

UNIVERSITY OF AARHUS

28-30 March 2022

**Training school for detection and analysis of circulating tumor DNA
(ctDNA) and circulating tumor cells (CTC)**



Biology of CTCs

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Biobanking : plasma – cells (>10 years)
 (associated biological & clinical data plus CTC count)

→ **Detection of other circulating biomarkers**

Technological challenges

Clinical trials

Precision medicine

Biopsie liquide

CTC
 micRNA
 Exosomes
 ctDNA

plaquelettes

Cancer biology

CANCERS

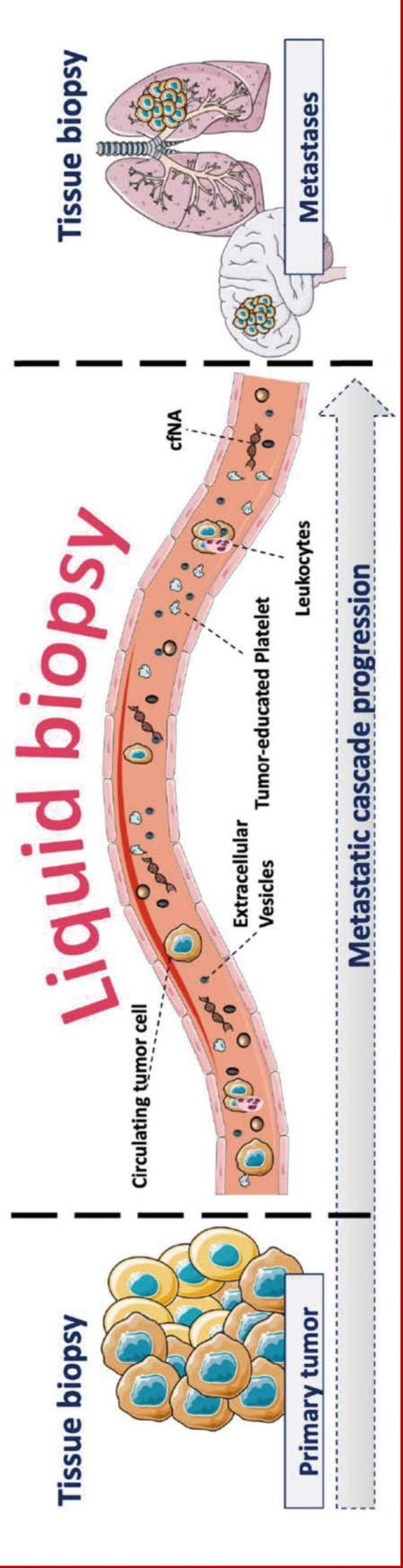
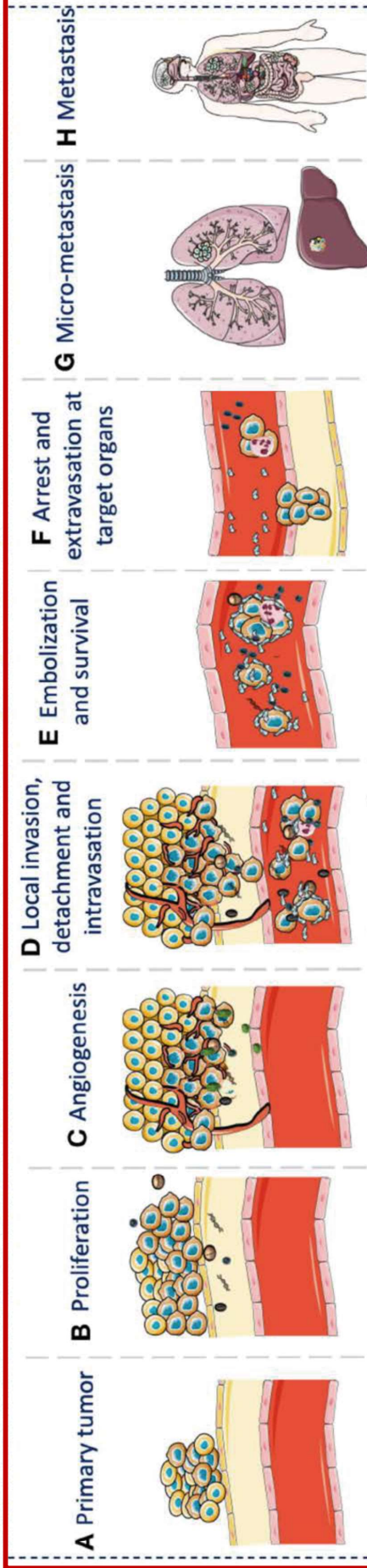
- Breast
- Ovarian
- Cervix
- Endometrial
- Prostate
- Colon
- Rectum
- Pancreas
- Lung
- Head & neck
- Low-grade glioma
- Melanoma
- Merkel cell carcinoma

