CENTRE DE RECHERCHE DES CORDELIERS

SITC – Biomarker session

National Harbor, November 9th 2017

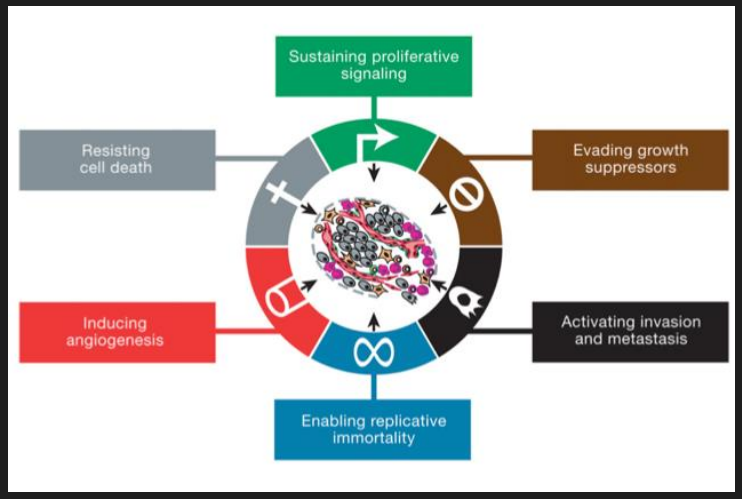
Inserm laboratory of Integrative Cancer Immunology

ROUND TABLE

Why immune biomarkers not yet really much used in the era of cancer immunotherapies ?

Jérôme GALON

Hallmarks of cancer



Hanahan & Weinberg, Cell 2000
Revised in 2011: emerging hallmark immunity

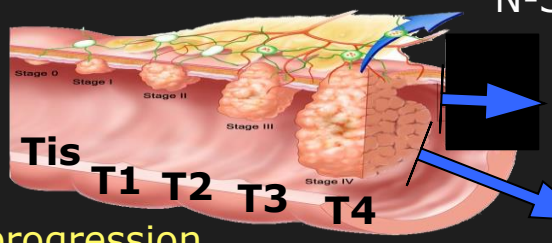
Cancer specialists

- Oncologists
- Geneticists
- Pathologists
- Surgeons
- Radiotherapists
- Cancer clinicians
- Organ specialists

TNM staging, Dukes 1932

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

Why the need for risk immune biomarkers ?

Today's cancer classifications – Routine biomarkers

Tumor cell extension and invasion	**T-STAGE**		**N-STAGE**		**M-STAGE**
Ways to classify	**Morphology**	**Cell of origin**	**Molecular pathway**	**Mutation status**	**Gene expression**
Tumor cell characteristics	Mucinous	Enterocyte	CIN	BRAF	CMS1
	Medullary	Goblet-like	MSI	APC	CMS2
	Adeno. NOS	Transit-amplifying-R	CIMP	KRAS	CMS3
	Serrated	Transit-amplifying-S		TP53	CMS4
	Signet ring cell	Inflammatory		CTNNB1	
	Micropapillary	Stem-like			
	Cribriform comedo -type				
Host immune response	**Immunoscore**	CD3+ T cells	CD8+ T cells	Density	Location (CT, IM)

