Global Engage

Metastasis-Competent Circulating Tumor Cells in Colon Cancer

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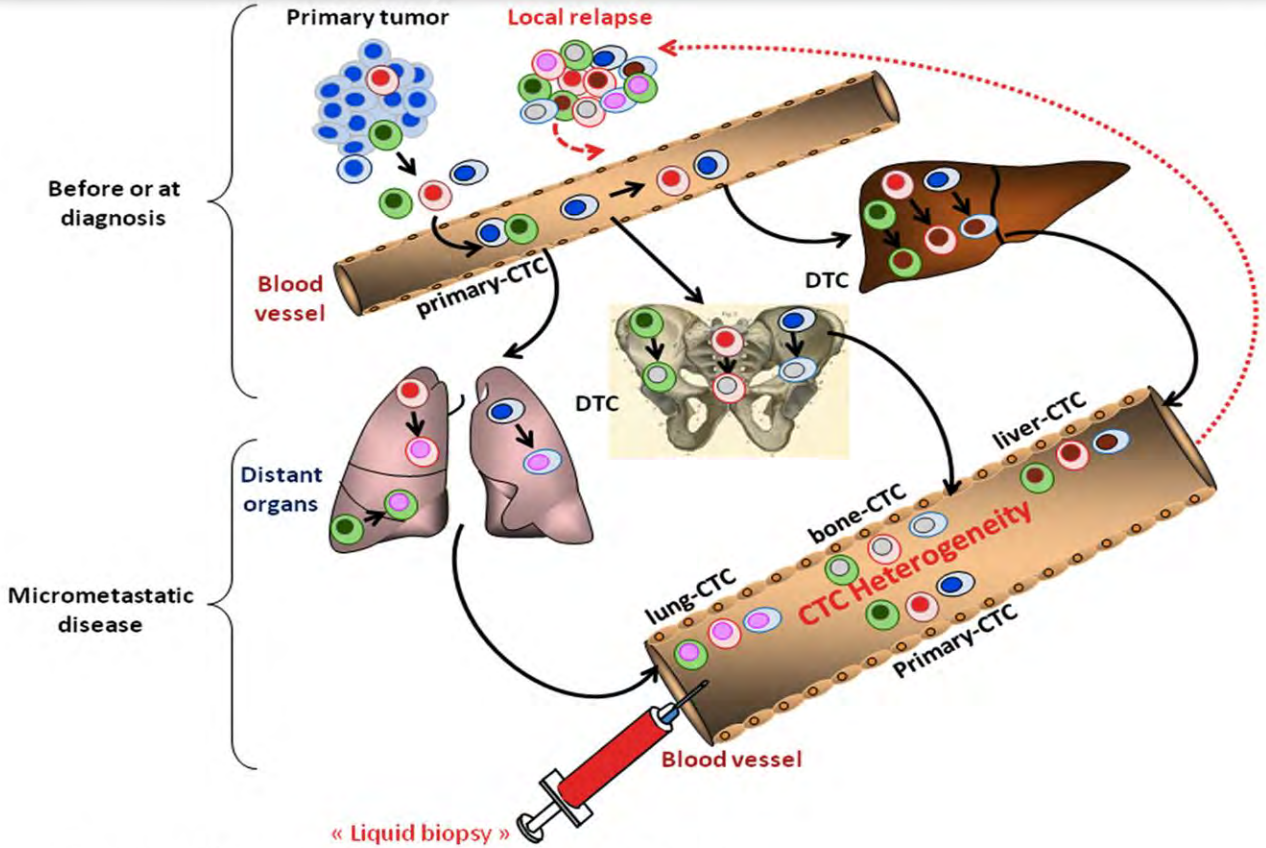
LCCRH
Laboratoire Cellules Circulantes Rares Humaines

CHU MONTPELLIER
CENTRE HOSPITALIER UNIVERSITAIRE

Real-Time *Liquid Biopsy*



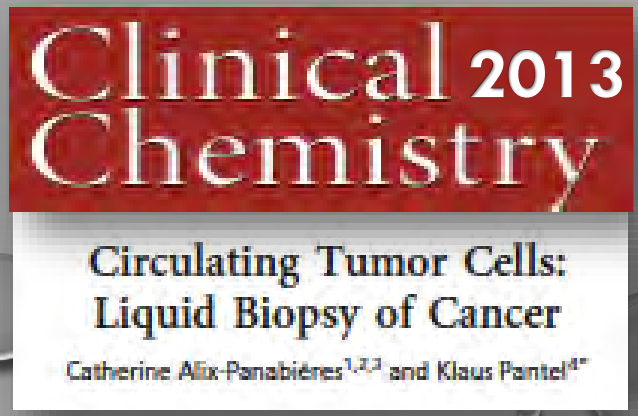
Genotype/Phenotype: CTCs ≠ Primary Tumor

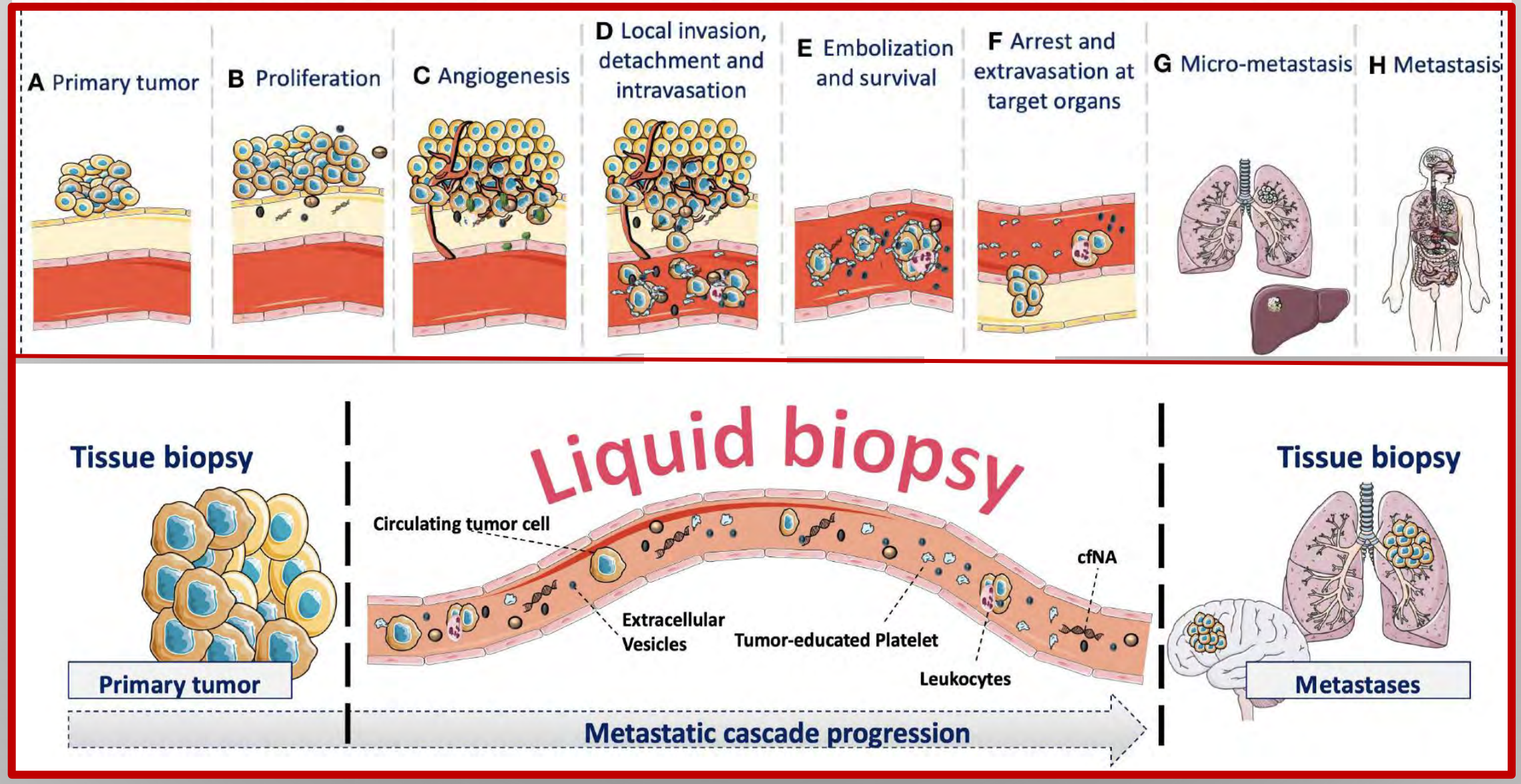
Patient { Stratification / Monitoring } → Personalized Therapies

DRUG RESISTANCE ?

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

- CTCs can harbor unique genomic alterations compared to the primary tumor
- CTCs can be minor clones missed in the tissue biopsy
- Biopsy of metastases is an invasive and sometimes not feasible procedure
- CTCs might reveal representative information on tumor heterogeneity





Eslami-S,… Alix-Panabières *et al. Frontiers in Oncology* 2020

cancers 2021

MDPI

Article

Is There *One* Key Step in the Metastatic Cascade?

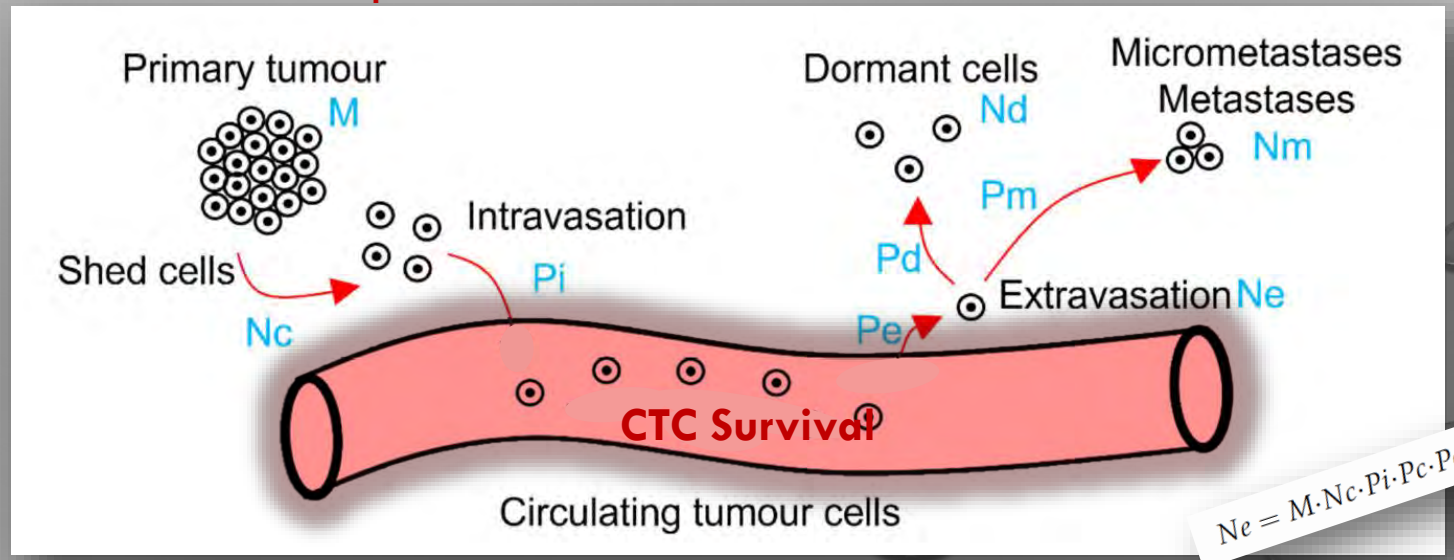
Conclusion

- The most critical parameter governing the formation of clinical metastases is the **survival duration of circulating tumor cells (CTCs)**.
- Administrating 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 ?

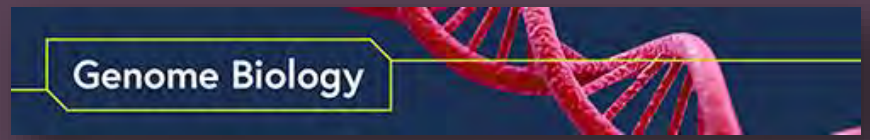
used simulations
vestigate the
step to the
SCADE

Frédéric Thomas

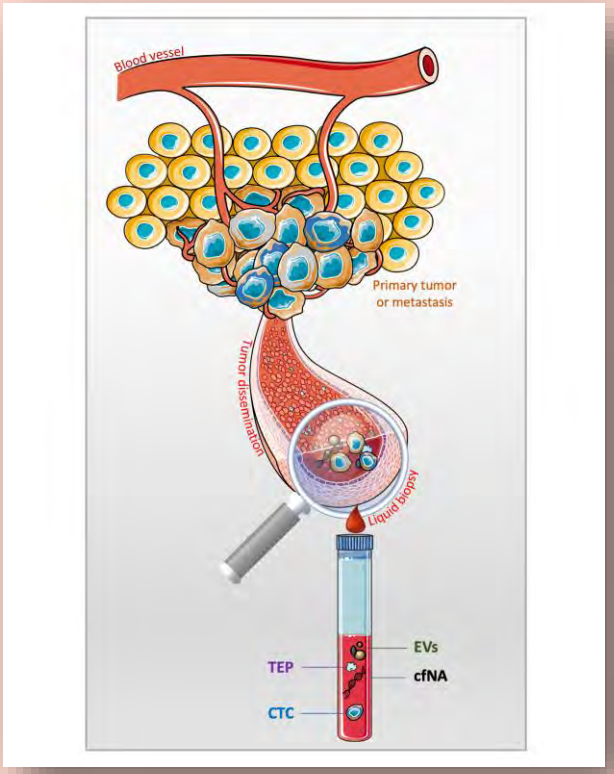
The metastatic Drake equation

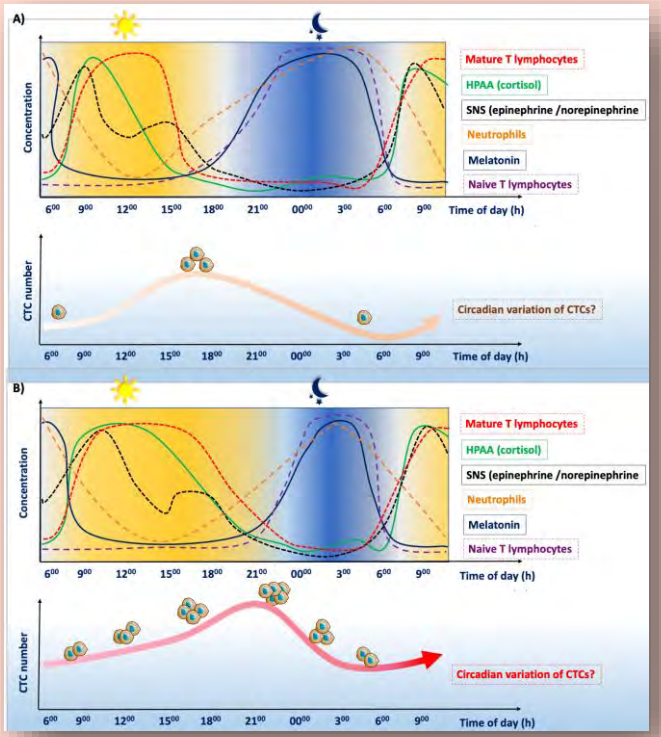


Do malignant cells sleep at night?



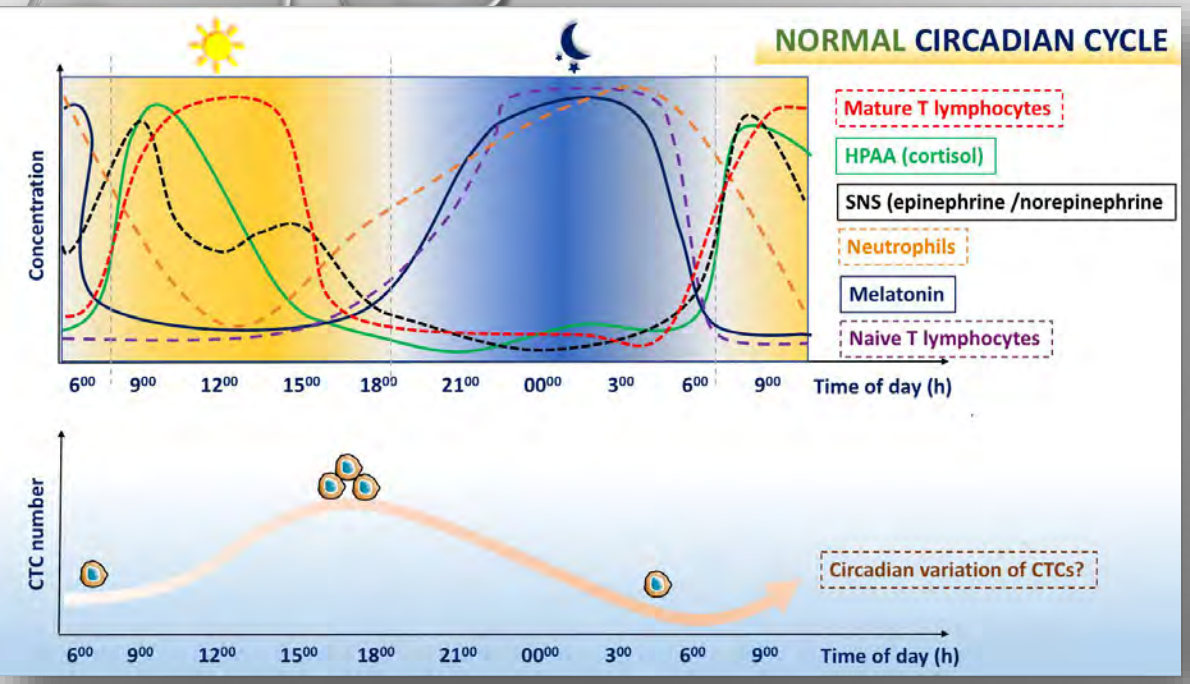
2020

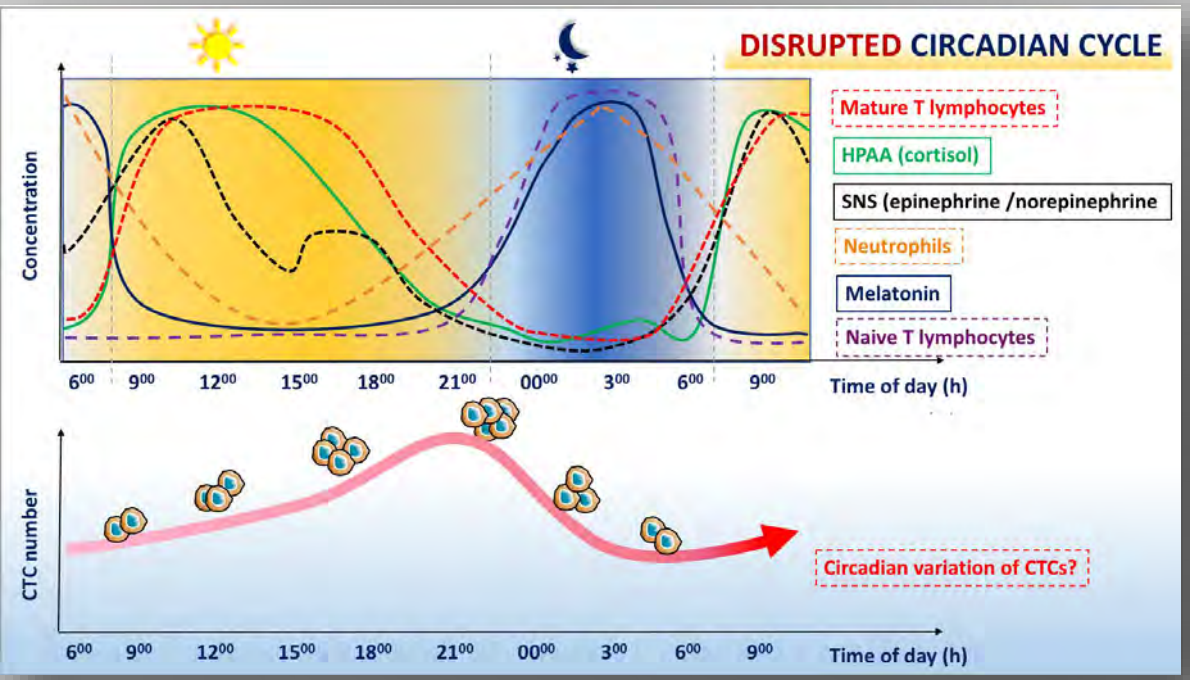




- *How ecological evolutionary concepts can be applied in cancer research?*
- *Does the circadian rythm/disruption has an implication in CTC fitness to survive and metastasize?*
- *Does this have clinical relevance in the applications of CTCs as liquid biopsy ?*

Cortes-Hernandez, Eslami-S….. Thomas & Alix-Panabières. *Genome Biology* **2020**

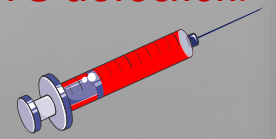




→ **Circadian cycle influences the neuroimmune-endocrine system with clear differences between ☀ & ☾**

→ **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.

