The Immunoscore: A proposal for a new classification of Cancer in the Era of immunotherapies

GALON Jérôme

A Strategic View of Immunoscore

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Cancer Classification using the Immunoscore: A Worldwide Task Force


Support from the World Immunotherapy Council (WIC), and support from societies including: ATTACK, BDA, CCIC, CRI/CIC, CIMT, CSCO, TIBT, DTIWP, ESCII, NIBIT, JACI, NCV-network, PIVAC, TVACT...
What to do for negative patients?

- Need innovative protocols for patients identified as unlikely to respond

If immunoscore negative patients do not make immune responses to immunotherapy, what does that tell us about our ability to prime anti-cancer immunity.

- Checkpoint blockade / Co-stim alone
- Role for next generation vaccines?
The next decade:

Defining immunoscore in other histologies.

Can gene signatures and immunoscore be combined to further improve biomarker?

Can a blood-based assay be used to characterize immunoscore (Cells/Sera).

Can imaging studies be used to assess immunoscore?

Why are immunoscore negative patients negative?
Immune response slows tumor growth

* Importance of natural coordinated anti-tumor adaptive immunity in Humans, regardless of the local extent and spread of the tumor.
Immunoscore – Immune Contexture:

Other cancers:
Likely Complex
Gene signature?
Methylation?

Immunoscore – Immune Contexture:

- DC
- Mast cell
- Macrophage
- MDSC
- Immature DC
- Tumour core
- Invasive margin
- Tumour bed
- FDC
- T\textsubscript{FH} cell
- CTL
- B cell
- Stroma
- TLS

What about other Cancers?
Association between immune infiltrate and outcome reported for 18 cancers

Table 1: The association of immune cell infiltrates with prognosis in cancer

<table>
<thead>
<tr>
<th>Cells</th>
<th>CD8⁺CD45RO⁺ T cells</th>
<th>T₈₁ cells</th>
<th>T₈₂ cells</th>
<th>T₈₁7 cells</th>
<th>T₈₉ cells</th>
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<tbody>
<tr>
<td>Melanoma</td>
<td>Good⁸⁻¹⁰</td>
<td></td>
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<tr>
<td>Head and neck cancers</td>
<td>Good⁹⁻¹²</td>
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<tr>
<td>Breast cancer</td>
<td>Good⁹⁻¹³</td>
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<tr>
<td>Bladder cancer</td>
<td>Good¹⁰⁻¹²</td>
<td></td>
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<tr>
<td>Ovarian cancer</td>
<td>Good¹⁰⁻¹³</td>
<td></td>
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<tr>
<td>Oesophageal cancer</td>
<td>Good¹⁰⁻¹⁴</td>
<td></td>
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<tr>
<td>Colorectal cancer</td>
<td>Good¹⁰⁻¹⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>Good¹⁰⁻¹⁶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostatic adenocarcinoma</td>
<td>Good¹⁰⁻¹⁷</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Lung carcinoma</td>
<td>Good¹⁰⁻¹⁸</td>
<td></td>
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</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Good¹⁰⁻¹⁹</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Good¹⁰⁻²⁰</td>
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<tr>
<td>Anal squamous cell carcinoma</td>
<td>Good¹⁰⁻²¹</td>
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<tr>
<td>Brain cancer</td>
<td>Good¹⁰⁻²²</td>
<td></td>
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<tr>
<td>Hepatocellular carcinoma</td>
<td>Good¹⁰⁻²³</td>
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<tr>
<td>Gastric cancer</td>
<td>Good¹⁰⁻²⁴</td>
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<tr>
<td>Medulloblastoma</td>
<td>Good¹⁰⁻²⁵</td>
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<tr>
<td>Merkel cell carcinoma</td>
<td>Good¹⁰⁻²⁶</td>
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<tr>
<td>Urothelial cell carcinoma</td>
<td>Good¹⁰⁻²⁷</td>
<td></td>
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<tr>
<td>Follicular lymphoma and Hodgkin's lymphoma</td>
<td>Good¹⁰⁻²⁸</td>
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Immunoscore: How is it defined?

Colon cancer: CD3 and CD8

For other cancers:
- Not yet known.
- Evaluation of other cell types.
- Evaluation of other parameters.
- Requires additional research and validation in large cohorts.
GOALS:
- Validate immunoscore as a prognostic biomarker?
- New Classification? – AJCC / COC

HURDLES:
- Industry has expressed interest.
- No support raised for project
- Individual centers bearing cost
- SITC providing coordination
- Control slides cut (Allesandro Lugli, Bern)
- Staining to start in November.
- *SITC supported data cloud with images available to the community?*
SITC Immunoscore Taskforce

October 2012 - 16 Countries participating

Diversity
- Genetic
- Dietary

World Immunotherapy Council (WIC): SITC, BDA, CCIC, CRI-CIC, CIMT, CSCO, TIBT, DTIWP, EATI, ESCII, NIBIT, JACI, NCV, PIVAC, ATTACK, TVACT
World Immunotherapy Council
INAUGURAL SUMMIT

FEBRUARY 21-24, 2012 • HYATT REGENCY CURACAO • CURACAO, DUTCH CARIBBEAN

SUMMIT GOAL: Provide a forum to facilitate rapid development and global dissemination of cancer immunotherapies through scientific exchange.

