Immunoscore and Immune Contexture in Cancer

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Disclosures

Co-founder and chairman of the scientific advisory board:
- HalioDx

Collaborative Research Agreement (grants):
- BioMerieux, Perkin-Elmer, IObiotech, MedImmune, Janssen

Participation to Scientific Advisory Boards:
- BMS, ImmunID, MedImmune, Astra Zeneca, Novartis, Definiens, IObiotech, Actelion

Consultant:
- BMS, Roche, Ventana, GSK, MedImmune, ImmunID, Nanostring, Compugen,
Definition of cancer

1) A tumor cell DNA disease – Cell-centric paradigm

2) Due to the acquisition of secondary key behavioral characteristics following tumor genomic changes (Hanahan & Weinberg, Cell 2000)

- Tumor invasion
- N-Stage
- Early-metastasis (venous emboli)
- M-Stage

Tumor progression
- Tis
- T1
- T2
- T3
- T4

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

-> Tumor aggressiveness, progression, invasion and recurrence define early and late stage cancers, and the severity of the disease
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.
T-cell based immunotherapy:
Unleashing the immune response

Key points

- T-cells & cytotoxic T-cells are essential to prevent tumor progression, invasion, recurrence, and death
- All immunotherapies are “just” modulating the pre-existing immune response of the patient
- Thus it is essential to “know” what is the immune contexture of the patient (Standardized Immune Assays)
- Stratifying patient based on immune parameters (Immunoscore) is a paradigm shift
- Knowing the immune “defect” of a patient will guide its optimal immunotherapy treatment
Effector Memory T Cells, Early Metastasis, and Survival in Colorectal Cancer

Franck Pagès, M.D., Ph.D., Anne Berger, M.D., Ph.D., Matthieu Camus, M.Sc., Fatima Sanchez-Cabo, Ph.D., Anne Costes, B.S., Robert Molidor, Ph.D., Bernhard Mlecnik, M.Sc., Amos Kirilovsky, M.Sc., Malin Nilsson, B.S., Diane Damotte, M.D., Ph.D., Tchao Meatchi, M.D., Patrick Bruneval, M.D., Ph.D., Paul-Henri Cugnenc, M.D., Ph.D., Zlatko Trajanoski, Ph.D., Wolf-Herman Fridman, M.D., Ph.D., and Jérôme Galon, Ph.D.*

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

Quantification of immune cell densities (6640 IHC) revealed the major positive role of cytotoxic and memory T cells for patient’s survival.

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 Kirillovsky,1 Bernhard Mlecnik,2 Christine Lagorce-Pagès,3 Marie Tosolini,‡ Matthieu Camus,1 Anne Berger,4 Philippe Wind,4 Franck Zinzindohoué,5 Patrick Bruneval,6 Paul-Henri Cugnenc,5 Zlatko Trajanoski,4 Wolf-Herman Fridman,1,7 Franck Pagès1,7,‡

Cohort 1: n= 415 patients
Validation cohorts: n= 188 patients

Galon J et al. Science 2006

The foundation a new concept

Immune contexture -> Immmunoscore

✓ Quantification of immune cell densities (6640 IHC) revealed the major positive role of cytotoxic and memory T cells for patient’s survival.
in situ analysis of cytotoxicity
Novel Paradigm

COX multivariate analysis (OS) in all stages I, II, III patients

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<td>Differentiation</td>
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<td>0.84</td>
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<td>Immunoscore</td>
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<td>0.00001</td>
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“Contexture: the act of assembling parts into a whole; an arrangement of interconnected parts”

“Invasive margin (IM) immune tumor Center of the tumor (CT) immune

“Immune Contexture” : nature, immune functional orientation, density, and location within distinct tumor regions, of a natural in situ immune reaction

Galon J et al. Science 2006
Galon J et al. Cancer Res. 2007
Prolonged survival in patients with high *Immunoscore* (Im) based on the evaluation of CD45RO-CT/IM and CD8-CT/IM

Tumor progression, invasion and recurrence are dependent on the immune contexture and Immunoscore.

