



SITC Workshop



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

GALON Jérôme

A Strategic View of Immunoscore

Bernard A. Fox



Galon lab.
INSERM, CRC, Paris, France

Franck Pagès
Amos Kirilovsky
Marie Tosolini
Matthieu Camus
Bernhard Mlecnik
Gabriela Bindea
Malika Benouchan
Tessa Fredriksen
Stéphanie Mauger

Cordeliers Research Center,
INSERM, Paris, France

Wolf-Herman Fridman

Institute for Genomics and
Bioinformatics, Graz, Austria

Pornpimol Charaoetong
Zlatko Trajanoski

Institute of Oncology and Radiology,
Belgrade, Serbia

Tijana Vujanović

Dpt. of General and Digestive
Surgery, HEGP, Paris, France

Anne Berger

Dpt. of Pathology, HEGP, Paris,
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Avicenne, Bobigny, France

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Cancer Classification using the Immunoscore: A Worldwide Task Force

Jérôme Galon^{1,2,3,4,5#}, Franck Pagès^{1,2,3,4}, Francesco M Marincola^{5,6}, Helen K Angell^{1,2,3}, Magdalena Thurin⁷, Alessandro Lugli⁸, Inti Zlobec⁸, Anne Berger⁴, Carlo Bifulco⁹, Gerardo Botti¹⁰, Fabiana Tatangelo¹⁰, Cedrik M. Britten¹¹, Sebastian Kreiter¹¹, Lotfi Chouchane¹², Paolo Delrio¹³, Arndt Hartmann¹⁴, Martin Asslaber¹⁵, Michele Maio¹⁶, Giuseppe V. Masucci¹⁷, Martin Mihm¹⁸, Fernando Vidal-Vanaclocha¹⁹, James P Allison²⁰, Sacha Gnjjatic²⁰, Leif Hakansson²¹, Christoph Huber¹¹, Harpreet Singh-Jasuja²², Christian Ottensmeier²³, Heinz Zwierzina²⁴, Luigi Laghi²⁵, Fabio Grizzi²⁵, Pamela S. Ohashi²⁶, Patricia A Shaw²⁷, Blaise A Clarke²⁷, Bradley G. Wouters²⁷, Yutaka Kawakami²⁸, Shoichi Hazama²⁹, Ena Wang⁶, Jill O'Donnell-Tormey³⁰, Christine Lagorce³¹, Graham Pawelec³², Michael I. Nishimura³³, Robert Hawkins³⁴, Rejean Lapointe³⁵, Andreas Lundqvist³⁶, Samir N. Khleif³⁷, Shuji Ogino³⁸, Peter Gibbs³⁹, Paul Waring⁴⁰, Noriyuki Sato⁴¹, Toshihiko Torigoe⁴¹, Kyogo Itoh⁴², Prabhu S. Patel⁴³, Shilin N. Shukla⁴³, Richard Palmqvist⁴⁴, Iris D. Nagtegaal⁴⁵, Yili Wang⁴⁶, Corrado D'Arrigo⁴⁷, Scott Kopetz⁴⁸, Frank A Sinicrope⁴⁹, Giorgio Trinchieri⁵⁰, Thomas F Gajewski^{5,51}, Paolo A Ascierto^{52,53}, Bernard A Fox^{5,54,55}

Galon, J. J. Transl Med. 2012

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...

Immunoscore: Strategic Considerations

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?

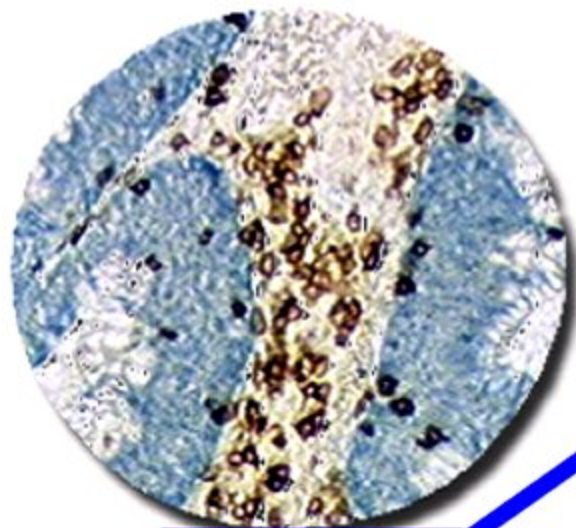
Can a blood-based assay be used to characterize immunoscore (Cells/Sera).

Can imaging studies be used to assess immunoscore?

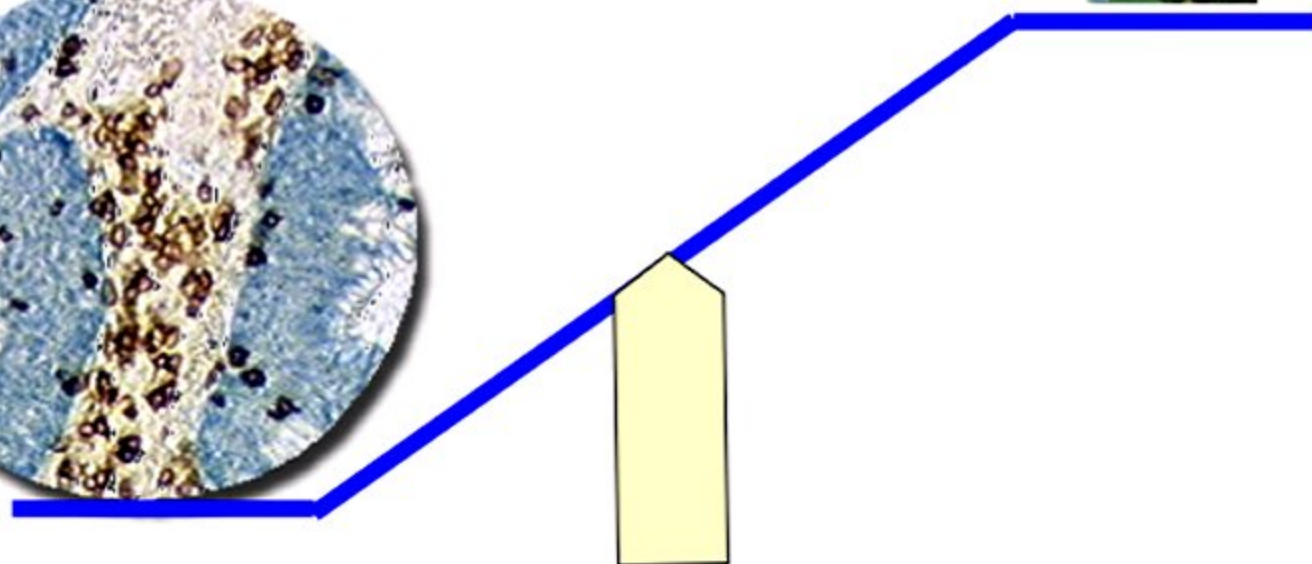
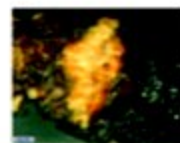
Why are immunoscore negative patients negative?

