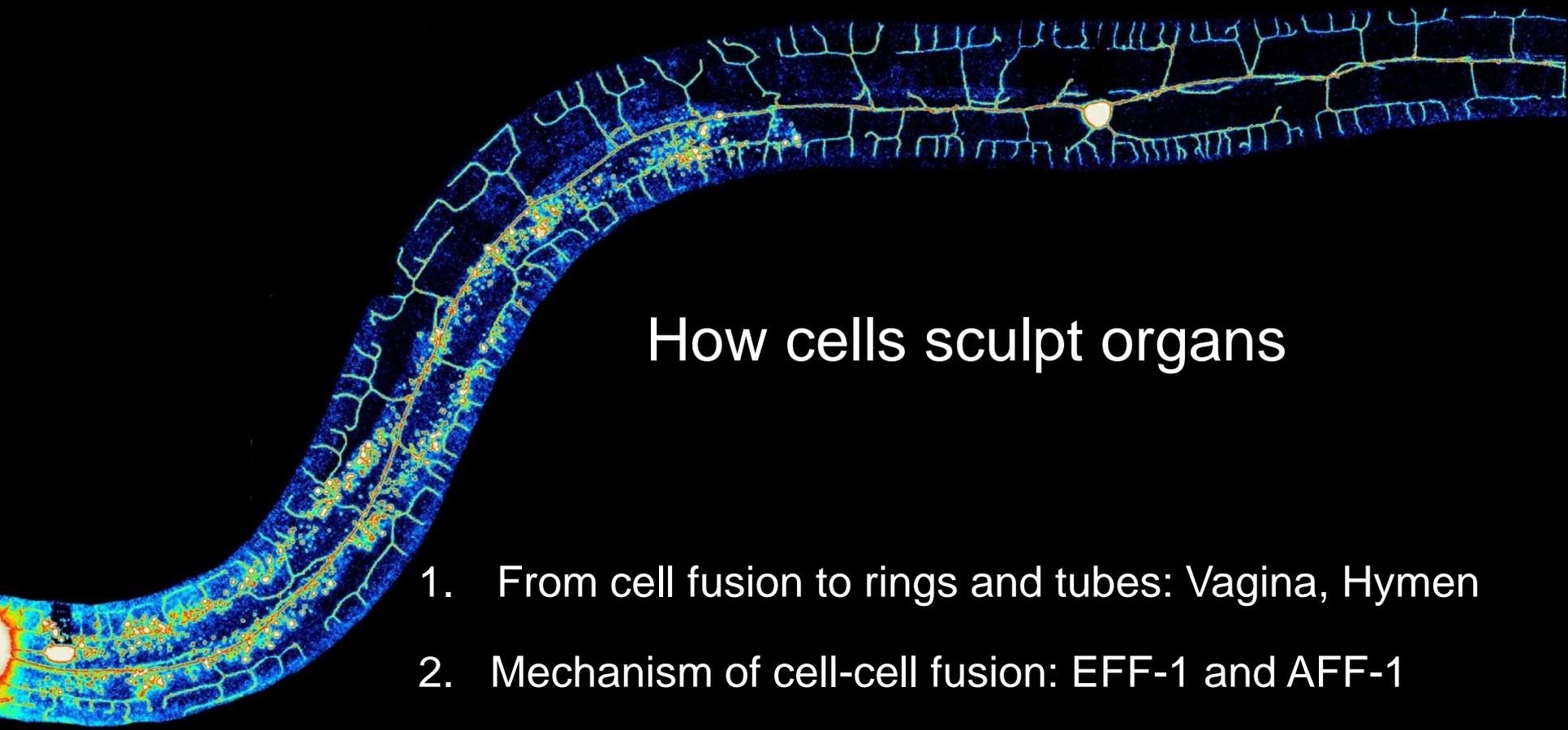
Benjamin Podbilewicz
Technion - Israel Institute of Technology

Conference on Bioscience and Society: Organisms as Living Systems,
Slovenia, October 21-22, 2010.



LJAZEV STOLP

Gali

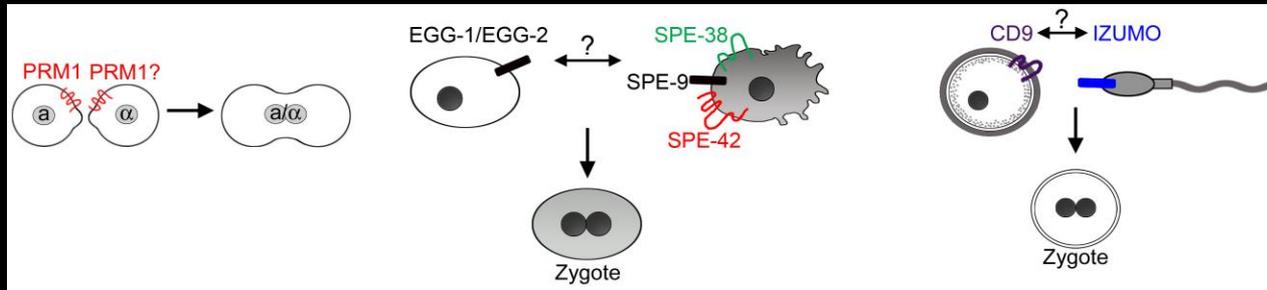


How cells sculpt organs

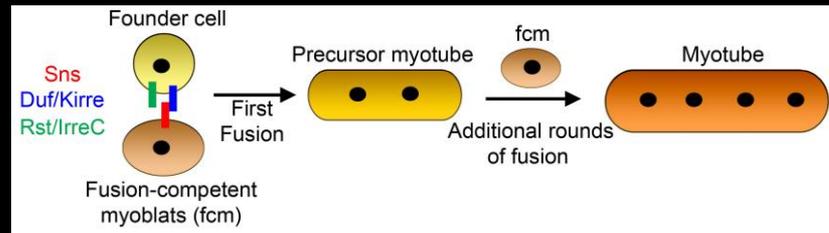
1. From cell fusion to rings and tubes: Vagina, Hymen
2. Mechanism of cell-cell fusion: EFF-1 and AFF-1
3. Cell fusion: Worm gynecology and neurology

1. From cell fusion to rings and tubes

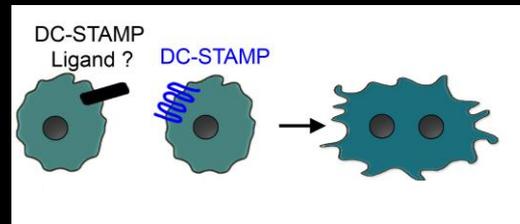
GAMETES



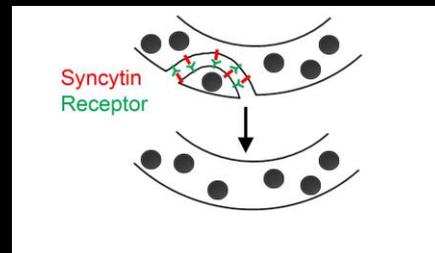
MUSCLES



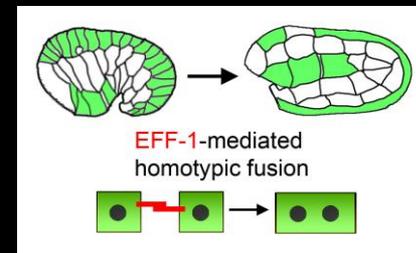
BONES



PLACENTA



EPIDERMIS



Caenorhabditis elegans



Resume

Name: *Caenorhabditis elegans*

Alias: *C. elegans*, the worm

Personal information

- 1mm long
- can be raised on agar
- 3.5 day life cycle
- self fertilizing hermaphrodites
- males arise rarely & spontaneously
- transparent at all stages
- fixed number of cells (959 nuclei)
- cell fates are invariant

Major accomplishments

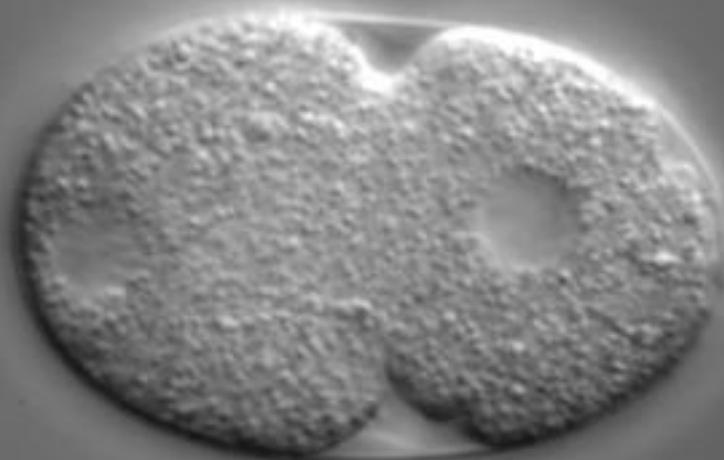
- Complete anatomy in electron micrographs
- Complete physical map of the genome
- Complete cell lineage and neural map
- Complete sequence of the genome
- Expression patterns (partial)
- Gene knockouts (partial)
- Discovery of RNAi
- Survived space shuttle Columbia accident

Honors and awards

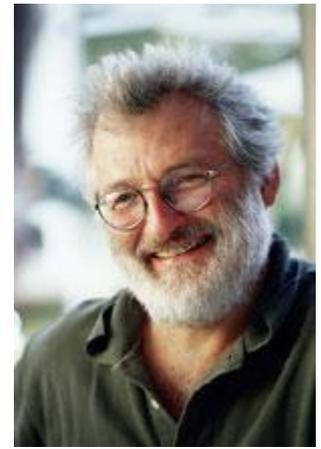
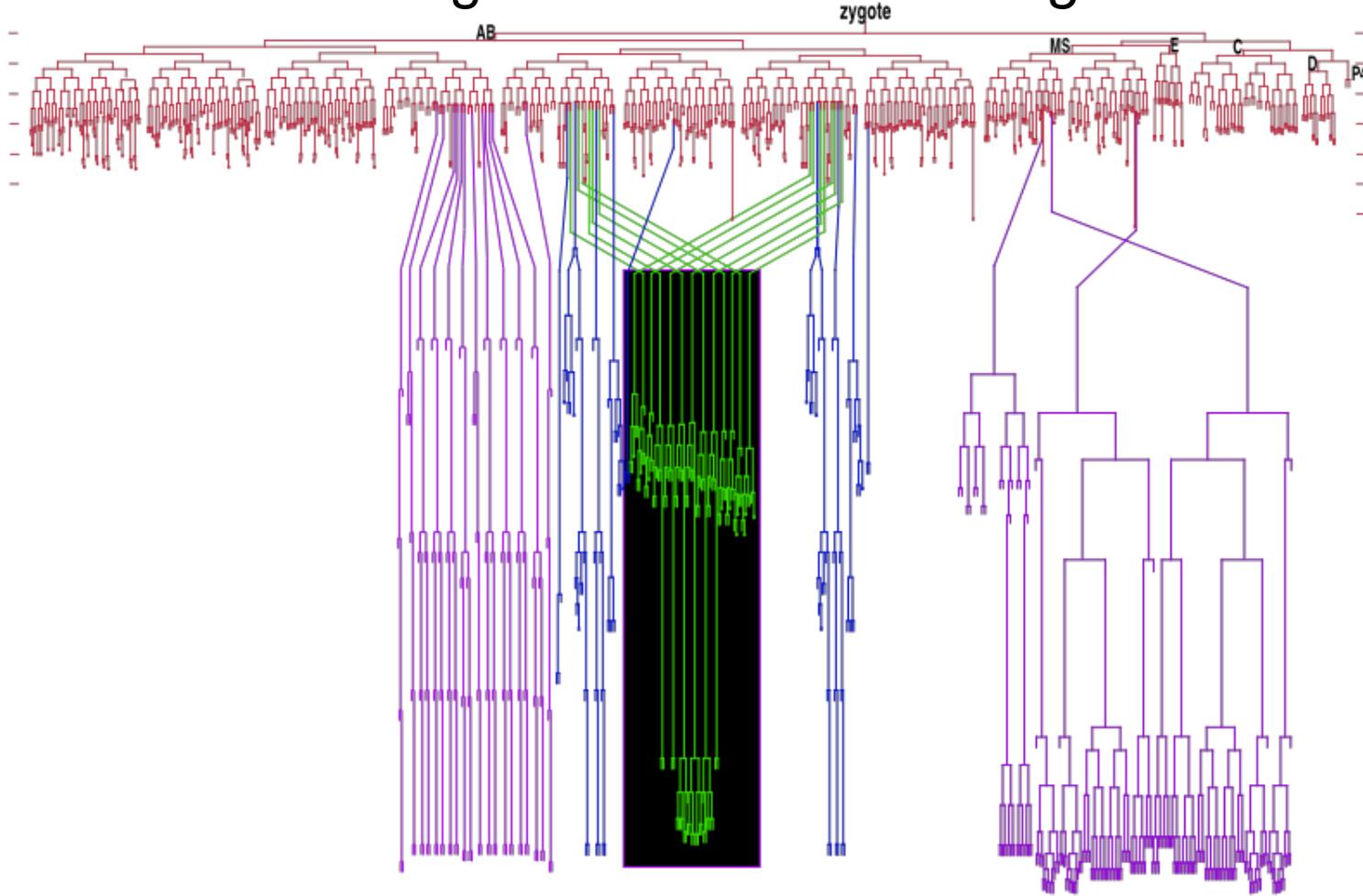
- Harvey Prize, Technion
- Dan David Prize, Tel-Aviv U.
- Nobel Prize 2002, 2006, 2008



Time Elapsed : 00 :00 :03



Cell lineage is invariant in *C. elegans*



John Sulston

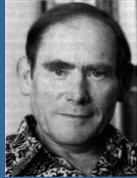


John White



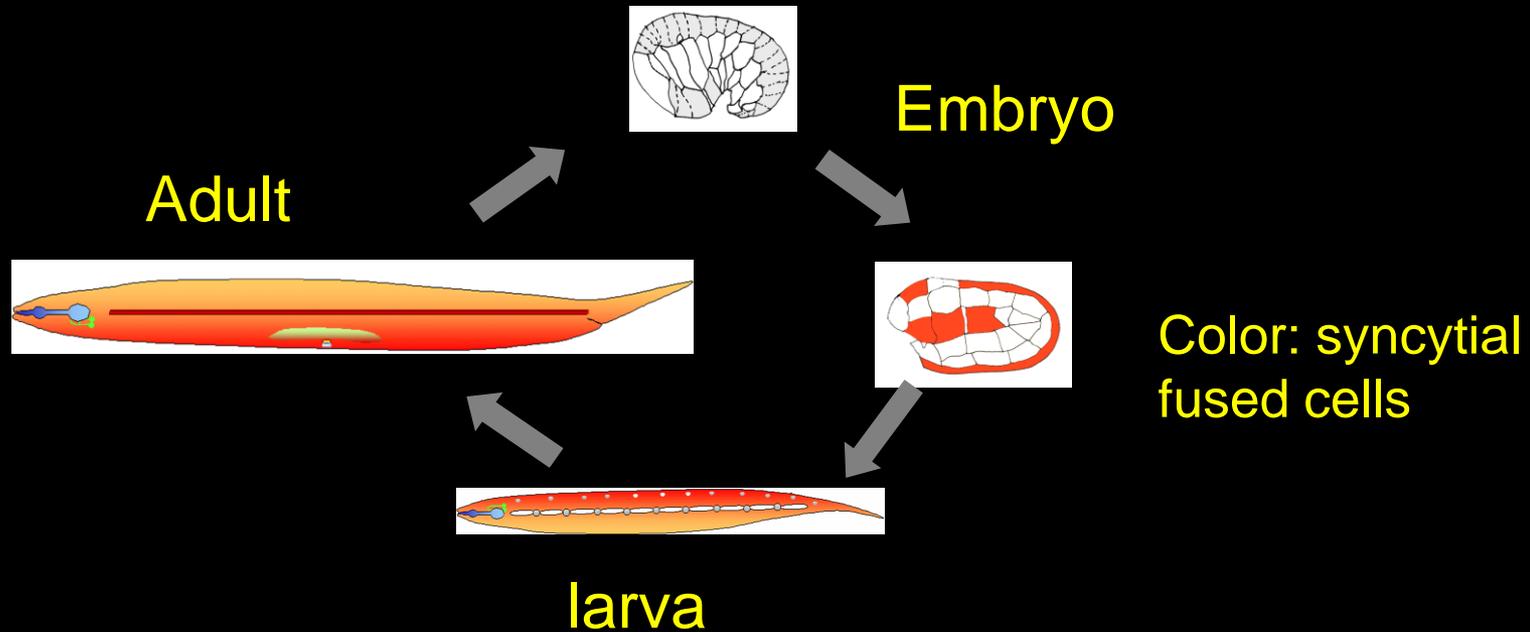
The *C. elegans* research community lineage

Sydney Brenner



Why study cell fusion in *C. elegans*?

