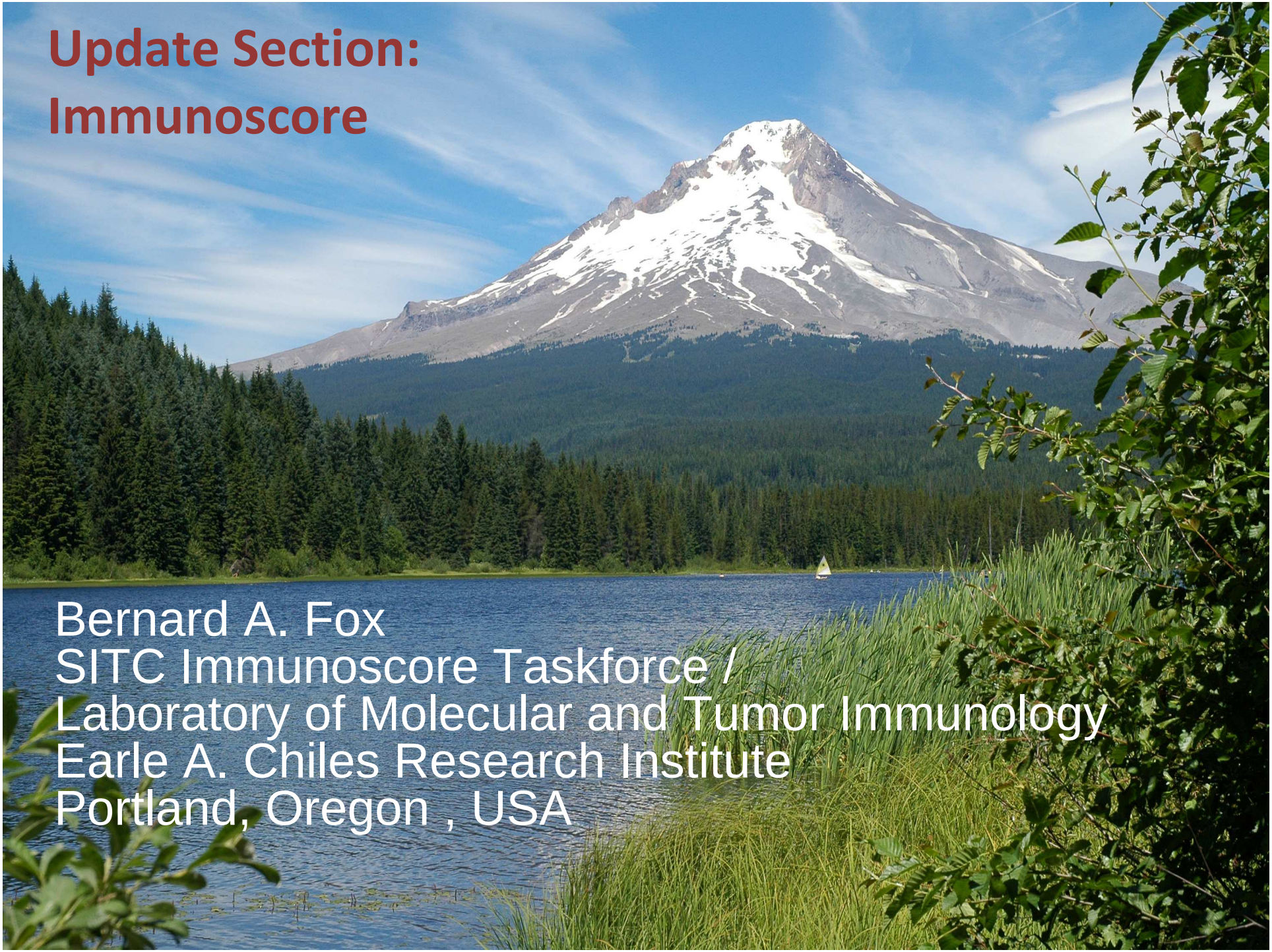
Update Section: Immunoscore



Bernard A. Fox
SITC Immunoscore Taskforce /
Laboratory of Molecular and Tumor Immunology
Earle A. Chiles Research Institute
Portland, Oregon , USA

I have Consultant/Advisory Roles or Research support/Grant to disclose.

Bristol-Myers Squibb, MannKind, Aduro (BioSante, Cell Genesys), Immunophotonics, Dendreon, Ventana/Roche, Definiens, Janssen/Johnson & Johnson, Nodality,

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

UbiVac, UbiVac-CMV, Insys Ther

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The practice of oncology is undergoing a transformation.

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Observation

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

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Appears to be a prognostic factor.

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Appears to be a prognostic factor.

WHY?

Hypothesis:

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

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Hypothesis:

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

CONTROVERSIAL….

