

# Metástasis

Asignatura pendiente de la Oncología de  
Precisión en el Siglo XXI

FERNANDO VIDAL VANACLOCHA

George Washington University

School of Medicine and Health Sciences

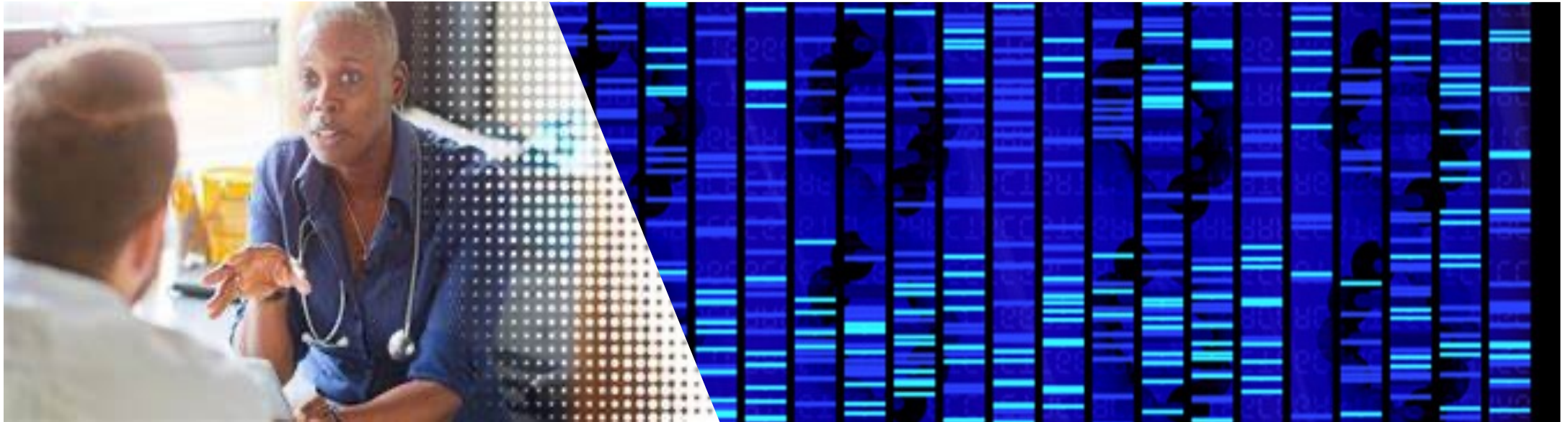
Washington, DC



# The XXI Century Health, Aging and Medicine

## Our current Medicine is transitioning:

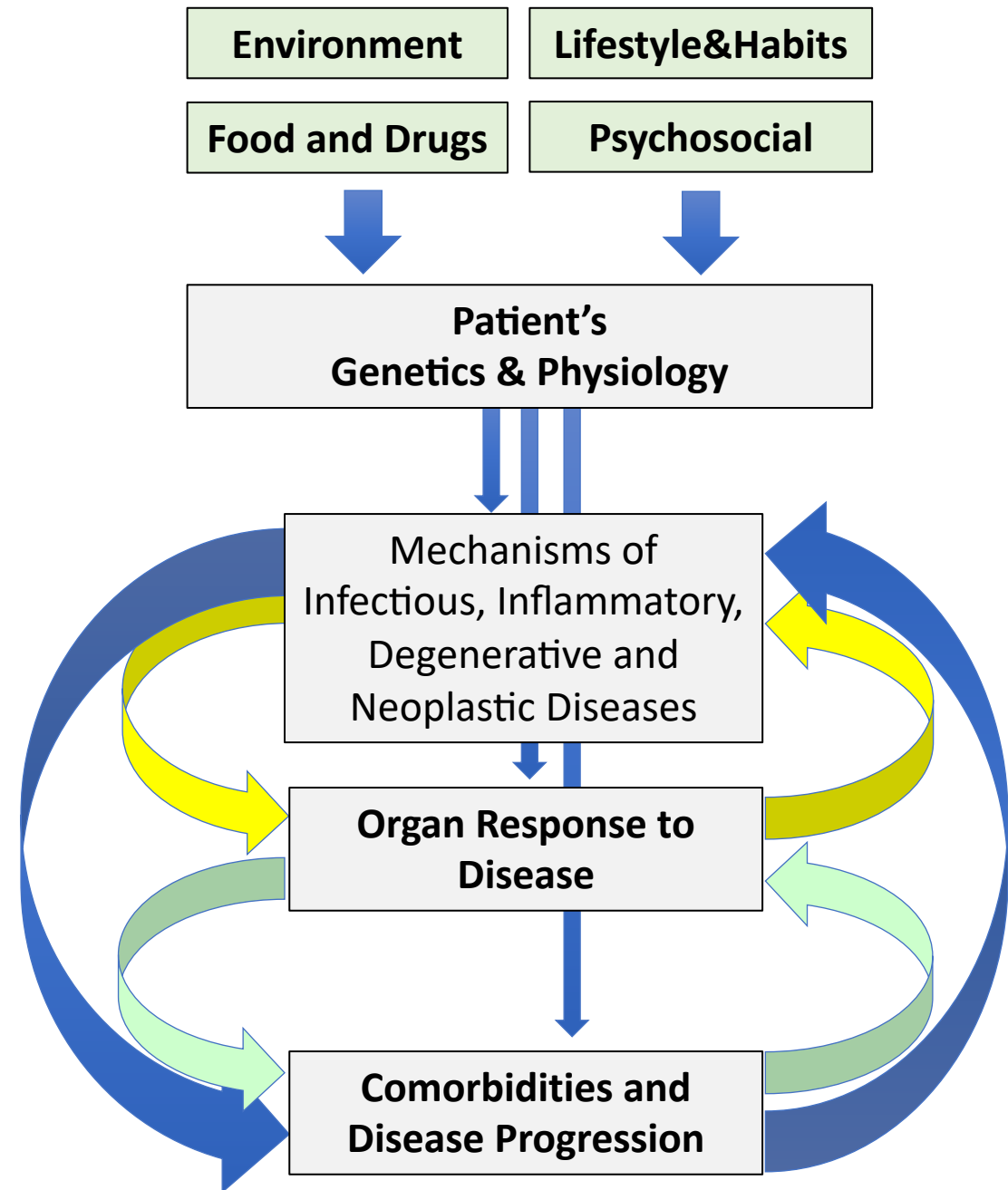
- From the old systems of the industrial age where everyone receives generalized **therapies designed for the masses**.
- To the 21st century, where **each patient is recognized as unique**.



# Precision Medicine

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The clinical practice based on diagnostics and therapeutics focused on genomic and molecular biomarkers and targets associated with predisposition, development and regulation of the disease and its response to treatments



# Dying from Metastatic Cancer

- Metastatic cancer (Stage IV cancer): a condition where a cancer has spread from its original location to distant organs, forming “metastases.”
- Most metastatic cancers are not curable and diagnosis is tightly associated with death.
- Most patients with metastatic disease respond transiently to treatments.
- Treatment slow metastasis growth and ease symptoms, improving quality of life.
- Planning for death with compassion is a part of caring for patients.
- Patients with metastatic cancer are advised to “get their affairs in order” and racing against time to address unfinished issues.
- Many illnesses affecting multiple organs do not usually lead to an early death.

**What is different about metastatic cancer that results in death?**

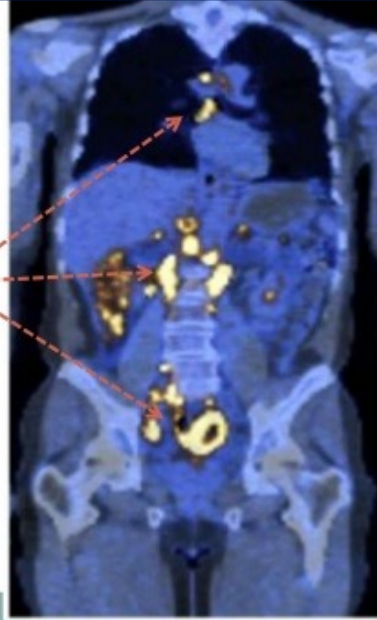
# How many deaths from cancer are caused by metastases?

## What is the process of Cancer Metastasis?

**Metastasis** is the process by which a tumor cell leaves the primary tumor, travels to a distant site via the circulatory system, and establishes a secondary tumor



Metastatic tumors



- **Death from cancer without metastatic disease as an underlying cause (10-35%):**
  - Cases where **local tumors affect vital organs.**
  - Cancer treatment **fatal side effects** (organ failure, bleeding due to thrombocytopenia, infections, interstitial pneumonitis, and tumor lysis syndrome).
  - **Surgical treatment fatal complications.**
- **Death from cancer metastasis (65-90%): Colorectal, lung, breast, ovarian cancers, melanoma)**





# History of Cancer Metastasis Disease

## XIX Century

To understand the clinical pathology of the disease:

- Pathology and Surgical aspects of as a clinical entity.

## XX Century

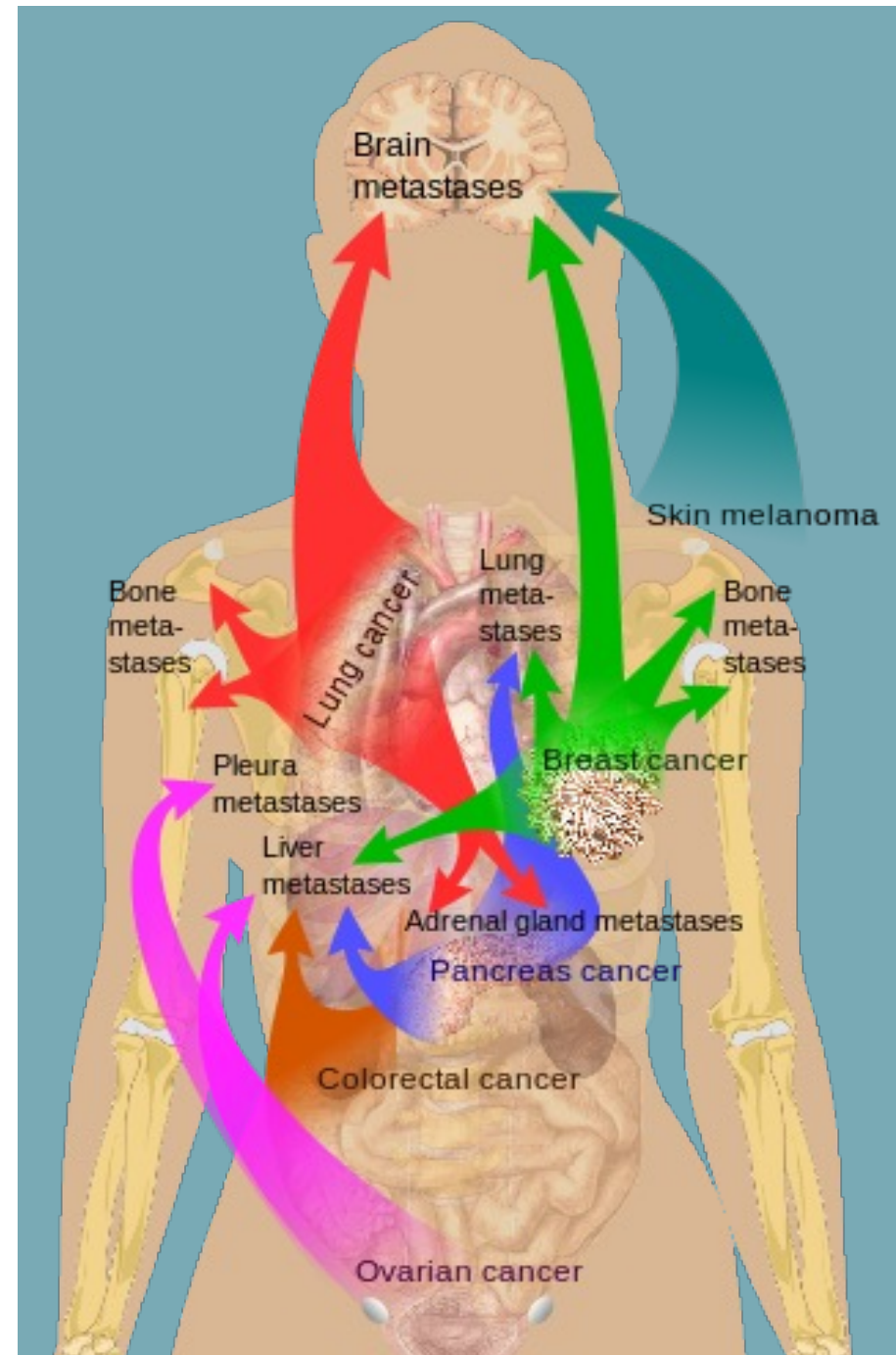
To understand biological mechanisms of the disease:

- Cell and Molecular processes.
- Anti-tumor Chemo-Immunotherapy-Radiotherapy.