~1/3 of the adult nuclei are part of syncytia



In addition:

Powerful genetics

Relatively small genome

Short life cycle and ~300 progeny per worm



7 October 2002

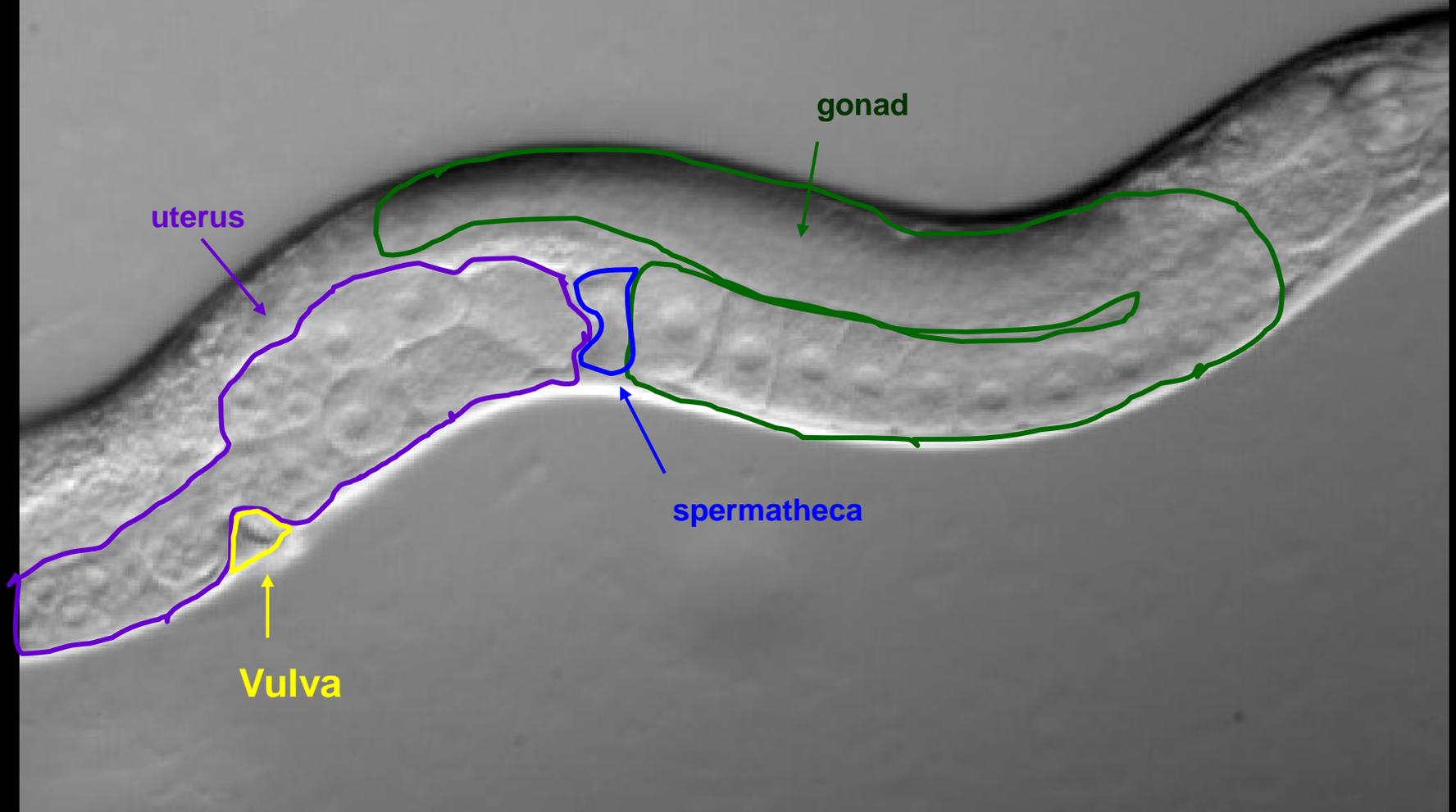
The Nobel Assembly at Karolinska Institutet
has today decided to award The Nobel Prize in Physiology or Medicine for 2002
jointly to

Sydney Brenner, H. Robert Horvitz and John E. Sulston

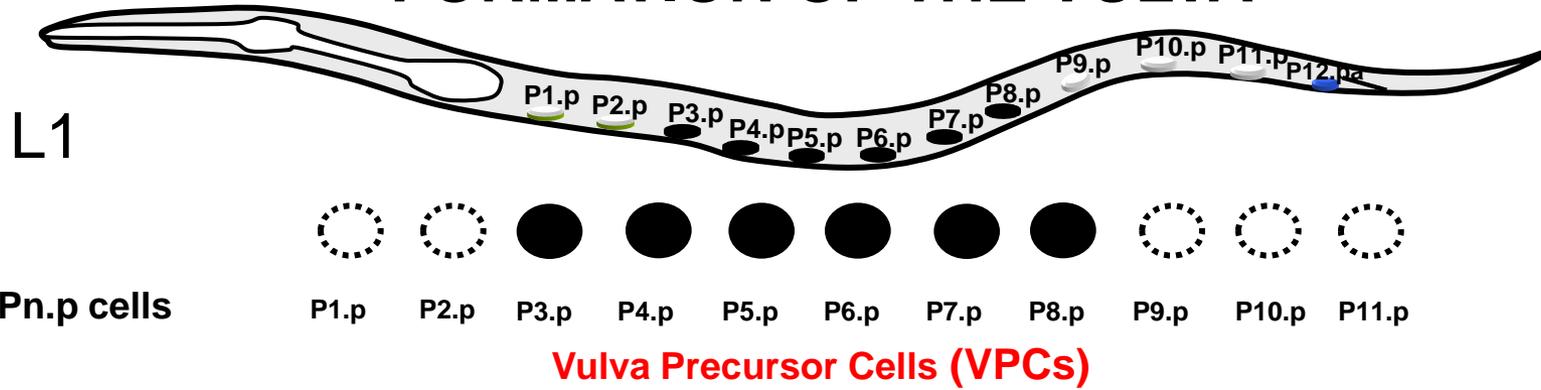
for their discoveries concerning

"genetic regulation of organ development and programmed cell death"

