Society for Immunotherapy of Cancer

Link Between Metastatic Genetic Heterogeneity and the Immune Contexture in Colorectal Cancer

Jérôme Galon

SITC
Houston, TX, USA
September 4th, 2019

Link Between Metastatic Genetic Heterogeneity and the Immune Contexture in Colorectal Cancer

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SORBONNE UNIVERSITÉ

CRC CENTRE DE RECHERCHE DES CORDELIERS

Disclosures

Co-founder and chairman of the scientific advisory board:

- *HalioDx*

Collaborative Research Agreement (grants) :

- *Perkin-Elmer, IObiotech, MedImmune, Janssen, Imcheck Therapeutics*

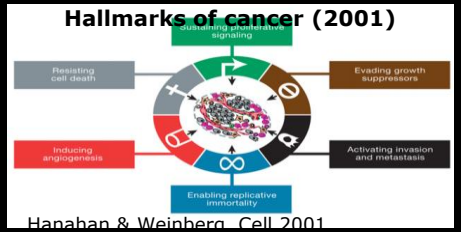
Participation to Scientific Advisory Boards:

- *BMS, MedImmune, Astra Zeneca, Novartis, Definiens, Merck Serono, IObiotech, ImmunID, Nanostring, Illumina, Northwest Biotherapeutics, Actelion, Amgen, Merck MSD*

Consultant :

- *BMS, Roche, GSK, Compugen, Mologen, Gilead, Sanofi*

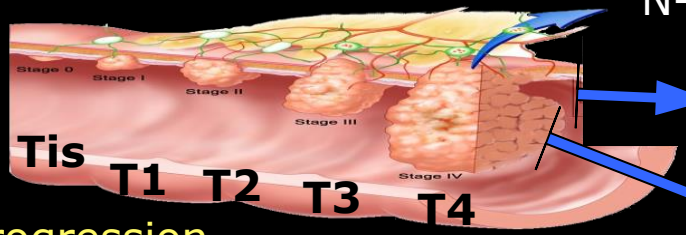
Definition of cancer



Hanahan & Weinberg, Cell 2001

Tumor invasion

N-Stage



Early-metastasis
(venous emboli)

T-Stage

M-Stage

Tumor progression

Tumor grade differentiation
Tumor aggressiveness
(driver mutations, CIN, MSI, CIMP…)

-> Tumor recurrence

-> Tumor aggressiveness, progression, invasion and recurrence define early and late stage cancers, and the severity of the disease

Novel paradigm

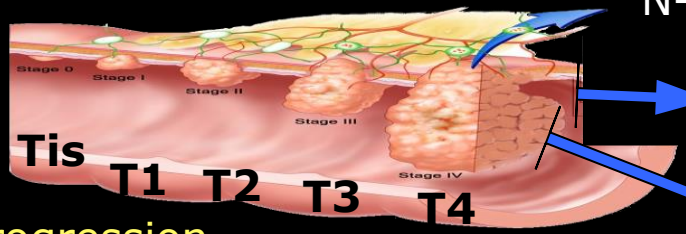
“Hot” Tumor

Immunoscore
Immune contexture

“Cold” Tumor

Tumor invasion

N-Stage



Early-metastasis
(venous emboli)

T-Stage

M-Stage

Tumor progression

Tumor grade differentiation
Tumor aggressiveness
(driver mutations, CIN, MSI, CIMP…)

-> Tumor recurrence

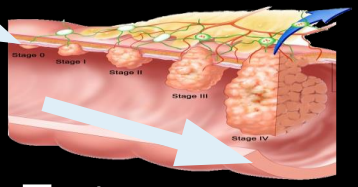
-> death

- ✓ Tumor progression, invasion and recurrence are dependent on pre-existing immunity and on Immunoscore
- ✓ Pre-existing immunity is determining the fate and survival of the patient
- ✓ Pre-existing immunity is determining the likelihood of response to immunotherapy

The Immune landscape and the importance of the immune contexture

Oncogenensis

Pre-cancer lesions



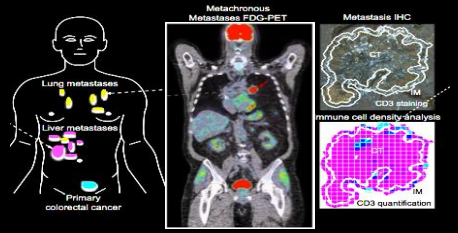
Progression

T-stage

VELIPI+ Dissemination

N+ Invasion

M+



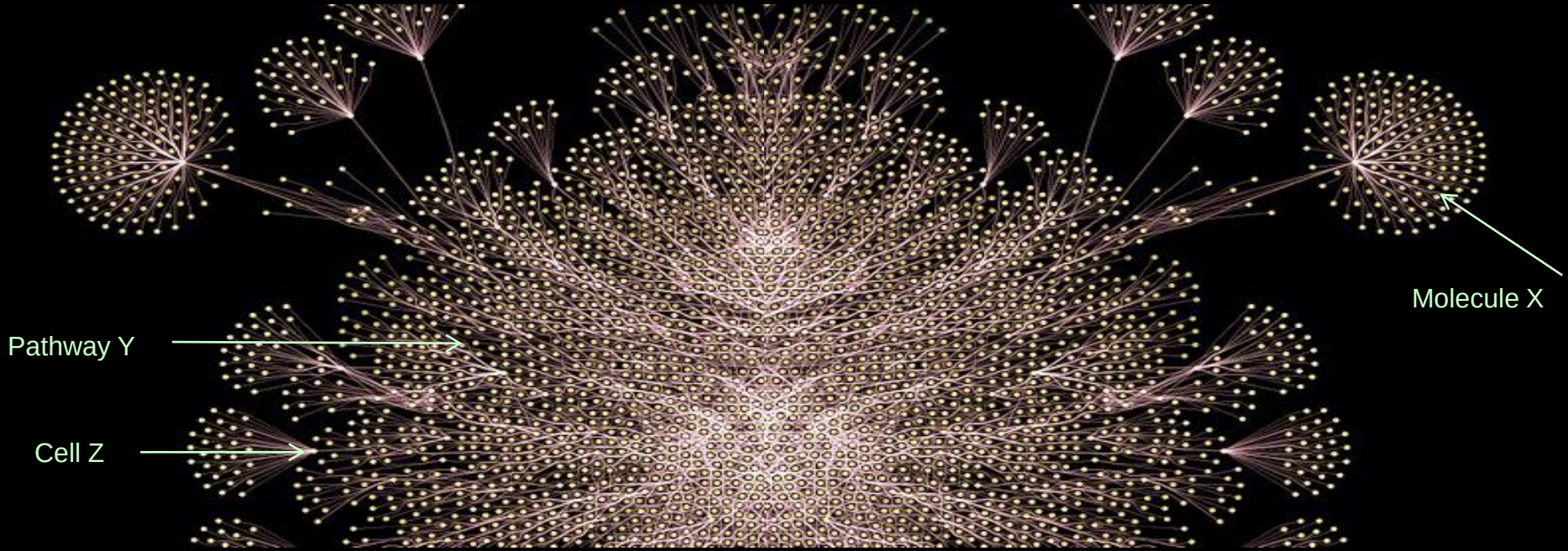
Prognosis

Recurrence

Death

Immunotherapy

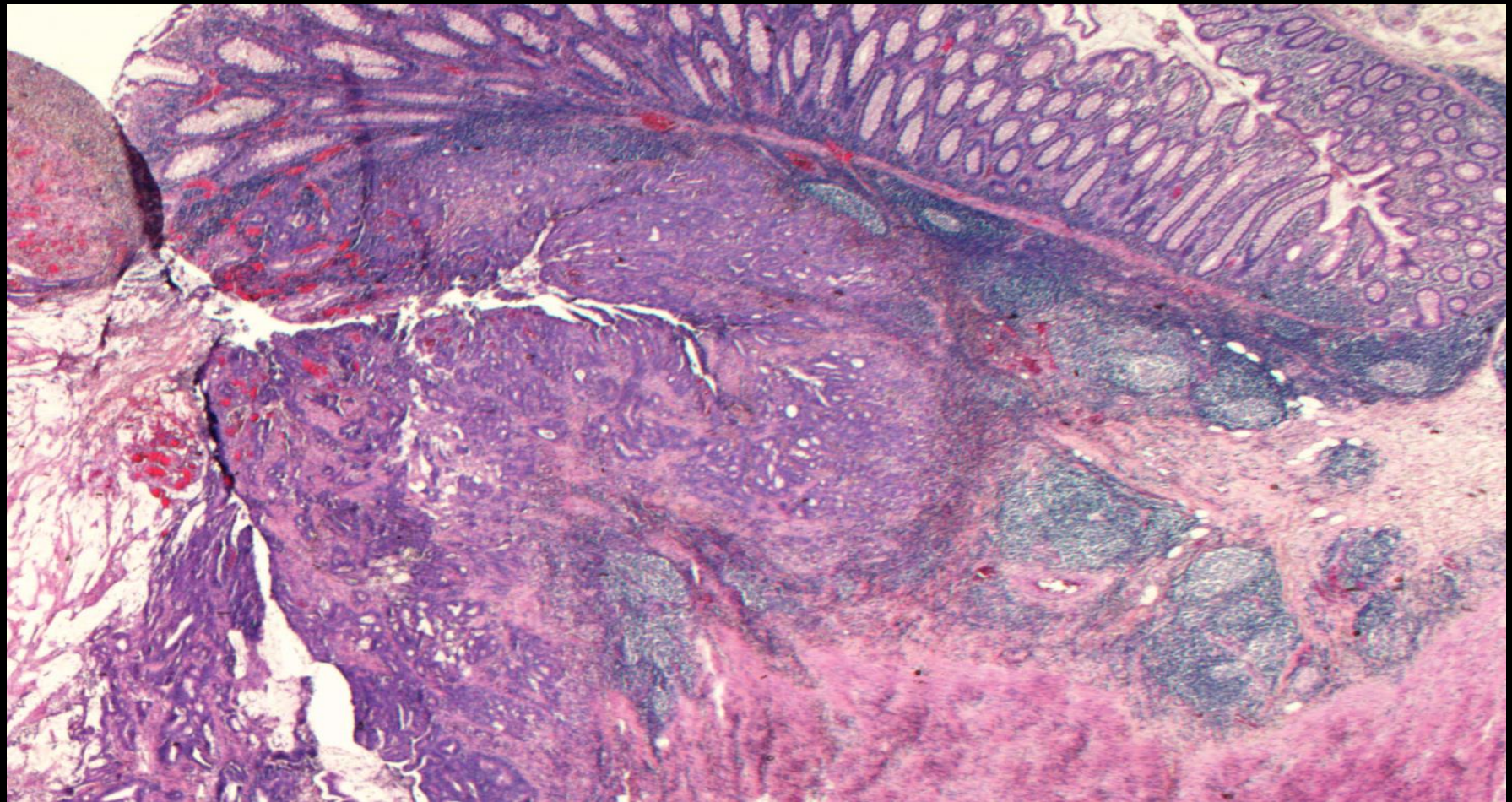
Cancer is one of the most complex biological system of all



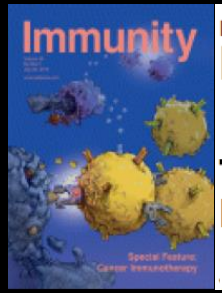
"*The whole is greater than the sum of its parts*", Aristotle

-> Systems biology in human cancer

Tumor microenvironment



The continuum of cancer immunosurveillance

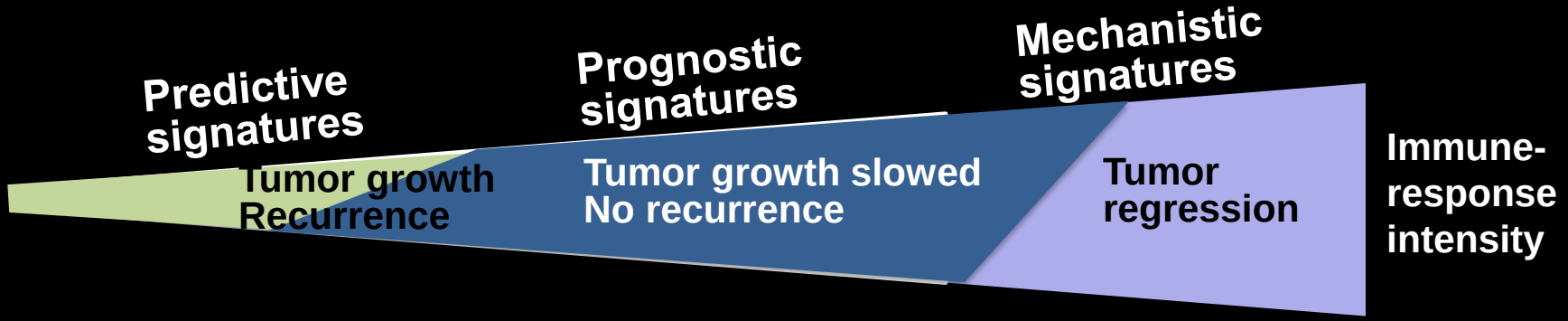


Immunity
Review

Cell PRESS

The Continuum of Cancer Immunosurveillance: Prognostic, Predictive, and Mechanistic Signatures

Jérôme Galon,[1,2,3,*] Helen K. Angell,[1,2,3] Davide Bedognetti,[4] and Francesco M. Marincola[4,5,*]



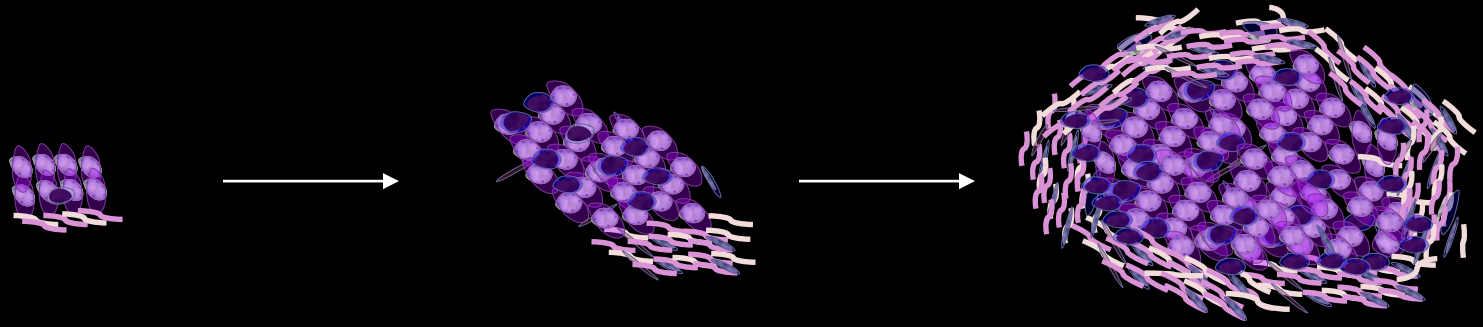
Galon J et al. ***Immunity*** 2013

The continuum of cancer immunosurveillance

Pre-cancerous lesions

Primary Carcinoma

Metastasis



Mascaux C. … Galon J.
Nature 2019

Pagès F. … Galon J.
Lancet 2018

Angelova M. … Galon J.
Cell 2018

What is the importance of the pre-existing immunity within tumors ? Does it matter ?