BDA, CCIC, CIMT, CRI-CIC, CSCO, DTIWP, EATI, ESCII, JACI, NCVE, NIBIT, PIVAC, SITC, TIBT, TVACT, ATTACK
2011
November: SITC BOD - Immunoscore Taskforce.
December: Galon, Ascierto, SITC leadership, NCI agree

2012
January: Immunoscore editorial published.

February:
- Ascierto & Galon - Immunoscore meeting, Naples –
  - Build consensus among key groups on digital imaging and analysis
  - Sets parameters - CD3 and CD8.
- World Immunotherapy Council endorses Immunoscore
THE IMMUNOSCORE AS A NEW POSSIBLE APPROACH IN THE CLASSIFICATION OF CANCER

NAPLES Feb 13th 2012
Organizers: ASCIERTO P. & GALON J.
2011
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TNM Staging in Colorectal Cancer: T Is for T Cell and M Is for Memory

Elizabeth K. Broussard and Mary L. Disis, Tumor Vaccine Group, Center for Translational Medicine in Women’s Health, University of Washington, Seattle, WA

What next?

• Could these data be reproduced?
• Who would organize the Global effort?
TNM Staging in Colorectal Cancer: T Is for T Cell and M Is for Memory

Elizabeth K. Broussard and Mary L. Disis, Tumor Vaccine Group, Center for Translational Medicine in Women’s Health, University of Washington, Seattle, WA
Receiver operating characteristic (ROC) curves for disease-free survival for patients with stage I to III tumors.

Better predictive performance of the immune score.
Multivariate proportional hazard COX analysis among all patients with AJCC/UICC-TNM Stage I/II/III colorectal cancer

According to clinical parameters and immune parameters

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<th>COX analysis for DFS</th>
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<td>0.0084</td>
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According to AJCC/UICC-TNM classification and immune score

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<td>HR</td>
<td>P-value</td>
<td>HR</td>
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<tr>
<td>AJCC/UICC-TNM</td>
<td>1.38</td>
<td>0.09</td>
<td>ns</td>
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<tr>
<td>Immune Score</td>
<td>0.64</td>
<td>&lt;0.0001</td>
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-> Validation in 2 independent cohorts of colorectal cancer patients
**Multivariate** proportional hazard COX analysis among all patients with AJCC/UICC-TNM Stage I/II/III colorectal cancer

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Histopathologic-Based Prognostic Factors of Colorectal Cancers Are Associated With the State of the Local Immune Reaction

Bernhard Mlecnik, Marie Tosolini, Amos Kirilovsky, Anne Berger, Gabriela Bindea, Tchao Meatchi, Patrick Bruneval, Zlatko Trajanoski, Wolf-Herman Fridman, Franck Pagès, and Jérôme Galon

Patients and Methods
We studied the intratumoral immune infiltrates in the center of the tumor and in the invasive margin of 599 specimens of stage I to IV colorectal cancers from two independent cohorts. We analyzed these findings in relation to the degree of tumor extension and to the frequency of recurrence.

Conclusion
Assessment of CD8+ cytotoxic T lymphocytes in combined tumor regions provides an indicator of tumor recurrence beyond that predicted by AJCC/UICC-TNM staging.
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The adaptive immune response is more relevant to DFS than the level of tumor invasion.
The adaptive immune response is more relevant to DFS than the level of tumor invasion.
Digital Pathology: Correlation with optical evaluation

CD8 counts (100 spots)

- Total CD8 T cells: $R^2 = 0.91$
- Intra-tumoral CD8 T cells: $R^2 = 0.99$

number of CD8 T cells per spot by digital counts

number of CD8 T cells per spot by optical counts
Digital Pathology: Jerome Galon and Franck Pagès used technology to objectively assess immune infiltrates – IM vs Tumor.
Digital Pathology: Jerome Galon and Franck Pagès used technology to objectively assess immune infiltrates.
Immune cells are present within the tumor

H&E sections

Tumor (blue)
CD3 T cells (brown)
Transformed cells

“Danger” signals
Tumor antigens
NKR ligands

Intrinsic tumor suppression
(senescence, repair, and/or apoptosis)

Normal tissue

Carcinogens
Radiation
Viral infections
Chronic inflammation
Inherited genetic mutations

Elimination

CD8+ T cell
CD8+ T cell
NKT cell
NK cell

CD4+ T cell
CD4+ T cell

Highly immunogenic transformed cell
Poorly immunogenic and immunoevasive transformed cells

Is there evidence that this happens with human tumors?

R D Schreiber et al.
Science 2011;331:1565-1570
Transformed cells

“Danger” signals 
Tumor antigens 
NKR ligands 

Intrinsic tumor suppression (senescence, repair, and/or apoptosis)

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R D Schreiber et al.
Science 2011;331:1565-1570
The cancer immunoediting concept.

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## Cancer and the Immune System

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Cancer and the Immune System

1900s  Ehrlich: Suggests immune system decreased prevalence of cancer.
1908   Coley: intratumoral injection of toxins
1957   Prehn and Main: Tumor-specific immunity
1959   Thomas: Immune Surveillance
Observation

- Advances in enumerating immune cells at the tumor provides significantly better staging of patients with colon cancer.

Hypothesis

- The immune system is the “agent” that improves outcome and cures people with metastatic solid cancer.
Observation

- Advances in enumerating immune cells at the tumor provides significantly better staging of patients with colon cancer.

Appears to be a prognostic factor.

WHY?
Observation

- Advances in enumerating immune cells at the tumor provides significantly better staging of patients with colon cancer.

Appears to be a prognostic factor.
Observation

- Advances in enumerating immune cells at the tumor provides significantly better staging of patients with colon cancer.
I have Consultant/Advisory Roles or Research support/Grant to disclose.

MicroMet (Amgen), BMS, MannKind, BioSante (Cell Genesys), Immunophotonics, Ventana/Roche, Dendreon

Yes, I have a Leadership Position and Stock Ownership to disclose.

UBIVAC