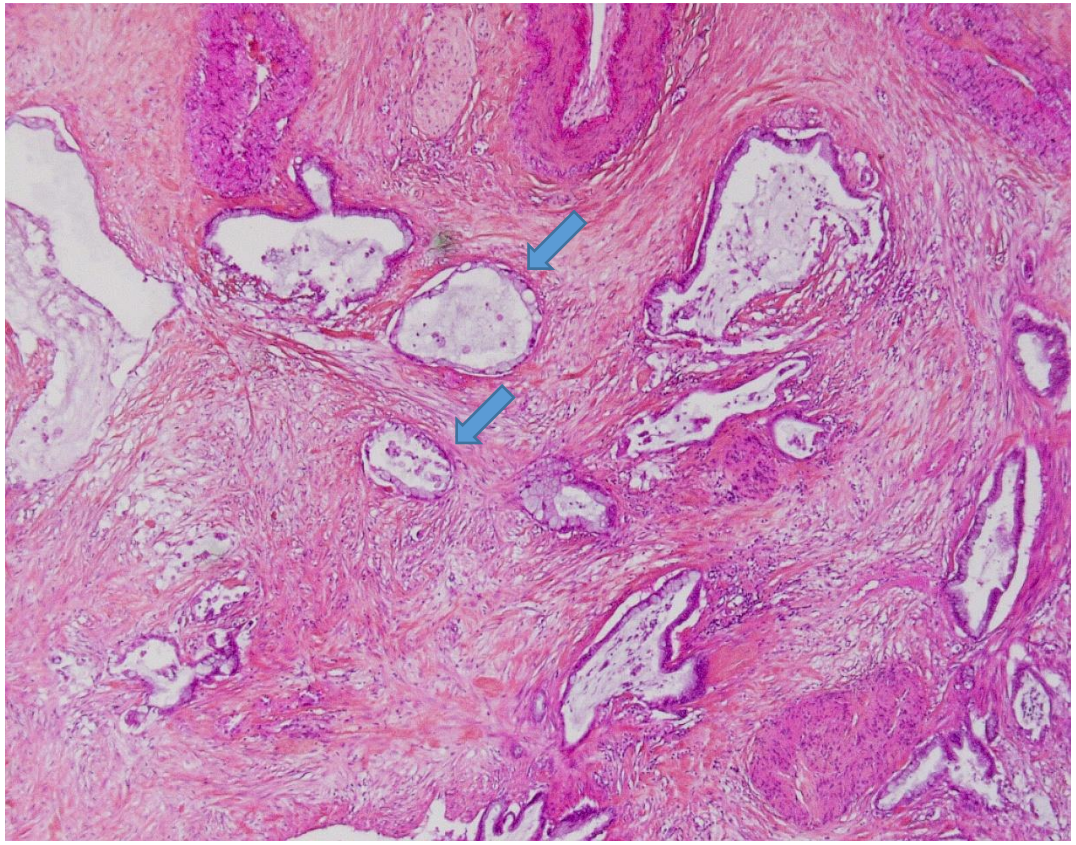
Tissue biomarkers in pancreatic ductal adenocarcinoma

Jerome Cros
Dpt of Pathology – INSERM U1149
Beaujon Hospital, Paris, France

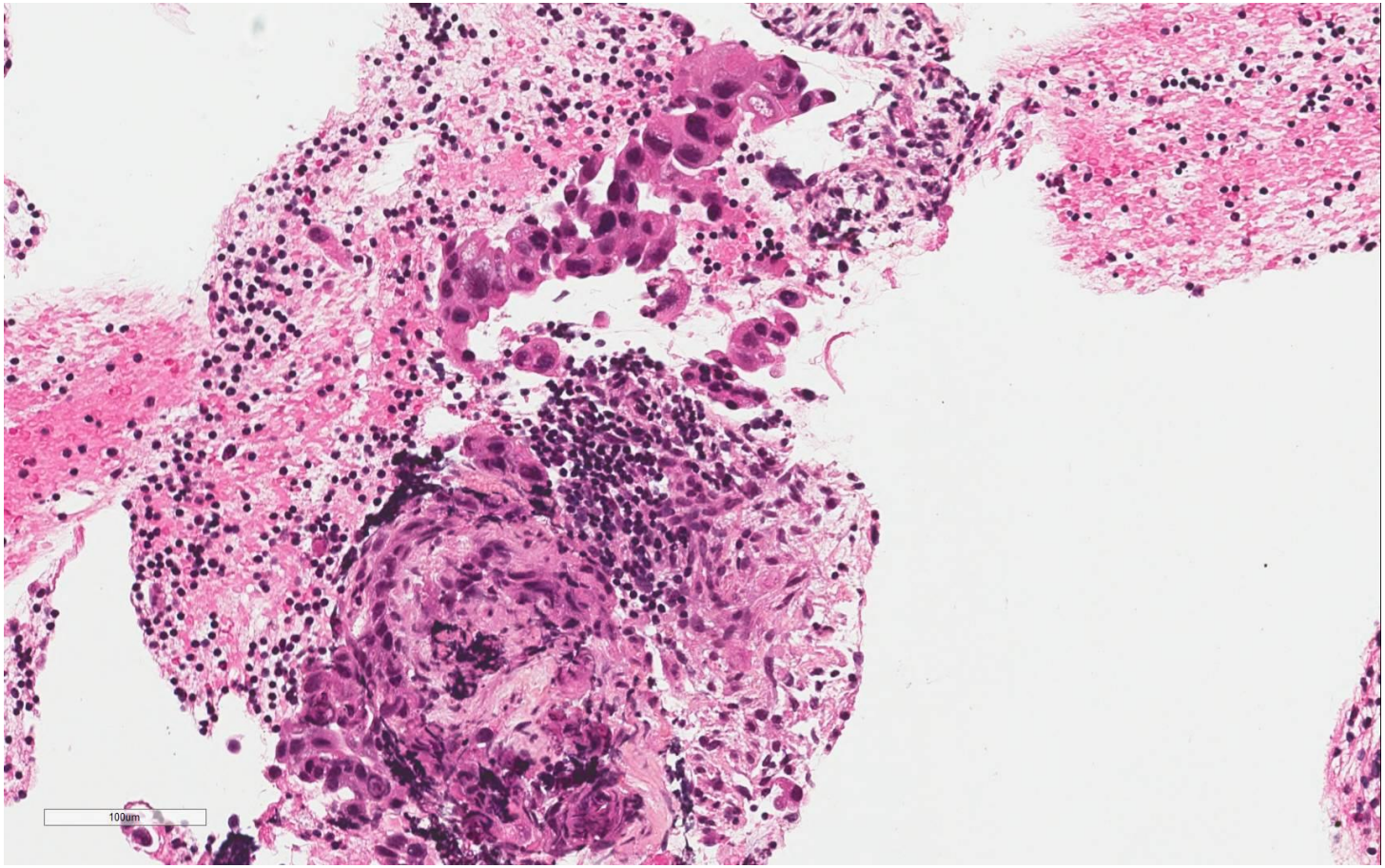
Challenges associated with tissue biomarker in pancreatic ductal adenocarcinoma



Tumor cells are rare in PDAC….

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

Challenges associated with tissue biomarker in pancreatic ductal adenocarcinoma



… and this is even worse in fine needle biopsies!