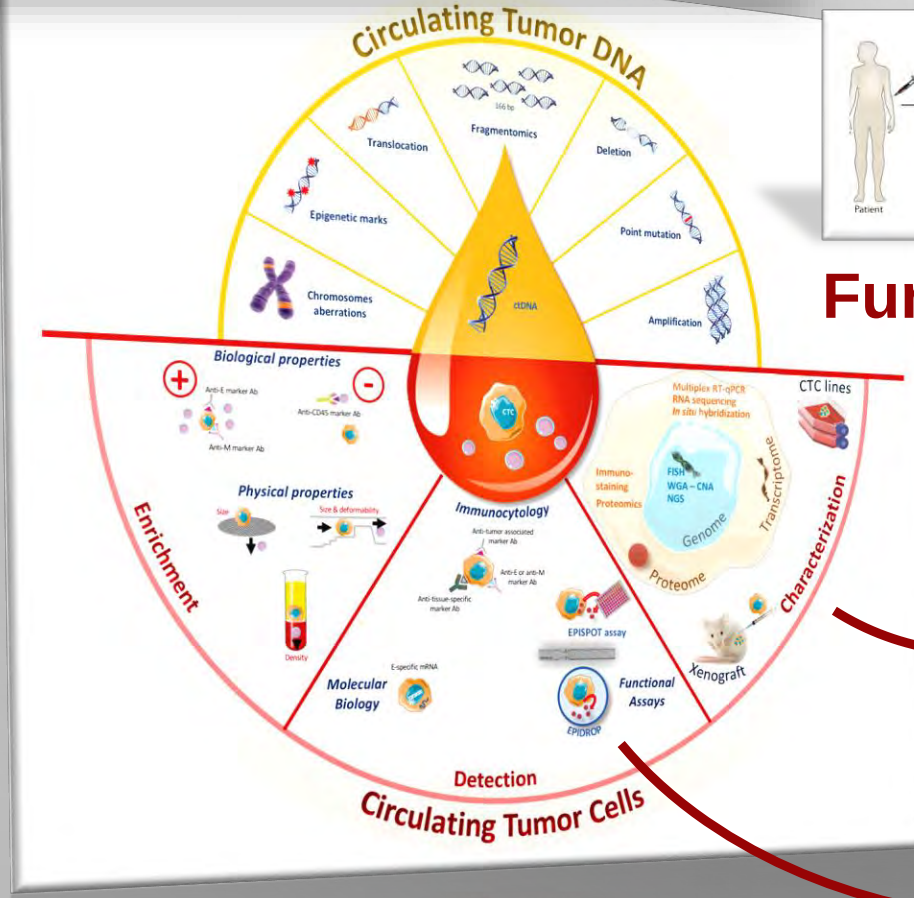


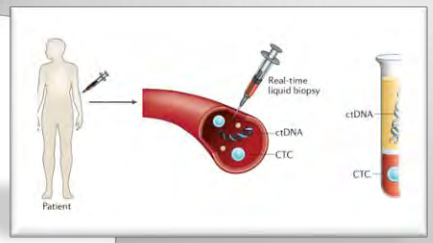
Cortes-Hernandez *et al. Genome Biology* **2020**

CANCER DISCOVERY 10
REVIEW 2021

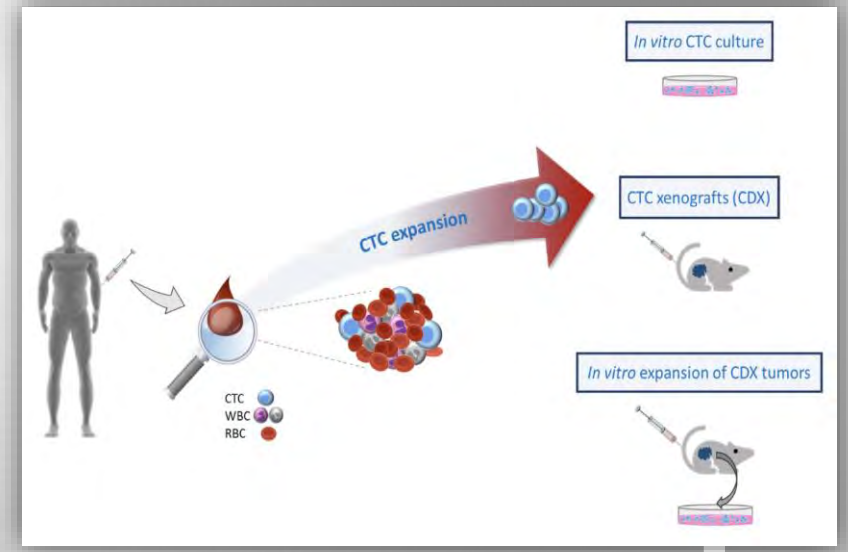
Liquid Biopsy: From Discovery to Clinical Application

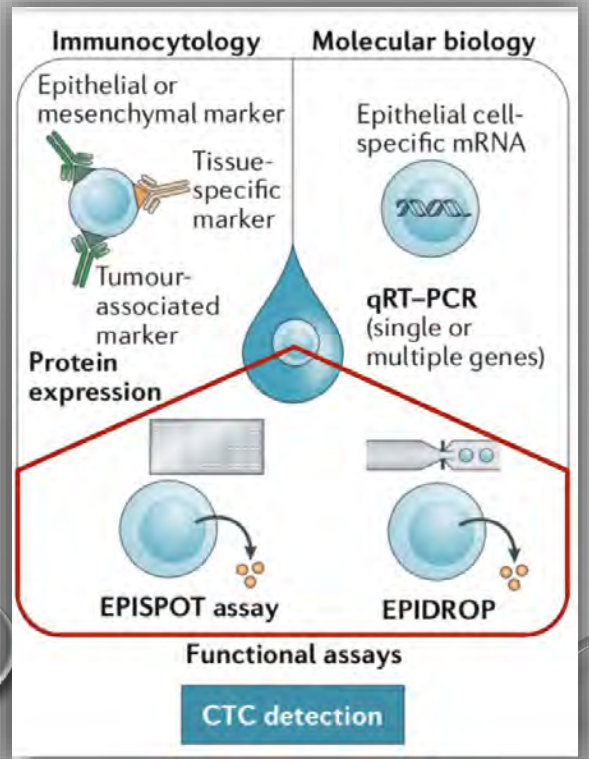
Catherine Alix-Panabières[1,2] and Klaus Pantel[3]

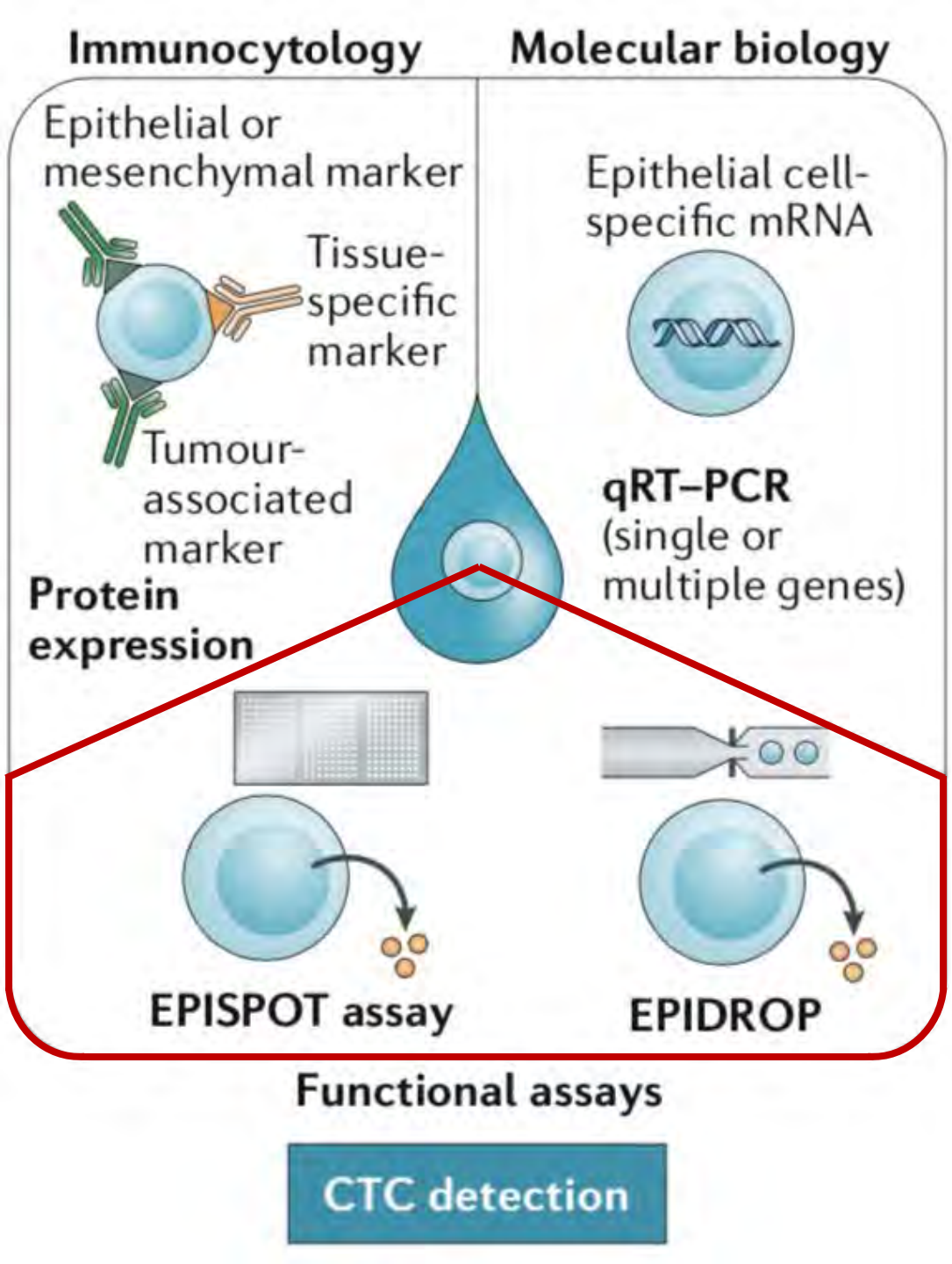




Functional studies on CTCs







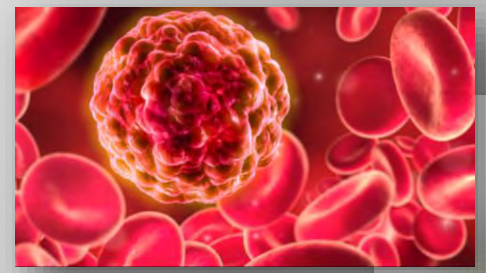
2019

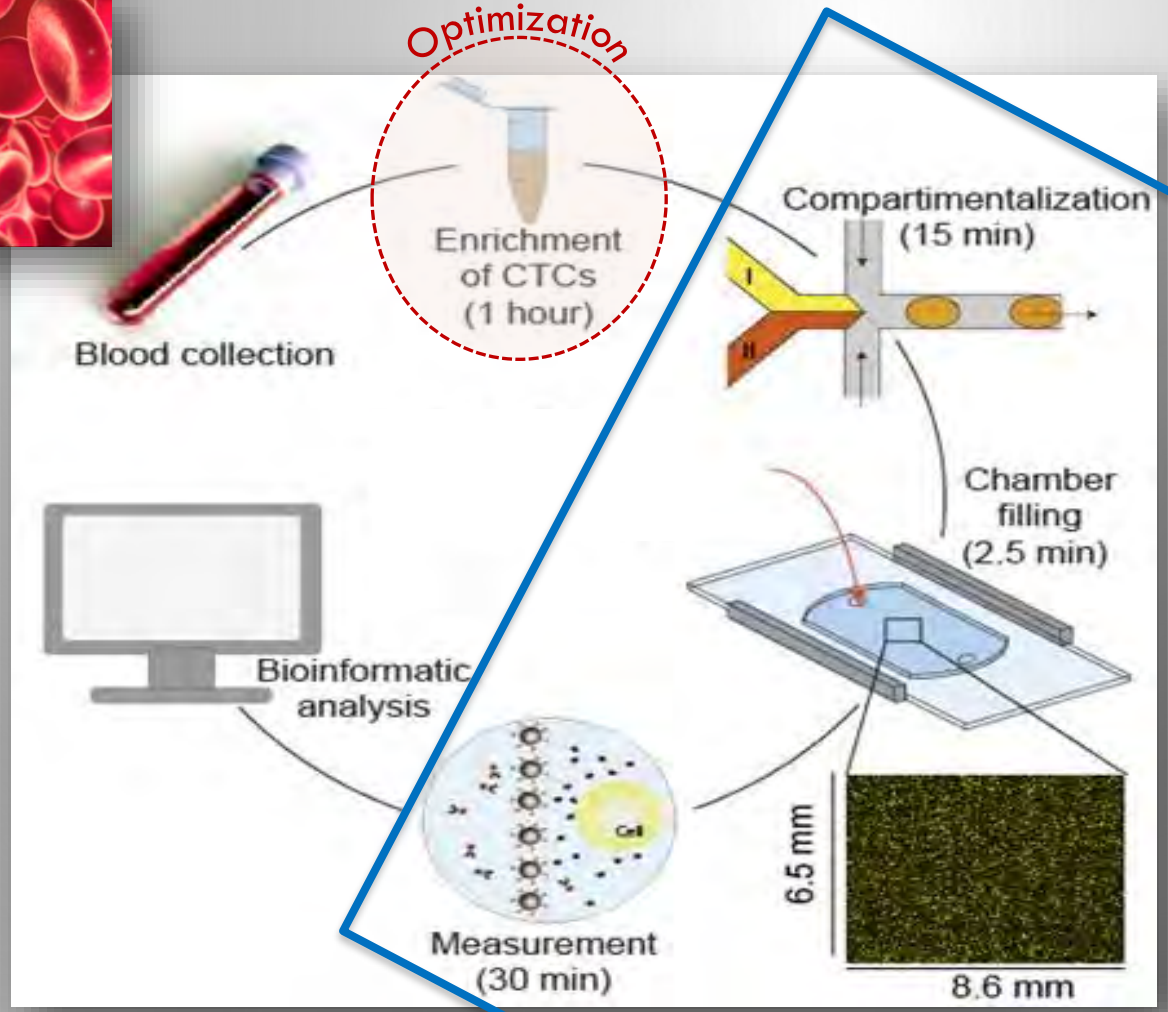
nature REVIEWS CLINICAL ONCOLOGY

Liquid biopsy and minimal residual disease — latest advances and implications for cure

*Klaus Pantel[1] * and Catherine Alix-Panabières[2]*

EPIDROP technology





« EPIspot in a DROP »

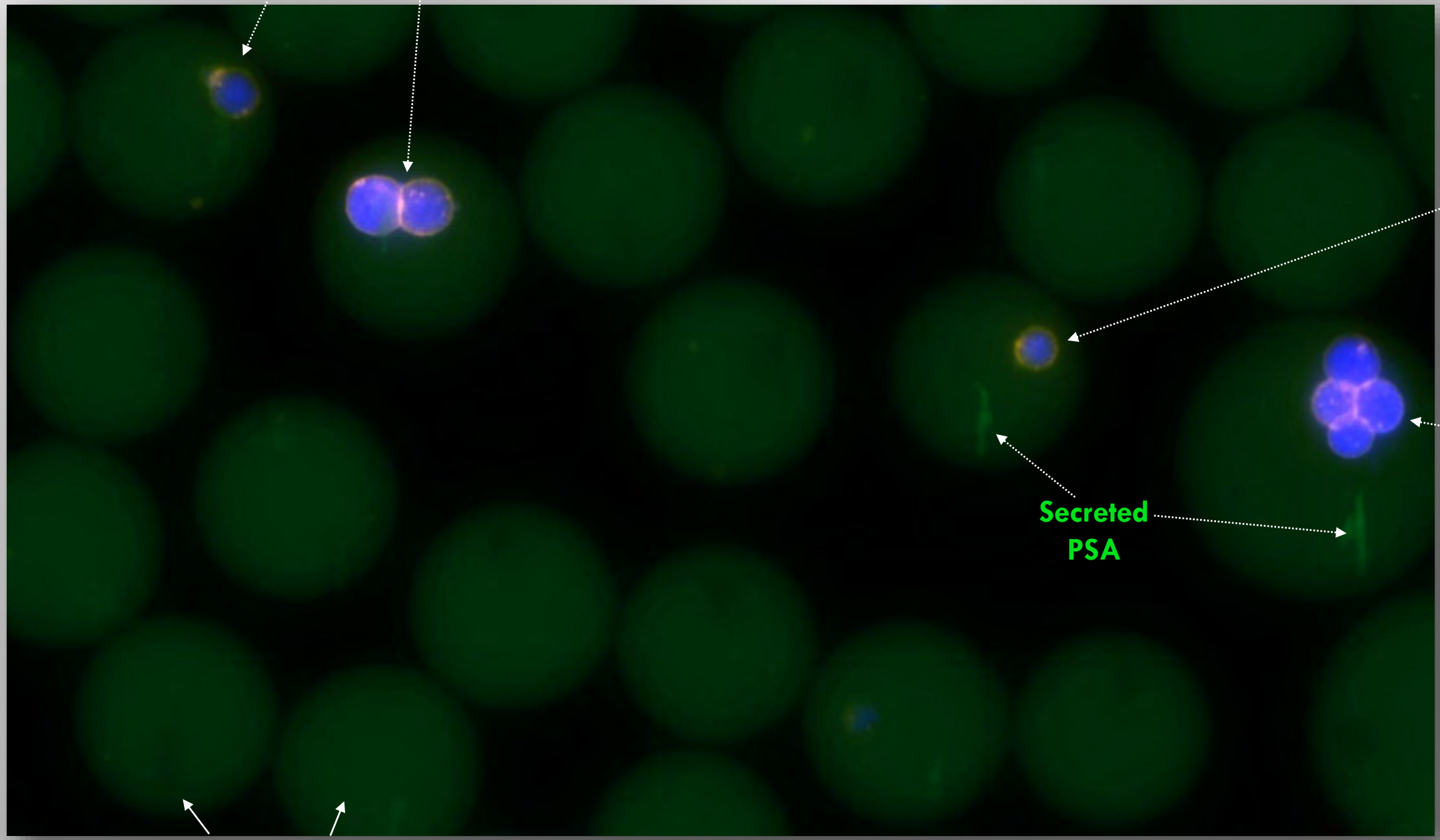
EpiDrop

LNCaP cancer cells

Prostate cancer

1 single LNCap cell
No secretion of PSA

1 cluster of 2 LNCap cells
No secretion of PSA



1 single LNCap cell
secreting PSA

1 cluster of 4 LNCap cells
secreting PSA

Secreted
PSA

Empty microdroplets

CHU MONTPELLIER

ESPCI PARIS

U.S. National Library of Medicine

ClinicalTrials.gov NCT04581109

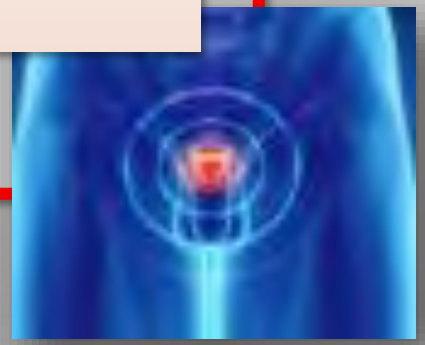
Clinical Trial recruiting patients

EPIDROP

Oncogram :

Precision medicine → Therapeutic choice at the diagnostic of cancer

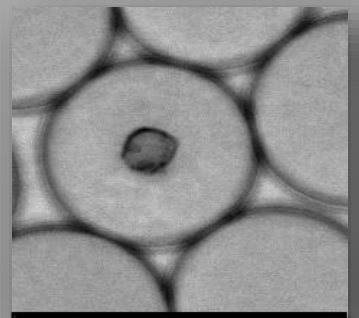
→ Monitoring treatment response



Prostate cancer

CellSearch

?