Pre-existing immunity is determining the fate and survival of the patient.

Tumor progression, invasion and recurrence are dependent on the immune contexture and Immunoscore.

Pre-existing immunity is determining the fate and survival of the patient.
The immune landscape in human tumors, and definition of the immune contexture

Immune contexture

- **Type**: Adaptive immunity, cytotoxic, memory T cells, T<sub>FH</sub> cells, B cells
- **Density**: Quantification (cells/mm<sup>2</sup>)
- **Location**: Tumor center, Margin, Tertiary lymphoid ilets
- **Immune Functional orientation**: IFNG, IL12, TBX21, IRF1, STAT1, GZMA, GZMB, GZMH, PRF, GLNY, CX3CL1, CXCL9, CXCL10, CCL5, CCL2, MADCAM1, ICAM1, VCAM1, ITGAE

CXCL13

IL21, IL15

Galon J et al. *Immunity* 2013
The overlap between the immune contexture, the immunologic constant of rejection and the Immunoscore

Immune contexture

Type: Adaptive immunity, cytotoxic, memory T cells
Density: Quantification (cells/mm²)
Location: Tumor center, Margin, Tertiary lymphoid ilets

Immunologic Constant of Rejection (other diseases)

CXCL13
IL21, IL15

Galon J et al. Immunity 2013
Prognostic signatures: better disease-free and overall survival

Predictive signatures: increased likelihood to respond to therapy

Mechanistic signatures: tumors studied during treatments that subsequently undergo complete regression
The overlap between prognostic, predictive and mechanistic immune signatures

NON-Immune signatures

Prognostic

Predictive

Mechanistic

IMMUNE signatures

Prognostic

Immune contexture

Predictive

ICR

Mechanistic

Immunoscore
Th1
Cytotoxicity
Chemokines
Cytokines
Adhesion

Galon J et al. *Immunity* 2013
Understanding the evolution of the immune response with tumor progression using systems biology

- Evolution of the tumor microenvironment with tumor progression?
- Immune escape mechanisms in human tumors?

-> Spatio-temporal dynamics of the immune response with tumor progression

Bindea G et al. *Immunity*, 2013
“Immunome” of purified immune cell subpopulations

Bindea G et al. *Immunity* 2013

Purified immune cell subpopulations: “Immunome”

Expression of 577 cell type specific genes

Cell types (n=28)

- B cells
- T cells
- T helper cells
- Tcm
- Tem
- Th1 cells
- Th2 cells
- TFH
- Th17 cells
- Treg
- CD8 T cells
- Tgd
- Cytotoxic cells
- NK cells
- NK CD56dim cells
- NK CD56bright cells
- DC
- iDC
- aDC
- pDC
- Eosinophils
- Macrophages
- Mast cells
- Neutrophils
- SW480 cancer cells
- Normal mucosa
- Blood vessels
- Lymph vessels

colon cancer

normal mucosa
Intratumor innate cells, adaptive cells, and vessels

IHC enzymatic stainings: -> Quantification (cells/mm²)
Cohort 1 (n=120 patients), cohort 2 (n=415 patients)

<table>
<thead>
<tr>
<th>CD20 /cs</th>
<th>CD68 /Tum</th>
<th>CD1A</th>
<th>IL3RA</th>
<th>Granulocyte</th>
<th>PDPN /cs</th>
<th>ENG</th>
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<table>
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<tr>
<th>CD3 / Tum</th>
<th>CD8 /Tum</th>
<th>CD57 /cs</th>
<th>CD45RO</th>
<th>FoxP3</th>
<th>CXCR5</th>
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<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /></td>
</tr>
</tbody>
</table>

Bindea G et al. *Immunity* 2013
Intratumor B cells, T cells and $T_{FH}$ cells

Bindea G et al. *Immunity* 2013
6-color multiplex IHC using multispectral technology
Understanding the evolution of the immune response with tumor progression: The immune landscape