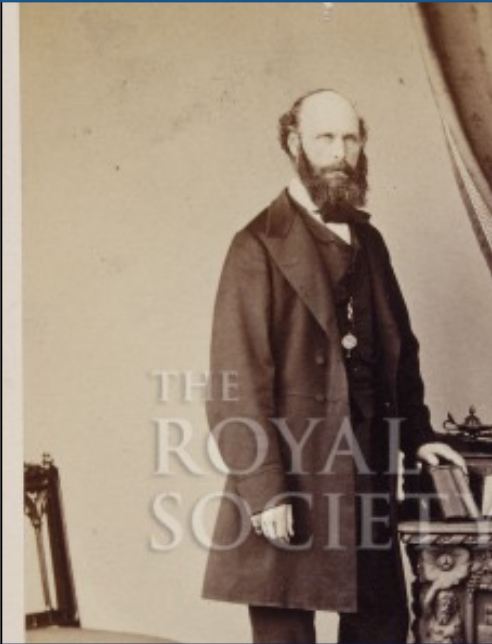
## XXI Century

To deploy a Precision Medicine practice:

- Transcriptional Phenotyping of Prometastatic Risk.
- Targeted therapies for cancer metastasis.

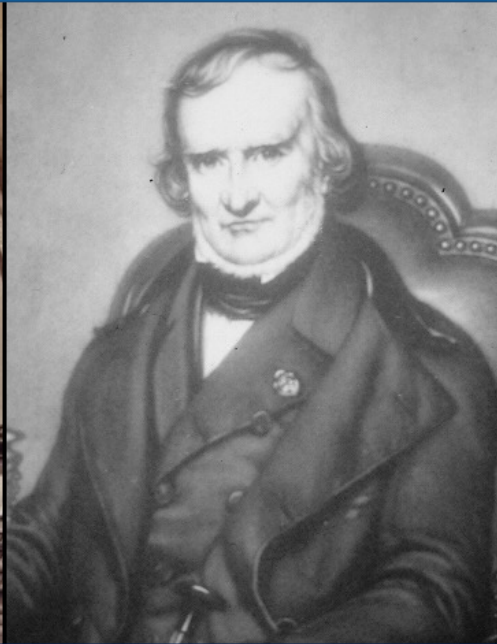


# Contribution of XIX Century Pathologists to the scientific study of Cancer Metastasis Disease



With the use of the microscope (XVIII), cancer spreads from primary tumor through lymph nodes to other sites (metastasis).

English surgeon  
Campbell De Morgan  
(1874)



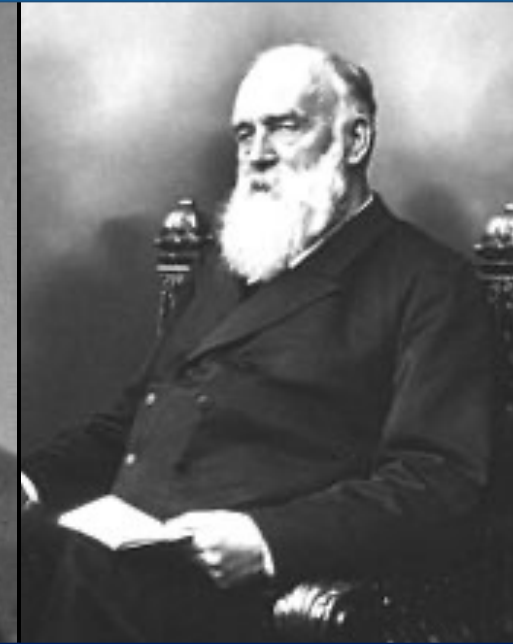
“Metastasis” is a secondary malignant tumor at a distant organ.

French surgeon  
Jean-Claude Recamier  
1820s



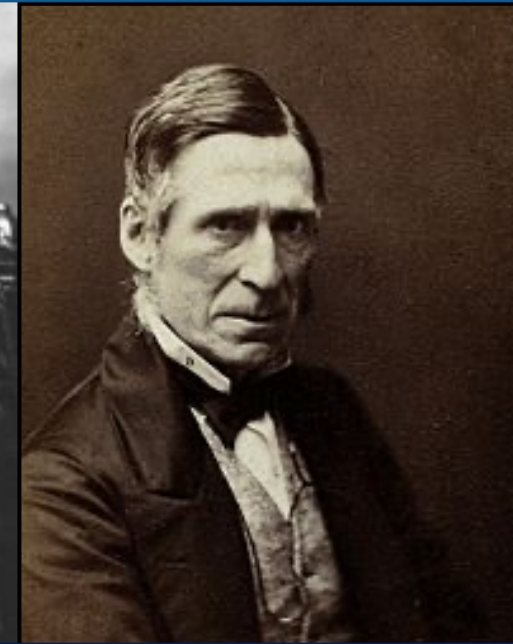
Cancers at sites of chronic inflammation.  
Pro/Anti-neoplastic roles of intratumor leukocytes.

German pathologist  
Rudolf Virchow, MD  
(1821 –1902)



Cancers metastasize through the spread of malignant cells and not of a humor.

German surgeon  
Karl Thiersch  
(1860s)

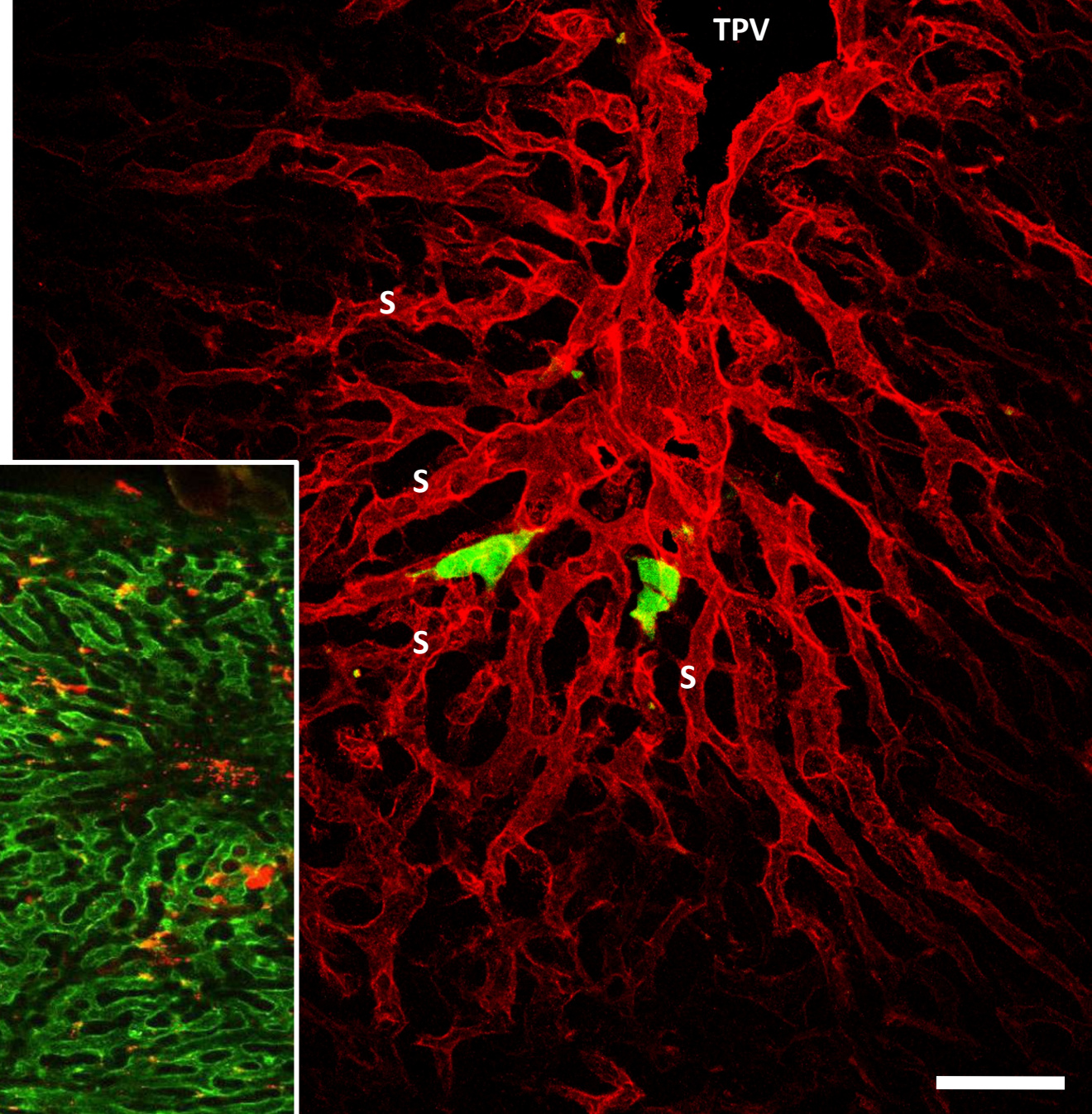
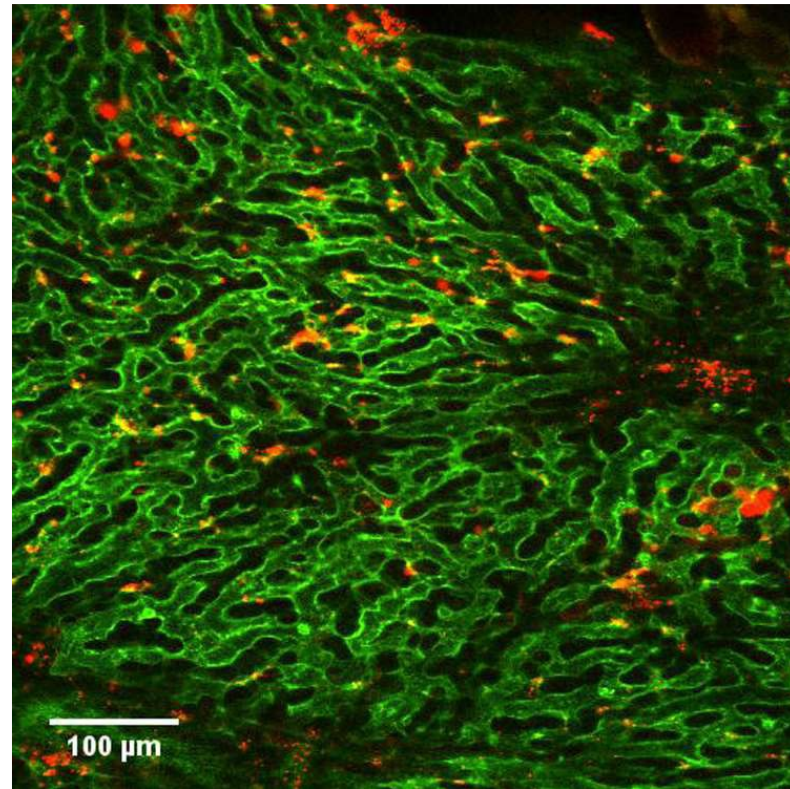
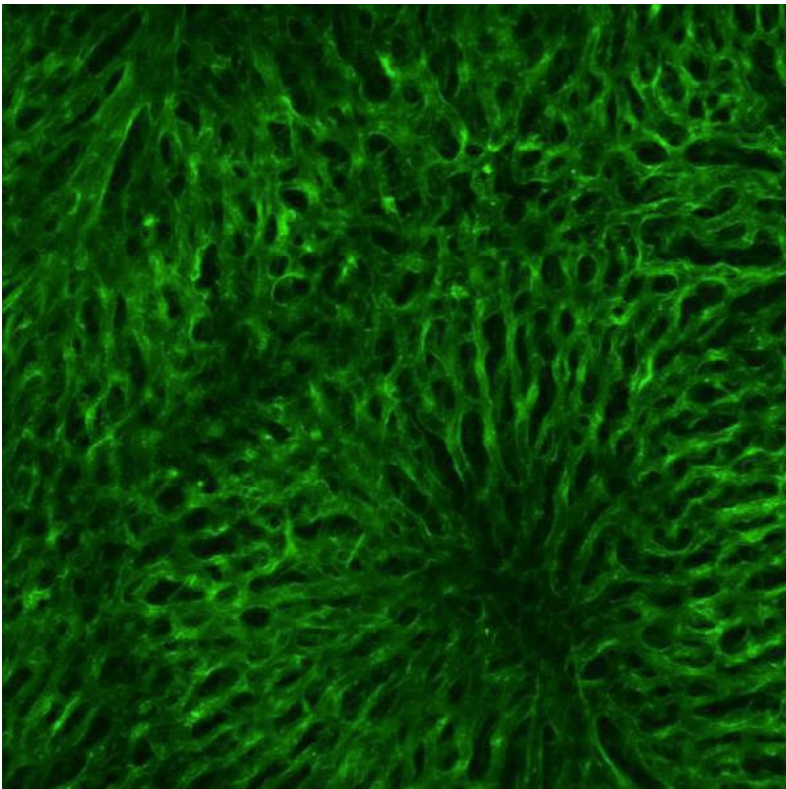