DNA-based biomarker in pancreatic ductal adenocarcinoma

TCGA, Cancer cell 2017

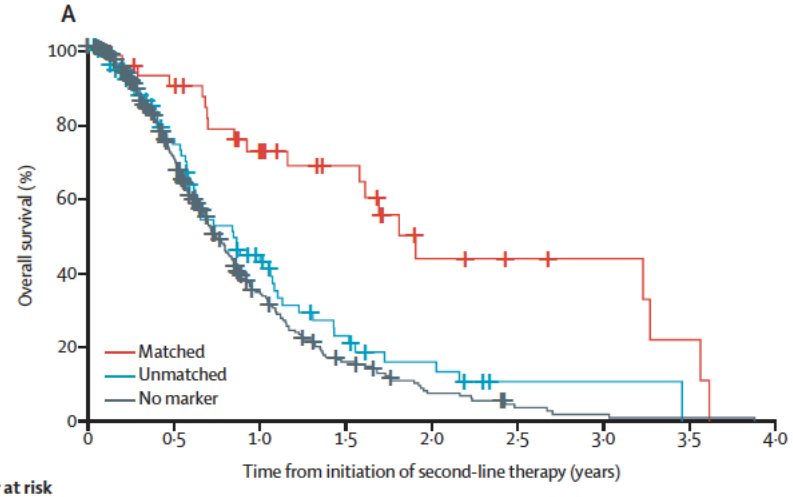
FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

DNA-based biomarker in pancreatic ductal adenocarcinoma

1082 received Perthera reports (282 with actionable molecular findings)
- 1005 pancreatic adenocarcinoma
- 11 adenosquamous carcinoma
- 12 acinar cell carcinoma
- 35 neuroendocrine tumour
- 19 other pancreaticobiliary

405 excluded
- 351 no documented first line of therapy
  - 195 being followed (168 surgical candidates)
  - 156 deceased (66 surgical candidates)
- 54 with neuroendocrine or other pancreaticobiliary tumours

677 patients in analysis cohort (189 with actionable molecular findings)



Number at risk (number censored)									
Matched therapy	39	33	23	16	7	5	4	2	0
	(0)	(2)	(4)	(6)	(4)	(2)	(1)	(0)	(0)
Unmatched therapy	83	49	24	11	6	1	1	0	0
	(0)	(15)	(6)	(3)	(2)	(3)	(0)	(0)	(0)
No marker	288	167	65	27	11	4	2	1	0
	(0)	(45)	(25)	(4)	(3)	(2)	(0)	(0)	(0)

Actionable molecular findings	Line of therapy	Time on therapy (months)	Second line of therapy (advanced setting)
ALK fusion	2	≥29	Crizotinib + IMRT + gemcitabine
MSI-H	2	≥16	Pembrolizumab
BRCA1 mutation	2	12	FOLFOX + olaparib
ATM mutation	2	≥11	Alternating chemotherapy
BRAF mutation	2	11	Trametinib + dabrafenib
MSI-H	2	≥10	Pembrolizumab
BRCA2 mutation	2	10	Olaparib
PALB2 mutation	2	≥10	Olaparib

+ *KRAS* G12C targeting therapy

*POLO trial

Pishvaian et al. Lancet oncol. 2020

DNA-based biomarker in pancreatic ductal adenocarcinoma

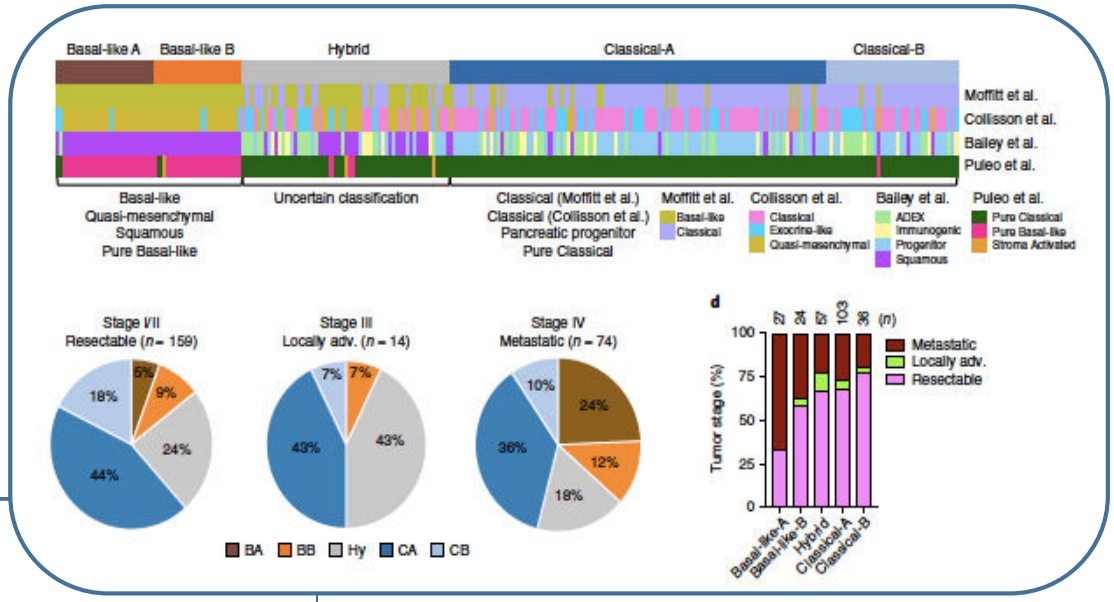
Ideal word : large NGS panel for all

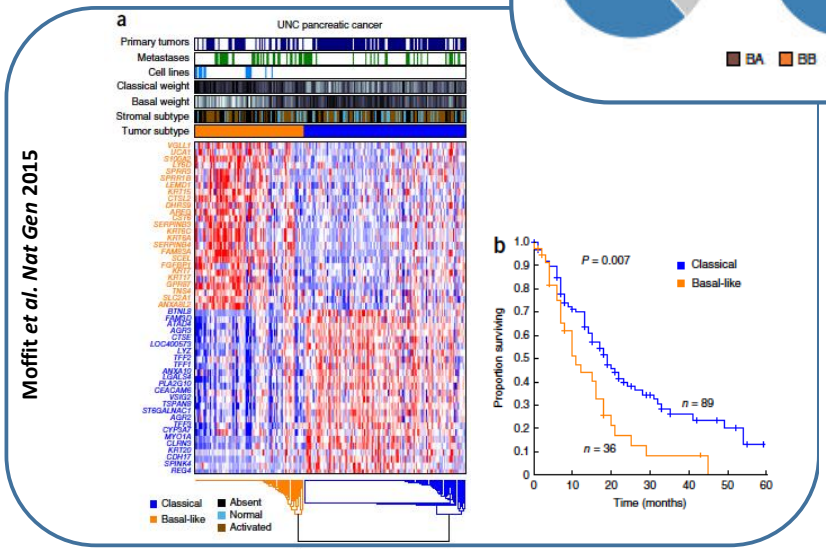
Minimal work up:

- *KRAS* seq, WT➜ look for fusion trancripts

- *BRCA1/2* seq ➜ Pt/olaparib/genetic conselling

RNA-based biomarker in pancreatic ductal adenocarcinoma





Chan-Seng-Yue et al Nat genetics 2020

How many subtypes?
Is it always back and white or a gradient?

