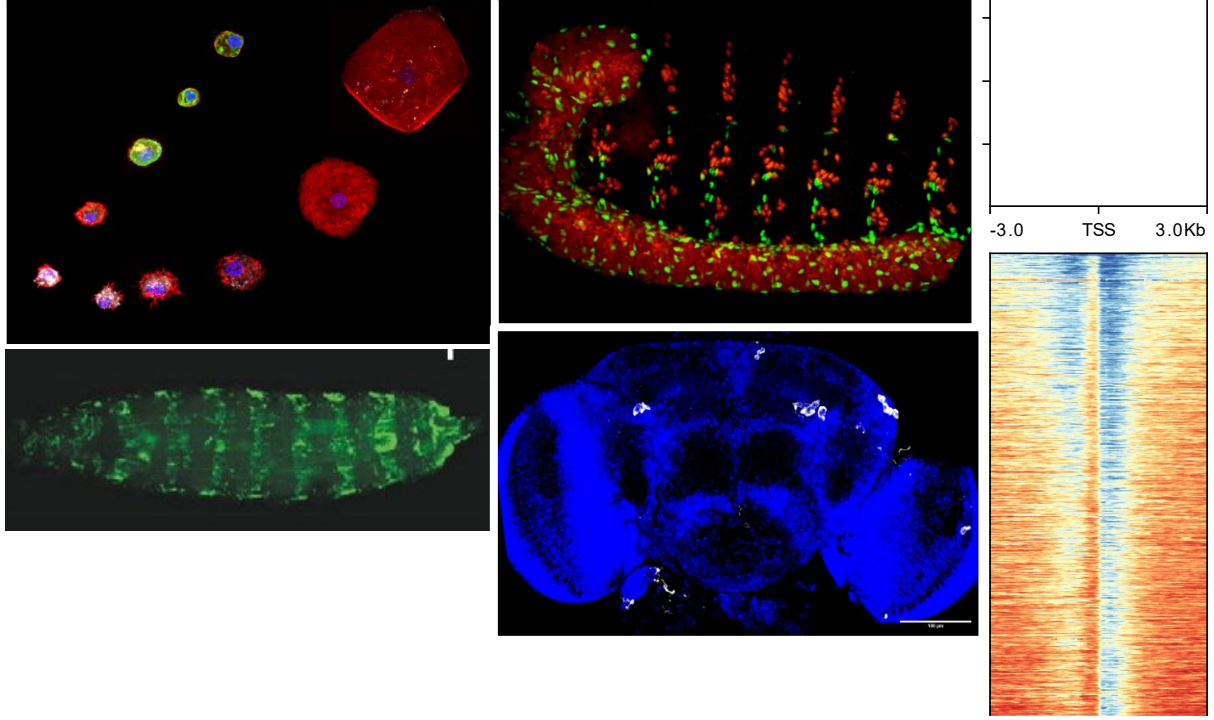
IMBB Crete June 21 2024



OF GLIA AND MACROPHAGES:

SIGNALING HUBS IN DEVELOPMENT AND HOMEOSTASIS

Angela GIANGRANDE

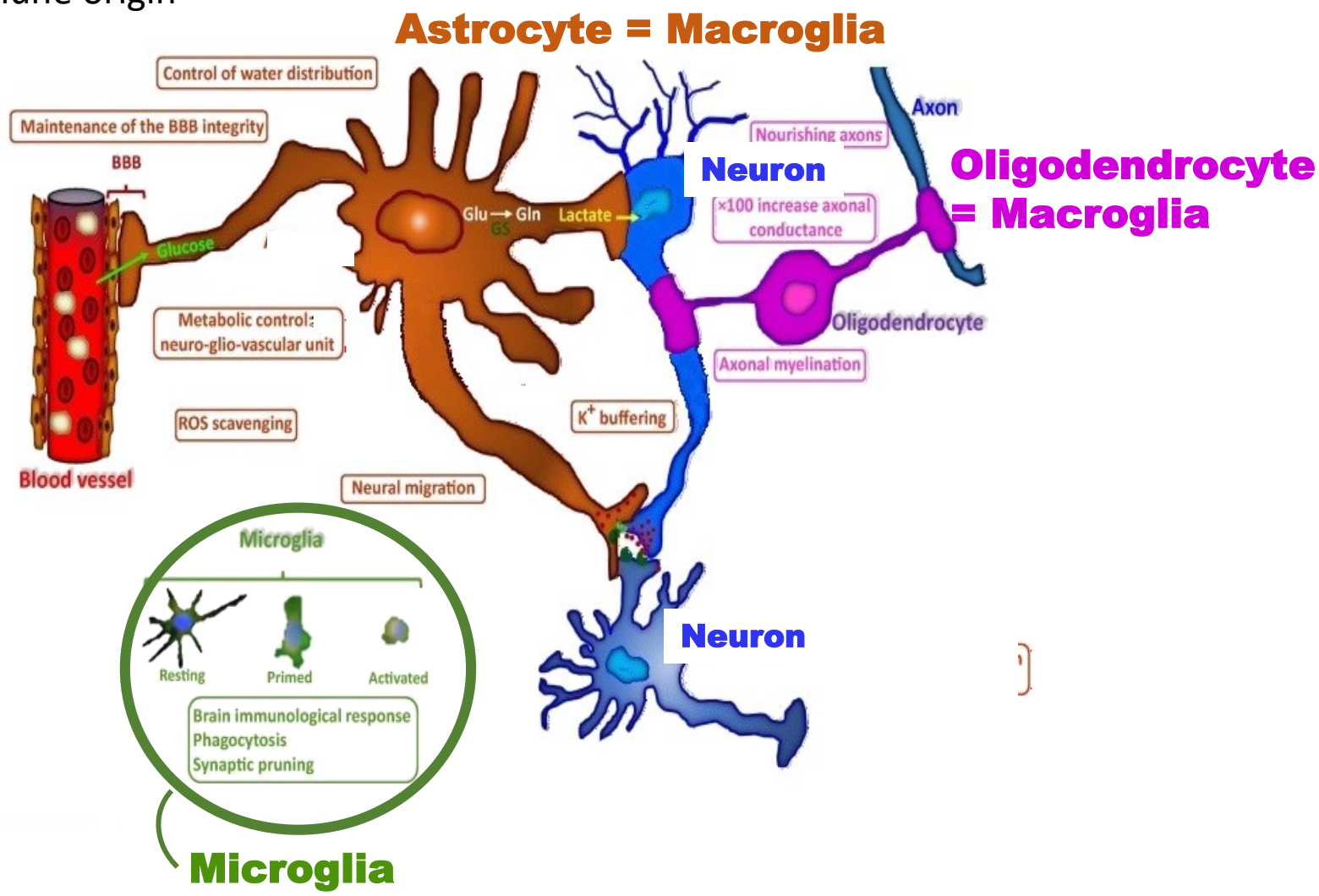
Transcriptional Regulation Of Immune And Neural Development