MacCarty WC, Mahle AE.
Relation of differentiation and lymphocytic infiltration to postoperative longevity in gastric carcinoma.
J Lab Clin Med 1921 ; 6:473.

A Novel Paradigm for Cancer

Science
AAAS

Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

Jérôme Galon,[1*†] Anne Costes,[1] Fatima Sanchez-Cabo,[2] Amos Kirilovsky,[1] Bernhard Mlecnik,[2] Christine Lagorce-Pagès,[3] Marie Tosolini,[1] Matthieu Camus,[1] Anne Berger,[4] Philippe Wind,[4] Franck Zinzindohoué,[5] Patrick Bruneval,[6] Paul-Henri Cugnenc,[5] Zlatko Trajanoski,[2] Wolf-Herman Fridman,[1,7] Franck Pagès[1,7†]

29 SEPTEMBER 2006 VOL 313 SCIENCE www.sciencemag.org

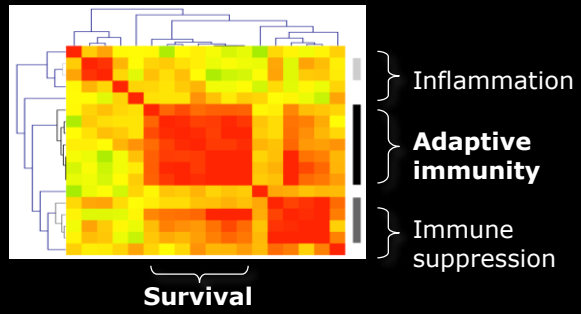
The foundation a new concept

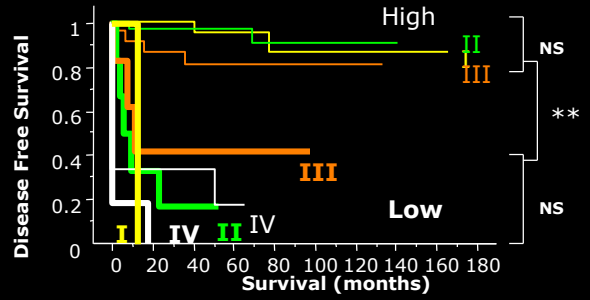
↓

Immune contexture

- ✓ Gene expression profiling
- ✓ Qualitative immune signature

- ✓ Immunohistochemistry (IHC)
- ✓ Digital Pathology
- ✓ Quantitative immune cell infiltration





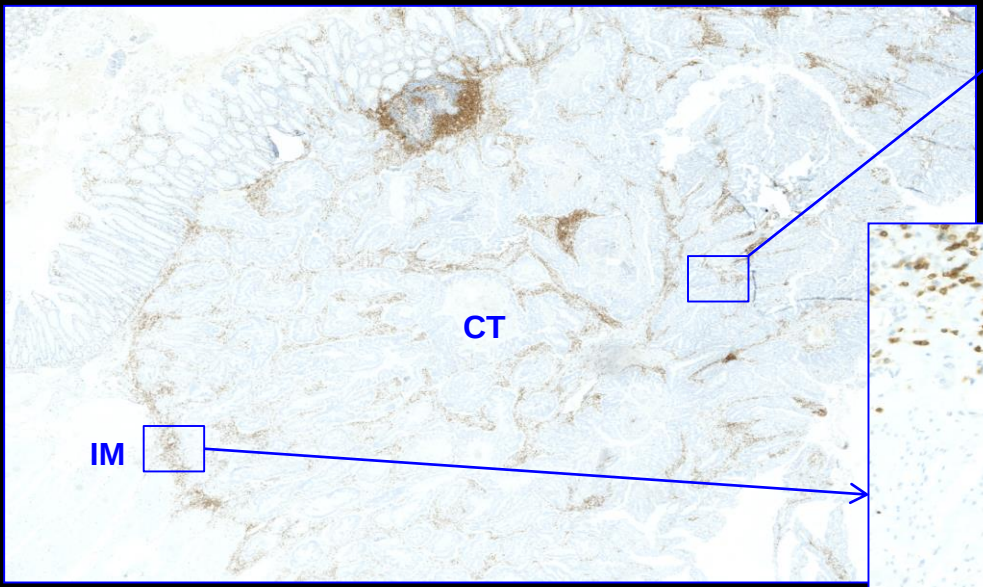
Optimized Immunosign

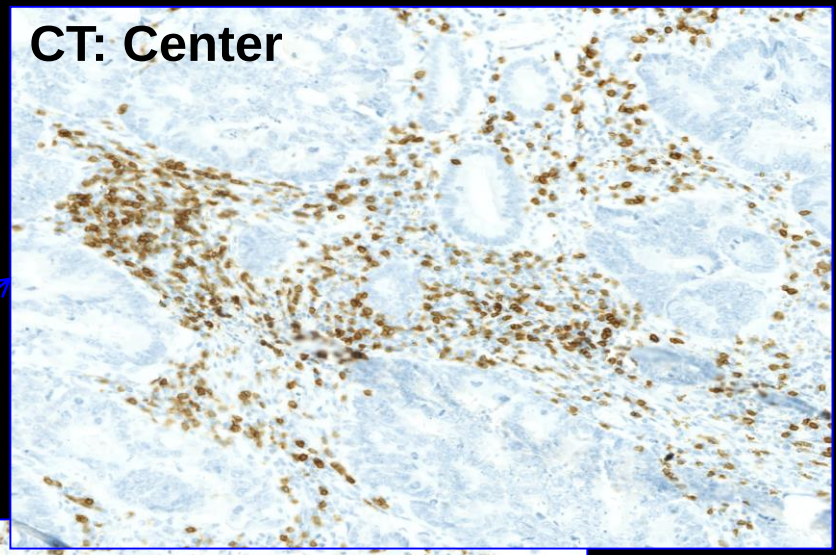
Quality

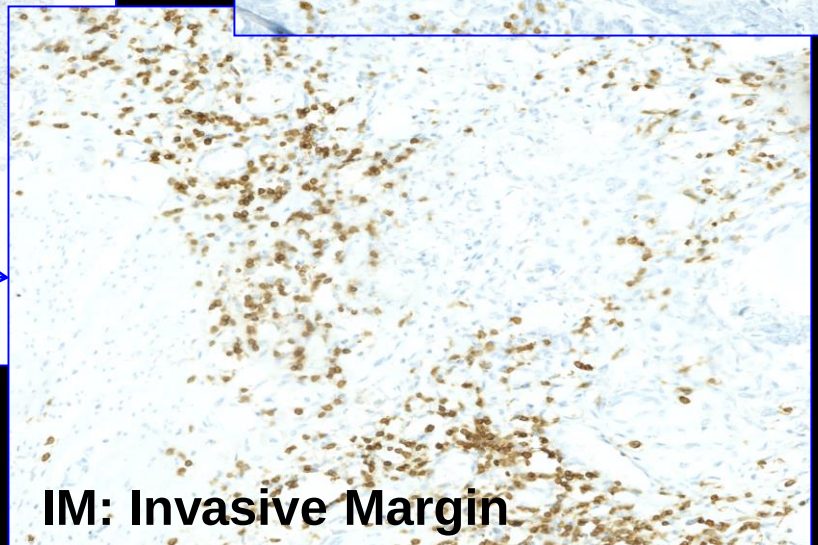
Type/Density/Location

Galon J et al. *Science* 2006

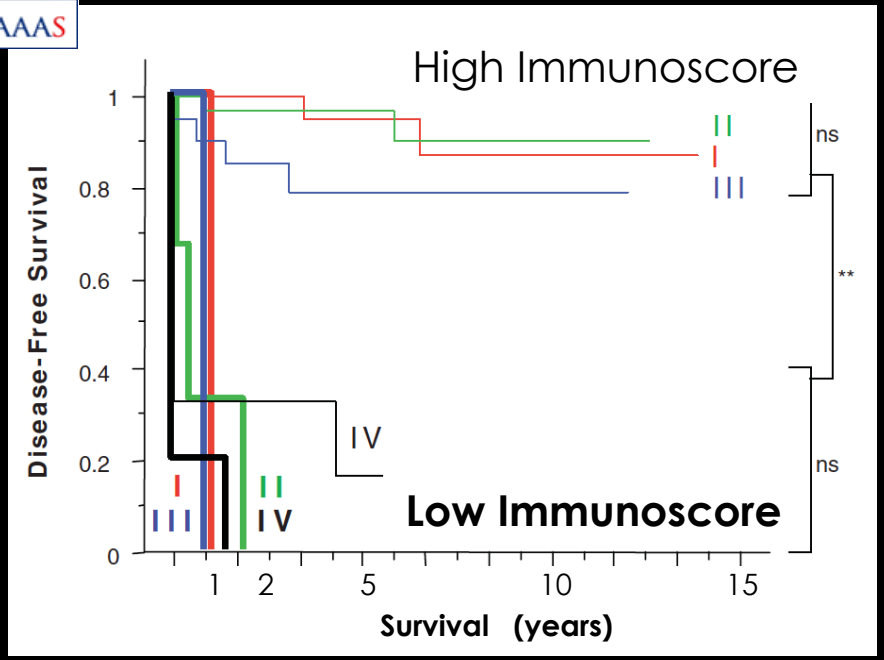
Digital quantification of immune cells infiltrating tumors: *Immunoscore*







Immunoscore: a novel paradigm for cancer



- ✓ High Immunoscore
- ✓ Inflammed tumors
- ✓ Strong pre-existing adaptive immunity

- ✓ Low Immunoscore
- ✓ Non-Inflammed tumors
- ✓ Weak/absent pre-existing adaptive immunity

Coordinated adaptive immune reaction (Immunoscore) more than tumor invasion predicts clinical outcome

Galon et al. ***Science*** 2006

A Novel Paradigm for Cancer

Multivariate Cox Analysis

Parameters	*HR*	*P* value
• T-stage	1.2	0.25
• N-stage	1.4	0.15
• Differentiation	1.1	0.84
• **Immunoscore**	1.9	0.00001

"***Immune Contexture***" :

Cells -> ✓**Type**

Quantity -> ✓**Density**

Spatial -> ✓**Location**

-> Immunoscore

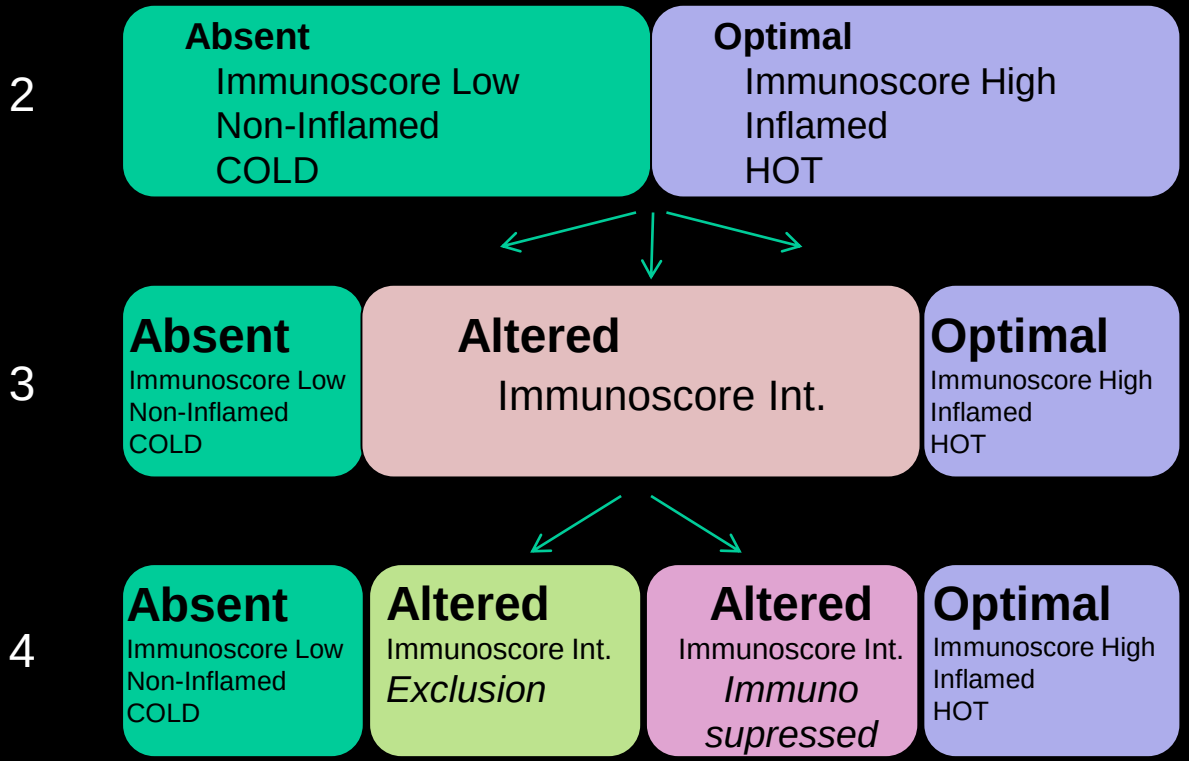
Quality -> ✓Immune **functional** orientation