Liquid Biopsy

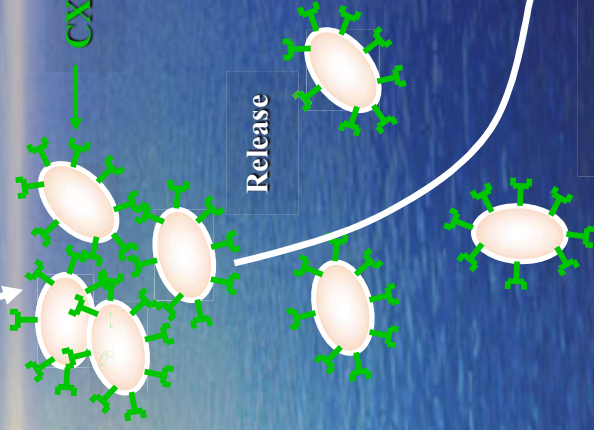


Objectives of the lesson

1. To define the notion of '*metastatic cascade*' in solid cancers
2. To define the notion of '*liquid biopsy*' in solid cancers
3. To know the biology of CTCs:
 - Hallmarks of CTCs
 - Epithelial-to-mesenchymal plasticity (EMP)
 - CTC clusters
 - Metastasis-initiator CTCs (MIC) with stemness
 - Tumor heterogeneity