Dept Functional Genomics and Cancer

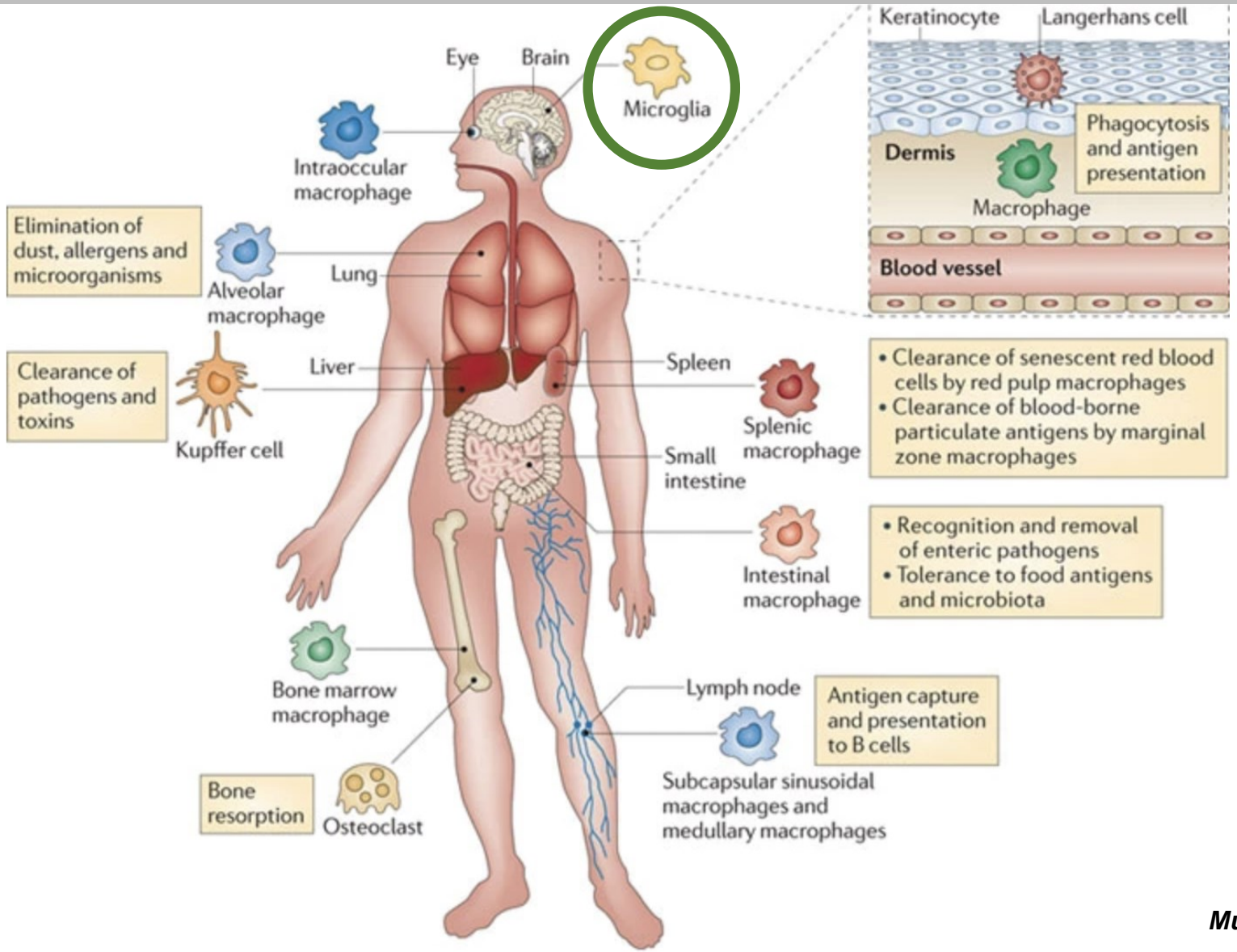
IGBMC

VERTEBRATE MACROGLIA AND MICROGLIA

Macroglia = neural origin
Microglia = immune origin

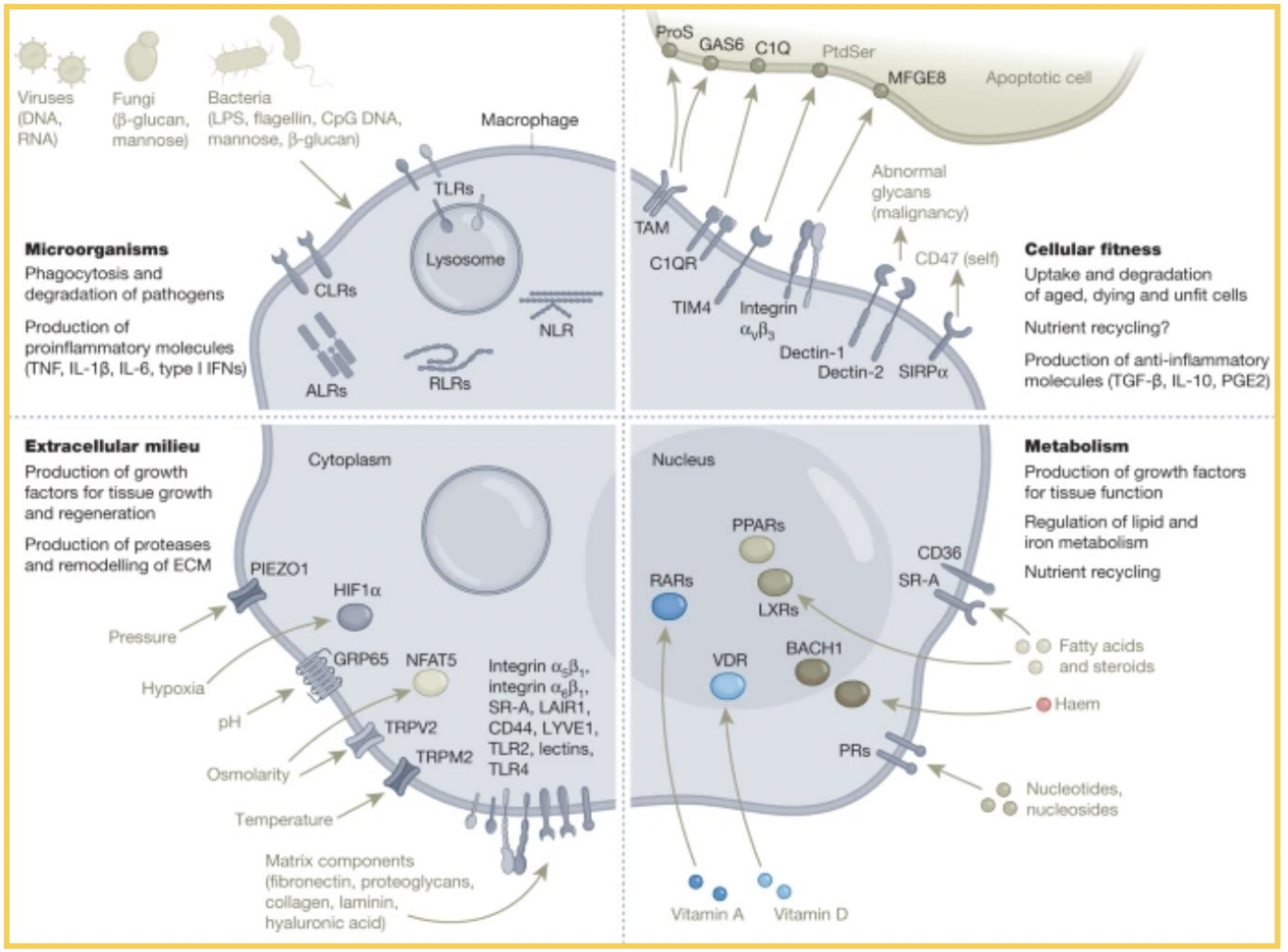


VERTEBRATE MACROPHAGE HETEROGENEITY



Murray 2011

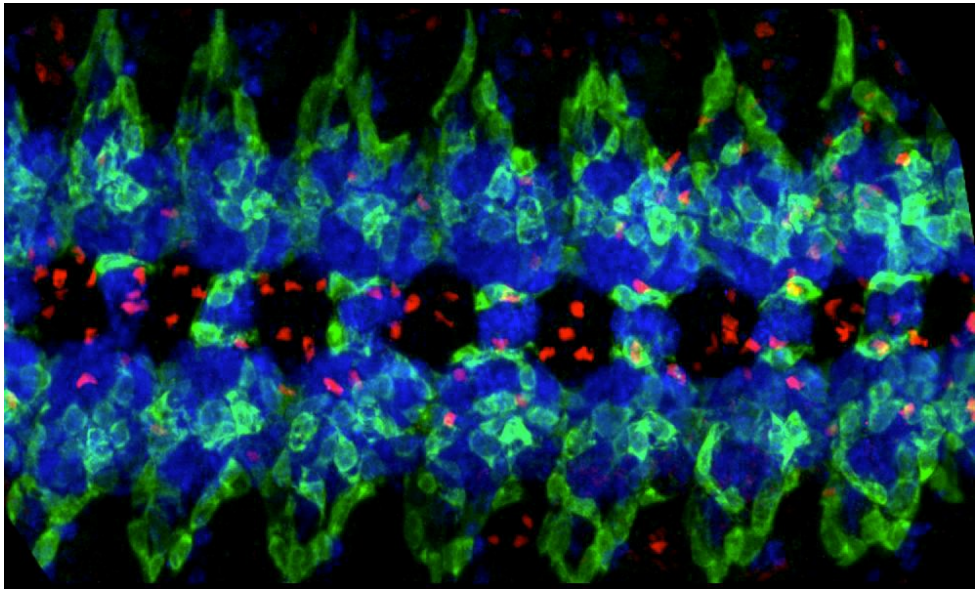