Galon et al. ***J Pathol***. 2014

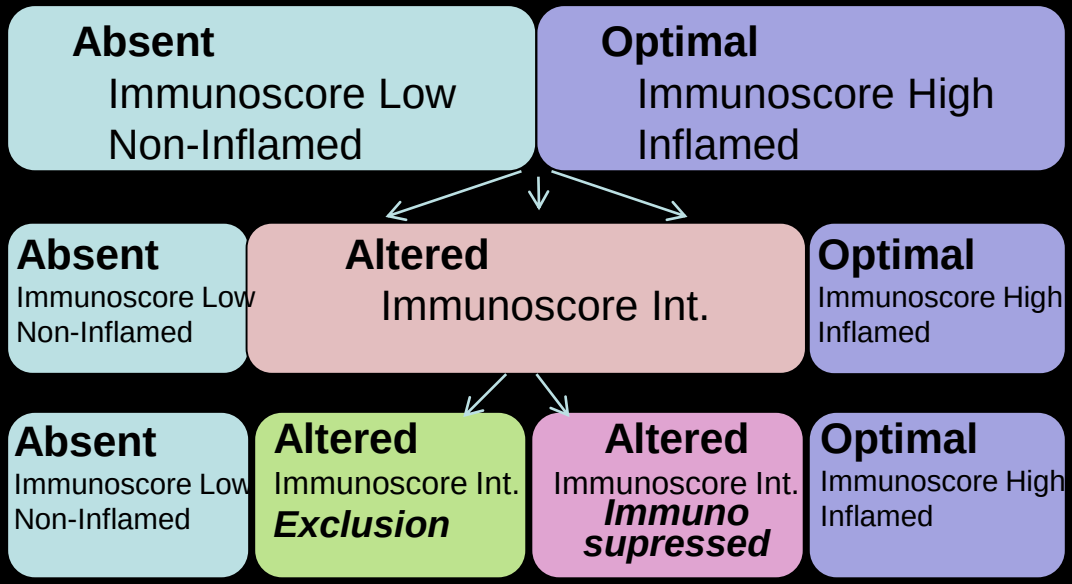
Definition of cancer

Two quite opposite qualities equally bias our minds:
habits and novelty.

Jean de la Bruyère, French philosopher (1645-1696)

Example of Immunoscore

Basic science



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

Definition of the Immune contexture
Hot/Cold tumors
Immunoscore > TNM

Camus & *Galon Cancer Res* 2009

Absent, altered, optimal immunity

Camus & *Galon Cancer Res* 2009

"TNM: T is T-cells, M is Memory"

Pages F et al. *JCO* 2009
Mlecnik B et al. *JCO* 2011
Mlecnik B et al. *Science Transl Med* 2016
Galon et al. *J Pathol* 2014
Mlecnik B et al. *Immunity* 2016
Mlecnik B et al. *JNCI* 2016

Translational research

JOURNAL OF TRANSLATIONAL MEDICINE
REVIEW Open Access
Cancer classification using the Immunoscore: a worldwide task force
Galon *et al. Journal of Translational Medicine* 2012, **10**:205

JOURNAL OF CLINICAL ONCOLOGY
Official Journal of the American Society of Clinical Oncology

Worldwide Immunoscore consortium (2012), ASCO 2016

Prospective Immunoscore study (2014)

European Immunoscore consortium (2015)

Immuno-oncology diagnostic company (2015)

halio dx

Immunoscore approved EMA as CE-IVD (12/2016)
Immunoscore available in CLIA lab (USA) (10/2017)

Characteristics of good biomarkers

Ways to routinely classify cancer based on:

Tumor cell characteristics

T-STAGE

N-STAGE

M-STAGE

Morphology
Mucinous, Serrated, Signet ring, …

Cell of origin
Enterocyte, Gobelet, Stem-like, …

Molecular pathway
CIN, MSI, CIMP, …

Mutation status
BRAF, KRAS, TP53, …

Gene expression
CMS1, CMS2, CMS3, …

Host-immune characteristics

-> Currently none

Hurdles for biomarker	TILs evaluation	**Immunoscore quantification**
• Routine	☑	☑
• Feasible	☑	☑
• Simple	☑	☑
• Rapid	☑	☑
• Robust	☐	☑
• Objective	☐	☑
• Specific	☐	☑
• Reproducible	☐	☑
• Quantitative	☐	☑
• Standardized	☐	☑
• Powerful	☐	☑
• Pathology-based	☑	☑

Why the need for predictive biomarkers ?

- ✓ Only a subgroup of patients responding to treatment
- ✓ Delayed responders
- ✓ Tumor ‘progression’ before evident regression
- ✓ Toxicity, irAE
- ✓ Combinatorial regimens
- ✓ Costly therapies

Why the need for predictive biomarkers ?

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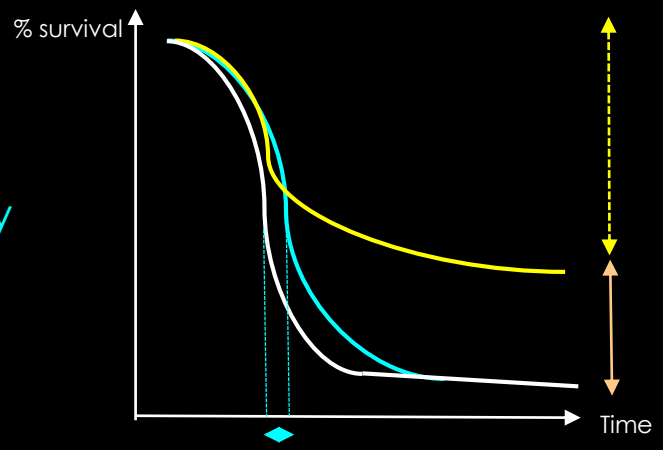
Chemotherapy
Targeted therapy
Immunotherapy



Inefficient

Responding subgroup
Long-term survival

Why the need for predictive biomarkers ?