-> Immunosign

Galon J et al. ***Science*** 2006

Essential role of the pre-existing immunity: The Immune contexture

Major immune categories of tumors



Galon et al. Science 2006
Galon et al. Cancer Res 2007

Galon et al. Science 2006
Camus & *Galon Cancer Res* 2009

Camus & *Galon Cancer Res* 2009

The Immunoscore as a New Possible Approach for the Classification of Cancer

World Immunotherapy Council inaugural meeting (Feb 2012)

Support (moral) from the World Immunotherapy Council (WIC), and support from societies including, EATI, BDA, CCIC, CIC, CRI, CIMT, CSCO, TIBT, DTIWP, ESCII, NIBIT, JACI, NCV-network, PIVAC, ATTACK, TVACT…

Worldwide Immunoscore consortium (PI: J Galon)

(17 countries: >3000 Stage I/II/III Colon cancer patients)

Assay harmonization

Immunoscore meetings :

- Feb 2012, Italy
- Dec 2012, Italy
- Nov 2013, SITC, USA
- Dec 2013, Italy
- Jan 2014, Qatar
- Jul 2014, Paris, France
- Nov 2014, SITC, USA
- Nov 2015, SITC, USA
- Dec 2015, Italy
- Feb 2016, USCAP, USA
- April 2016, USA
- Nov 2016, SITC, USA
- Dec 2016, Italy
- Feb 2017, USCAP, USA
- Dec 2017, Italy

THE LANCET

International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study

Franck Pagès, Bernhard Mlecnik, Florence Marliot, Gabriela Bindea, Fang-Shu Ou, Carlo Bifulco, Alessandro Lugli, Inti Zlobec, Tilman T Rau, Martin D Berger, Iris D Nagtegaal, Elisa Vink-Börger, Arndt Hartmann, Carol Geppert, Julie Kolwelter, Susanne Merkel, Robert Grützmann, Marc Van den Eynde, Anne Jouret-Mourin, Alex Kartheuser, Daniel Léonard, Christophe Remue, Julia Y Wang, P Bavi, Michael H A Roehrl, Pamela S Ohashi, Linh T Nguyen, SeongJun Han, Heather L MacGregor, Sara Hafezi-Bakhtiari, Bradly G Wouters, Giuseppe V Masucci, Emilia K Andersson, Eva Zavadova, Michal Vocka, Jan Spacek, Lubos Petruzelka, Bohuslav Konopasek, Pavel Dundr, Helena Skalova, Kristyna Nemejcova, Gerardo Botti, Fabiana Tatangelo, Paolo Delrio, Gennaro Ciliberto, Michele Maio, Luigi Laghi, Fabio Grizzi, Tessa Fredriksen, Bénédicte Buttard, Mihaela Angelova, Angela Vasaturo, Pauline Maby, Sarah E Church, Helen K Angell, Lucie Lafontaine, Daniela Bruni, Carine El Sissy, Nacilla Haicheur, Amos Kirilovsky, Anne Berger, Christine Lagorce, Jeffrey P Meyers, Christopher Paustian, Zipei Feng, Carmen Ballesteros-Merino, Jeroen Dijkstra, Carlijn van de Water, Shannon van Lent-van Vliet, Nikki Knijn, Ana-Maria Mușină, Dragos-Viorel Scripcariu, Boryana Popivanova, Mingli Xu, Tomonobu Fujita, Shoichi Hazama, Nobuaki Suzuki, Hiroaki Nagano, Kiyotaka Okuno, Toshihiko Torigoe, Noriyuki Sato, Tomohisa Furuhata, Ichiro Takemasa, Kyogo Itoh, Prabhu S Patel, Hemangini H Vora, Birva Shah, Jayendrakumar B Patel, Kruti N Rajvik, Shashank J Pandya, Shilin N Shukla, Yili Wang, Guanjun Zhang, Yutaka Kawakami, Francesco M Marincola, Paolo A Ascierto, Daniel J Sargent, Bernard A Fox, Jérôme Galon*

Pages et al. *The Lancet* 2018

International validation of the consensus Immunoscore for the classification of colon cancer:

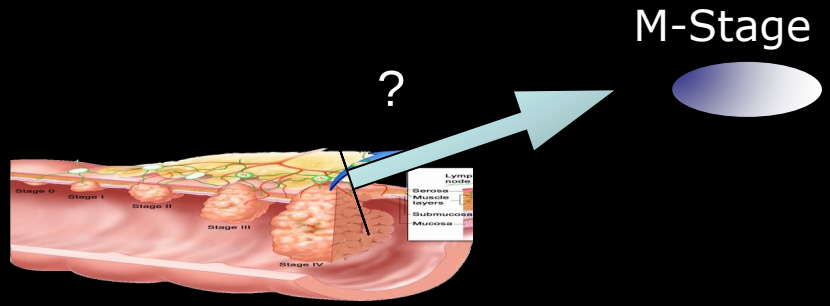
irAEs: immune-related Adverse Effects.

irRC: immune-related Response Criteria
(Wolchock et al. Clin Can Res 2009).

irRECIST: immune-related Response Evaluation Criteria In Solid Tumor
(Wong et al. NEJM 2017).

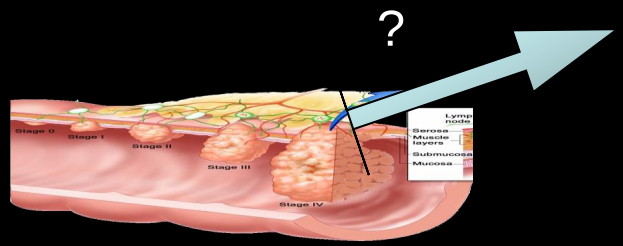
Strong arguments for introducing a "I" for Immune into the classification of cancer: TNM-I

What are the parameters associated with the dissemenation to distant metastasis? What is driving metastasis ?

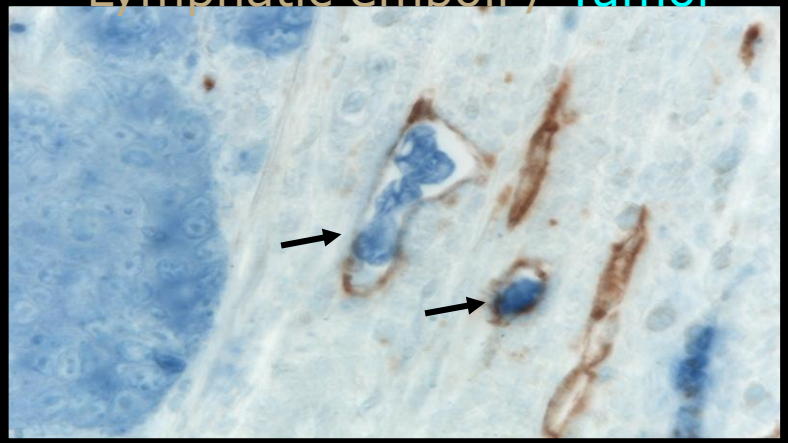


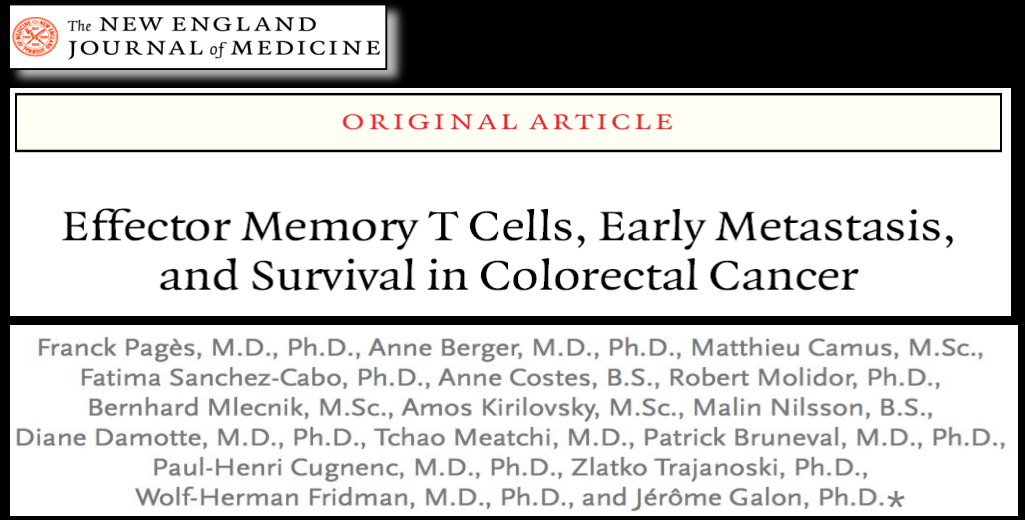
What are the mechanisms of early-metastatic dissemenation ?

VELIPI: Venous Emboli, Lymphatic Invasion, Perineural Invasion



Lymphatic emboli / Tumor





Memory T cells, in particular, T_{EM} correlate with the absence of early-metastatic invasion, and improved clinical outcome in colorectal carcinoma.

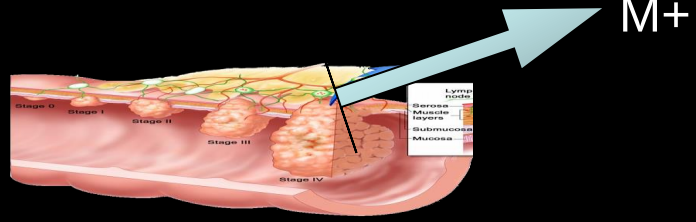
Pagès F, et al. ***N Engl J Med***. 2005

Pagès F & Galon J. ***N Engl J Med***. 2006

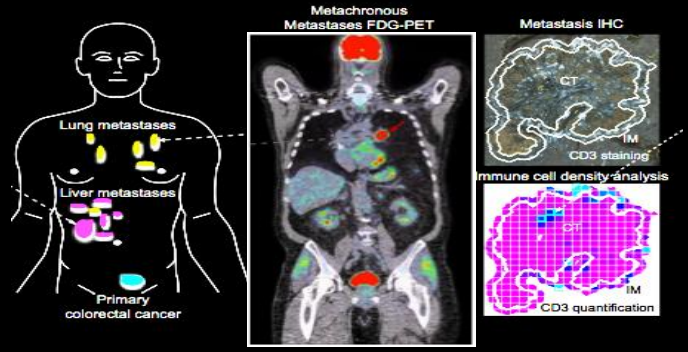
Is there an immune escape at the metastatic stage ?

Stage IV

Immunoscore in Stage IV metastatic colon cancer



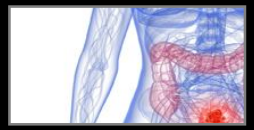
M+



Metastasis analysis

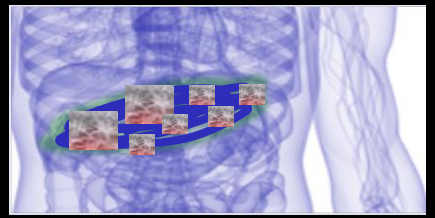
One primary tumor

Colorectal cancer



Multiple metastatic sites

Liver Metastasis



Lung Metastasis

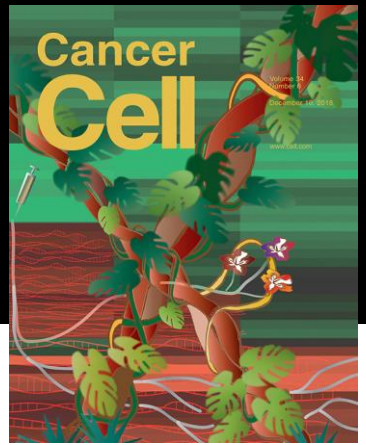
N=603 metastases

- Immunoscore within multiple metastases at different sites

Mlecnik et al. ***JNCI*** 2018

Van den Eynde M. *et al*. ***Cancer Cell 2018***

Metastasis analysis



CellPress

Cancer Cell
Article

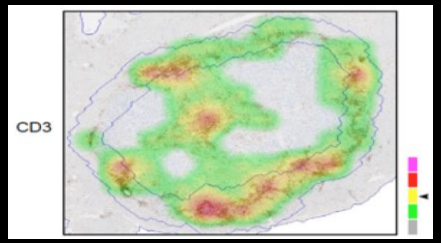
The Link between the Multiverse of Immune Microenvironments in Metastases and the Survival of Colorectal Cancer Patients

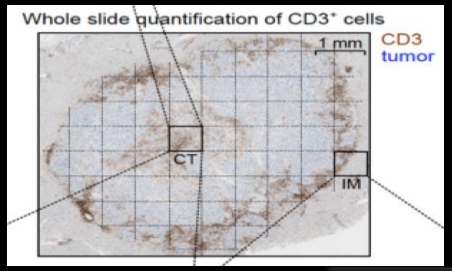
Marc Van den Eynde,[1,2,9] Bernhard Mlecnik,[2,3,9] Gabriela Bindea,[2,9] Tessa Fredriksen,[2] Sarah E. Church,[2] Lucie Lafontaine,[2] Nacilla Haicheur,[4] Florence Marliot,[2,4] Mihaela Angelova,[2] Angela Vasaturo,[2] Daniela Bruni,[2] Anne Jouret-Mourin,[1] Pamela Baldin,[1] Nicolas Huyghe,[1] Karin Haustermans,[5,6] Annelies Debucquoy,[5] Eric Van Cutsem,[7] Jean-Francois Gigot,[1] Catherine Hubert,[1] Alex Kartheuser,[1] Christophe Remue,[1] Daniel Léonard,[1] Viia Valge-Archer,[8] Franck Pagès,[2,4] Jean-Pascal Machiels,[1] and Jérôme Galon[2,10,*]

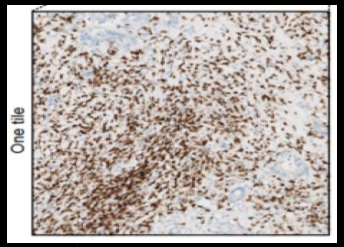
- Immunoscore within multiple metastases at different sites

