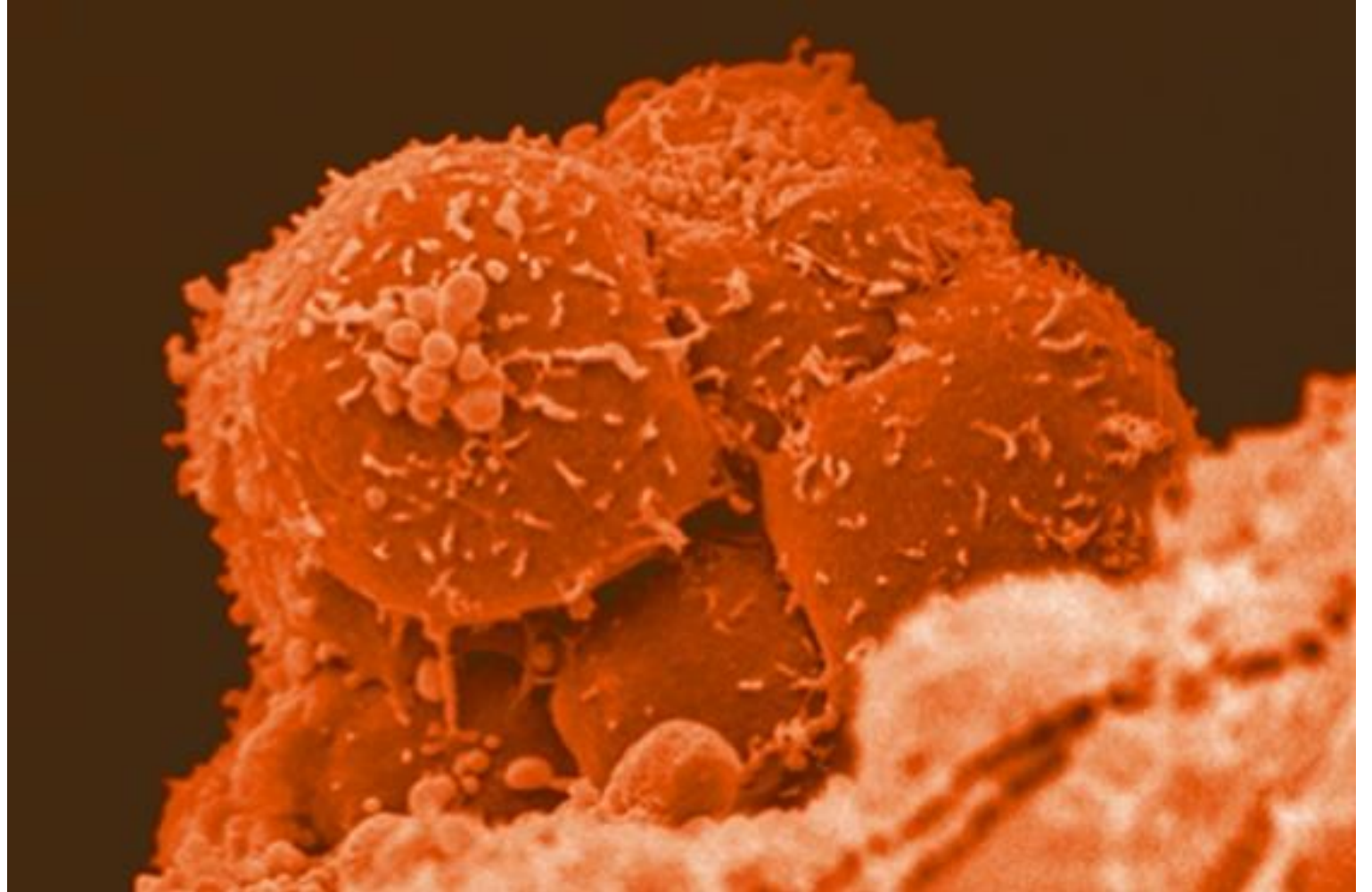


INVESTIGATION OF *IN VIVO* HAEMATOPOIESIS AND IMMUNITY: TOWARDS PRECISION MEDICINE



July 1-3, 2025

Dr. Karima KISSA
INSERM
University of Montpellier

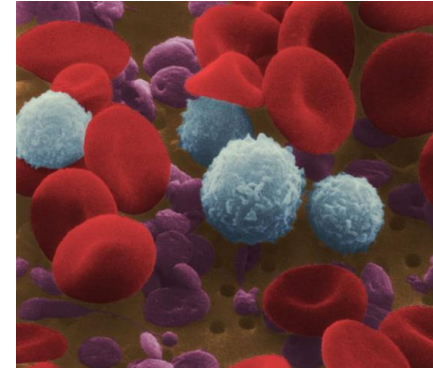


HAEMATOPOIETIC STEM CELLS AND HAEMATOLOGICAL DISEASES

5,000,000 cas/an en Europe
(WHO, ESID, Medscape Ref)