Organ-specific metastasis patterns.  
Organ environment and cancer cell behavior.  
Seed and Soil Theory of Cancer Metastasis.

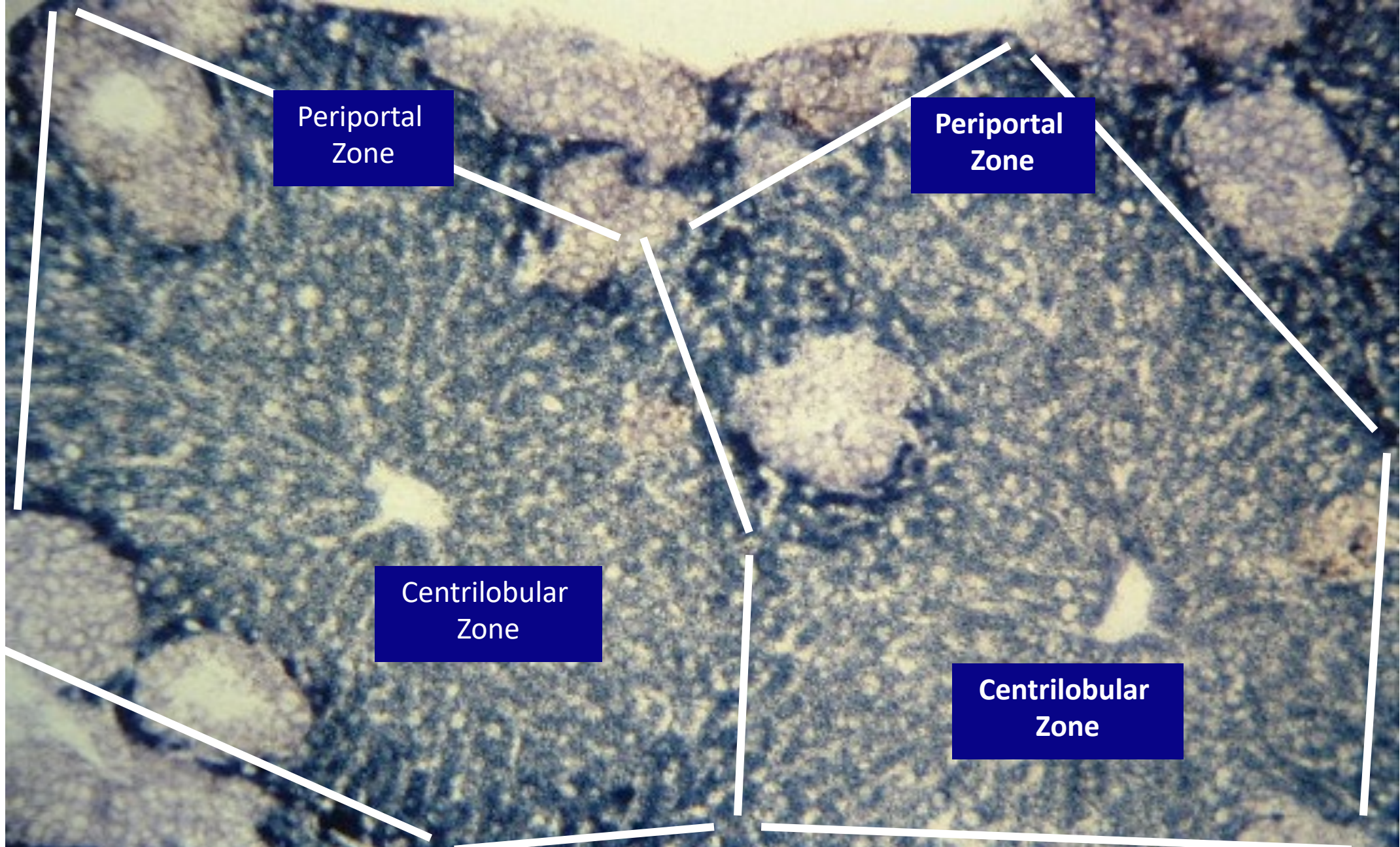
English Pathologist  
Stephen Paget  
(1889)



# INTRAHEPATIC TRAFFICKING OF CIRCULATING CANCER CELLS







Periportal  
Zone

Periportal  
Zone

Centrilobular  
Zone

Centrilobular  
Zone

Barberá-Guillem E, Alonso-Varona A., Vidal-Vanaclocha F. Selective implantation of experimental hepatic metastasis in acinar zone one. *Cancer Res.* 49: 4003-4010 (1989).