Immune response slows tumor growth

Immune reaction

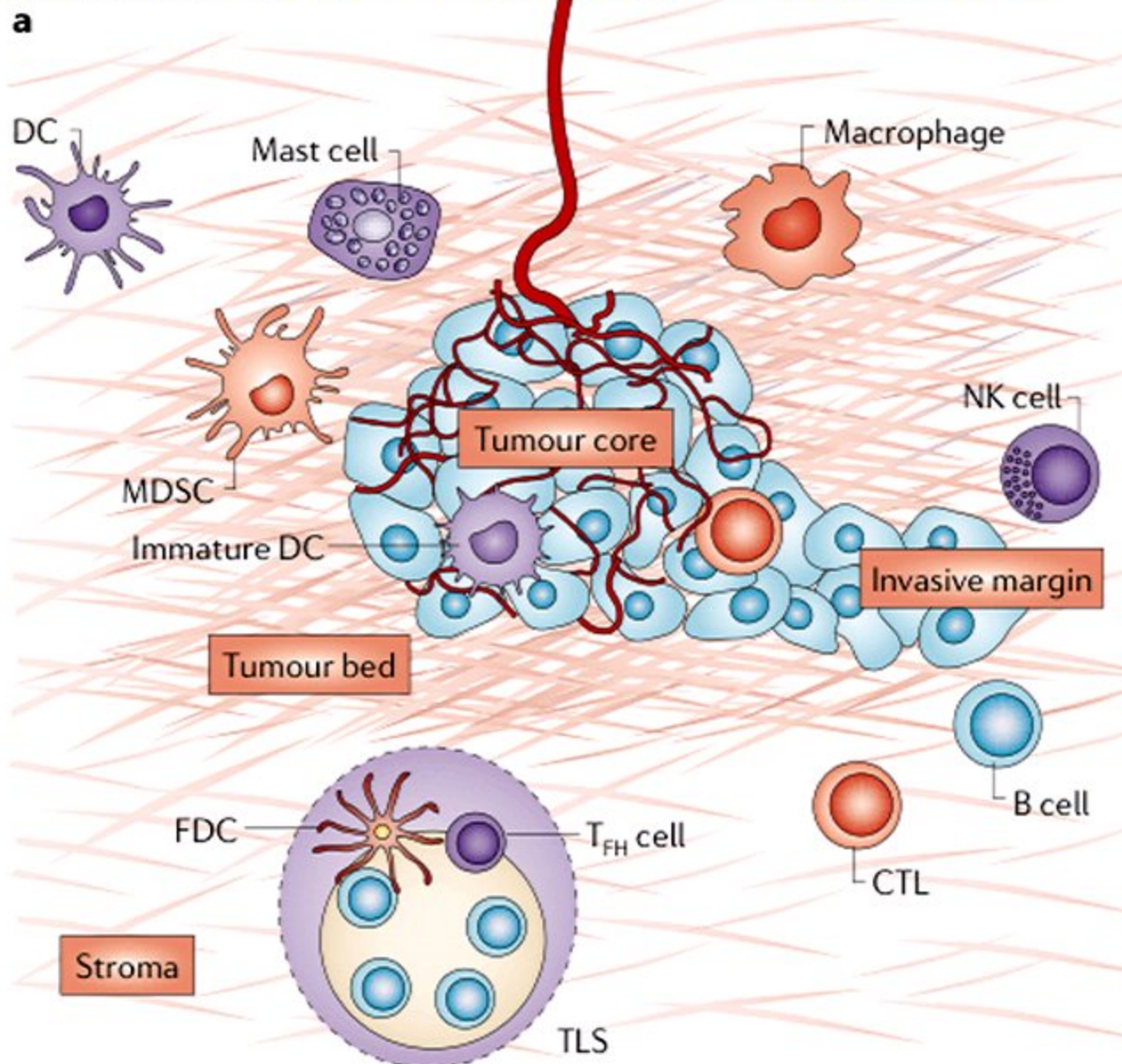


Tumoral extension



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

Immunoscore – Immune Contexture:



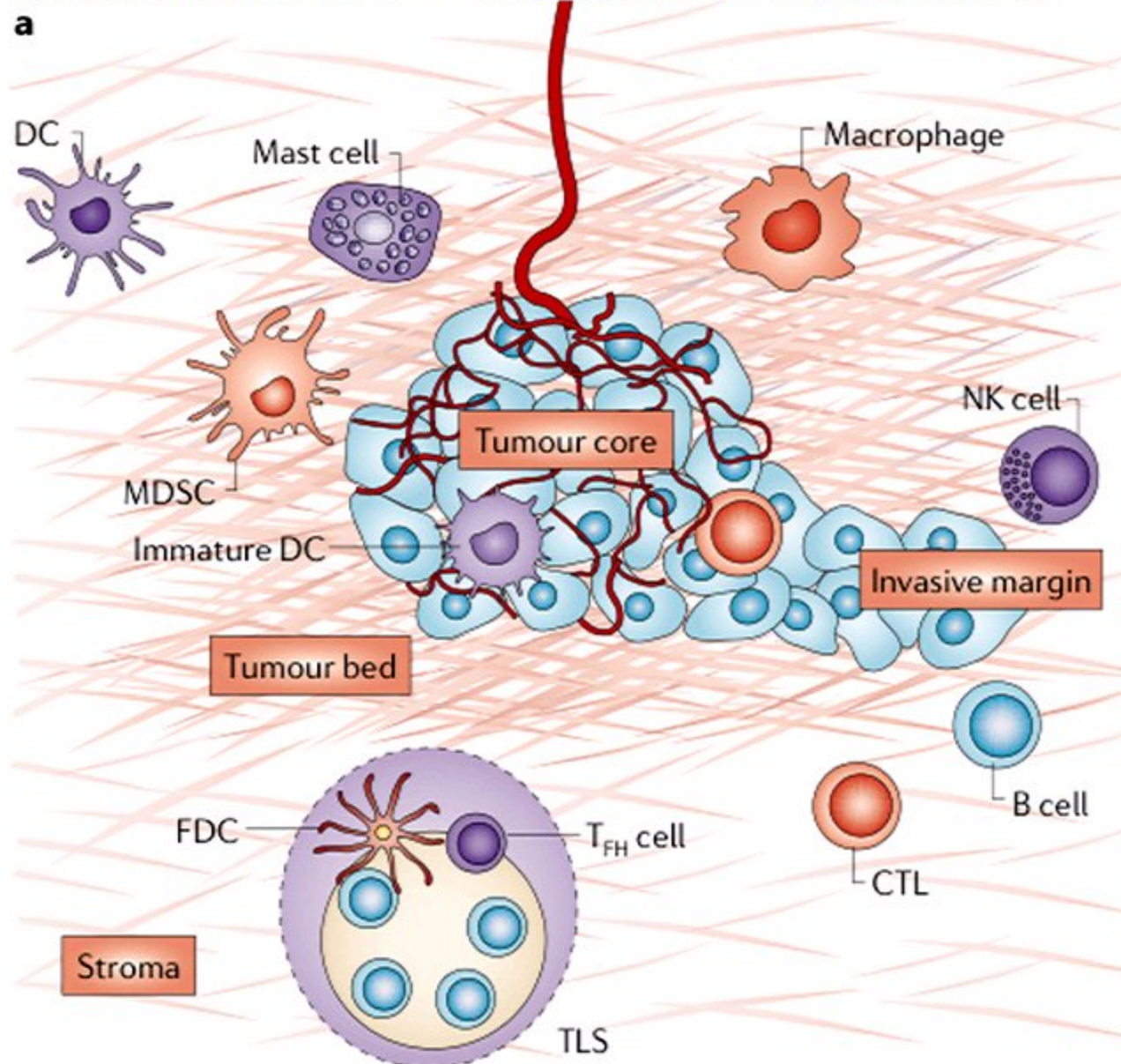
Other cancers:

Likely Complex

Gene
signature?

Methylation?

Immunoscore – Immune Contexture:



Fridman WH., et al., Nature Reviews Cancer, March 15, 2012

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

Cells	CD8 ⁺ CD45RO ⁺ T cells	T _H 1 cells	T _H 2 cells	T _H 17 cells	T _{reg} cells
Melanoma	Good ¹⁰¹⁻¹⁰⁴				• None ^{11,19} • Poor ^{102,108}
Head and neck cancers	Good ^{10,109,110}			None ²⁶	Good ^{26,111}
Breast cancer	Good ¹¹¹⁻¹¹⁴	• Good ^{115,116} • None ¹¹⁷	• Good ¹² • None ¹¹⁷		• None ¹⁵ • Poor ^{17,28}
Bladder cancer	Good ^{118,119}				Good ¹⁸
Ovarian cancer	Good ¹¹⁹⁻¹²²	Good ^{113,114}	Poor ¹¹¹	Good ¹²⁰	• Good ^{113,115} • Poor ¹⁵
Esophageal cancer	Good ^{115,127}	Good ¹¹⁸		Good ¹²⁹	
Colorectal cancer	Good ^{6,128,129,140,141,138-148}	Good ^{136,139}	None ²⁶	Poor ^{15,140}	• Good ^{13,14-16} • None ¹⁵
Renal cell carcinoma	• Good ¹⁵ • Poor ¹⁵	Good ¹¹			Poor ¹⁵
Prostatic adenocarcinoma	Good ^{11-15,13}				
Lung carcinoma	• Good ^{11,14-15,13} • None ¹³⁸	Good ¹¹		Poor ¹³⁸	Poor ¹³⁸⁻¹⁴²
Pancreatic cancer	Good ¹⁰⁴		Poor ^{104,145}		Poor ¹¹⁵
Cervical cancer		Good ¹¹⁸			
Anal squamous cell carcinoma					None ¹¹
Brain cancer					None ^{11,24}
Hepatocellular carcinoma	• Good ^{107,105} • Poor ¹⁸	Good ¹⁰⁴		Poor ¹⁷⁰	Poor ^{18,100}
Gastric cancer		Good ¹⁷¹	Poor ¹⁷¹	Good ¹⁷²	
Medulloblastoma		Good ¹⁷¹			
Merkel cell carcinoma	Good ¹⁷⁴				
Urothelial cell carcinoma	Good ¹⁷⁴				
Follicular lymphoma and Hodgkin's lymphoma			Good ¹¹		• Good ^{11,17} • None ¹⁷ • Poor ¹¹

T_H1: T helper; T_{reg}: regulatory T cell.

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.

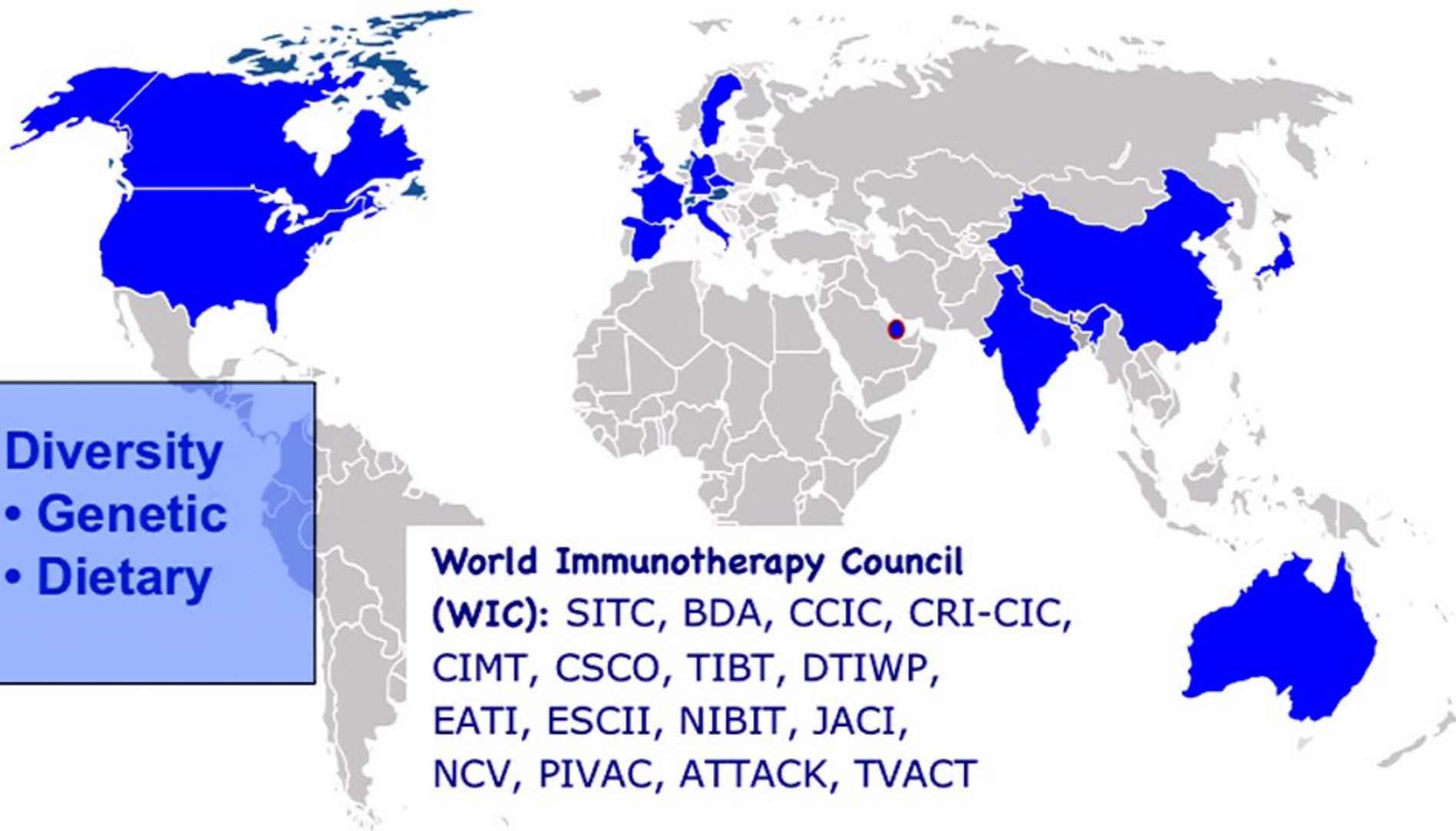
GOALS:

- 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?*

October 2012 - 16 Countries participating



Diversity

- Genetic
- Dietary

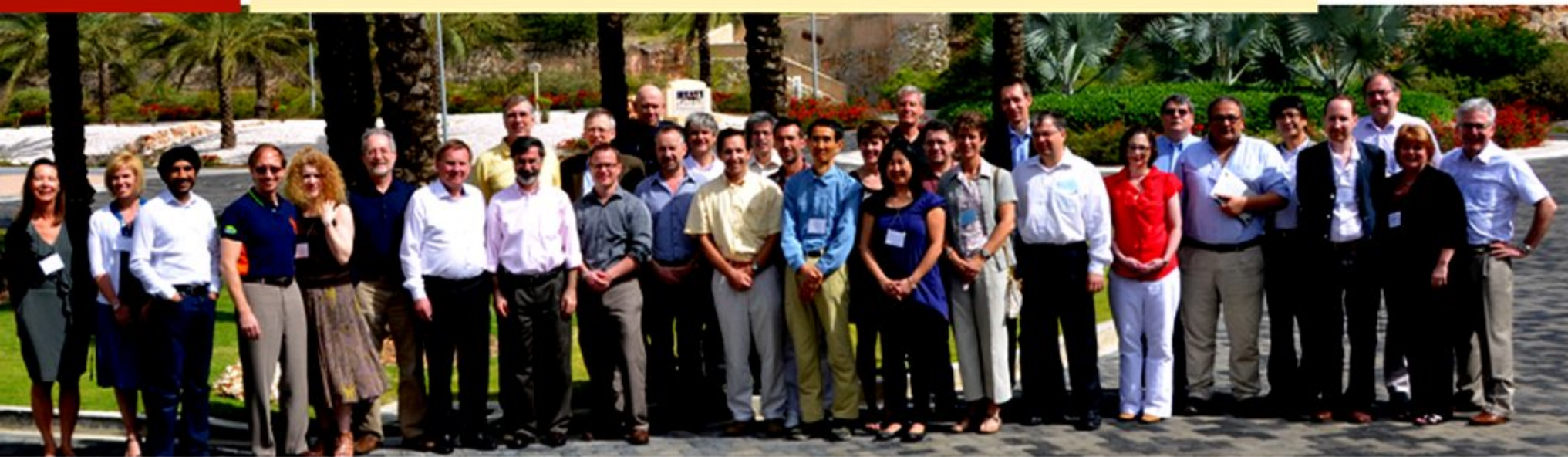
World Immunotherapy Council (WIC): SITC, BDA, CCIC, CRI-CIC, CIMT, CSCO, TIBT, DTIWP, EATI, ESCII, NIBIT, JACI, NCV, PIVAC, ATTACK, TVACT



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.