New source of transplantable cells -
Regenerative medicine



HSC
Haematopoietic Stem Cell
Physiological conditions

Blood cells

Origin of haematopoietic stem cells

Role of macrophages in haematopoiesis and cancer

Humanization of zebrafish embryo

HAEMATOPOIETIC STEM CELL PRODUCTION DURING EMBRYOGENESIS

Production of HSCs *in vivo*
during embryogenesis

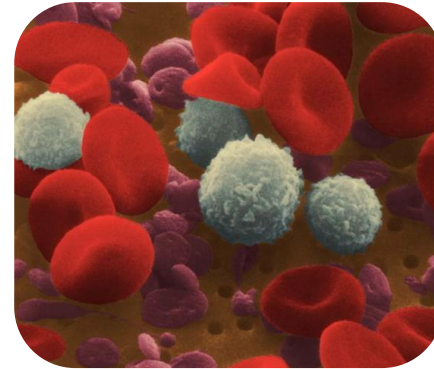


HSC

Haematopoietic Stem Cell
Physiological conditions



New source of transplantable cells -
Regenerative medicine



Blood cells

Origin of haematopoietic stem cells

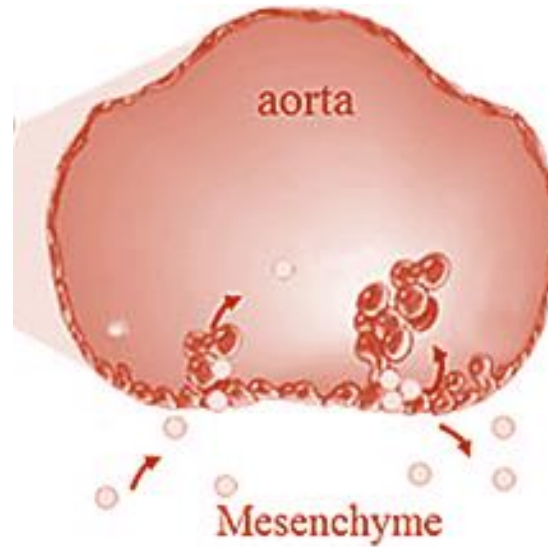
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HAEMATOPOIETIC STEM CELL PRODUCTION DURING EMBRYOGENESIS

32-day human embryo

AGM
Aorta-Gonad-Mesonephros



CSH ○
Cellules Souches Hematopoïétiques

Adaptated from Tavian et al, 2001
Bertrand et al; PNAS, 2005, R&D illustration

***AGM : Aorta-Gonad-Mesonephros**

○HSC : Hematopoietic Stem Cells

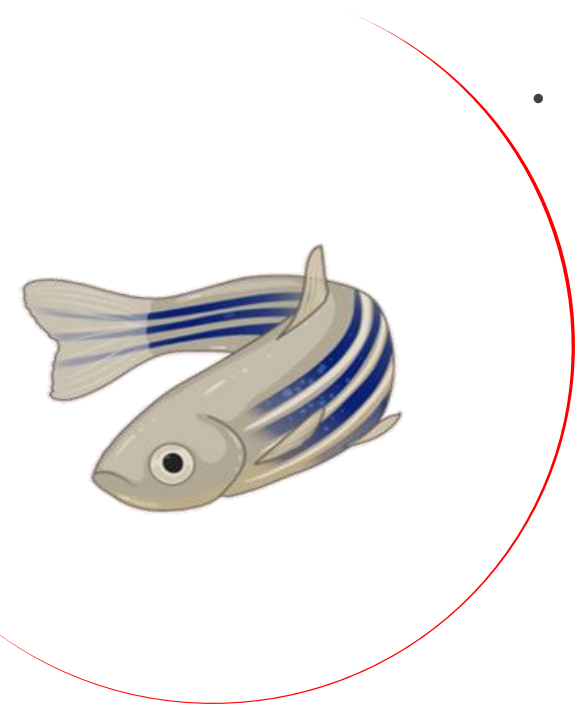
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Humanization of zebrafish embryo

THE ZEBRAFISH EMBRYO

- Easy handling and cost-efficient
 - Hundreds of eggs per week
 - 70% orthology with human genes
 - External and rapid development
 - Transparent and compatible with live-imaging techniques
 - Many transgenic lines availables



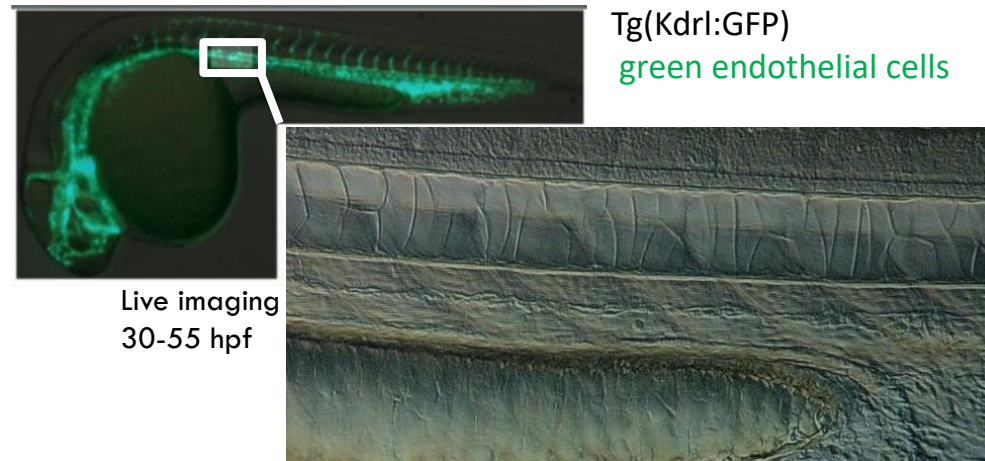
Nomarski live imaging in the zebrafish embryo