# Biology of Cancer Metastasis Process

1) Cancer Cell Invasion at the Primary Tumor Site

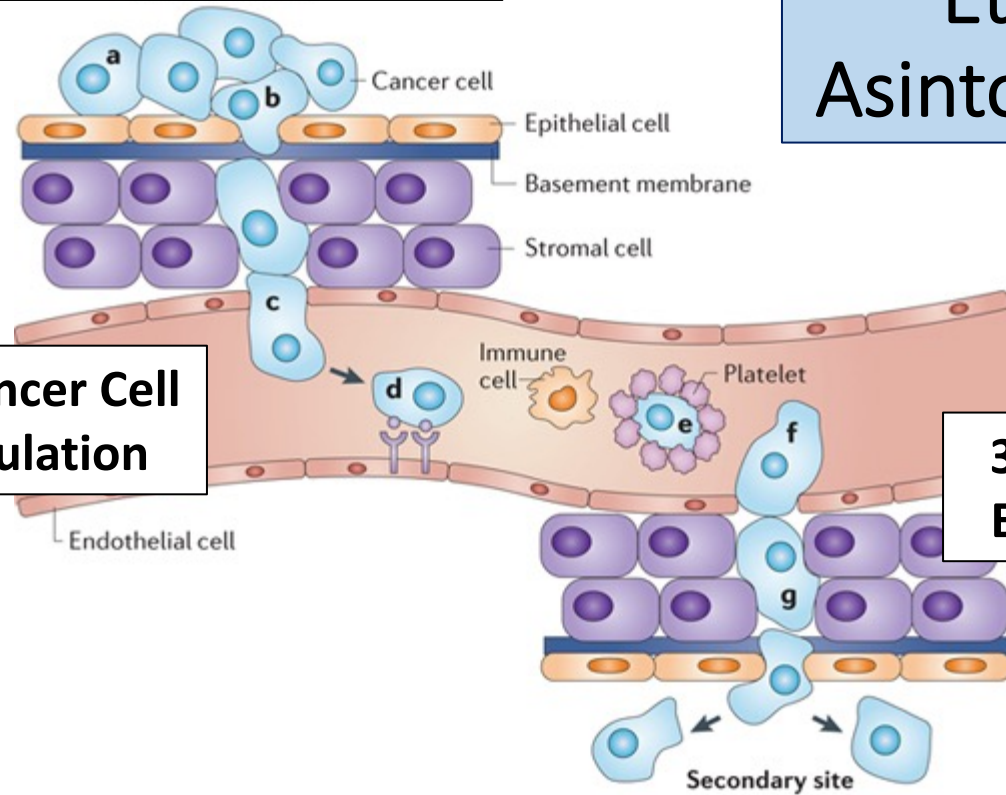
Etapa Asintomática

2) Cancer Cell Circulation

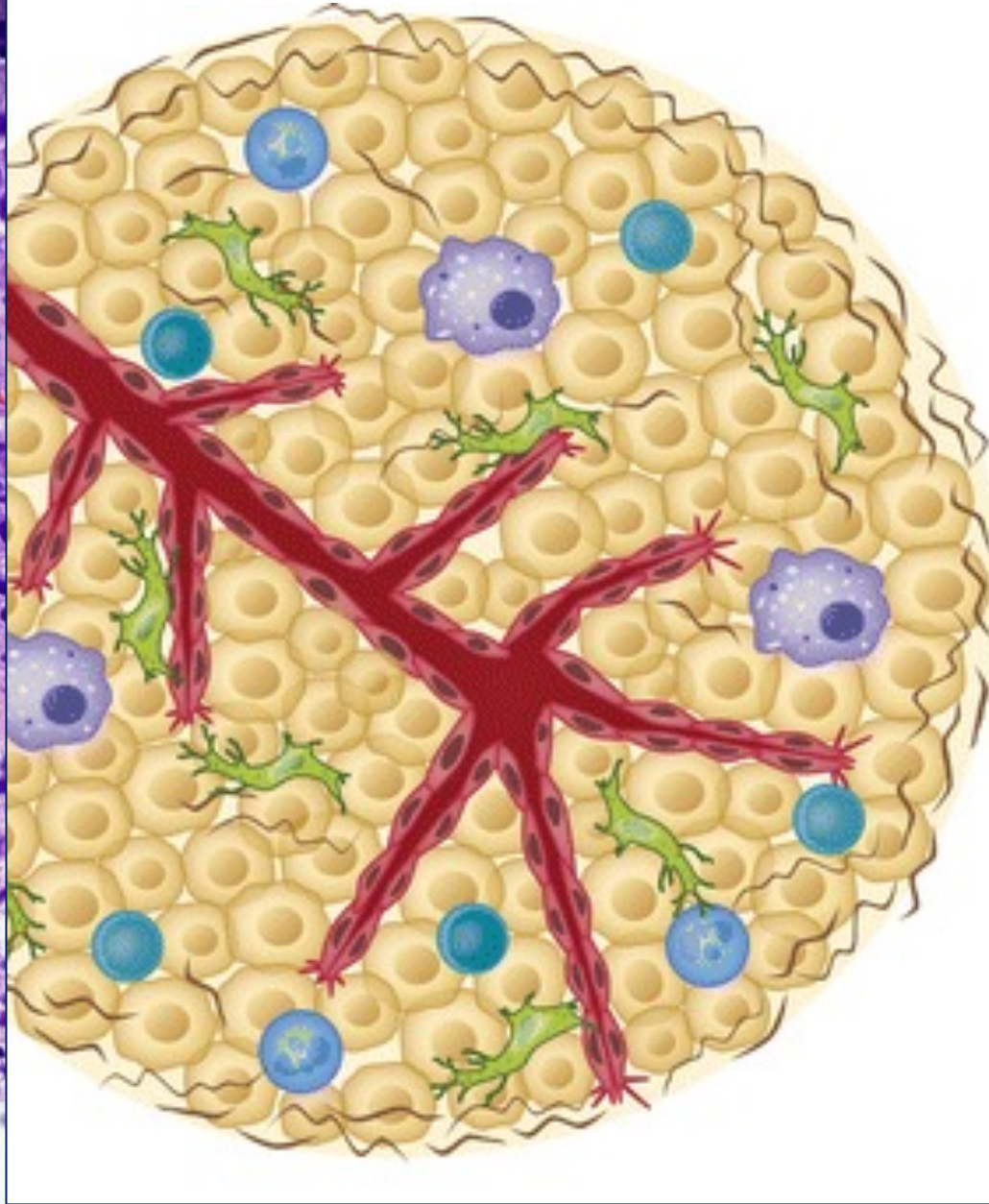
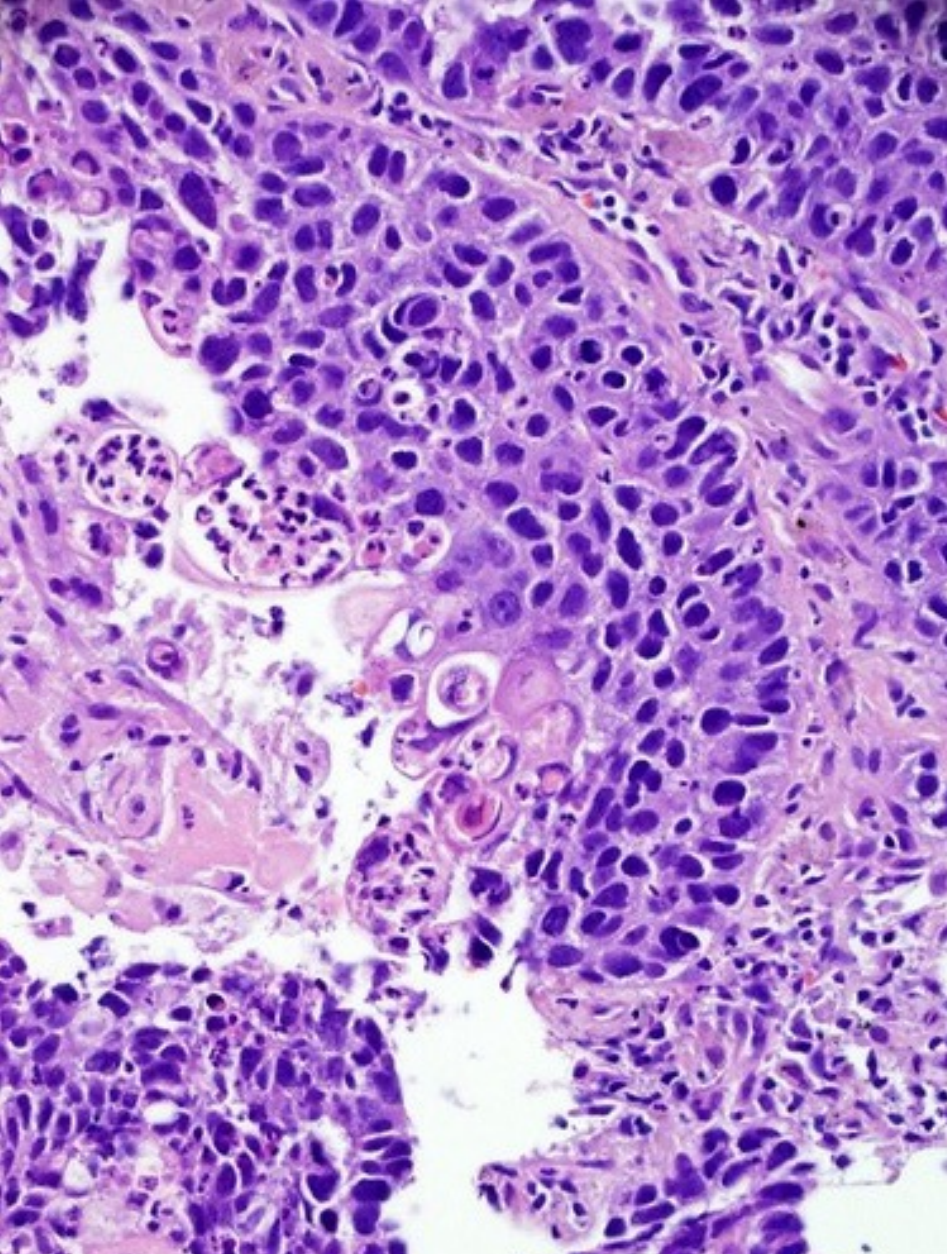
3) Cancer Cell Extravasation








Etapa Sintomática

4) Metastatic cancer Cell Invasion and Growth at a Remote Organ Site





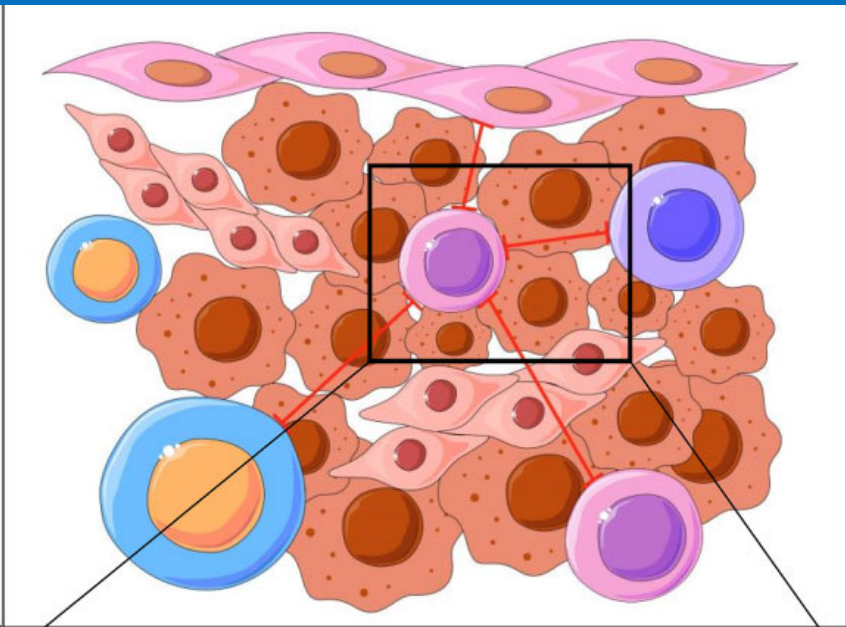
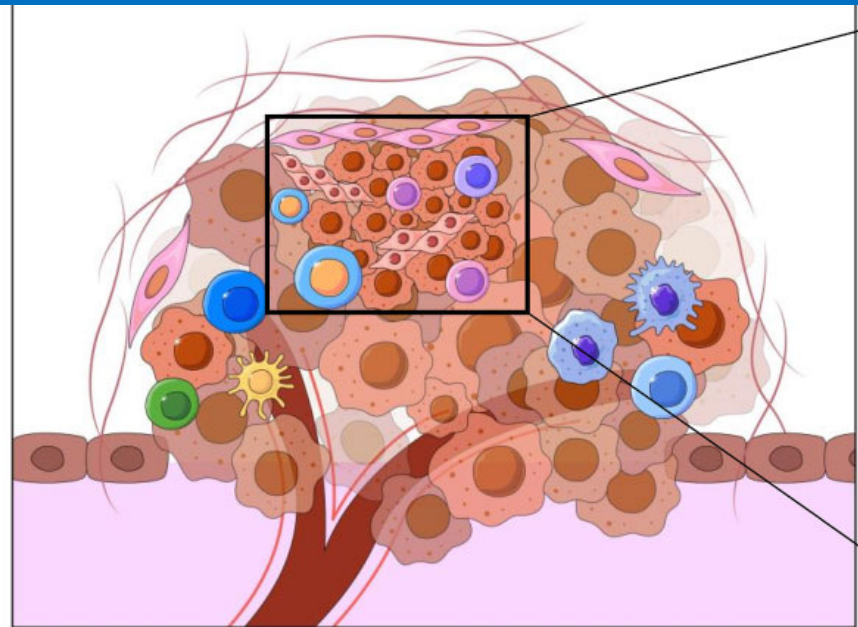




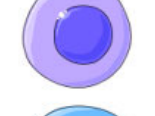







-  Cancer cell
-  Fibroblast
-  T cell
-  Neutrophil
-  Macrophage
-  Endothelial cell
-  Extracellular matrix

# The Cellular Composition of the Tumor Microenvironment

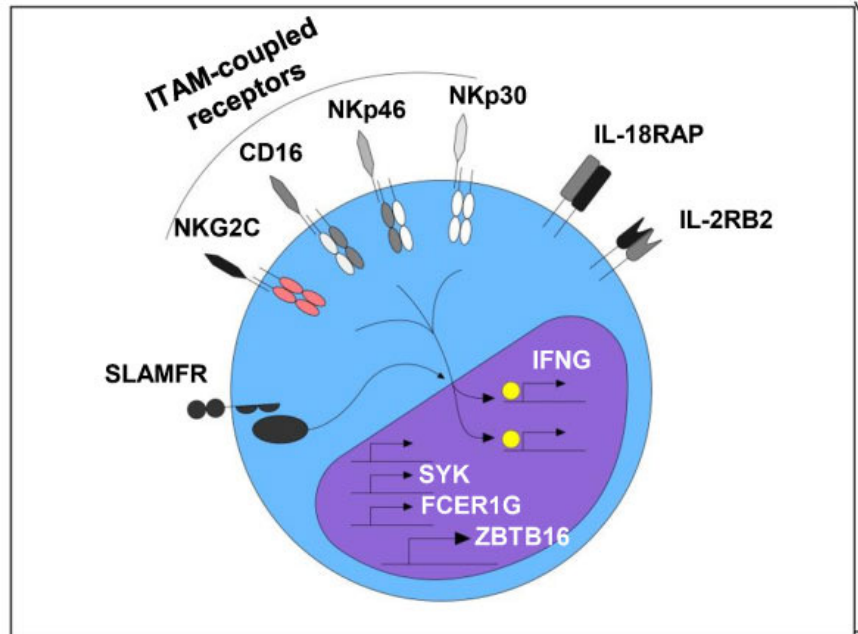


# Transcriptional Immunophenotyping of Developing Cancers

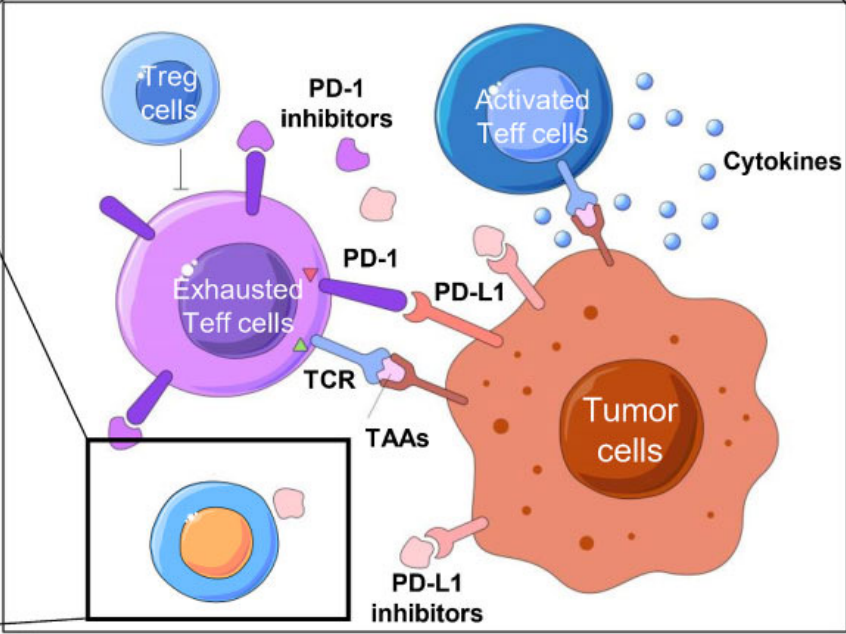


-  Cancer cells
-  Exhausted effector T cells
-  Activated effector T cells
-  Natural killer cells
-  Treg cells
-  Macrophages
-  Dendritic cells
-  B cells
-  MDSCs
-  CAFs