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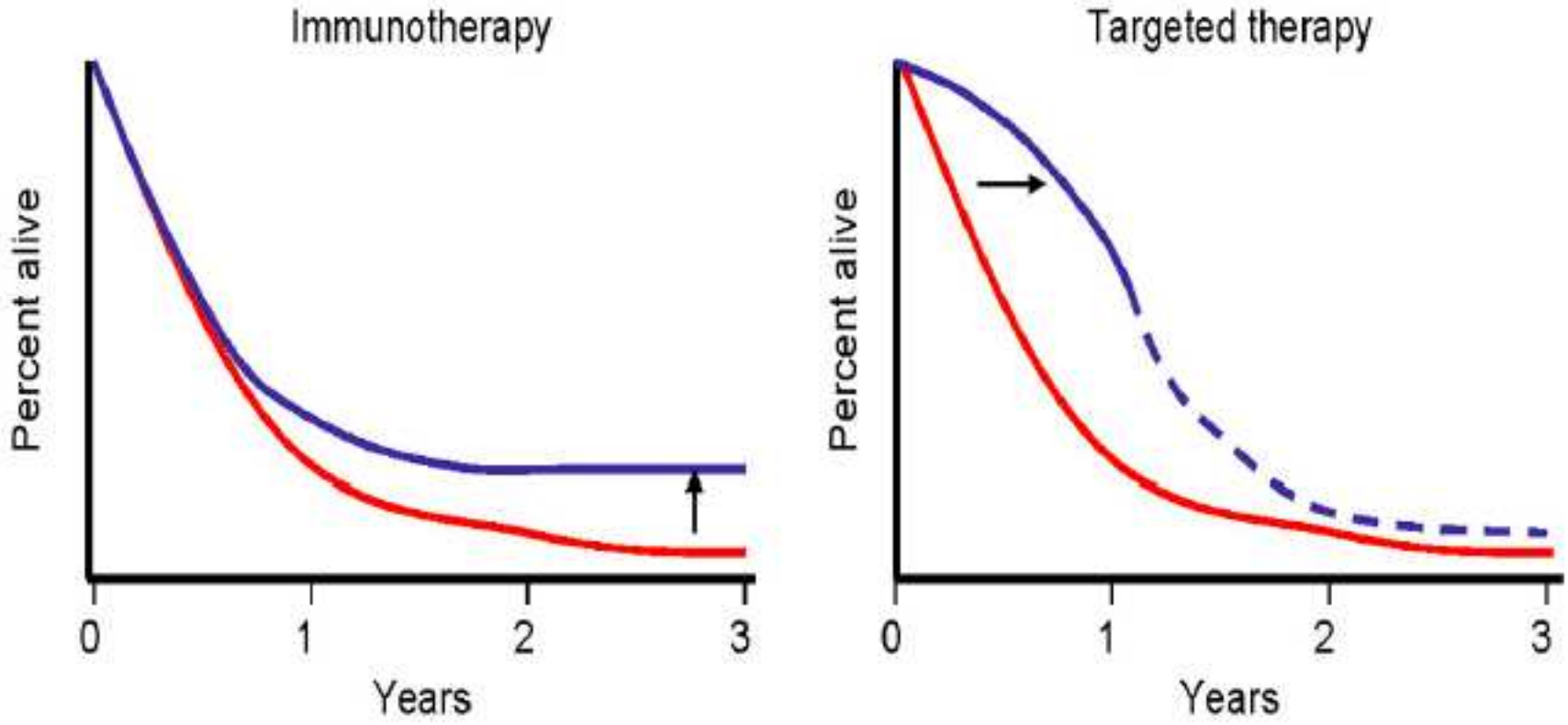
Effects of Immunotherapy and Targeted Therapy on Melanoma



Ribas A et al. *Clin Cancer Res* 2012;18:336-341

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Cure….

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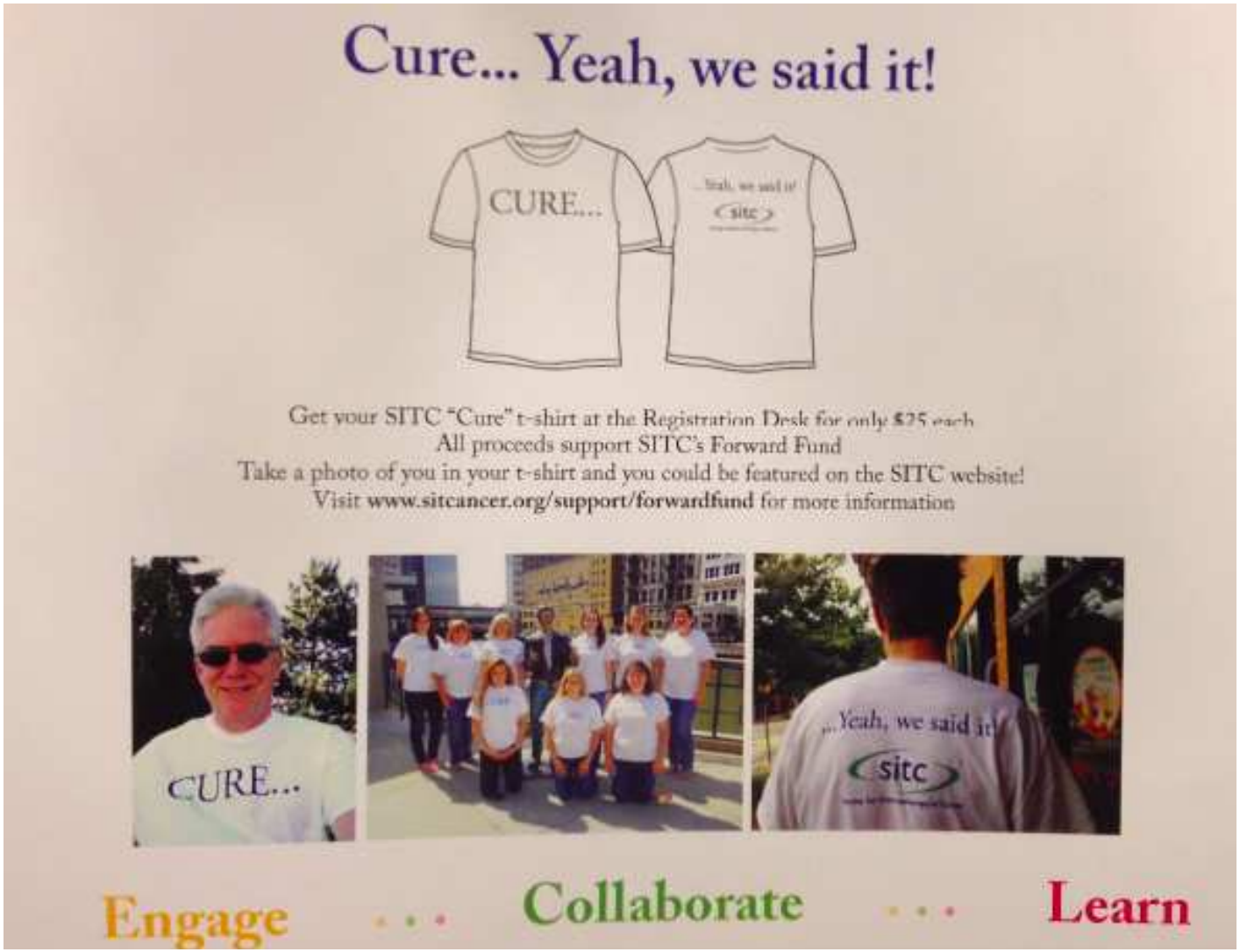
Cure…. Yeah, we said it!!!!!