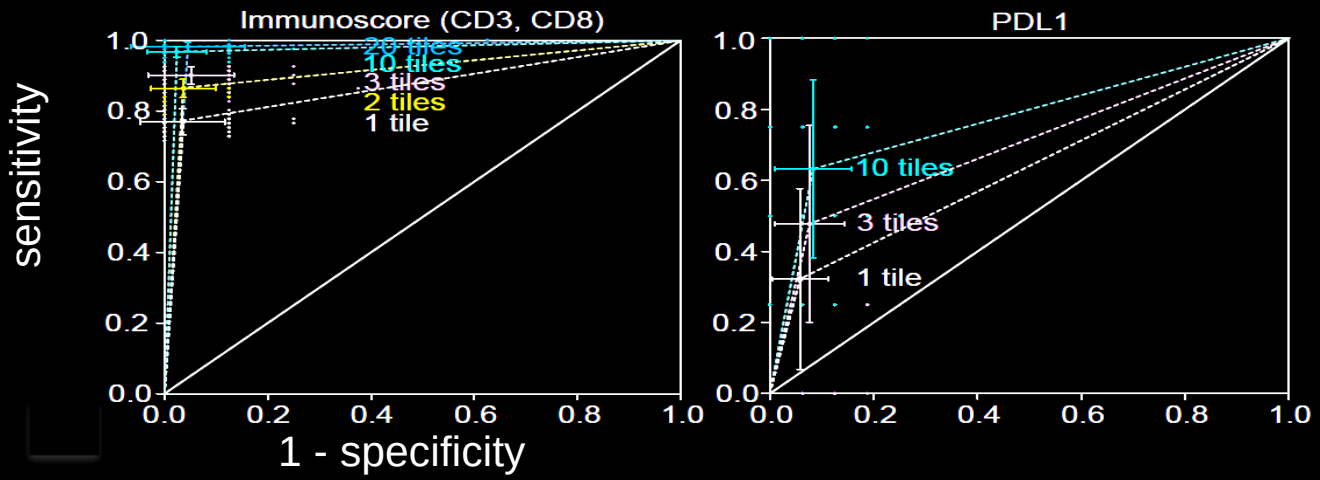
Van den Eynde et al. ***Cancer Cell*** 2018

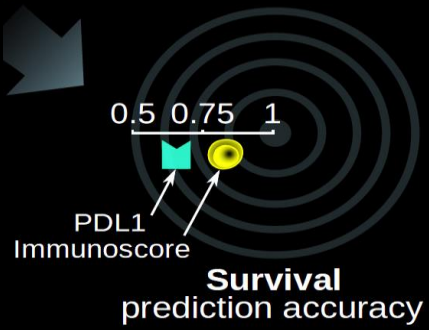
ROC curves illustrating the predictive value of 1, 2, 3, 10 biopsies compared to whole slide metastasis evaluation











✓ *Immunoscore Biopsy* is more reliable than PD-L1 expression

Van den Eynde M. et al. ***Cancer Cell*** 2018

What drives metastasis ?

What are the metastatic escape mechanisms ?

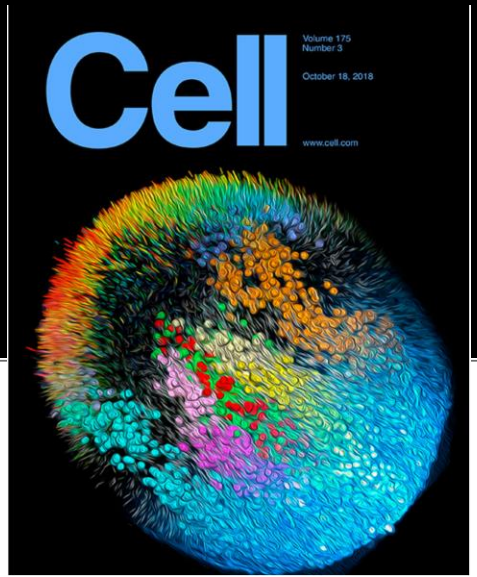
A Novel theory of cancer evolution ?

Current theories of cancer evolution

Models

LINEAR	NEUTRAL	BIG-BANG	BRANCHED
			
Immune pressure from Darwinian selection			
NO	**NO**	**NO**	**NO**

- The 4 proposed theories of cancer evolution
- All theories are tumor cell-centric. None involves a role of the immune system.



Article

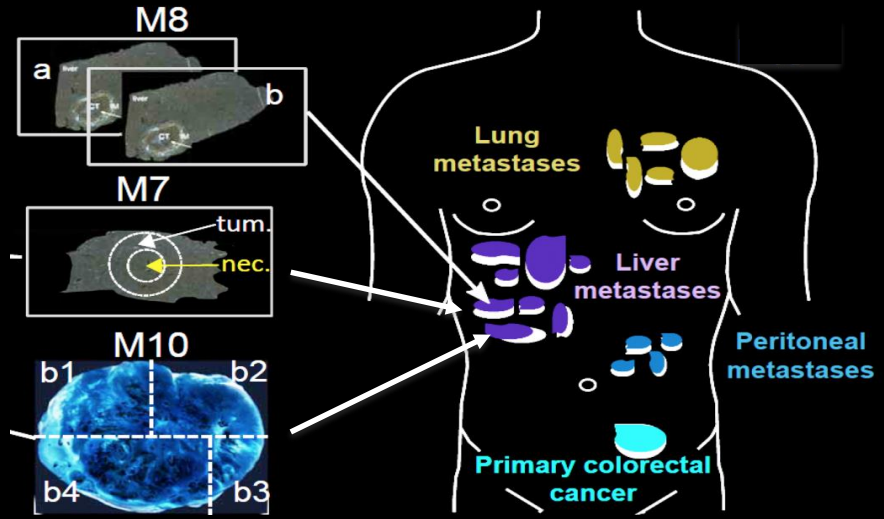
Cell

Evolution of Metastases in Space and Time under Immune Selection

Mihaela Angelova,[1] Bernhard Mlecnik,[1,2] Angela Vasaturo,[1] Gabriela Bindea,[1] Tessa Fredriksen,[1] Lucie Lafontaine,[1] Bénédicte Buttard,[1] Erwan Morgand,[1] Daniela Bruni,[1] Anne Jouret-Mourin,[3] Catherine Hubert,[3] Alex Kartheuser,[3] Yves Humblet,[3] Michele Ceccarelli,[4,5] Najeeb Syed,[6] Francesco M. Marincola,[7,8] Davide Bedognetti,[9,10] Marc Van den Eynde,[1,3,10] and Jérôme Galon[1,11,*]

Angelova M. *et al.* ***Cell*** 2018

What drives metastasis?



Primary tumors

↓

Synchronous metastases

↓

Metachronous metastases

↓

Metachronous metastases

↓

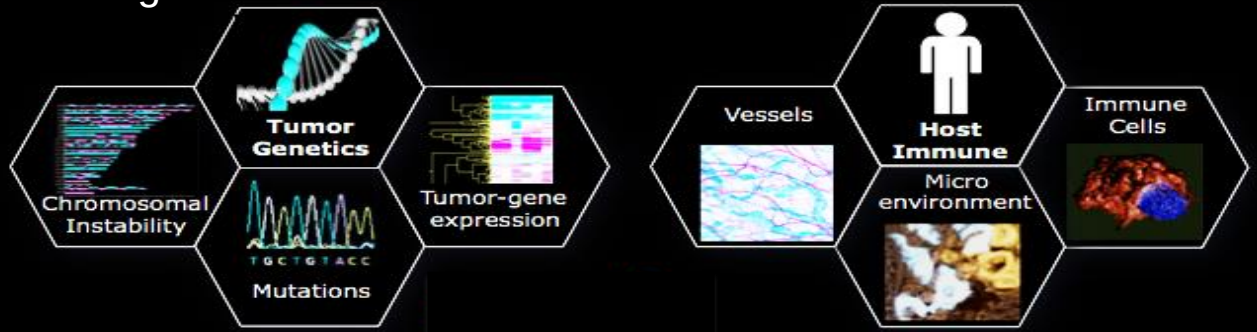
Metachronous metastases

↓

Etc.

> 11 years

Multi-Omics technologies

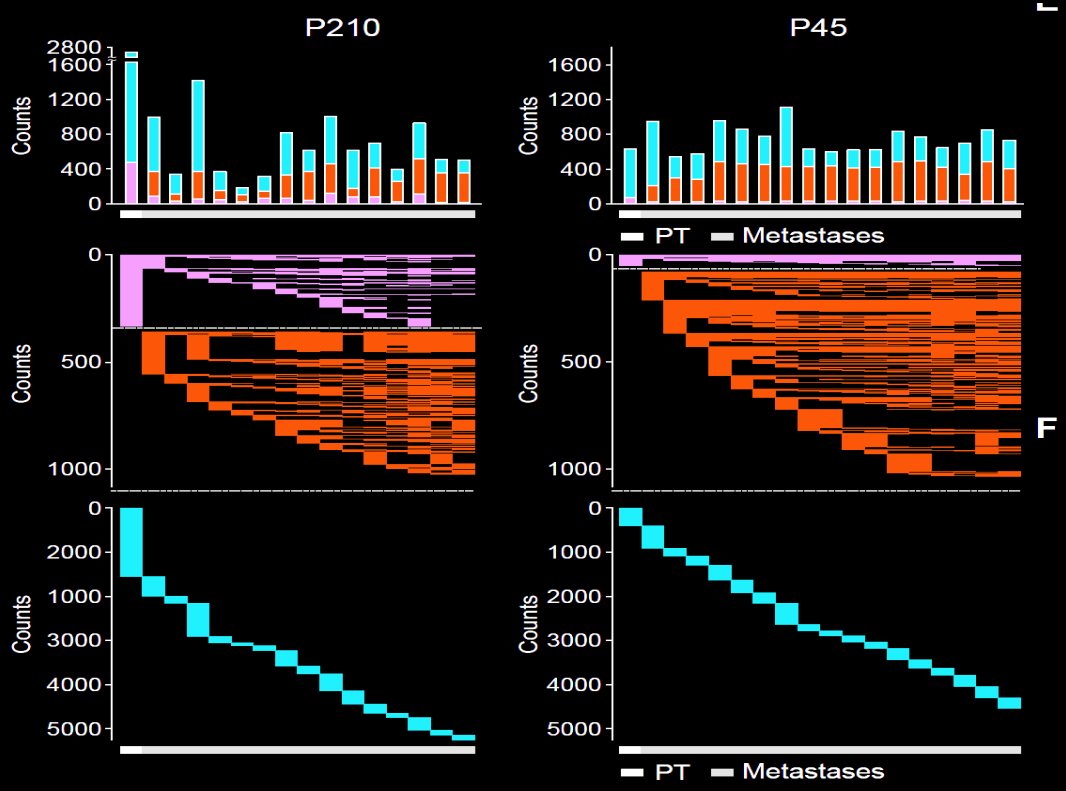


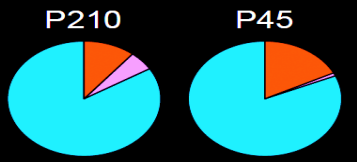
Mutational landscape across metastases

Shared between Meta

Shared between primary and Meta

Unique





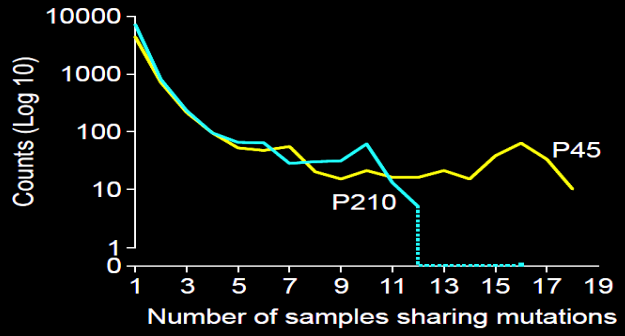
Mutations: Varscan2 + Mutect

Unique counts per sample

Shared mutations

Among PT and metastases

Among metastases



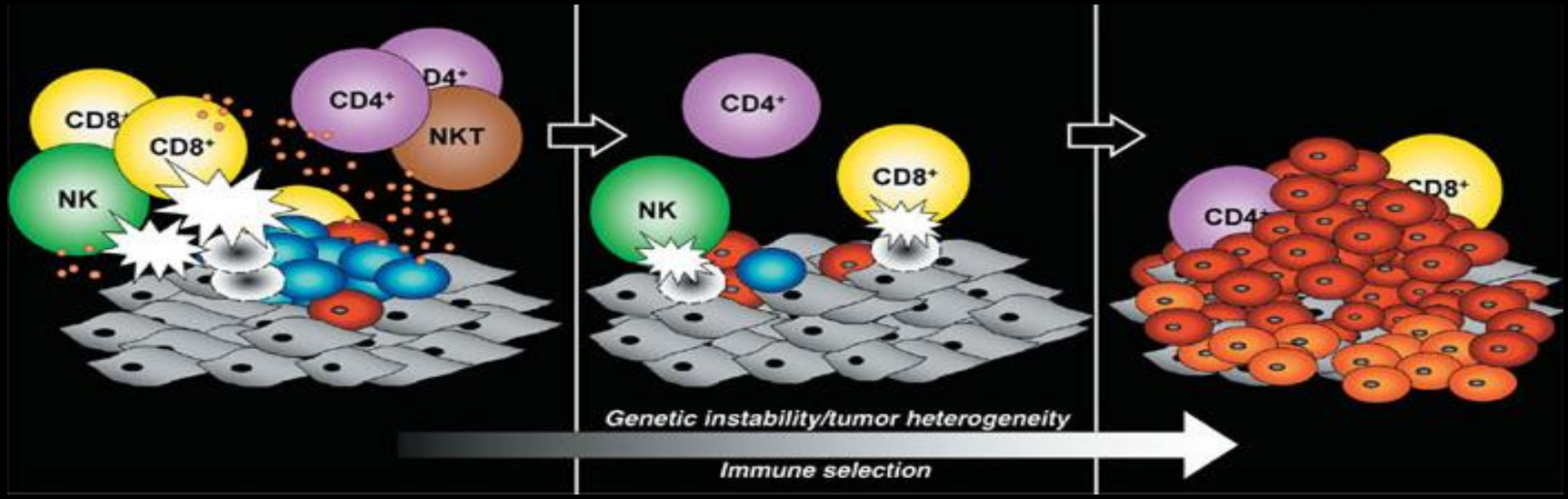
✓ ExomeSeq deep analysis of all synchronous and metachronous metastases

Genomics of primary tumors and metastases

✓ Highly heterogeneous genomic patterns between metastases

Immunoediting of cancer cells

Schreiber et al. *Science* 2011



Elimination

refers to effective immune surveillance for clones that express TSA

Shankaran et al. *Nature* 2001
Immunosurveillance RAG-/- STAT1-/-

Equilibrium

refers to the selection for resistant clones (red)

Koebel et al. *Nature* 2007
Immunoediting / Equilibrium

Escape

refers to the rapid proliferation of resistant clones in the immunocompetent host

Matsushita et al. *Nature* 2012
Immunoediting / Escape

Tumor and microenvironment evolution: immunoediting in Human

Genetic evidence for immunoediting in tumors and tumor-intrinsic resistance to cytolytic activity

Rooney MS et al. *Cell* 2015

Demonstration of the existence of immunoediting in Human with genetic evidence for missense and frameshift mutations

Mlecnik B et al. *Immunity* 2016

Anti-PD1 immunotherapy induces changes in the mutational burden of tumors, with loss of certain neoantigens, clonal T-cell expansion, and changes in immune contexture (mechanistic signature)

Riaz N et al. *Cell* 2017

First demonstration that Immunoscore and immunoediting in Human shape the evolution of specific tumor clones. Darwinian selection of immune-escape variant tumor clones throught parallel immune selection model.