VERTEBRATE MACROPHAGE HETEROGENEITY



Lazarov 2023

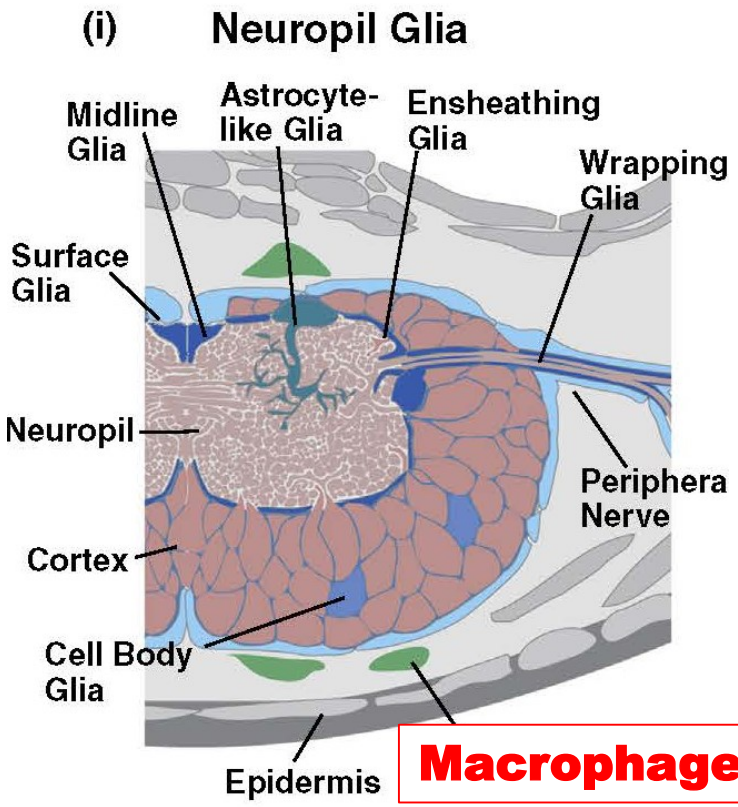
DROSOPHILA VENTRAL CORD

3D reconstruction
of embryonic ventral cord segments



Glia (Repo-mCD8GFP)
Neurons (Elav)
Hemocytes = Macrophages (Serpent)

Section of the larval ventral cord

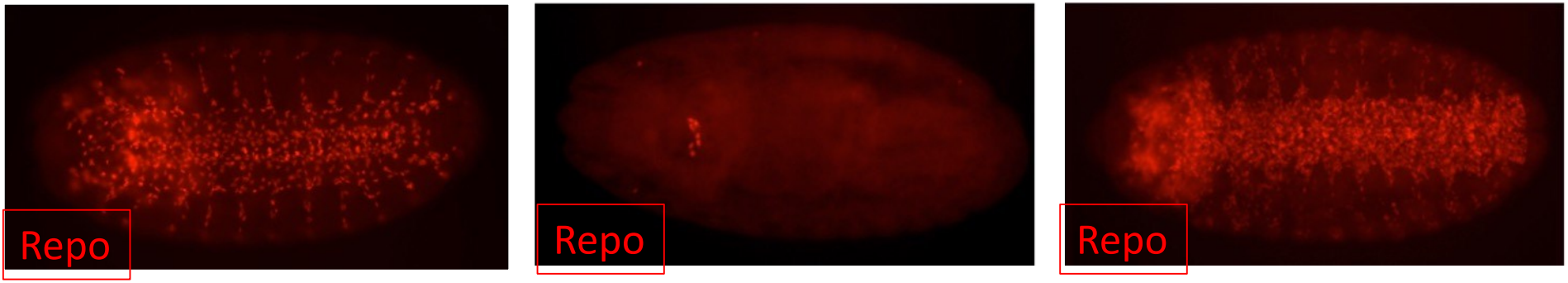


(Omoto 2016)