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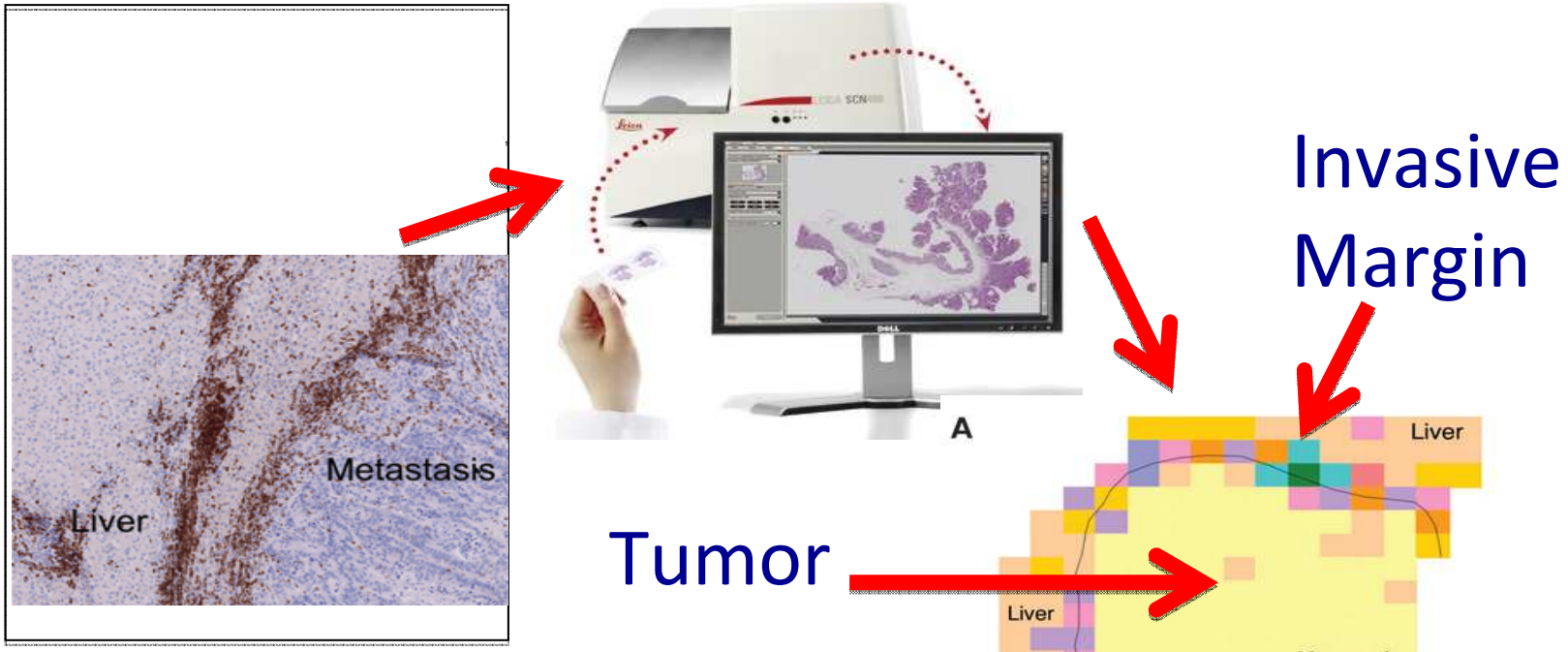
Digital Pathology : Jerome Galon and Franck Pagès used technology to objectively assess immune infiltrates – IM vs Tumor.

Science 313 : 29 September, 2006



Halama N., et al; Cancer Res 2011;71:5670-5677.

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VOLUME 29 · NUMBER 6 · FEBRUARY 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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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Multivariate proportional hazard COX analysis among all patients with AJCC/UICC-TNM Stage I/II/III colorectal cancer

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

SITC Immunoscore Taskforce!

Cancer classification using the Immunoscore: a worldwide task force

Galon *et al.*

BioMed Central

Galon *et al. Journal of Translational Medicine* 2012, **10**:205
http://www.translational-medicine.com/content/10/1/205

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GOALS:

- Validate immunoscore as a prognostic biomarker?