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Combinations

- ✓ 25 targets
- ✓ Sequential / concomitant = x2
- ✓ 3 doses: x3
- ✓ 20 cancer types: x20
- ✓ 3 stages (IV, NeoAdj, Adj): x3
- ✓ **= 4.97 Million clinical trials**

Why immune biomarkers not yet really much used in the era of cancer immunotherapies ?

Why immune biomarkers not yet really much used in the era of cancer immunotherapies ?

Non-scientific issues

- ✓ Cancer field is dominated by oncologists, geneticists, tumor cell specialists,…
- ✓ Cancer was defined as a genetic disease: driver mutation mutation, mutation
- ✓ Pathologists were trained and focus on any tumor cell abnormality
- ✓ New biomarkers have to stand the test of time
- ✓ Immune > TNM is a new paradigm
- ✓ Digital pathology is the tool of the 21st century for pathologists, but conservatism …
- ✓ Drug are very expensive but biomarkers are very poorly valued and reimbursed
- ✓ Pharma prefered not to use biomakers unless they have to, or if it is becoming a leaverage

Why immune biomarkers not yet really much used in the era of cancer immunotherapies ?

Scientific issues

- ✓ Relevant Immune markers are often prognostic, predictive and mechanistic [1]
- ✓ Immune cells are plastic
- ✓ Immune markers are dynamic (feedback loop mechanisms, …)
- ✓ Intratumoral markers are more relevant, stronger, more specific
- ✓ Peripheral markers are more convenient,
- ✓ Tumors are heterogeneous (primary and metastases)
- ✓ Intra-tumoral and Inter-tumoral immune heterogeneity (multiple meta = multiple disease)
- ✓ Assays should be consensus, robust, reproducible, quantitative

1 Galon et al. *Immunity* 2013

PDL-1 companion diagnostic

Dynalic

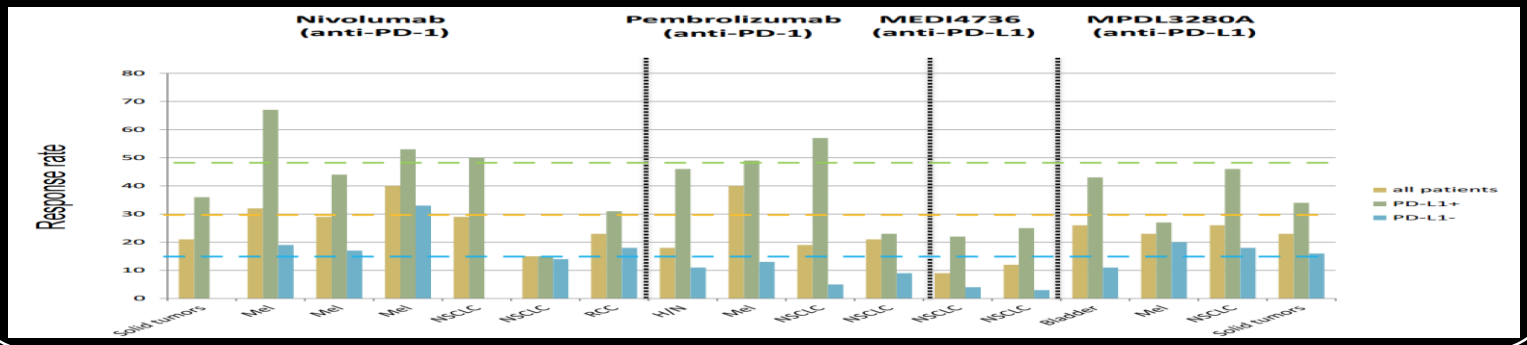
Different antibodies

Scoring Methods

Thresholds

subjective

Increased response rate to anti-PD1/L1 in PD-L1+ tumors [4]