Origin of haematopoietic stem cells

Role of macrophages in haematopoiesis and cancer

Humanization of zebrafish embryo

HAEMATOPOIETIC STEM CELL PRODUCTION DURING ZEBRAFISH EMBRYOGENESIS



Murayama et al, Immunity. 2006

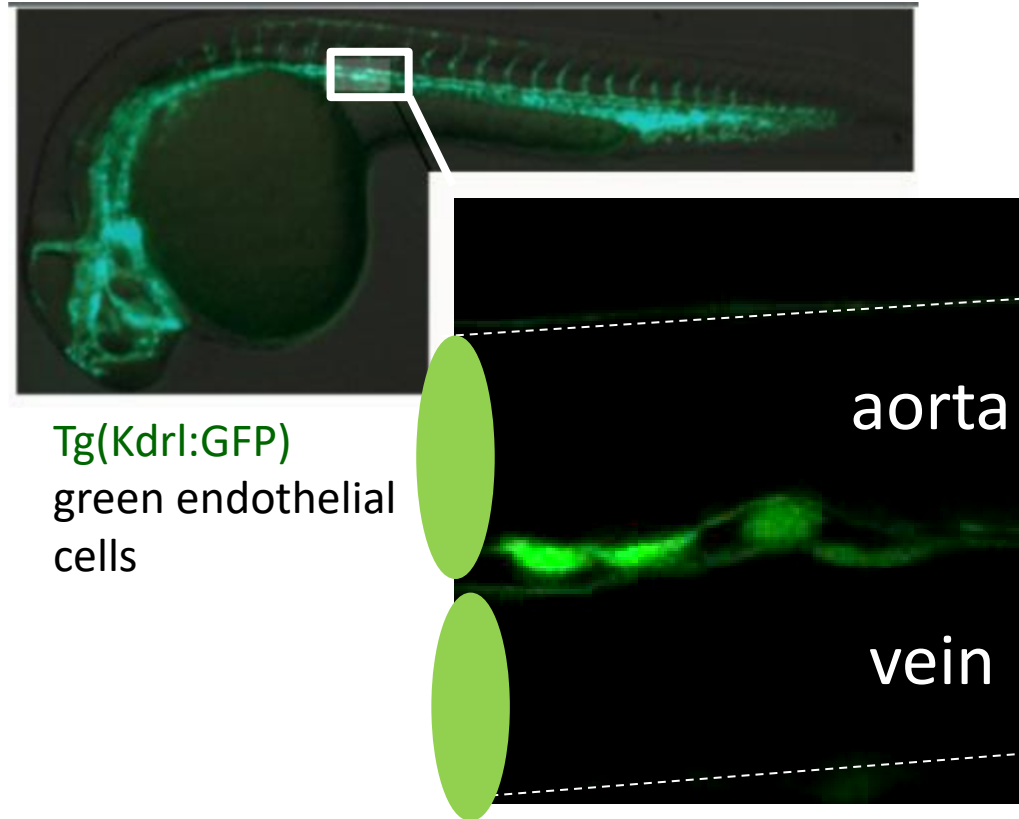
Kissa K et al, Blood. 2008.

Origin of haematopoietic stem cells

Role of macrophages in haematopoiesis and cancer

Humanization of zebrafish embryo

HAEMATOPOIETIC STEM CELLS EMERGE FROM THE AORTA



Kissa K & Herbomel P. Nature. 2010

Haematopoietic stem cells
emerge from the aorta by
endothelial hematopoietic
transition

Origin of haematopoietic stem cells

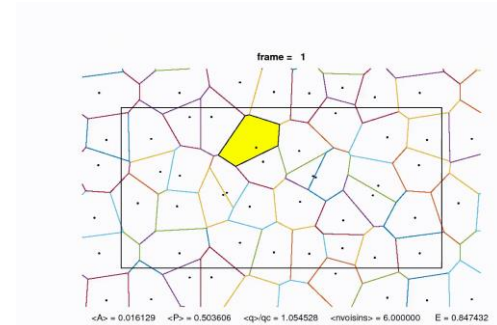
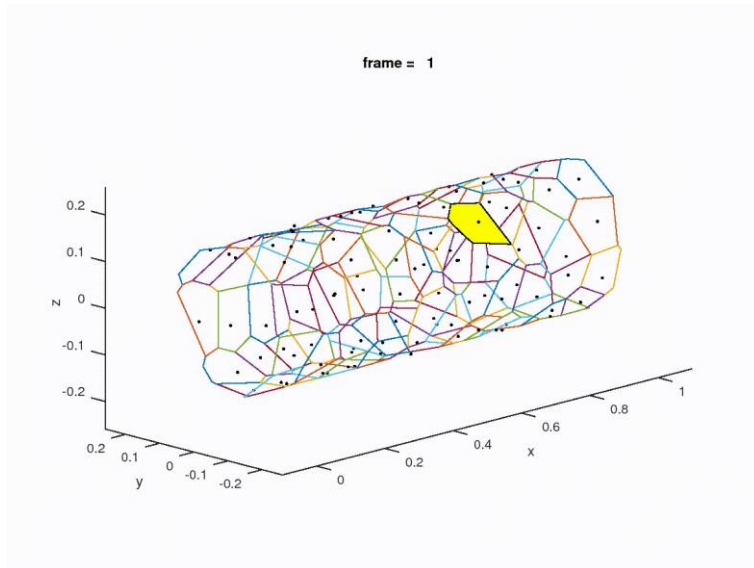
Role of macrophages in haematopoiesis and cancer

Humanization of zebrafish embryo

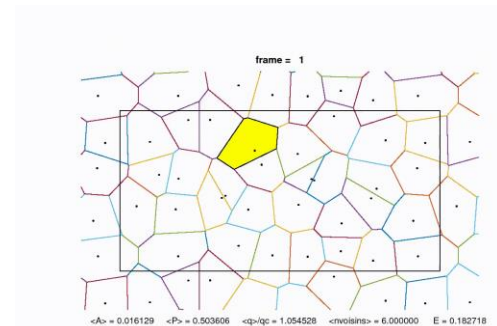
MODELING STEPS OF EHT

Physical principles of tissue organisation explaining cell motility

Laboratory Charles Coulomb (L2C)
A Parmeggiani
Dep of Physics, Russia
Sergei Rochal
Ivan Golushko
Dmitrii Chalin