- Modify TNM Classification? AJCC / COC

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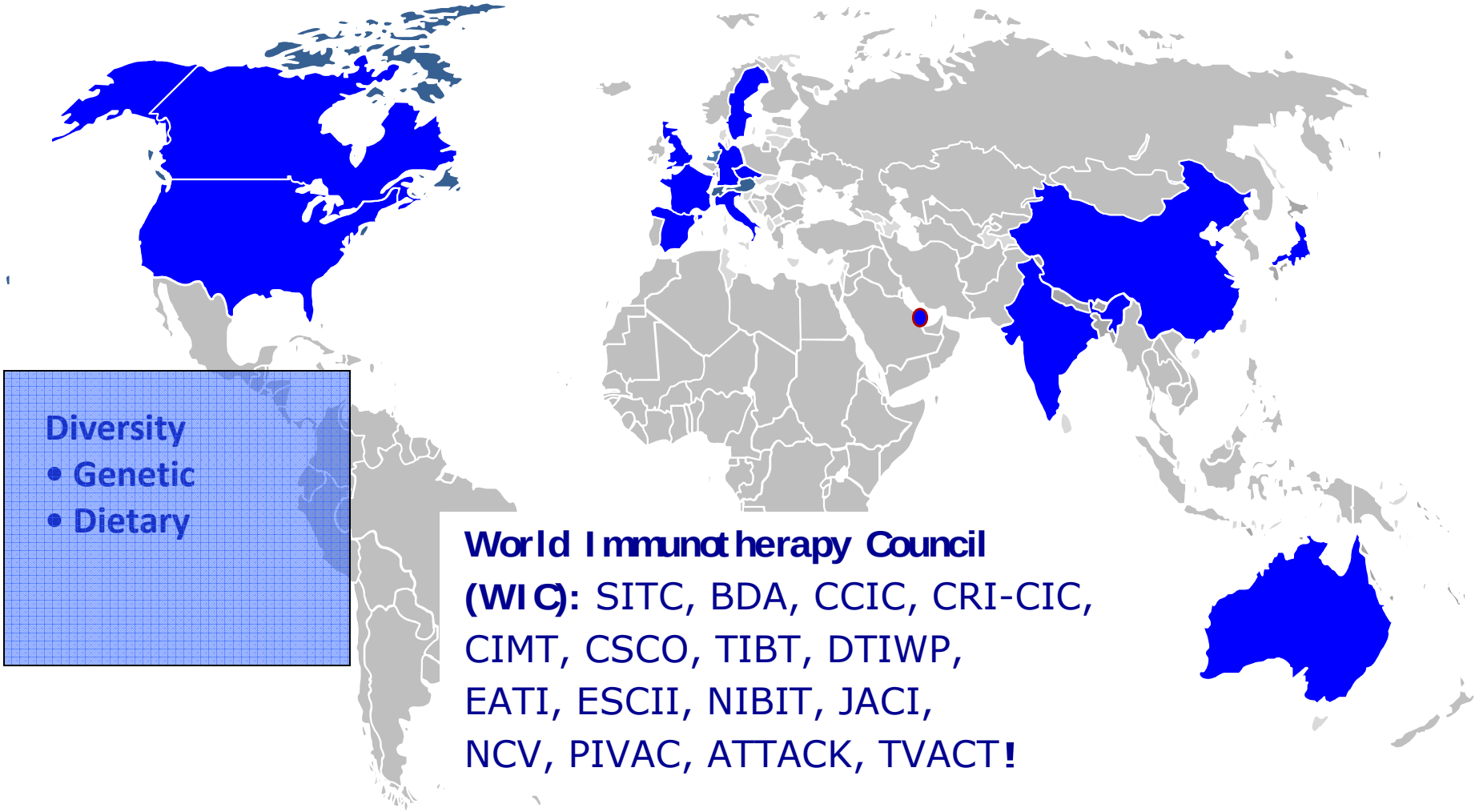
SITC Immunoscore Taskforce!