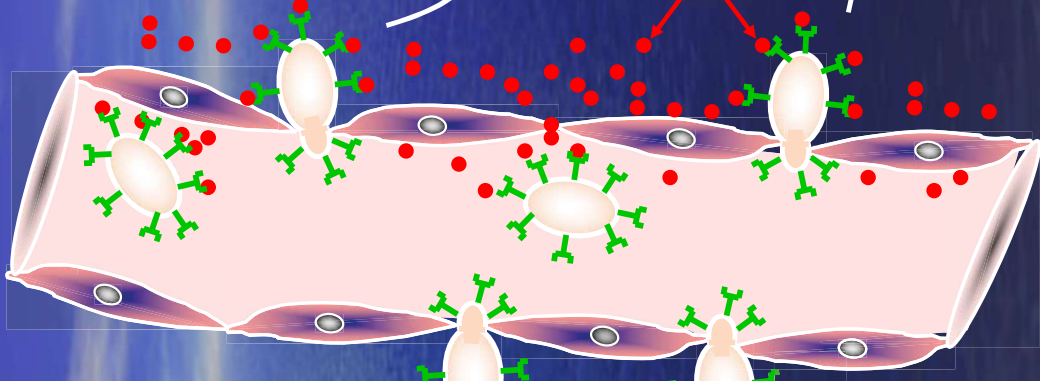


Breast

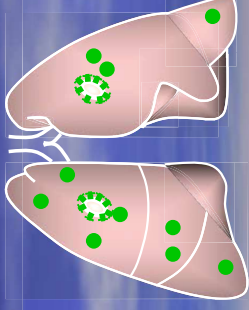


Migration and entry in the circulation

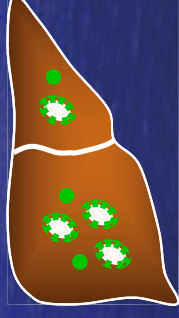
Bloodstream



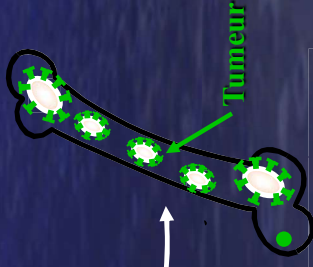
Secondary organs



Lung metastases



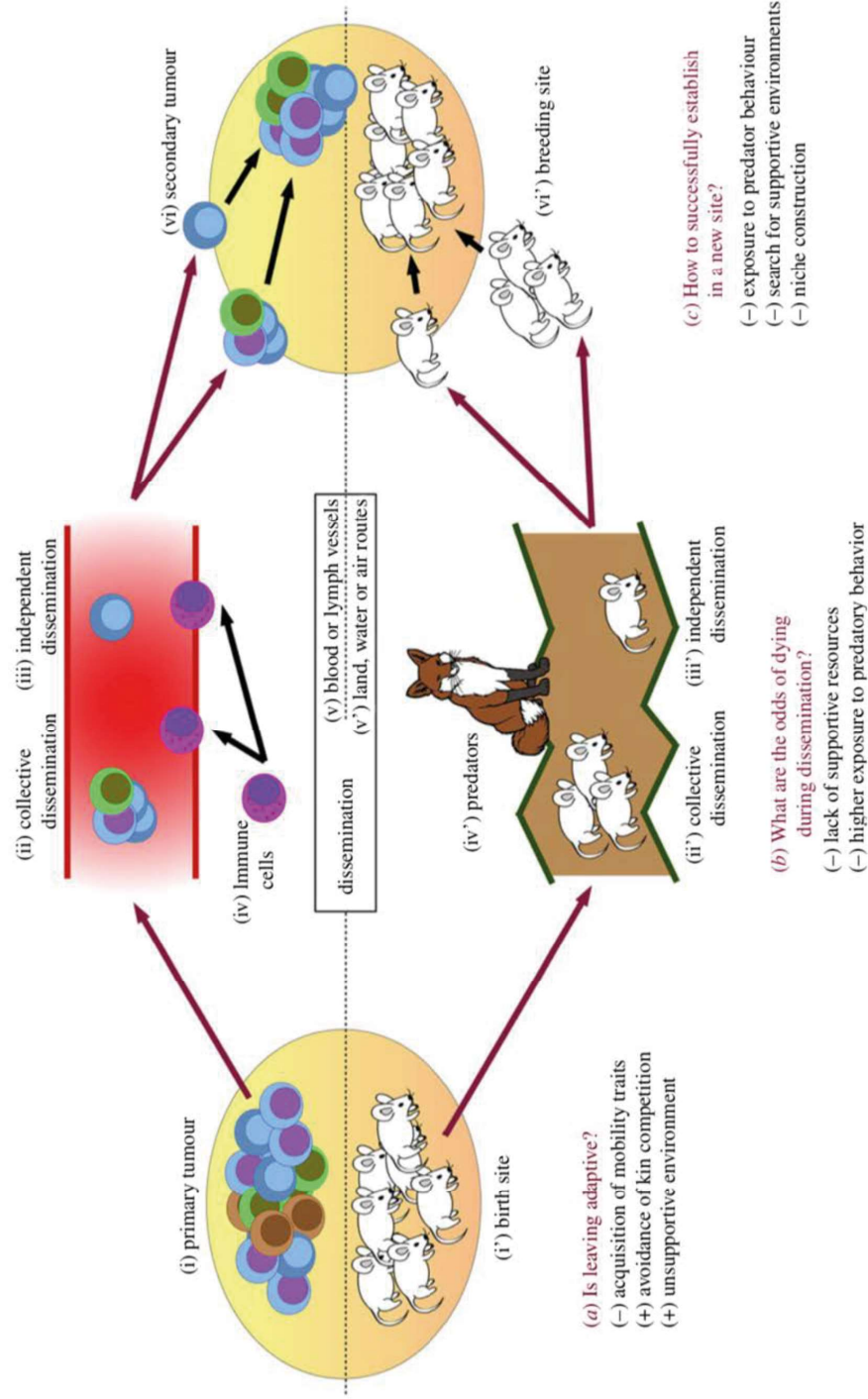
Liver metastases



Bone metastases

Metastasis and the evolution of dispersal

Tazio Tissot^{1,2}, François Massol^{3,4}, Beata Ujvari⁵, Catherine Alix-Panabieres⁶,
Nicolas Loeuille¹ and Frédéric Thomas⁷





Article

Is There One Key Step in the Metastatic Cascade?

Antoine M. Dujon ^{1,2,*}, Jean-Pascal Capp ^{3,t}, Joel S. Brown ⁴, Pascal Pujol ^{1,5}, Robert A. Gatenby ⁴, Beata Ujvari ^{2,6}, Catherine Alix-Panabieres ^{1,7,*} and Frédéric Thomas ^{1,t}

Drake equation



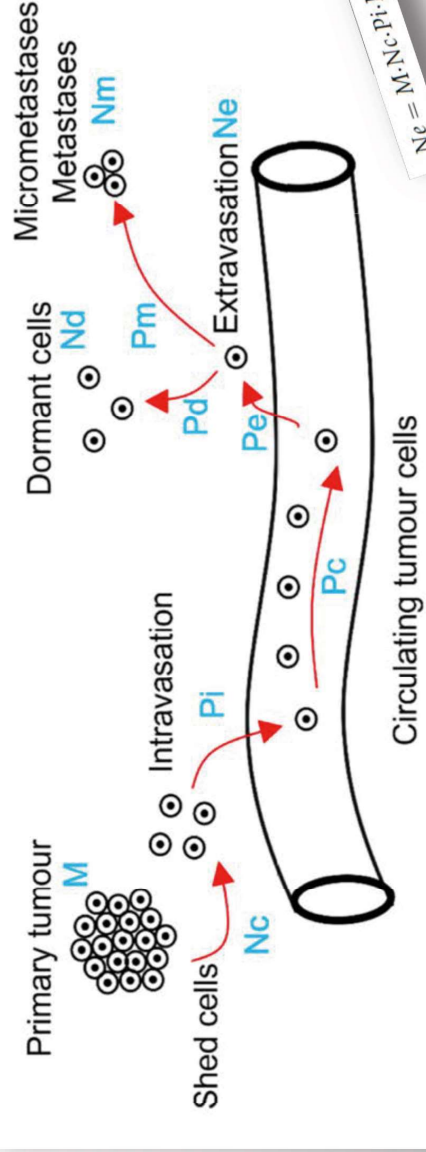
the emergence of intelligent civilizations in the MilkyWay (1961)

- within this framework, we used simulations on breast cancer to investigate the **contribution of each step to the METASTATIC CASCADE**



Frédéric Thomas

The metastatic Drake equation





Is There One Key Step in the Metastatic Cascade?