No microglia in the fly.
Once the BBB is formed end of embryogenesis, macrophages stay outside the nervous system

GCM IN THE EMBRYONIC GLIA

Control | ***gcm* null mutant** | ***gcm* overexpression**



Vincent 1996; Miller 1998; Bernardoni 1997, 1998; Van de Bor 2000, 2001, 2002

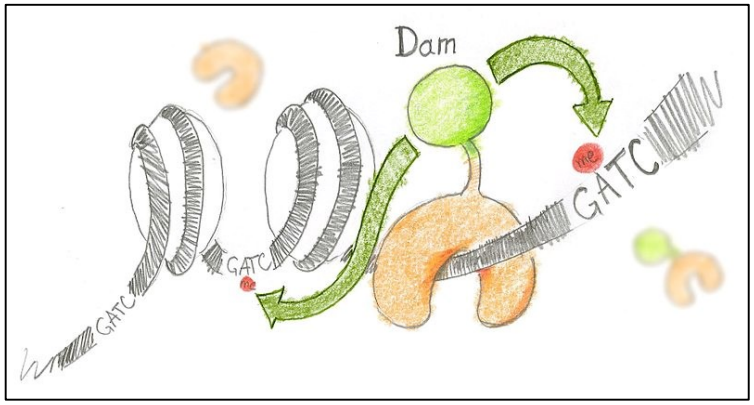
Gcm, a zinc finger transcription factor required and sufficient for glia

Gcm interacts with the HAT CBP

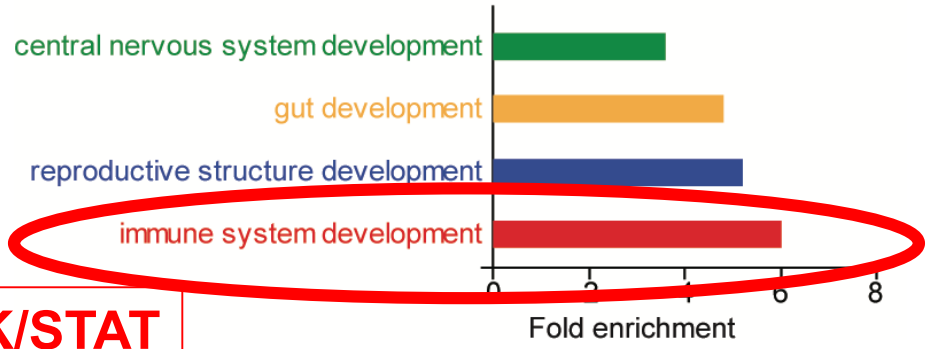
<u>ONGOING:</u> **Gcm, a novel pioneer transcription factor? Role of CBP?**
Lara, Pierre (ANR JCJC) (A Hamiche, IGBMC)

GCM DIRECT TARGETS: AN ANTI-INFLAMMATORY CASCADE?

Dam ID SCREEN



Go term sorted by category p-value > 10-5
at least five genes fold enrichment > 1.5 FDR <2%



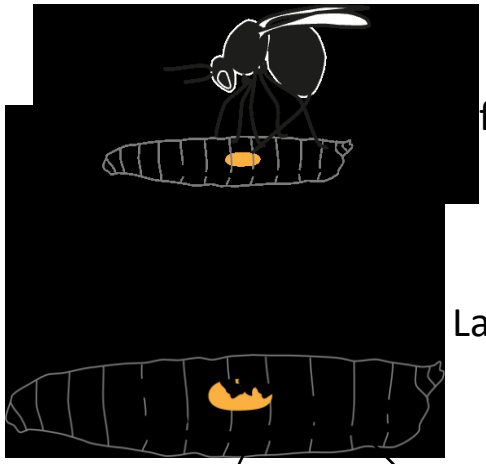
JAK/STAT

Gcm activates the expression of SOCS and PTP, inhibitors of the JAK/STAT proinflammatory pathway