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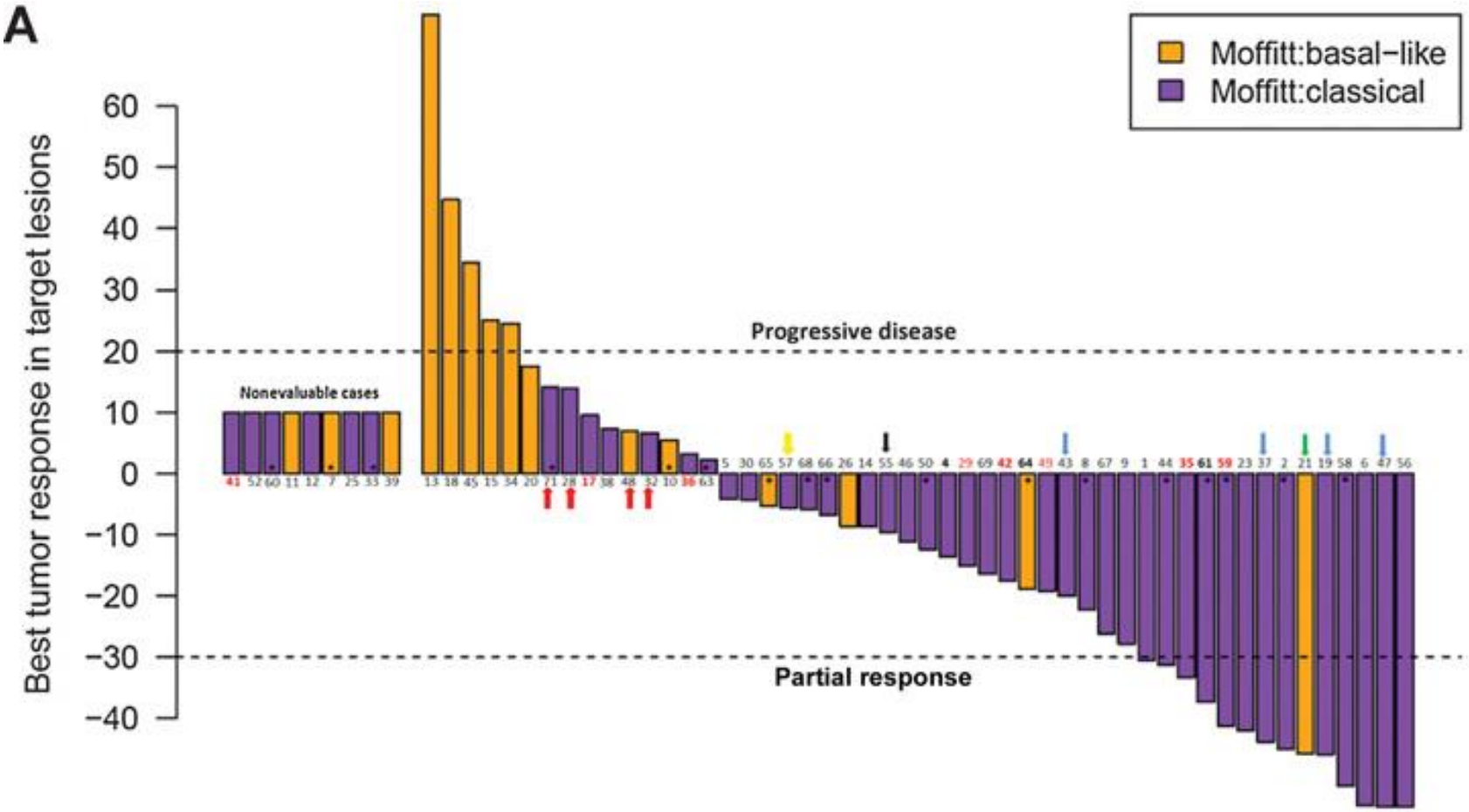
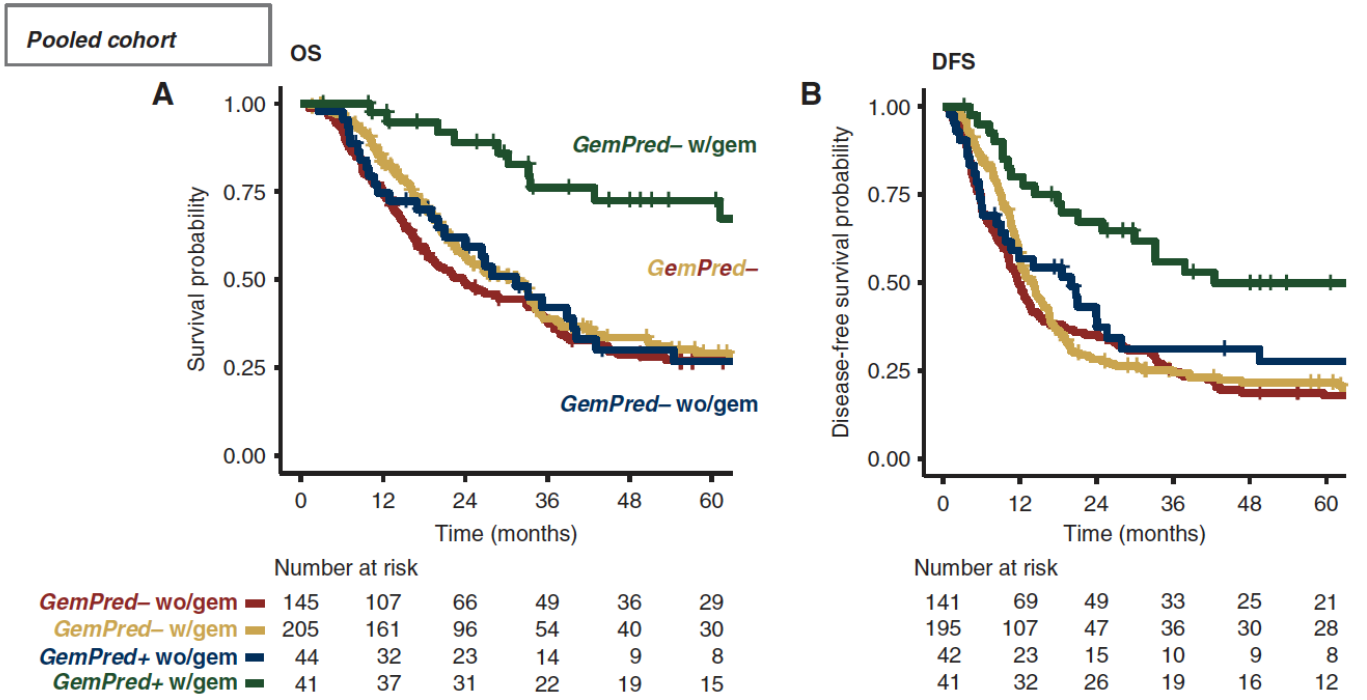
Reconnue d'utilité publique

RNA-based biomarker in pancreatic ductal adenocarcinoma



Aung *et al. Clin can res* 2018

RNA-based biomarker in pancreatic ductal adenocarcinoma



GemPred: RNA-based signature to predict response to gemcitabine in PDAC

More signatures to come?

Nicolle *et al. Ann oncol* 2021

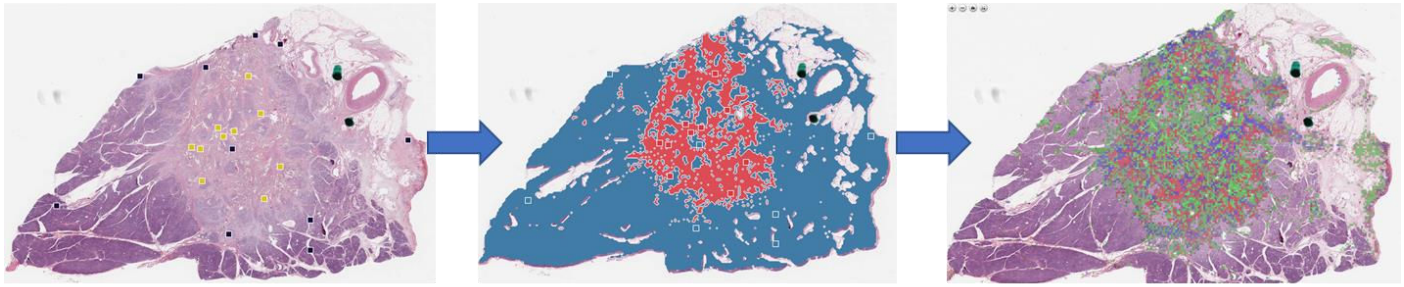
RNA-based biomarker in pancreatic ductal adenocarcinoma

RNA signatures have a strong prognostic/predictive value

- RNAseq in routine practice is challenging
- Signature determination is complex in highly contaminated samples
- Methylation-based signatures?