Angelova M et al. *Cell* 2018

Observed compared to expected frameshift and missense epitopes (immunogenic mutations) using ExomeSeq data

Genetic analysis of missense and frameshift immunogenic mutations (epitopes)

- ✓ ExomeSeq
- ✓ RNAseq
- ✓ Mutations detection
- ✓ Variant calling
- ✓ HLA haplotypes prediction
- ✓ Epitopes prediction
- ✓ HLA / TCR peptide binding prediction
- ✓ Immunogenicity scores

Silent mutations

↕

PanCancer rate (n=3659 Pts.)

↕

Non-immunogenic mutations

↕

Expected immunogenic mutations

↕

Observed immunogenic mutations

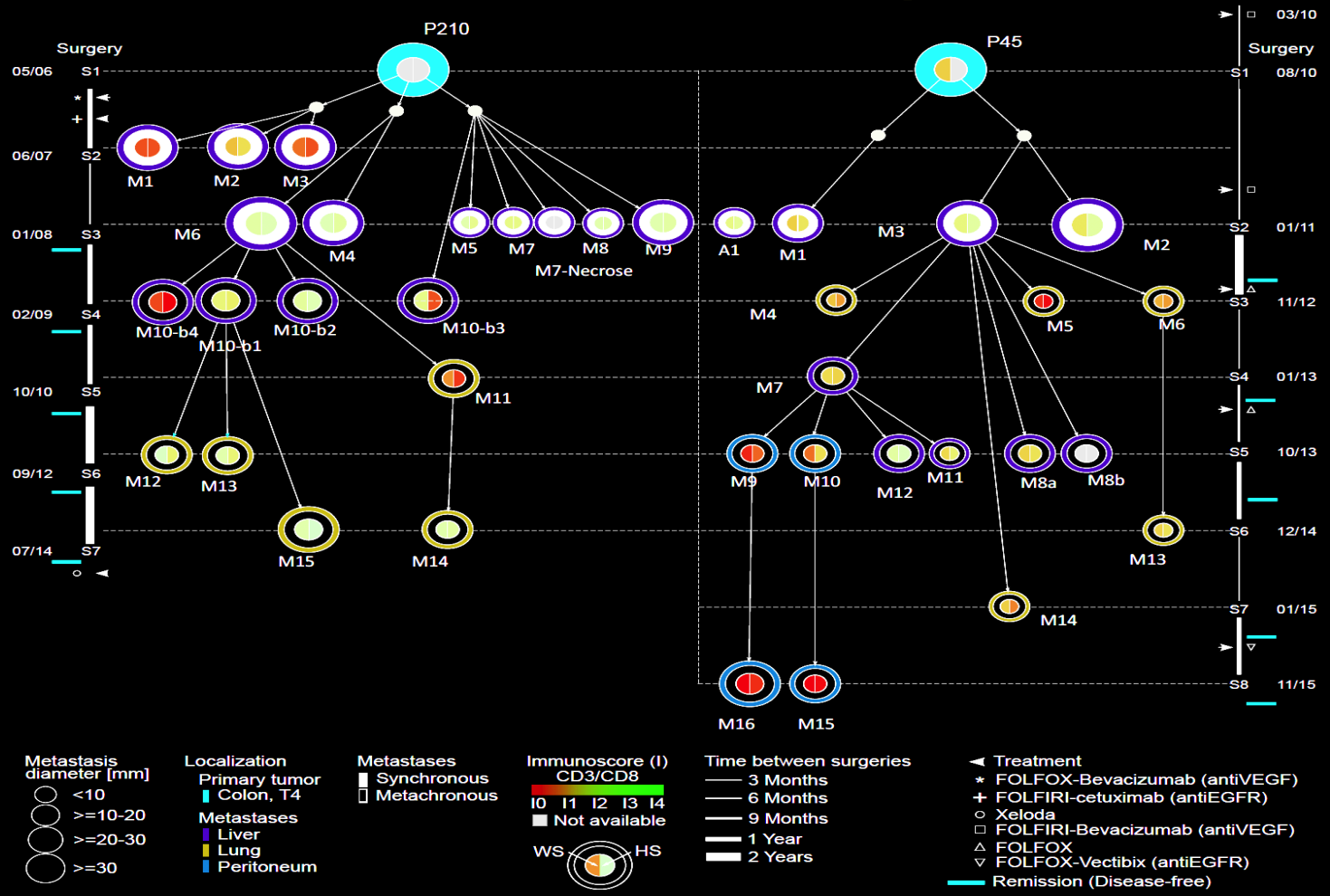
Clonal dissemination – Parent/child-relationship

Primary tumors

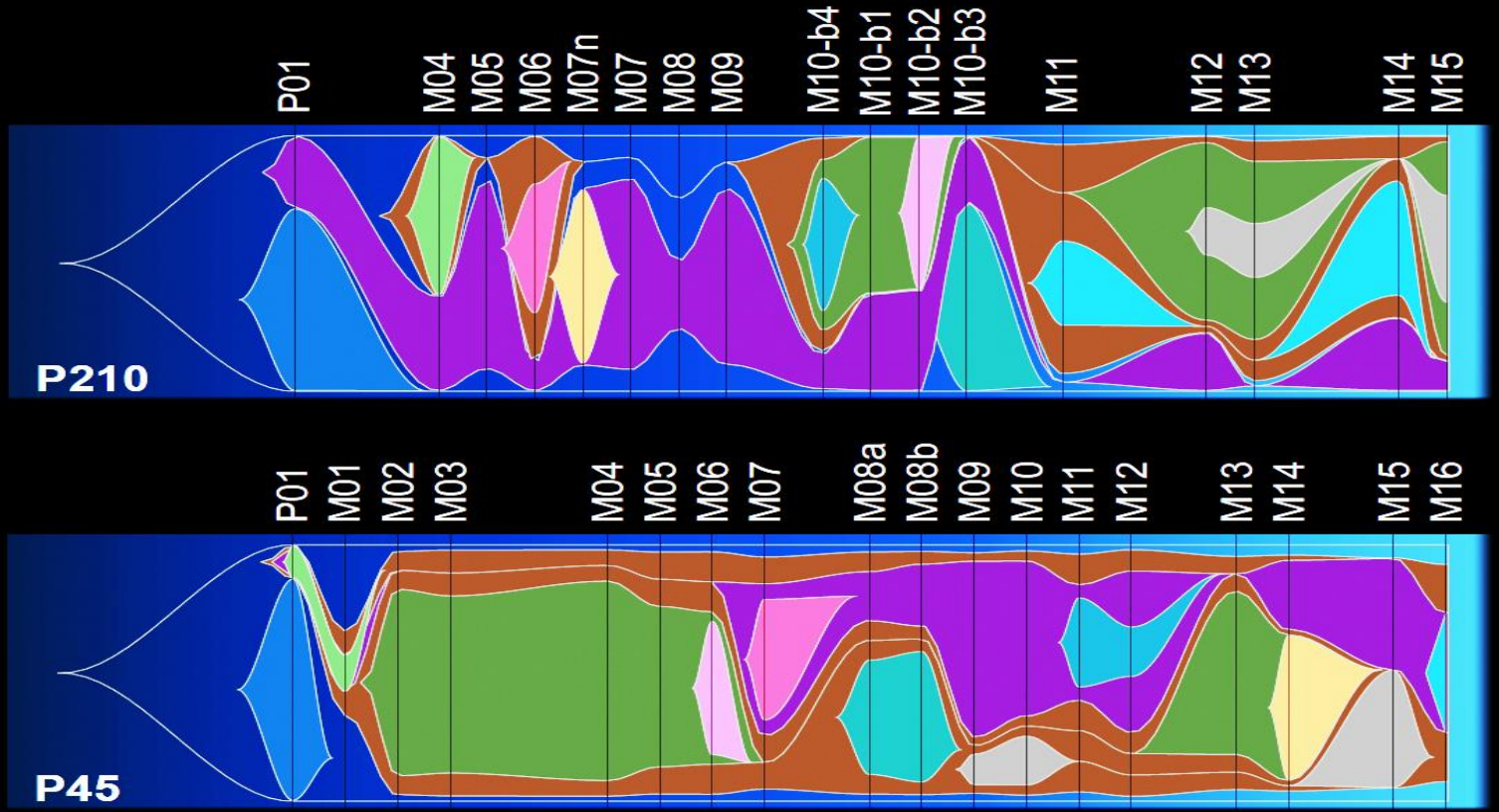
Synchronous meta

Metachronous meta

11 years



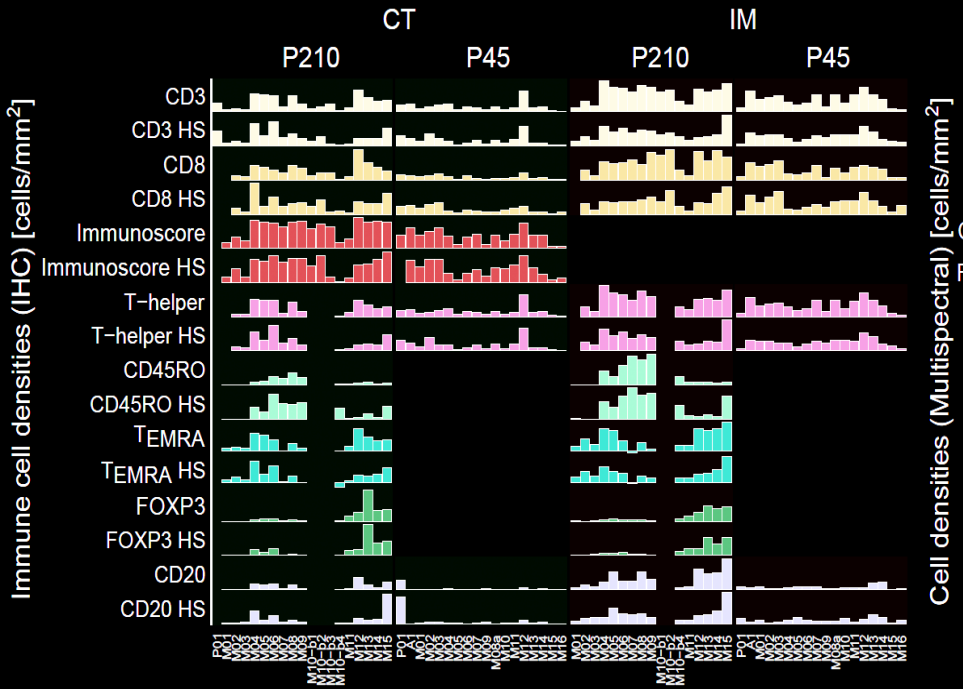
Evolvogram of tumor clones

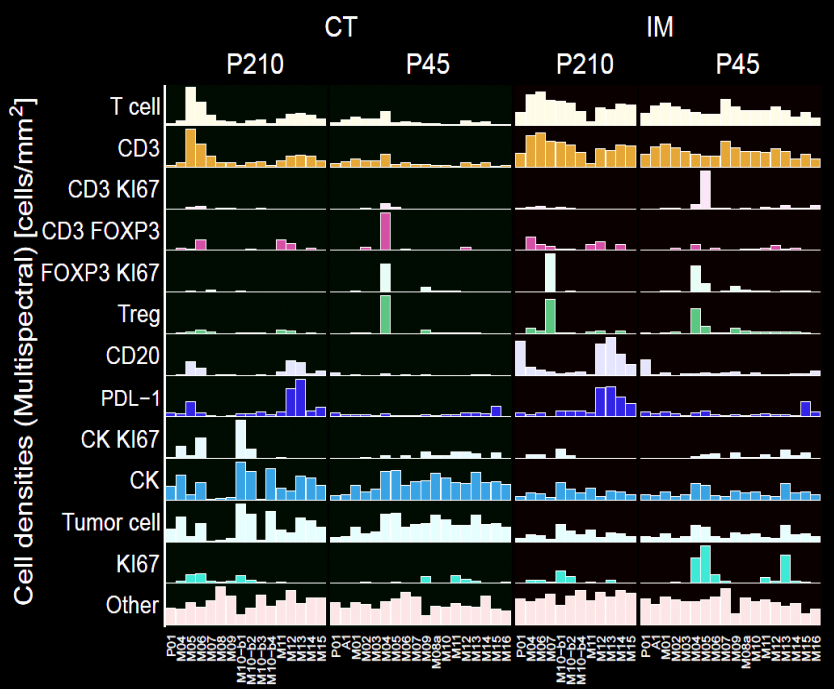


- ✓ Clonal evolution and cancer evolvogram
- ✓ Non-recurrent clones are immunoedited. Progressing clones are immune privileged

Immune microenvironment

Immune cell densities (cells/mm^2)