Cattenoz 2013, Bazzi 2018

GCM HAS AN ANTI-INFLAMMATORY ROLE

Wasp infestation



fly larva

Late fly larva

Wasp egg encapsulated by fly activated macrophages

"Melanotic tumors" of fly activated macrophages

Control

gcm RNAi

Higher response

gcm OE

Lower response

Inflammatory response

Bazzi 2018

GCM HAS AN ANTI-INFLAMMATORY ROLE

Inflammatory challenge

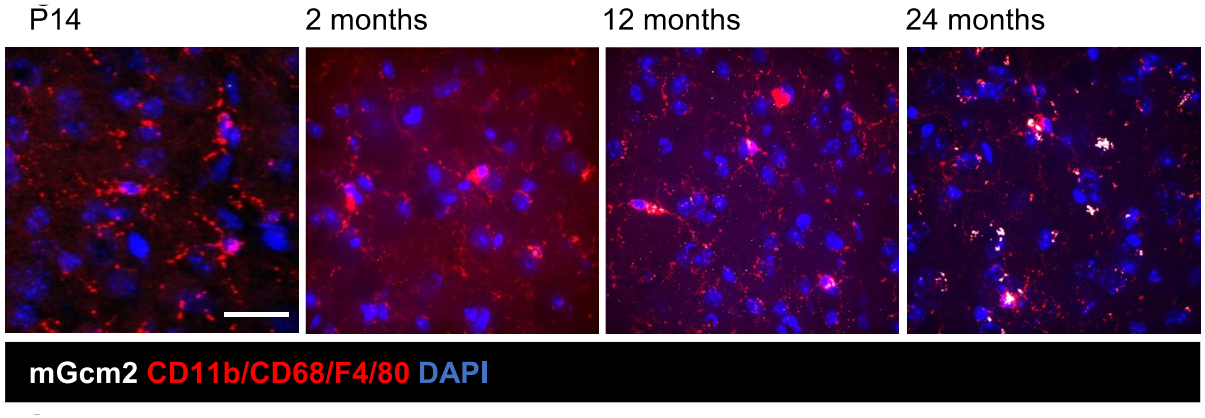
Acute inflammation: wasp infestation

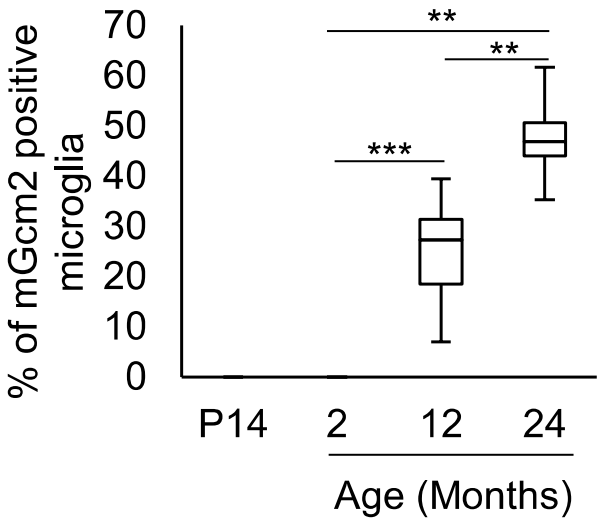
Chronic inflammation: aging, JAK/STAT or TOLL overexpression

Inflammatory response

Is the anti-inflammatory role of Gcm conserved in evolution?

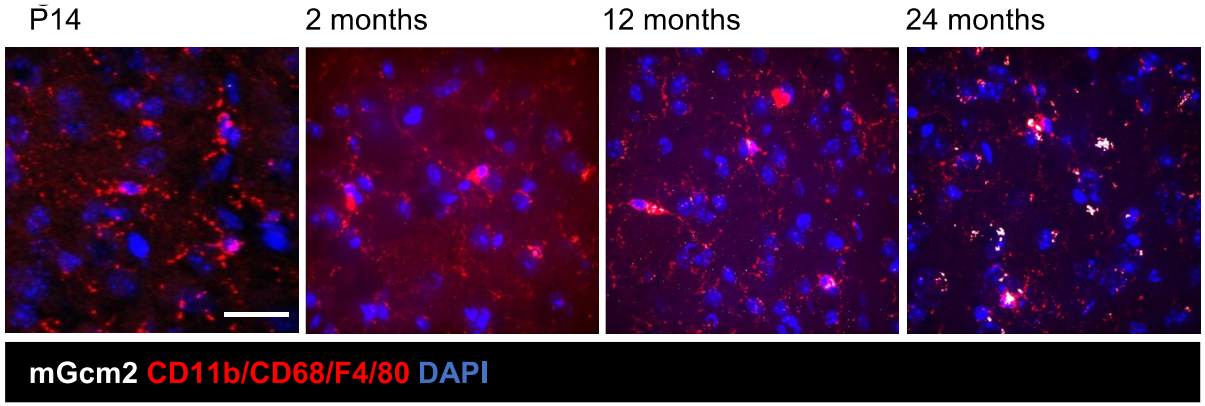
1 MGCM2 IS EXPRESSED AND REQUIRED IN AGING MICROGLIA