EpiDrop

CLINICAL RELEVANCE EPISPOT

Clinical Chemistry 60:1
214–221 (2014)

Cancer Diagnostics

Breast – 2014

Prognostic Relevance of Viable Circulating Tumor Cells Detected by EPISPOT in Metastatic Breast Cancer Patients

Jean-Marie Ramirez,[1] Tanja Fehm,[2] Mattea Orsini,[3] Laure Cayrefourcq,[1] Thierry Maudelonde,[4] Klaus Pantel,[5†] and Catherine Alix-Panabières[1,3†*]

cancers

MDPI

Colon – 2021

Article

Clinical Relevance of Viable Circulating Tumor Cells in Patients with Metastatic Colorectal Cancer: The COLOSPOT Prospective Study

Thibault Mazard [1,2,*], Laure Cayrefourcq [3,4], Françoise Perriard [5], Hélène Senellart [6], Benjamin Linot [7], Christelle de la Fouchardière [8], Eric Terrebonne [9], Eric François [10], Stéphane Obled [11], Rosine Guimbaud [12], Laurent Mineur [13], Marianne Fonck [14], Jean-Pierre Daurès [5], Marc Ychou [1], Eric Assenat [2] and Catherine Alix-Panabières [3,4,*]

SCIENTIFIC REPORTS

Prostate – 2016

OPEN

Improved detection of circulating tumor cells in non-metastatic high-risk prostate cancer patients

Received: 16 August 2016
Accepted: 28 November 2016
Published: 21 December 2016

Andra Kuske[1], Tobias M. Gorges[1], Pierre Tennstedt[2], Anne-Kathrin Tiebel[2], Raisa Pompe[2], Felix Preißer[2], Sandra Prues[2], Martine Mazel[3], Athina Markou[4], Evi Lianidou[4], Sven Peine[5], Catherine Alix-Panabières[3], Sabine Riethdorf[1], Burkhard Beyer[2], Thorsten Schlomm[2] & Klaus Pantel[1]

r Cells detected by
sy
runo Segui[2], Antoine Faix[2],

Clinical Chemistry 65:10
000-000 (2019)

Cancer Diagnostics

Head & Neck – 2019

Circulating Tumor Cells as a Prognostic Factor in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: the CIRCUTEC Prospective Study

Renaud Garrel,[1] Martine Mazel,[2] Françoise Perriard,[3] Marie Vinches,[4] Laure Cayrefourcq,[2] Joël Guigay,[5] Laurence Digue,[6] Karine Aubry,[7] Marc Alfonsi,[8] Jean-Pierre Delord,[9] Benjamin Lallemant,[10] Caroline Even,[11] Jean-Pierre Daurès,[3] Paul Landais,[3] Didier Cupissol,[4] and Catherine Alix-Panabières[2*]

cells 2019

MDPI

Melanoma – 2019

Article

S100-EPISPOT: A New Tool to Detect Viable Circulating Melanoma Cells

Laure Cayrefourcq [1], Aurélie De Roeck [2], Caroline Garcia [2], Pierre-Emmanuel Stoebner [2], Fanny Fichel [2], Françoise Garima [1], Françoise Perriard [3], Jean-Pierre Daures [3], Laurent Meunier and Catherine Alix-Panabières [1,*,†]

Clinical Chemistry 59:9
1384–1392 (2013)

Cancer Diagnostics

Colon – 2013

Capture of Viable Circulating Tumor Cells in the Liver of Colorectal Cancer Patients

Eric Denève,[1] Sabine Riethdorf,[2] Jeanne Ramos,[3] David Nocca,[1] Amandine Coffy,[4] Jean-Pierre Daurès,[4] Thierry Maudelonde,[5] Jean-Michel Fabre,[1] Klaus Pantel,[2†] and Catherine Alix-Panabières[4,5,6†*]

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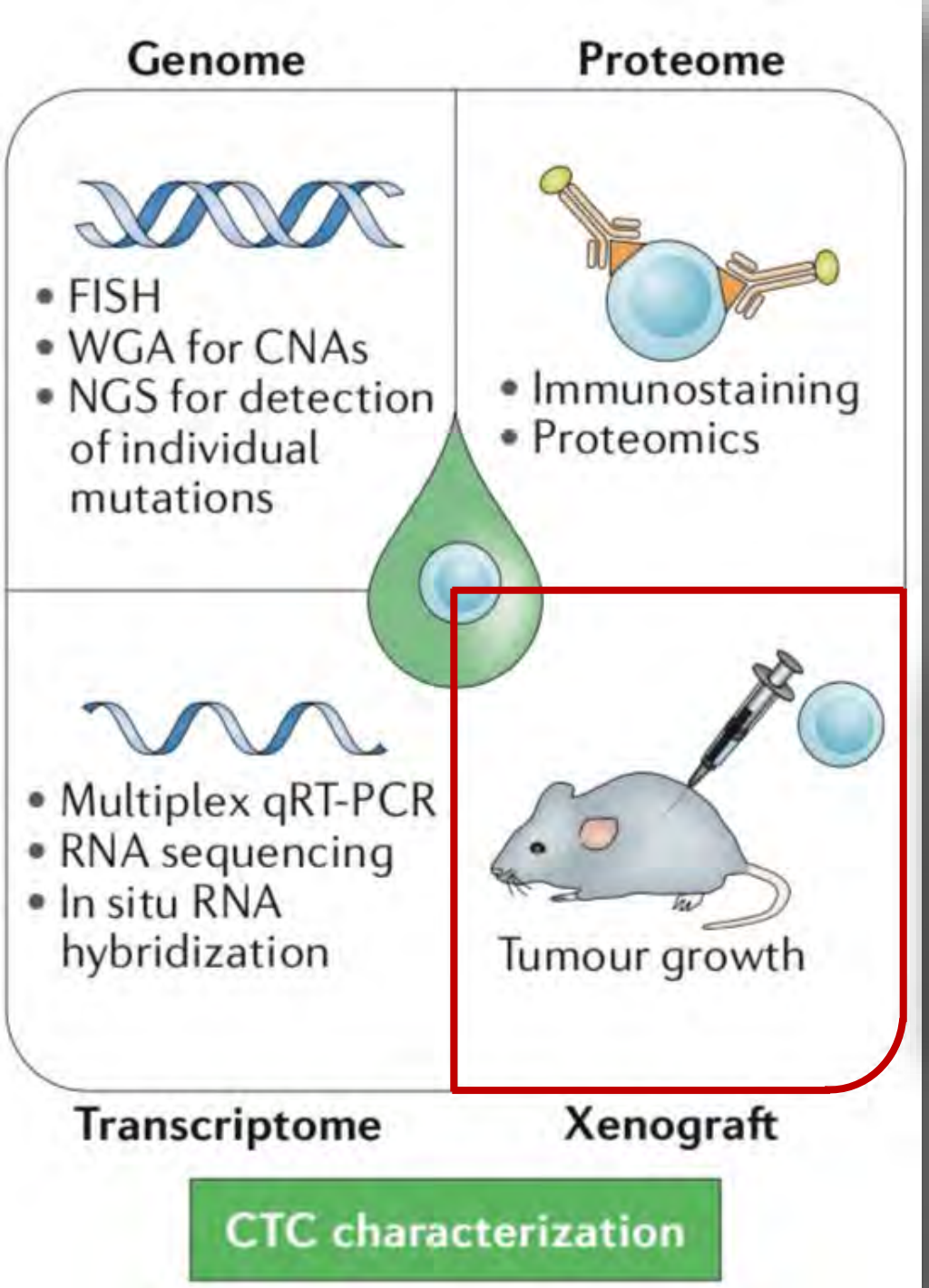
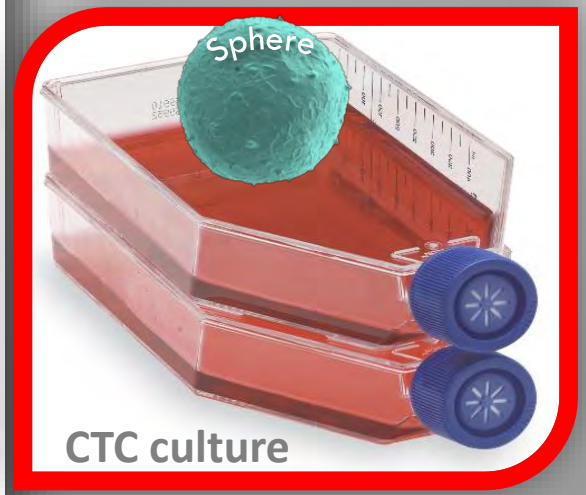


nature REVIEWS CLINICAL ONCOLOGY 2019

Liquid biopsy and minimal residual disease — latest advances and implications for cure

*Klaus Pantel[1] * and Catherine Alix-Panabières[2]*



Identification of metastasis-competent CTCs

- Higher number of CTCs
- CTCs with stemness properties/self renewal

Luis Enrique Cortes-Hernandez

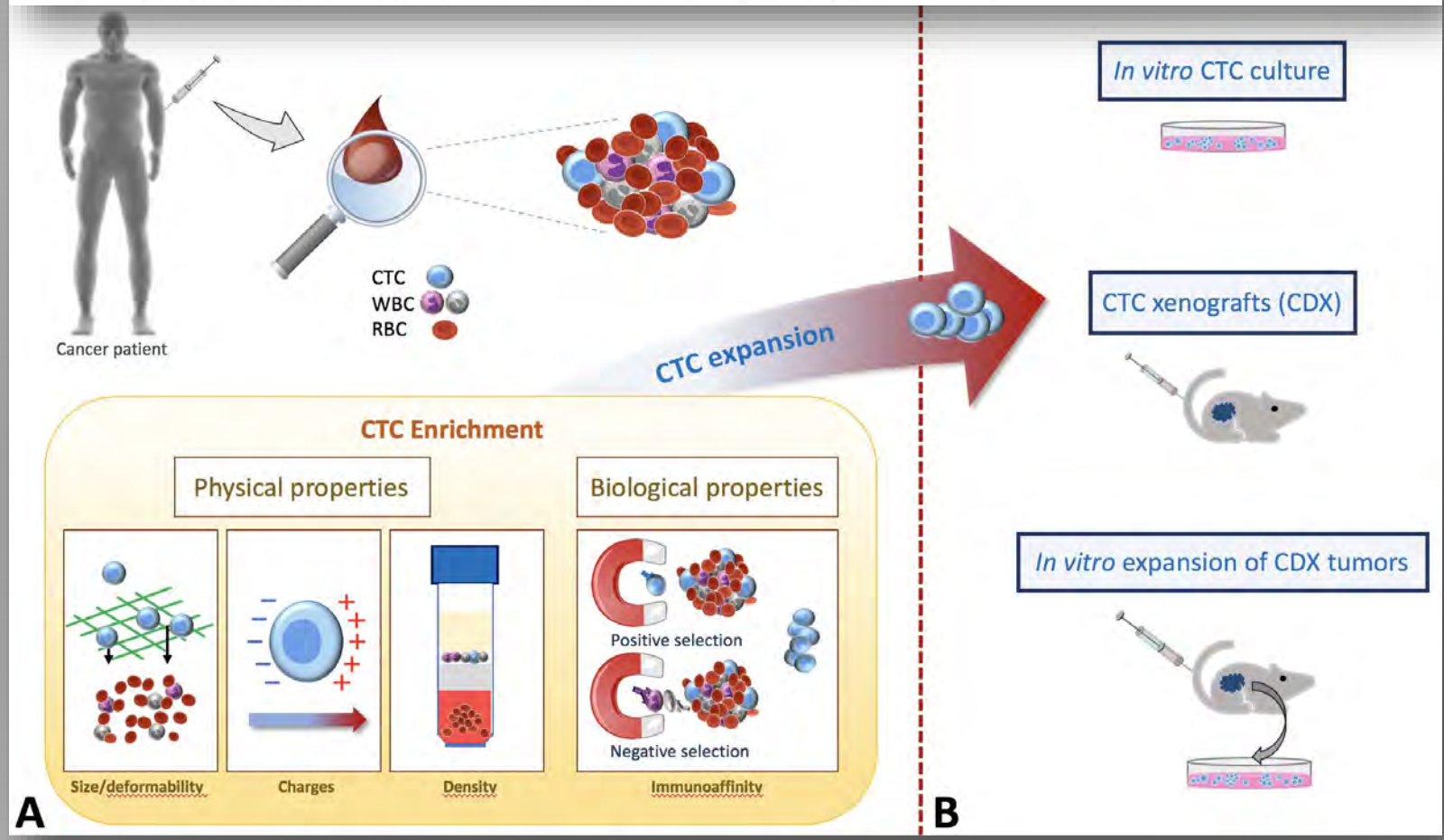
Contents lists available at ScienceDirect

Molecular Aspects of Medicine 2019

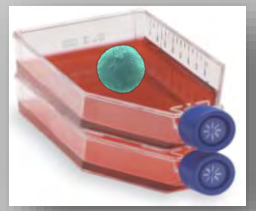
journal homepage: www.elsevier.com/locate/mam

Circulating tumor cell as the functional aspect of liquid biopsy to understand the metastatic cascade in solid cancer

Luis Enrique Cortés-Hernández[1], Zahra Eslami-S[1], Catherine Alix-Panabières*

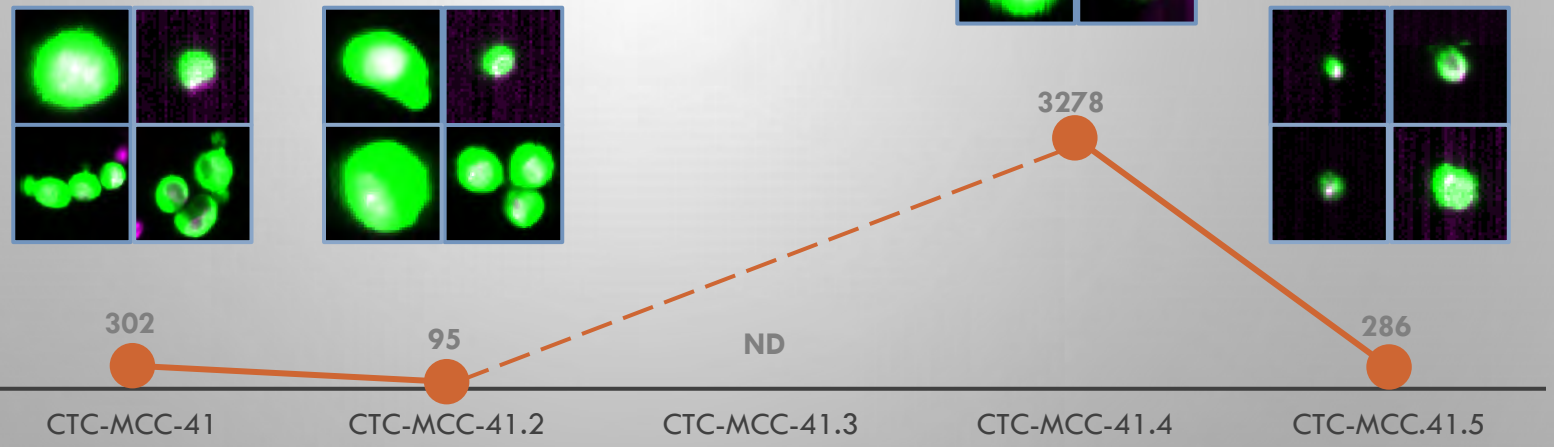


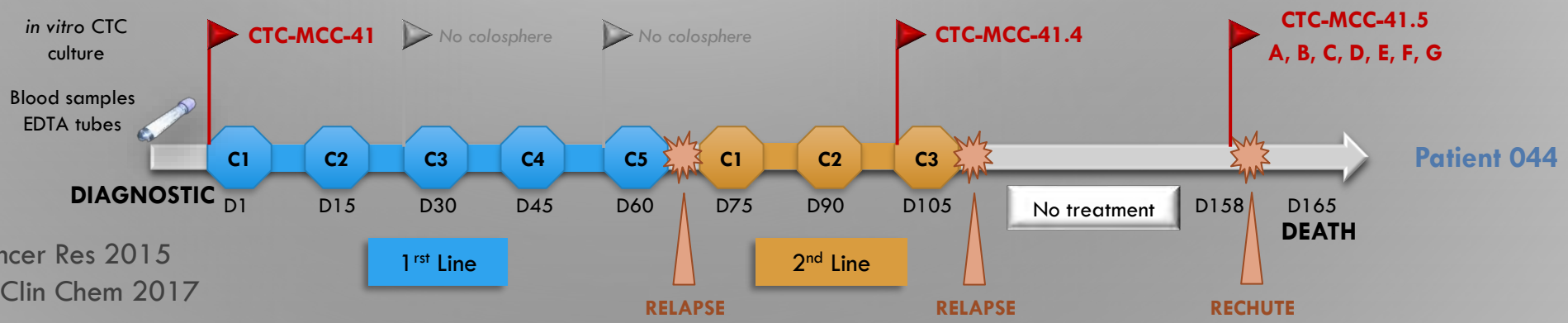
9 CTC-MCC Lines



Colon cancer

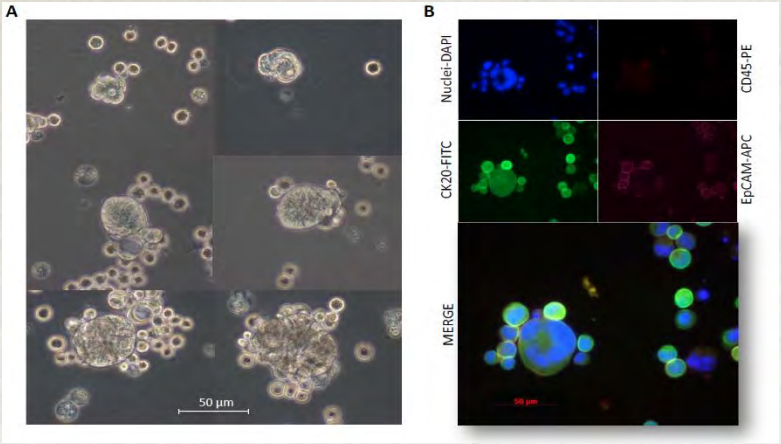
CellSearch





Cayrefourcq *et al*, Cancer Res 2015
Alix-Panabières *et al*, Clin Chem 2017

Soler *et al. Sci Rep. 2018*



Tumor and Stem Cell Biology

Cancer Research 2015

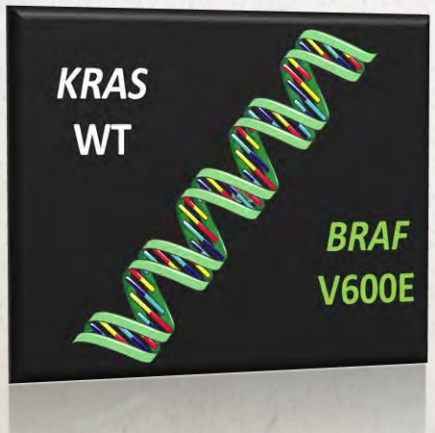
Establishment and Characterization of a Cell Line from Human Circulating Colon Cancer Cells