"Small" p_0



"Large" p_0

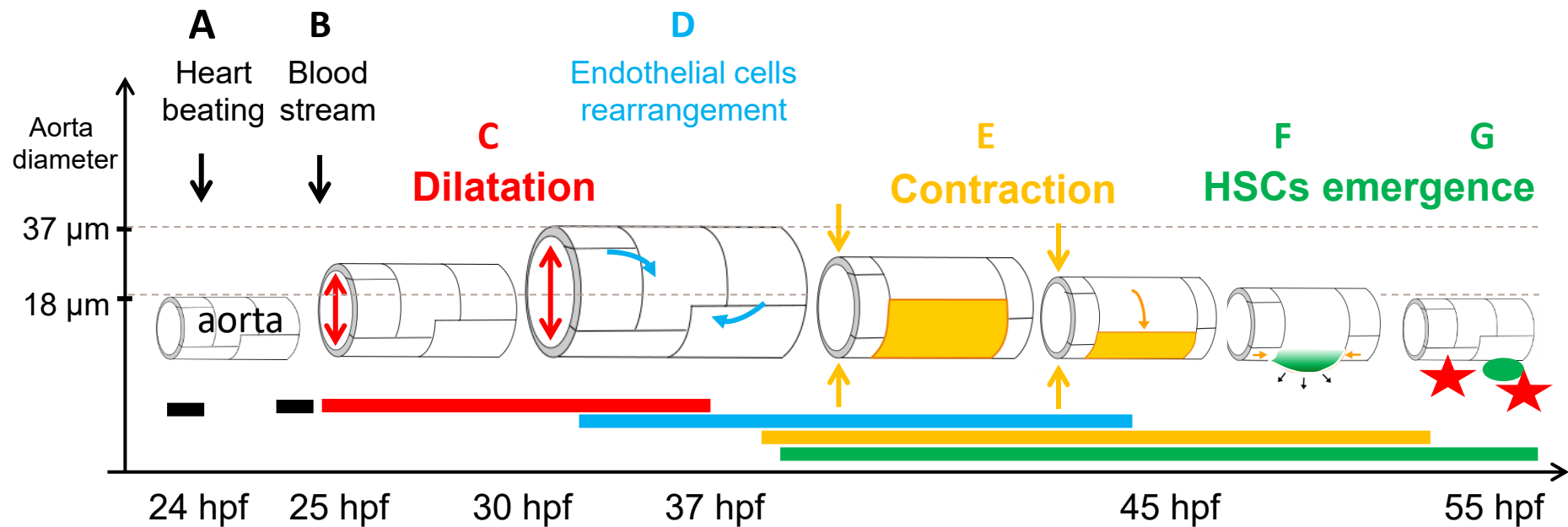
Poullet, Cell Mol Life Sci. 2020
Chalin D, Sci Rep. 2021

Origin of haematopoietic stem cells

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HAEMATOPOIETIC STEM CELLS EMERGE FROM THE AORTA BY ENDOTHELIAL HEMATOPOIETIC TRANSITION



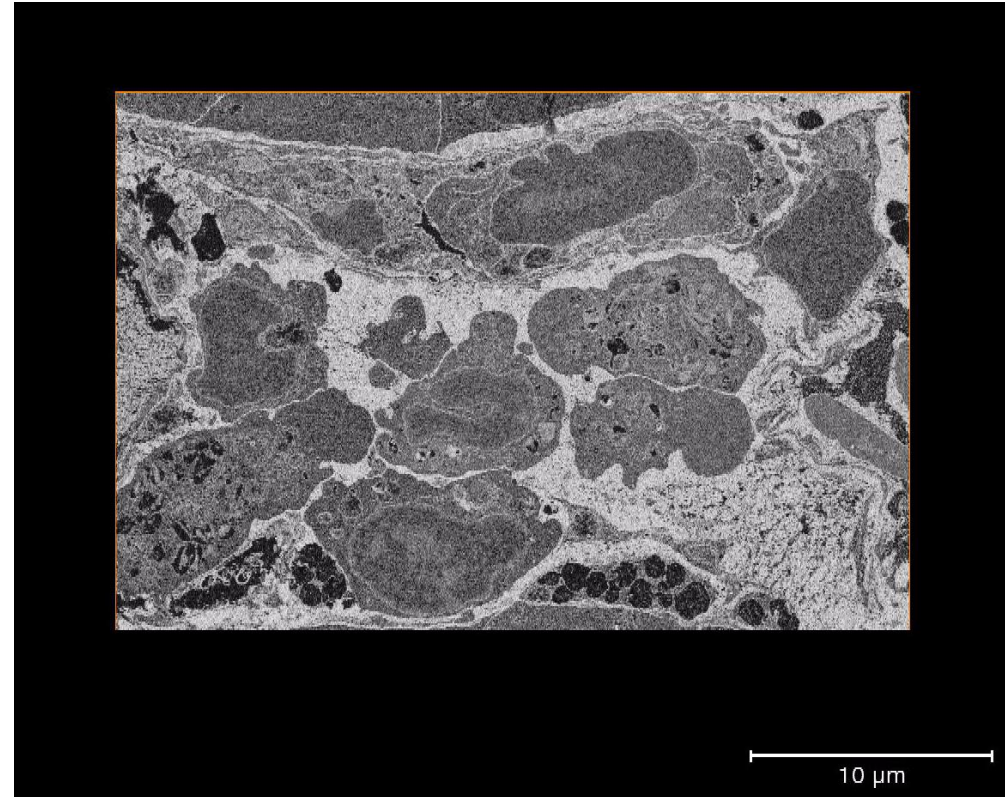
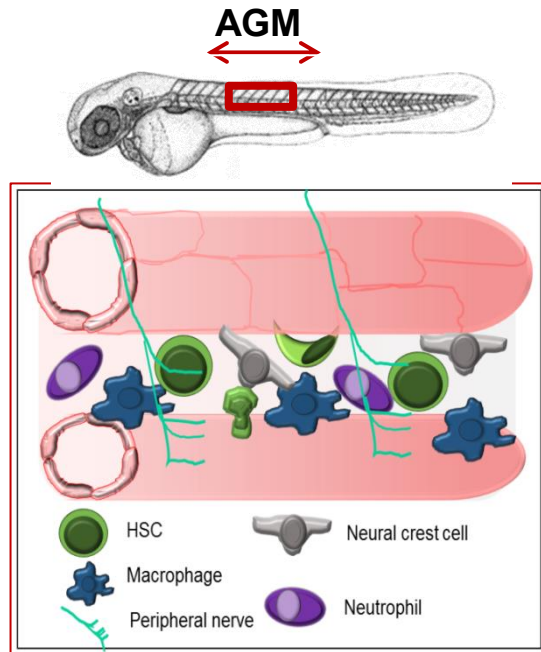
Poullet, Cell Mol Life Sci. 2020