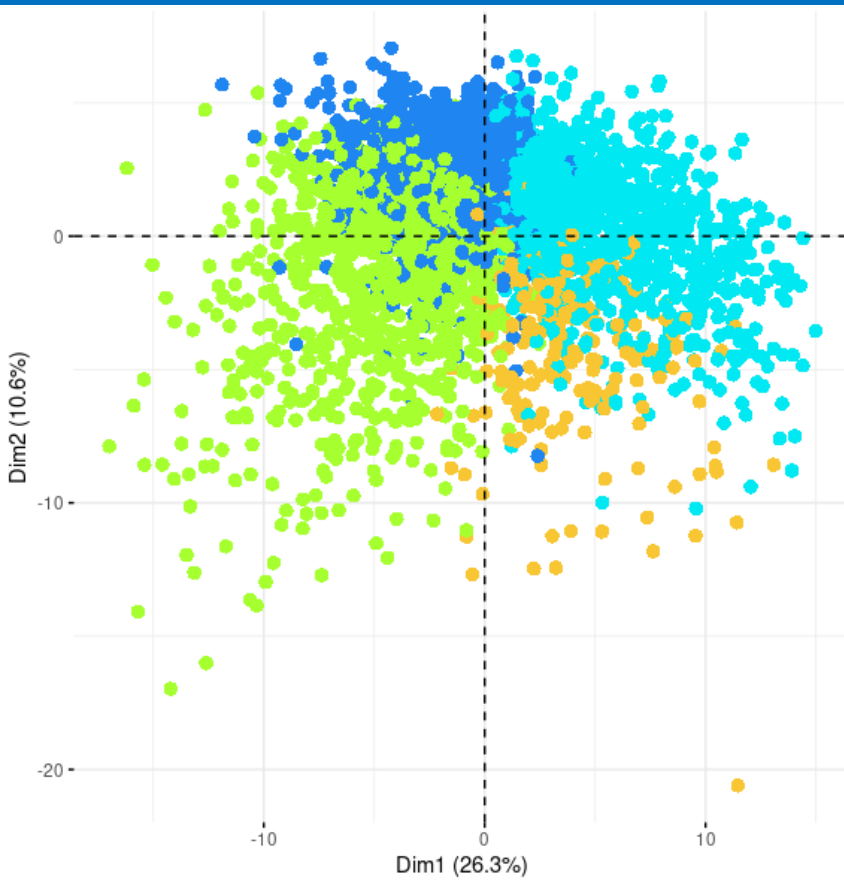
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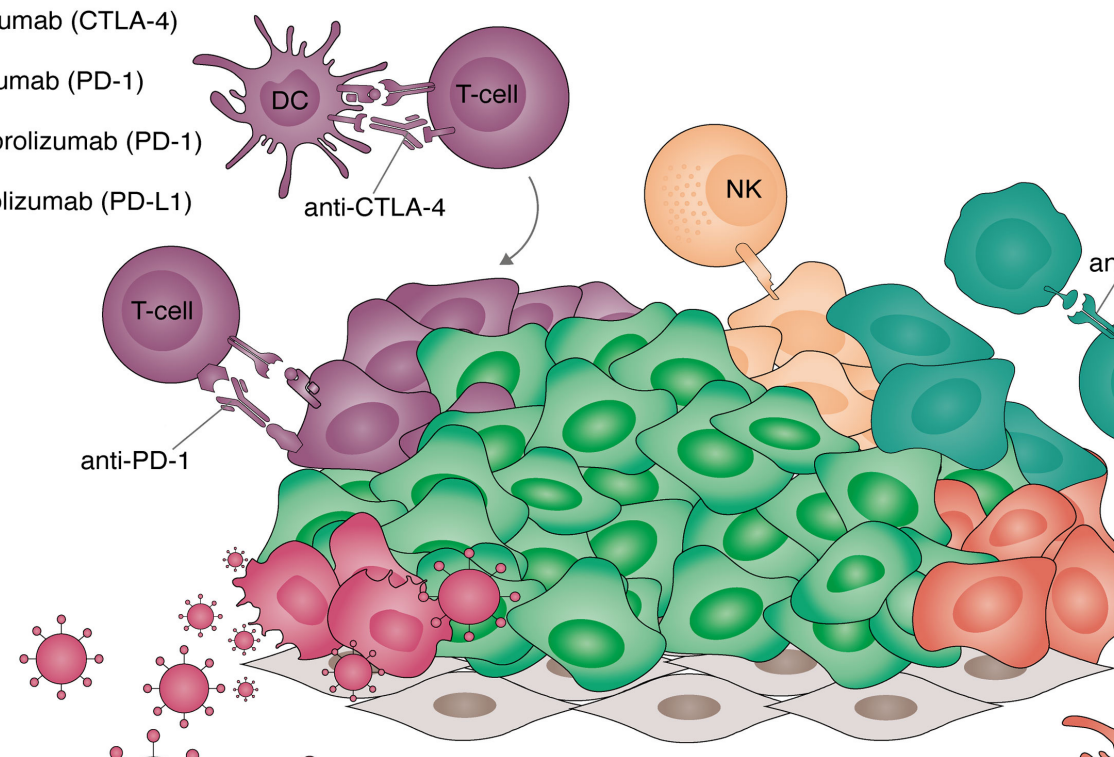


# Cancer Metastasis Immunotherapy



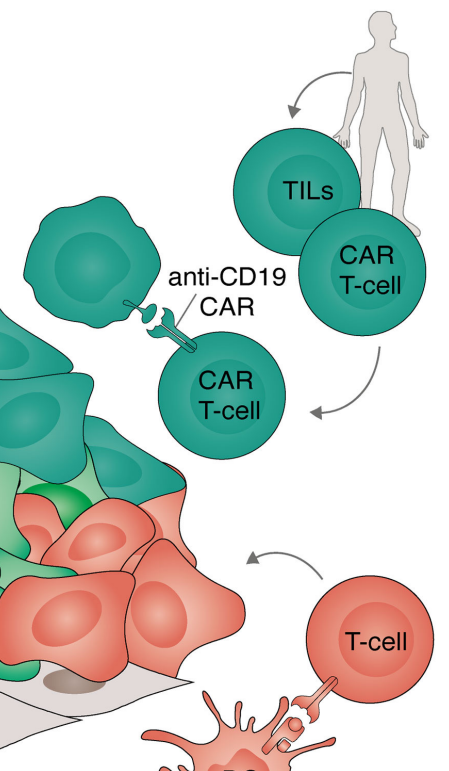
## Checkpoint Inhibitors

- Ipilimumab (CTLA-4)
- Nivolumab (PD-1)
- Pembrolizumab (PD-1)
- Atezolizumab (PD-L1)

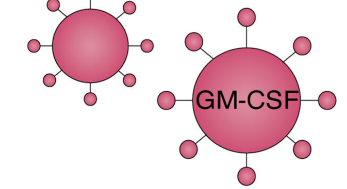


## Adoptive T Cells

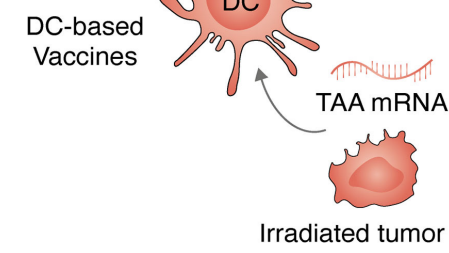
- Axicabtagene Ciloleucel (CD19)
- Tisagenlecleucel (CD19)
- Lisocabtagene Maraleucel (CD19)
- Brexucabtagene Autoleucel (CD19)
- Idecabtagene Vicleucel (BCMA)



- T-VEC



## Oncolytic Viruses



## Cancer Vaccines

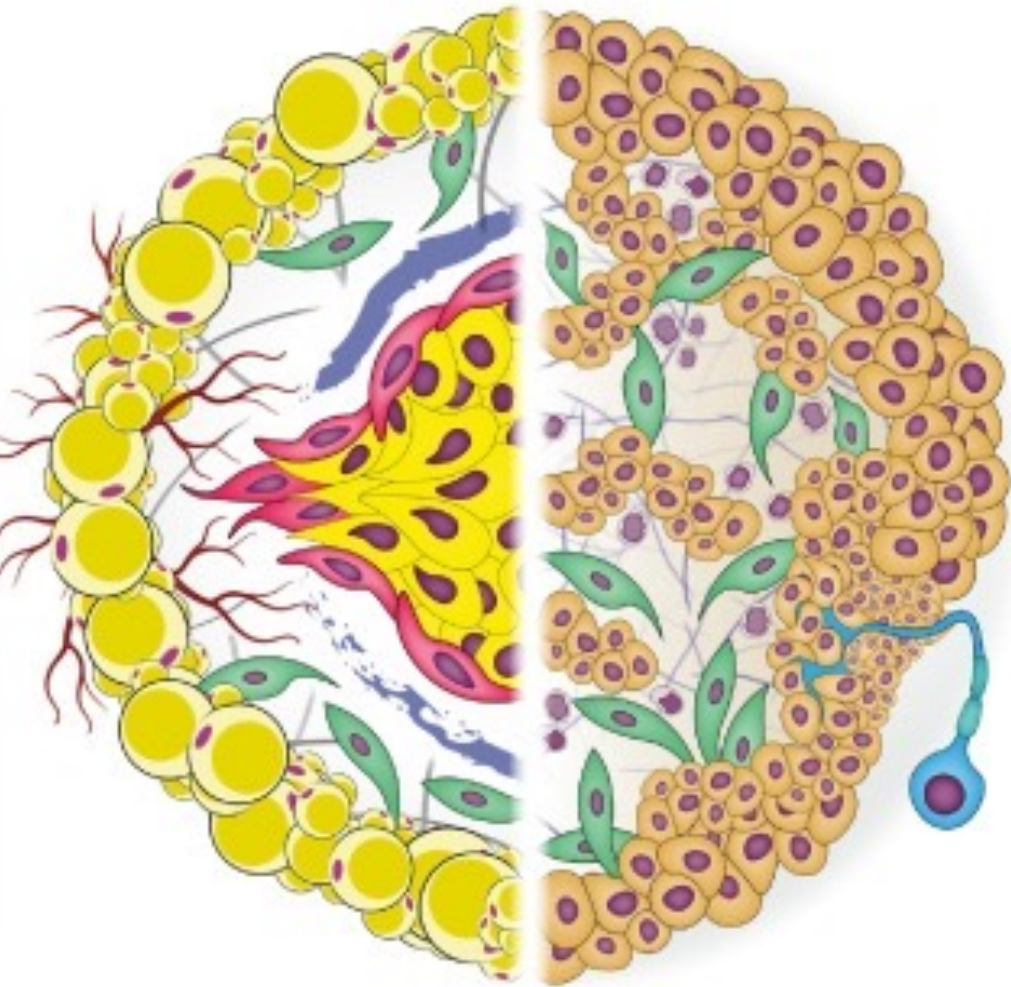
- Sipuleucel-T

- Immune checkpoint inhibitors.
- Adoptive T-cell therapy.
- Cancer vaccines.
- Oncolytic viruses.