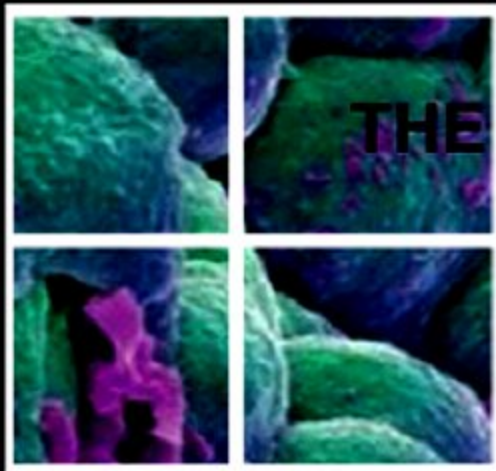
December: Galon, Ascierto, SITC leadership, NCI agree

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*

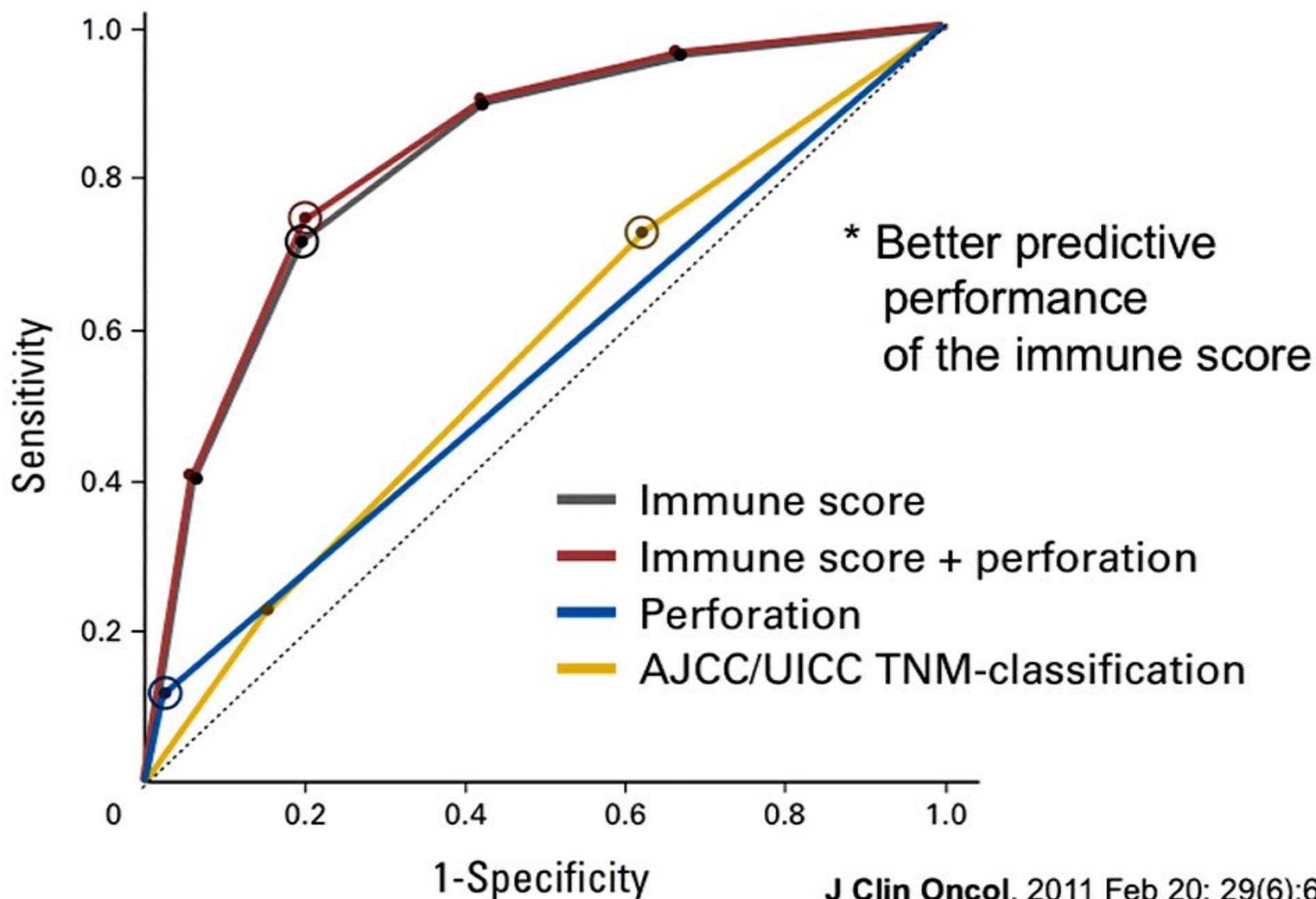
What next?

- 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.



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

COX analysis for DFS	HR	Log Rank P-values	
Tumor (T) stage	1.24	0.29	■
N Stage	1.31	0.17	■
Gender	1.47	0.18	■
Number of total lymph nodes	1.13	0.68	■
Histological grade	0.69	0.29	■
Mucinous Colloide	1.29	0.47	■
Occlusion	1.03	0.94	■
Perforation	4.03	0.0084	■
Immune Score	0.65	0.0003	■

According to AJCC/UICC-TNM classification and immune score

COX analysis	DFS		OS		DSS	
	HR	P-value	HR	P-value	HR	P-value
AJCC/UICC-TNM	1.38	0.09 ns	1.18	0.29 ns	1.43	0.10 ns
Immune Score	0.64	<0.0001	0.71	<0.0001	0.63	<0.0001

-> Validation in 2 independent cohorts of colorectal cancer patients

Mlecnik et al. *J Clin Oncol* 2011

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.

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
- 2001 Shankaran (Old & Schreiber): Role for IFN γ and lymphocytes in tumor development (Rag $^{-/-}$)
- 2004 Dunn, Old & Schreiber: Immunoediting
- 2005/6 Pages / Galon: Immunoscore in Colon CA

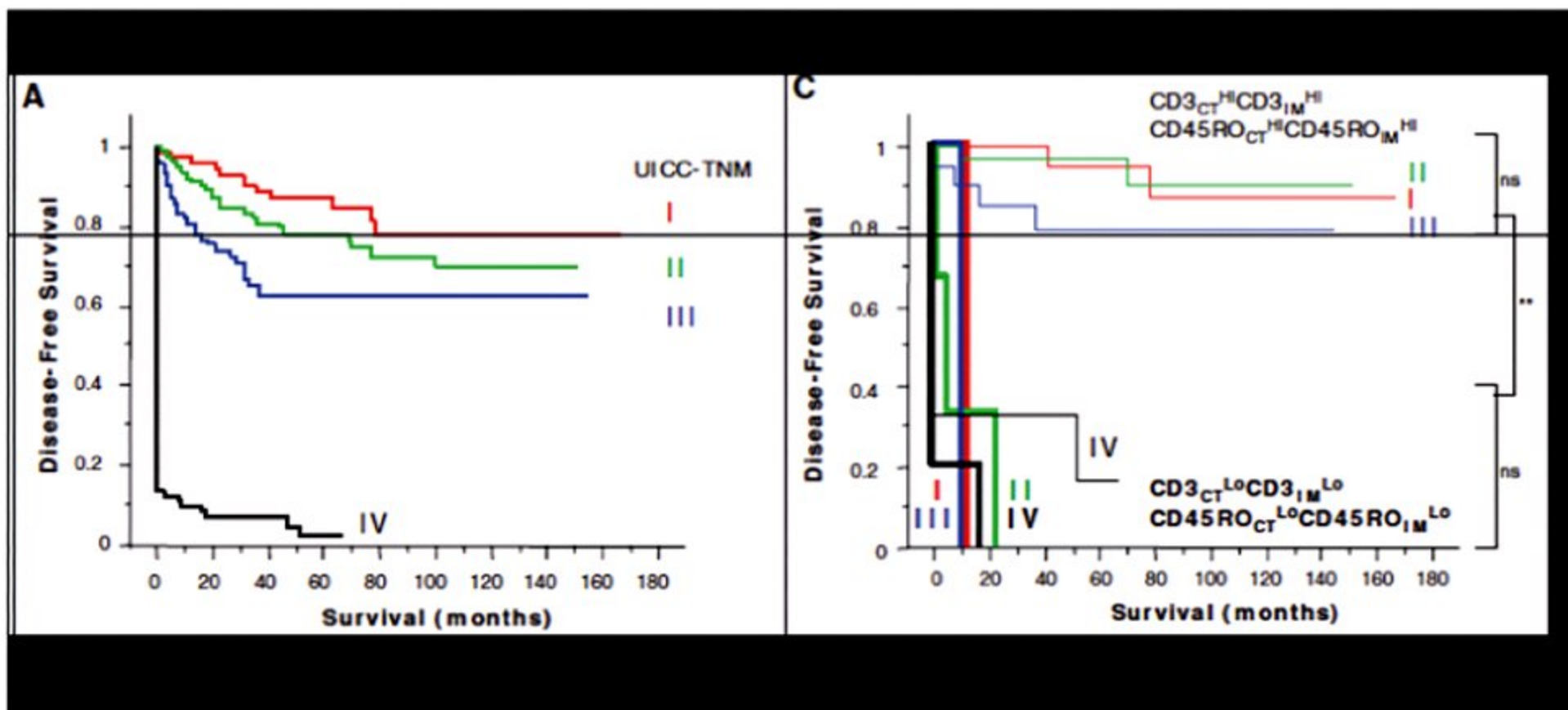
The adaptive immune response is more relevant to DFS than the level of tumor invasion.