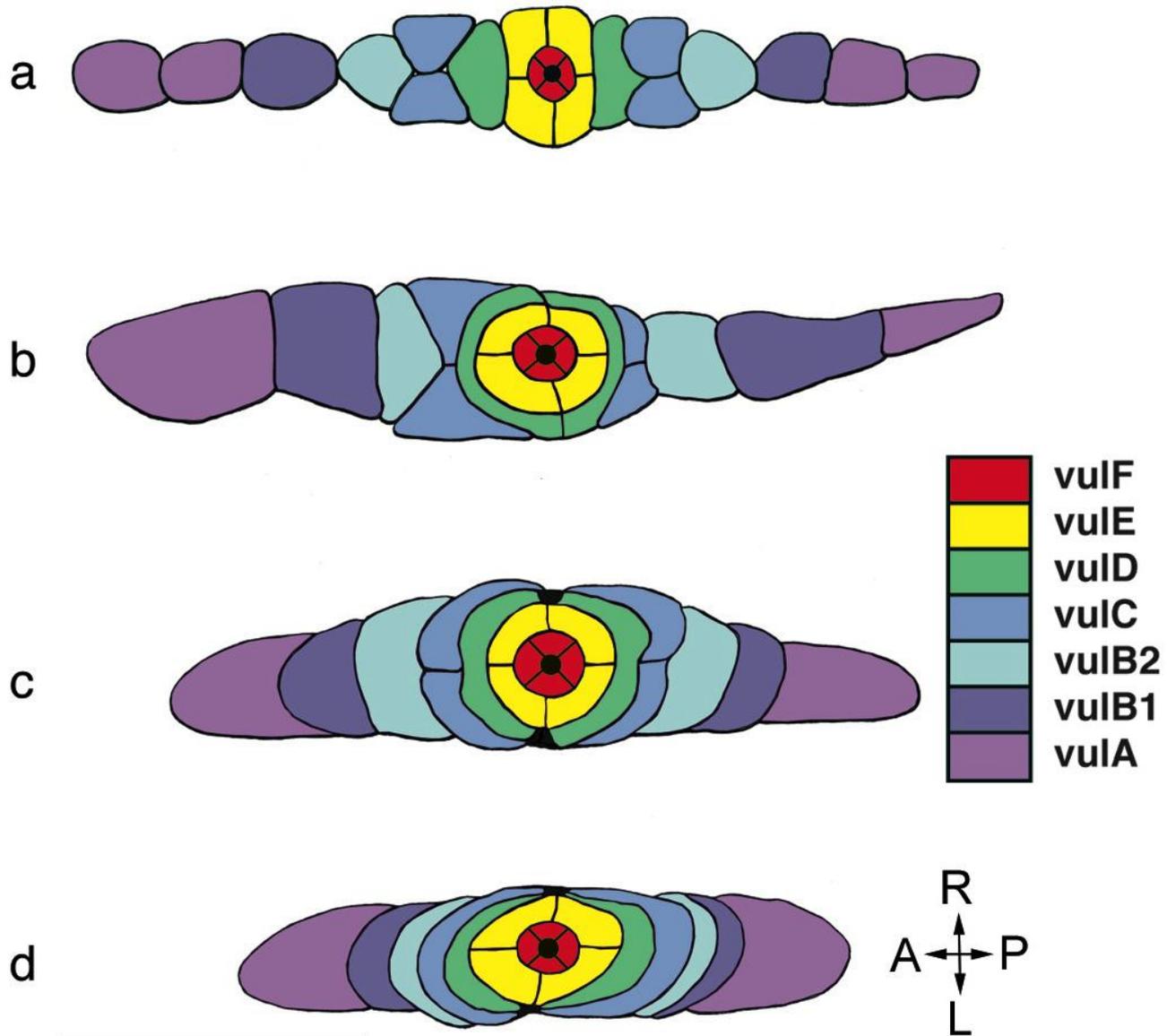
ORGANOGENESIS: VULVA FORMATION



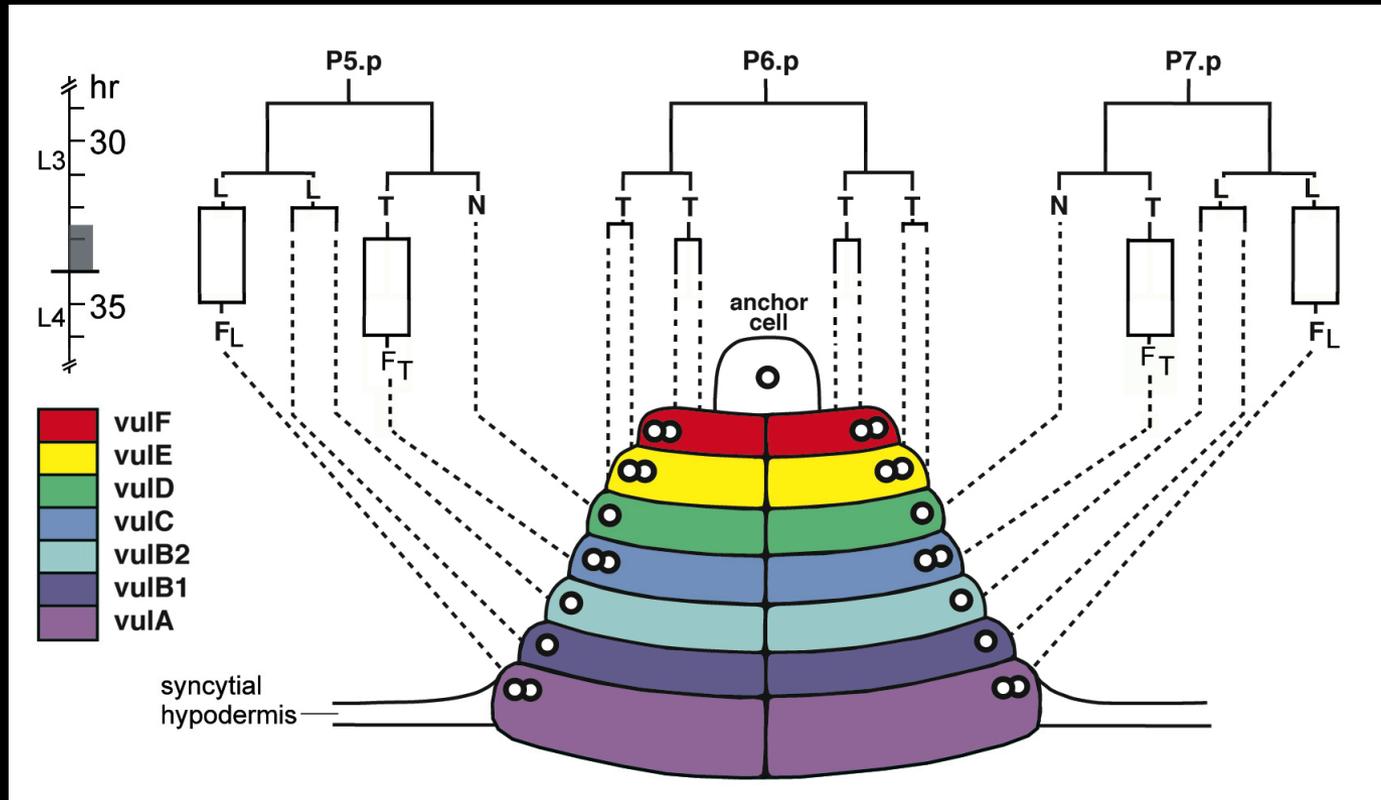
FORMATION OF THE VULVA



How to make rings and tubes



RINGS forming TUBES

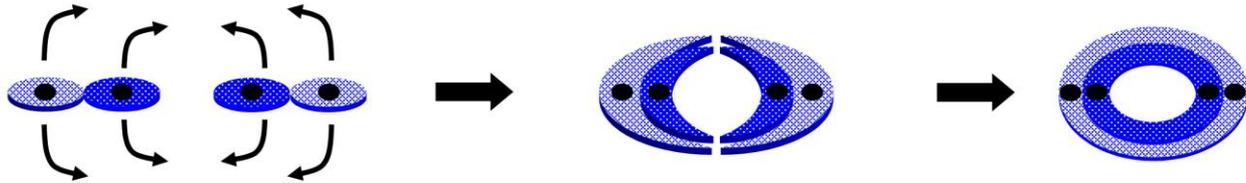


The ring hypothesis

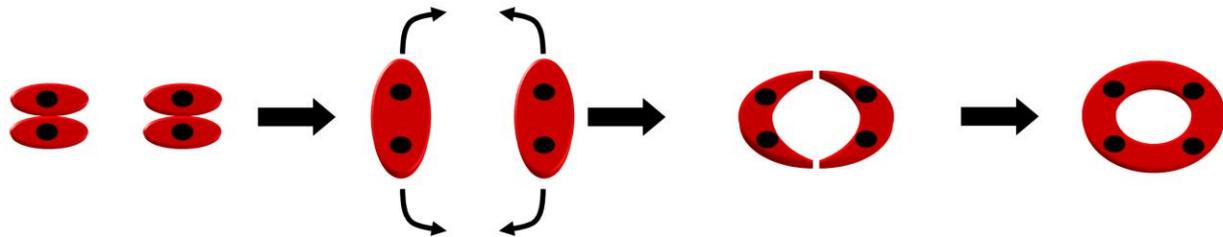
1. U (all)



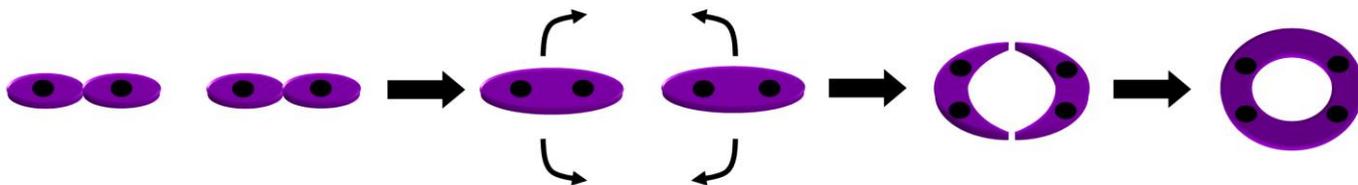
2. L (all)



3. T (all)



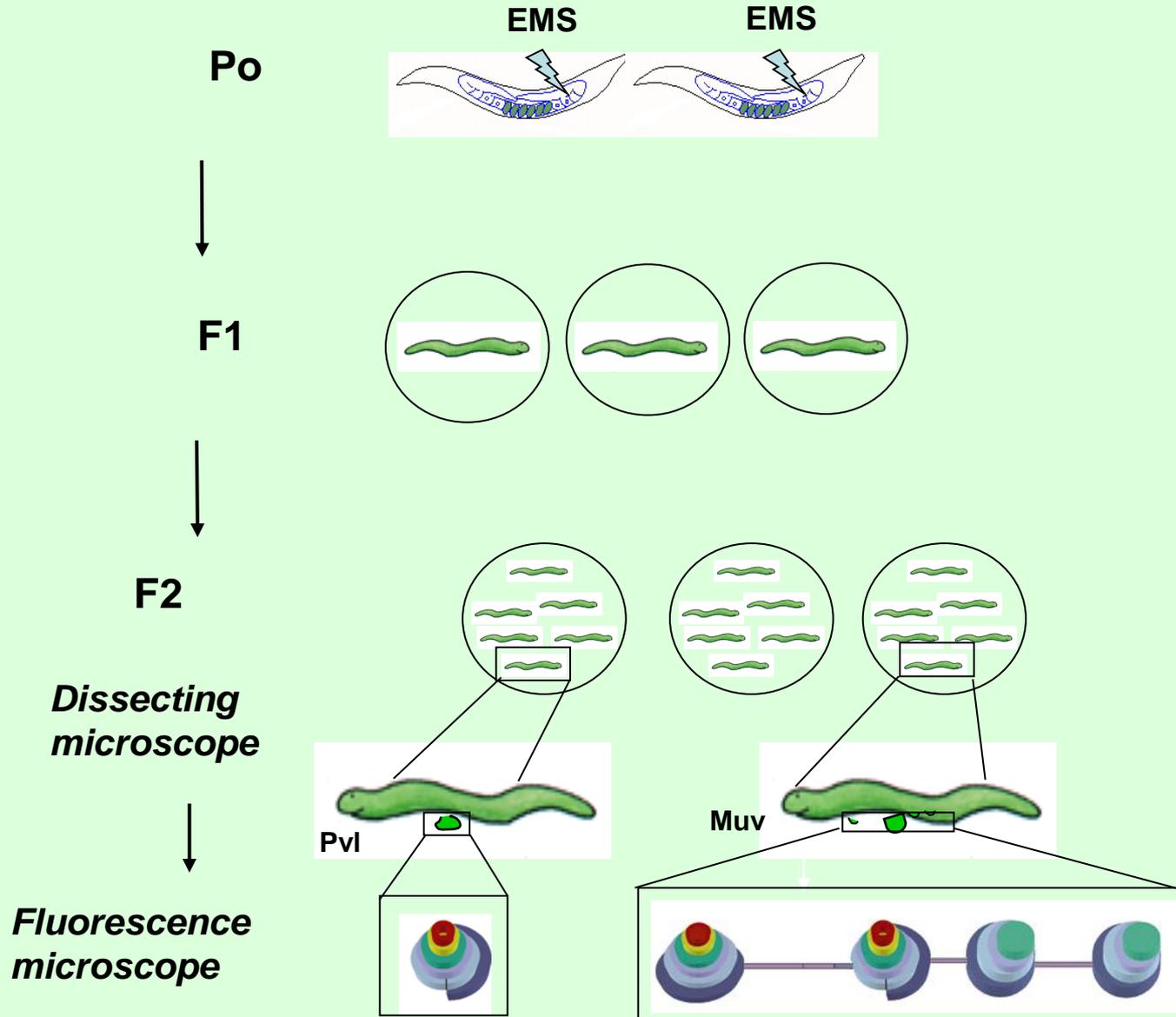
4. L (vulA)



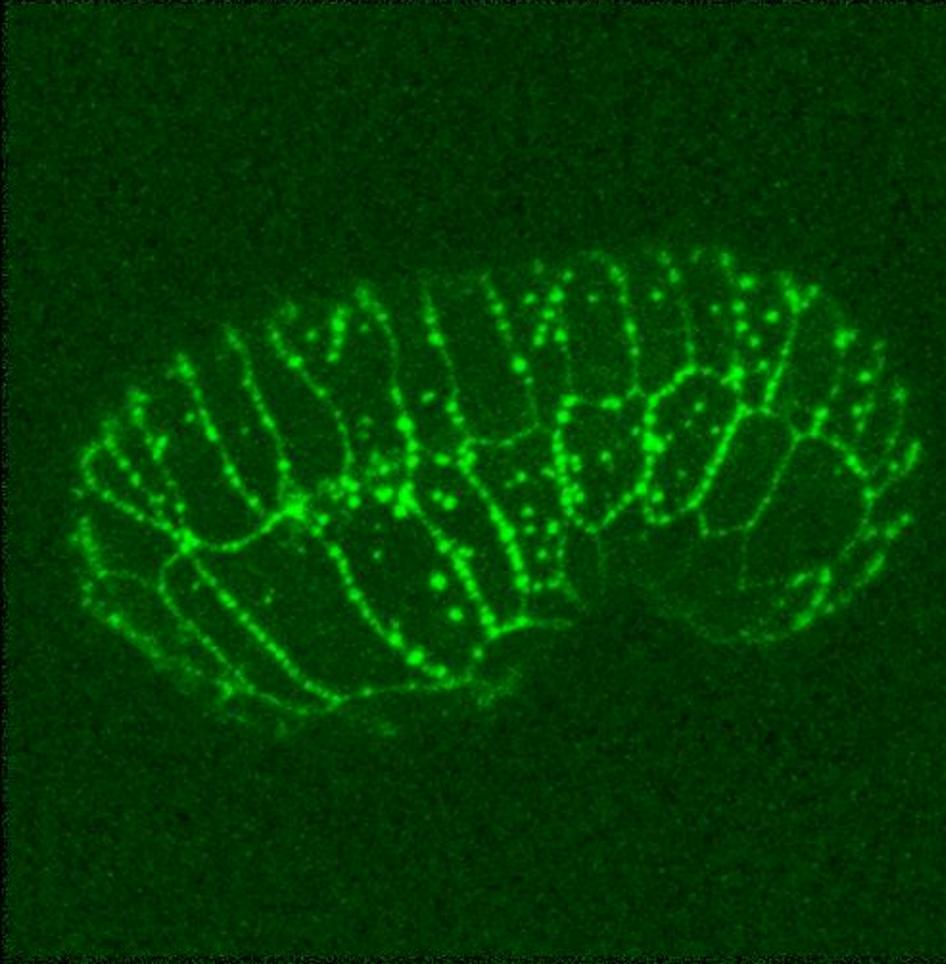
Rings: A; B1; B2; D; F

2. Mechanism of cell-cell fusion

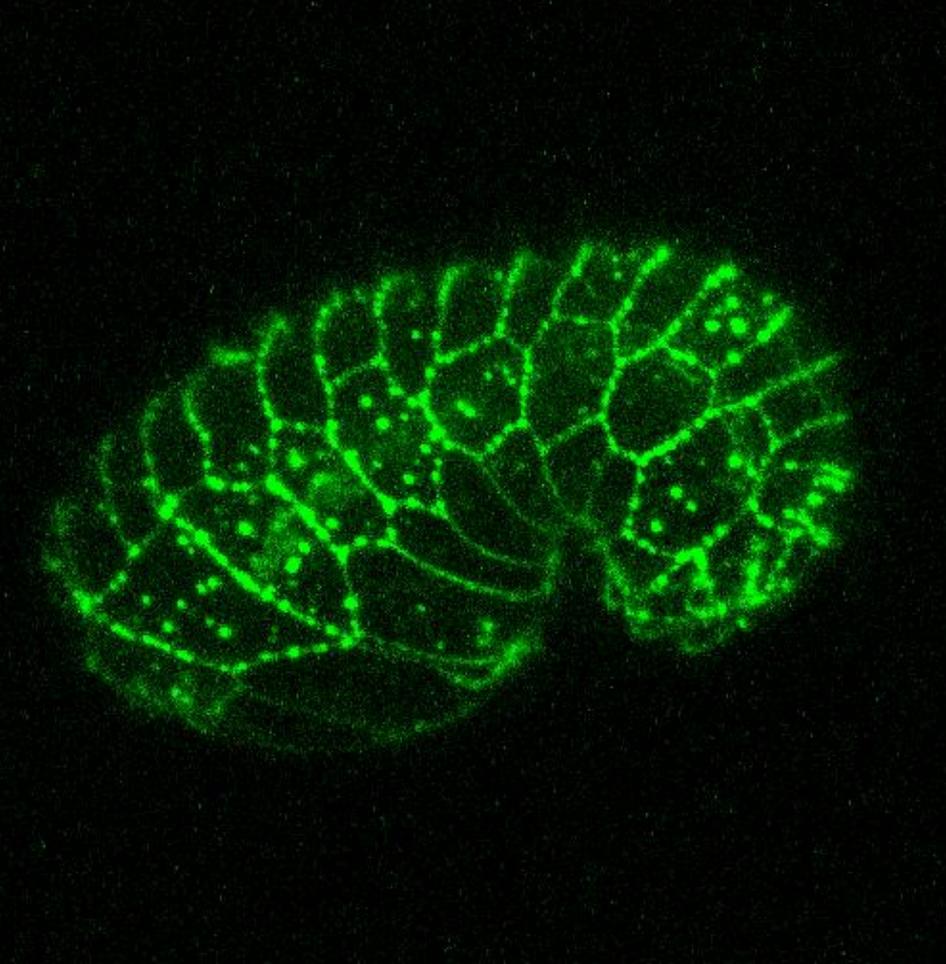
Genetic screen for viable cell fusion defective mutants



Wild-type



eff-1 (epithelial fusion failure)