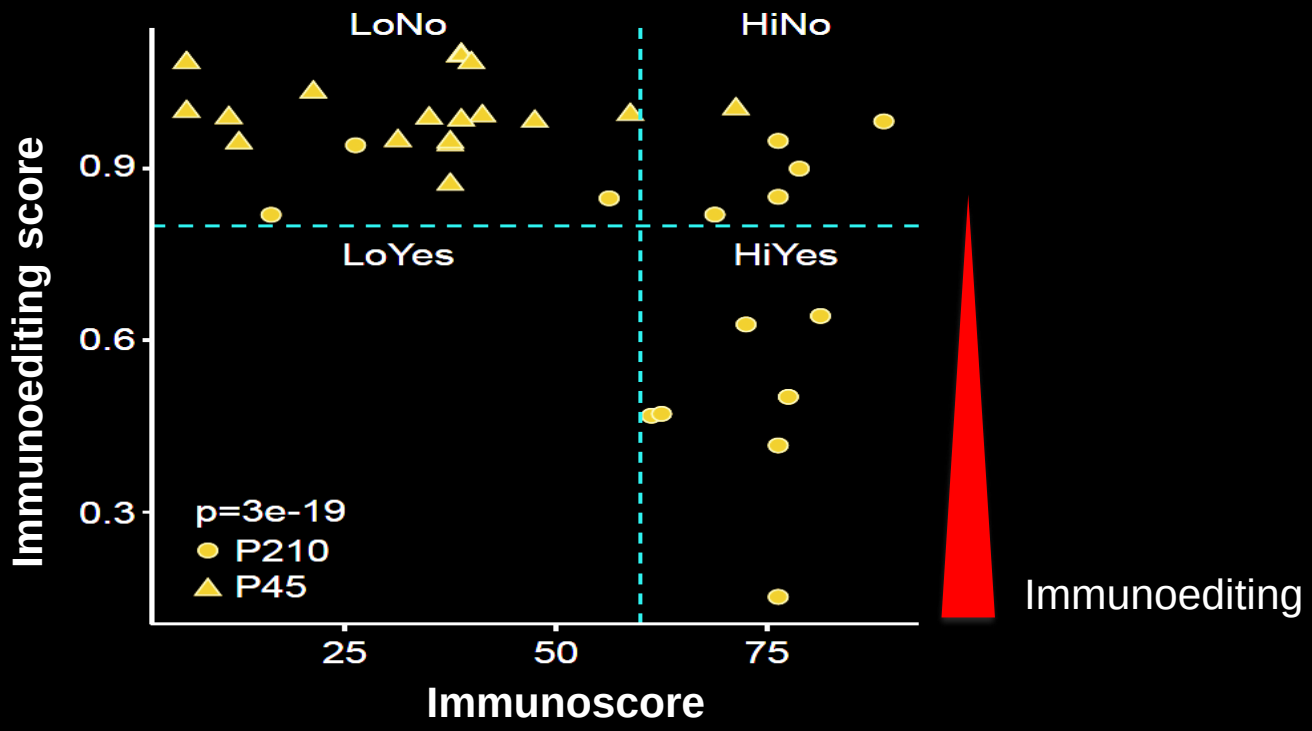




✓ Highly heterogeneous Immunomics patterns and immune cell infiltration between metastases

Angelova M. et al. *Cell* 2018

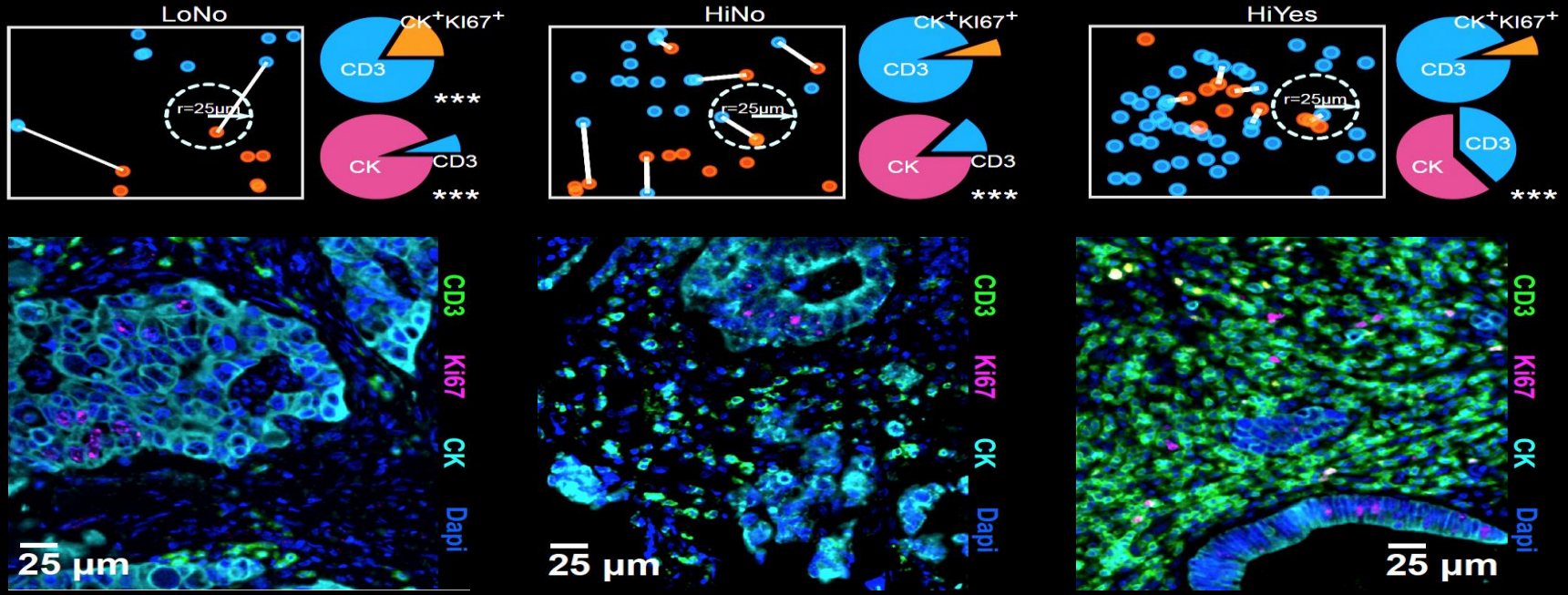
Immunoscore and Immunoediting within metastases



- ✓ For Immunoediting to occur, High-Immunoscore is necessary
- ✓ Immunoscore is not sufficient, since High-Immunoscore may not show immunoediting

What drives metastasis?

Spatial mapping of the metastatic microenvironment

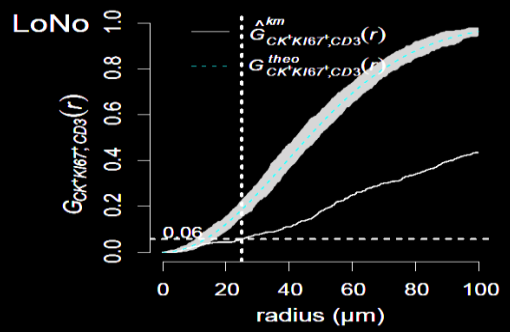


- Distance between CD3 + cells and tumor cells Ki67+ are associated with Immunoscore and Immunoediting groups, and with metastasis recurrence.

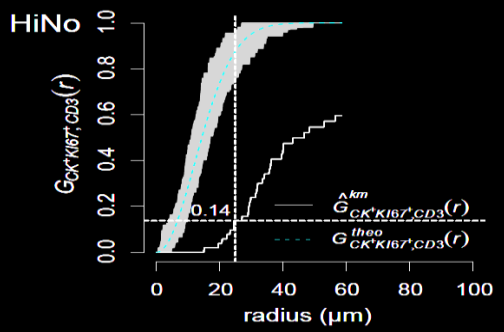
What drives metastasis?

Immunoscore - Immunoediting

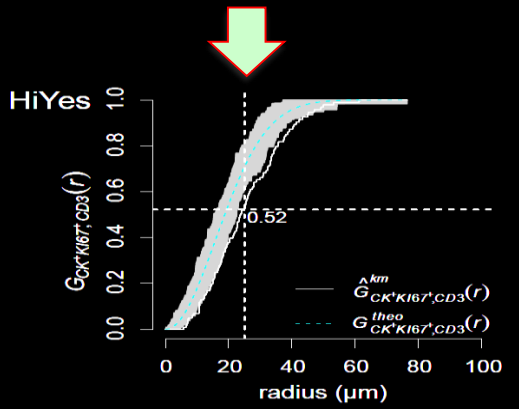
Lo-No



Hi-No

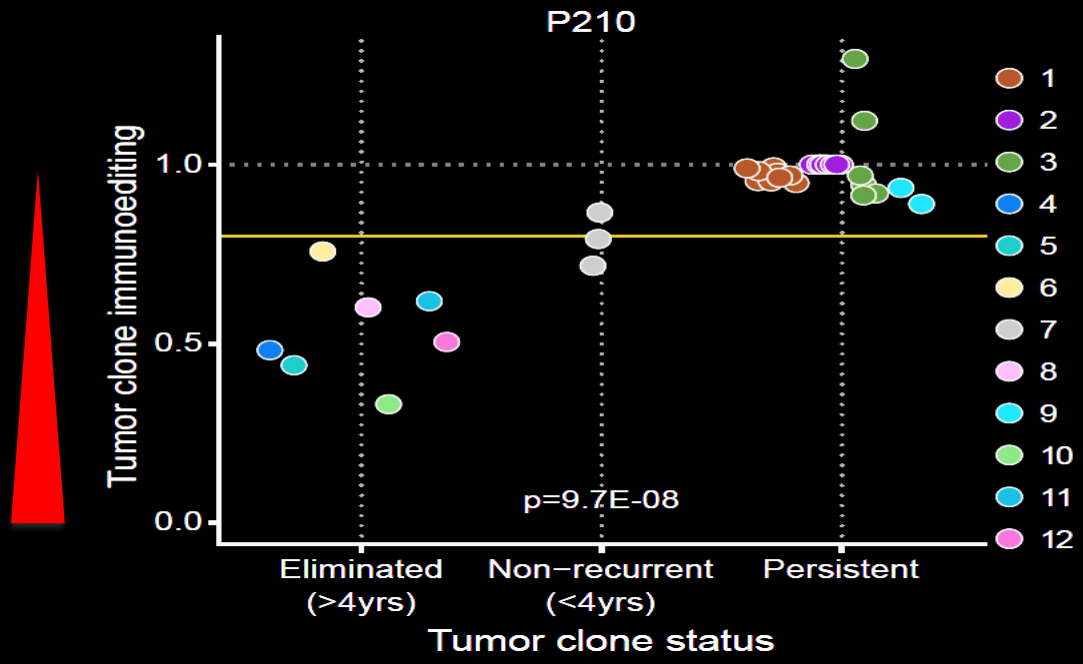


Hi-Yes



- ✓ **HiYes** metastases had shorter average mutual neighbor distances between $CD3^+$ and CK^+Ki67^+ cells
- ✓ **HiYes** metastases had on average 50% of the proliferating tumor cells in CT surrounded by $CD3^+$ T-cells within a radius of 25µm

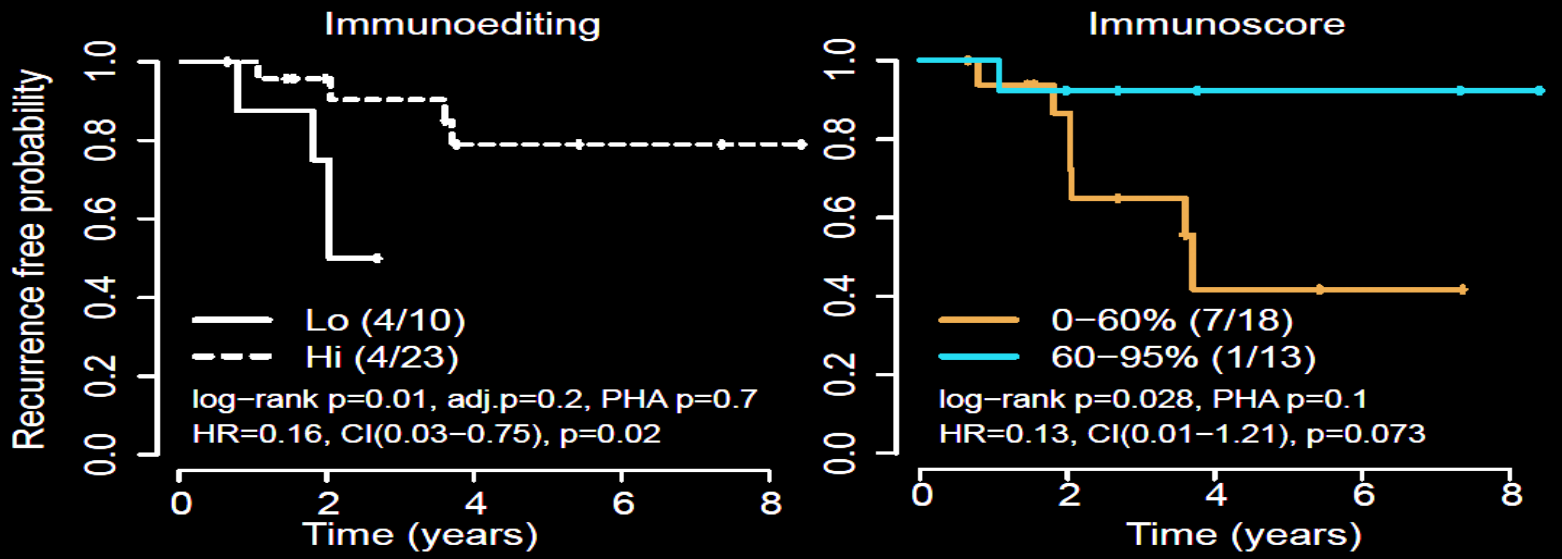
Elimination of Immunoedited clones



- ✓ Eliminated clones are immunoedited
- ✓ Non-recurrent clones (<4 years) have a low immunoediting score
- ✓ Persistent clones are immune privileged (not-immunoedited)