UICC-TNM
Staging system

CD3_{CT}^{hi}CD3_{IM}^{hi}
evaluation

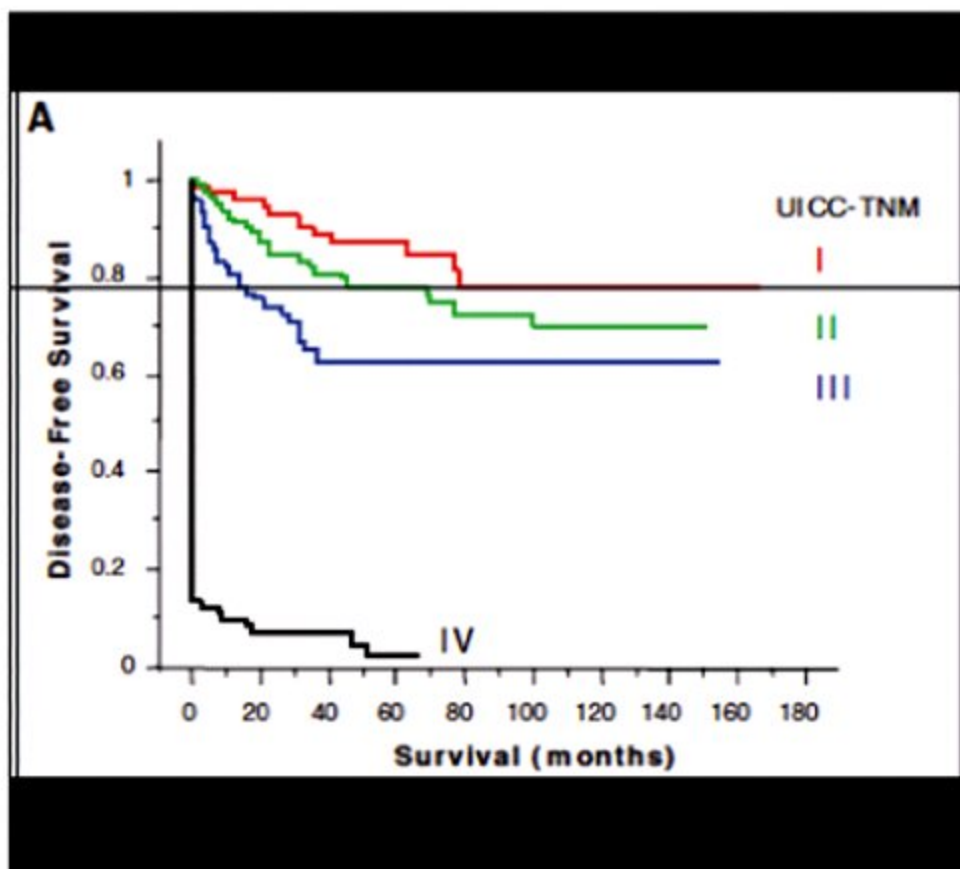
+

CD45RO_{CT}^{hi}CD45RO_{IM}^{hi}
evaluation

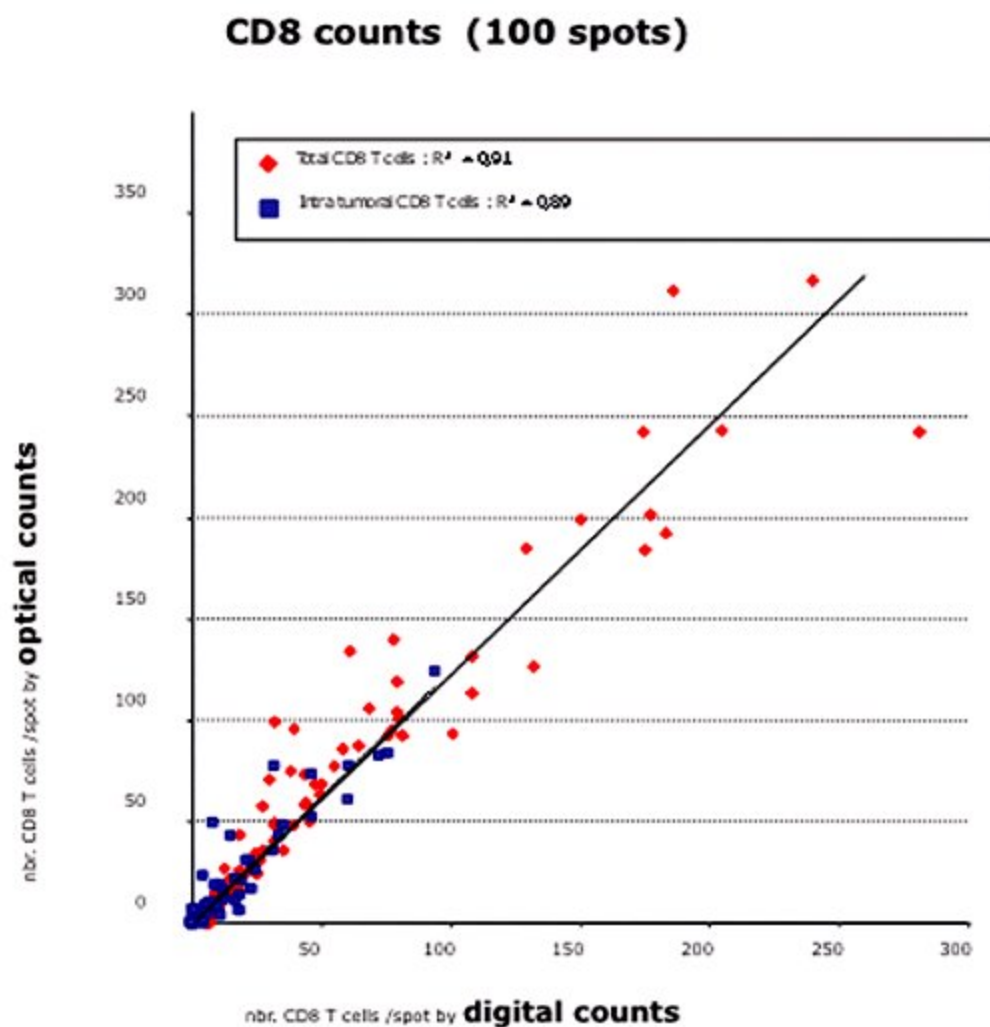


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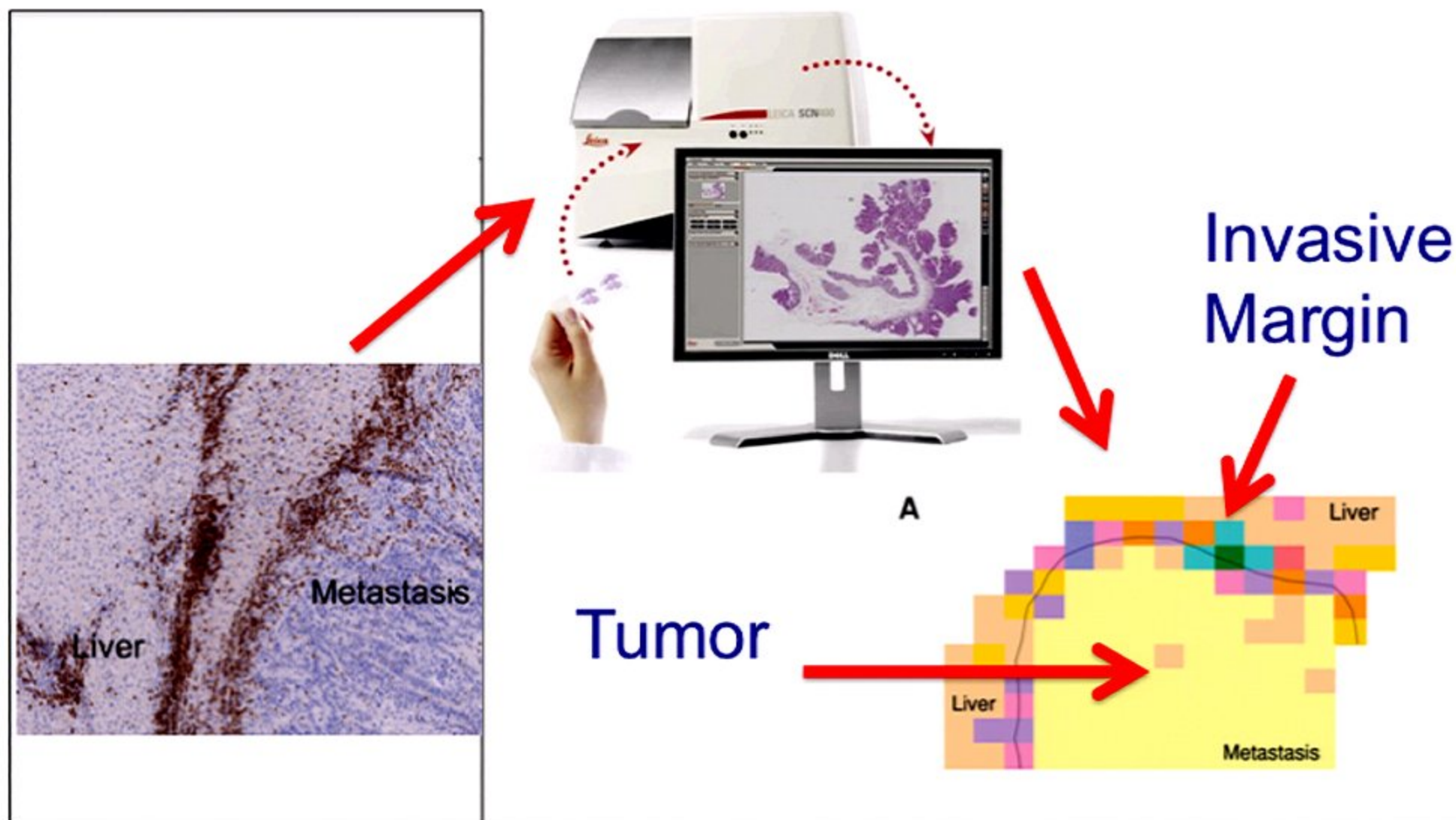
UICC-TNM
Staging system