Bindea G et al. *Immunity* 2013

tumor progression

Cell density (cells/mm²)

Invasive margin (IM)
Center of the tumor (CT)
Understanding the evolution of the immune response with tumor progression: The immune landscape

Bindea G et al. *Immunity* 2013

**tumor recurrence**

**Good**

**Bad**

**Hazard ratio**

**Impact on DFS**

**Invasive margin (IM)**

**Center of the tumor (CT)**

**B-cells**

**T$_{FH}$**

**T$_{H17}$**
ONLINE COVER: Protecting Against Metastasis. Notre Dame de Paris gargoyles guard over the city of Paris to frighten off and protect from any evil or harmful spirits. In this issue of Science Translational Medicine, Mlecnik et al. describe the protective role of cytotoxic immune infiltrate, Immunoscore, and lymphatic vessels against metastatic invasion in human cancer. These results support the use of T cell based immunotherapy at early stage disease.
What drives metastasis?

- Early-Metastasis (venous emboli, perineural invasion)
- Synchronous Metastasis (M1)
- Metachronous Metastasis (recurrence)

Genomic alterations in tumors

Chromosomal instability pattern (CIN)

Mutation pattern

Tumor gene expression pattern

- No significant difference between M0 and M1 cancer patients
What drives metastasis?

- Chromosomal Instability
- Tumor Genetics
- Tumor-gene expression
- FBXW7 mut

M1 stage

Blood and Lymph vessels, CD8+ cell and GZMB+ cell densities within primary tumors

Cohort 1 (n=108)

Cohort 2 (n=415)
Metastasis risk depending on lymph vessels and GZMB densities

Risk of metastasis increases:
- from 0% (blue) for tumors with High lymph vessels (IM) + high High GZMB (CT)
- to 49% (red) for tumors with Low lymph vessels (IM) + Low High GZMB (CT)

Quantification of blood and lymph vessel densities and GZBM+ cell densities within primary tumors (CT and IM regions)

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Integrative Analyses of Colorectal Cancer Show Immunoscore Is a Stronger Predictor of Patient Survival Than Microsatellite Instability

Bernhard Mlecnik,1,2,3,19 Gabriela Bindea,1,2,3,19 Helen K. Angell,1,2,3,4 Pauline Maby,1,2,3,5 Mihaela Angelova,1,2,3,6 David Tougeron,5,7,8 Sarah E. Church,1,2,3 Lucie Lafontaine,1,2,3 Maria Fischer,6 Tessa Fredriksen,1,2,3 Maristella Sasso,1,2,3 Amélie M. Bilocq,1,2,3 Amos Kirilovsky,1,2,3 Anna C. Obenauf,9 Mohamad Hamieh,5 Anne Berger,1,10 Patrick Bruneval,11 Jean-Jacques Tuch,12 Jean-Christophe Sabourin,13 Florence Le Pessot,13 Jacques Mauillon,13,14 Arash Rafii,15 Pierre Laurent-Puig,2,16 Michael R. Speicher,9 Zlatko Trajanoski,9 Pierre Michel,7 Richard Sesboüe,5 Thierry Frebourg,5,16 Franck Pagès,1,2,3,17 Vlja Valge-Archer,4,18 Jean-Baptiste Latouche,5,8 and Jérôme Galon1,2,3,*

TCGA CRC cohort: n=270 patients
Inserm cohort: n=689 patients
Specific genotype and gene profiling in MSI-H patients

Chromosomal instability, mutation patterns, and gene expression profiling in 270 MSI-H and MSS patients
Most of over-expressed genes in MSI-H patients correspond to immune-related genes

Gene functions and gene distribution analysis using ClueGO software

Mlecnik et al. Immunity 2016
Patients with MSI-H have multiple Frameshift mutations (Fsmut)

ExomeSeq

Multiplex FSmut validation

Mlecnik et al. *Immunity* 2016
Patients with MSI-H have decreased observed compared to expected frameshift and missense epitopes