Transforsm these signatures into routine-ready tools

AI-based



Tumor detection

Molecular subtype determination

Saillard *et al. unpublished*

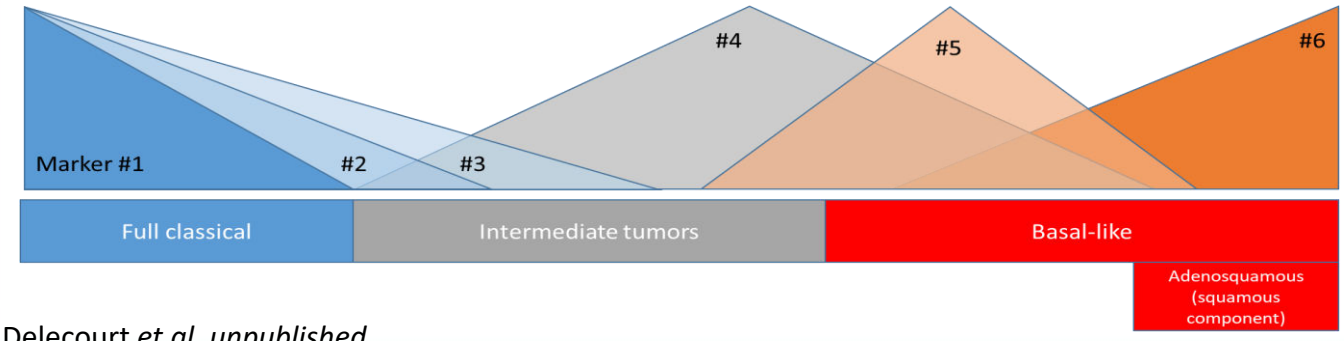
RNA-based biomarker in pancreatic ductal adenocarcinoma

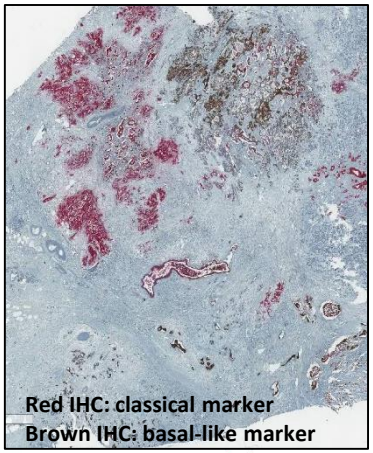
RNA signatures have a strong prognostic/predictive value

- RNAseq in routine practice is challenging
- Signature determination is complex in highly contaminated samples
- Methylation-based signatures?

Transforsm these signatures into routine-ready tools

IHC-based





Delecourt *et al. unpublished*

Protein-based biomarker in pancreatic ductal adenocarcinoma

- SO MANY PROGNOSTIC MARKERS….
  - None used

- No predictive marker in routine practice
  - hENT1/CDA for gemcitabine
  - SLFN11 for irinotecan…

Tissue biomarkers in pancreatic ductal adenocarcinoma

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Key messages:

- Adequate sampling is key to biomarker determination in PDAC

- Should all patients have at least a *KRAS* and *BRAC1/2* seq?

- RNA-based signature may help stratify patients if they can be robustly determined

Journée scientifique
CANCER DU PANCRÉAS

Journée scientifique
CANCER DU PANCRÉAS

WHAT CAN WE LEARN FROM THE BLOOD ?

CIRCULATING TUMOR CELLS (CTCs) IN PANCREATIC CANCER

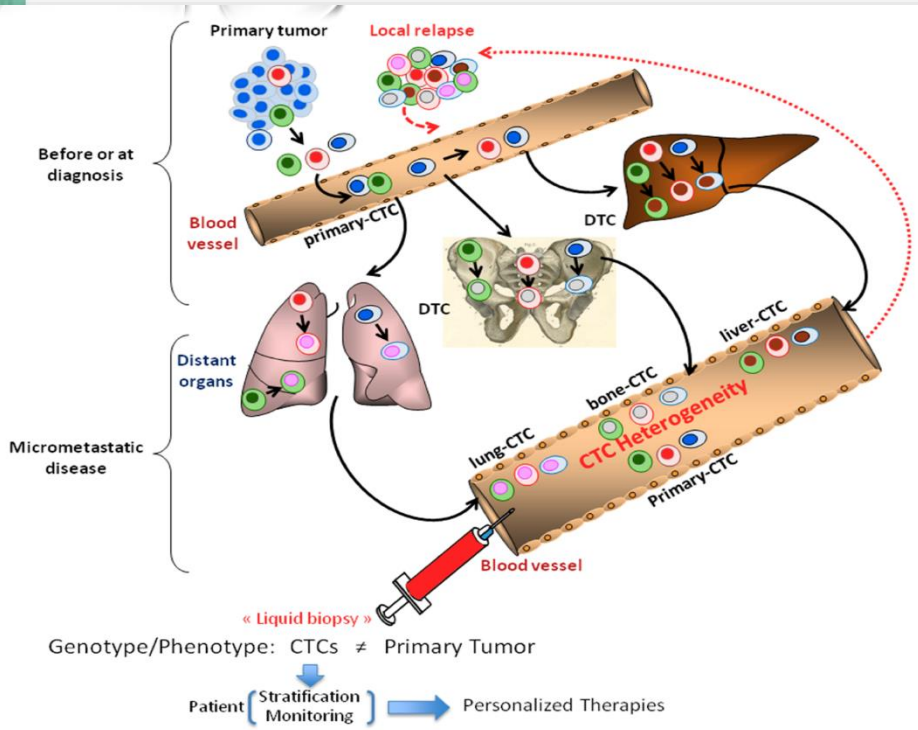
LIQUID BIOPSY

Dr. Catherine Alix-Panabières

CHU et Université de Montpellier

c-panabieres@chu-montpellier.fr

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique



DRUG RESISTANCE ?