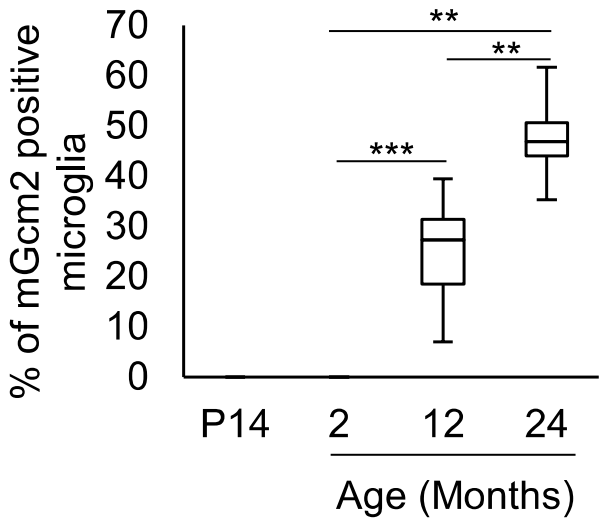


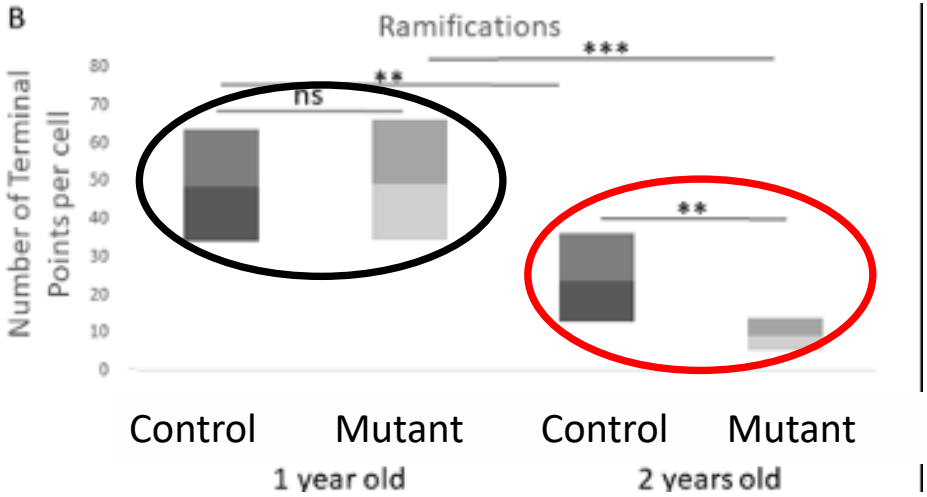


Pavlidaki 2022

1 MGCM2 IS EXPRESSED AND REQUIRED IN AGING MICROGLIA



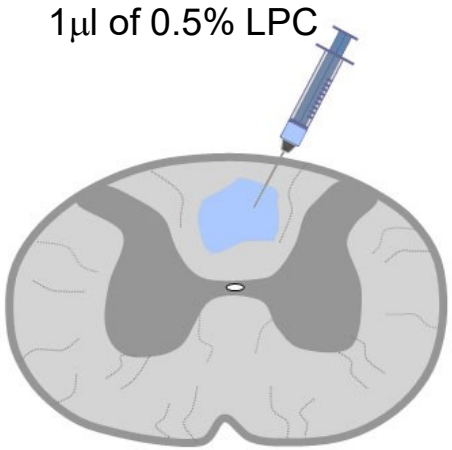




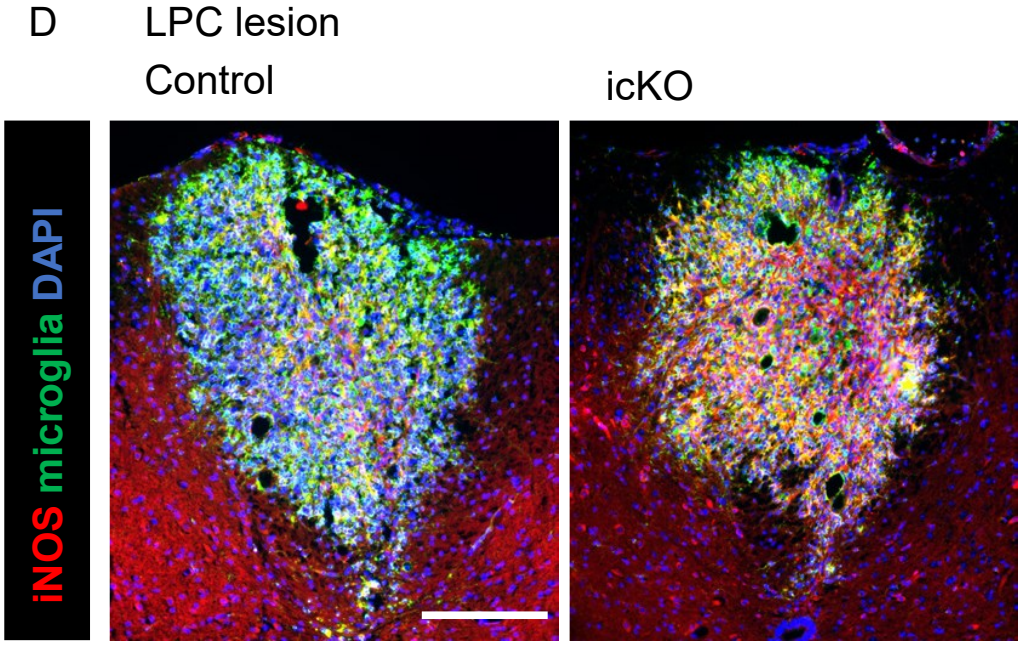
Pavlidaki 2022

More ameboid (activated) microglia AND **higher inflammatory state (INOS+)** in the mutant mice

2 ENHANCED INFLAMMATORY STATE IN mGCM2 KO MICROGLIA UPON ACUTE CHALLENGE



thoracic spinal cord



➢ **Lysolecithin (LPC) model of focal demyelination**

Dr. Brahim NAIT OUMESMAR – ICM Paris

Pavlidaki 2022

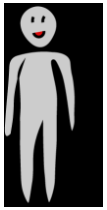
AN ANCESTRAL ANTI-INFLAMMATORY PATHWAY

Gcm expression in immune cells within/outside the fly nervous (glia/macrophages)

Gcm has an anti-inflammatory role upon chronic/acute challenge

The murine Gcm2 gene expressed in microglia (but not in macroglia)

mGcm2 supresses the inflammatory state upon chronic/acute challenge



The human GCM2 gene is expressed in active plaques of Multiple Sclerosis patients

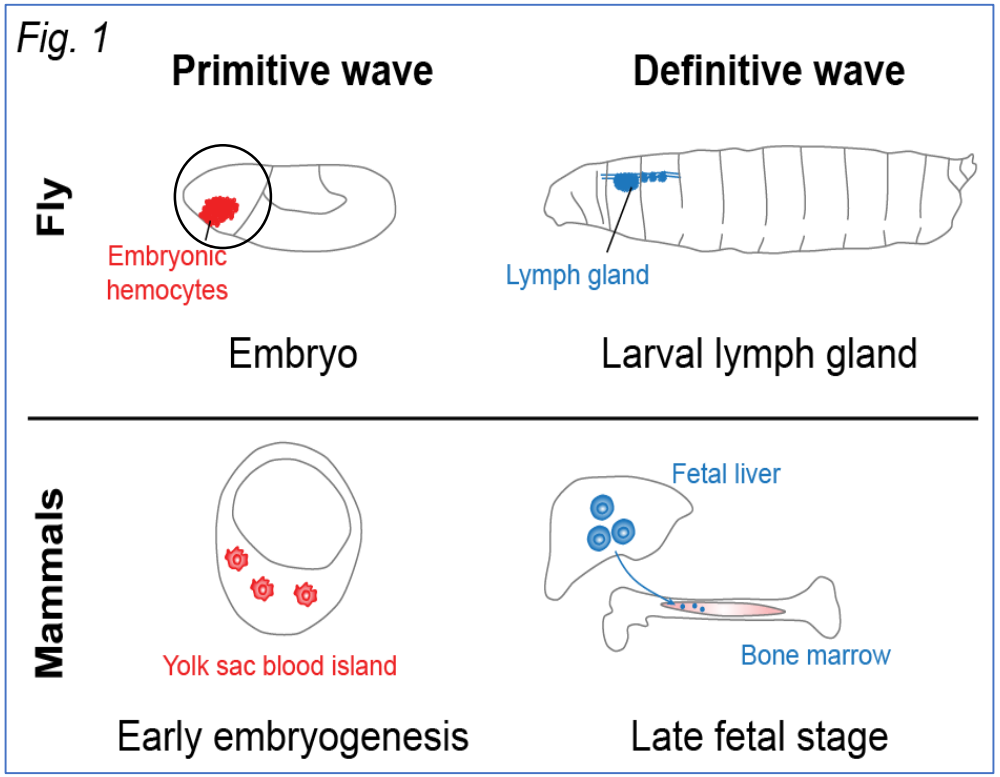
<u>ONGOING</u>: Impact and role of Gcm in degenerative models

Tarek, Sara

(S Birman, ESCPI, Paris, B Nait-Ouemesmar, ICM, Paris)

STRATIFIED HEMATOPOIESIS

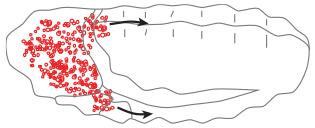
Early macrophages: resident population



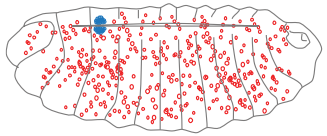
Bernardoni 1997; Kammerer 2001; Jacques 2009; Cattenoz 2016; Giangrande & Hartenstein 2018; Bazzi 2018

WAVE-SPECIFIC ROLE OF MACROPHAGES?