Genetic analysis of missense and frameshift immunogenic mutations (epitopes) compared to nonsense (silent) mutations

**Missense Immunogenic Mutations (epitopes)**

- Decreased in frameshift immunogenic mutations in MSI patients compared to silent mutations
- Less than expected number of missense immunogenic mutations in CRC patients, and particularly MSI patients compared to silent mutations

*Genetic evidence of immunoediting*

- Decreased in frameshift immunogenic mutations in MSI patients compared to silent mutations
- Less than expected number of missense immunogenic mutations in CRC patients, and particularly MSI patients compared to silent mutations

Mlecnik et al. *Immunity* 2016
Patients with MSI-H have increased intratumoral T-cell proliferation

Triple immunofluorescence quantification *in situ*

Increased CD3+Ki67+ cells in the center, invasive margin and tertiary lymphoid structures in patients with MSI-H

Mlecnik et al. *Immunity* 2016
MSI-H patients with TGFBR2 FSmut have anti-TGFBR2-FSmut T-cells in their tumor.
Functional T-cell assays

**AAPP : Artificial APC**

- **retroviral vectors encoding**
  - HLA-A*0201
  - β2-microglobulin
  - B7.1 (CD80)
  - ICAM-1 (CD54)
  - LFA-3 (CD58)

- Transduced with a dicistronic vector encoding a puromycin resistance element and one frameshift peptide

- Mutated TGFBR2 peptide

- **Cytotoxic assay: Target cancer cells labeled with $^{51}$Cr**

  Mlecnik et al. *Immunity* 2016
MSI-H patients with TGFBR2 FSmut have anti-TGFBR2-FSmut T-cells able to kill APC\(^{A2.1/FSmutP2}\) cells.
Immunoscore high (I3, I4) patients have prolonged survival regardless of the MSI status.

Cox multivariate analysis for DSS.
Most MSI and a subgroup of MSS patients have high intratumoral adaptive immune gene expression.

Functional effector anti-frameshift mutation CTLs kill tumor cells in MSI patients.

Genetic evidence of immunoediting in human CRC, in particular for MSI patients.

Immunoscore gives an indicator of tumor recurrence and survival beyond MSI staging.

Mlecnik et al. *Immunity* 2016
How to explain “Hot” and “Cold” immune infiltrated tumors?

Patient 1 (weak)

Patient 2 (moderate)

Patient 3 (strong)

**Immunoscore**
- Im0
- Im2
- Im4

CD3/CD8 Center/Margin

Median OS (death)
- < 2 years
- 4.9 years
- > 15 years
Mechanisms associated with T cells infiltration

Attraction

- CXCL9
- CXCL10
- CCL2
- CCL5
- CX3CL1

Adhesion

- MADCAM1
- VCAM1
- ICAM1

T cells

Memory T cells

TH1 Cytotoxic

TFH B cells

Local lymphocyte proliferation

IL15


Mlecnik et al. *Gastroenterology* 2010

Bindea et al. *Immunity* 2013
Deciphering the tumor immune microenvironment: Clinical implications

Predictions
- Need T-cell priming
- Cancer vaccine
- CAR-T cells

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

But it is not as simple since biology is complex and is not dichotomized in good & bad
Deciphering the tumor immune microenvironment: Clinical implications

"Non-T cell inflamed" Tumor
Immunoscore I0

"T cell inflamed" Tumor
Immunoscore I4

CD3 Tumor

Immunoscore I1 I2 I3 I4

immune defects W X Y Z

-> Immunotherapies based on Immunoscore and immune defects
Implications for cancer classification and therapies

From the **Immune contexture**

(Complexity of intratumor immune reaction)