Breast tumour

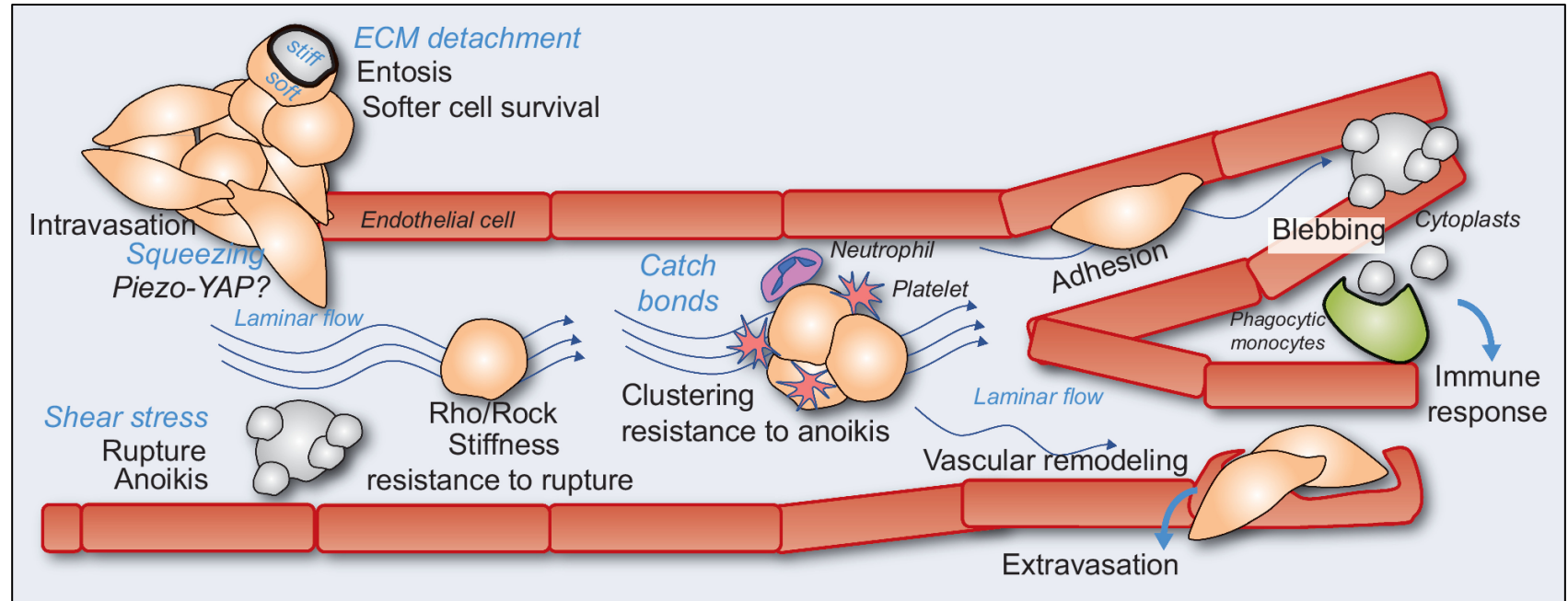
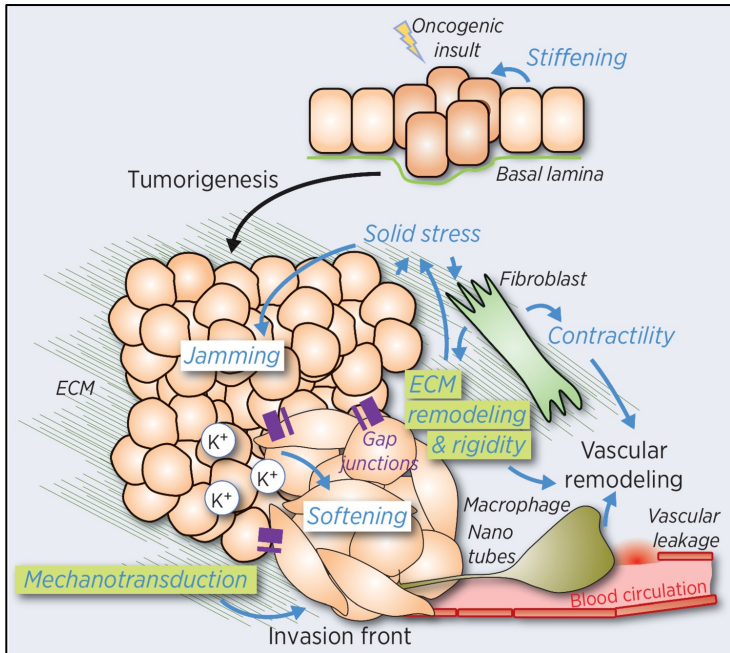
Pancreatic tumour



## Molecules that contribute to the process of cancer metastasis

- Tissue/Organ-specific growth factors (adipokines, hepatokines, hematopoietic factors, etc)
- Immuno-inflammatory molecular mediators.
- Pro-angiogenic factors, extracellular matrix-remodelling molecules.
- Transcription factors that regulate tumor invasion-metastasis. (Slug, Snail, Goose-coid, Twist, and ZEB1)
- Genes associated with embryogenesis, tissue morphogenesis, and wound healing.
- Reactive oxygen species and antioxidants.
- Metabolic factors
- Mechano-sensing factors

# Biophysical forces act at multiple stages of the metastatic process

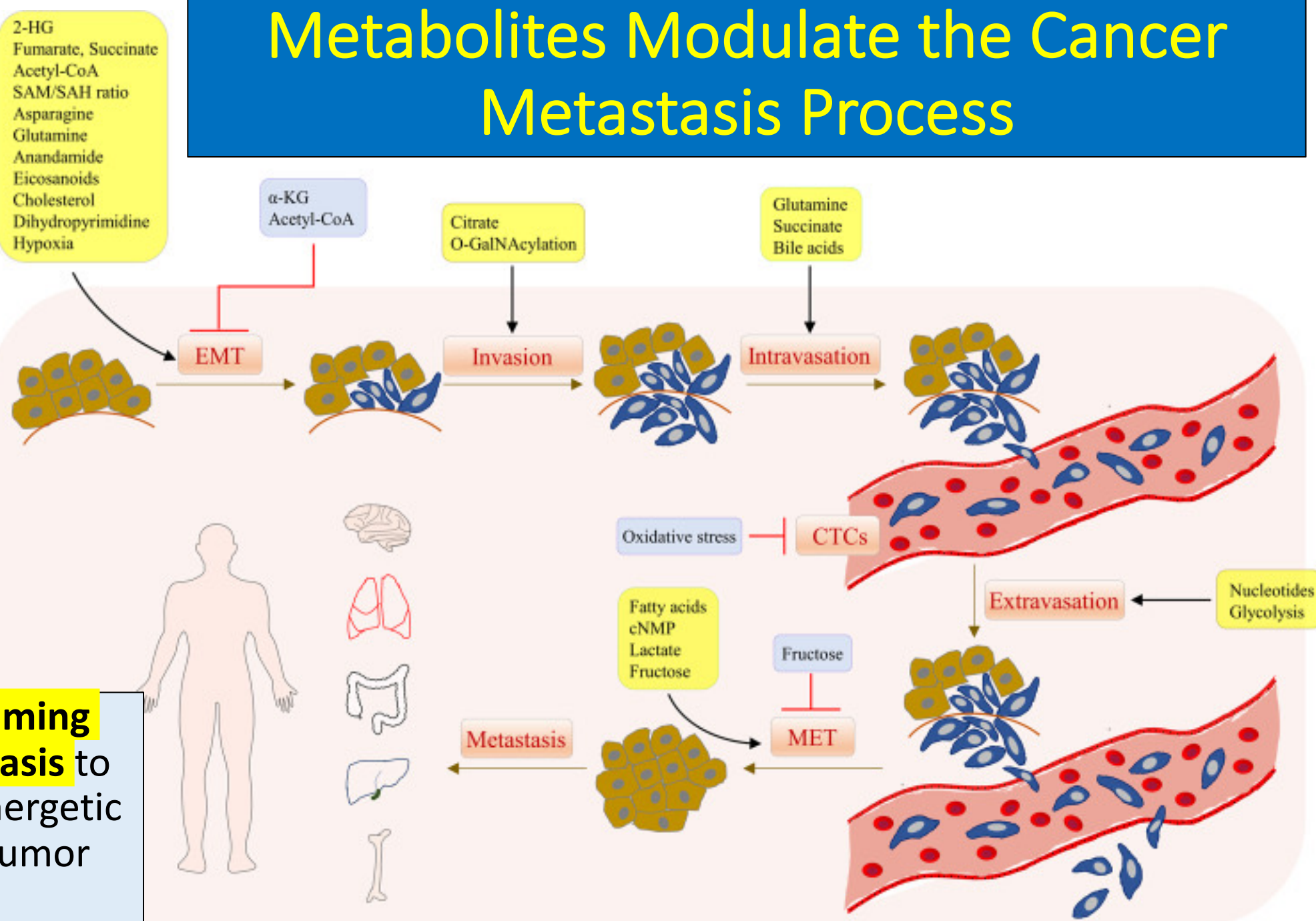




# Metabolites Modulate the Cancer Metastasis Process

## Role of metabolites in different stages of the cancer metastasis:

- Epithelial-mesenchymal transition (EMT)
- Invasion, intravasation, survival in circulation.
- Extravasation and outgrowth into detectable metastasis.



**Metabolic reprogramming during cancer metastasis** to meet the changing energetic requirements at the tumor microenvironment

# Biological Mechanisms of Cancer Metastasis

- **The Clonal Selection model:**
  - Primary cancer cells with the genetic prerequisites for metastasis.
  - The cell subpopulations that metastasize.
- **The Cancer Stem Cell (CSC) model:**
  - CSCs are the only cell subset initiating tumor invasion and growth.
  - They have all of the necessary attributes to result in a metastasis.
- **The Epithelial-Mesenchymal Transition (EMT) model:**
  - The loss of epithelial properties (cell-cell adhesion and junction, polarity).
  - The gain of mesenchymal properties (ability to invade through extracellular matrix).
- **The Prometastatic Niche model:**
  - Primary tumors release soluble factors that remotely induce an appropriate or permissive organ environment prior to the seeding of metastatic cells in the secondary target organ.
- **The Genetic Metastasis model:**
  - Prometastatic gene signatures expressed by cancer cells and predictive of metastasis.
  - They often occurred early during tumor progression.
  - They classify tumors into metastasis risk subtypes and differential treatments or no treatment.
- **The Immunocarcinogenic Metastasis model:**
  - Prometastatic gene signatures expressed by cancer cells and predictive of metastasis.



# Cancer Pathogenesis

Patient Genetics & Life Style & Psycho-Social Profile & Pathophysiologic Background