Laure Cayrefourcq[1,2], Thibault Mazard[3], Simon Joosse[4], Jérôme Solassol[5], Jeanne Ramos[6], Eric Assenat[3], Udo Schumacher[7], Valérie Costes[6], Thierry Maudelonde[2,5], Klaus Pantel[4], and Catherine Alix-Panabières[1,2]

AACR AWARD 2017

CHARACTERIZATION OF THE CTC-MCC-41 LINE

- Permanent CTC line
- Shares main characteristics with the primary tumor
- Shows an epithelial phenotype with a certain plasticity with stem cell properties
- Induces *in vitro* angiogenesis and xenogafts in immunodeficient mice



TRANSCRIPTOMIC ANALYSIS OF CTC-MCC-41

Clinical Chemistry 63:3
700–713 (2017)

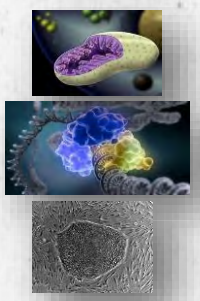
Clinical Chemistry

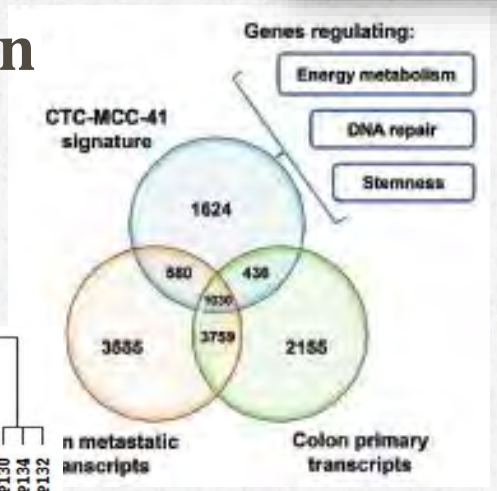
Cancer Diagnostics

Molecular Portrait of Metastasis-Competent Circulating Tumor Cells in Colon Cancer Reveals the Crucial Role of Genes Regulating Energy Metabolism and DNA Repair

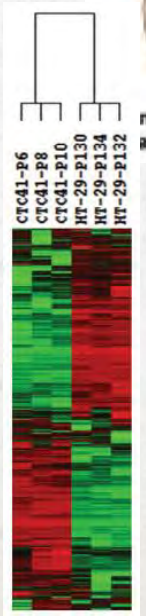
Catherine Alix-Panabières,[1,2*] Laure Cayrefourcq,[1,2] Thibault Mazard,[3,4] Thierry Maudelonde,[5,2] Eric Assenat,[6] and Said Assou[7,8*]

- **CTC signature, with overexpression**
  - Energetic metabolism
  - DNA repair
  - Stem cell properties





- **Different signatures**
  - CTC line *vs* primary tumors lines
  - CTC line *vs* metastases lines



COMPARAISON CTC-MCC-41 *vs* PRIMARY & METASTATIC COLON CANCER CELL LINES

cells 2020

MDPI

Article

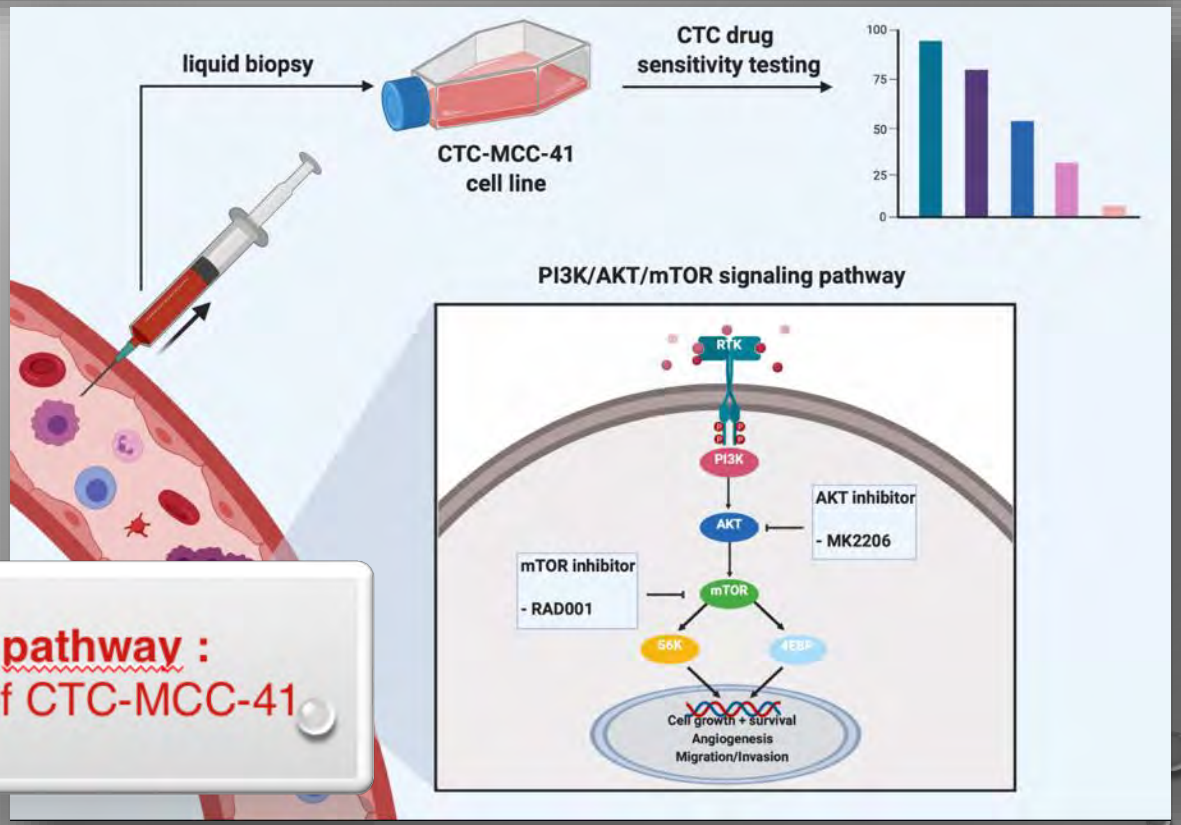
High Sensitivity of Circulating Tumor Cells Derived from a Colorectal Cancer Patient for Dual Inhibition with AKT and mTOR Inhibitors

Daniel J. Smit [1], Laure Cayrefourcq [2], Marie-Therese Haider [3], Nico Hinz [1], Klaus Pantel [4], Catherine Alix-Panabières [2] and Manfred Jücker [1,*]

Daniel Smit

Regulation of essential functions:

- Protein biosynthesis
- Cell growth
- Cell cycle control
- Survival
- Migration



CONCLUSION PI3K/AKT/mTOR signaling pathway : Key role in the proliferation of CTC-MCC-41

Cayrefourcq *et al. Molecular Cancer* (2021) 20:30
https://doi.org/10.1186/s12943-021-01326-6

Molecular Cancer

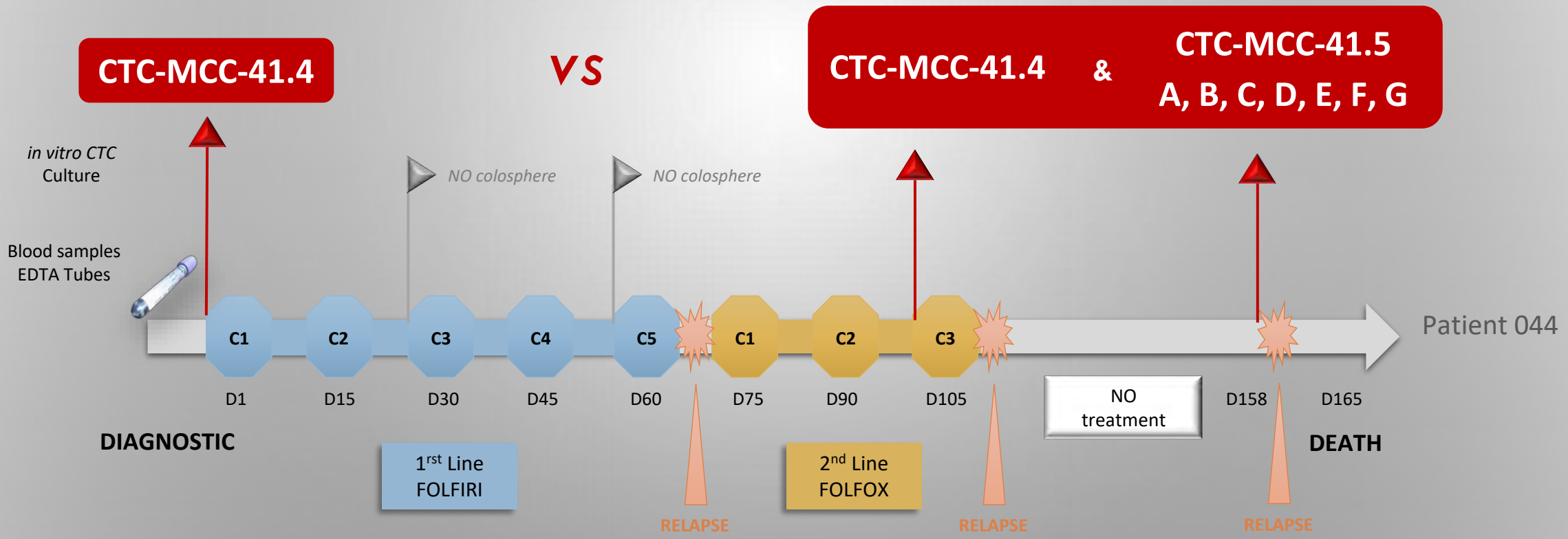
2021

LETTER TO THE EDITOR

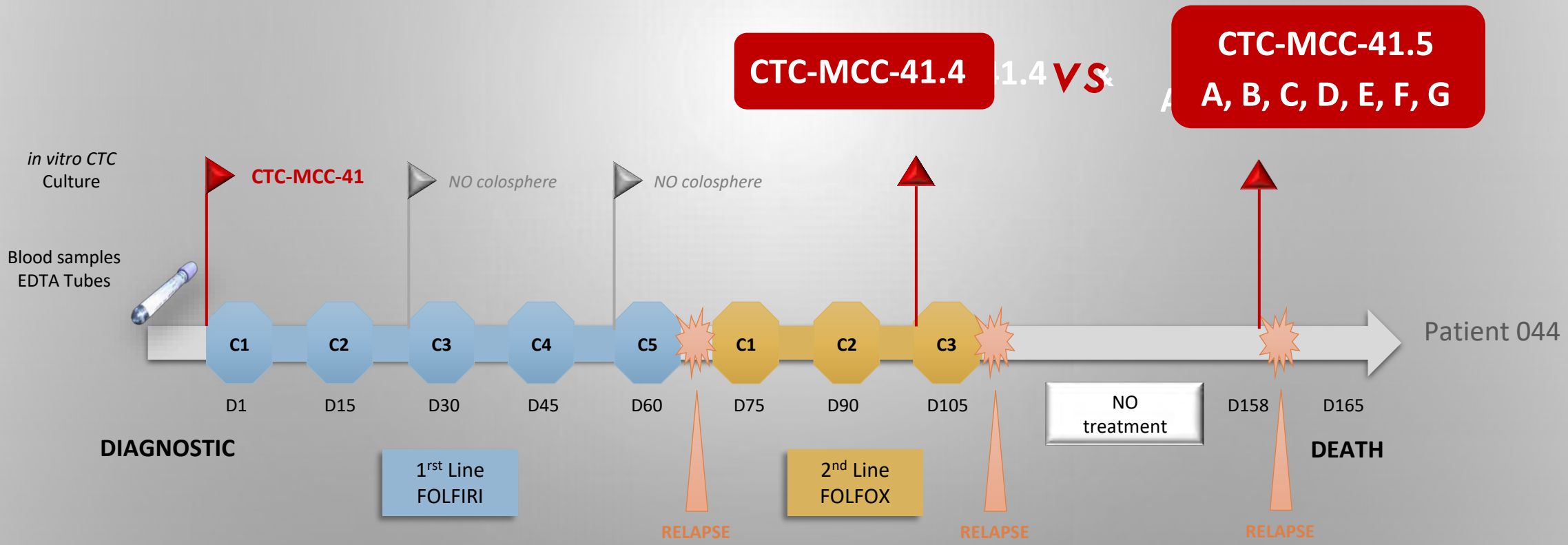
Open Access

Selective treatment pressure in colon cancer drives the molecular profile of resistant circulating tumor cell clones

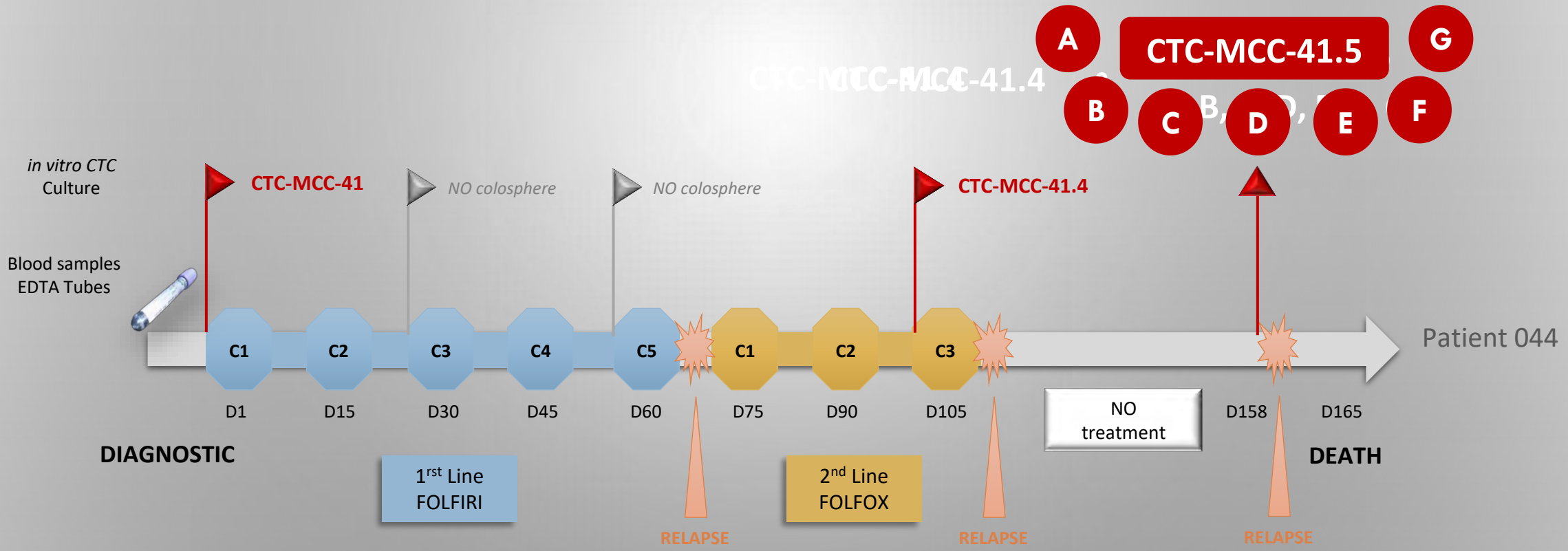
Laure Cayrefourcq[1,2], Frédéric Thomas[2], Thibault Mazard[3], Eric Assenat[4], Said Assou[5*] and Catherine Alix-Panabières[1,2*]