Origin of haematopoietic stem cells

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CHARACTERISING THE CELLULAR ENVIRONMENT



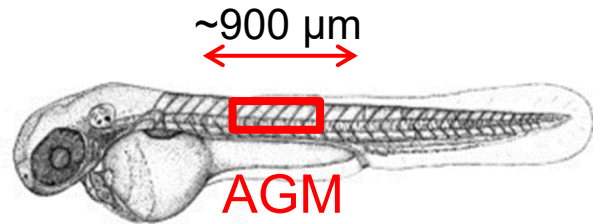
CLEM: Correlative Light and Electron Microscopy

Origin of haematopoietic stem cells

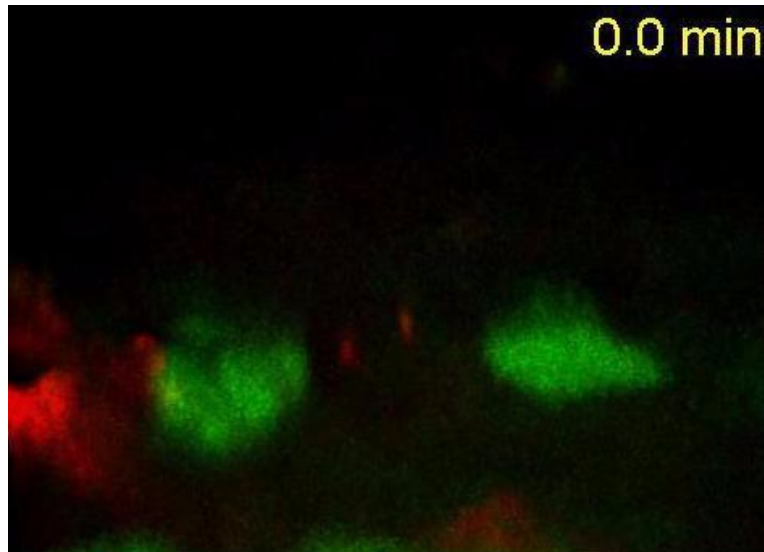
Role of macrophages in haematopoiesis and cancer

Humanization of zebrafish embryo

PRIMITIVE MACROPHAGES CONTROL HSPC MOBILISATION AND HAEMATOPOIESIS



High resolution OMX microscopy

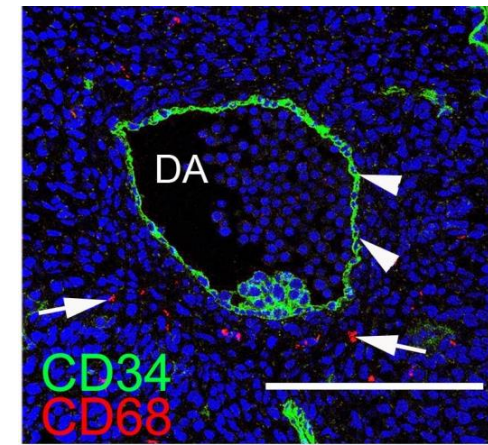


Tg(Mpeg1-mCherry) / Tg(CD41:GFP)

Macrophage

HSC

Human embryo 34 days



E. Julien, M. Tavian

CD34 – Vascular endothelium - arrowheads
CD68 – Macrophages - arrows

Travnickova J. Sci Rep. 2021

Origin of haematopoietic stem cells

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Humanization of zebrafish embryo