Cancer Cell & Soluble Factors

Tumor Microenvironment

Paraneoplastic Syndrome

# Pathophysiology of the Cancer Patient

Interorgan Prometastatic Communication

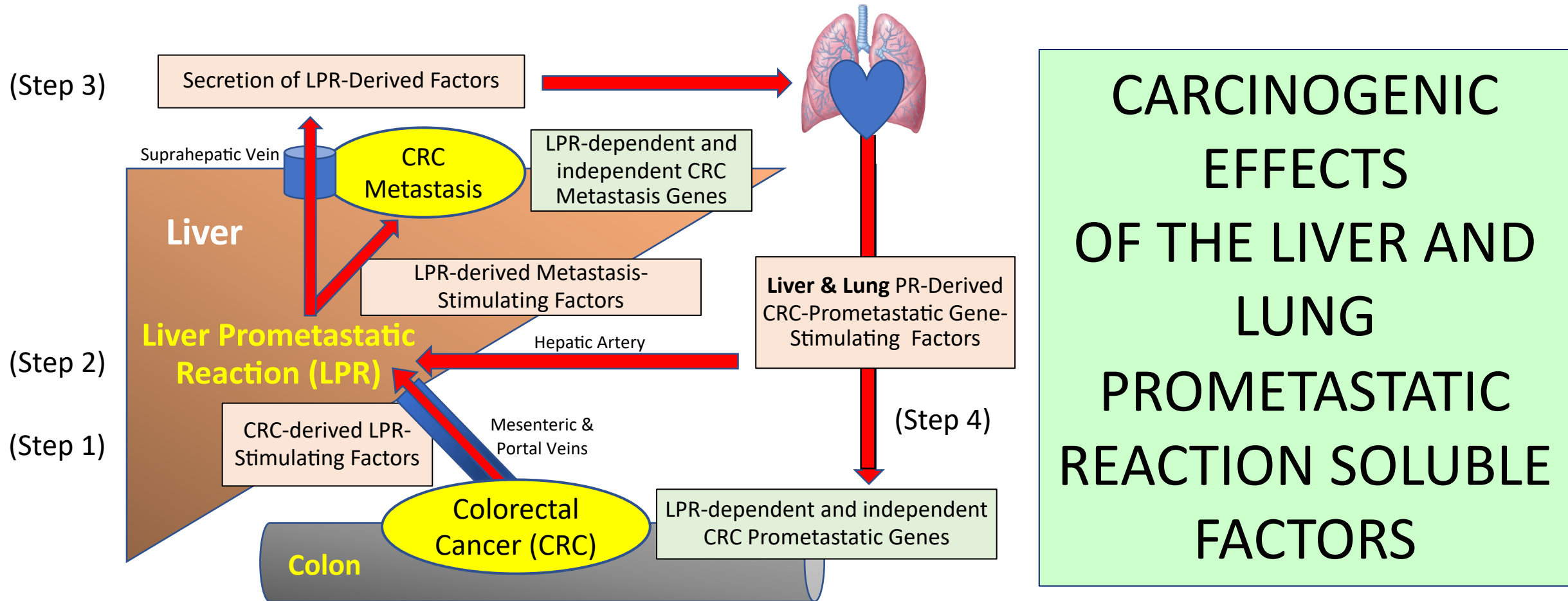
Organ-Specific Prometastatic Reaction-1

Organ-Specific Prometastatic Reaction-2

Pre/Prometastatic Niches

Pre/Prometastatic Niches

# Colorectal Cancer soluble factor-Triggered Liver Prometastatic Reaction and Intercommunication Axis\*



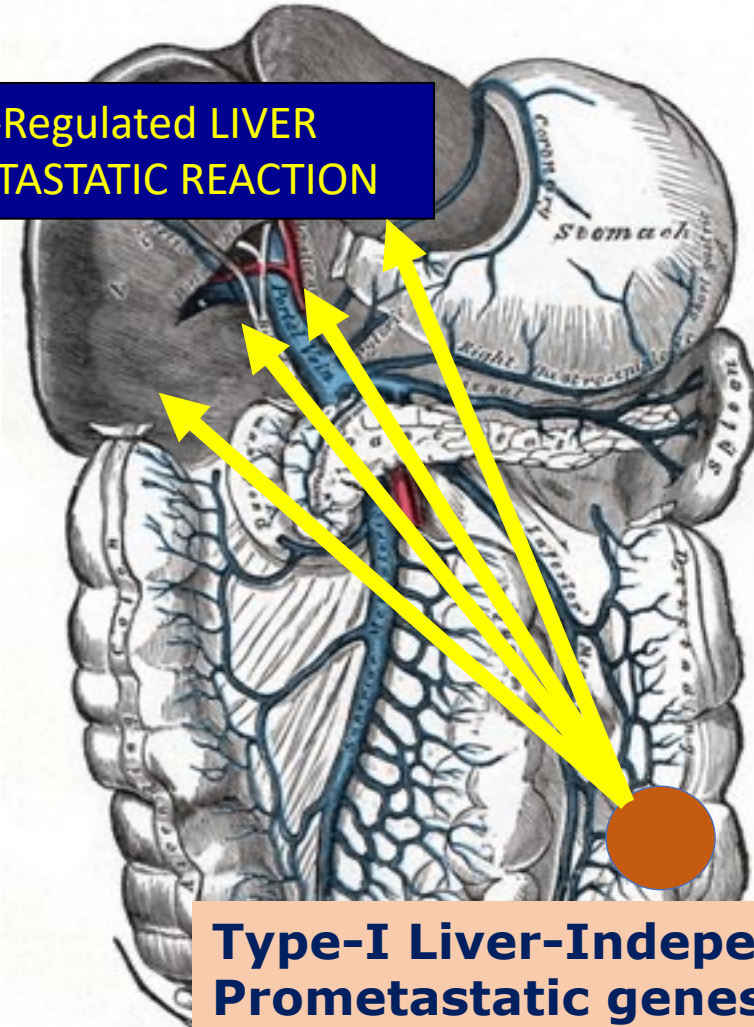
\*Vidal-Vanaclocha F, Crende O., Sotomayor EM. Liver prometastatic reaction: Stimulating factors and responsive cancer phenotypes. Semin Cancer Biol. 2020:S1044-579X(20)30171-1. doi: 10.1016/j.semcancer.2020.08.001.



# Colorectal Cancer Prometastatic Genes inducing (Subtype I) and regulated by (Subtype II) the Liver Prometastatic Reaction

(Step I)

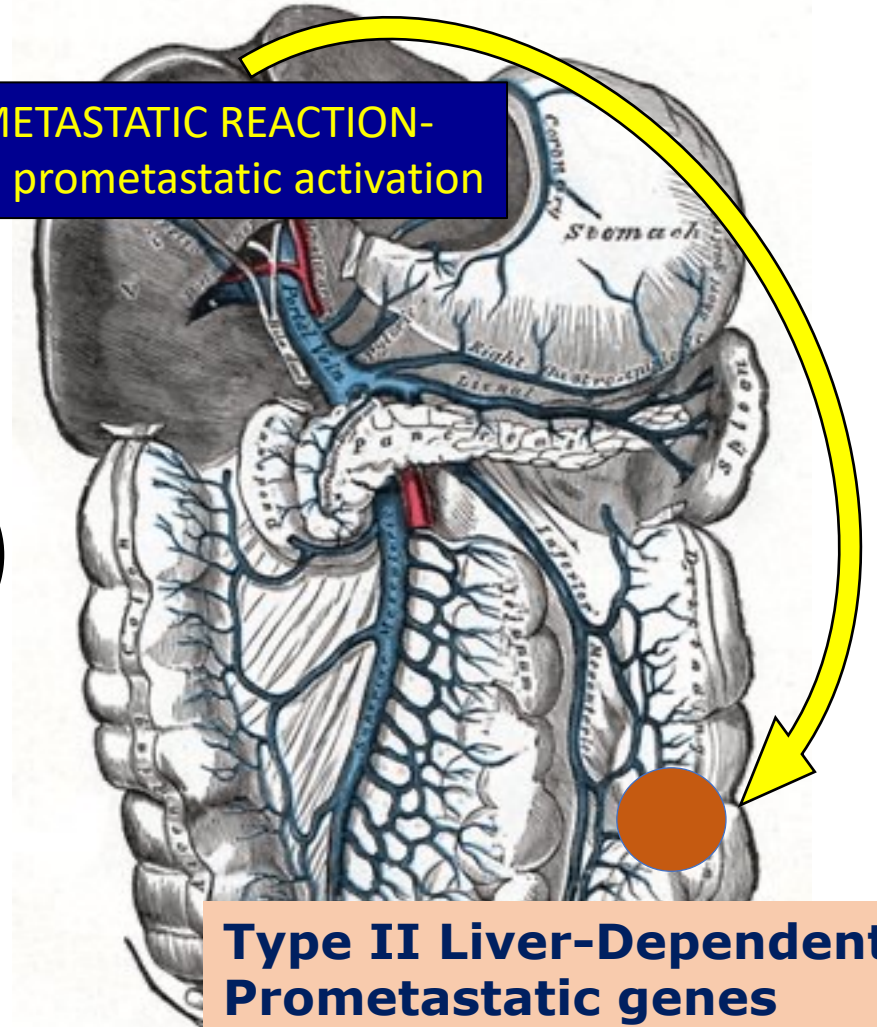
CRC-Regulated LIVER PROMETASTATIC REACTION



**Type-I Liver-Independent Prometastatic genes** remotely inducing the Liver Prometastatic Reaction

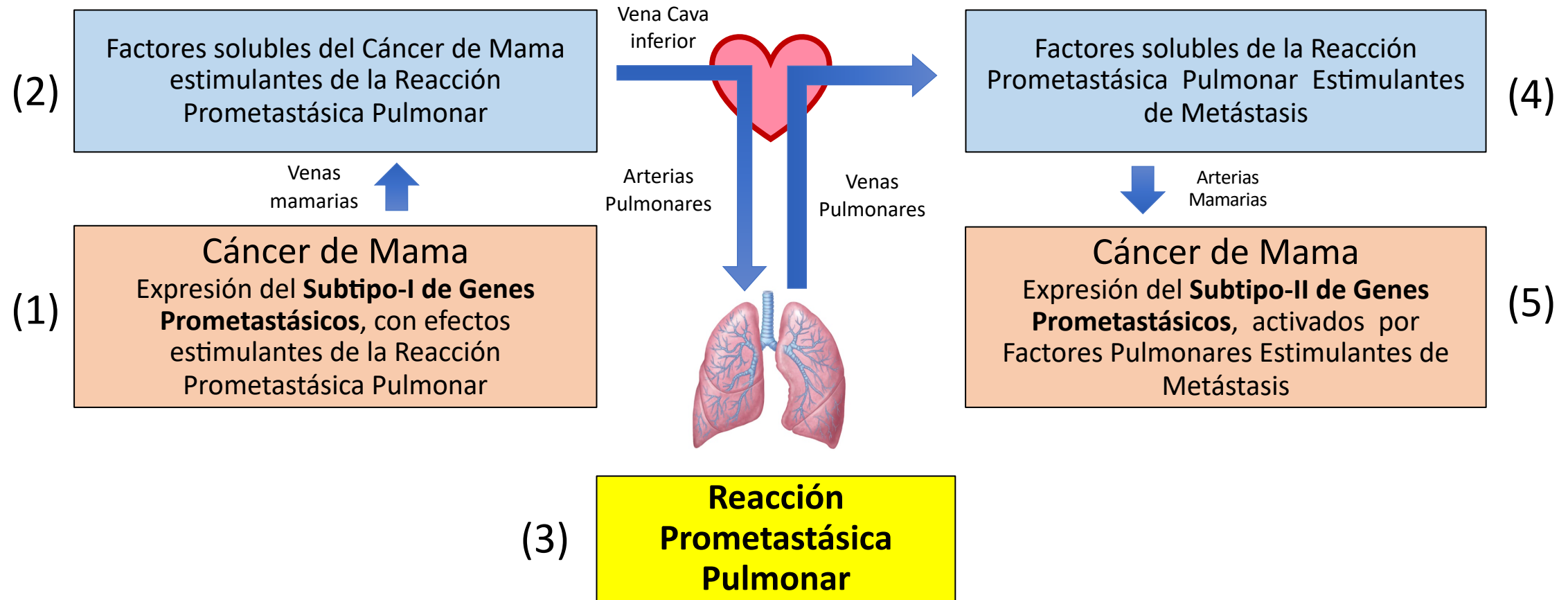
(Step II)