Wild-type

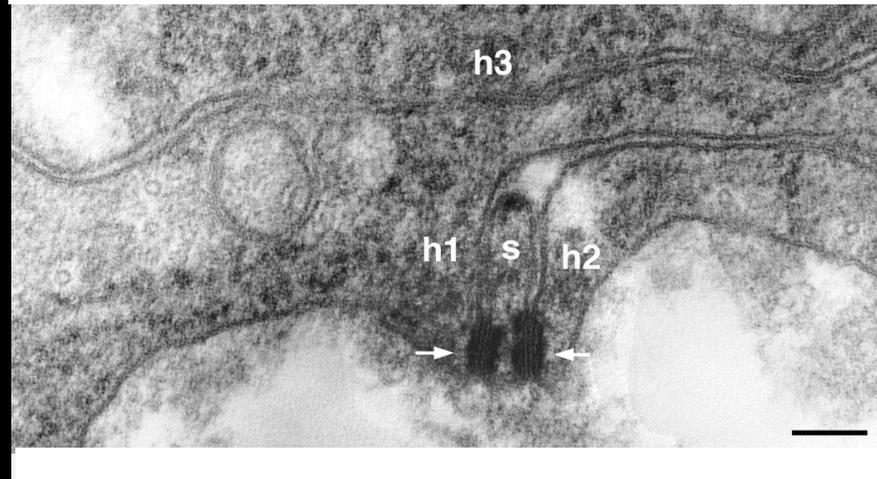
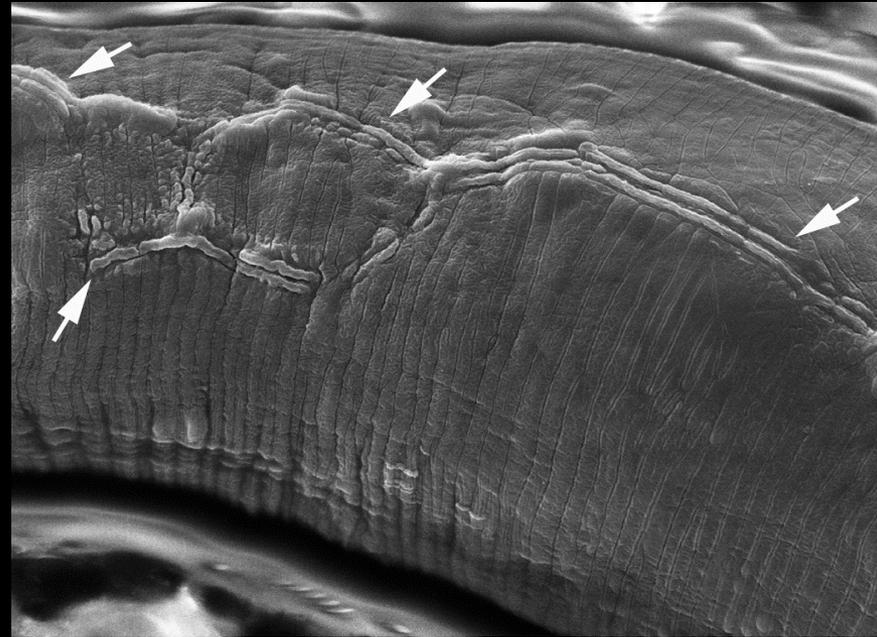


eff-1



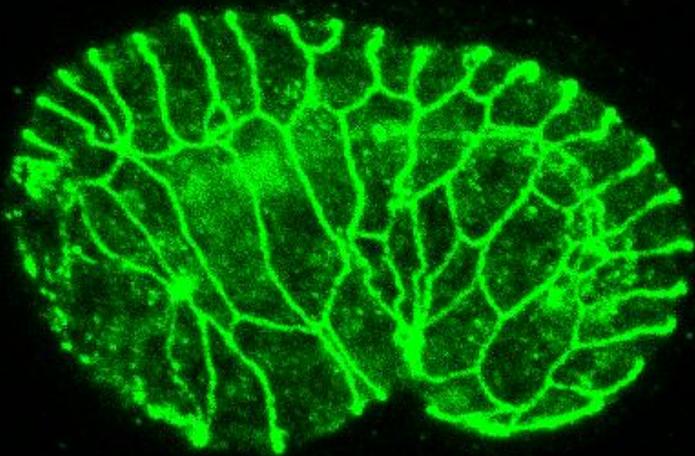
Functions of regulated cell fusion

Cells fail to initiate fusion in *eff-1(-)* mutant

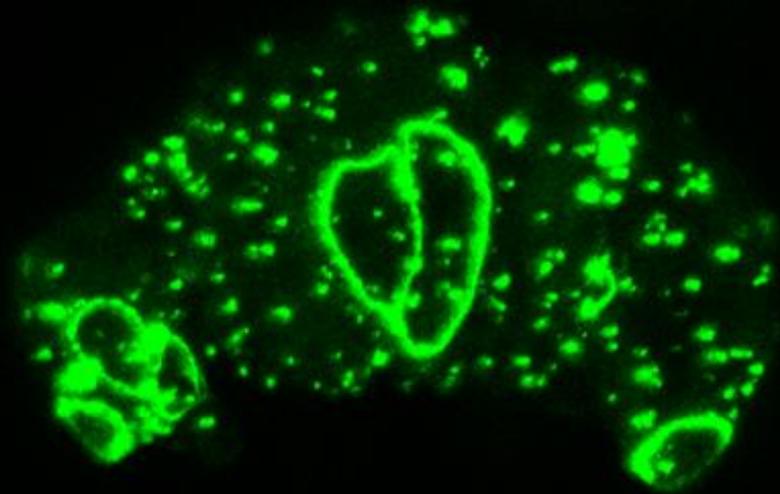


*Unfused plasma membranes
are separated by 9-13 nm*

eff-1 is sufficient for embryonic fusion

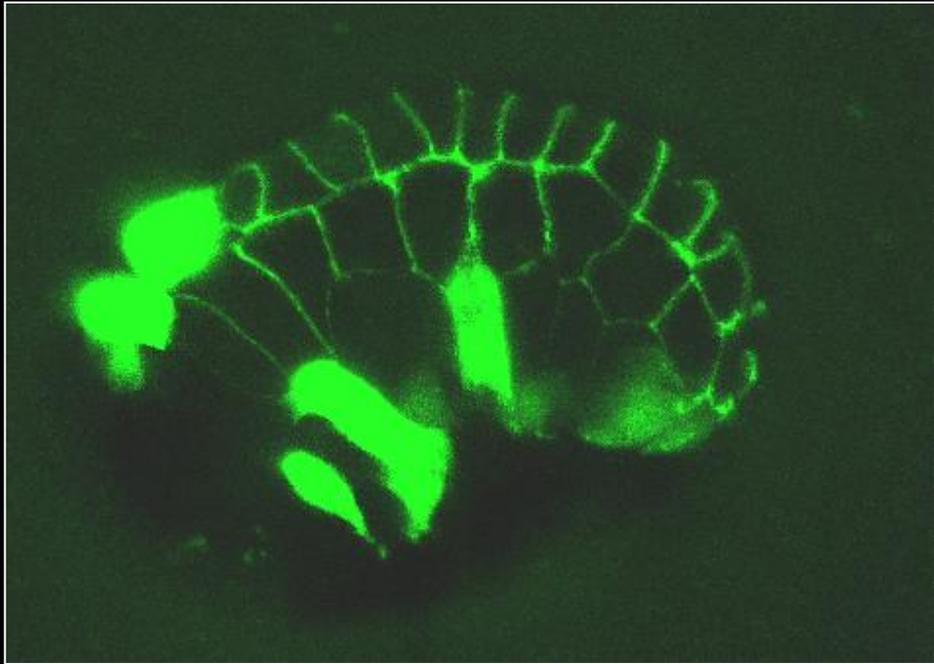


WT/*eff-1*(-)

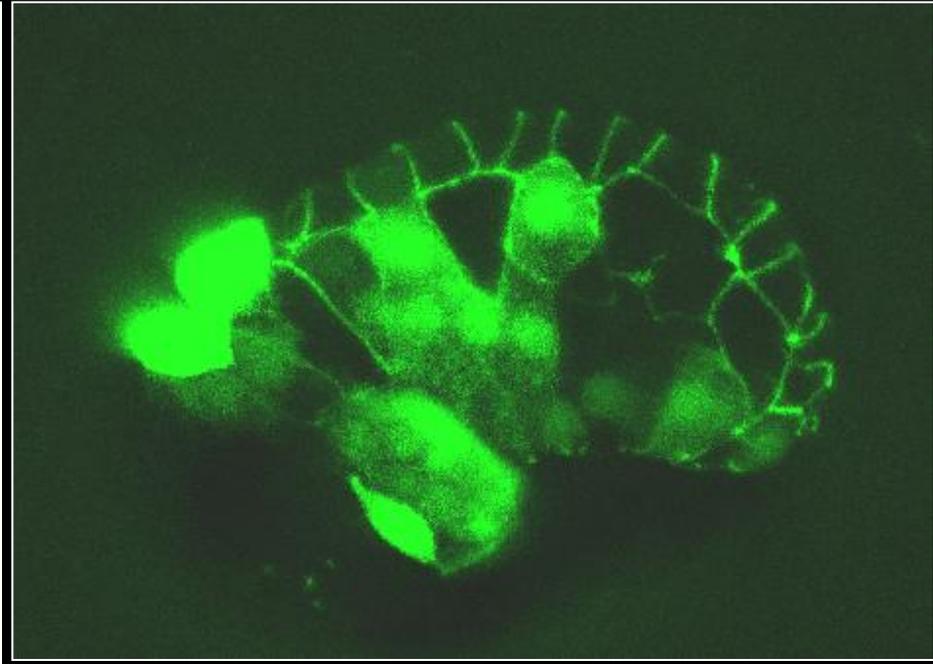


Ectopic EFF-1

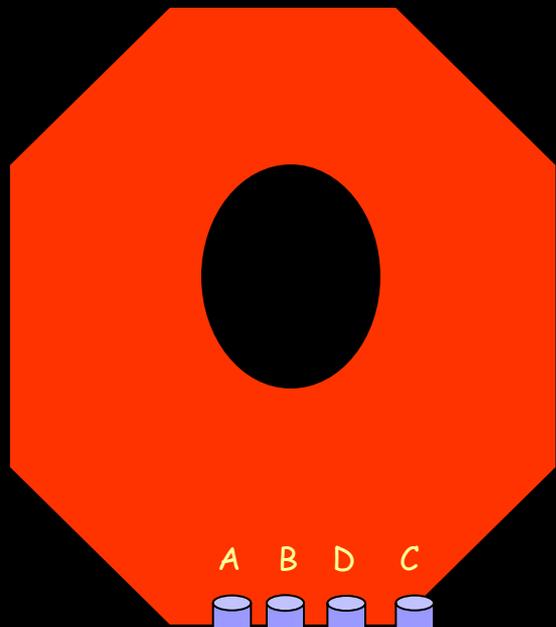
This is complete fusion:
The cytoplasms mix!



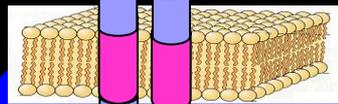
0'



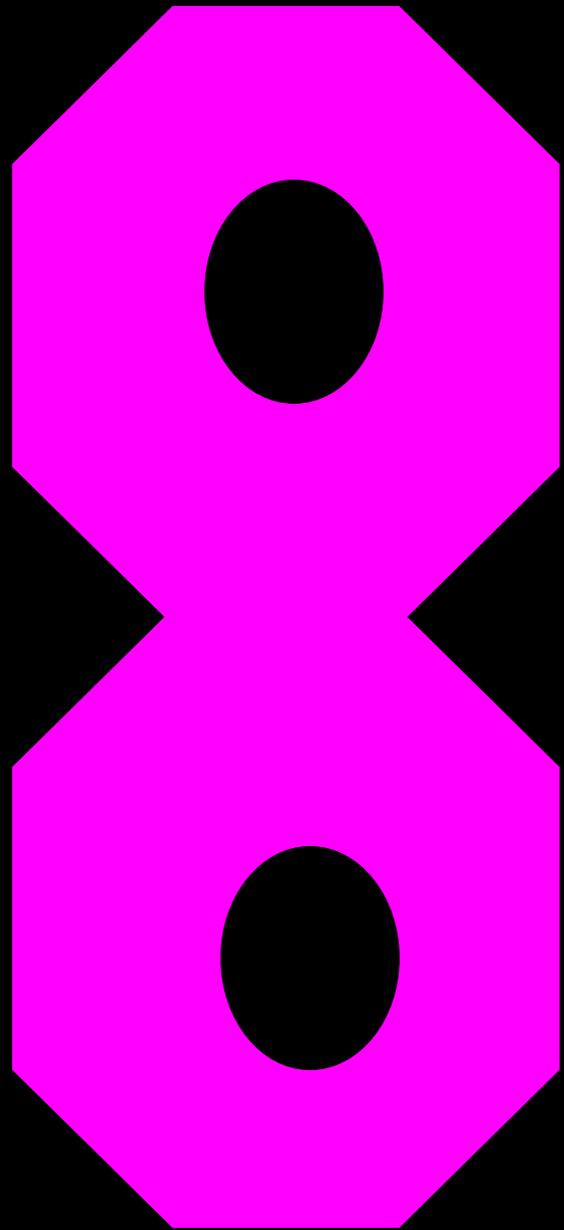
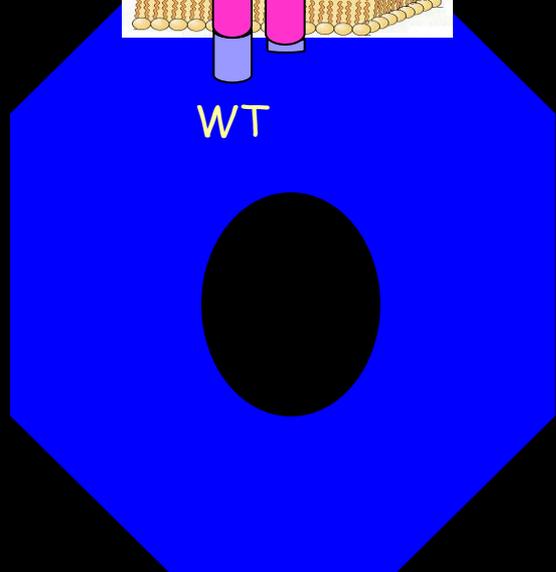
22'