*Tumor
microenvironment*

CAR

CAART

INFECTIOUS DISEASES

Cancer



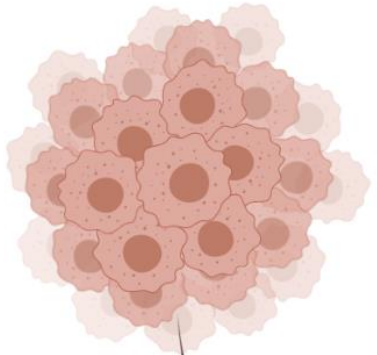
Inflammatory diseases

Brest cancer

Liver cancer

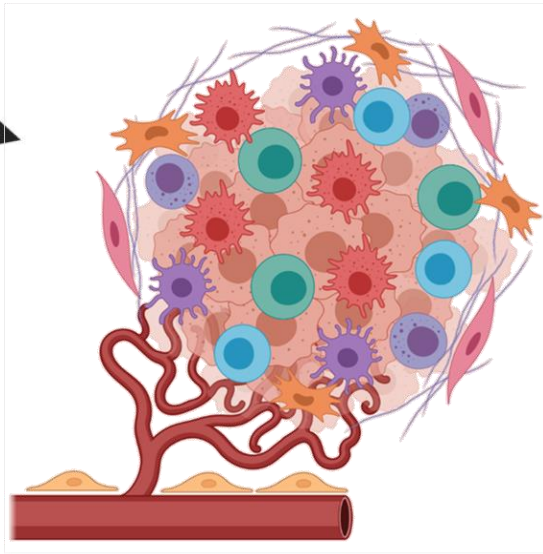
Drug delivery

WHY STUDYING TUMOR MICROENVIRONMENT (TME) ?



- For decades, cancer was considered as a **chaotic aggregate of cells** able to proliferate in an anarchic manner.
- At this point, the **complex interaction** between tumor cells and their microenvironment was **neglected**.

→ The treatment aims to target cancer cells.



- With the discovery of the **key role** of the **TME in cancer progression**
- The objective is now to **characterize cellular interactions** between **cancer cells** and **surrounding cell populations**.

→ To understand how TME influence proliferation and metastatic dissemination.