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

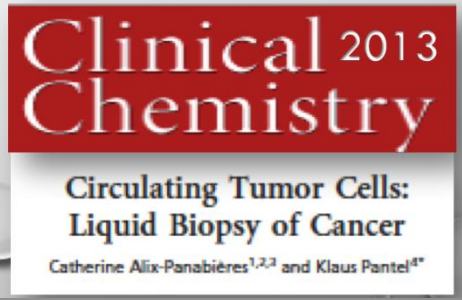
Real-Time *Liquid Biopsy*

- 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



Molecular Oncology

JUNE 2019

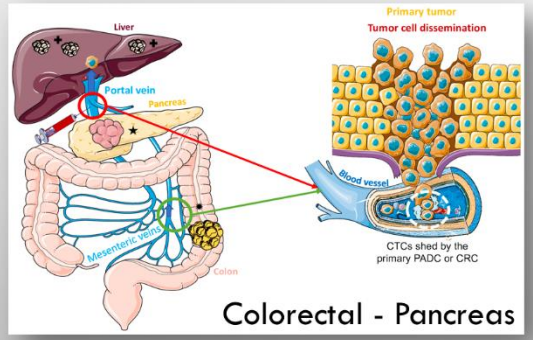
Review | Open Access

Tumor-proximal liquid biopsy to improve diagnostic and prognostic performances of circulating tumor cells

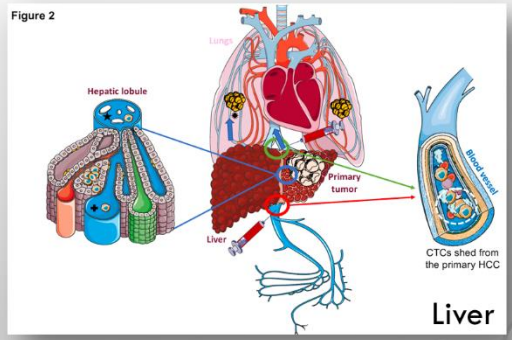
Etienne Buscail, Laurence Chiche, Christophe Laurent, Véronique Vendrely, Quentin Denost, Jérôme Denis, Matthieu Thumerel, Jean-Marc Lacorte, Aurélie Bedel, François Moreau-Gaudry, Sandrine Dabernat, Catherine Alix-Panabières ... See fewer authors

Sandrine Dabernat

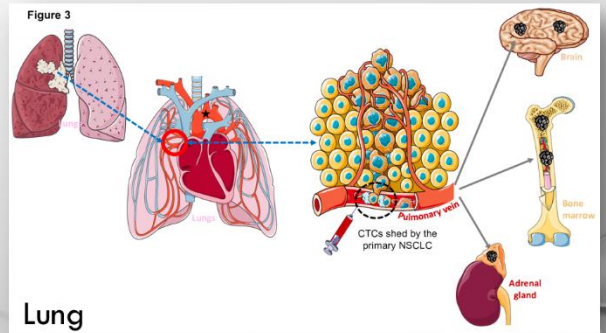
Etienne Buscail



Colorectal - Pancreas



Liver



Lung

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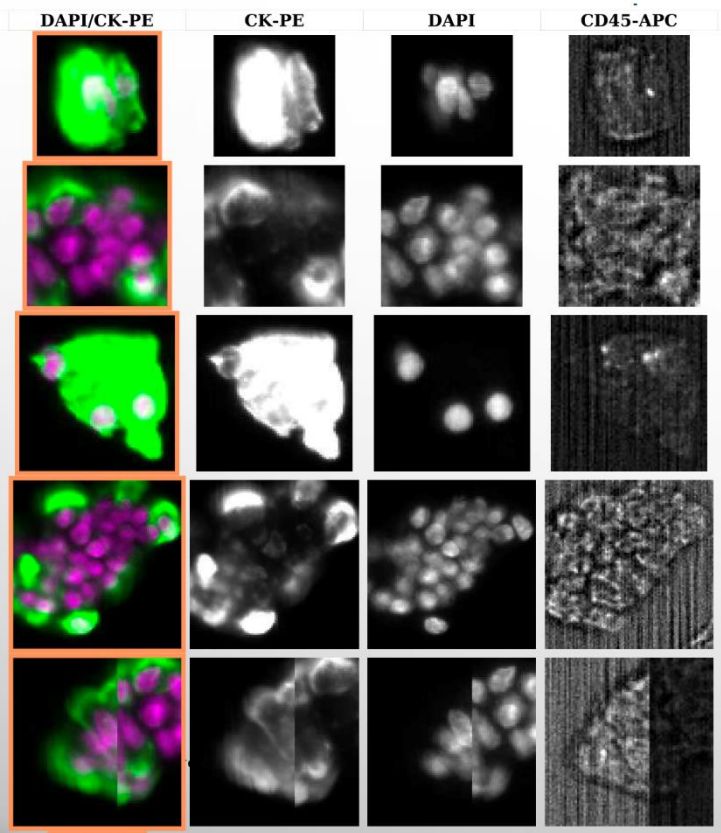
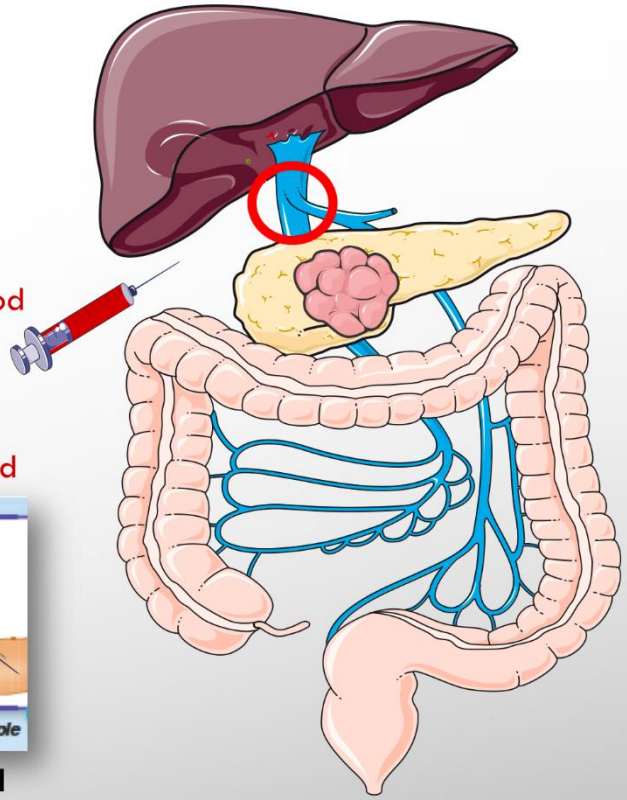
Reconnue d'utilité publique