Embryo



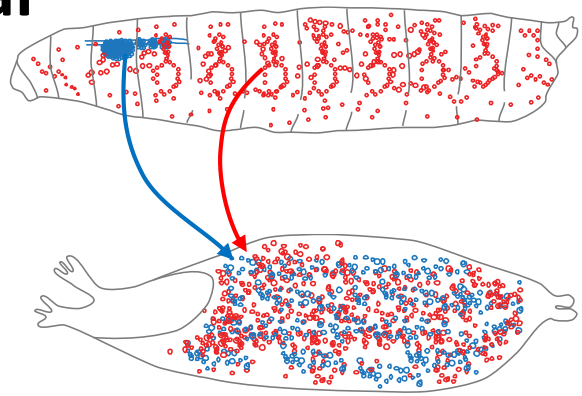
Early wave macrophages



Lymph gland growth and differentiation

3rd Instar Larva

Pupa

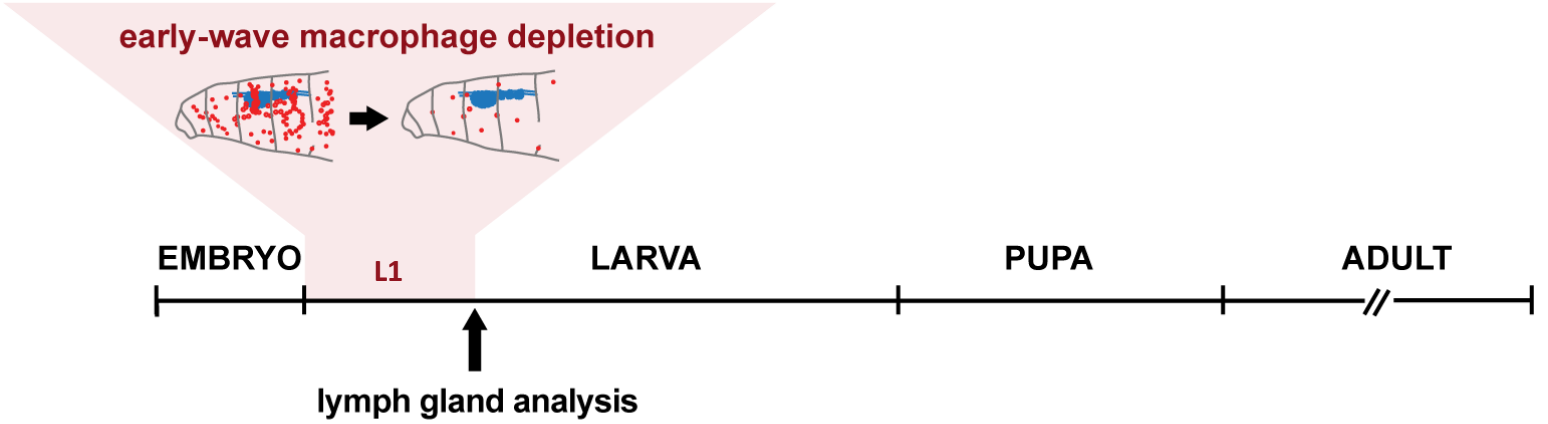


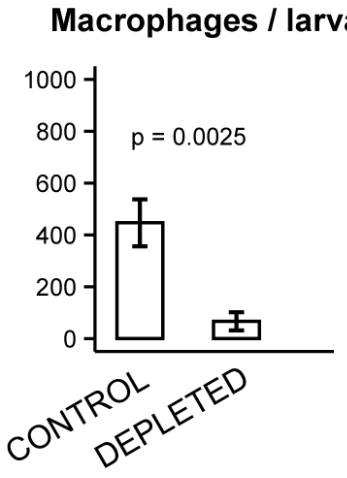
Lymph gland histolysis at pupal stage

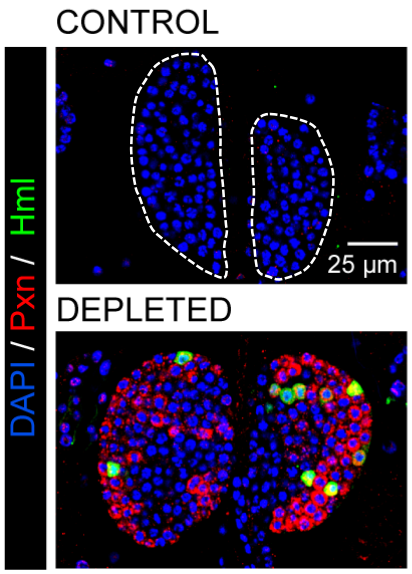
ADULT: 2/3 early-wave derived macrophages
1/3 lymph gland derived macrophages

From W Wood, P Martin; 2017

THE LOSS OF EARLY-WAVE MACROPHAGES ACCELERATES LATE HEMATOPOIESIS







Overgrowth and earlier cell differentiation
(Pxn in red =marker of differentiated macrophages)

CONTROL: ***w;HmlΔGal4,UAS-2XEGFP/+;tubulinGal80^{TS}/+***

DEPLETED: ***w;HmlΔGal4,UAS-2XEGFP/UAS-hid;tubulinGal80^{TS}/+***

Monticelli 2024

A DEVELOPMENTAL ROLE OF MACROPHAGES

The depletion of early-wave macrophages accelerates the development of the lymph gland, site of late hematopoiesis.

ECM molecules secreted by early-wave macrophages ensure a proper architecture of the lymph gland and modulate its maturation.

Early-wave macrophages depletion during mouse fetal liver hematopoiesis triggers premature differentiation of Hematopoietic Stem Cells sustaining late hematopoiesis.

Acceleration of late hematopoiesis associates with defective ECM in the fetal liver niche.

<u>ONGOING</u>: **Impact of macrophages on development and disease**

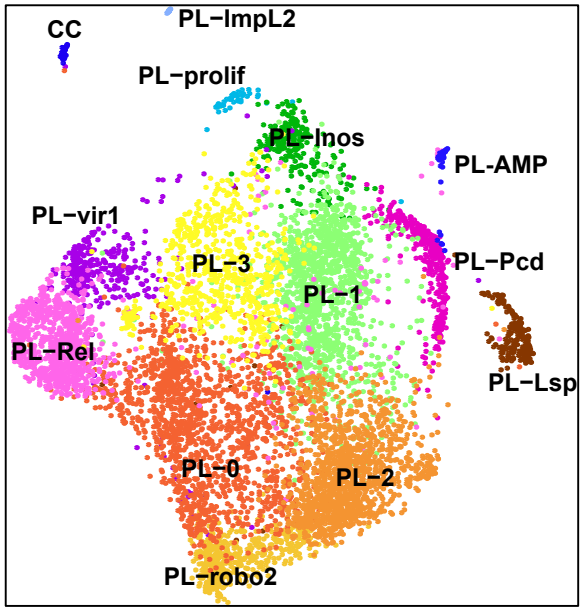
Sara, Pierre, Zeinab, Smrithi, Tarek, Sajad