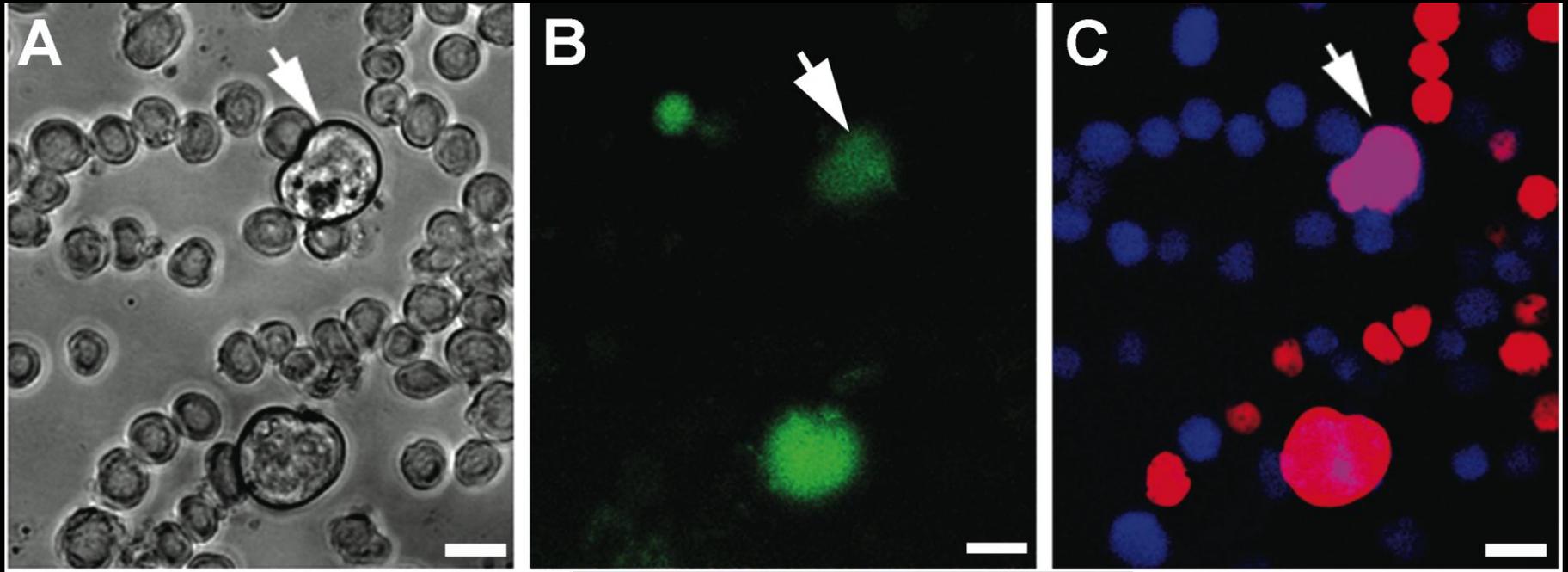
A B D C



WT

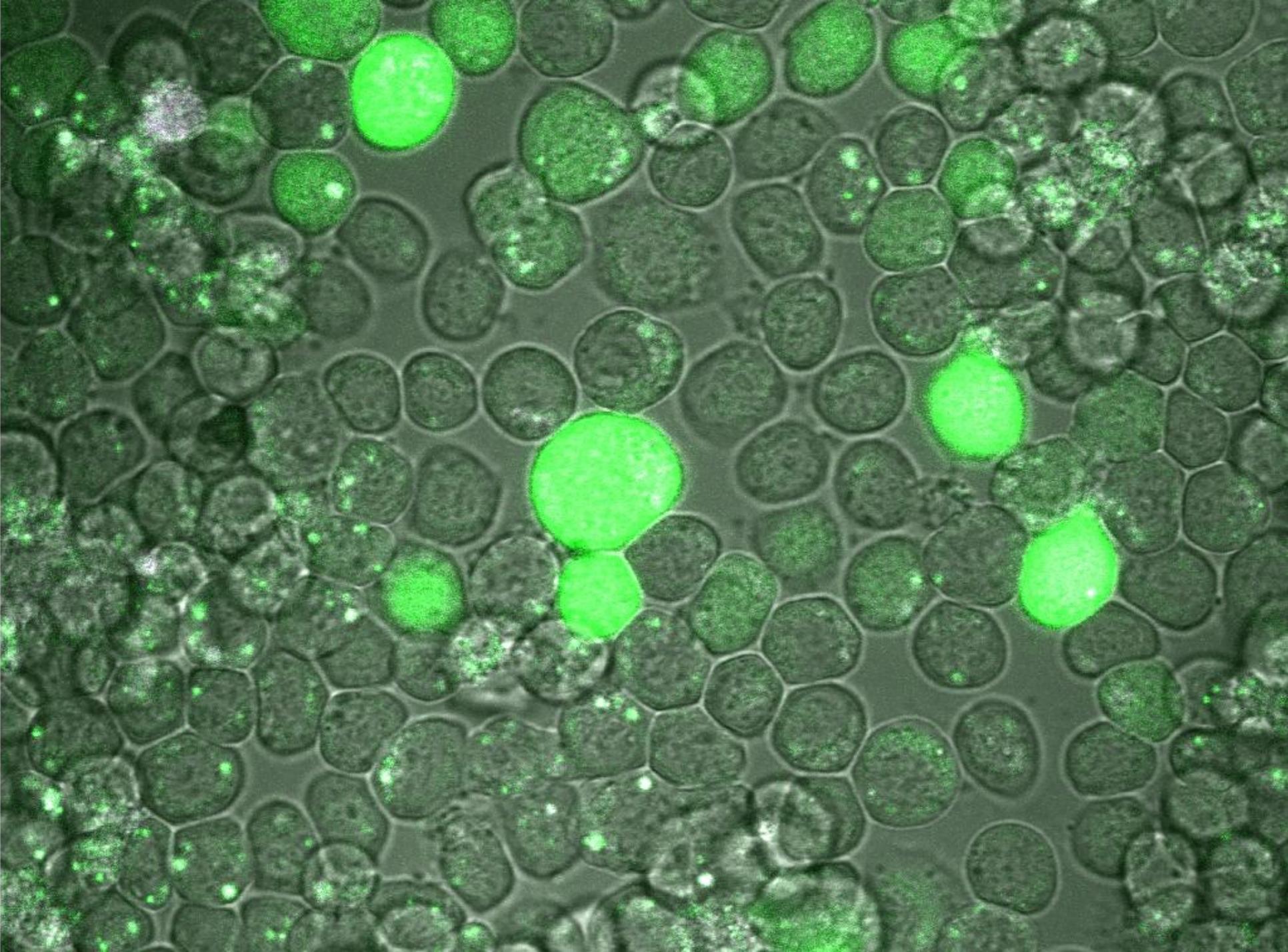


EFF-1 fuses insect cells

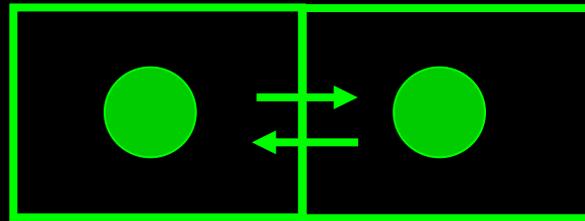


Green cells express **EFF-1**

Red cells fuse with **blue** cells

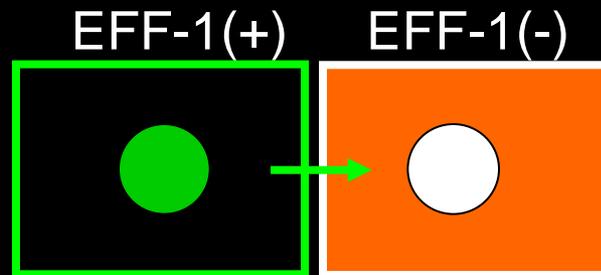


Predicted models for EFF-1 mode of function



Fusion or no-fusion?

EFF-1 in BOTH fusing partners

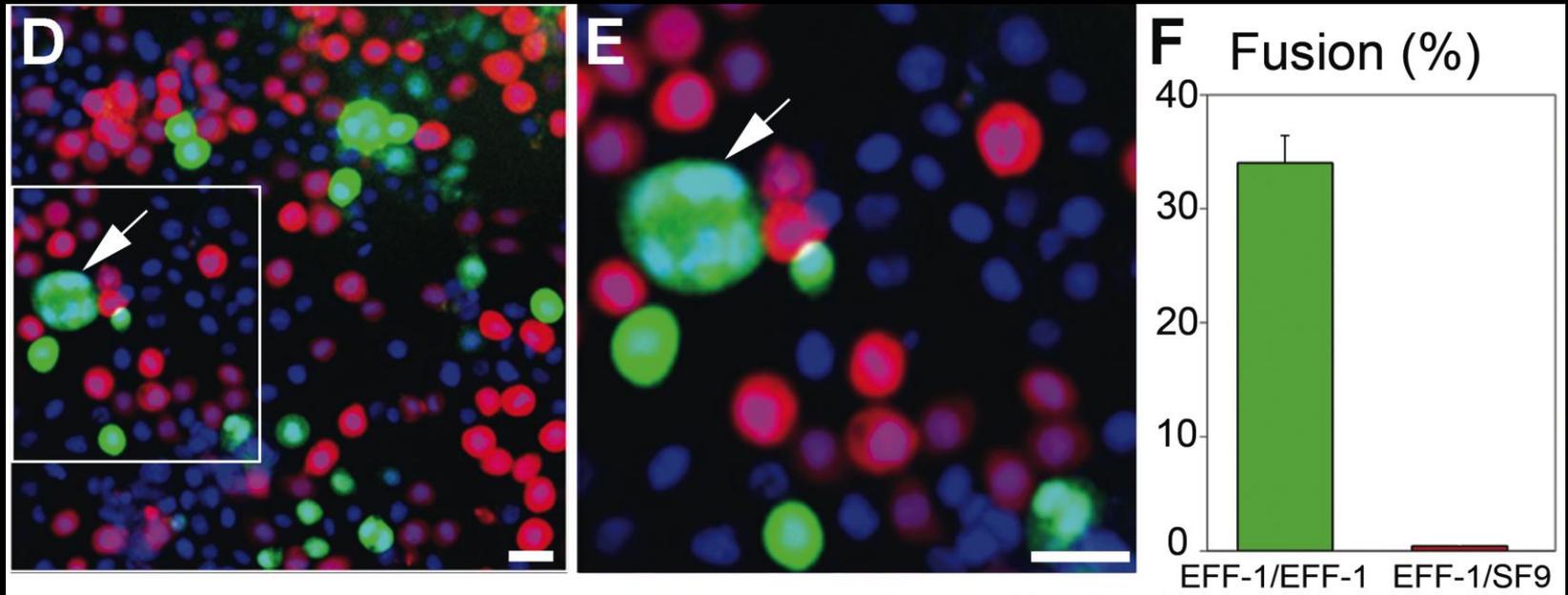


EFF-1 in ONE of the fusing partners

 *eff-1 (+)*

 *eff-1 (-)*

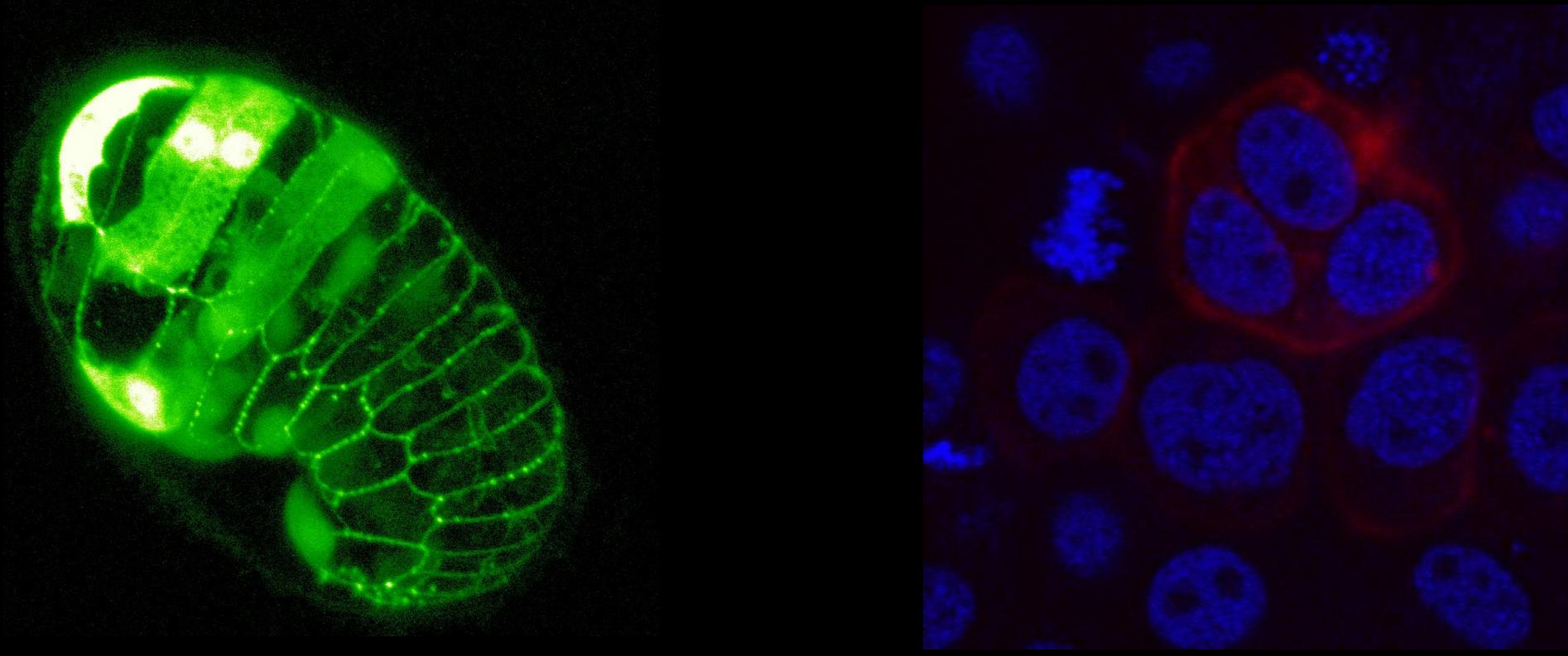
EFF-1-expressing cells do not fuse with innocent cells



Cell fusion is homotypic

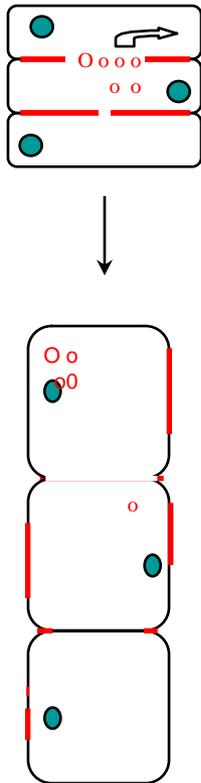
EFF-1 summary

1. EFF-1 is essential for cell fusion
2. EFF-1 is required in both fusing cells
3. EFF-1 is sufficient to fuse cells
4. EFF-1 can fuse heterologous insect cells