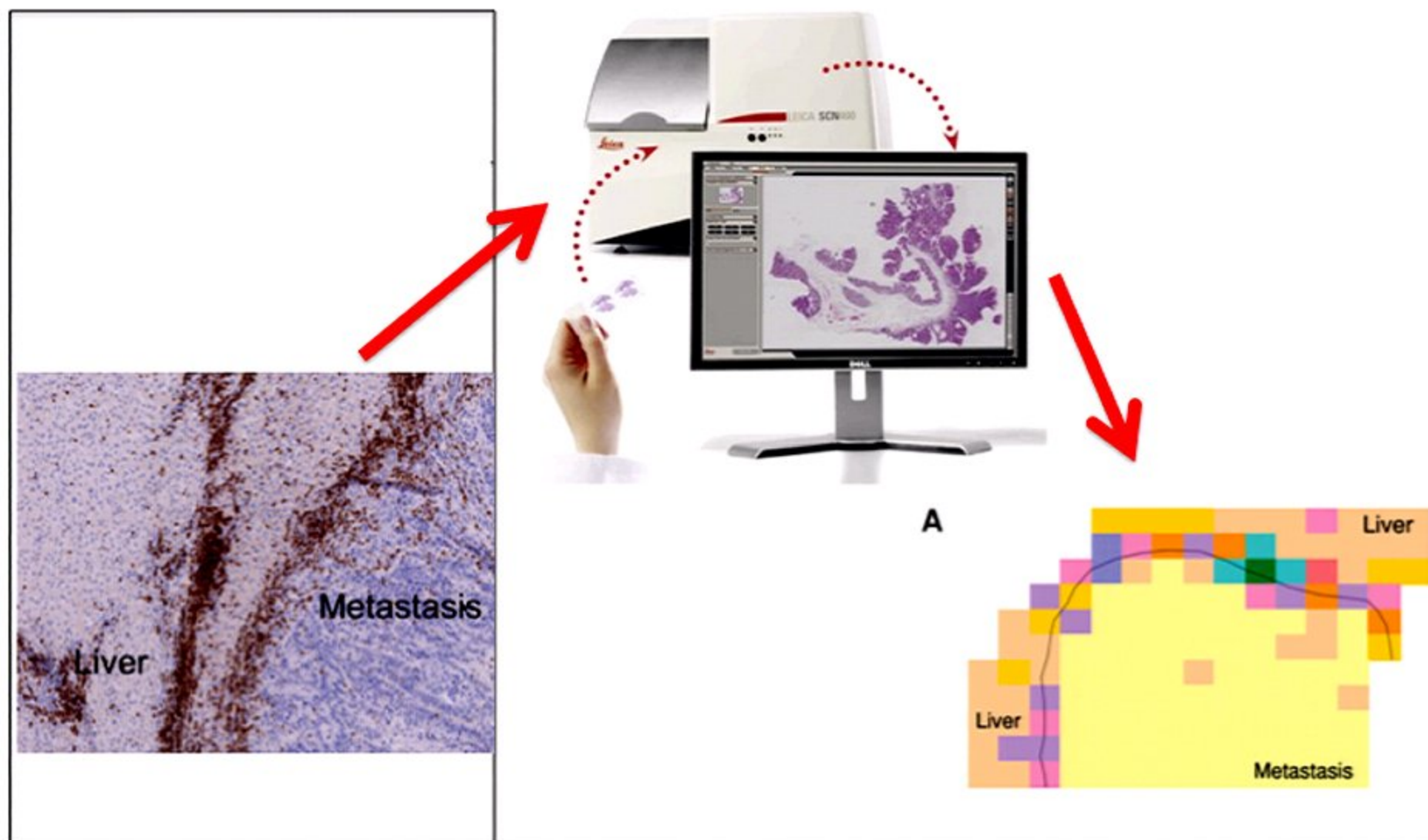
Digital Pathology : Correlation with optical evaluation



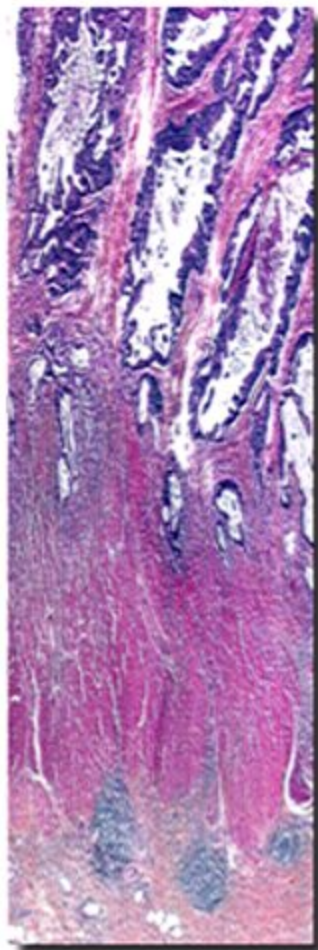
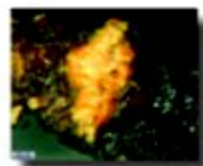
Digital Pathology : Jerome Galon and Franck Pagès used technology to objectively assess immune infiltrates – IM vs Tumor.