Angelova M. et al. *Cell* 2018

Metastasis recurrence



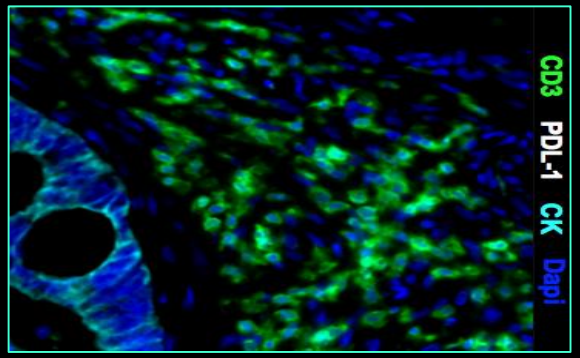
- ✓ Immunoediting and Immunoscore are associated with metachronous metastasis recurrence

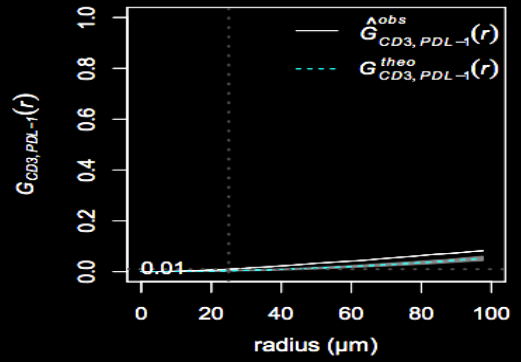
Spatial mapping of the metastatic microenvironment

Cumulative distribution function of nearest neighbors between CD3+ and PD-L1+

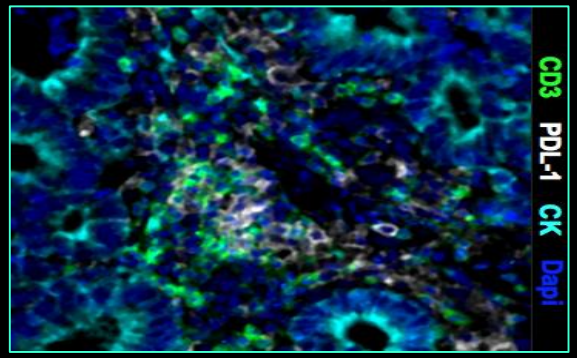
Immunoscore - Immunoediting

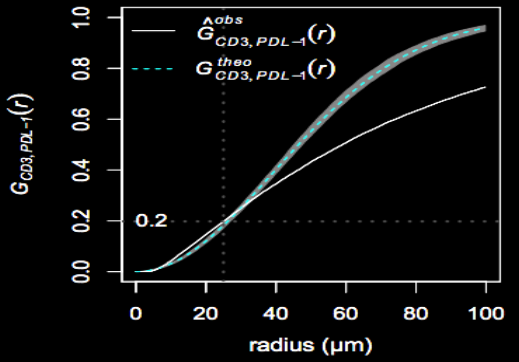
Lo-No



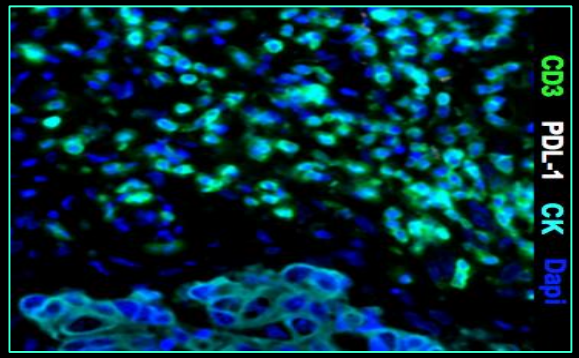


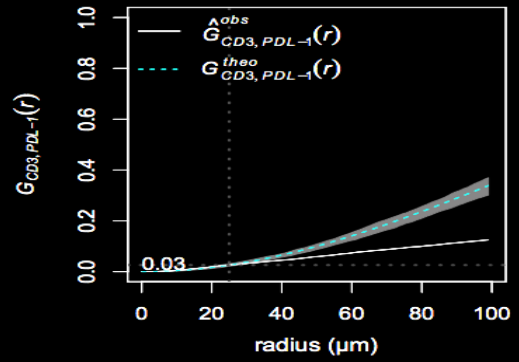
Hi-No





Hi-Yes

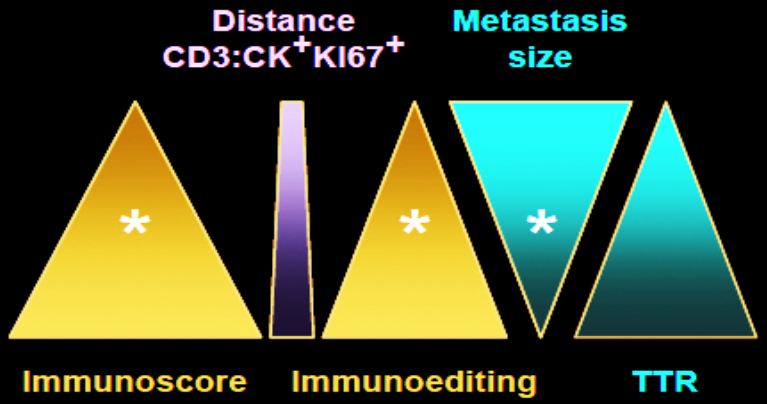




HiNo metastases have a higher percentage of T cells ($CD3^{+}$) that have the nearest PD-L1+ within a radius of 25μm

Multivariate analysis of all genomics and immunomics parameters

	Df	First recurrence		Multiple recurrences	
Excluded variable		AIC	log(HR)	AIC	log(HR)
<none>		43.3		124	
CD3 to CK+KI67+ mutual neighbor distance (Hi)	1	43.7	-2.2	124.1	-1.6
Immunoscore (>60%)	1	46.2	**-3.1**	124.8	**-1.8**
Immunoediting (Low)	1	48.1	**-3.1**	133	**-1.9**
Meta Size (log)	1	45.9	**2.5**	133.7	**2.6**

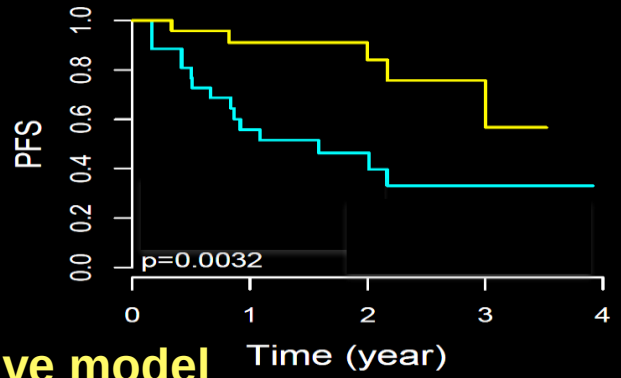


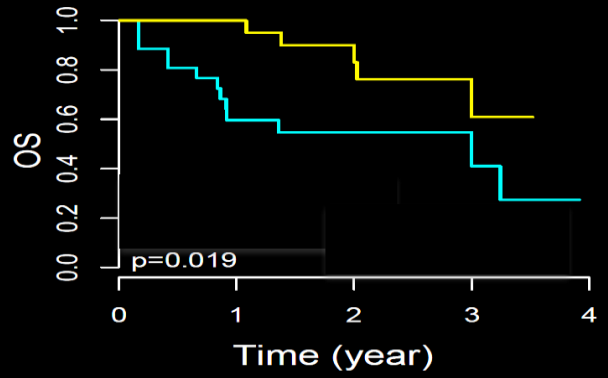
- ✓ Cox multivariate analysis revealed 4 parameters associated with metastatic dissemination:
- ✓ Immunoscore, Immunoediting, the distance between CD3 T-cells and Ki67+ tumor cells, and the size of the parent metastasis

Validation Study

CRC Primary tumor recurrence (n=132 patients)