LIVER PROMETASTATIC REACTION-Regulated CRC prometastatic activation



**Type II Liver-Dependent Prometastatic genes** remotely regulated by LPR-Stimulating factors

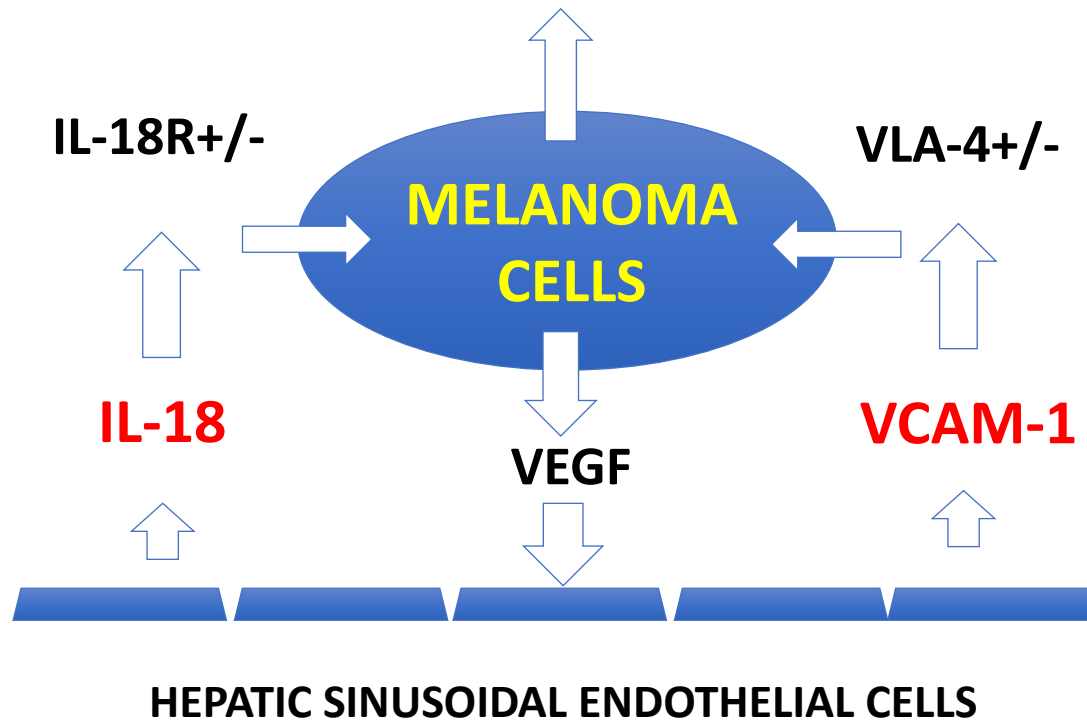
# Regulación Prometastásica del Cáncer de Mama: Subtipos de Genes asociados a la Reacción Prometastásica Pulmonar



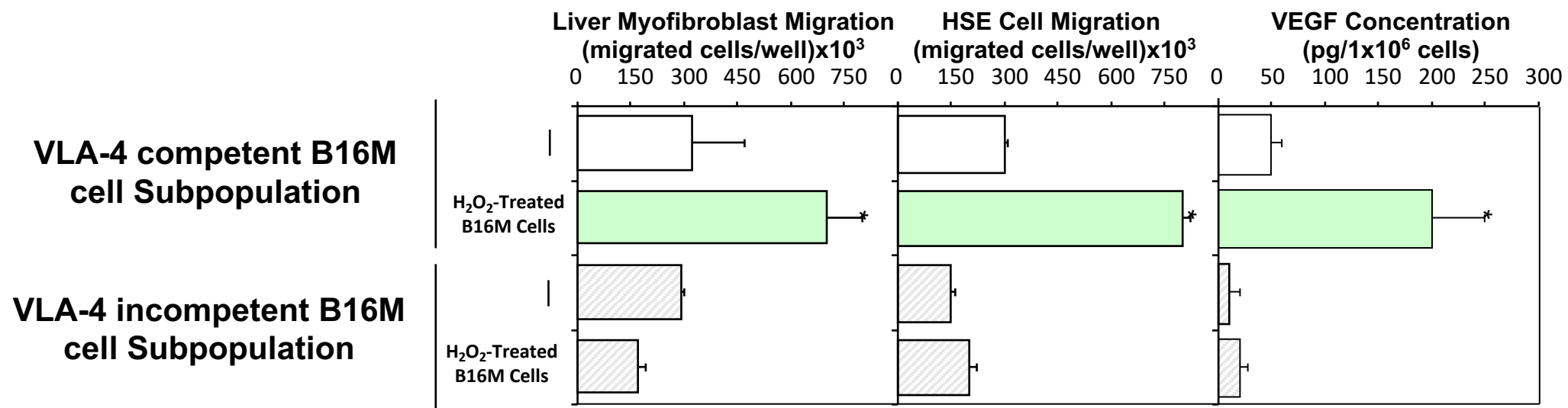
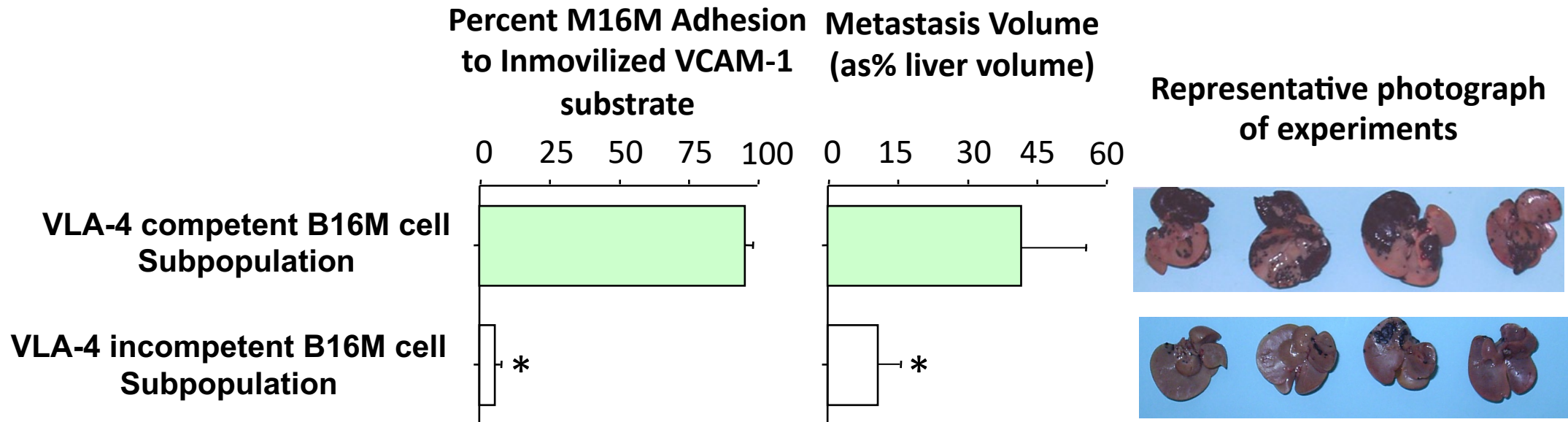


# The Liver Prometastatic Reaction Responsive Melanoma: Signature genes in metastatic lesions from patients with Stage-IV melanoma

**GENE EXPRESSION PROFILING of THE LIVER PROMETASTATIC REACTION RESPONSIVE MELANOMA (including CSC/ICP genes)**

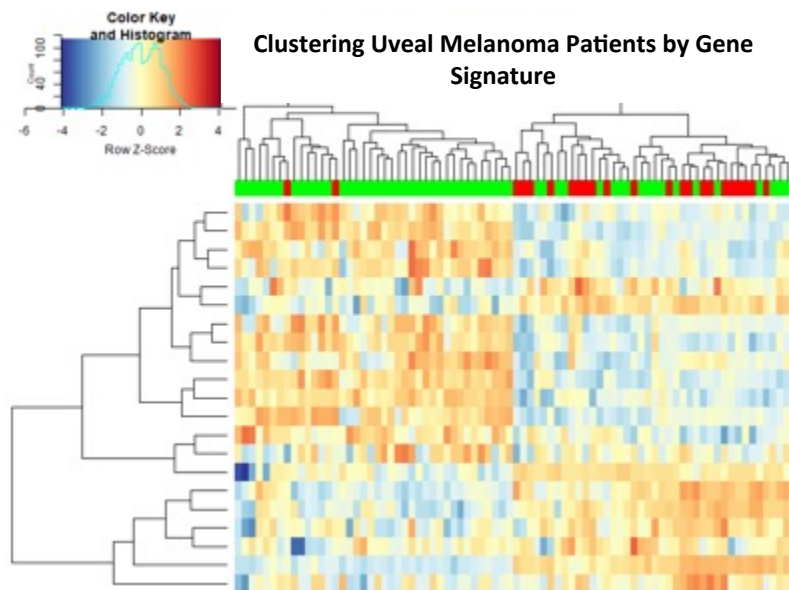
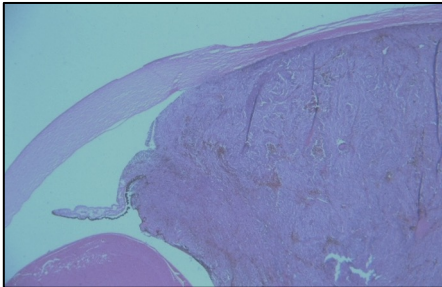


# The Liver Prometastatic Reaction Responsive Phenotype of Intrasplically-injected VLA-4-expressing B16 Melanoma Cells

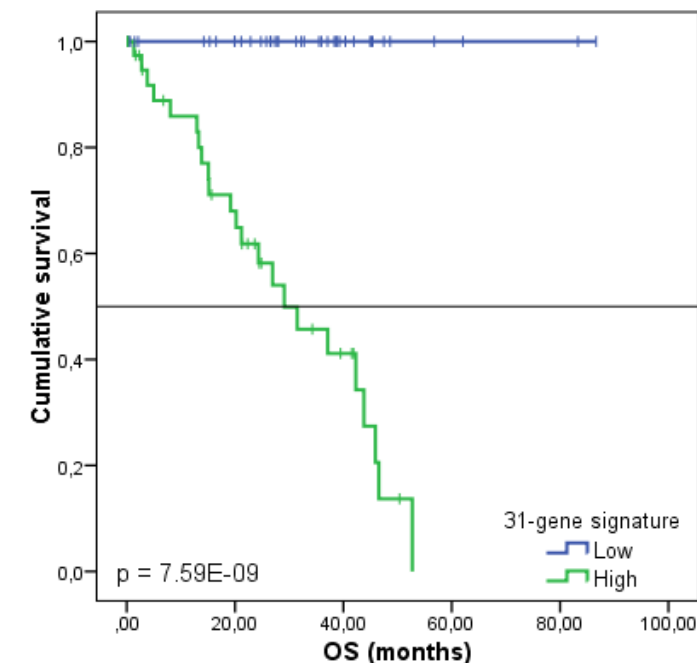




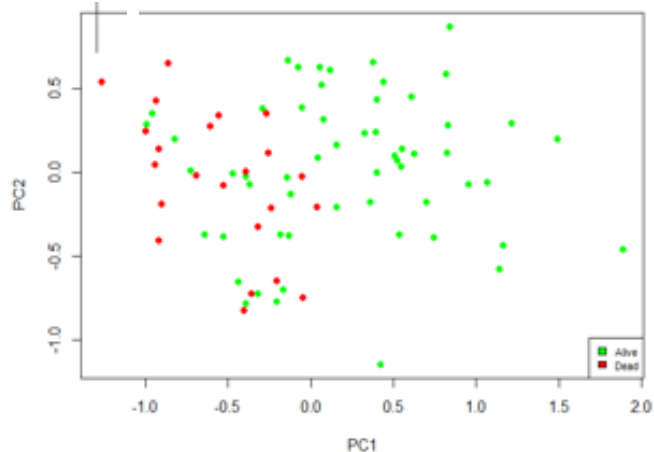
# VLA4-Regulated Prometastatic Gene Signature to Identify and Treat Patients with Recurrent Uveal Melanoma



- Each year there are around 5,000 cases of **eye melanoma** in the USA
- **Melanoma** of the eye spreads to the liver and leads to **death** in 40% of patients.
- **Melanoma cell response to liver prometastatic reaction molecules defines a gene signature to predict and treat recurrent uveal melanoma**



Sorting Uveal Melanoma patients by Overall Survival Rate



## The results of the Prometastatic Gene Signature allow:

- To predict metastatic recurrence.
- To decide follow-up level, including appropriate imaging and blood screening of circulating melanoma cells.
- To open possibilities for FDA-approved target-oriented therapies

# Cancer Metastasis: From Biological Concepts to Precision Medicine Deployment

(1)

- **Prometastatic Risk Clinical Management.**

- Prometastatic gene expression signatures at early cancer stage.
- Prometastatic target organ reaction.

(2)

- **Organ-Site Specific Occult Micrometastasis Risk.**

- Liver, Brain, Lung, Bone Marrow

- **Immunocarcinogenic phenotyping.**

- Transcriptional Immunophenotype.
- Immunometabolic phenotype.