Conclusion

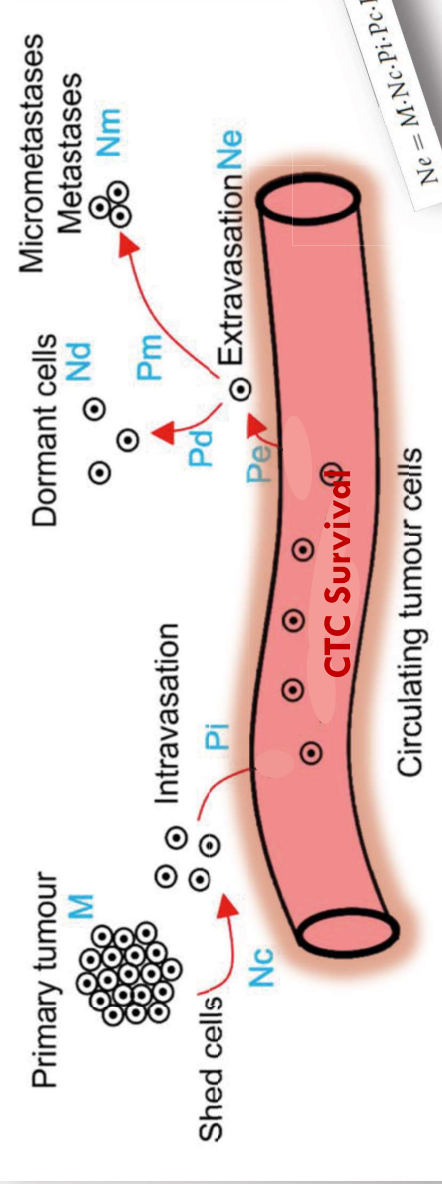
- The most critical parameter governing the formation of clinical metastases is the **survival duration of circulating tumor cells (CTCs)**.
- Administering to people in the second part of life, when most cancers appear, a systematic medication aimed at reducing the life expectancy of CTCs could be highly protective against the eventuality of metastatic cancers, no ?



Frédéric Thomas

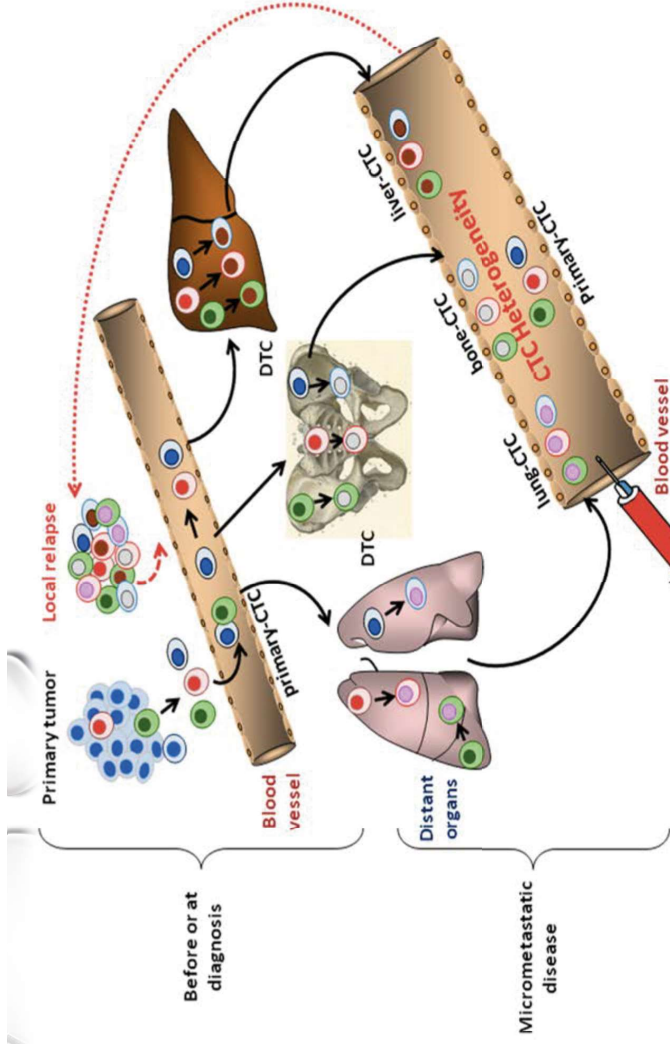


The metastatic Drake equation



Real-Time Liquid Biopsy

- Metastases evolve many years after primary tumor resection and can harbor unique genomic alterations
- Biopsy of metastases is an invasive and sometimes dangerous procedure
- Intra-patient heterogeneity of metastases at different sites
- CTC/ctDNA might reveal representative information on metastatic cells located at different sites



Genotype/Phenotype: CTCs ≠ Primary Tumor

Patient (Stratification Monitoring) → Personalized Therapies

DRUG RESISTANCE ?