↓

To **Immunoscore**

(A simple and powerful Immune Test)
# Colorectal cancer classifications

<table>
<thead>
<tr>
<th>Tumor cell extension and invasion</th>
<th>T-STAGE</th>
<th>N-STAGE</th>
<th>M-STAGE</th>
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<td>Ways to classify</td>
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<tr>
<td>Morphology</td>
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<tr>
<td>Mucinous</td>
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<td>Medullary</td>
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<td>Adeno. NOS</td>
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<td>Serrated</td>
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<td>Signet ring cell</td>
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<td>Micropapillary</td>
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<td>Tumor cell characteristics</td>
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<td>CD3+ T cells</td>
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<td>CD8+ T cells</td>
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<td>Density</td>
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<td>Location (CT, IM)</td>
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</table>

Prognostic importance of the *in situ* immune reaction in patients with early-stage (Stage I/II) colorectal cancer

**Stage I cancer**

CD45RO<sub>CT/IM</sub> CD8<sub>CT/IM</sub> $P < .0001$

**Stage II cancer**

CD45RO<sub>CT/IM</sub> CD8<sub>CT/IM</sub> $P < .0001$

Metastasis analysis

Multiple primary tumors

Melanoma  Breast cancer  Kidney cancer  Lung cancer

Other cancers

One metastatic site

Brain Metastasis


- Immunoscore within brain metastasis
Immunoscore in brain metastasis and survival

Immunoscore quantification (CD3, CD8, in CT and IM regions) within Brain Metastases (n=116 patients)

Immunoscore predicts overall survival and long-term survival in patients with Brain Metastases

THE IMMUNOSCORE
AS A NEW POSSIBLE APPROACH IN THE CLASSIFICATION OF CANCER

Naples, Italy, Feb 2012
Organizer: P Ascierto, J. Galon,
Principal investigator: J. Galon
Immunoscore steering committee: B. Fox, F. Marincola, C. Bifulco, P. Ascierto, J. Galon

IMMUNOSCORE®

-> Standardized Operating Procedure
-> Today’s tools for modern pathologists

IHC automate

High-resolution scanner

whole slide quantification

Digital pathology

-> Conceptual and technological challenge


Immunoscore
Immunoscore (I) using whole slide FFPE

Routine whole slide stainings & precise image quantification

Immunostaining

Definition of Tumor Regions

Density plots

HE  CD8  CD3  I

CT  IM  Tissue
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)

(23 Centers, 17 countries: >3000 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
Worldwide Immunoscore consortium (PI: J Galon)

Training Set (TS):
- France
- Germany
- Switzerland
- Sweden
- Czech R
- Japan
- USA
- Canada

Internal Validation Set (IVS):
- France
- Germany
- Switzerland
- Sweden
- Czech R
- Japan
- USA
- Canada

External Validation Set (EVS):
- India
- China
- Netherland
- Belgium
- France
- Germany
- Italy
- Switzerland

Control slides Center
Clinical data Center
External Statistician
Management Communication

Referent Center
Steering Committee
Meetings Organizers
PathForce Image Server

Meetings Organizers
PathForce Image Server
Worldwide Immunoscore consortium (PI: J Galon)

Study design

Referent Center

SOP

Control slides Center

All Centers

Slides

Referent Center

QA/QC

All Centers

Slides

Referent Center

QA/QC

All Centers

Slides

Referent Center

QA/QC

All Centers

Immunoscore

Raw data

Referent Center

QA/QC

External Statistician (Mayo)

Clinical data

Encrypted data

Analysis

TS

>1000

IVS

>1000

EVS

>1000 Pts.
Stratification of cancer based on the immune status

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<th>Tumor classification</th>
<th>MSI-H</th>
<th>MSS(^\wedge)</th>
<th>MSS/CIMP.hi</th>
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<th>MSS-CIMP.lo</th>
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<tr>
<td>Immune classification</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
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</table>

-> Importance of having standardized immune Assays
PostDoctoral position available now

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  Florence Marliot  
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  Amélie Bilocq  
  Bénédicte Buttard  
  Amos Kirilovsky  
  Marie Tosolini  
  Maximilian Waldner  
  Sarah Church  
  Pauline Maby  
  Helen Angell  
  Mihaela Angelova  
  Angela Vasaturo  
  Bernhard Mlecnik  
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  Christopher Becker  

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