(C Delidakis IMBB, E Gomez Perdiguero Pasteur Institute, T Mukherjee InStem India, S Birman ESCPI)

THE FIRST SINGLE CELL ATLAS OF THE FLY IMMUNE SYSTEM

- Phagocytic
- Proliferative
- Secretory
- Antimicrobial peptides
- Unspecified
- …

3rd INSTAR LARVA, 14 clusters



ONGOING: **Macrophage identity (space/time) and heterogeneity**

Lara, Sara, Pierre, Thomas, Gege

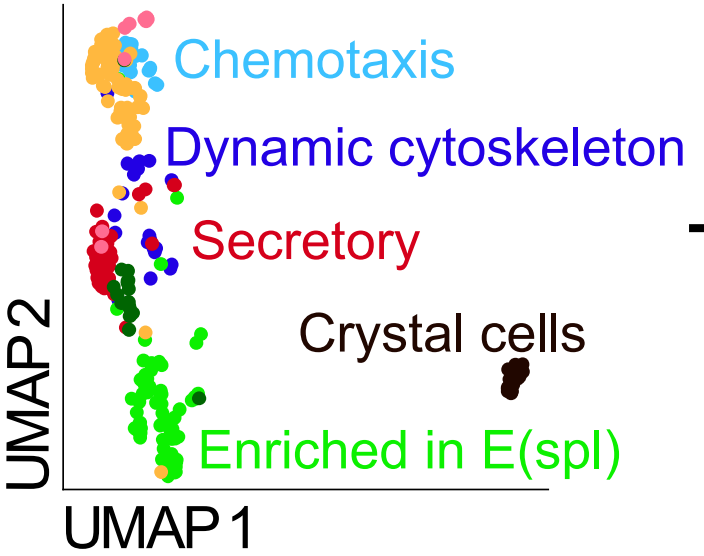
Longitudinal analysis, Lineage tracing, Metabolic challenges

(D Siekhaus UCLA, K Kierdorf U Freiburg, T Mukherjee InStem India, L Ciapponi U La Sapienza, Roma)

Cattenoz 2020, 2021, Bazzi 2023

MACROPHAGE HETEROGENEITY: NATURE VS. NURTURE

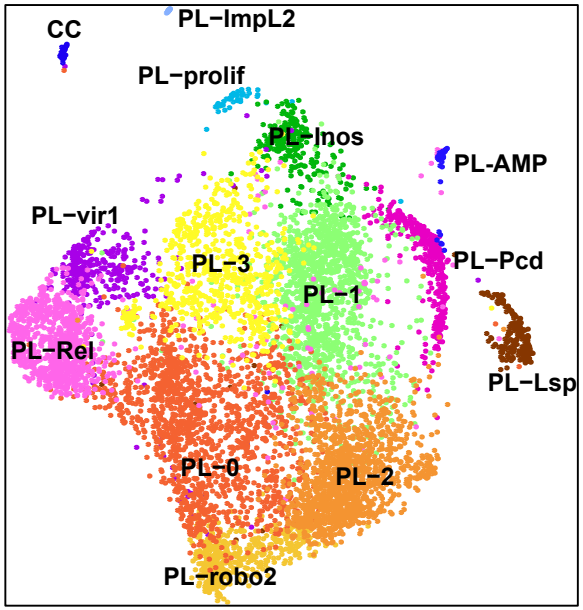
LATE EMBRYO, 8 clusters

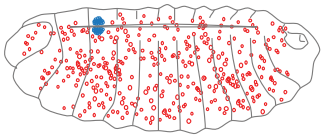


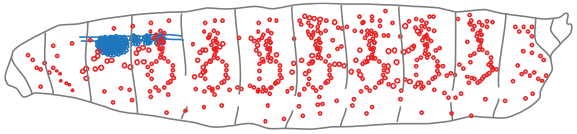
Proliferation
Homing
Diversification

L1 L2
Feeding
Breathing
…

3rd INSTAR LARVA, 14 clusters



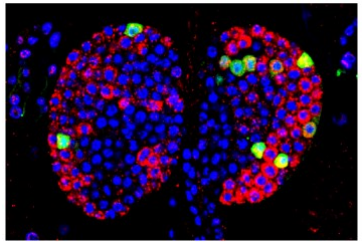




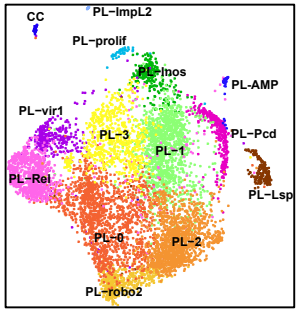
Pierre Cattenoz, Sara Monticelli, Lara El Berjawi with Tao Ye (GenomEast IGBMC) and D Siekhaus (IST Austria, UCLA)

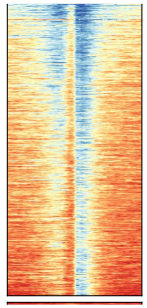
Gcm, a potent and evolutionarily conserved transcription factor

Stratified hematopoiesis and homeostatic interactions between waves

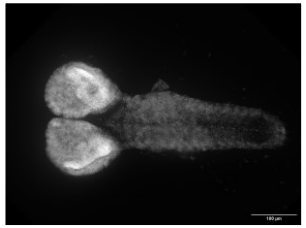


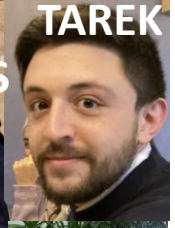
Macrophages, an heterogeneous and plastic cell population

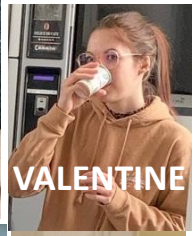


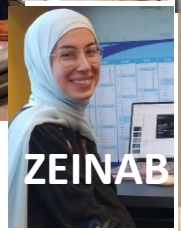


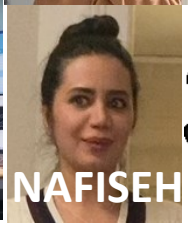
Macrophages, signaling hubs during development and in pathological conditions











THE TEAM

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Sajad Ahmad Najar co-supervised PhD (InStem)

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Holy ANDRIAMAMPIANINA AI INSERM

THE IGBMC

THE FACILITIES

Imaging, Genomeast, Screening, FACS, EM, Mouse, Cell culture…

IBMC MS Platform

THE FLY COMMUNITY

International Research Project
IRP CNRS/INSERM/Unistra
with InStem INDIA