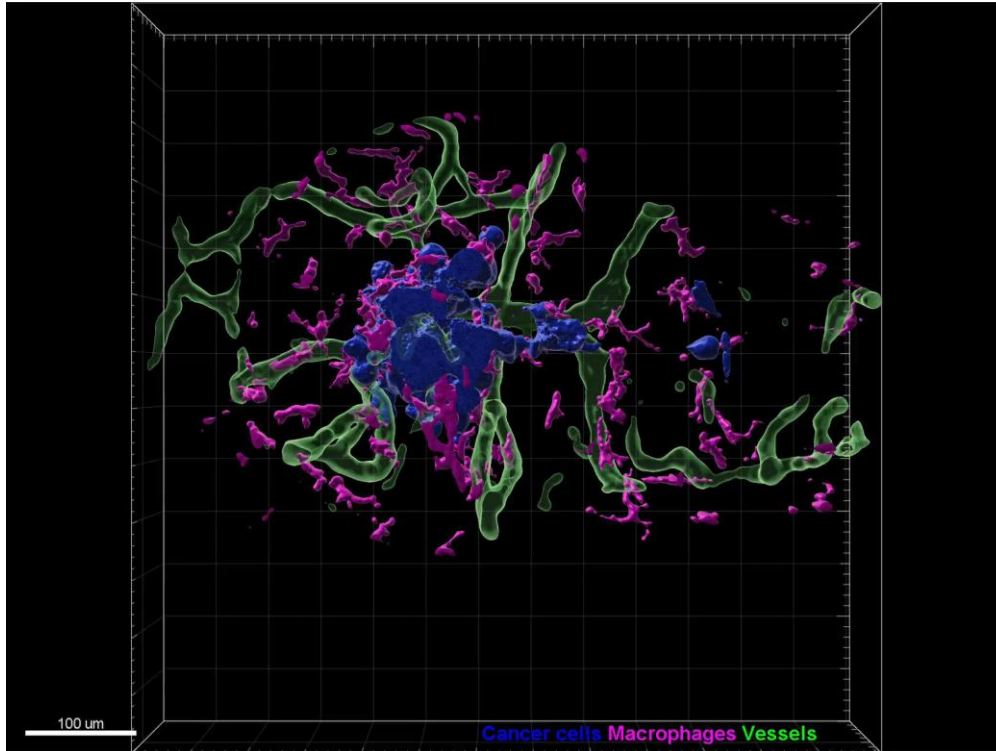
Origin of haematopoietic stem cells

Role of macrophages in haematopoiesis and cancer

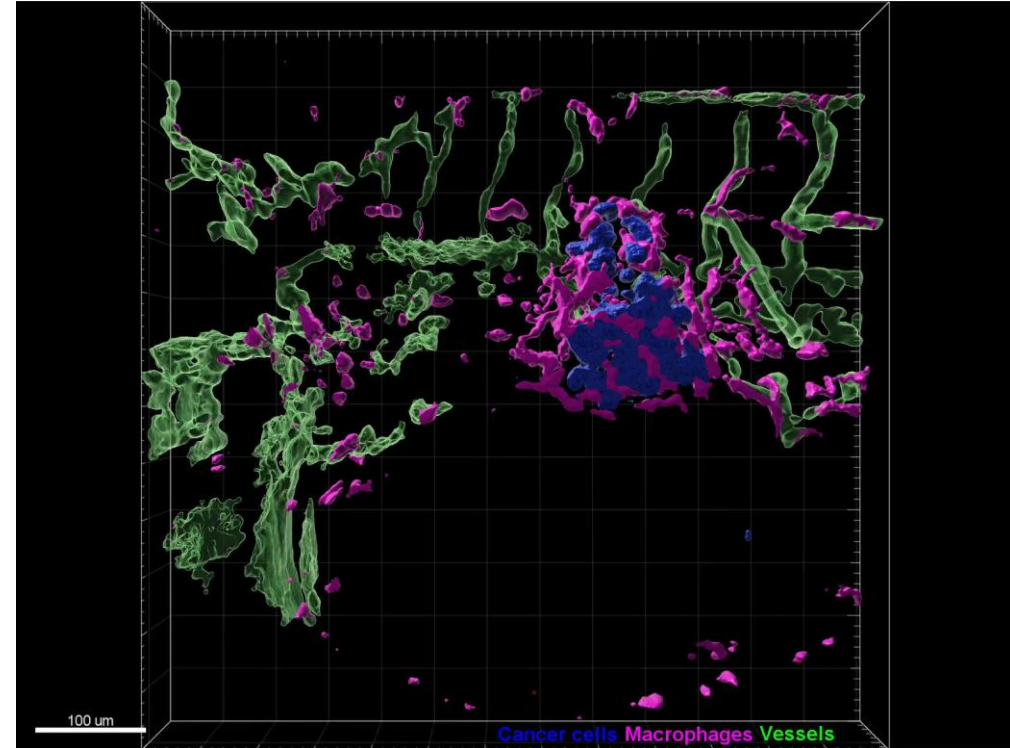
Humanization of zebrafish embryo

MODELLING 3D TUMOUR MICROENVIRONMENT *IN VIVO*

Glioblastoma model



Melanoma model



3D reconstruction : Glioblastoma TME model after injection in zebrafish head
Melanoma TME model after injection in the peritoneal cavity

cancer cells in blue
vessels in green
macrophages in magenta

Marines J. Curr Issues Mol Biol. 2023

Lorenzini F. Cell Death Discov. 2025

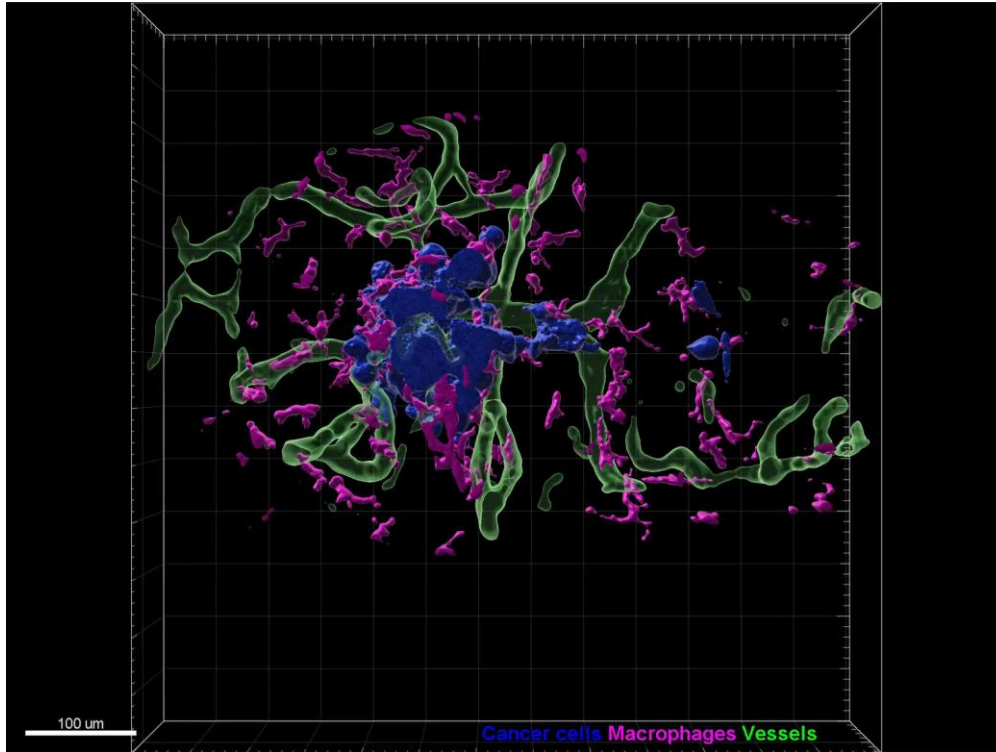
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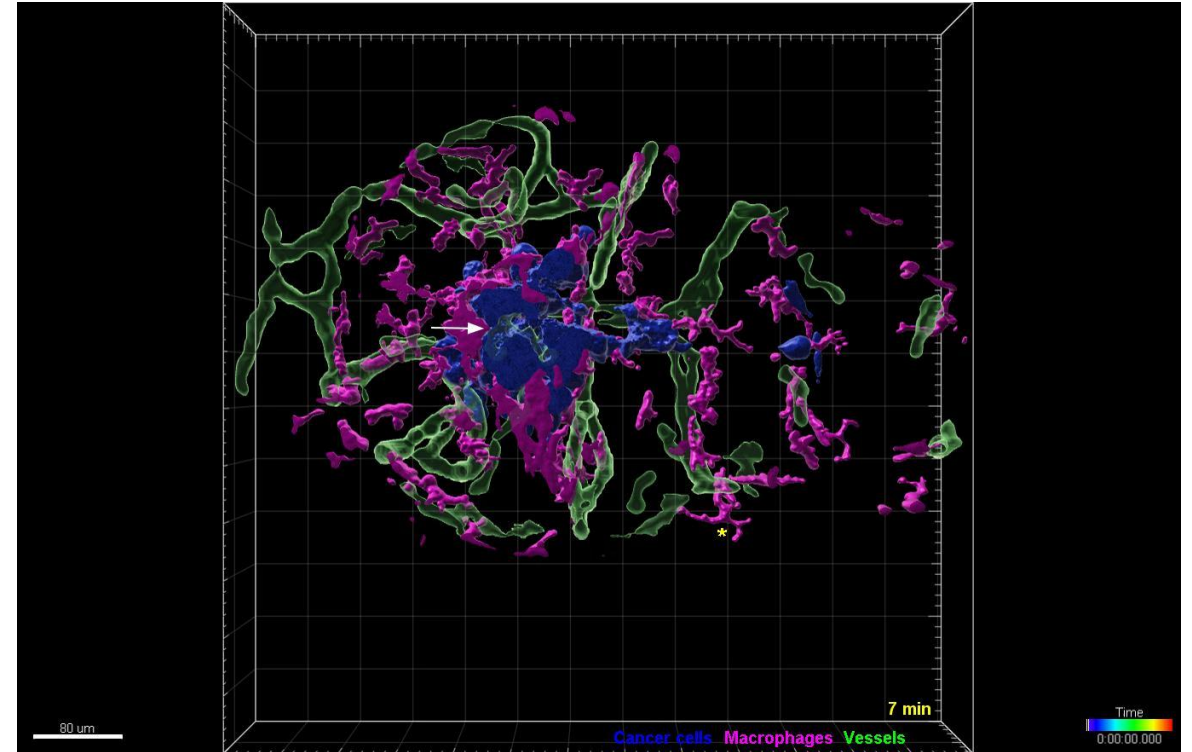
Humanization of zebrafish embryo