I- IMPACT OF THE TREATMENT

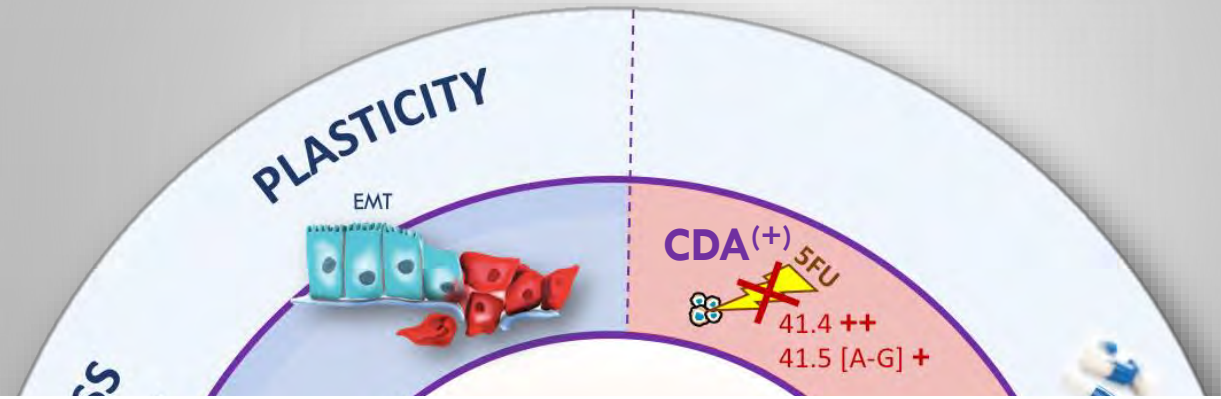


II- PROGRESSION OF THE DISEASE AFTER TREATMENT



III- Final Clonal Heterogeneity

Hallmarks of CTC-MCC clones resistant to therapies



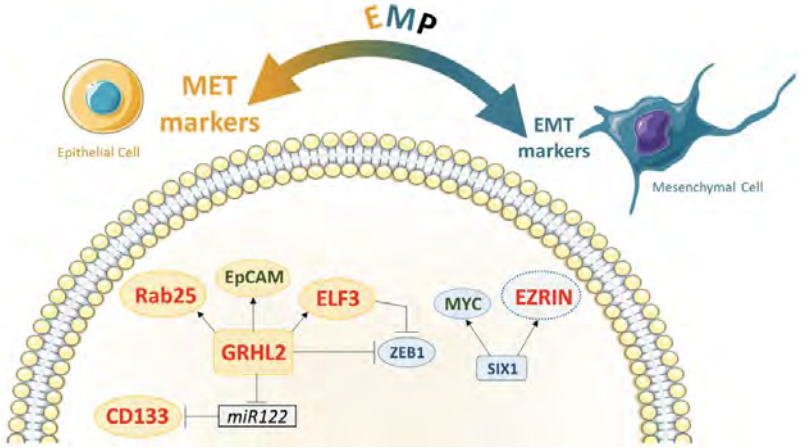
cancers 2021 In Press

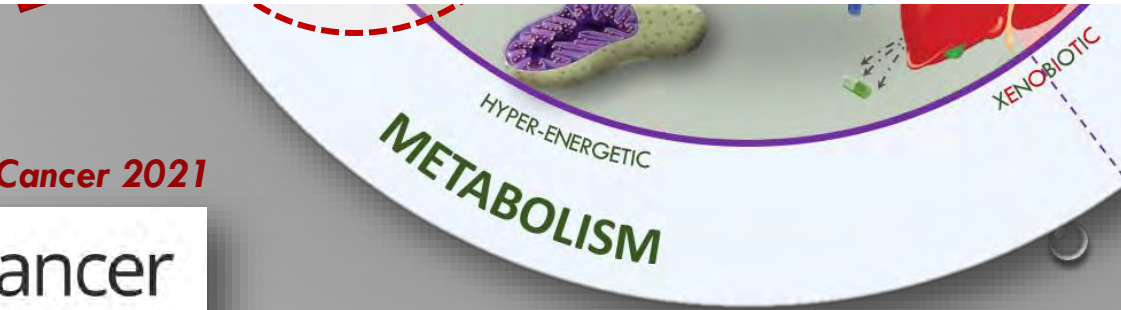
MDPI

Article

Sequential circulating tumor cell lines from a patient with colorectal cancer display increased epithelial-to-mesenchymal plasticity

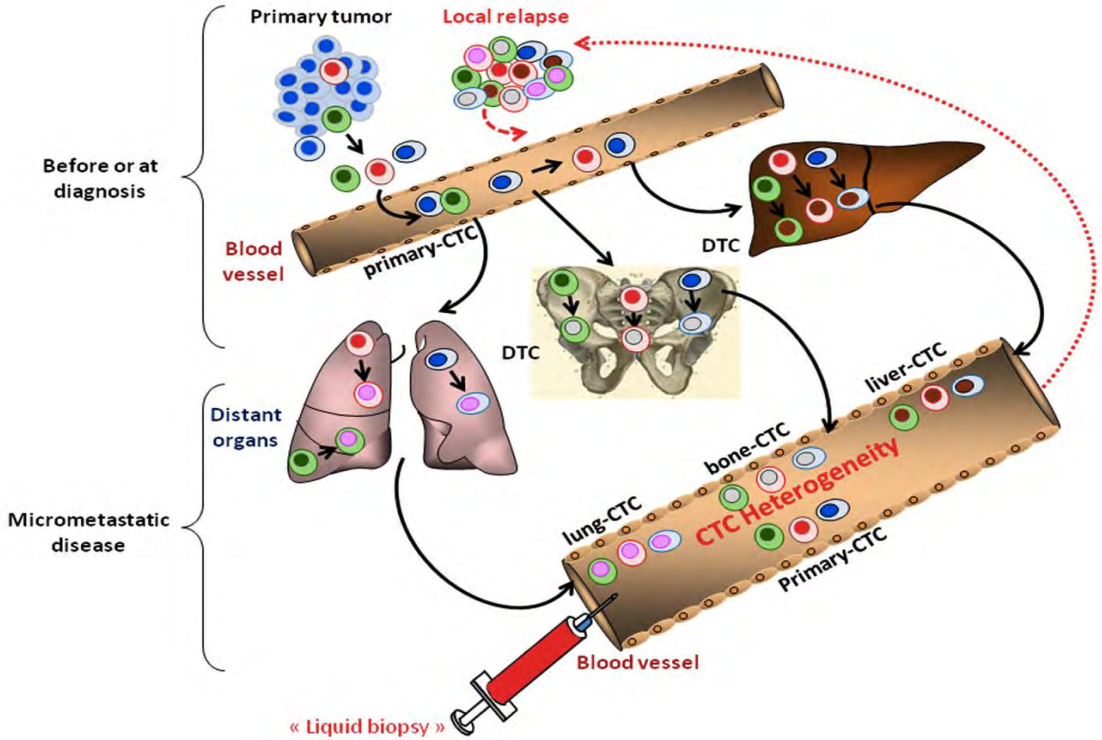
Pelin Balcik-Ercin[1], Laure Cayrefourcq[2,3], Rama Soundararajan[4], Sendurai A. Mani[4], Catherine Alix-Panabières[2,3*]





Cayrefourcq *et al.* ***Mol Cancer 2021***

Molecular Cancer



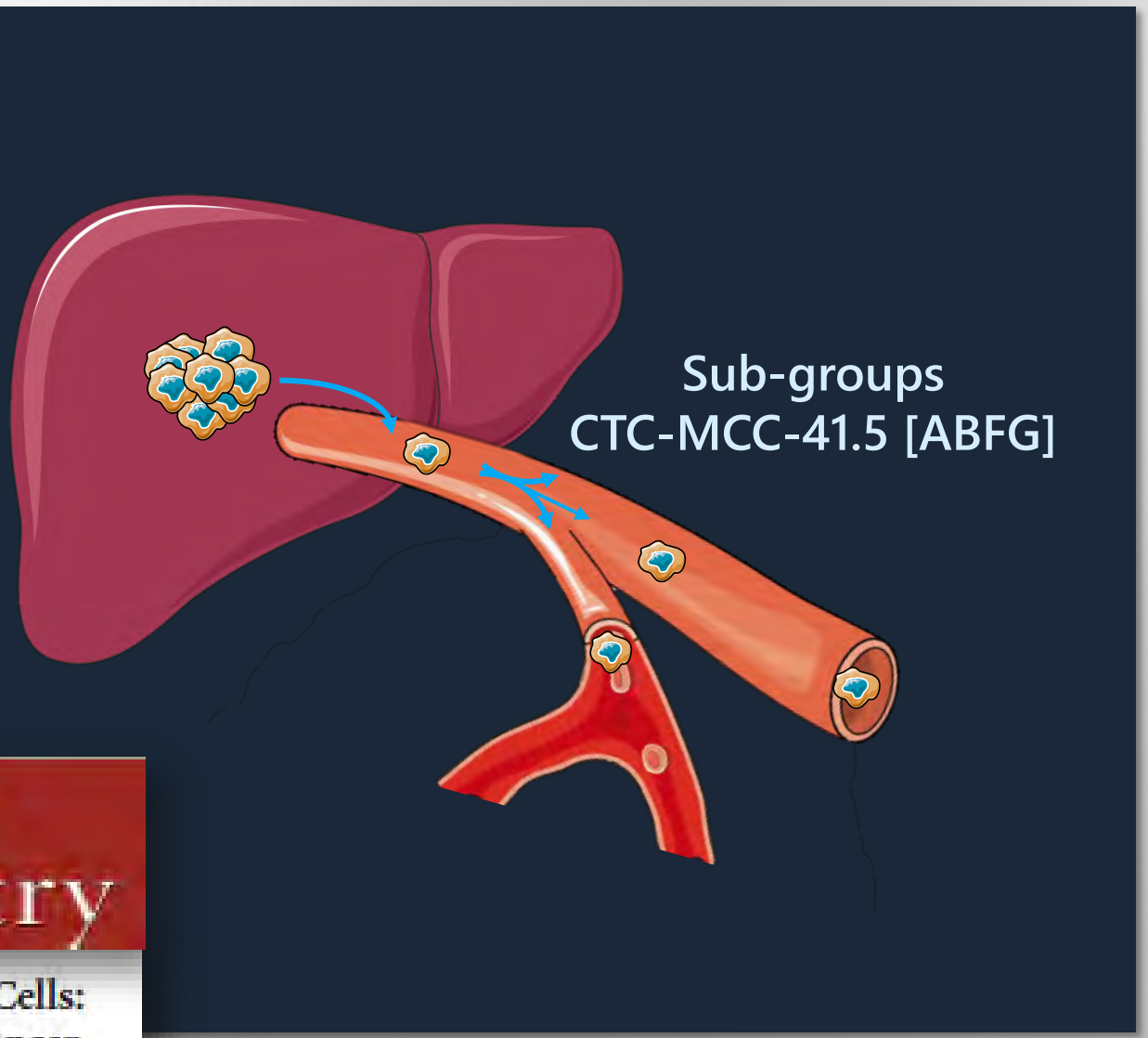
Genotype/Phenotype: CTCs ≠ Primary Tumor

Patient { Stratification / Monitoring } → Personalized Therapies

DRUG RESISTANCE ?

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

origin



Sub-groups
CTC-MCC-41.5 [ABFG]

Clinical Chemistry

Circulating Tumor Cells: Liquid Biopsy of Cancer

Catherine Alix-Panabières[1,2,3] and Klaus Pantel[4]*

Comprehensive outlook on the molecular events involved in colon cancer progression and provides ***potential CTC biomarkers*** that may help developing new therapies to specifically **target CTCs with stem cell properties** that escape the immune system, cause metastases and tumor relapse in patients with colon cancer

Klaus Pantel

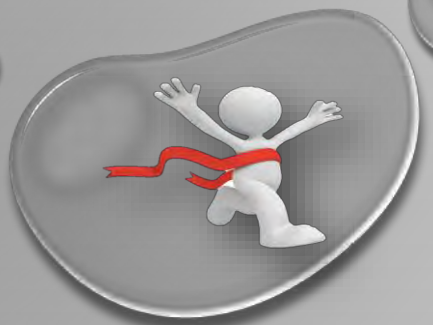
Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

EMBO 2020 Molecular Medicine

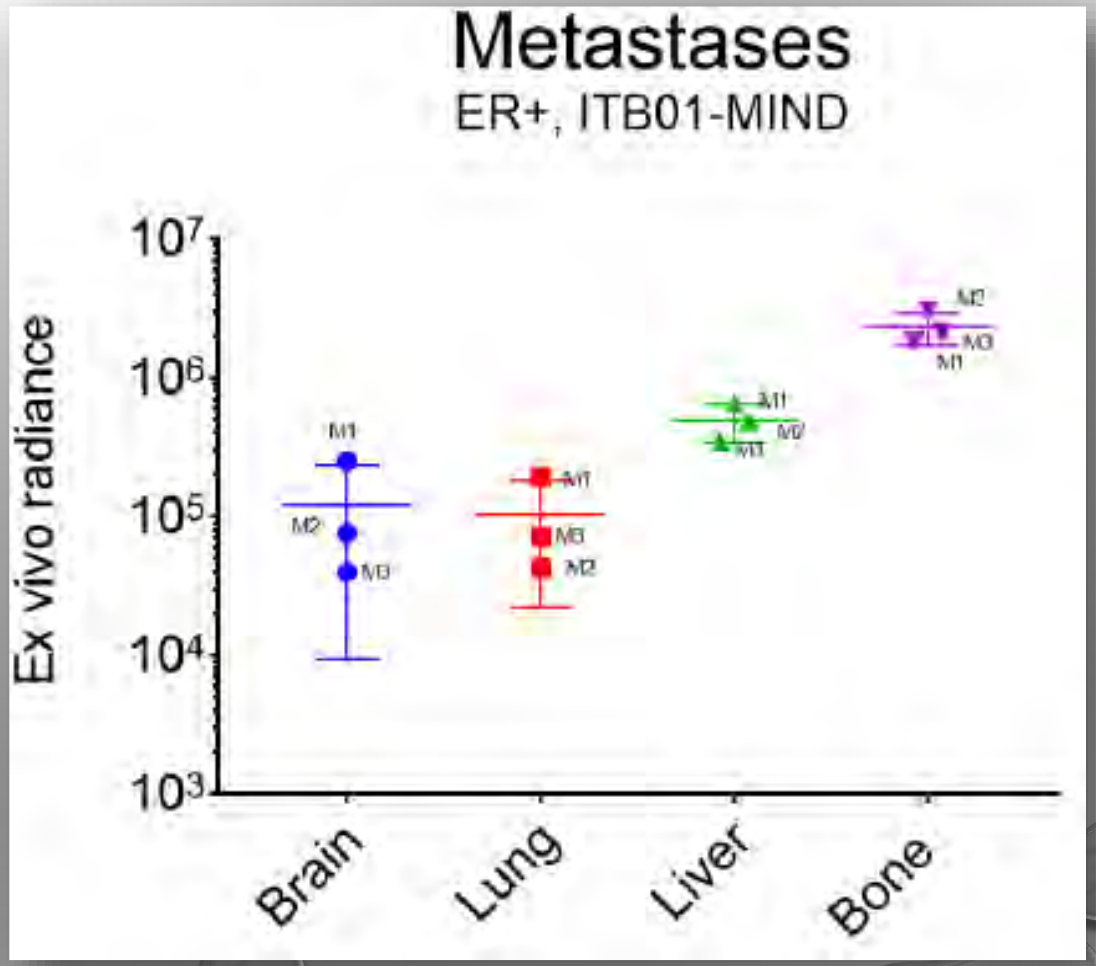
Characterization of circulating breast cancer cells with tumorigenic and metastatic capacity

Claudia Koch[1,†], Andra Kuske[1,†], Simon A Joosse[1], Gökhan Yigit[2], George Sflomos[3], Sonja Thaler[4], Daniel J Smit[5], Stefan Werner[1], Kerstin Borgmann[6], Sebastian Gärtner[1], Parinaz Mossahebi Mohammadi[1], Laura Battista[3], Laure Cayrefourcq[7,8], Janine Altmüller[9], Gabriela Salinas-Riester[10], Kaamini Raithatha[10], Arne Zibat[2], Yvonne Goy[6], Leonie Ott[1], Kai Bartkowiak[1], Tuan Zea Tan[11], Qing Zhou[12], Michael R Speicher[12], Volkmar Müller[13], Tobias M Gorges[1], Manfred Jücker[5], Jean-Paul Thiery[14], Cathrin Brisken[3,15,‡], Sabine Riethdorf[1,‡], Catherine Alix-Panabières[7,8,‡] & Klaus Pantel[1,*]



CHU MONTPELLIER CENTRE HOSPITALIER UNIVERSITAIRE

In vivo growth and metastasis of a new human EK+ CTC line after intra-mammilar injection into immunodeficient mice



Koch, Riethdorf, Alix-Panabieres, Pantel et al, *EMBO Mol. Med.* 2020

DETECTION & MONITORING OF CTCs

CTC CHARACTERIZATION (DNA, RNA, PROTEINS)

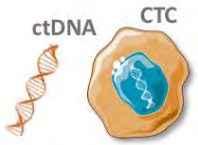
THERAPEUTIC TARGETS (HER2, ER, PD-L1), VIRUS

RESISTANCE MECHANISMS (ARv7)

CANCER DISCOVERY 10
REVIEW 2021

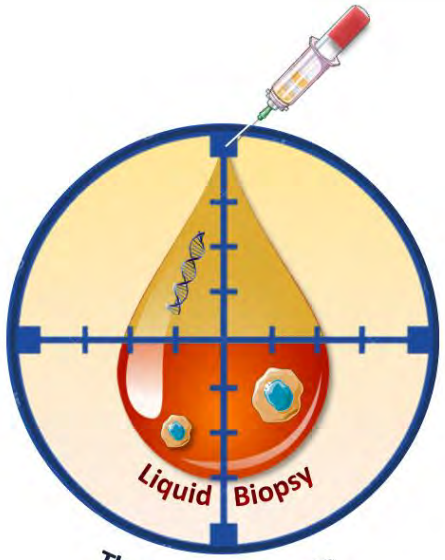
Liquid Biopsy: From Discovery to Clinical Application

Catherine Alix-Panabières[1,2] and Klaus Pantel[3]



Genome Analysis

- AR-targeting therapy — *PC* — AR
- Taxane resistance — *PC* — TMPRSS2-ERG
- Anti-EGFR therapy — *NSCLC* — EGFR
- EGFR-therapy resistance — *CRC* — NRAS
- EGFR-therapy resistance — *CRC* — KRAS
- BRAF inhibitors — *Melanoma (V600E, V600K)* *NSCLC (non-V600E variants)* *CRC (non-V600E variants)* — BRAF
- ALK-inhibitors resistance — *LC* — ALK
- ALK/ROS1-inhibitors crizotinib resistance — *LC* — ROS1
- Endocrine therapy resistance — *BC* — PIK3CA
- Fulvestrant resistance — *ER(+) BC* Chemotherapy resistance — *CRC* — ESR1



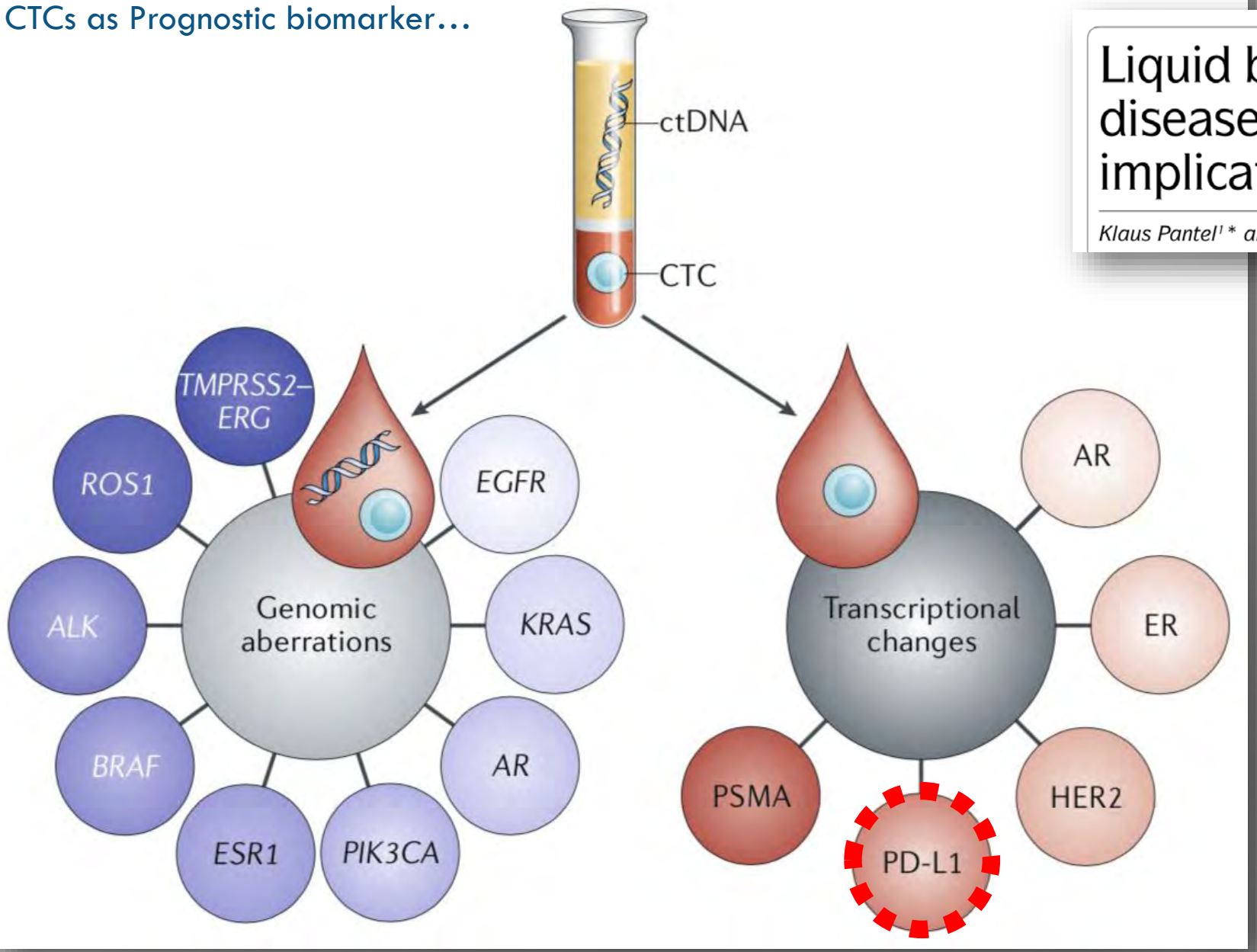
Therapeutic targets
Resistance mechanisms