LIQUID BIOPSY AND PORTAL VEIN



300 CTCs and clusters/7.5 ml portal blood

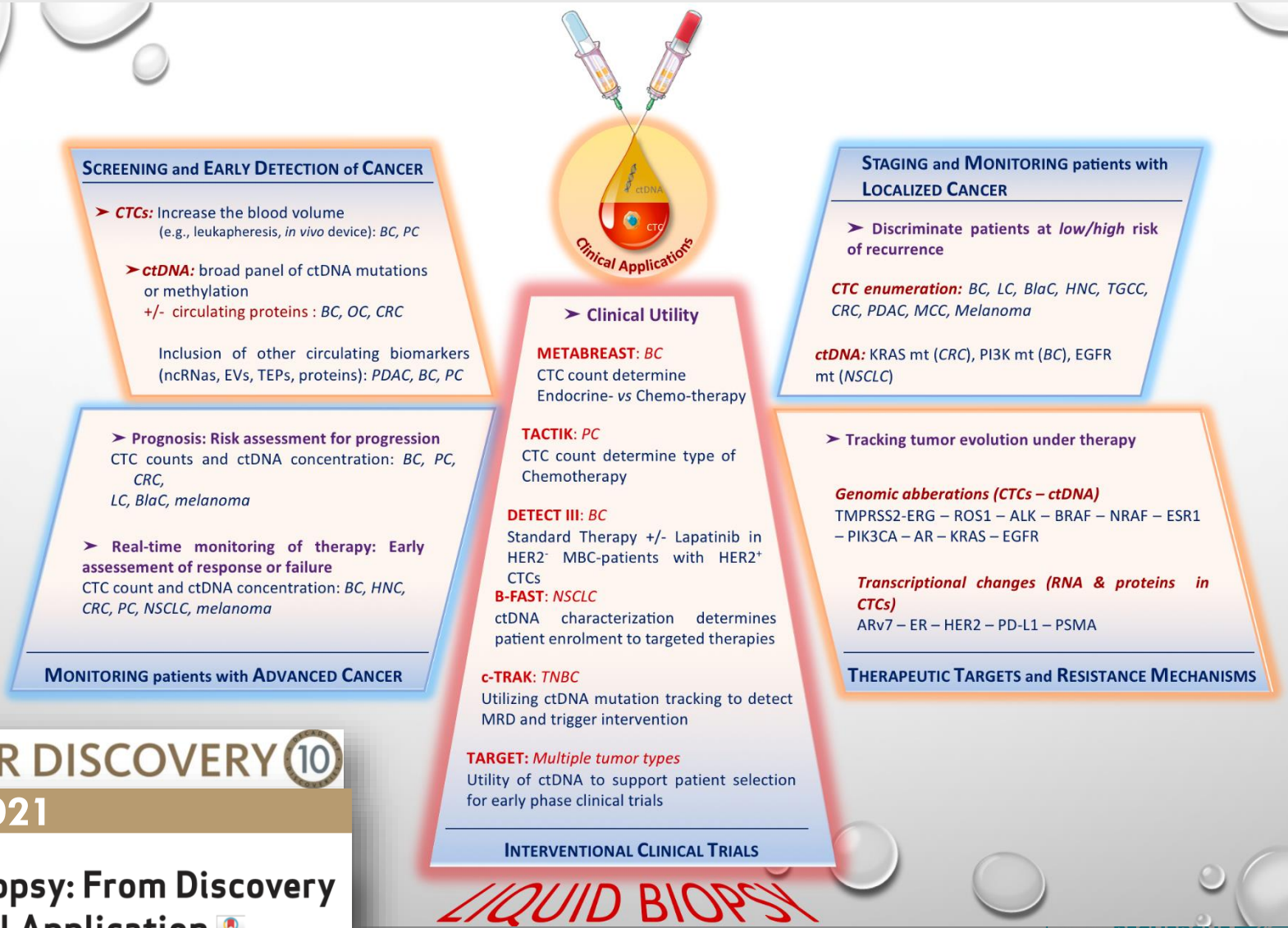
LOCALIZED PANCREATIC CANCER



0 CTCs/7.5 ml peripheral blood

Buscail, Alix-Panabières *et al.* CANCERS 2019

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique



CANCER DISCOVERY 10
REVIEW 2021

Liquid Biopsy: From Discovery to Clinical Application

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

cancers 2019

MDPI

Review

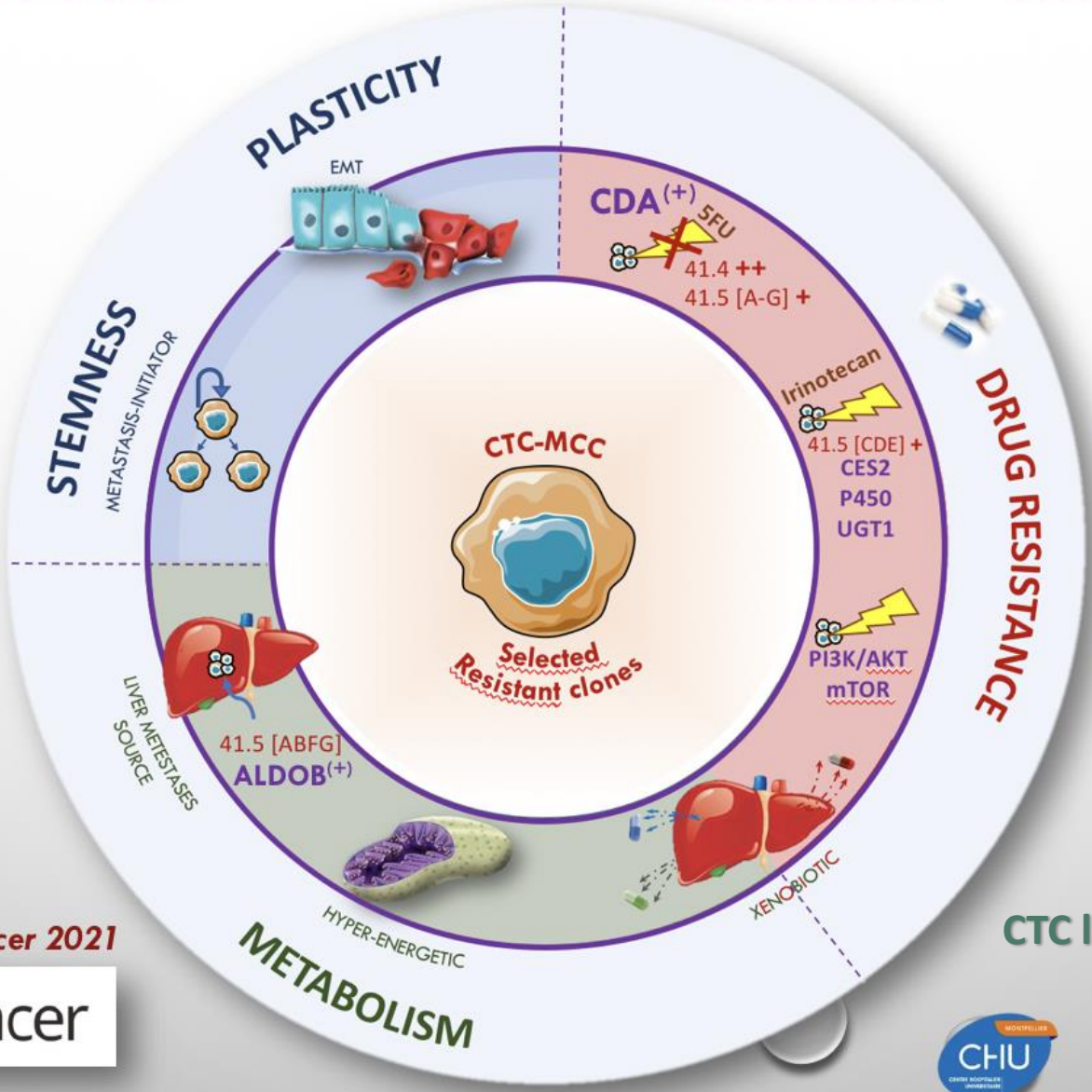
Liquid Biopsy Approach for Pancreatic Ductal Adenocarcinoma

Etienne Buscail [1,2], Charlotte Maulat [3,4], Fabrice Muscari [3,4], Laurence Chiche [1,2], Pierre Cordelier [3], Sandrine Dabernat [1], Catherine Alix-Panabières [5] and Louis Buscail [3,6,*]

Clinical relevance of CTCs

→ Presence of CTCs from resected, locally advanced, or metastatic tumours was associated with poor PDAC patient prognosis, an increased number of metastases and an increased likelihood of relapse.