CTCs	Treatments
PROTEINS	
ER+	Endocrine therapy
Her2/ <i>neu</i> +	Trastuzumab
DNA MUTATIONS	
KRAS mutations	EGFR targeted therapies
PI3K mutations	HER2/ <i>neu</i> targeted therapies

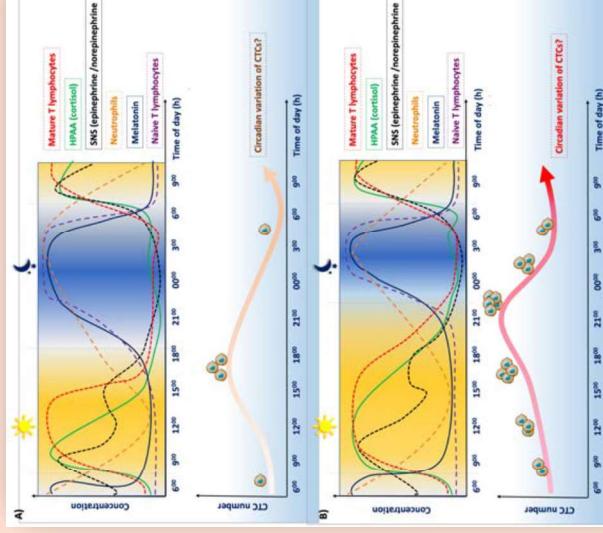
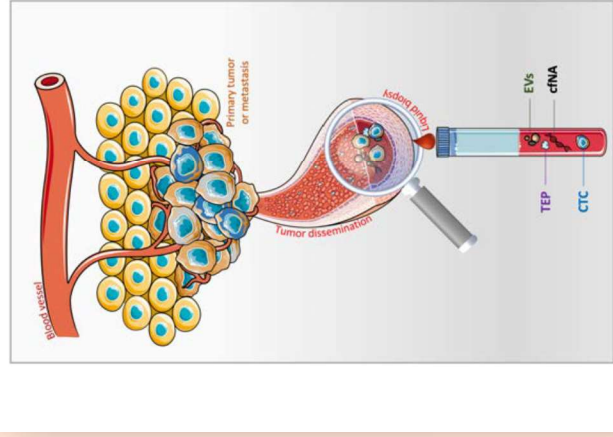
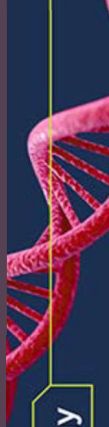
Clinical 2013
Chemistry

Circulating Tumor Cells:
Liquid Biopsy of Cancer
Catherine Alix-Panabières^{1,2,3} and Klaus Pantel^{4*}

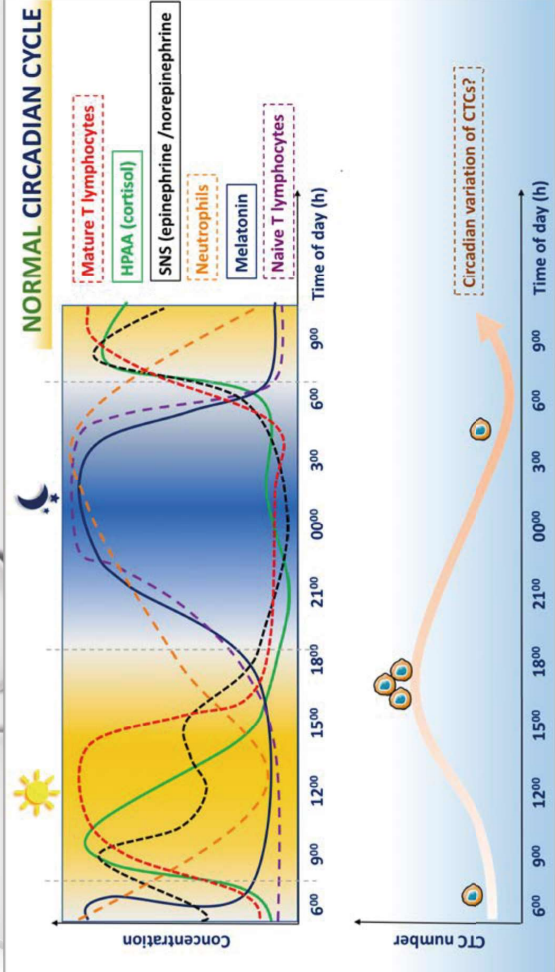
Do malignant cells sleep at night?