Transcript/Protein Analyses

- ARv7 — AR-targeting-therapy resistance — *PC*
- PSMA — PSMA-targeted therapy — *PC*
- HER2 — HER2-targeting therapies — *BC*
- PD-L1 — Immunotherapy — *NSCLC, BC, HNC, Melanoma*
- ER — Endocrine therapy — *BC*

Therapeutic targets and resistance mechanisms

CTCs as Prognostic biomarker…



Liquid biopsy and minimal residual disease — latest advances and implications for cure

*Klaus Pantel[1] * and Catherine Alix-Panabières[2]*

nature REVIEWS CLINICAL ONCOLOGY 2019

cancers 2020

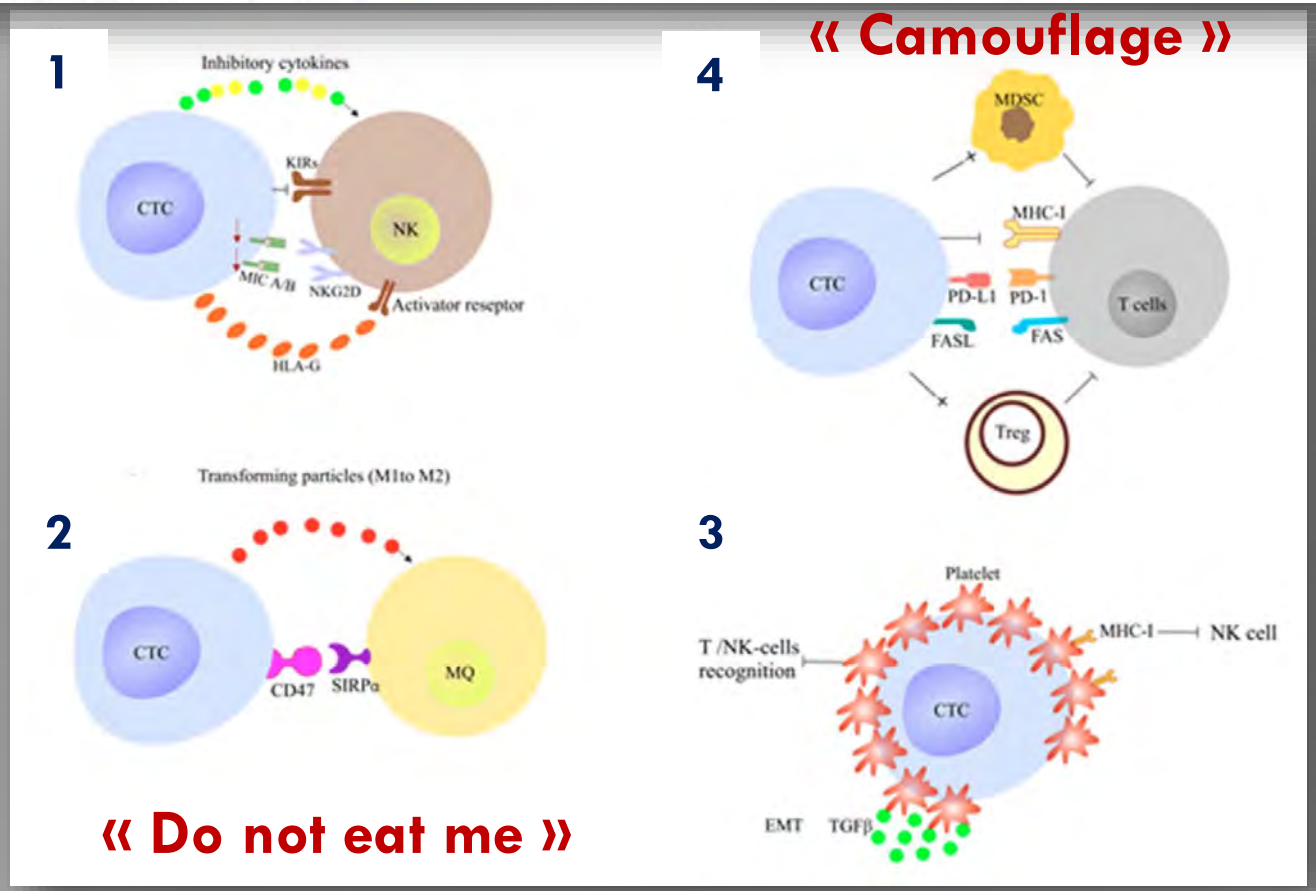
MDPI

Review

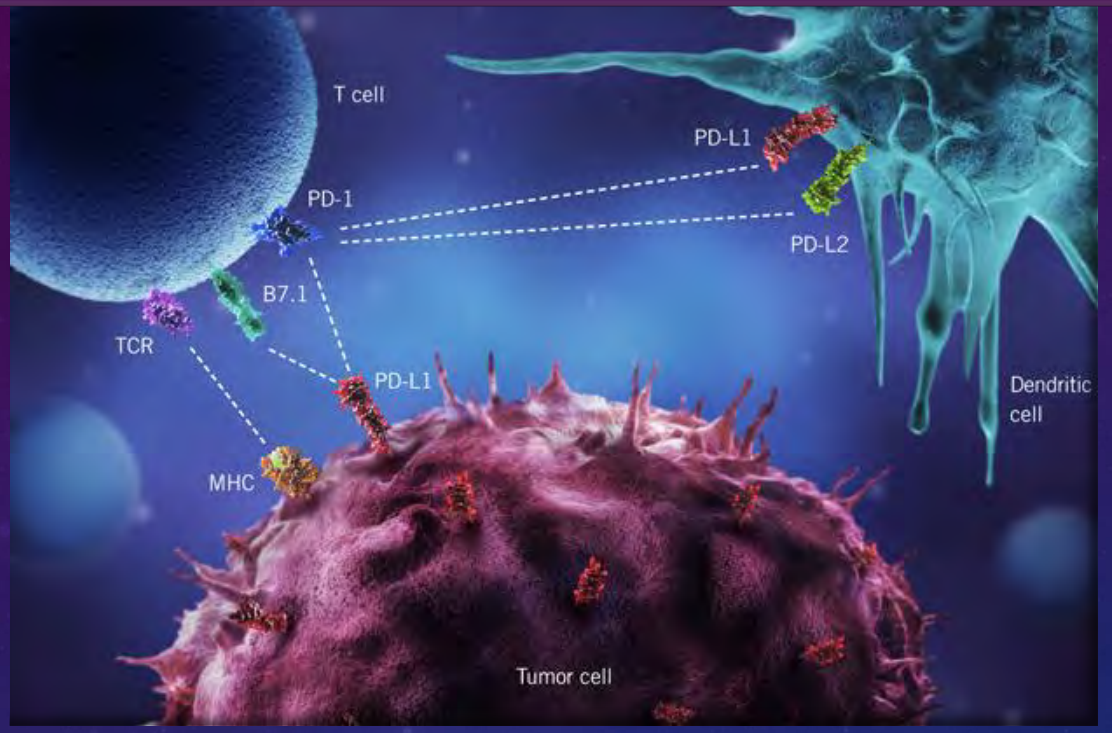
The Role of Circulating Tumor Cells in the Metastatic Cascade: Biology, Technical Challenges, and Clinical Relevance

Hassan Dianat-Moghadam [1,2], Mehdi Azizi [3], Zahra Eslami-S [4], Luis Enrique Cortés-Hernández [4], Maryam Heidarifard [5], Mohammad Nouri [1] and Catherine Alix-Panabières [4,*]

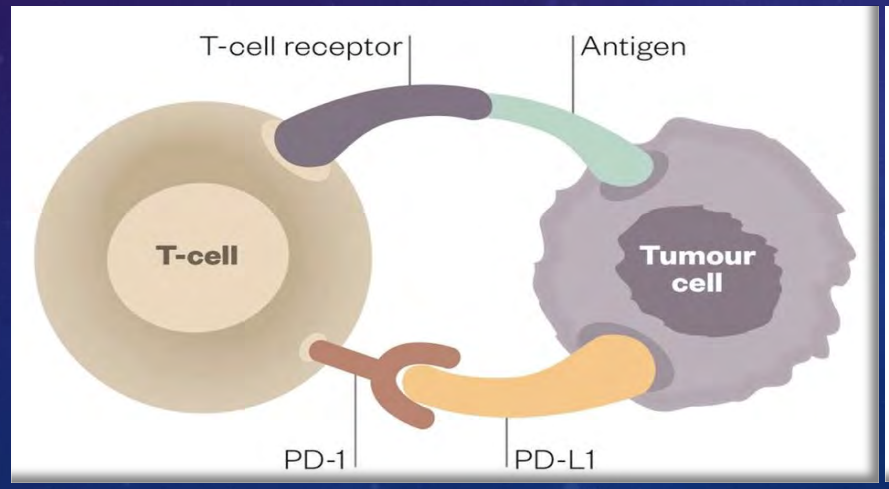
CTCs *evade the immune systems* in several ways



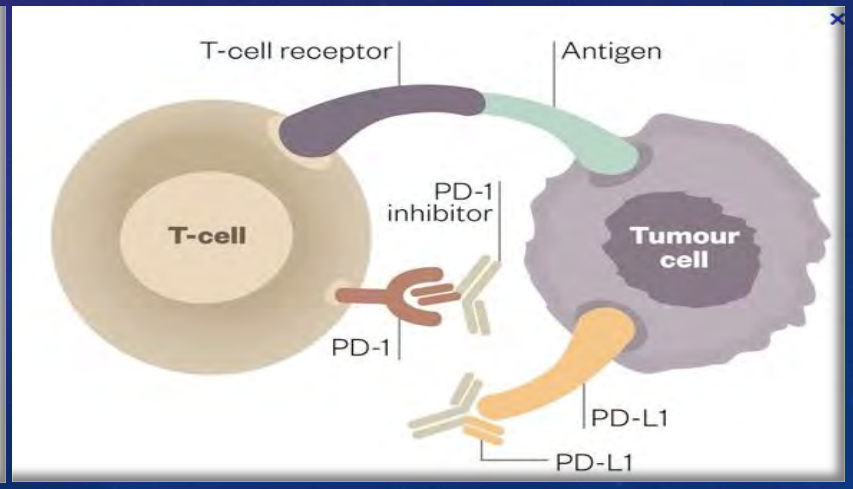
PD-L1 “CAMOUFLAGE” OF CANCER CELLS



Deactivation



Activation



THE LANCET Oncology

PD-L1 expression by circulating breast cancer cells Rachel David

PD-L1 expression by circulating breast cancer cells

Metastatic breast cancer cells express PD-L1, the ligand for the immune checkpoint receptor PD-1, according to new research. The findings suggest that it might be possible to predict which patients will benefit from PD-1 blockade, a promising therapeutic approach in cancer.

The team, led by Catherine Alix-Panabières (University of Montpelier, Montpelier, France), used a tool called CellSearch to detect circulating tumour cells (CTCs) in blood samples from hormone-receptor-positive, HER2-negative patients with metastatic breast cancer. They assessed the samples for expression of PD-L1 with an antibody validated using western blotting and flow cytometry.

The analysis showed that PD-L1 expression is common among CTCs derived from breast tumours. Although the sample size was small (one male patient and 15 female patients), 11 of 16 samples had a subpopulation of cells expressing PD-L1, either at low or high levels.

This high frequency of PD-L1 expression contrasts with previous work suggesting that breast cancer cells have low PD-L1 expression. According to Alix-Panabières, this discrepancy could be the result of higher PD-L1 expression by CTCs than by primary tumours, and potential differences in methods.

The team now wants to investigate whether their technique could be used as a "liquid biopsy" to identify patients who will benefit from treatment with PD-1 inhibitors—molecules that bind PD-1 and interfere with the checkpoint that enables cancer cells to evade the immune system. This technique could help to avoid exposing patients to any toxicities associated with PD-1 inhibitor treatment.

"It would be nice to see whether we can really stratify patients, and decide whether they will start, or not, immunotherapy", she commented. Additionally, the technique offers opportunities to "monitor patients during immunotherapy".

Daniel Hayes (University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA) agreed that this could be a valuable method to determine "entry into clinical trials and as a pharmacodynamic monitoring tool". However, he cautioned that further research is necessary to assess the clinical usefulness of measuring PD-L1 expression by CTCs, since "it is not clear that tissue PD-L1 measurement in cancer cells is sufficiently predictive for patient selection for PD-L1 inhibitor therapy".

Rachel David

Study Detects PD-L1 Expression on Breast Cancer Patient CTCs, Points to Potential New CellSearch Use

Jul 15, 2015
Turna Ray
Premium

NEW YORK (GenomeWeb) – Using a platform for assessing circulating tumor cells (CTCs), researchers have demonstrated the ability to gauge PD-L1 expression from liquid biopsies of metastatic breast cancer patients.

genomeweb

Frequent expression of PD-L1 on circulating breast cancer cells

2015

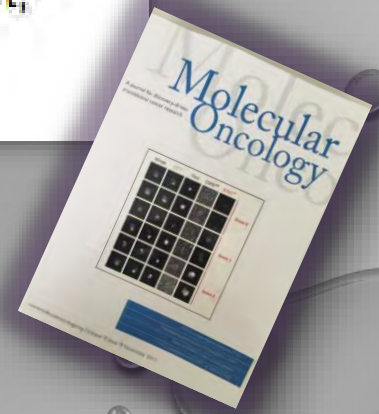
Martine Mazel, William Jacot, Klaus Pantel, Kai Bartkowiak, Delphine Topart,

Laure Cayrefourcq, Delphine Rossille, Thierry Maudelonde, Thierry Fest,

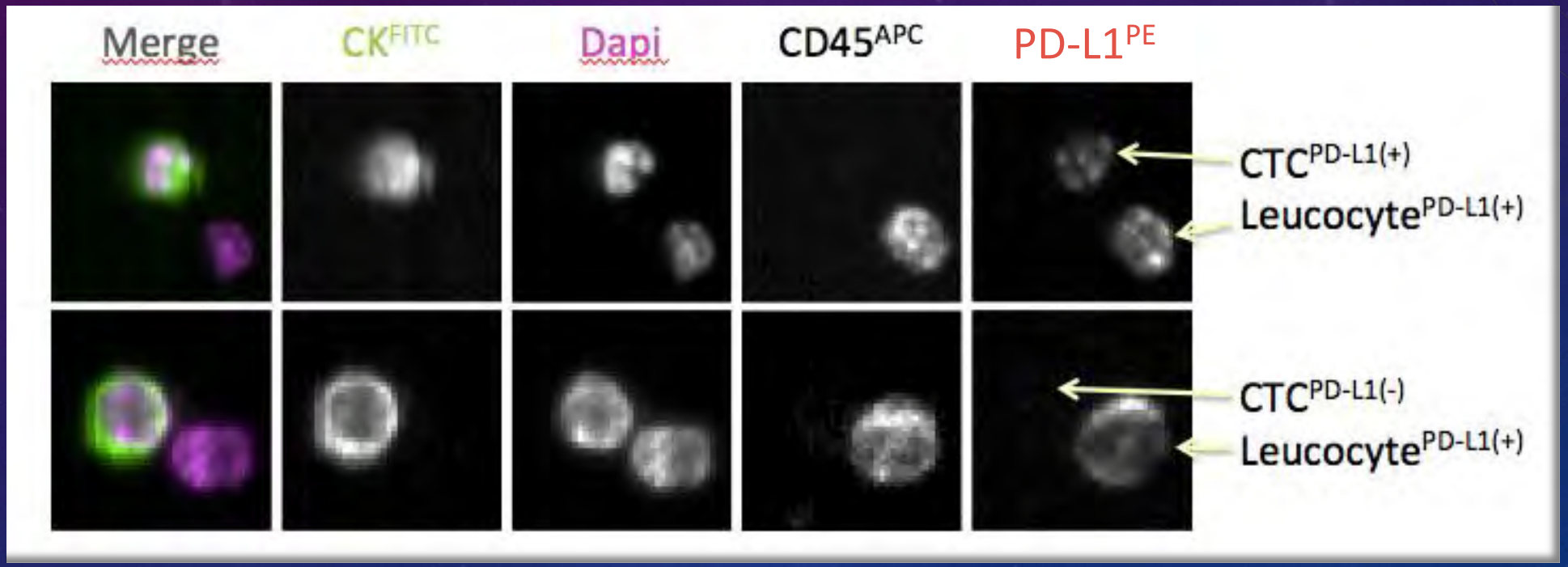
Catherine Alix-Panabières

Molecular Oncology

William Jacot



METASTATIC BREAST CANCER PATIENTES



Mazel *et al.*, *Mol Oncol* 2015
(Editorial by R. David in *Lancet Oncol.* 2015)