MACROPHAGE RECRUITMENT AND DYNAMIC

Glioblastoma model



Macrophages dynamic



3D reconstruction : Glioblastoma TME model after injection in zebrafish head
Melanoma TME model after injection in the peritoneal cavity

cancer cells in blue
vessels in green
macrophages in magenta

Marines J. Curr Issues Mol Biol. 2023
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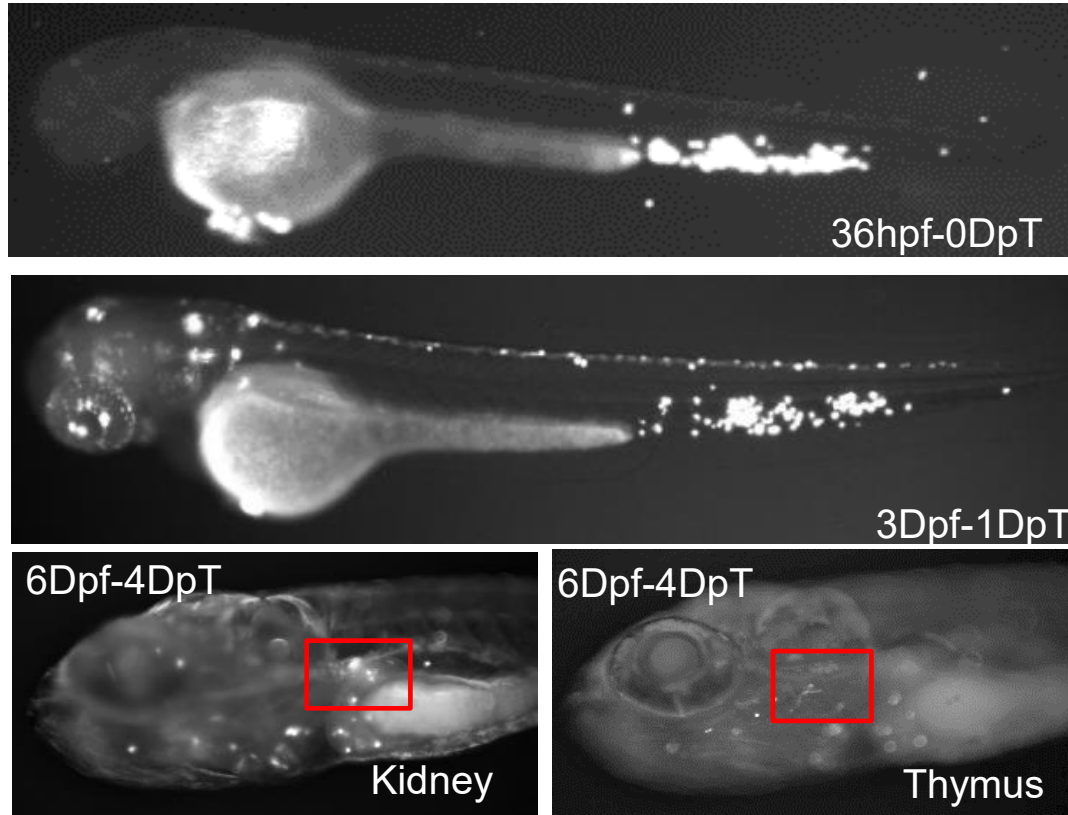
Role of macrophages in haematopoiesis and cancer

Humanization of zebrafish embryo

HUMAN HAEMATOPOIESIS IN THE ZEBRAFISH LARVAE

Manuela Tavian - EFS
Eric Robinet - Lymphobank

Mimic the human tumour microenvironment *in vivo*



Chimeric **Zebrafish / Human** HSCs CD34-GFP



R El Omar, 2024, Cell Death & Disease.

Origin of haematopoietic stem cells

Role of macrophages in haematopoiesis and cancer

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Thank you for your attention

Inserm

Institut national
de la santé et de la recherche médicale



Karima Kissa
Naoill Abdellaoui
Suma Choorapoikayil
Lukáš Höchtberger
Etienne Lelièvre
Sandra Nicolas
Nausicaa Pouillet
Sandra Than
Jana Travnickova



***Systèmes Complexes et
Phénomènes Non Linéaires***

Andrea Parmeggiani
Ivan Golushko
Vladimir Lorman



Noel Converset
Fabrice Schmitt