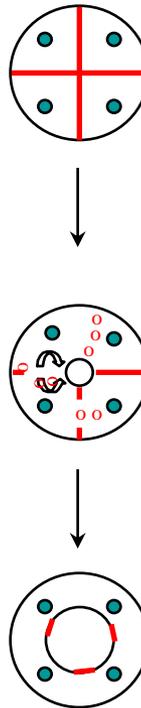


The fusomorphogenetic hypothesis: cell fusion and tube formation

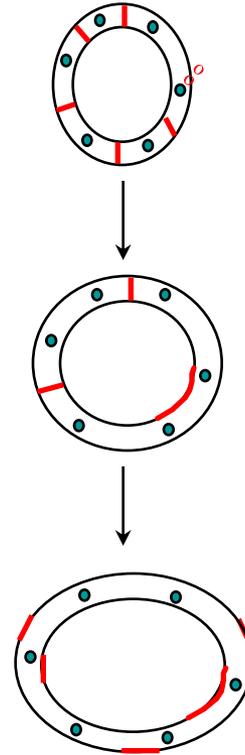
A Epidermis, muscles



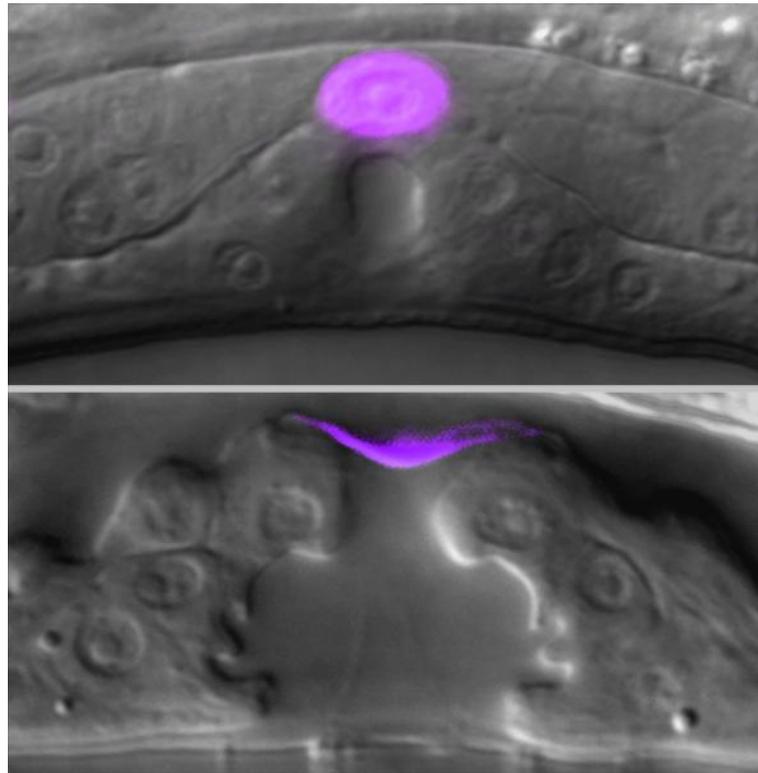
B Vulva, Uterus



C Placenta



The Anchor cell (AC) invades the vulva
and then fuses to form the hymen



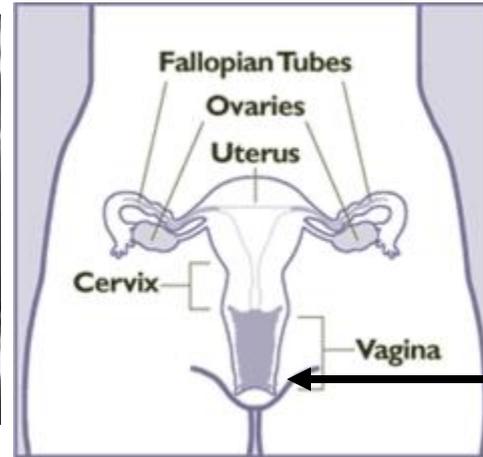
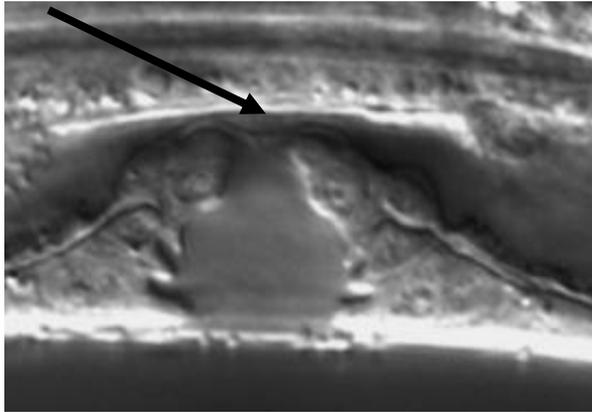
AC fusion occurs in *eff-1* mutants

C. elegans Hymen is analogous to the Hymen in mammals



Hymen: the marriage god, son of Aphrodite and Dionysus

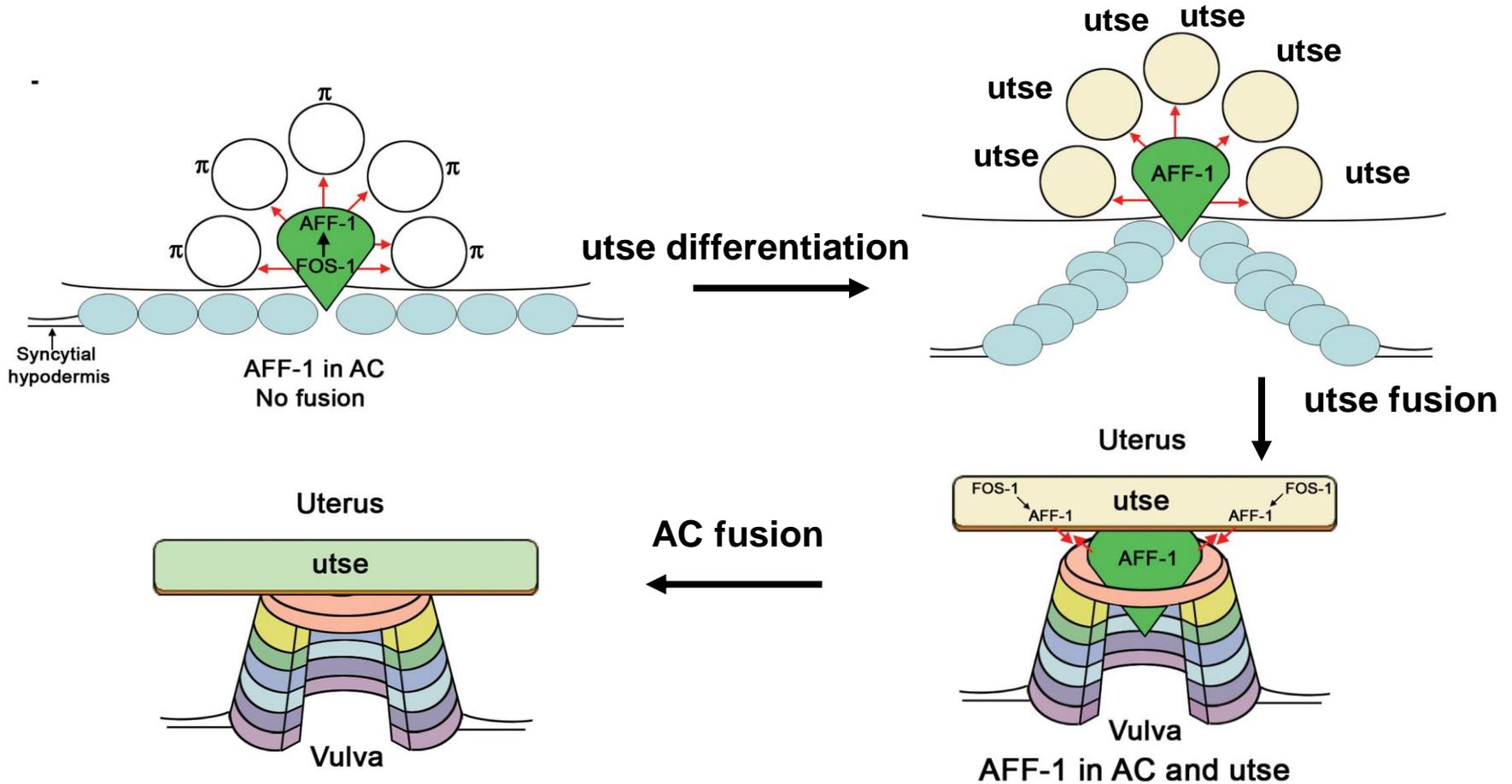
Vulva uterus
junction

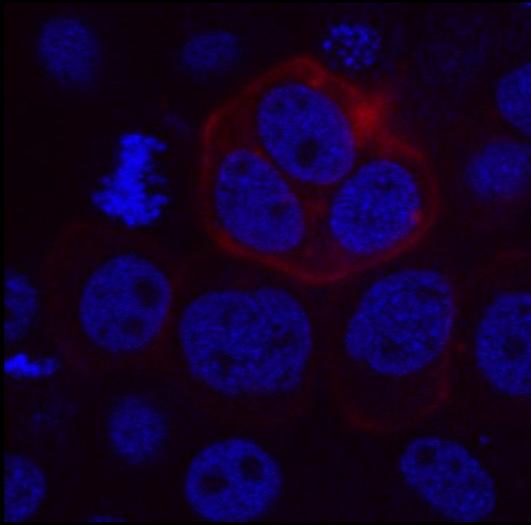


In the outer
region of the
vagina

What is it good for?

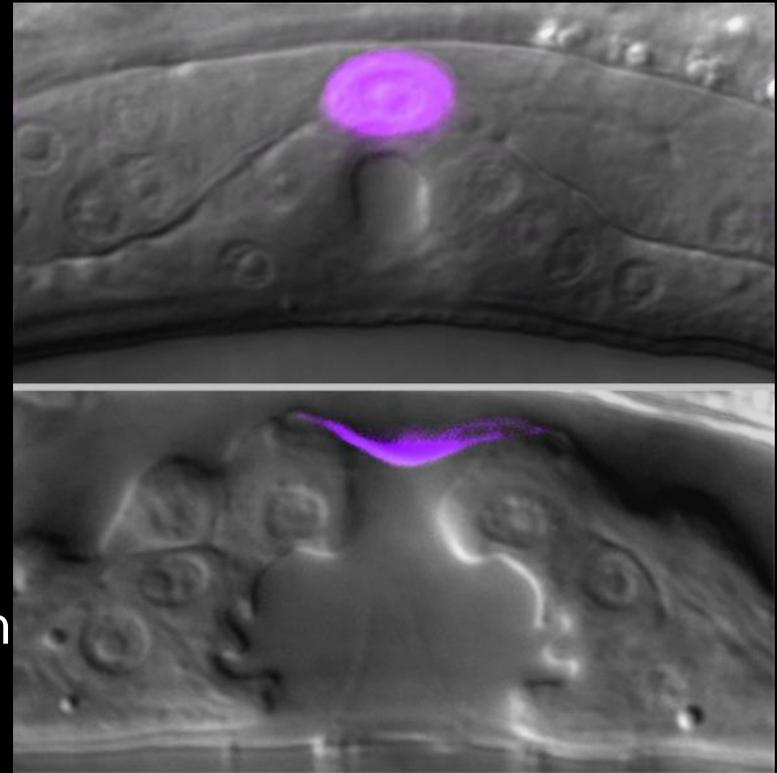
AFF-1 fuses the AC and connects two tubes





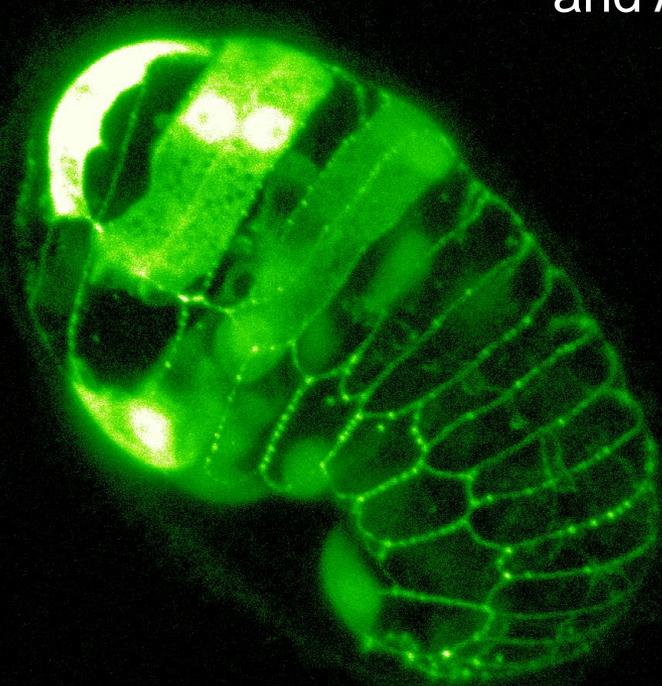
EFF-1 & AFF-1

Essential for Epithelial
and Anchor cell fusion

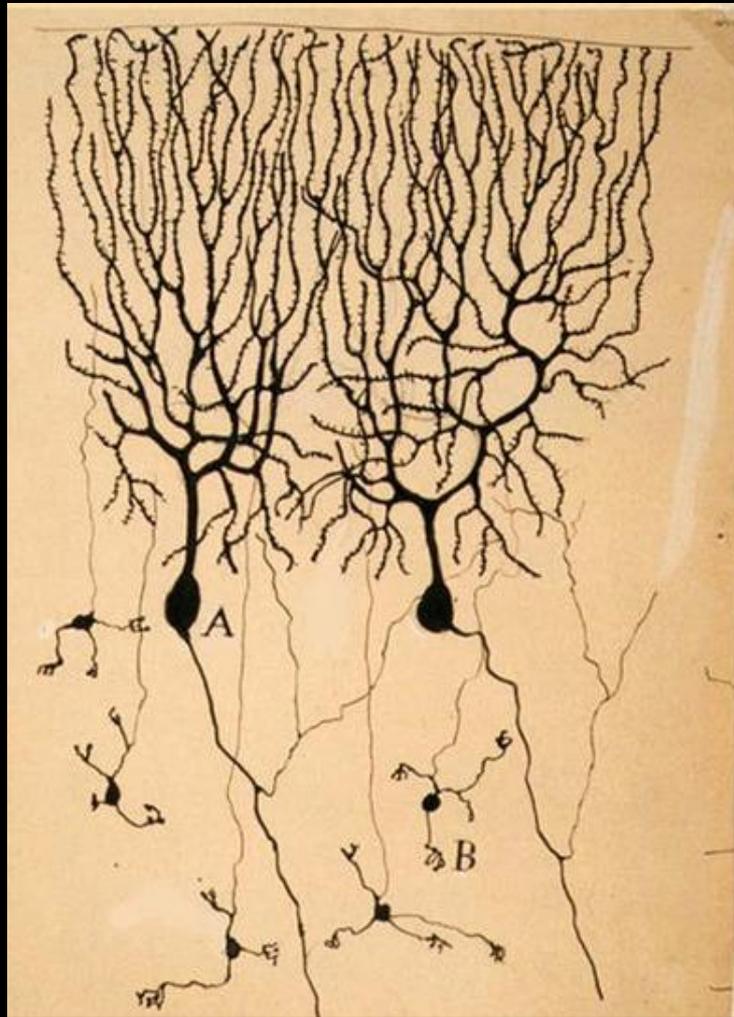


Fuse heterologous cells

First eukaryotic Fusogens



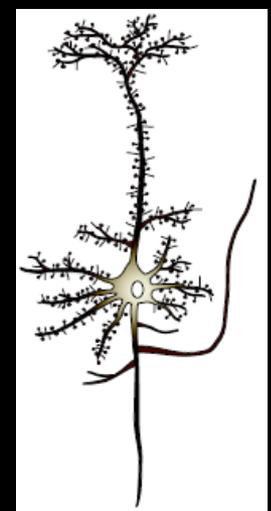
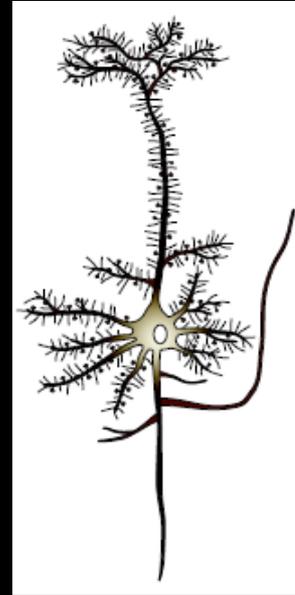
3. Development of dendritic arbors