Predictive markers to immunotherapies: the cancer Immunogram

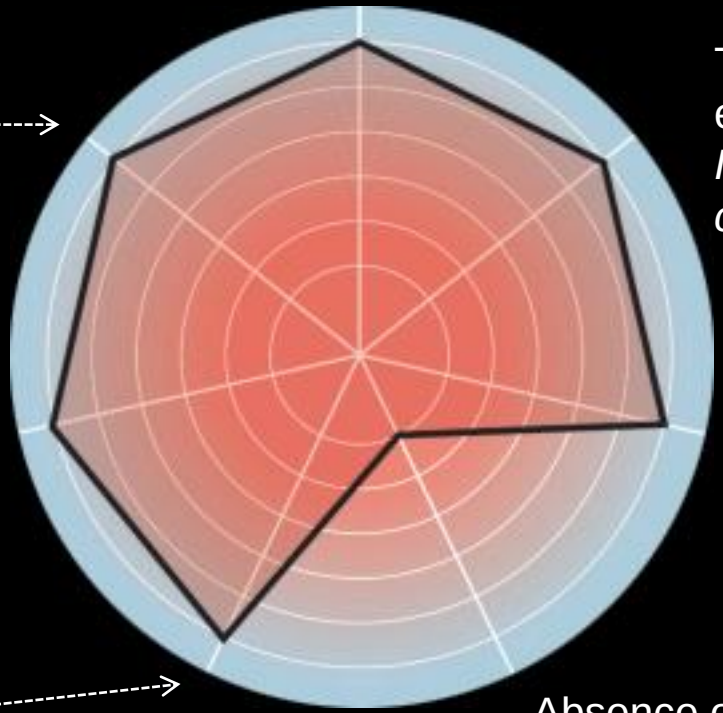
Peripheral

Intra-tumoral

Tumor foreignness
*Mutational load, MSI **

Peripheral immune status
Lymphocyte count

Tumor sensitivity to immune effectors
IFNG, MHC, cytokines, chemokines,



Abscence of inhibitory tumor metabolism
LDH, glucose

Immune cell infiltration
Immunoscore

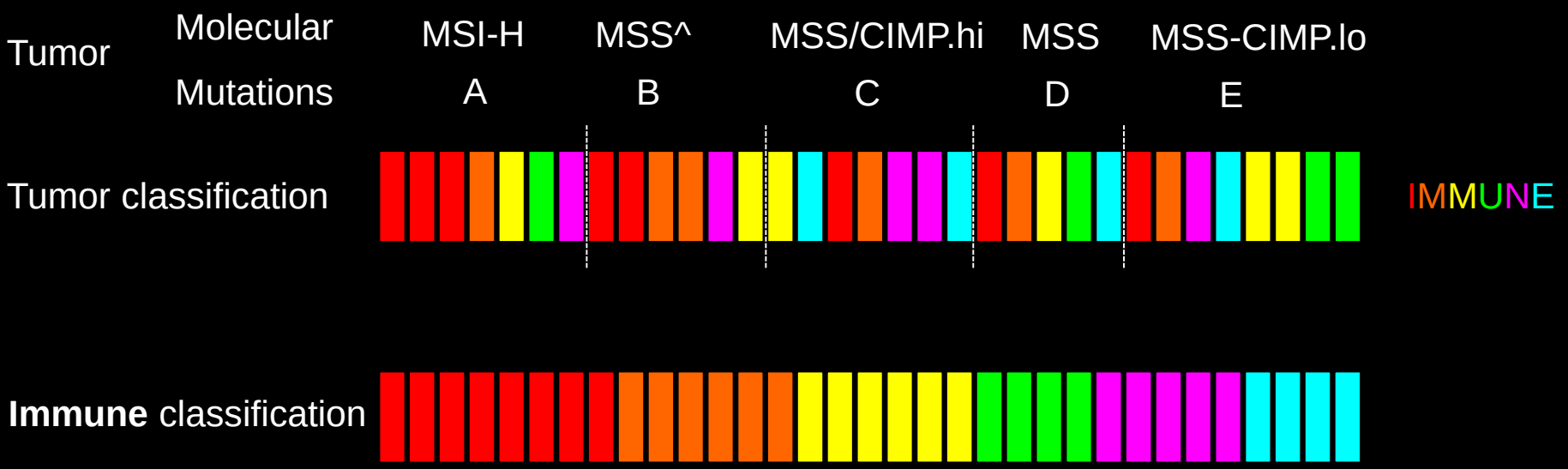
Abscence of soluble inhibitors
IL-6, CRP

Absence of checkpoint
*PD-L1 **

** FDA approved*

Adapted from Blank C et al. "The cancer immunogram" Science 2016

Stratification of cancer based on the immune status



-> Importance of having standardized immune Assays