Genome Biology

2020



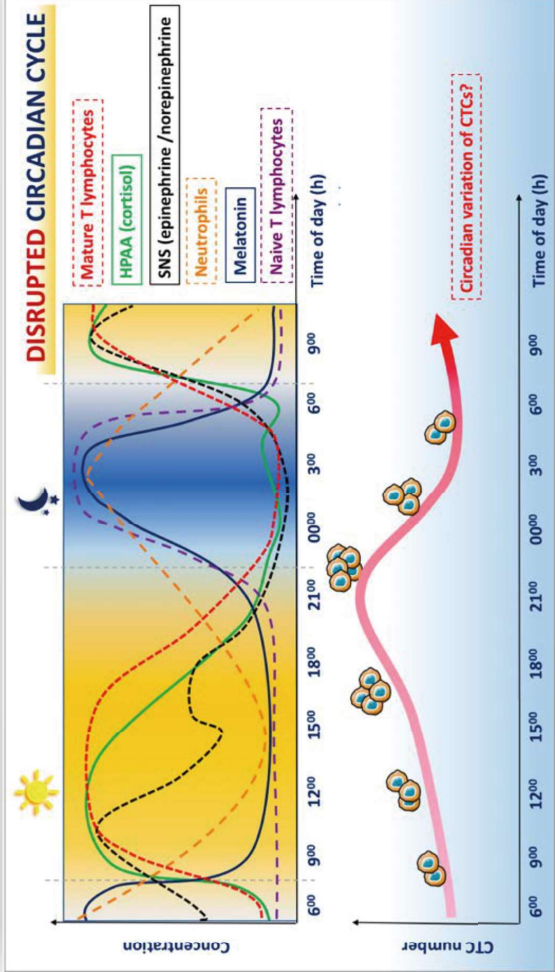
- How ecological evolutionary concepts can be applied in cancer research?
- Does the circadian rhythm/disruption has an implication in CTC fitness to survive and metastasize?
- Does this have clinical relevance in the applications of CTCs as liquid biopsy ?



→ Circadian cycle influences the neuroimmune-endocrine system with clear differences between ☀️ & 🌙

→ **CANCER CELLS** must adapt to efficiently progress through the metastatic cascade

→ Possible fluctuations related to the biological cycles may play a crucial role in defining the best moment for blood sampling to increase the chance of CTC detection.



Circulating tumour cells in cancer patients: challenges and perspectives

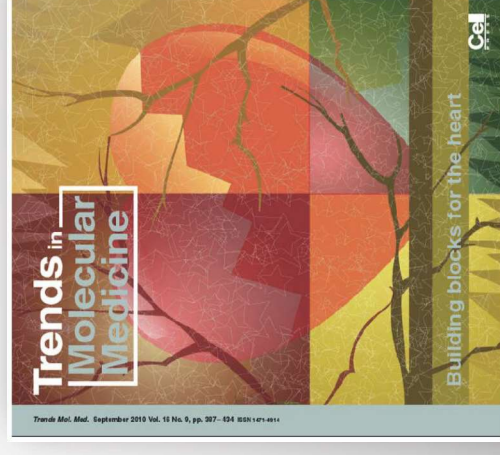
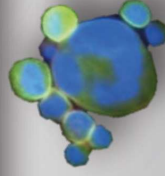
Klaus Pantel¹ and Catherine Alix-Panabières^{2,3}

¹Institute of Tumour Biology, Centre of Experimental Medicine, University Medical Centre Hamburg Eppendorf, Hamburg, Germany

²University Medical Centre, Saint-Eloi Hospital, Institute of Research in Biotherapy, Laboratory of Rare Human Circulating Cells, Montpellier, France