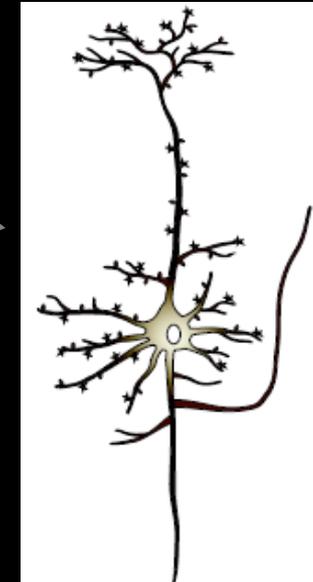
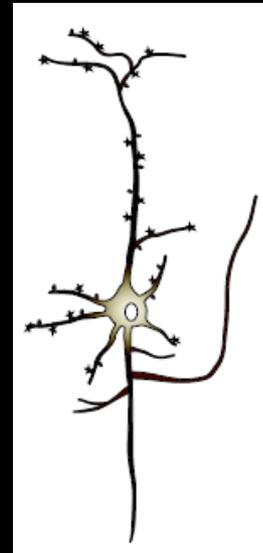
Santiago Ramon y Cajal,
Nobel laureate, 1906

Dendrite abnormalities in human diseases

- Schizophrenia
- Down's syndrome
- Autism
- Fragile X syndrome
- Angelman's syndrome
- Rett's syndrome

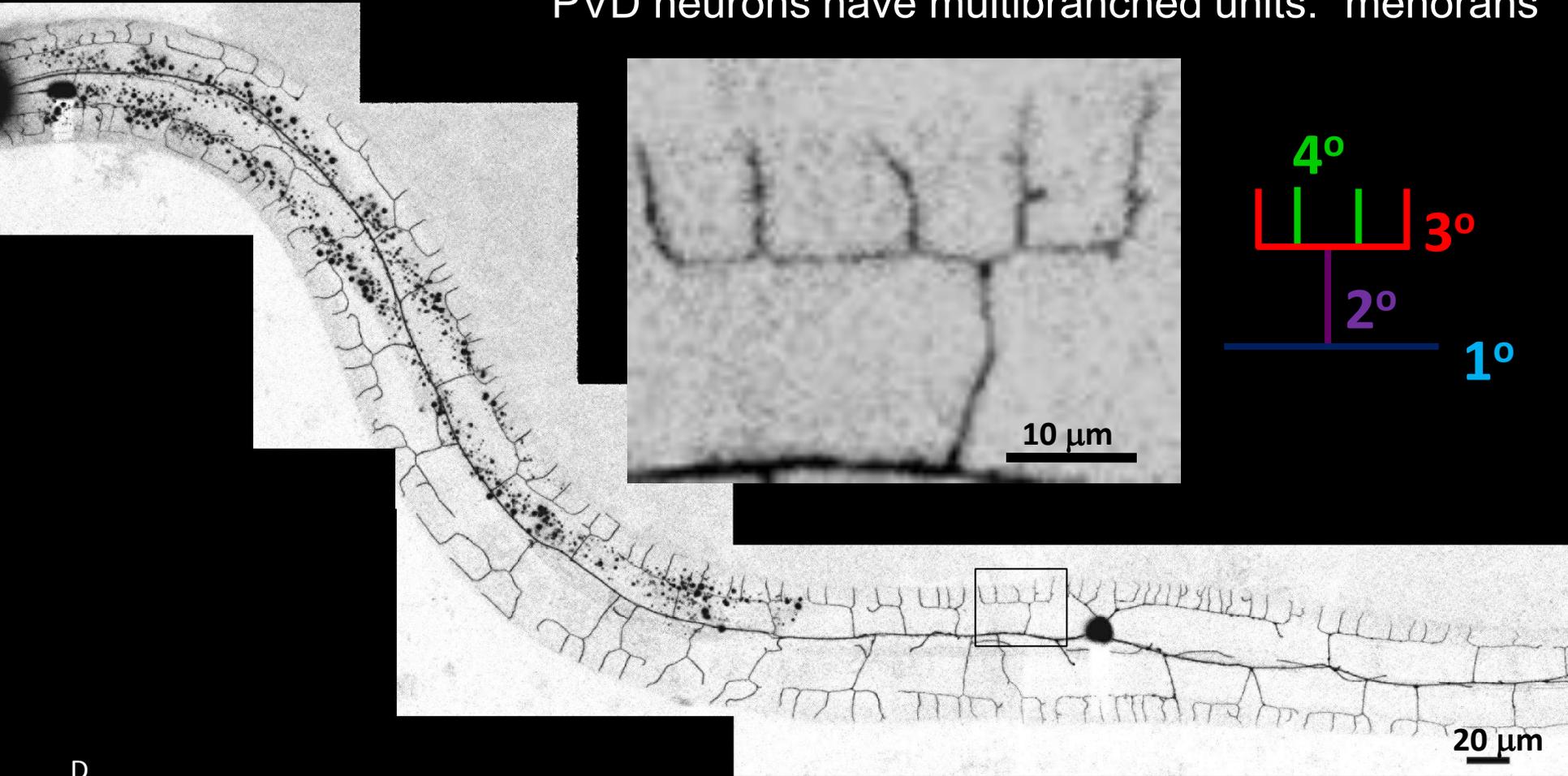


Healthy neuron

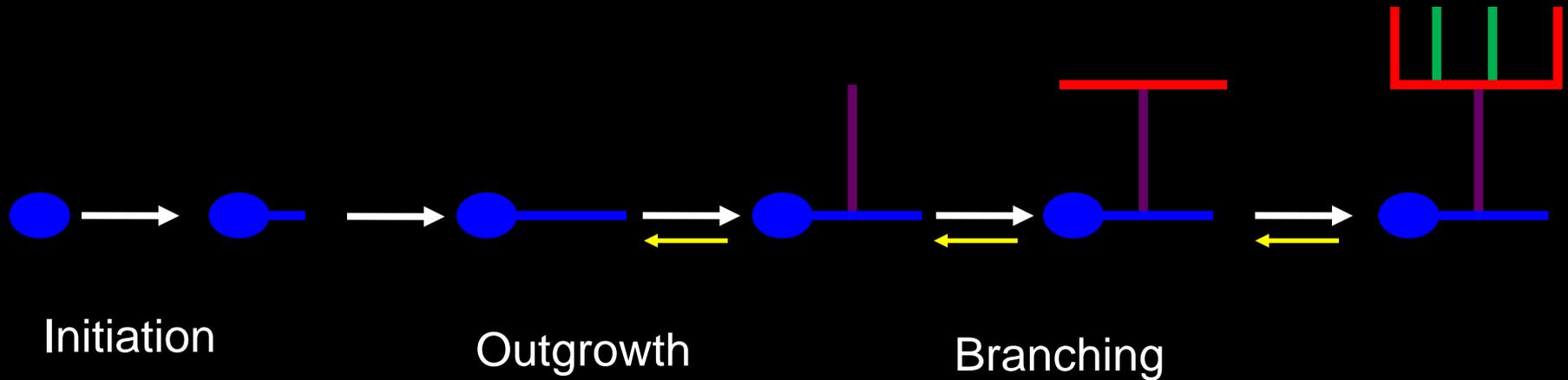


The PVD neurons as a model to study arborization in *C. elegans*

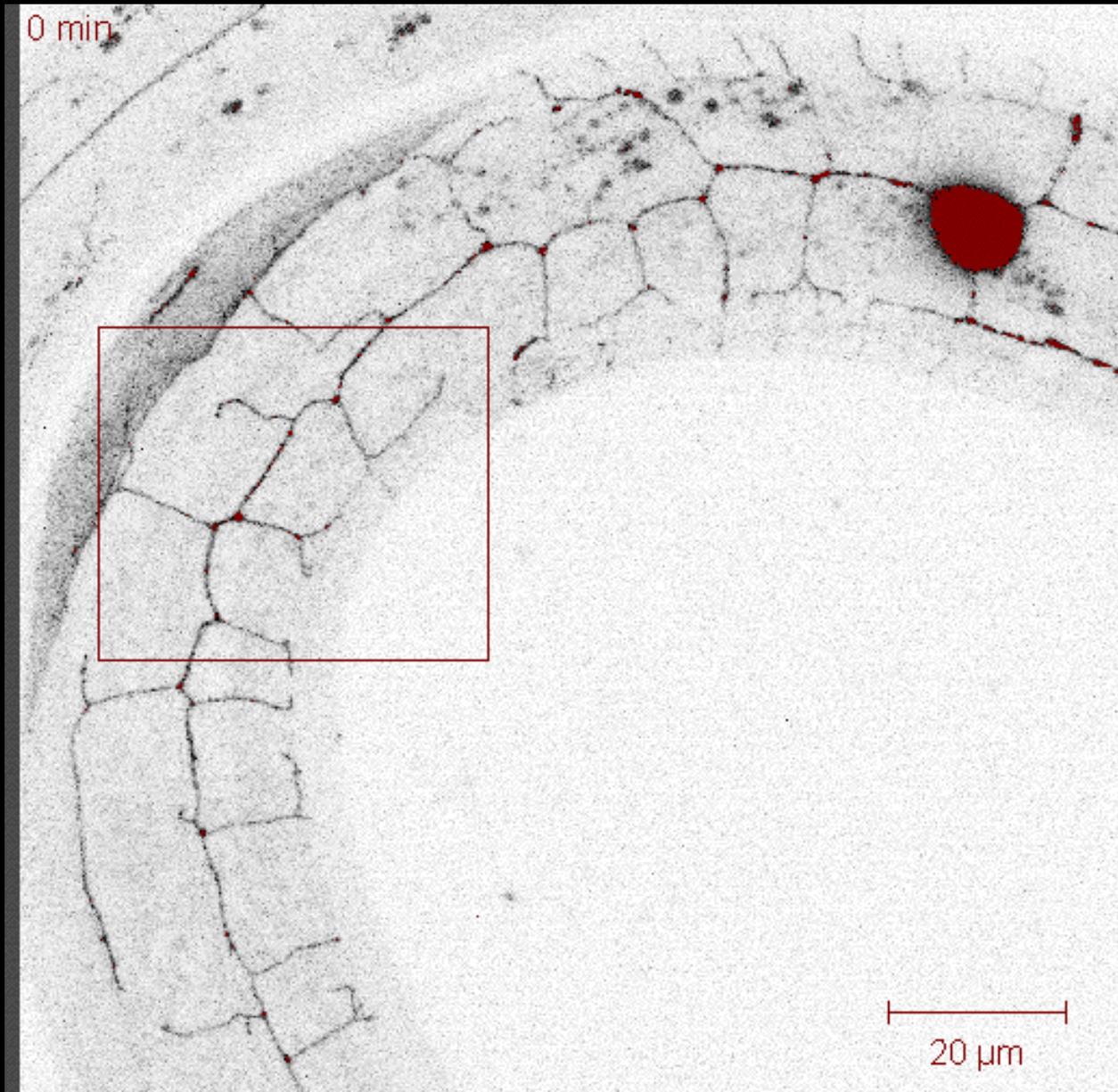
PVD neurons have multibranching units: “menorahs”



Morphogenetic pathway of arborization

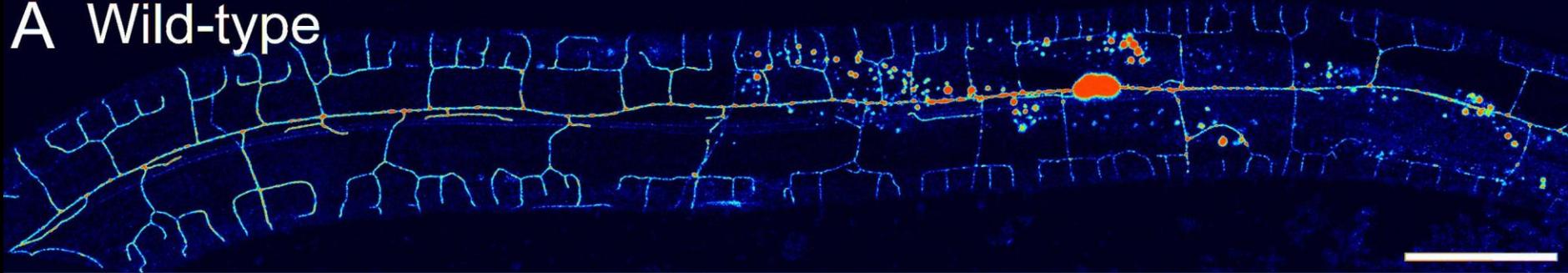


Live imaging reveals neuronal plasticity



PVD stereotyped pattern is disrupted in *eff-1* mutants

A Wild-type



B *eff-1(hy21)*





The Nobel Prize in Physiology or Medicine 1906

"in recognition of their work on the structure of the nervous system"



Camillo Golgi

1/2 of the prize

Italy

Pavia University
Pavia, Italy

b. 1843
d. 1926



Santiago Ramón y Cajal

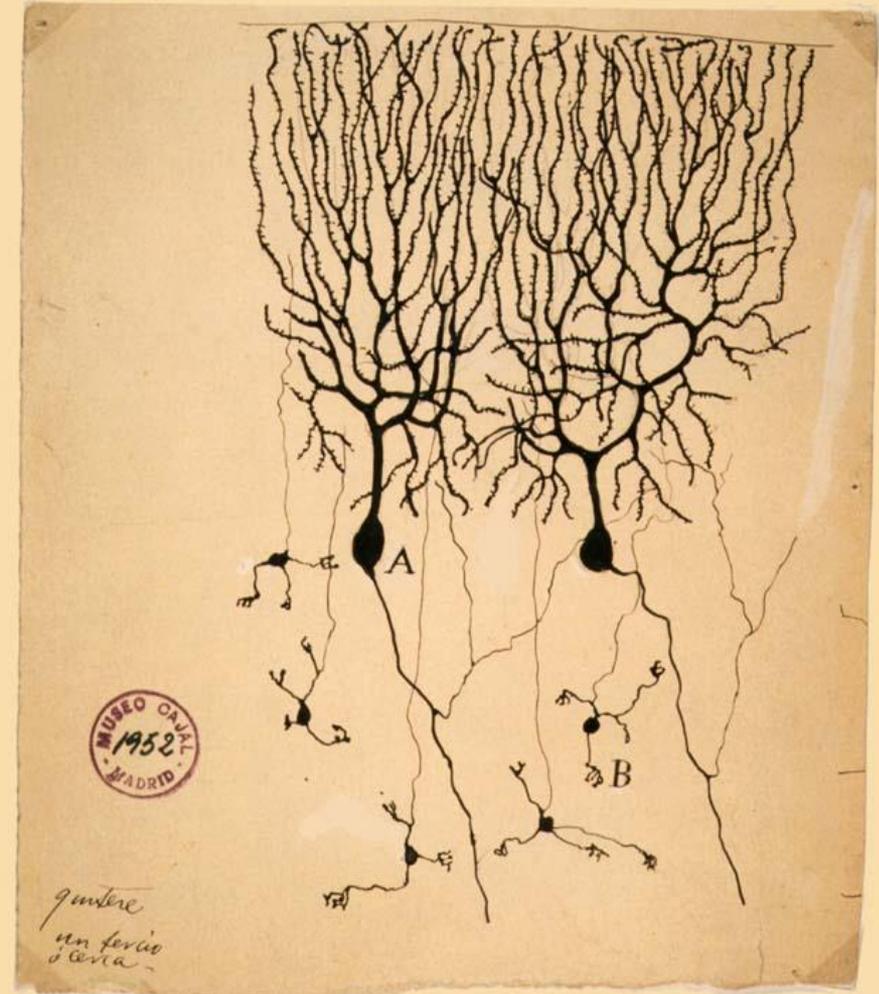
1/2 of the prize

Spain

Madrid University
Madrid, Spain

b. 1852
d. 1934

Titles, data and places given above refer to the time of the award.
Photos: Copyright © The Nobel Foundation