April 2013 - 17 Countries / 23 Sites



Diversity
- **Genetic**
- **Dietary**

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

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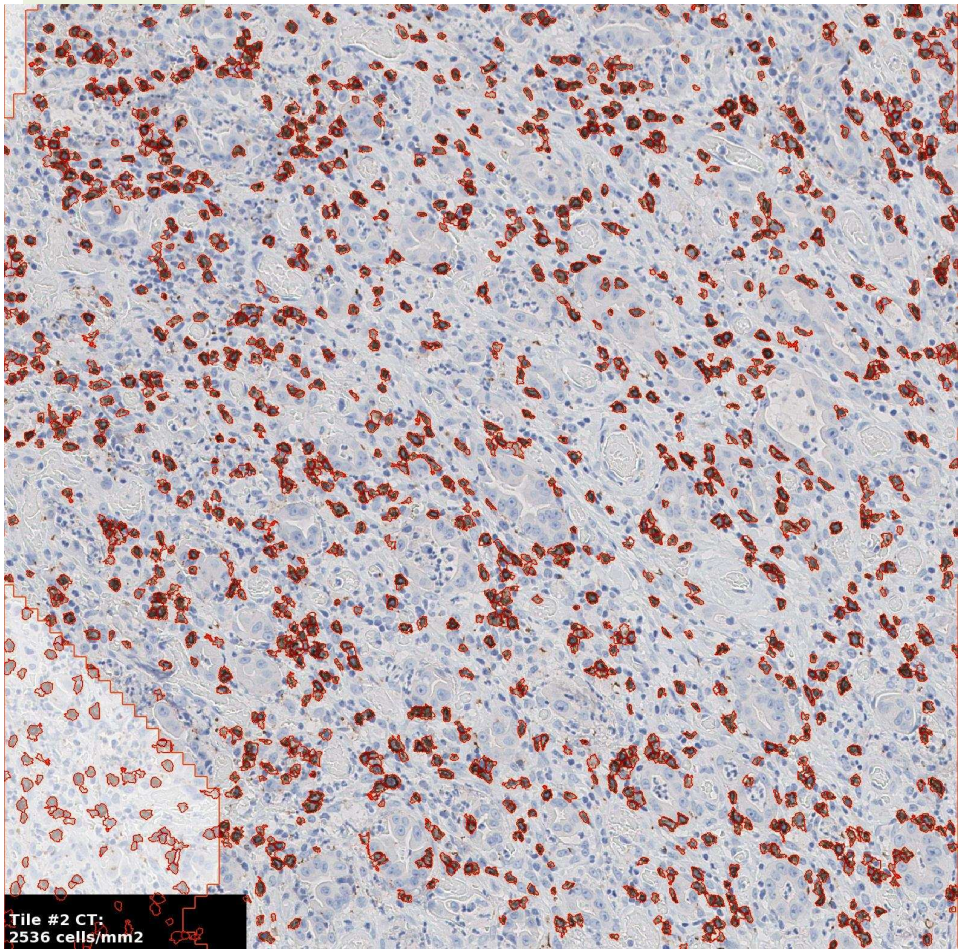
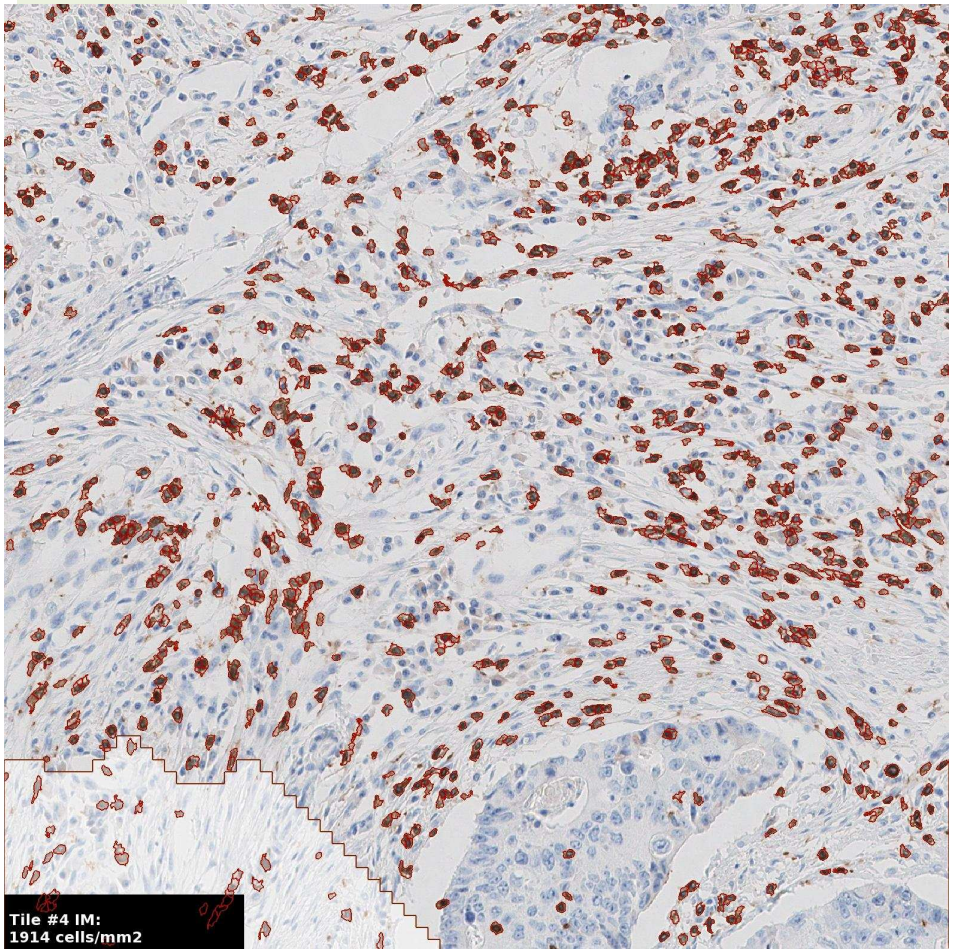
CD8