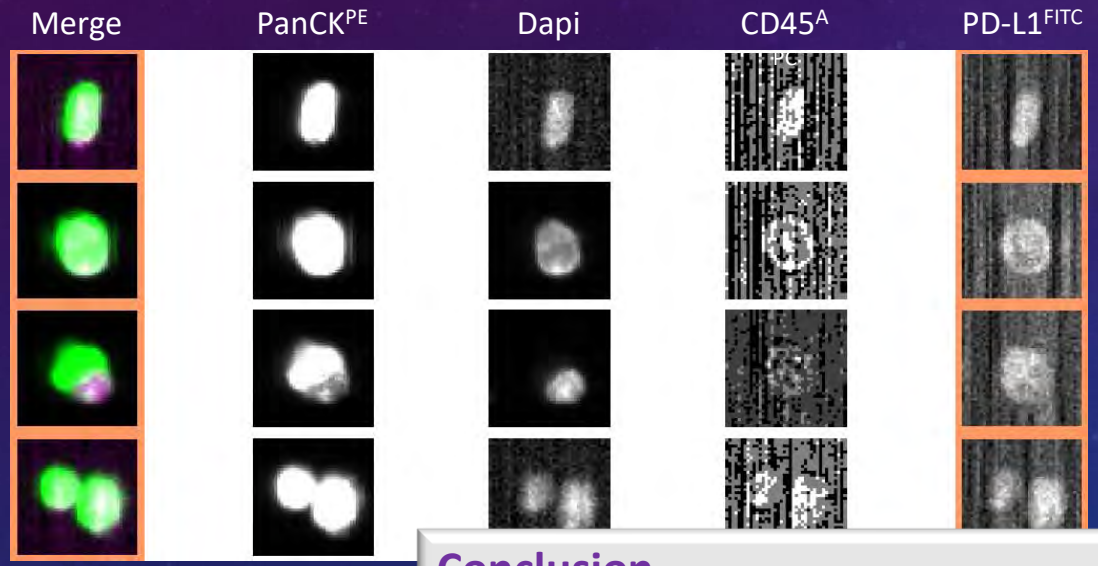
PD-L1 is frequently expressed on CTCs (> 60% of patients) in metastatic breast cancer patients

CTC DETECTION & PD-L1 EXPRESSION
METASTATIC BREAST CANCER

CANCER ID

ALCINA 1

- **72 MBC patients**
- Median Age 65 yrs old (range 35-87)
- Subtypes of breast cancer: **ER$^{(+)}$/HER2$^{(-)}$** 69.4%; **HER2$^{(+)}$** 18.1%, **TN** 12.5%



Clinical Chemistry 0:0
1093–1101 (2020)

Clinical Chemistry 2020

Cancer Diagnostics

Clinical Correlations of Programmed Cell Death Ligand 1 Status in Liquid and Standard Biopsies in Breast Cancer

William Jacot, Martine Mazel, Caroline Mollevi, Stéphane Pouderoux, Véronique D'Hondt, Laure Cayrefourcq, Céline Bourgier, Florence Boissiere-Michot, Fella Berrabah, Evelyne Lopez-Crapez, François-Clément Bidard, Marie Viala, Thierry Maudelonde, Séverine Guiu, and

Conclusion

- ❑ PD-L1 expression : tumor *vs* CTCs → no correlation (p=0.589)
- ❑ Presence of CTC$^{PD\text{-}L1(+)}$: independent biomarker for shorter PFS

CTC Detection & PD-L1 Expression
Metastatic Non-Small Lung Cancer

ALCINA 1

- **54 MNSCLC patients**
- Mean Age 64.5 yrs old
- 57.4% were men and 86% were smokers

Clinical Chemistry 00:0
1–10 (2021)

Clinical Chemistry **2021**

Cancer Diagnostics

Programmed Cell Death Ligand 1-Expressing Circulating Tumor Cells: A New Prognostic Biomarker in Non-Small Cell Lung Cancer

Léa Sinoquet,[a] William Jacot,[a,b] Ludovic Gauthier,[c] Stéphane Pouderoux,[a] Marie Viala,[a] Laure Cayrefourcq,[d,e] Xavier Quantin,[a,b] and Catherine Alix-Panabières[d,e,*]

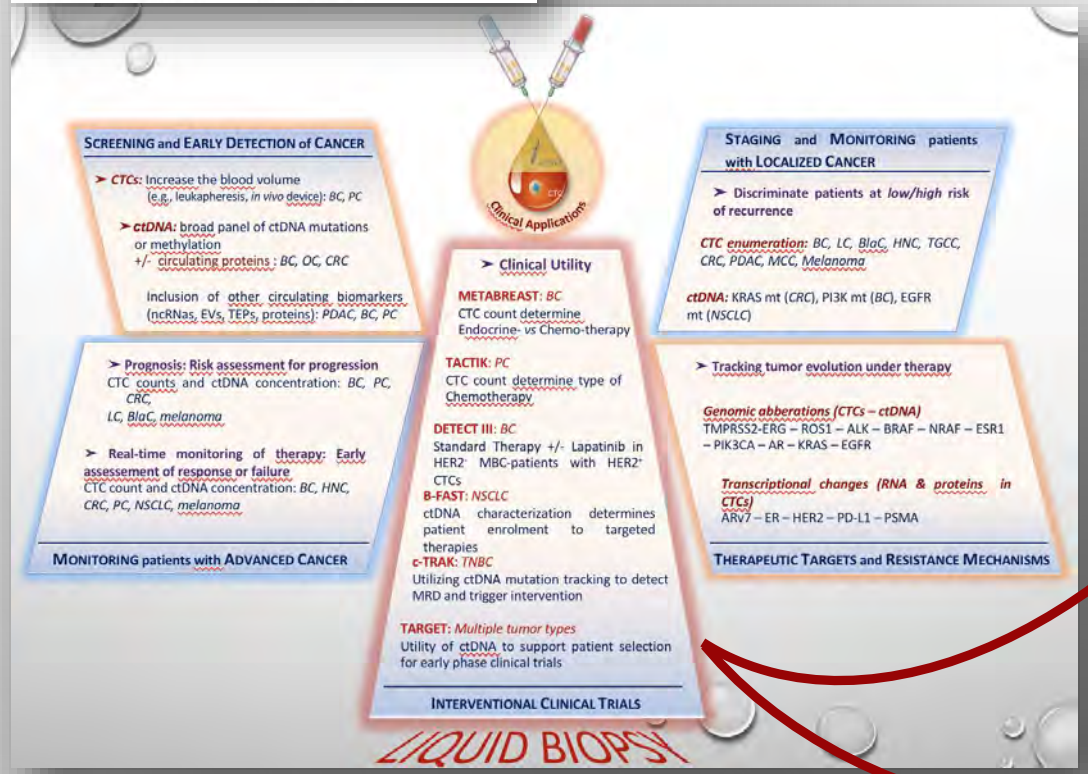
- CTCs detected in 23/53 patients (43.4%)
- $CTC^{PD\text{-}L1(+)}$ observed in 5 patients (9.4%).

CANCER DISCOVERY 10

REVIEW 2021

Liquid Biopsy: From Discovery to Clinical Application

Catherine Alix-Panabières[1,2] and Klaus Pantel[3]



HAS HAUTE AUTORITÉ DE SANTÉ

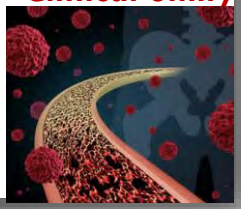
Original Investigation 2020

Circulating Tumor Cell Count–Driven vs Clinician-Driven First-line Therapy Choice in Hormone Receptor–Positive, ERBB2-Negative Metastatic Breast Cancer

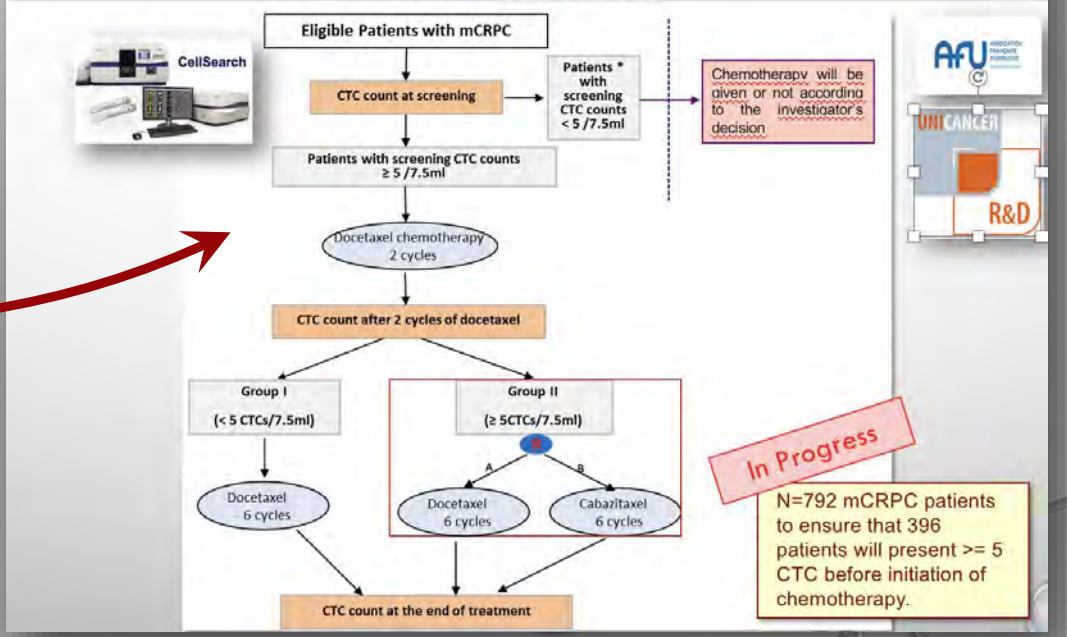
The STIC CTC Randomized Clinical Trial

François-Clément Bidard, MD, PhD; William Jacot, MD, PhD; Nicolas Kiavue, MBBS; Sylvain Dureau, PharmD; Amir Kadi, PhD; Etienne Brain, MD, PhD; Thomas Bachelot, MD; Hugues Bourgeois, MD; Anthony Gonçalves, MD, PhD; Sylvain Ladoire, MD, PhD; Hervé Naman, MD; Florence Dalenc, MD, PhD; Joseph Gligorov, MD, PhD; Marc Espié, MD; George Emile, MD; Jean-Marc Ferrero, MD; Delphine Loirat, MD, PhD; Sophie Frank, MD; Luc Cabel, MD; Véronique Diéras, MD; Laure Cayrefourcq, MSc; Cécile Simondi, MSc; Frédérique Berger, MSc; Catherine Alix-Panabières, PhD; Jean-Yves Pierga, MD, PhD

→ Clinical utility



Personalized Treatment of Metastatic castrate-resistant prostate cancer according to CTC kinetic during chemotherapy:
TACTIK Project



Review

2010

Circulating tumour cells in cancer patients: challenges and perspectives

Klaus Pantel[1] **and Catherine Alix-Panabières**[2,3]

[1] Institute of Tumour Biology, Centre of Experimental Medicine, University Medical Centre Hamburg Eppendorf, Hamburg, Germany
[2] University Medical Centre, Saint-Eloi Hospital, Institute of Research in Biotherapy, Laboratory of Rare Human Circulating Cells, Montpellier, France
[3] University Institute of Clinical Research, UM1-EA2415, Epidemiology, Biostatistics and Public Health, Montpellier, France

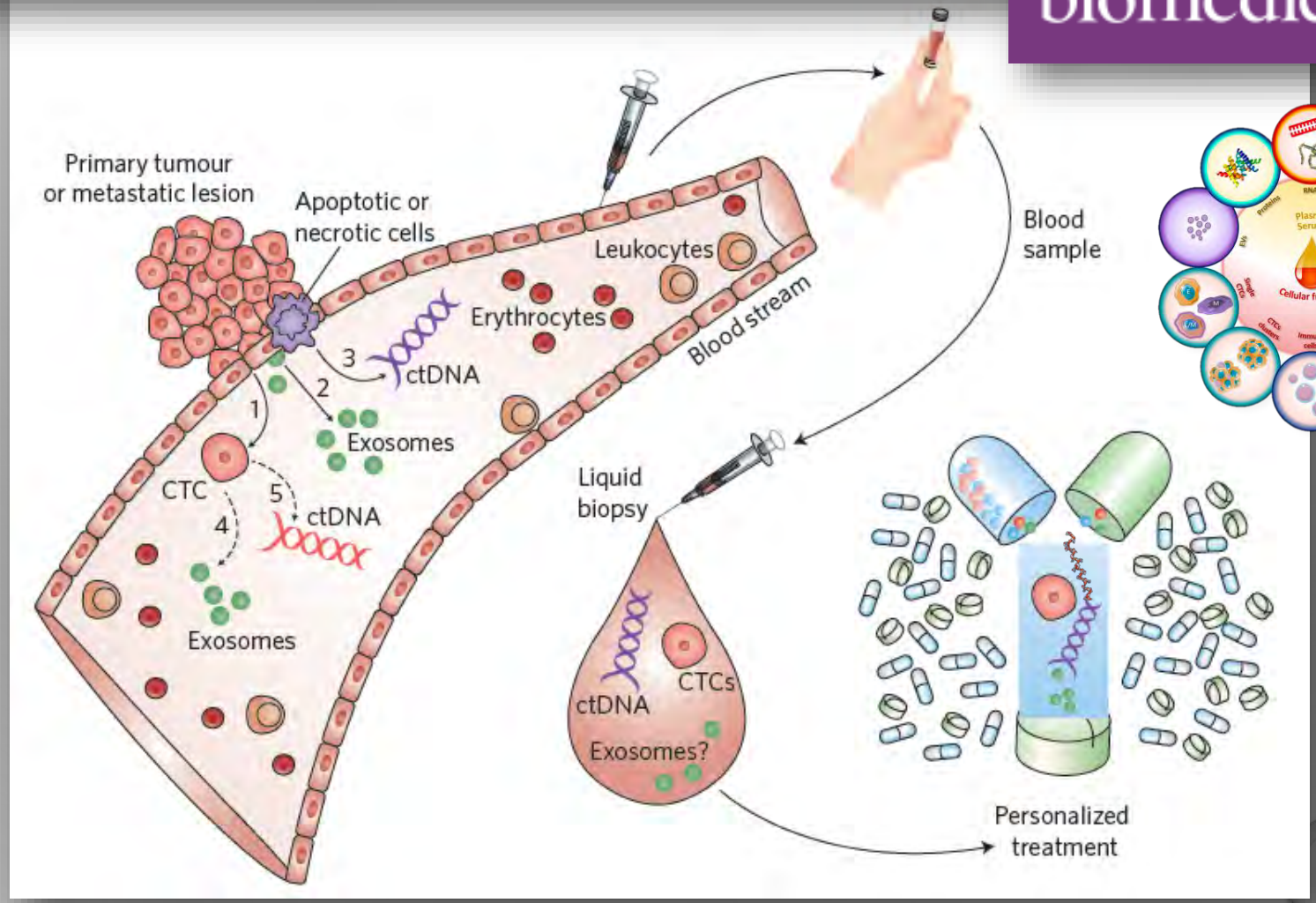
or resistance. Although promising data from patients with advanced disease demonstrate the value of CTC analysis as "liquid biopsy", studies on cancer patients at earlier stages are hampered by the low CTC counts. It remains unclear if

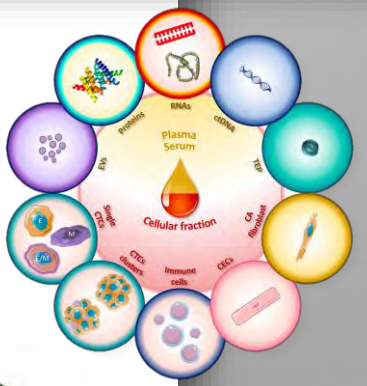
Clinical prospects of liquid biopsies

Catherine Alix-Panabières and Klaus Pantel

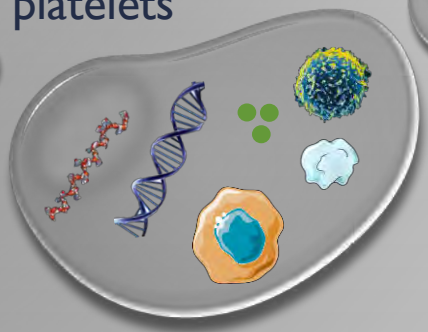
nature biomedical engineering 2017

INDEX ALGORITHM





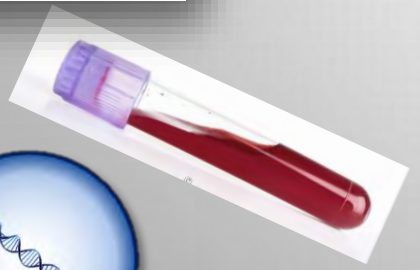
CTCs
ctDNA
miRNA
Evs (exosomes)
Proteins
Immune cells
Tumor-educated platelets