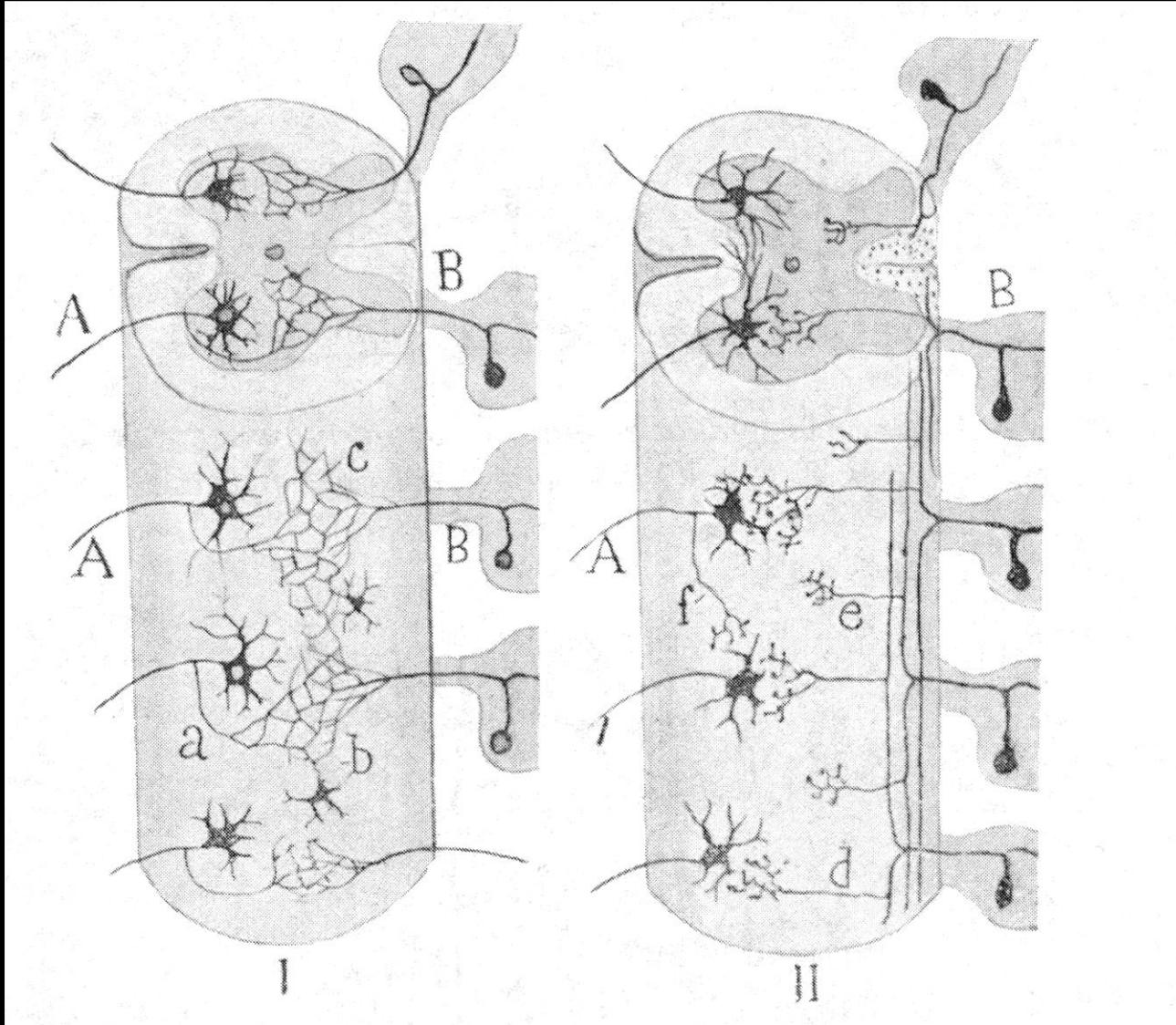


"Pigeon cerebellum. A, Purkinje cell, B, granule cell
Modified from a photograph taken from the original
(14X15.5 cm). Drawn on sheet/paper. P.Y. 1899. S.R.
y Cajal Institute - CSIC - Madrid, Spain.

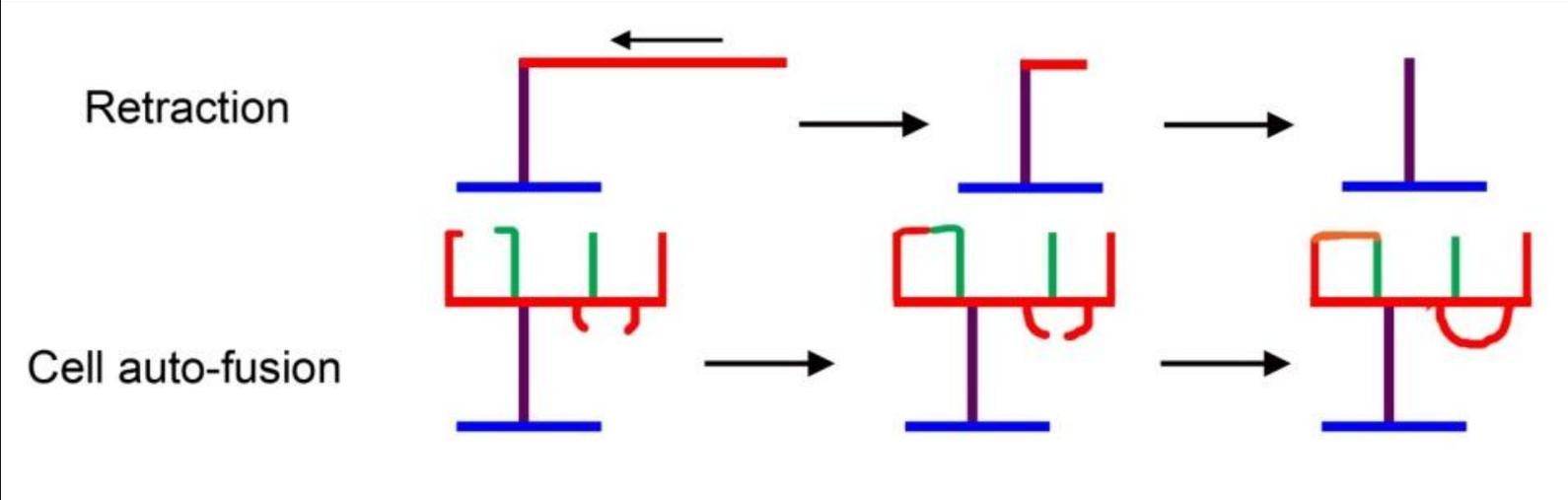
Reticulum versus Synapse

Golgi

Ramón y Cajal



EFF-1 restricts branching by retraction and auto-fusion

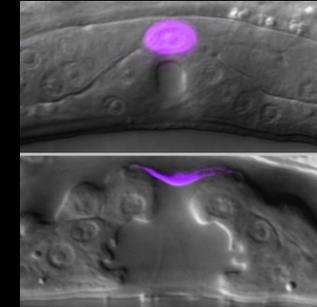


Conclusions

1. EFF-1 and AFF-1 are the first developmental cell-cell fusion proteins



2. EFF-1 and AFF-1 sculpt rings and tubes to form organs (vagina, uterus, hymen and neurons)



3. Hypothesis: FFs, or other proteins sculpt human organs

Technion, Haifa, Israel

Clari Valansi
Ori Avinoam
Lilach Fridlander
Ksenia Smurova
Jorge Verdin
Hadas Raveh
Dganit Melamed
Karen Fridman
Meital Oren-Suissa
Gidi Shemer, UNC
Amir Sapir, Caltech



Albert Einstein School of Medicine, NY

David Hall and Ken Nguyen

NIH, Bethesda

Leonid Chernomordik and Evgenia Leikina

Institut Pasteur, Paris

Felix Rey and Jimena Perez Vargas

Baylor College of Medicine, Houston

Anna Newman and Jaebok Choi

The Hebrew University, Jerusalem

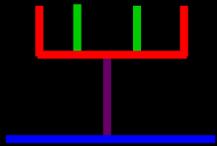
Millet Treinin

Yossi Gruenbaum

The Caenorhabditis Genetics Center (CGC)



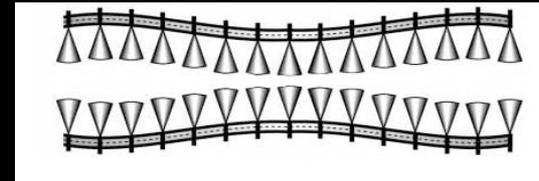
Maintenance of menorah structure by controlling high curvature of neuronal tubes



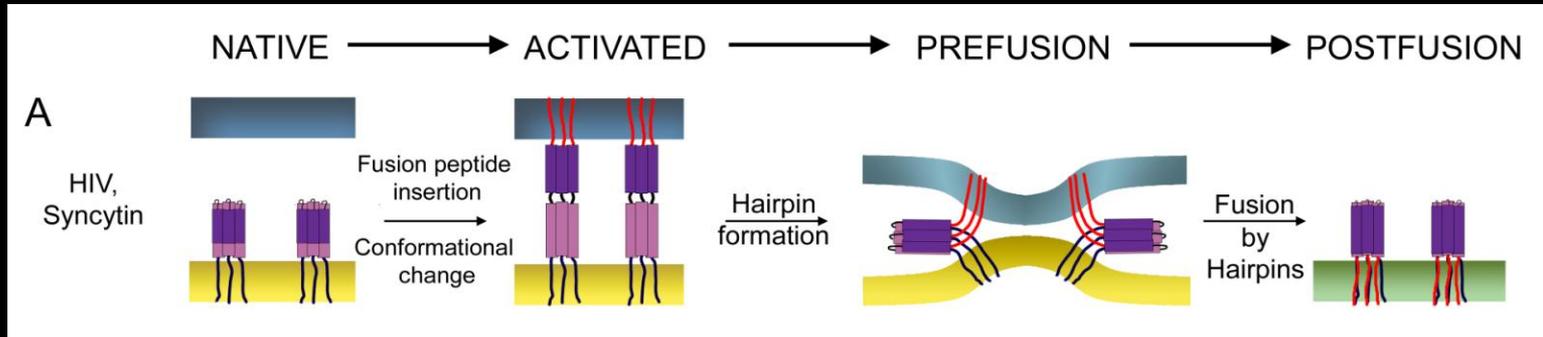
Bending



Fusion

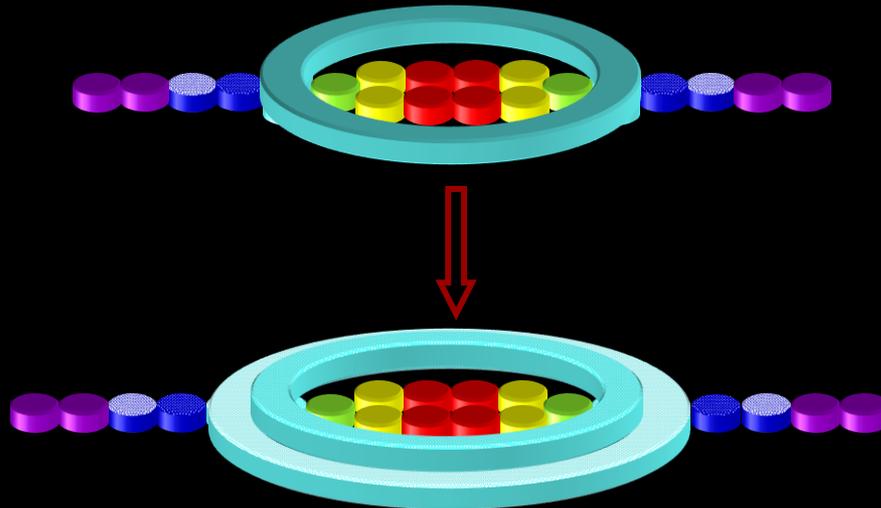
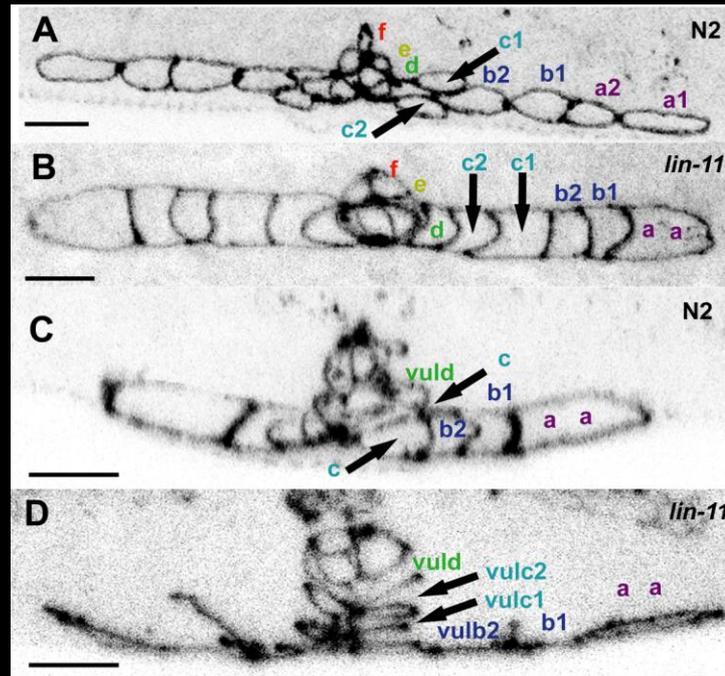


A unified model for membrane fusion?



Testing the ring hypothesis

C. elegans lin-11 mutation results in abnormal A-P division instead of L-R



Number of rings in species related to *C.elegans*