CD3



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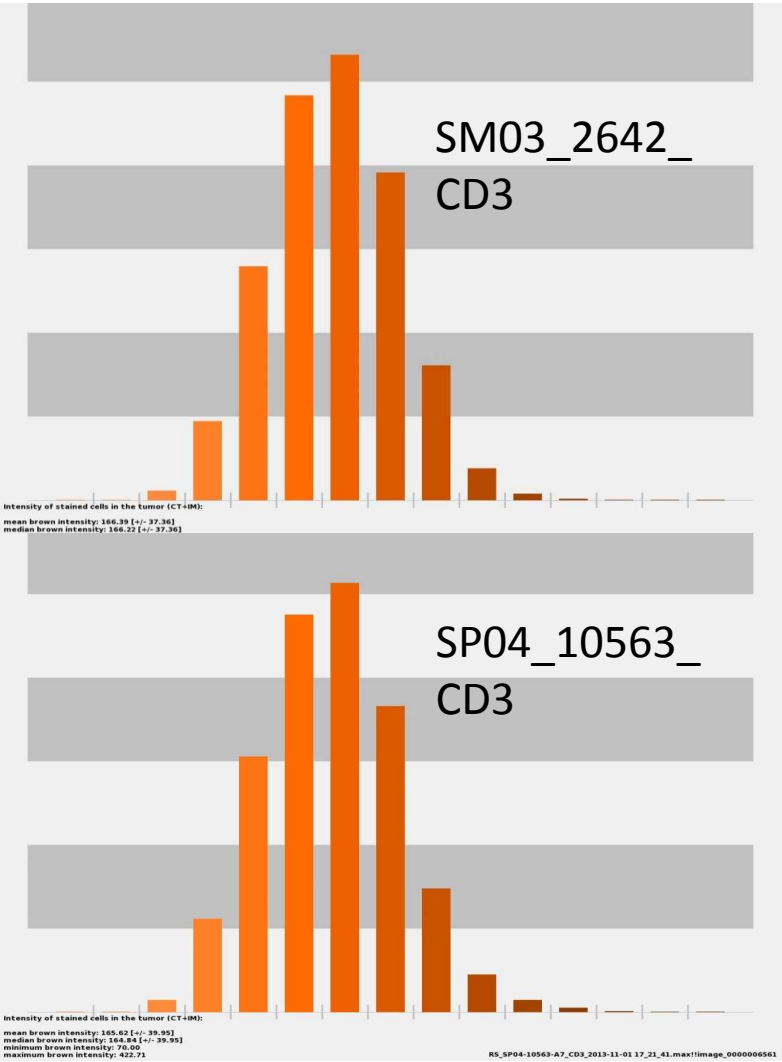
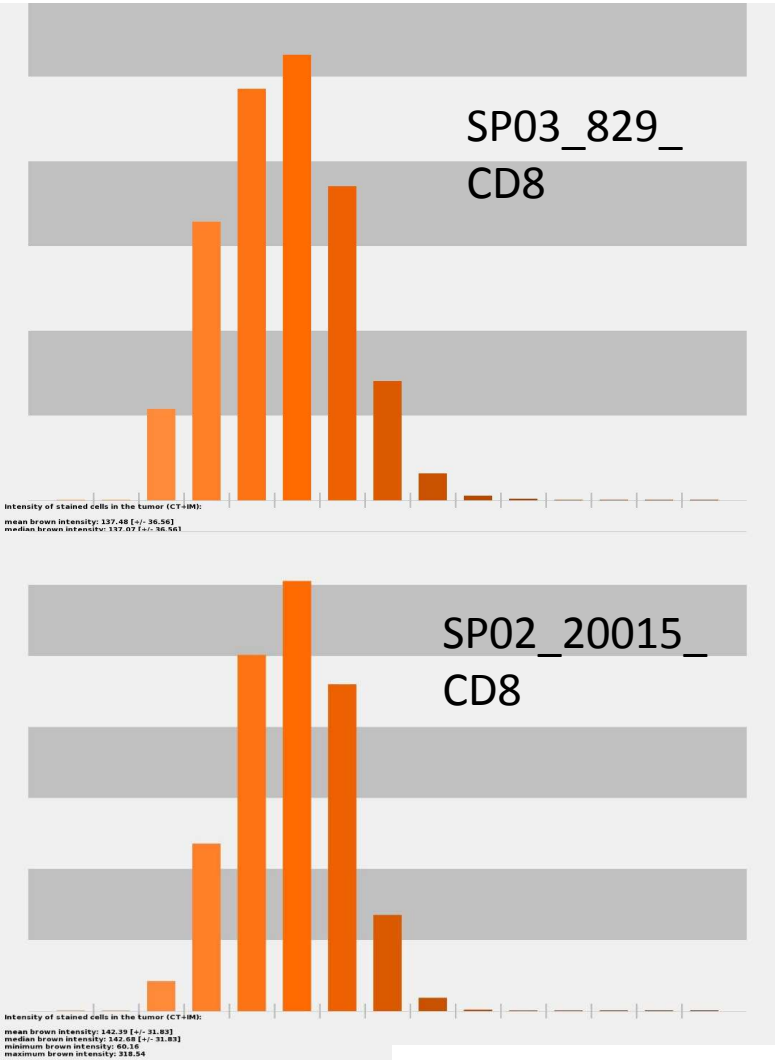
Sample staining intensity histogram





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Immunoscore task force progress (Nov 2013)

City, Country		Melbourne, Australia	Graz, Austria	Toronto, Canada	Xi'an, China	Paris, France	Erlangen, Germany	Napoli, Italy	Milan, Italy	Siena, Italy	Sapporo, Japan	Doha, Qatar	Madrid, Spain	Stockholm, Sweden	Umea, Sweden	Bern, Switzerland	Nijmegen, Netherlands	Dorchester, UK	Portland, OR, USA	Rochester, MN, USA	Houston, TX, USA	Tokyo, Japan	Ahmedabad, India	Prague, Czech Republic
Steps	**Expected time**																							
Joint analysis of all data	October 2013																							
All Immunoscore quantification performed	September 2013																							
All stained slides scanned	September 2013																							
All IHC stainings performed following guidelines	September 2013																							
300 patients with Immunoscore quantification performed	September 2013																							
300 patients with stained slides scanned	September 2013																							
300 patients with IHC stainings performed following guidelines	September 2013																							
200 patients with Immunoscore quantification performed	June 2013																							
200 patients with stained slides scanned	June 2013																							
200 patients with IHC stainings performed following guidelines	June 2013																							
100 patients with Immunoscore quantification performed	May 2013																							
100 patients with stained slides scanned	May 2013																							
100 patients with IHC stainings performed following guidelines	May 2013																							
Some Immunoscore quantification performed	May 2013																							
Some stained slides scanned	April 2013																							
Some IHC stainings performed following guidelines	April 2013																							
All slides cut and ready for staining	May 2013																							
Some slides cut and ready for staining	March 2013																							
clinical data and follow-up data table ready	April 2013																							
Control IHC slides passed quality controls	February 2013																							
Control IHC slides stained	January 2013																							
All blocks recovered from hospital archives	September 2012																							
Some blocks recovered from hospital archives	July 2012																							
Selection of patients for the study done	April 2012																							