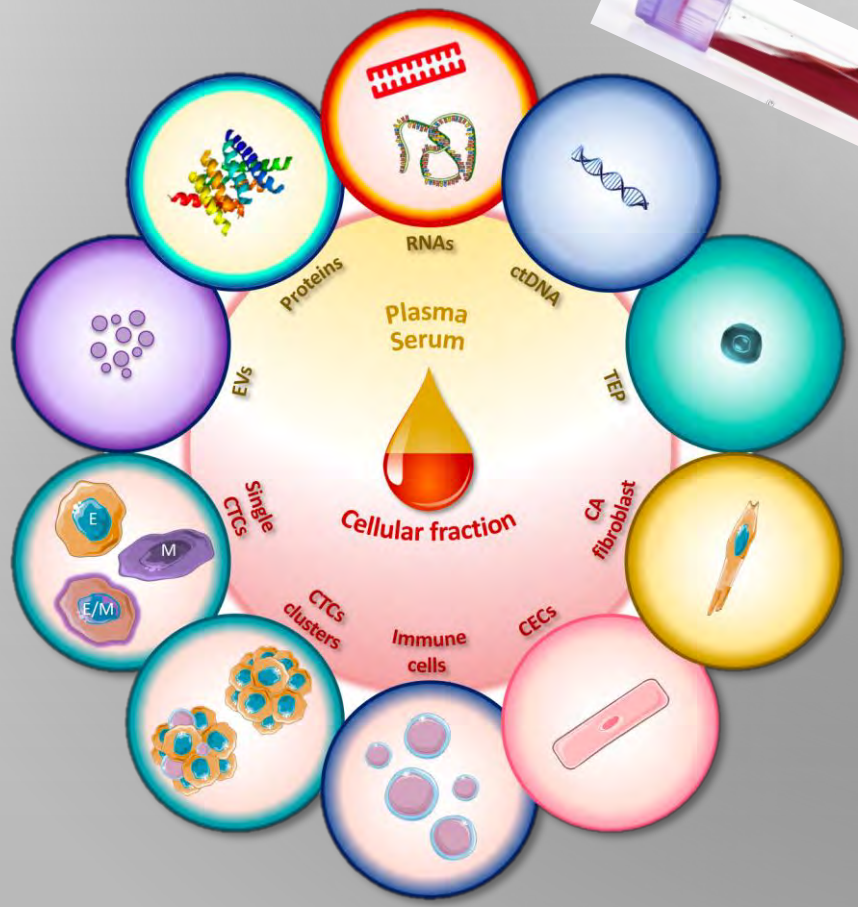


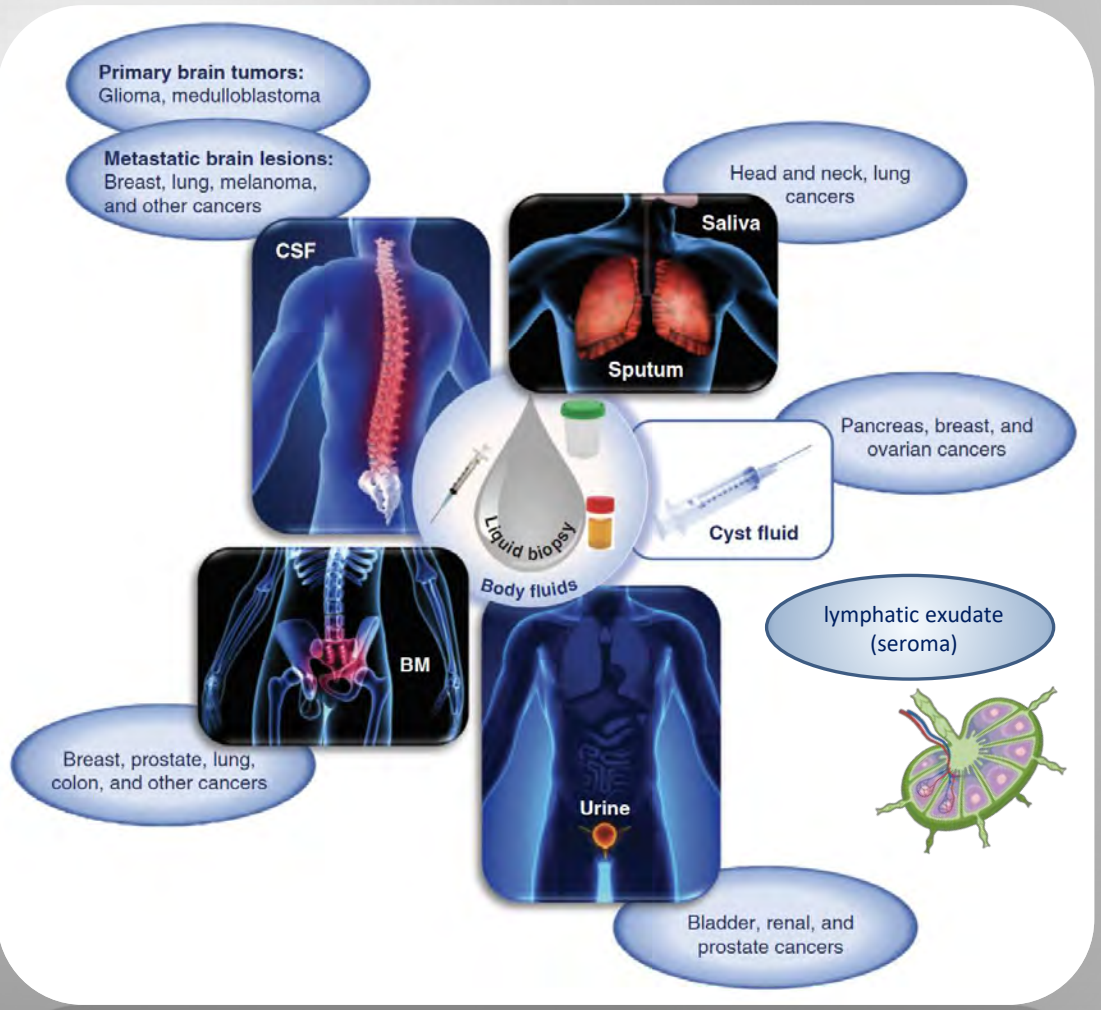
CANCER DISCOVERY 10
REVIEW 2021

Liquid Biopsy: From Discovery to Clinical Application

Catherine Alix-Panabières[1,2] and Klaus Pantel[3]







Perspective: The future of liquid biopsy

Nature | Vol 579 | 26 March 2020

Catherine Alix-Panabières

Cancer diagnosis

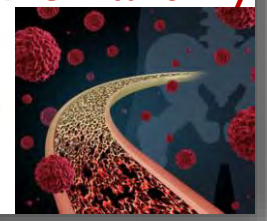
nature

JAMA Oncology | Original Investigation 2020

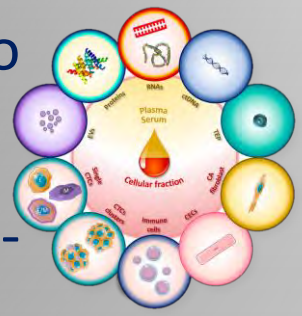
Efficacy of Circulating Tumor Cell Count–Driven vs Clinician-Driven First-line Therapy Choice in Hormone Receptor–Positive, ERBB2-Negative Metastatic Breast Cancer
The STIC CTC Randomized Clinical Trial

François-Clément Bidard, MD, PhD; William Jacot, MD, PhD; Nicolas Kiavue, MBBS; Sylvain Dureau, PharmD; Amir Kadi, PhD; Etienne Brain, MD, PhD; Thomas Bachelot, MD; Hugues Bourgeois, MD; Anthony Gonçalves, MD, PhD; Sylvain Ladoire, MD, PhD; Hervé Naman, MD; Florence Dalenc, MD, PhD; Joseph Gligorov, MD, PhD; Marc Espié, MD; George Emile, MD; Jean-Marc Ferrero, MD; Delphine Loirat, MD, PhD; Sophie Frank, MD; Luc Cabel, MD; Véronique Diéras, MD; Laure Cayrefourcq, MSc; Cécile Simondi, MSc; Frédérique Berger, MSc; Catherine Alix-Panabières, PhD; Jean-Yves Pierga, MD, PhD

→ Clinical utility



- To push liquid biopsy into widespread use, **more intervention studies are needed**;
- To develop **an algorithm** that can **combine different circulating biomarkers** to obtain a precise tumour profile;
- To **define guidelines and SOP** for *liquid biopsy*: technical variability in the pre-analytical and analytical steps



→ **Big consortia to achieve these goals : e.g. ELBS**

THE EUROPEAN LIQUID BIOPSY SOCIETY

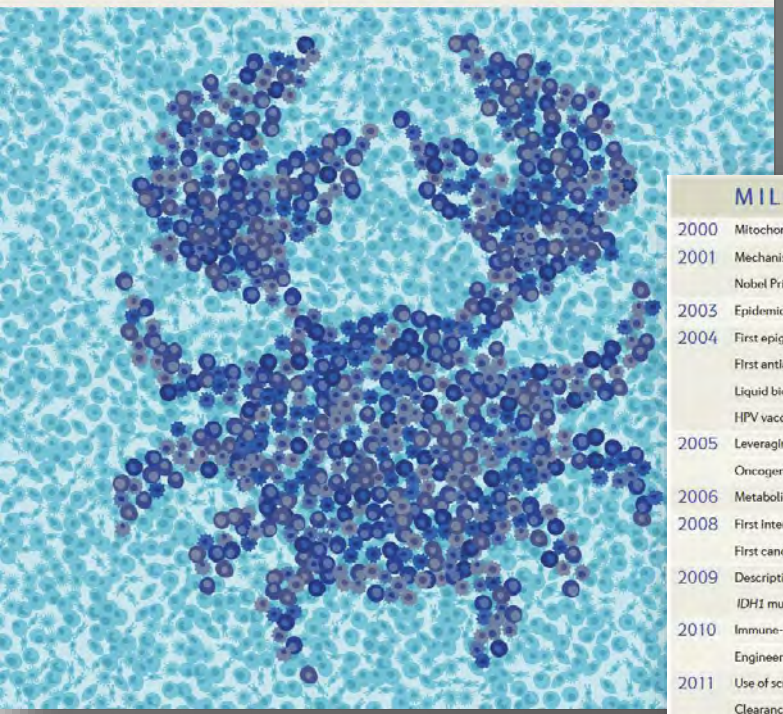
International Liquid Biopsy Standardization Alliance (ILSA)

CHU

www.nature.com/collections/cancer-milestones December 2020

nature milestones

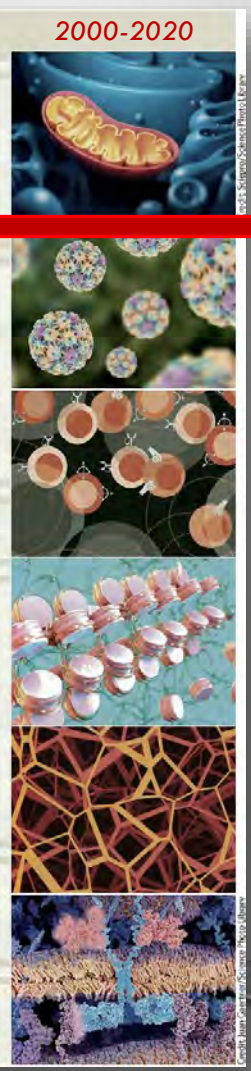
Cancer



During the last 20 yrs…

MILESTONES IN CANCER 2000-2020

2000	Mitochondrial complex II mutations found in tumours
2001	Mechanisms of resistance to targeted treatment (MILESTONE 1)
	Nobel Prize awarded for "discoveries of key regulators of the cell cycle"
2003	Epidemiological link between cancer and obesity
2004	First epigenetic drug to gain FDA approval
	First antiangiogenic agent to gain FDA approval for cancer treatment
	Liquid biopsies for non-invasive diagnosis and monitoring of patients (MILESTONE 2)
	HPV vaccines to prevent cervical cancer (MILESTONE 3)
2005	Leveraging synthetic lethality for treatment (MILESTONE 4)
	Oncogene-induced senescence in premalignant tissues and cancer (MILESTONE 5)
2006	Metabolic adaptations in cancer (MILESTONE 6)
2008	First interim analysis published by The Cancer Genome Atlas
	First cancer whole-genome sequence (MILESTONE 7)
2009	Description of colorectal cancer organoids
	IDH1 mutations leading to the generation of 2-hydroxyglutarate
2010	Immune-checkpoint inhibitors from bench to bedside (MILESTONE 8)
	Engineering T cells to kill cancer cells (MILESTONE 9)
2011	Use of screening to decrease mortality from lung cancer
	Clearance of senescent cells by the immune system
2012	Epigenetic drivers of tumour initiation and progression (MILESTONE 10)
	Clonal diversity of tumour cells as a basis for cancer progression and treatment resistance (MILESTONE 11)
	Full-length single-cell mRNA sequencing of individual tumour cells
	Anti-tumour role of metabolite depletion
2013	Targeting 'undruggable' non-kinase proteins (MILESTONE 12)
	Gut microbiome influences on anti-tumour immune responses (MILESTONE 13)
2015	The Big Bang theory of cancer evolution is proposed
	Driver mutations found in healthy tissue
	First FDA approval for a combination of immunotherapies
2016	First FDA approval for an anti-PD-L1 inhibitor
2017	Potential of artificial intelligence in cancer diagnosis and monitoring (MILESTONE 14)
	First FDA approval of a treatment on the basis of tumour genomics alone
	First inhibitor of mutant IDH2 approved for clinical use
2018	Nobel Prize awarded for "discovery of cancer therapy by inhibition of negative immune regulation"
2019	Clinical trial of CAR T cells to target BCMA in patients with multiple myeloma
	Nobel Prize awarded for "discoveries of how cells sense and adapt to oxygen availability"
2020	Pan-cancer analysis of whole genomes
	Clinical trial of CD19-targeting CAR–Natural Killer cells in patients with CD19⁺ cancers



MILESTONE 2

Diana Romero,
Nature Reviews Clinical Oncology

Tracking cancer in liquid biopsies

The diverse clinical applications that derived from analysis of circulating tumour material eventually led to the coining of the term 'liquid biopsy' by Pantel and Alix-Panabières in 2010. In subsequent investigations,

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On the need for integrating CANCER into ONE HEALTH perspective

Antoine DUJON [1,2,3], Joel S. BROWN[4*], Delphine DESTOUMIEUX-GARZON[5], Marion VITTECOQ[1,2,6], Rodrigo HAMEDE[7], Aurélie TASIEMSKI[8,9], Justine BOUTRY[1,2], Sophie TISSOT[1,2], Catherine ALIX-PANABIERES[1,2,10], Pascal PUJOL[1,2,11], François RENAUD[1,2], Frédéric SIMARD[2], Benjamin ROCHE[1,2], Beata UJVARI[3,7*], Frédéric THOMAS[1,2*]

ONE HEALTH

The "One World - One Health" concept, initiated in 2004, recognizes the close connections between health of humans and that of other animals and our shared environment. The importance of this concept is evidenced by the accelerated emergence or re-emergence of zoonoses (*e.g.* Ebola, current COVID-19 pandemic) over the last decades [1].

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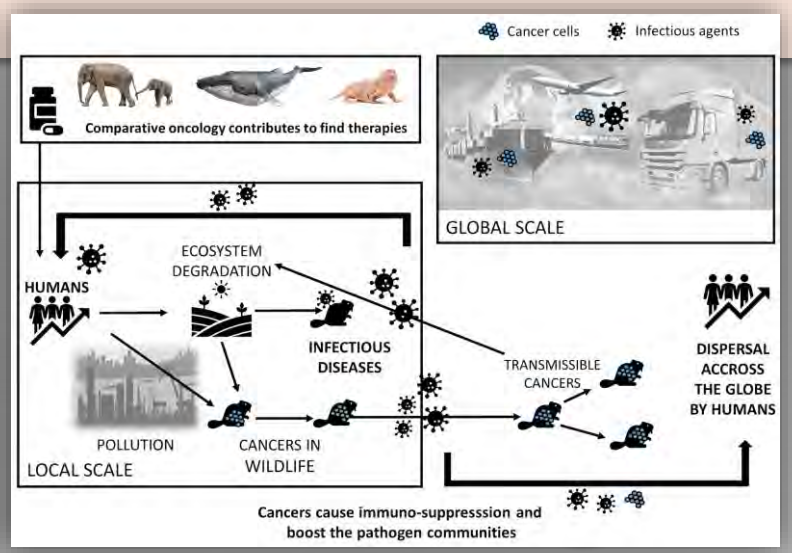
We argue that cancers should be an additional key focus in the One Health approach:

1- Human activities are oncogenic to other animals, exacerbating the dynamics of oncogenesis, causing immuno-suppressive disorders in wildlife with effects on host-pathogen interactions ;

2- The emergence of transmissible cancers in animal species (or even humans) has the potential to accelerate biodiversity loss across ecosystems and to become pandemics ;

3- Translating knowledge of tumor suppressor mechanisms found across the Animal Kingdom to human health offers novel insights into cancer prevention and treatment strategies.

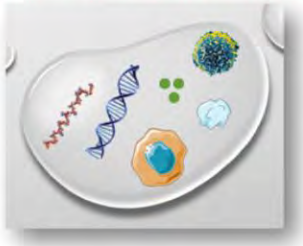


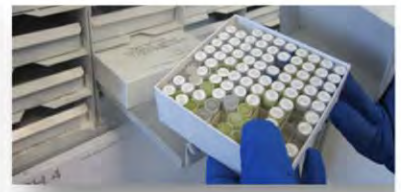
LCCRH

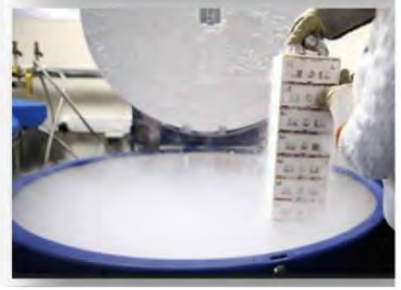
Laboratoire Cellules Circulantes Rares Humaines

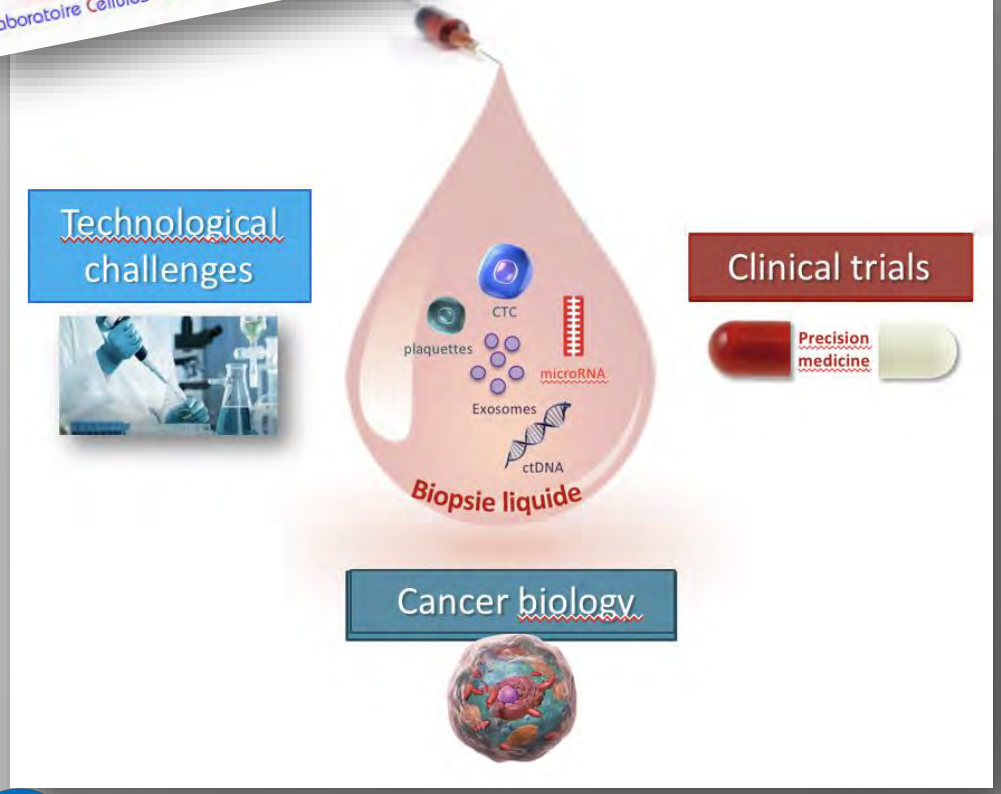
Biobanking : plasma – cells (>10 years)
(associated biological & clinical data plus CTC count)

→ **Detection of other circulating biomarkers**









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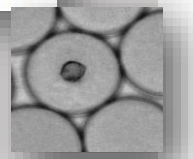

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SUPPORTS

FP6 EU STREP 'DISMAL'
TRANSCAN '**CTCSCAN**' 2012
TRANSCAN '**PROLIPSY**' 2
IMI '**CANCER-ID**' 2015
Marie Curie '**ELBA**' 2017

FUI **PANTHER** 2016
INCa - ARC - La Ligue
Fondation de France - MINEFI - SIRIC
MENARINI/ROCHE

GRANTS

Transcan 'PROLIPSY'

Prostate Cancer
(CTCs, ctDNA & exosomes)

Merkel Carcinoma
(CTCs, circulating nucleic acids)

Ministère des Solidarités et de la Santé

Prostate Cancer
(CTCs)

PHRC - TACTIK

European Liquid Biopsies Academy

Marie Curie

Lung Cancer
(CTCs, ctDNA, miRNA, exosomes, platelets)

MECA-CTC

Breast & Colon Cancer

CIRCUTEC

Head & Neck Cancer
(CTCs)

IMI CALL

Breast & lung Cancers
(CTCs, ctDNA, exosomes)

COLOSPOT

Colon Cancer
(CTCs)

Laboratory Circulating Rare Human Cells

CHU MONTPELLIER CENTRE HOSPITALIER UNIVERSITAIRE

LCCRH Laboratoire Cellules Circulantes Rares Humaines

UNIVERSITÉ DE MONTPELLIER

CREEC Centre de Recherches Écologiques & Évolutives sur le Cancer

THE EUROPEAN LIQUID BIOPSY SOCIETY

CANECEV

http://canecev.org/

CNRS International French-Australian Lab

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MONTPELLIER CANCER
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FEDER
la Région Languedoc Roussillon
Thank you for your attention