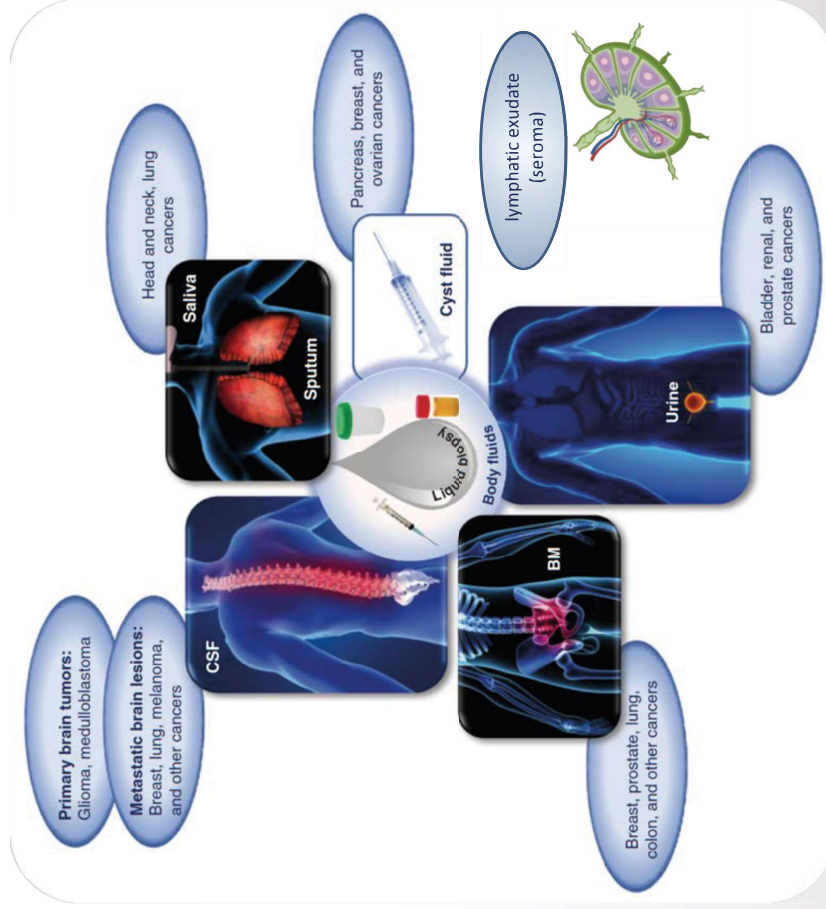
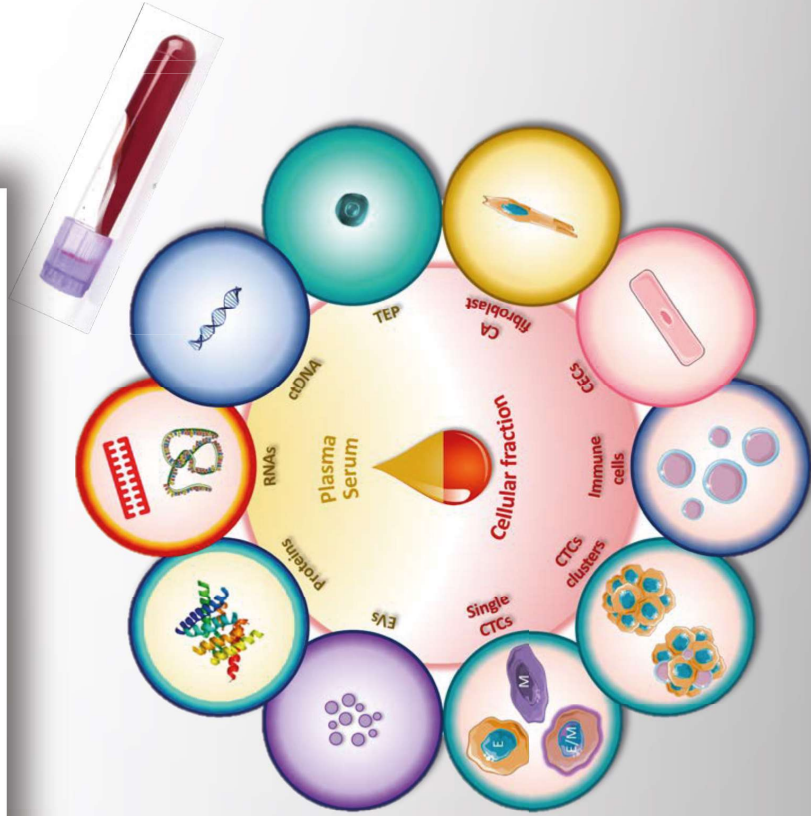
³University Institute of Clinical Research, UM1-EA2415, Epidemiology, Biostatistics and Public Health, Montpellier, France

or resistance. Although promising data from patients with advanced disease demonstrate the value of CTC analysis as “liquid biopsy”, studies on cancer patients at earlier stages are hampered by the low CTC counts. It remains unclear if



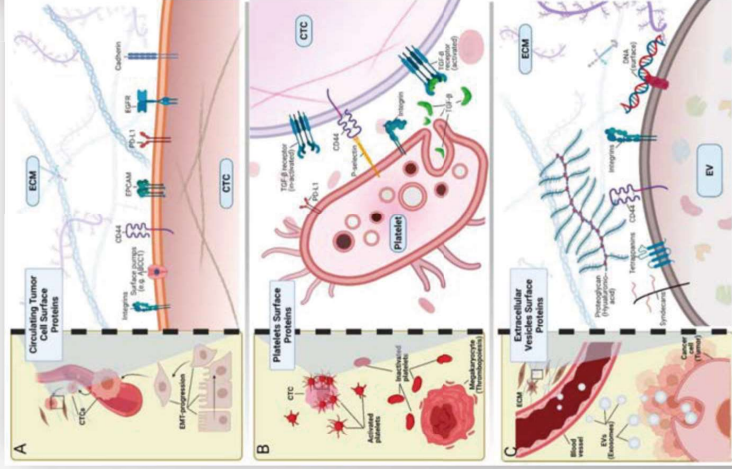
Liquid Biopsy: From Discovery to Clinical Application

Catherine Alix-Panabières^{1,2} and Klaus Pantel³



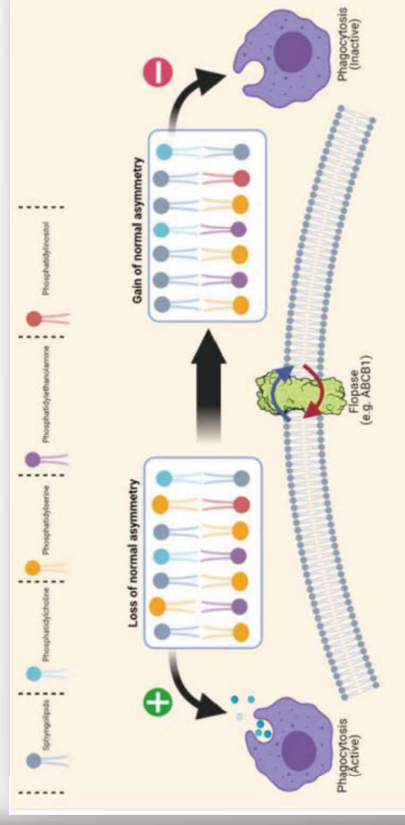
In this review, we briefly describe some of the most important **SURFACE COMPONENTS** of **Circulating Tumor Cells (CTCs)** and **Extracellular Vesicles** as well as their interactions, putting an emphasis on how they are involved in the different steps of the metastatic cascade and how they can be exploited by the different liquid biopsy technologies.

Surface PROTEINS

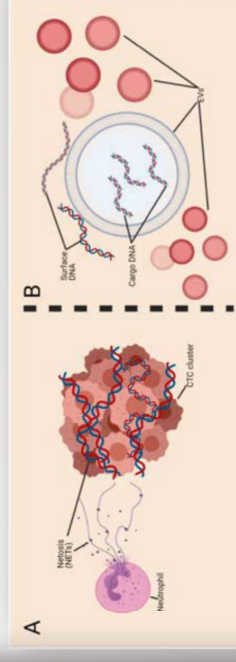


Luis Enrique Cortés-Hernández ^{1,2,†}, Zahra Eslami-S ^{1,2,†}, Bruno Costa-Silva ³ and Catherine Alix-Panabières ^{1,2,*}

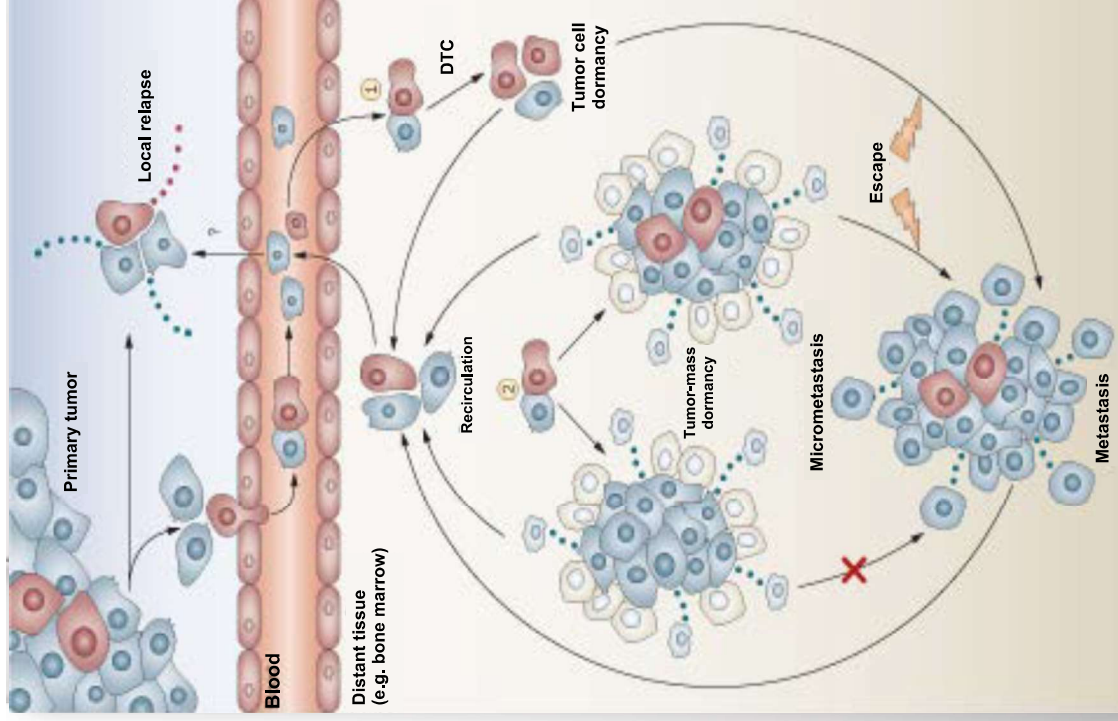
PHOSPHOLIPID composition



Surface DNA



Modèle de circulation des cellules tumorales circulantes et dormance cancéreuse



Cancer micrometastases

Klaus Pantel, Catherine Alix-Panabières and Sabine Riethdorf