Good, Done
Ongoing
Not done, To Do

Update Date: -> November 2013

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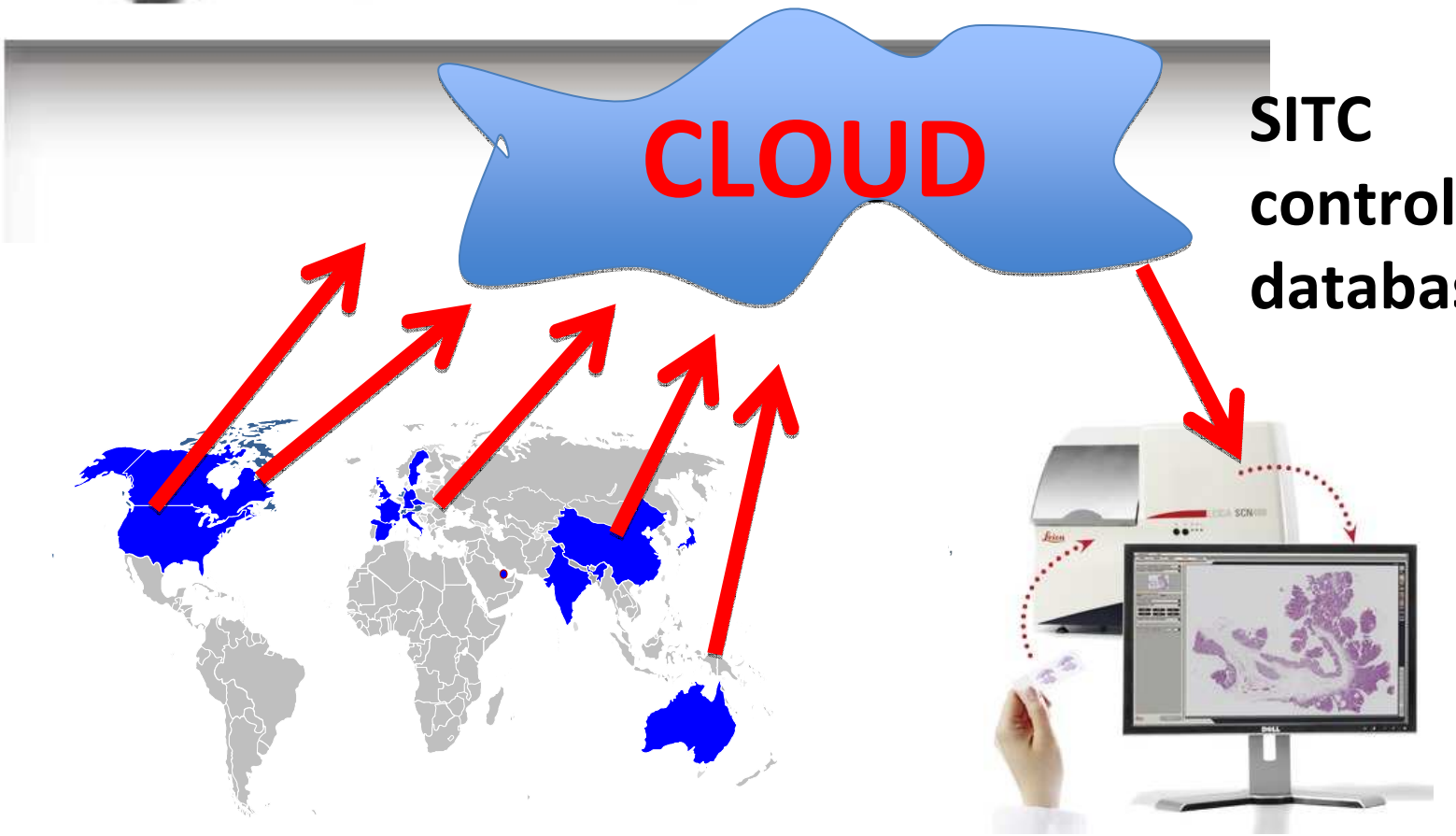
Understanding Images



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2013 REVIEW ISSUE
FREE ONLINE

The Journal of Pathology
Understanding Disease

Towards the introduction of the Immunoscore in the classification of malignant tumors.

Galon J, Mlecnik B, Bindea G, Angell HK, Berger A, Lagorce C, Lugli A, Zlobec I, Hartmann A, Bifulco C, Nagtegaal ID, Palmqvist R, Masucci GV, Botti G, Tatangelo F, Delrio P, Maio M, Laghi L, Grizzi F, Asslaber M, D'Arrigo C, Vidal-Vanaclocha F, Zavadova E, Chouchane L, Ohashi PS, Hafezi-Bakhtiari S, Wouters BG, Roehrl M, Nguyen L, Kawakami Y, Hazama S, Okuno K, Ogino S, Gibbs P, Waring P, Sato N, Torigoe T, Itoh K, Patel PS, Shukla SN, Wang Y, Kopetz S, Sinicrope FA, Scripcariu V, Ascierto PA, Marincola FM, Fox BA, Pagès F.

J Pathol. 2013 Oct 3. doi: 10.1002/path.4287. [Epub ahead of print]

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EDITORIAL Open Access

The additional facet of immunoscore: immunoprofiling as a possible predictive tool for cancer treatment

Paolo A Ascierto[1*], Mariaelena Capone[1], Walter J Urba[2], Carlo B Bifulco[2], Gerardo Botti[1], Alessandro Lugli[3], Francesco M Marincola[4], Gennaro Ciliberto[1], Jérôme Galon[5,6,7] and Bernard A Fox[2,8]

Table 1 Differences between immunoscore and immunoprofiling

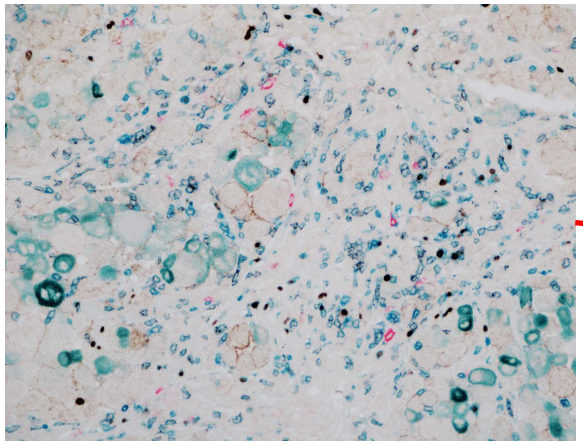
	Immunoscore Prognostic/Predictive(?)	Immunoprofiling Prognostic/Predictive(?)
Number of immune markers	2-4	1 – Several
Immunoscore markers	CD3/CD8	
Immunoscore-like markers	CD3/CD8/CD20/FoxP3	Immune gene signatures
	CD3/CD8/CD45RO	Multiplex assays
	CD4/CD8/CD68	CD137, Galectin1, LAG-3, OX40, PD-
	CD3/CD8/CD20, CD3/GZMB	
	CD8/FoxP3	
	CD8/IL17	
	(others)	
Possible application	• Staging in colorectal cancer (already tested)	• Prognostic assay
	• Staging in Melanoma, Breast cancer, Ovarian cancer, NSCLC, Prostate cancer, Pancreatic cancer, Head & Neck cancer (to be defined).	• Predictive assay • Personalized immune-treatment