Immunoediting

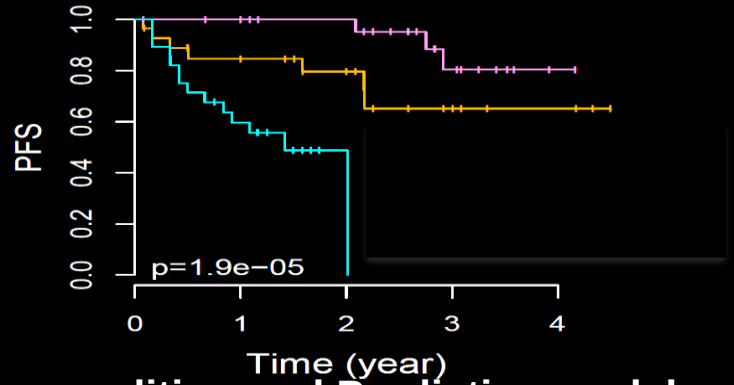




Immunoediting

No Immunoediting

Predictive model

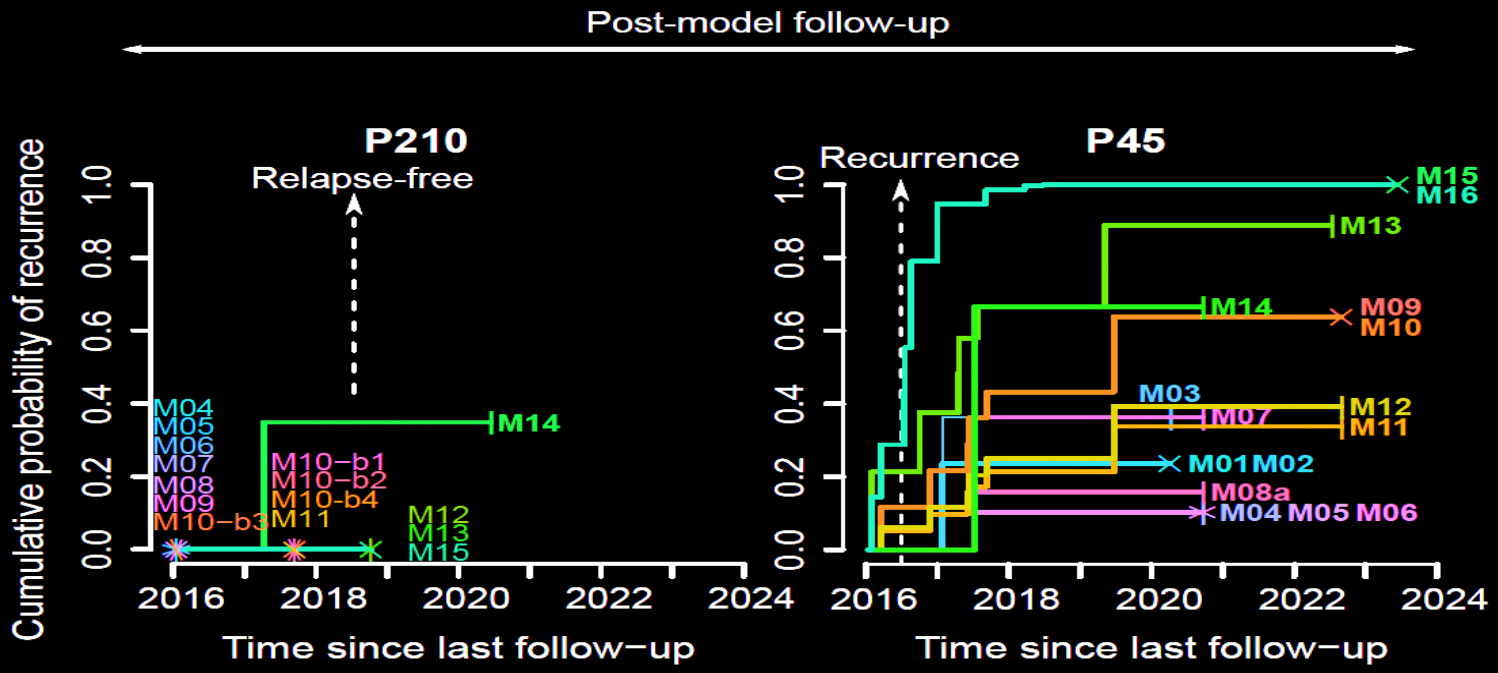


Predictive model
Recurrence probability
Low
Int
High

- **Immunoediting and Predictive model are predictive factors of recurrence.**

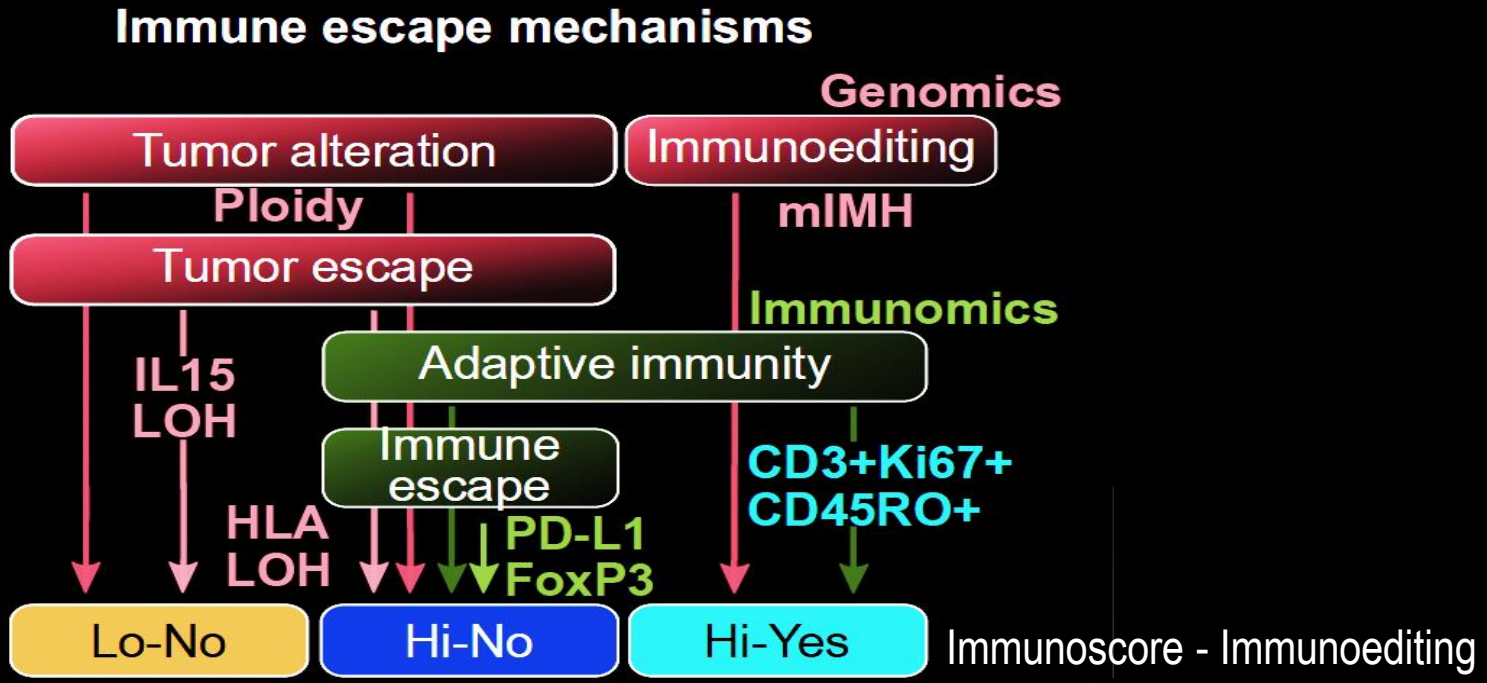
Angelova M. et al. *Cell* 2018

Predictive model of dissemination



- ✓ Model for cumulative probability of recurrence
- ✓ -> Prediction model

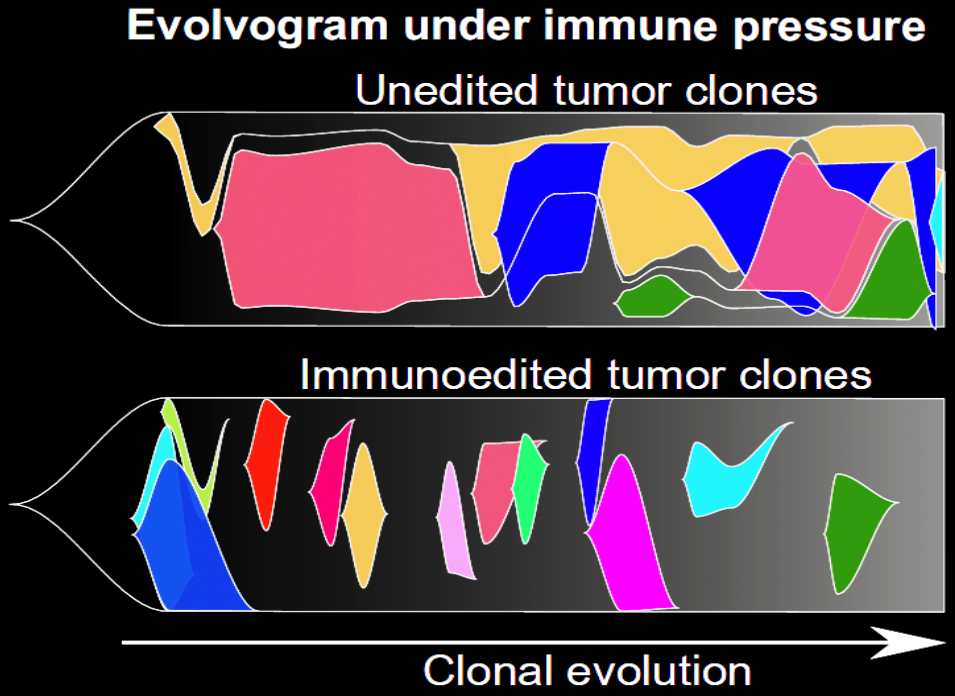
What drives metastasis? Conclusions



- Different escape mechanisms delineated by lack of adaptive immunity or immunoediting.

Angelova M. et al. *Cell* 2018

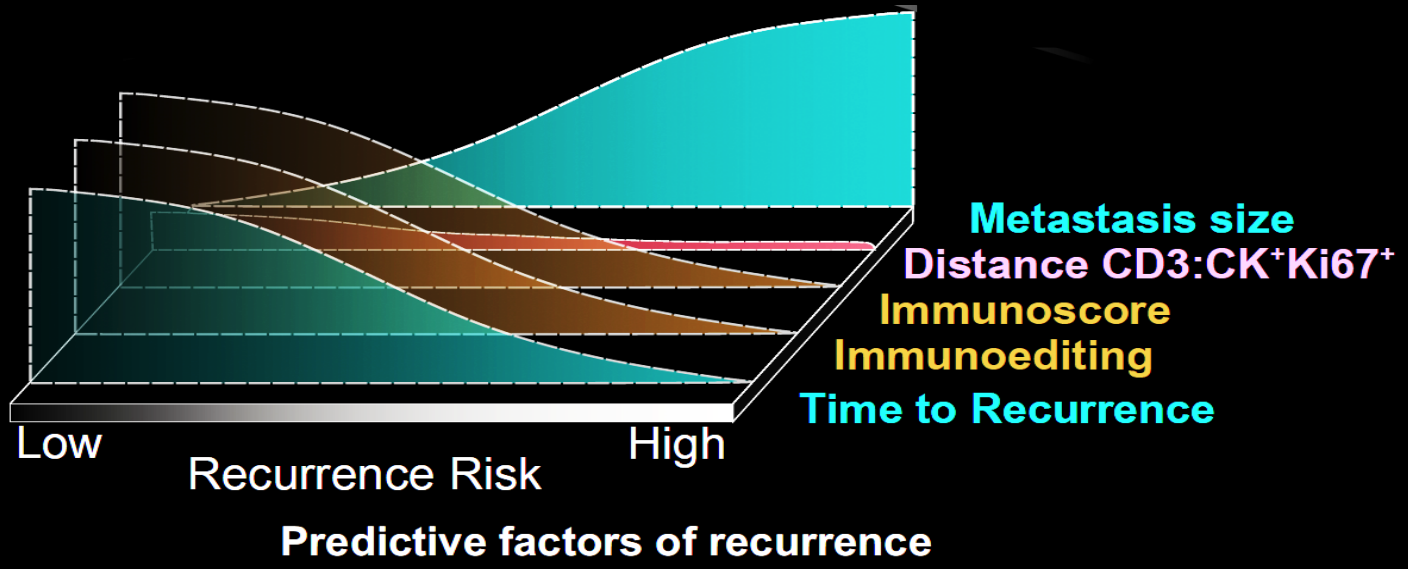
What drives metastasis? Conclusions (2)



- Multiverse of metastases evolution in space and time under immune selection
- Evolution of tumor clones is linked to the intra-metastatic immune contexture.
- Non-recurrent clones are immunoedited. Progressing clones are immune privileged.

Angelova M. et al. *Cell* 2018

What drives metastasis? Conclusions (3)



- Parallel selection model describes tumor evolution during the metastatic process.
- Immunoediting and Immunoscore are predictive factors of metastasis recurrence.
- Distance between CD3 + cells and tumor cells Ki67+ and metastasis size are also associated metastasis recurrence.

Angelova M. et al. *Cell* 2018

A Novel theory of cancer evolution

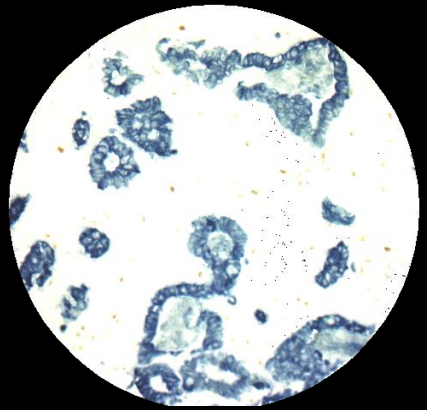
Models

LINEAR	NEUTRAL	BIG-BANG	BRANCHED	SELECTION
				
Immune pressure from Darwinian selection				
NO	**NO**	**NO**	**NO**	**YES**

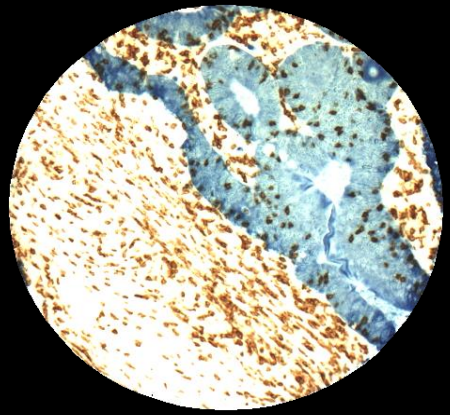
- **Parallel immune selection model**
- Dynamic interaction of tumor-cells with immune-cells and Darwinian selection of immune escape variant, with parallel evolution and multiverse of metastases.

Deciphering the tumor immune microenvironment: Clinical implications

"Cold" Tumor
I 0



CD3
Tumor



"Hot" Tumor
I 4

Clinical implications

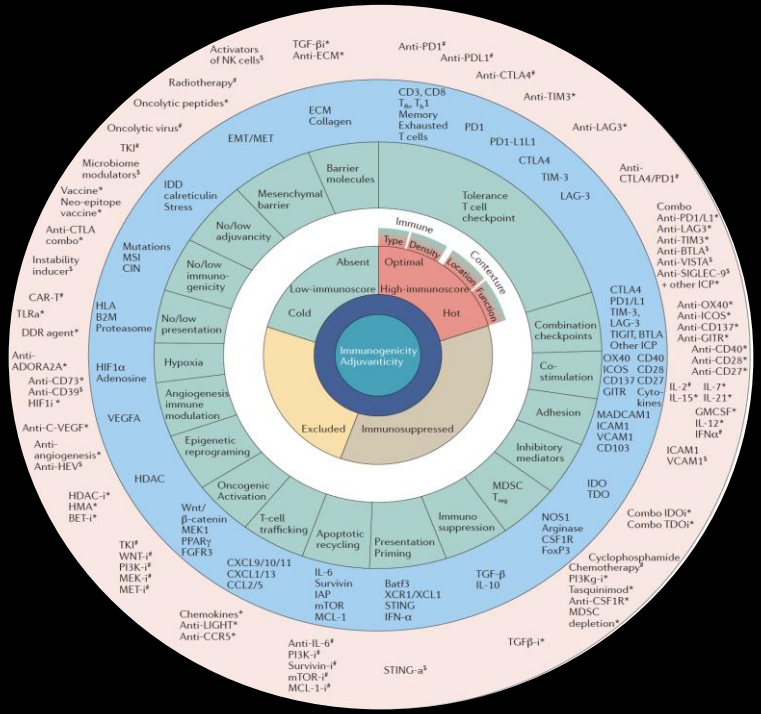
Predictions

Need T-cell priming
Cancer vaccine

Response to immunotherapies
(CTLA4, PD1, PDL1, …)

But it is not as simple since biology is complex and is not dichotomized in good & bad

Treating hot, altered and cold immune tumors with immunotherapy



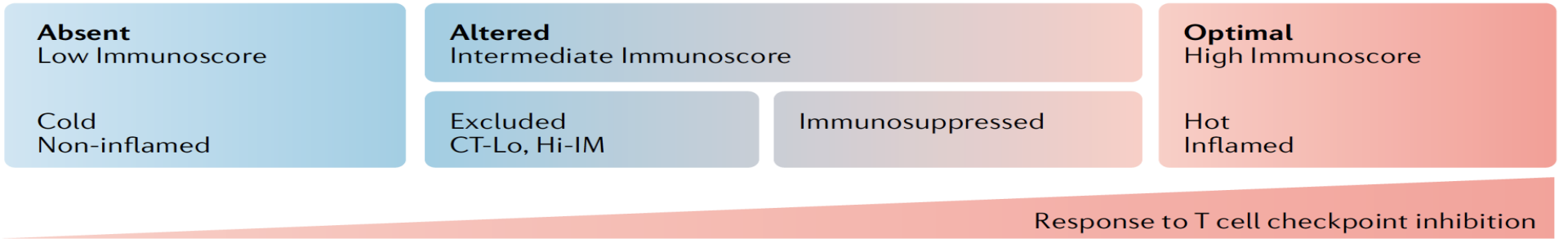
Galon J. & Bruni D.
Nature Reviews Drug Discovery 2019

NATURE REVIEWS | DRUG DISCOVERY

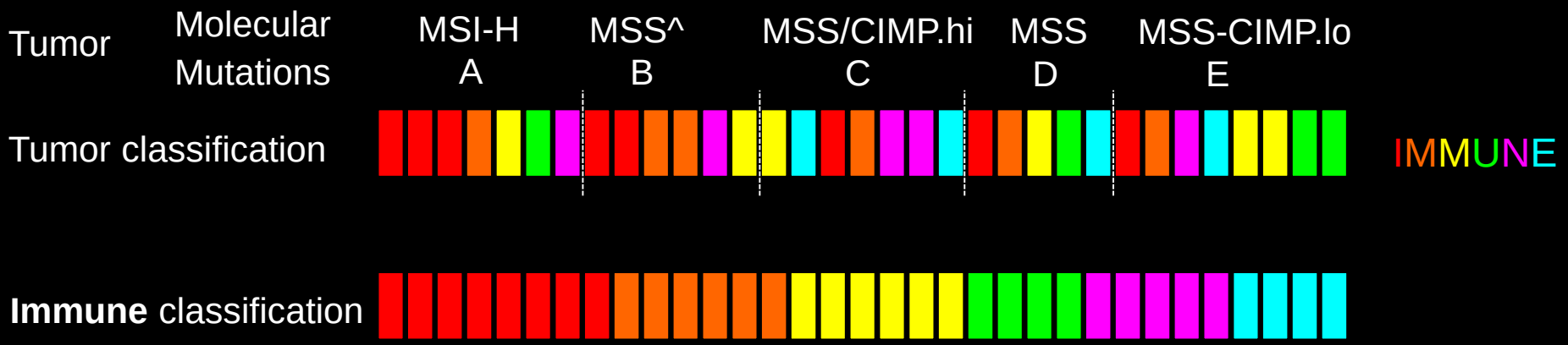
Approaches to treat immune hot, altered and cold tumours with combination immunotherapies

Jérôme Galon * *and Daniela Bruni*

2019



Stratification of cancer based on the immune status



-> Importance of having standardized immune Assays

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