Hallmarks of CTC-MCC clones resistant to therapies



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

Molecular Cancer

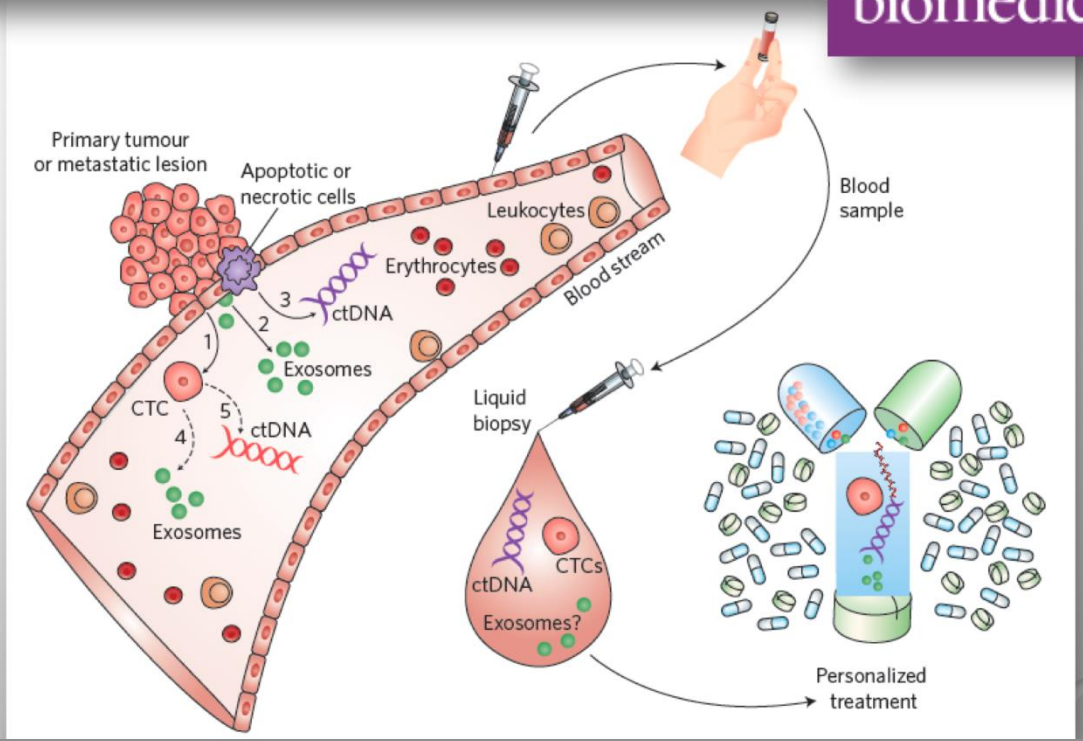
CTC lines…

***CTC-MCC**: **C**irculating **T**umor **C**ells – **M**etastatic **C**olon **C**ancer

Clinical prospects of liquid biopsies

Catherine Alix-Panabières and Klaus Pantel

nature biomedical engineering 2017



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


George Calin

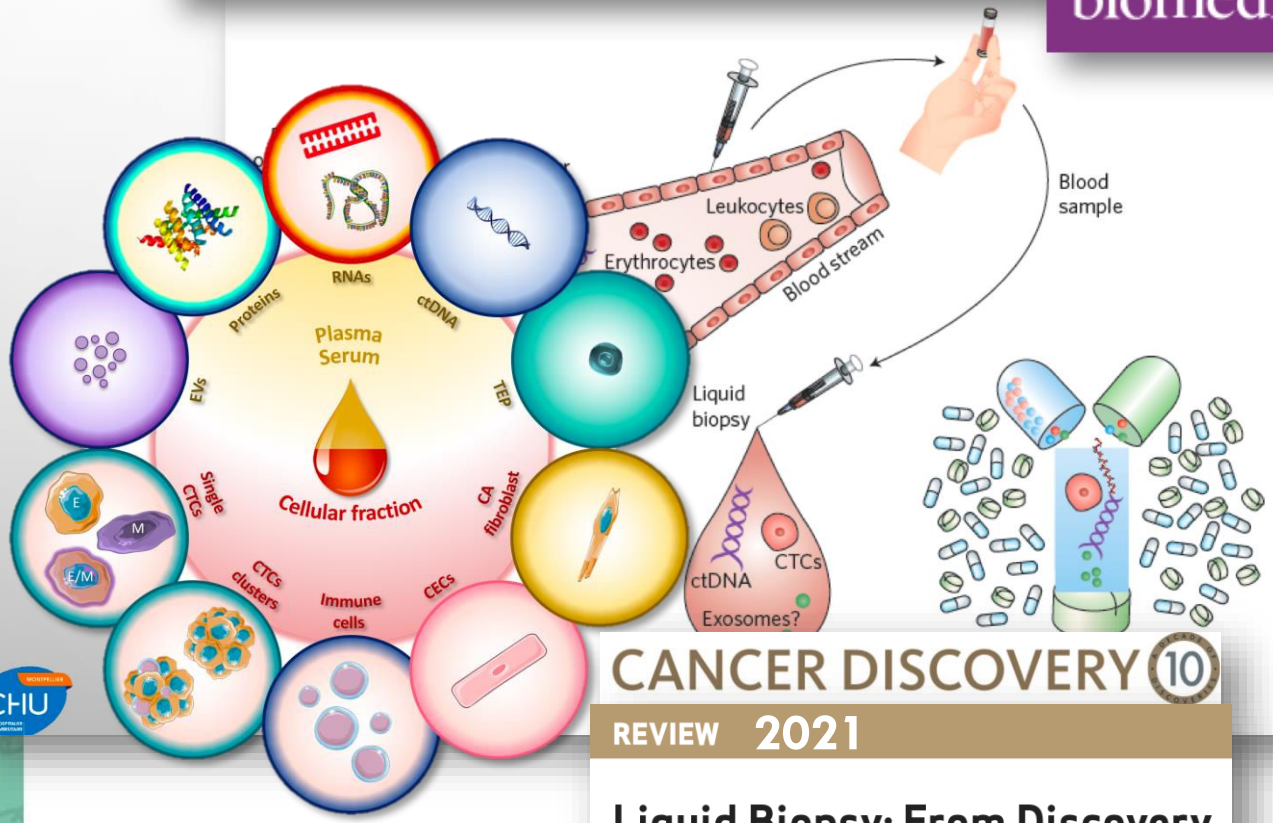

Bruno Costa


Tom Würdinger

Clinical prospects of liquid biopsies

Catherine Alix-Panabières and Klaus Pantel

nature biomedical engineering 2017



CTCs
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CANCER DISCOVERY 10

REVIEW 2021

Liquid Biopsy: From Discovery to Clinical Application

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

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

cancers 2019

MDPI

Article

High Clinical Value of Liquid Biopsy to Detect Circulating Tumor Cells and Tumor Exosomes in Pancreatic Ductal Adenocarcinoma Patients Eligible for Up-Front Surgery

Etienne Buscail [1,2,3], Catherine Alix-Panabières [4], Pascaline Quincy [1,2,3], Thomas Cauvin [1,2,3], Alexandre Chauvet [1,2,3], Olivier Degrandi [1,2,3], Charline Caumont [2,3], Séverine Verdon [2], Isabelle Lamrissi [1,3], Isabelle Moranvillier [1,3], Camille Buscail [5], Marion Marty [2], Christophe Laurent [1,2,3], Véronique Vendrely [1,2,3], François Moreau-Gaudry [1,2,3], Aurélie Bedel [1,2,3], Sandrine Dabernat [1,2,3,*,†] and Laurence Chiche [1,2,3,†]