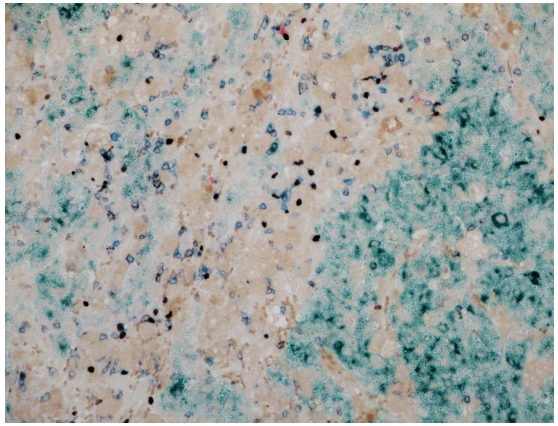
J. Transl Med. 11: 54 2013

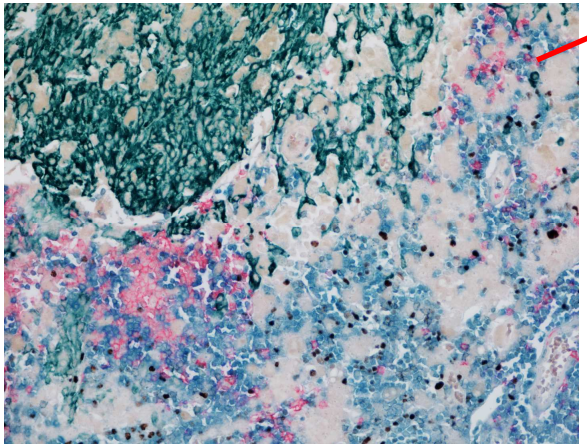
5-Plex Chromogenic Staining on Melanoma

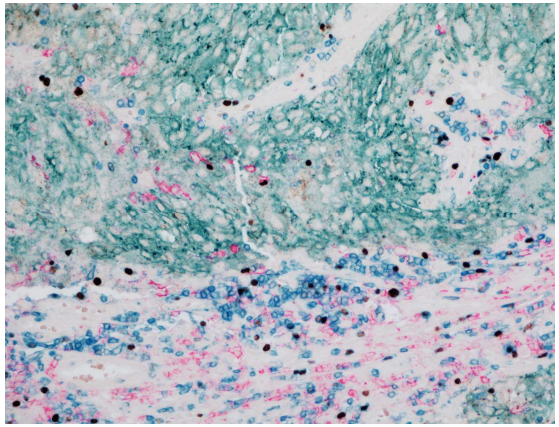
Collaboration between Bernard A. Fox, Carlo Bifulco and Zip Feng of the Earle A. Chiles Res. Inst and Noemi Sebastiao, Jean Bird and Alisa Tubbs of Ventana Medical systems

FoxP3 – DAB (dark brown)
CD8 – Gray/black
CD3 - Blue
CD20 – Red/magenta
S100 – Melanoma cocktail









200x

Melanoma TIL Study
EACRI - Ventana collaboration
TMA # FS13-10145, 241837

Earle A. Chiles Research Institute

SITC Immunoscore Taskforce!

EDITORIAL Open Access

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 Thurin [7], Alessandro Lugli [8], Inti Zlobec [8], Anne Berger [4], Carlo Bifulco [9], Gerardo Botti [10], Fabiana Tatangelo [10], Cedrik M. Britten [11], Sebastian Kreiter [11], Lotfi Chouchane [12], Paolo Delrio [13], Arndt Hartmann [14], Martin Asslaber [15], Michele Maio [16], Giuseppe V. Masucci [17], Martin Mihm [18], Fernando Vidal-Vanaclocha [19], James P Allison [20], Sacha Gnjatic [20], Leif Hakansson [21], Christoph Huber [11], Harpreet Singh-Jasuja[22], Christian Ottensmeier [23], Heinz Zwierzina [24], Luigi Laghi [25], Fabio Grizzi [25], Pamela S. Ohashi [26], Patricia A Shaw [27], Blaise A Clarke [27], Bradly G. Wouters [27], Yutaka Kawakami [28], Shoichi Hazama [29], Ena Wang [6], Jill O'Donnell-Tormey [30], Christine Lagorce [31], Graham Pawelec [32], Michael I. Nishimura [33], Robert Hawkins [34], Rejean Lapointe [35], Andreas Lundqvist [36], Samir N. Khleif [37], Shuji Ogino [38], Peter Gibbs [39], Paul Waring [40], Noriyuki Sato [41], Toshihiko Torigoe [41], Kyogo Itoh [42], Prabhu S. Patel [43], Shilin N. Shukla [43], Richard Palmqvist [44], Iris D. Nagtegaal [45], Yili Wang [46], Corrado D'Arrigo [47], Scott Kopetz [48], Frank A Sinicrope [49], Giorgio Trinchieri [50], Thomas F Gajewski [5, 51], Paolo A Ascierto [52,53], Bernard A Fox [5,54,55]

Galon, J. J. Transl Med. 2012

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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…