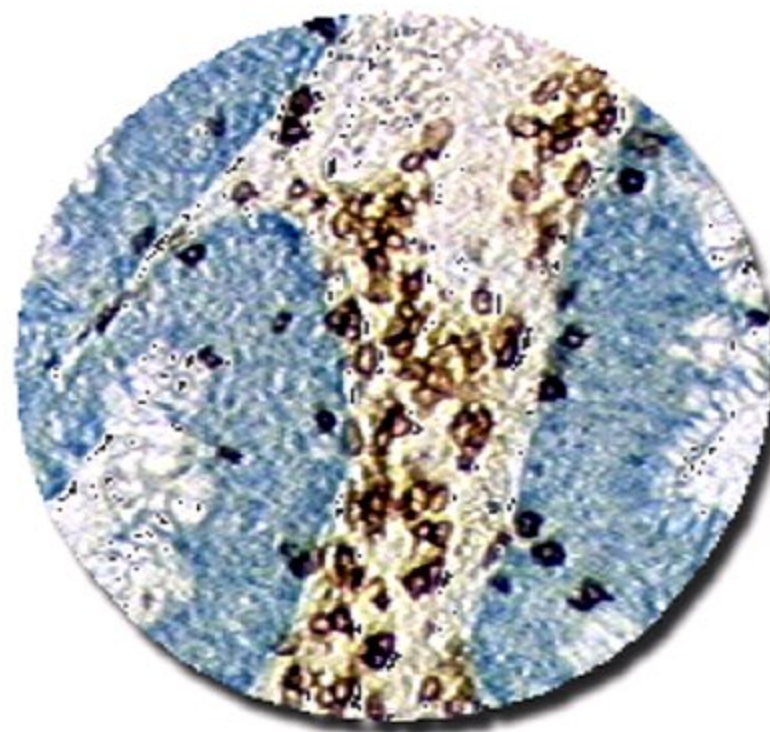
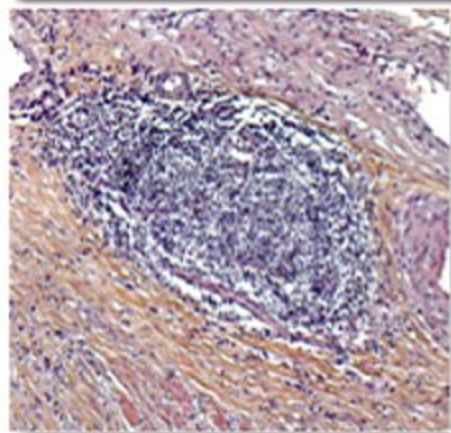
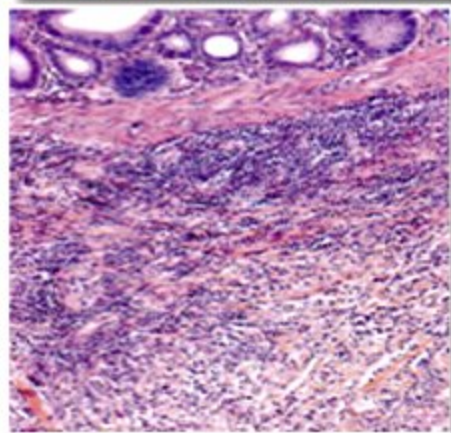
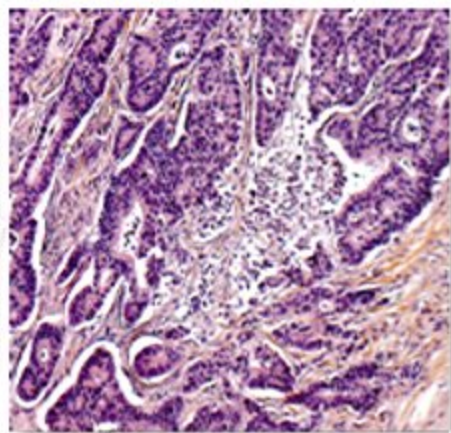
Digital Pathology : Jerome Galon and Franck Pagès used technology to objectively assess immune infiltrates.



Immune cells are present within the tumor

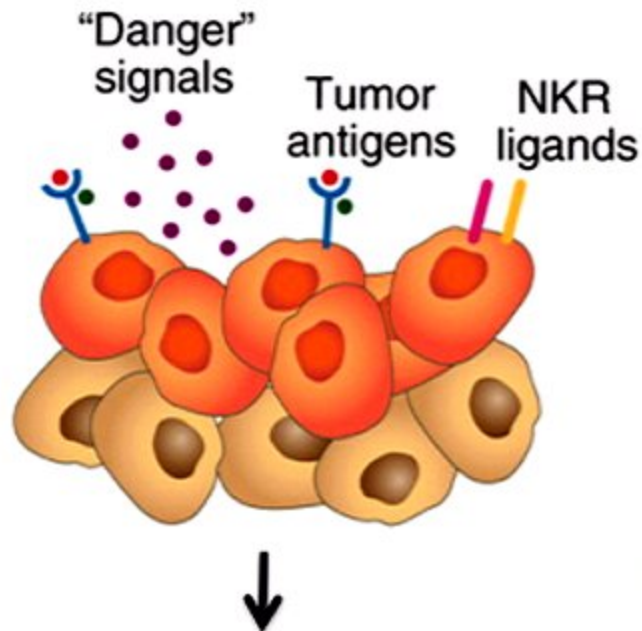


H&E sections



Tumor (blue)
CD3 T cells (brown)

Transformed cells



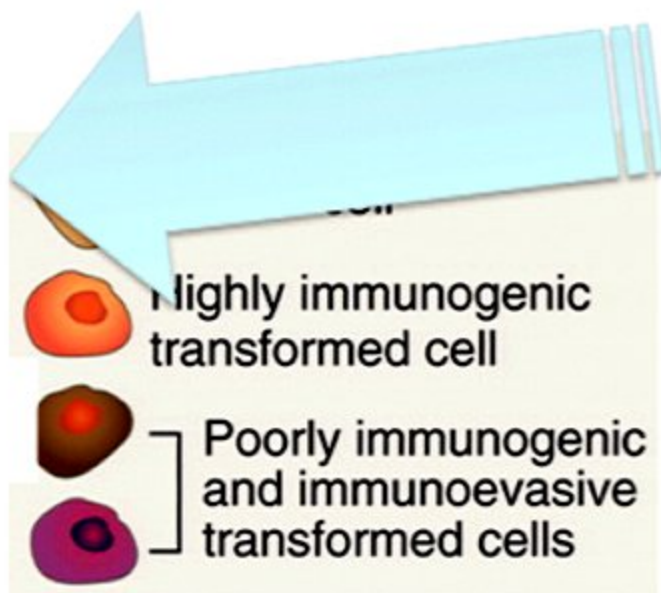
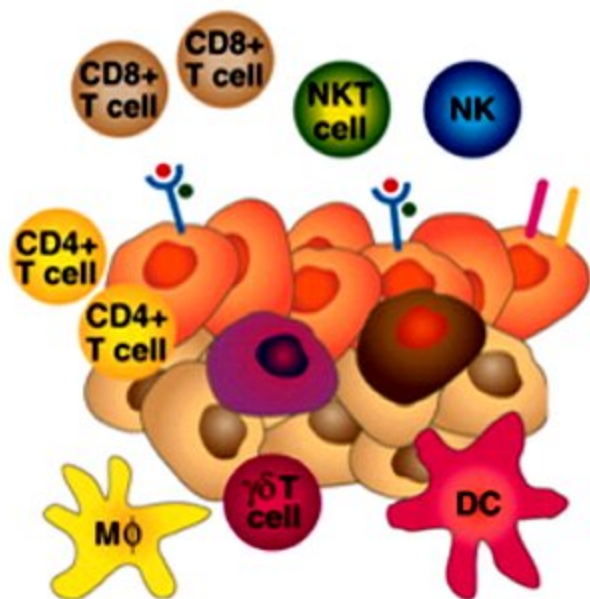
Intrinsic tumor suppression
(senescence, repair,
and/or apoptosis)

Carcinogens
Radiation
Viral infections
Chronic inflammation
Inherited genetic mutations

Normal
tissue

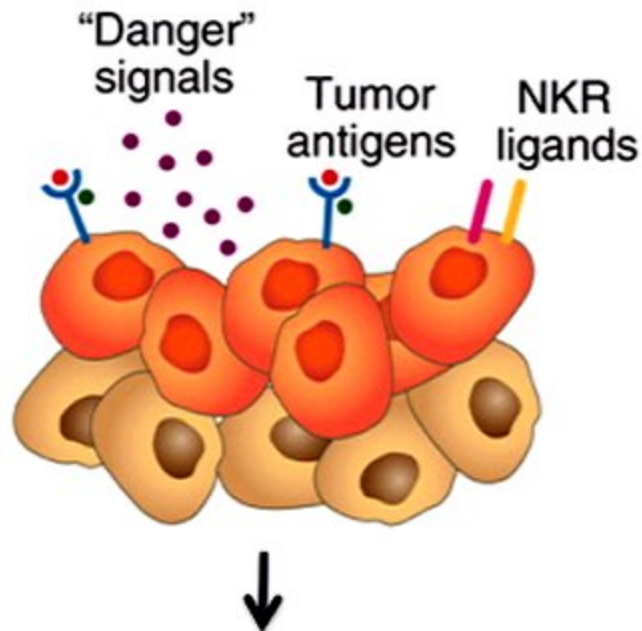


Elimination



Is there
evidence
that this
happens
with human
tumors?

Transformed cells



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

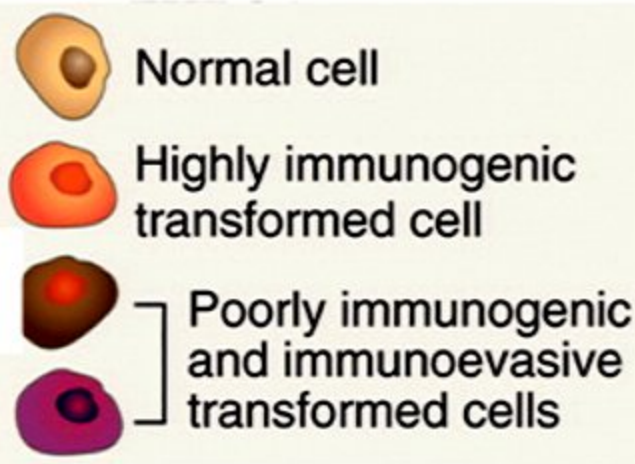
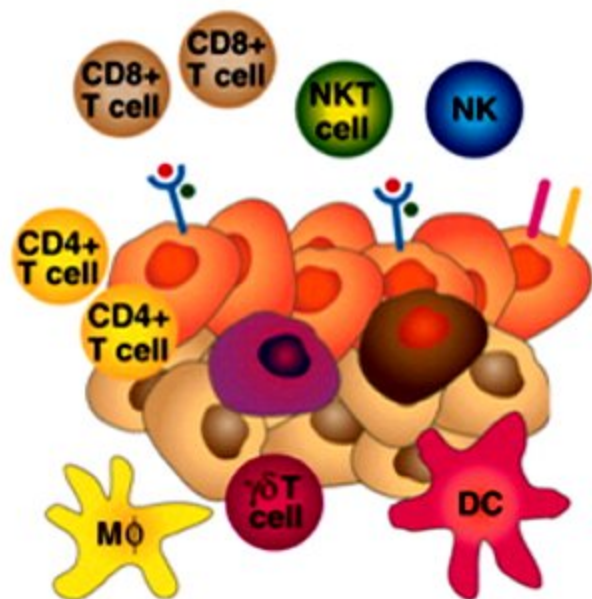


Carcinogens
Radiation
Viral infections
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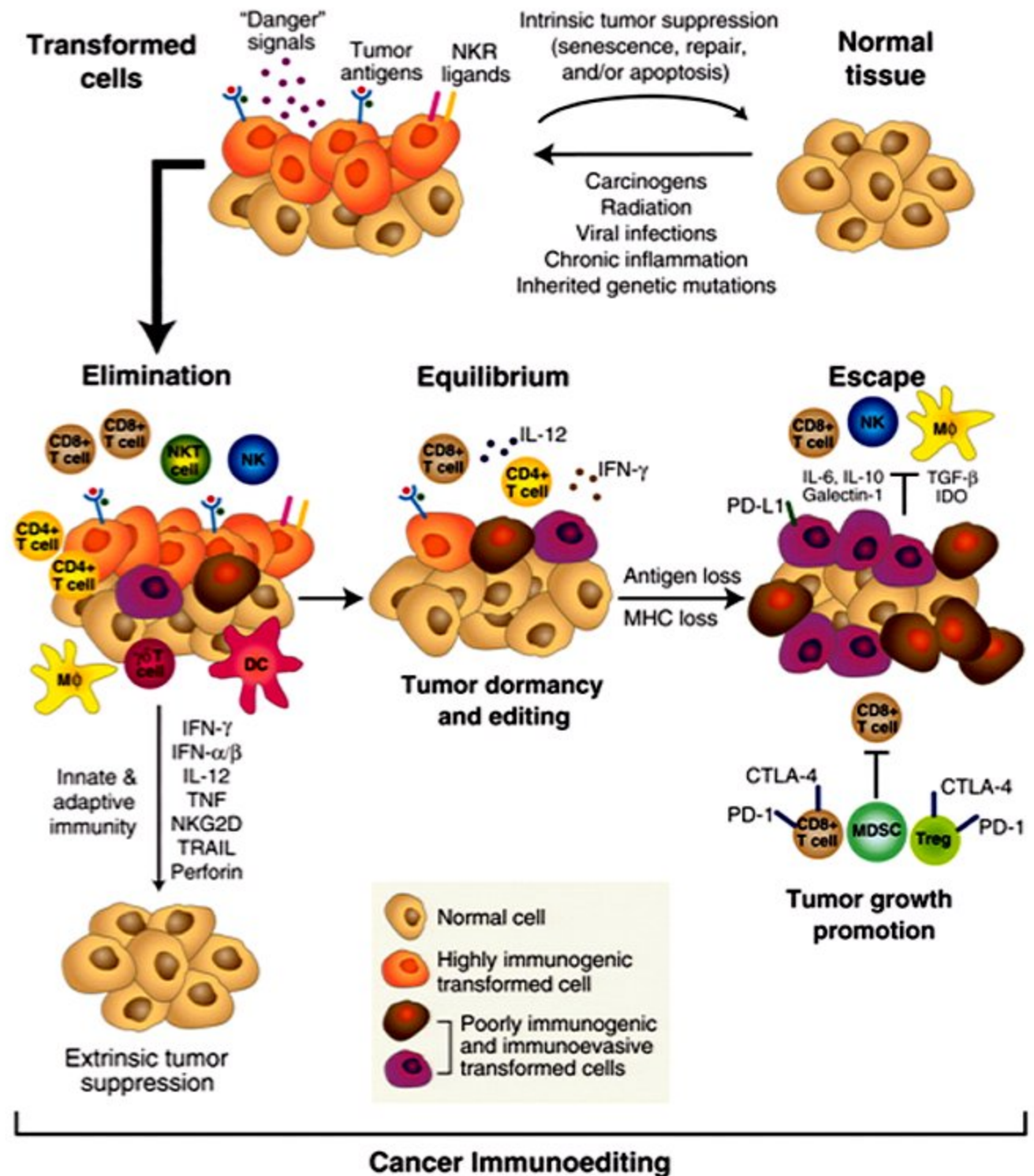
Normal tissue



Elimination



The cancer immunoeediting concept.



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

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 - 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

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**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

Victor





Victor