CHU

REVIEW 2021

Liquid Biopsy: From Discovery to Clinical Application

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

Bruno Costa

Tom Würdinger

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER

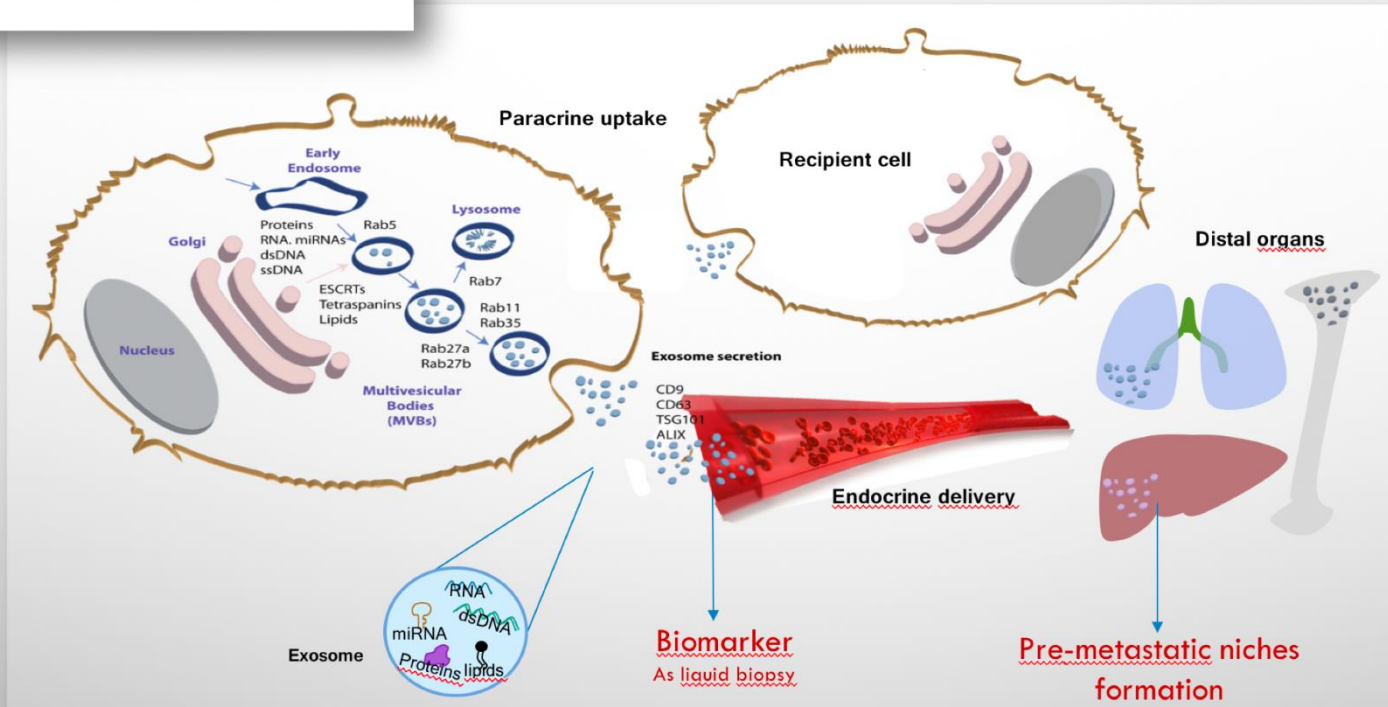
Reconnue d'utilité publique

ARTICLE

doi:10.1038/nature15756

Tumour exosome integrins determine organotropic metastasis

Ayuko Hoshino[1]*, Bruno Costa-Silva[1]*, Tang-Long Shen[1,2]*, Goncalo Rodrigues[1,3], Ayako Hashimoto[1,4], Milica Tesic Mark[5], Henrik Molina[5], Shinji Kohsaka[6], Angela Di Giannatale[1], Sophia Ceder[7], Swarnima Singh[1], Caitlin Williams[1], Nadine Soplop[8], Kunihiro Uryu[8], Lindsay Pharmer[9], Tari King[9], Linda Bojmar[1,10], Alexander E. Davies[11], Yonathan Ararso[1], Tuo Zhang[12], Haiying Zhang[1], Jonathan Hernandez[1,13], Joshua M. Weiss[1], Vanessa D. Dumont-Cole[14], Kimberly Kramer[14], Leonard H. Wexler[14], Aru Narendran[15], Gary K. Schwartz[16], John H. Healey[17], Per Sandstrom[10], Knut Jørgen Labori[18], Elin H. Kure[19], Paul M. Grandgenett[20], Michael A. Hollingsworth[20], Maria de Sousa[1,3], Sukhwinder Kaur[21], Maneesh Jain[21], Kavita Mallya[21], Surinder K. Batra[21], William R. Jarnagin[13], Mary S. Brady[1,22], Oystein Fodstad[23,24], Volkmar Muller[25], Klaus Pantel[26], Andy J. Minn[27], Mina J. Bissell[11], Benjamin A. Garcia[28], Yibin Kang[29,30], Vinagolu K. Rajasekhar[31], Cyrus M. Ghajar[32], Irina Matei[1], Hector Peinado[1,33], Jacqueline Bromberg[34,35] & David Lyden[1,14]



Can we assess the preparation of the pre-metastatic niches in PDAC ?

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

Perspective: The future of liquid biopsy

Nature | Vol 579 | 26 March 2020

Catherine Alix-Panabières

Cancer diagnosis

nature

JAMA Oncology | Original Investigation 2020

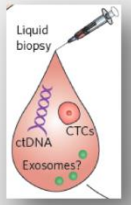
Efficacy of Circulating Tumor Cell Count–Driven vs Clinician-Driven First-line Therapy Choice in Hormone Receptor–Positive, ERBB2-Negative Metastatic Breast Cancer
The STIC CTC Randomized Clinical Trial

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 consortium to achieve these goals : ELBS**



THE EUROPEAN LIQUID BIOPSY SOCIETY

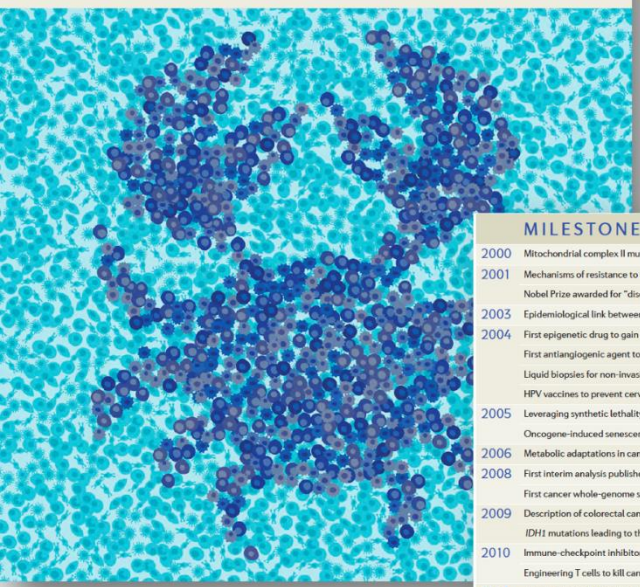
CHU MONTPELLIER

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

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

Tracking cancer in liquid biopsies

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

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

nature milestones

Cancer

MILESTONE 2

Tracking cancer in liquid biopsies

In homage to Bertrand Kamal

SUMMARY

CIRCULATING TUMOUR-DERIVED KRAS MUTATIONS IN PANCREATIC CANCER CASES ARE PREDOMINANTLY CARRIED BY VERY SHORT FRAGMENTS OF CELL-FREE DNA

Dr. Florence Le Calvez-Ke

- *The shorter the amplicon size, the higher the mutant allelic fraction.*
- *The specific biological fragmentation characteristics of ctDNA should be taken into account when performing liquid biopsies based assays.*
- *Enrichment of short cfDNA molecules should increase the ability to detect tumour-derived mutations in liquid biopsy.*

Tissue biomarkers in pancreatic ductal adenocarcinoma

Dr Jérôme Cro

- *Adequate sampling is key to biomarker determination in PDAC*
- *Should all patients have at least a KRAS and BRAC1/2 seq?*
- *RNA-based signature may help stratify patients if they can be robustly determined*

(strong prognostic/predictive value)

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique