Principles of Immunotherapy

Bernard A. Fox
Harder Family Endowed Chair for Cancer Research
Laboratory of Molecular and Tumor Immunology
Robert W. Franz Cancer Research Center
Earle A. Chiles Research Institute
Providence Portland Medical Center

Department of Molecular Microbiology and Immunology; and
Knight Cancer Institute, OHSU, Portland, Oregon , USA

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

Bristol-Myers Squibb, MannKind, Aduro (BioSante, Cell Genesys), Immunophotonics, Micromet (Amgen), Dendreon, Ventana/Roche, Nodality, Definiens, Janssen/Johnson & Johnson, 3M, PerkinElmer, MedImmune/AstraZeneca, NeoStem, Viralytics, *Immune Design, NanoString*

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

UbiVac, UbiVac-CMV, Insys Ther

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Objective for this talk:

1) Paradigm shift in Oncology
   - What cures people
     - Proof of concept
   - Its just not for melanoma

2) Identification of good/bad risk factors /
   - Immunoprofiling
   - tailoring treatment / combinations

3) The next five years – How to get to 100%
   "Thinking outside the box"

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The practice of oncology is undergoing a transformation.

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Why?

New Paradigm

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

New Paradigm

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- The immune system is the "agent" that improves outcome and **CURES** people with metastatic solid cancer.
- **Fundamental shift in our understanding of cancer.**

New Paradigm

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CONTROVERSIAL…

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Source: The New York Times, Los Angeles Times

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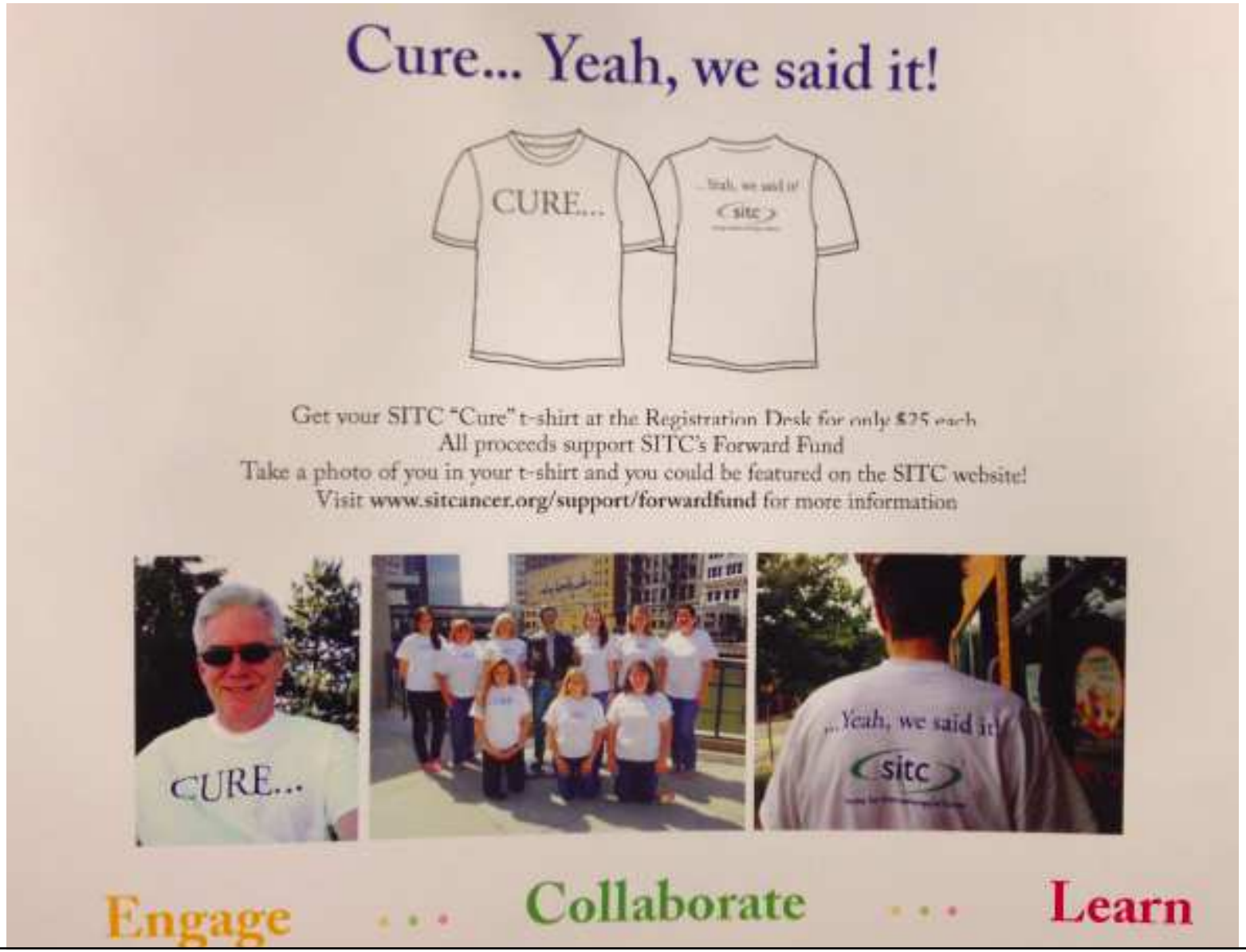
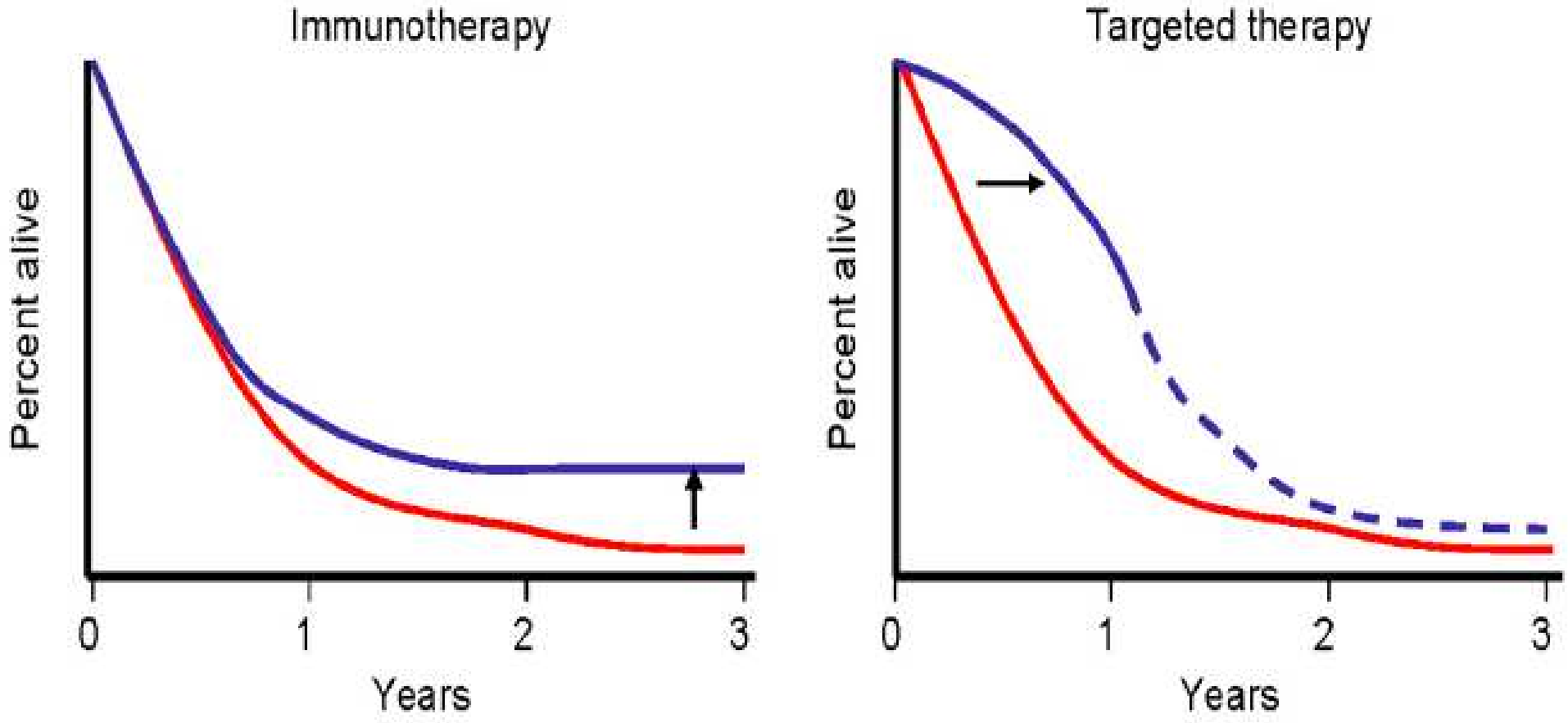
Source: The New York Times, Los Angeles Times

SITC Immunoscore Taskforce!

Cure…. Yeah, we said it!!!!!

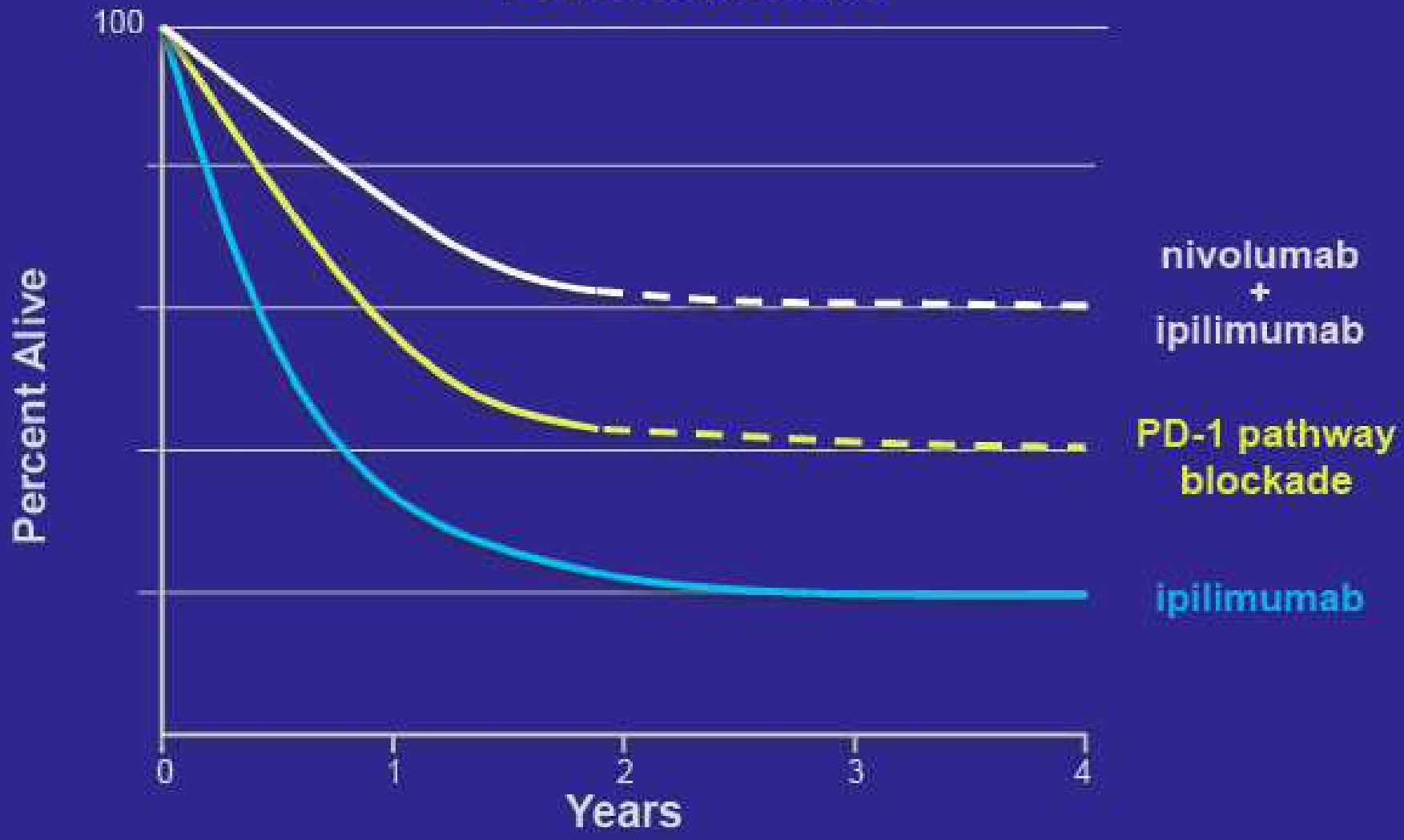


Effects of Immunotherapy and Targeted Therapy on Melanoma

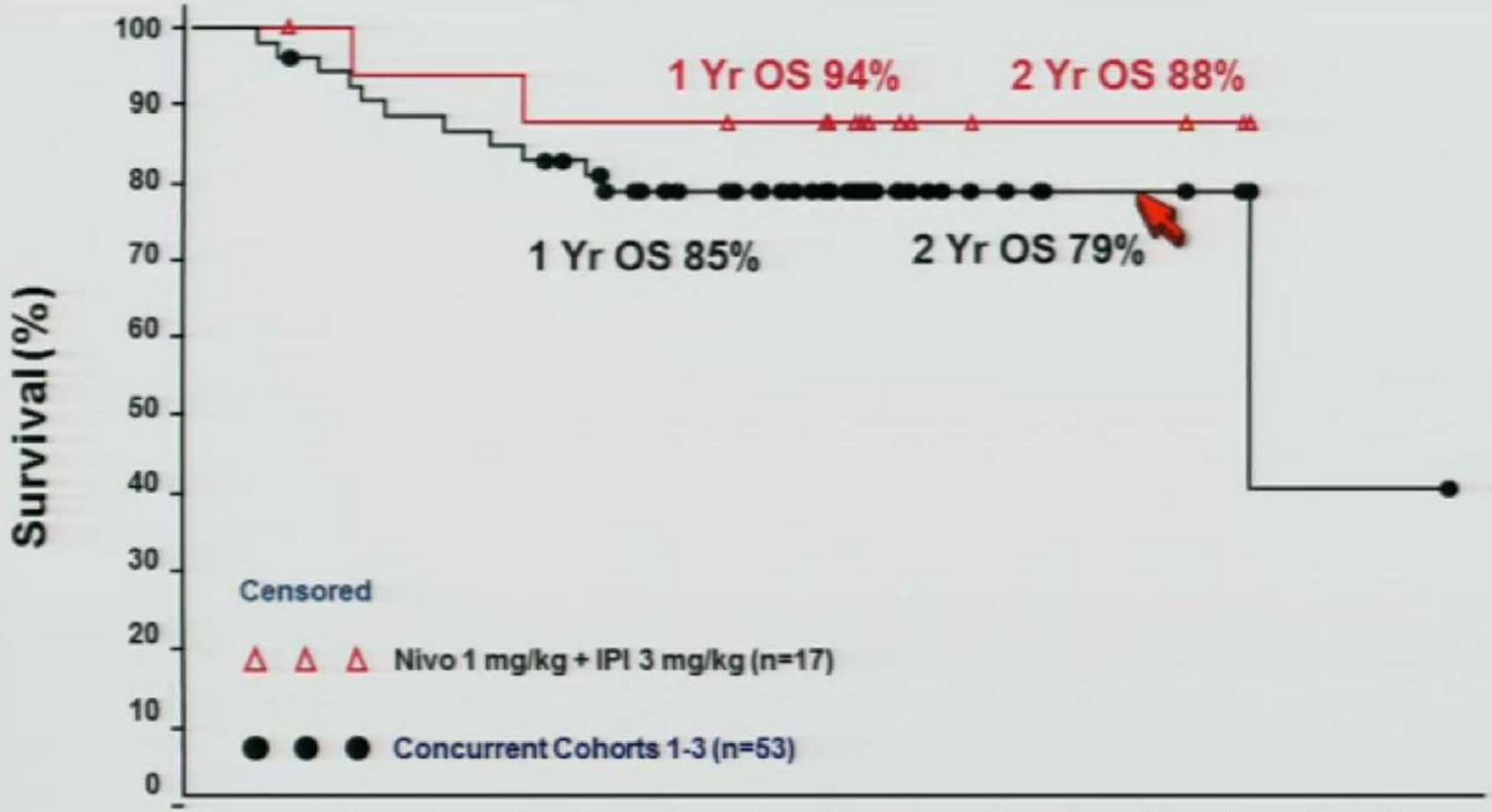


Ribas A et al. *Clin Cancer Res* 2012;18:336-341

Overall Survival After Checkpoint Blockade



Overall Survival for Concurrent Therapy by Dose Cohort



Pts at Risk																	
Nivo 0.3_IPI 3	14	13	11	10	8	7	7	7	7	7	5	2	2	2	1	1	0
Nivo 1_IPI 3	17	17	16	15	15	14	14	13	9	4	3	3	3	2	0	0	0
Nivo 3_IPI 1	16	16	15	15	15	13	4	2	0	0	0	0	0	0	0	0	0
Nivo 3_IPI 3	6	6	6	6	6	6	6	6	3	0	0	0	0	0	0	0	0
Concurrent	53	52	48	46	44	40	31	28	19	11	8	5	5	4	1	1	0

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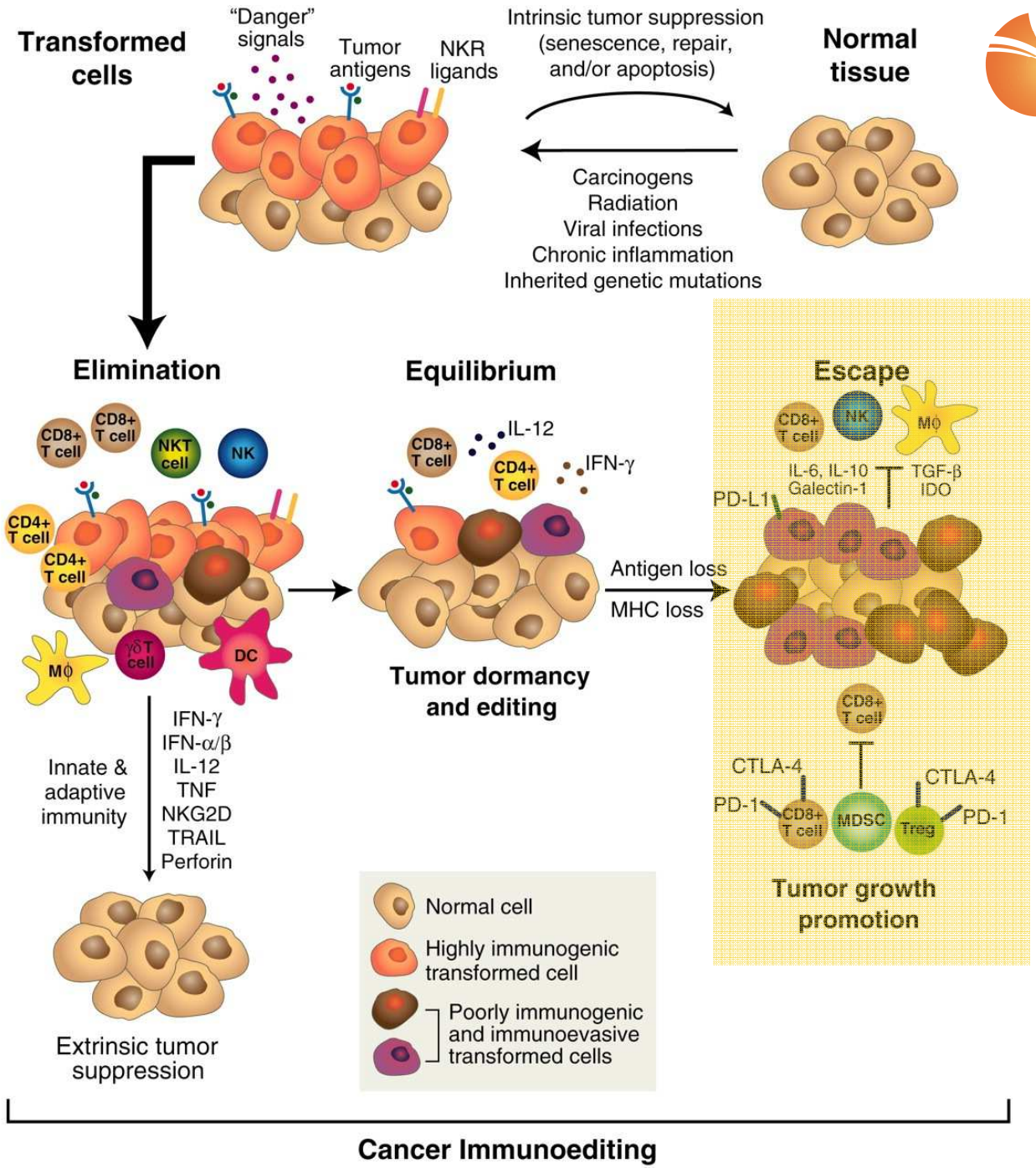
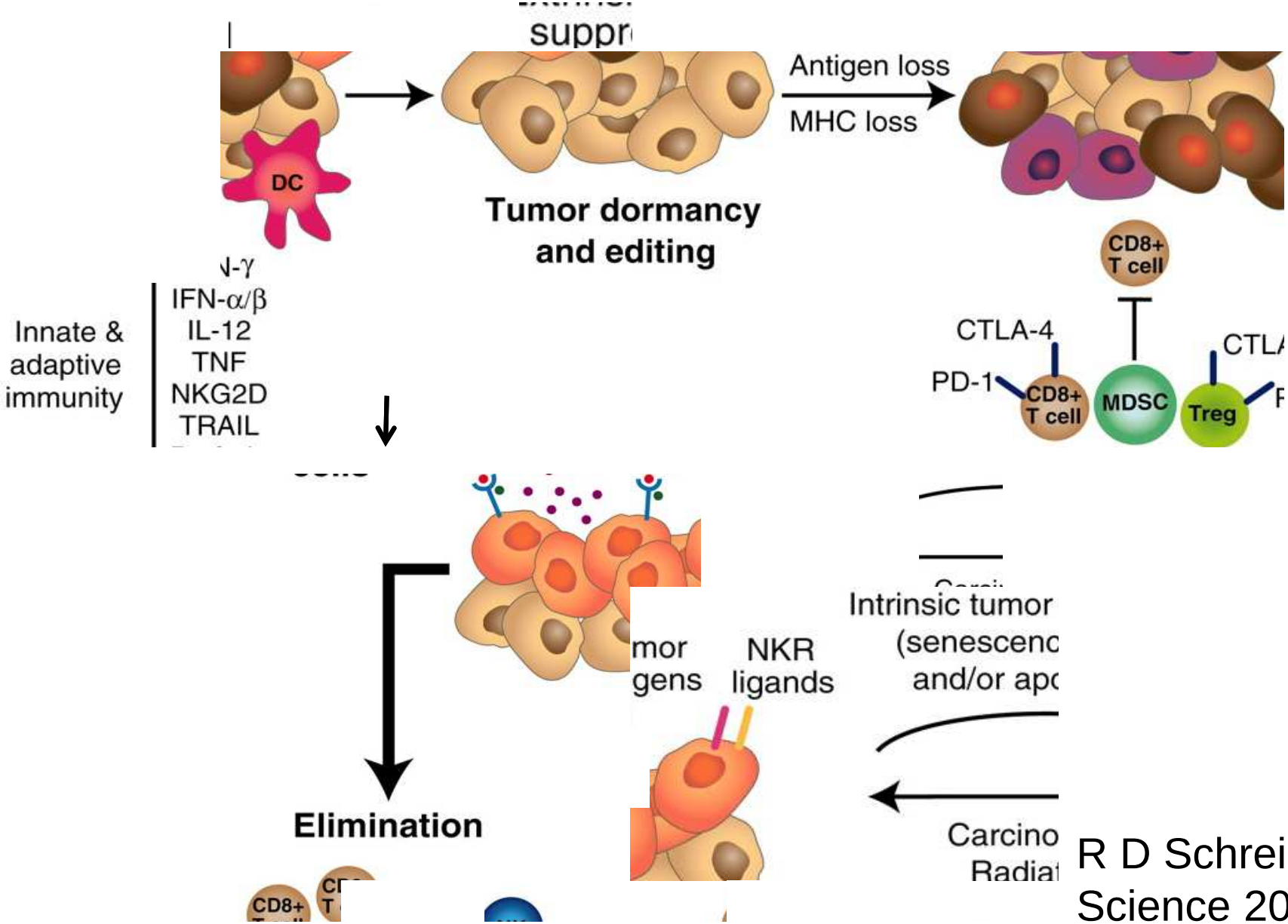


The cancer immunoediting concept.

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



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

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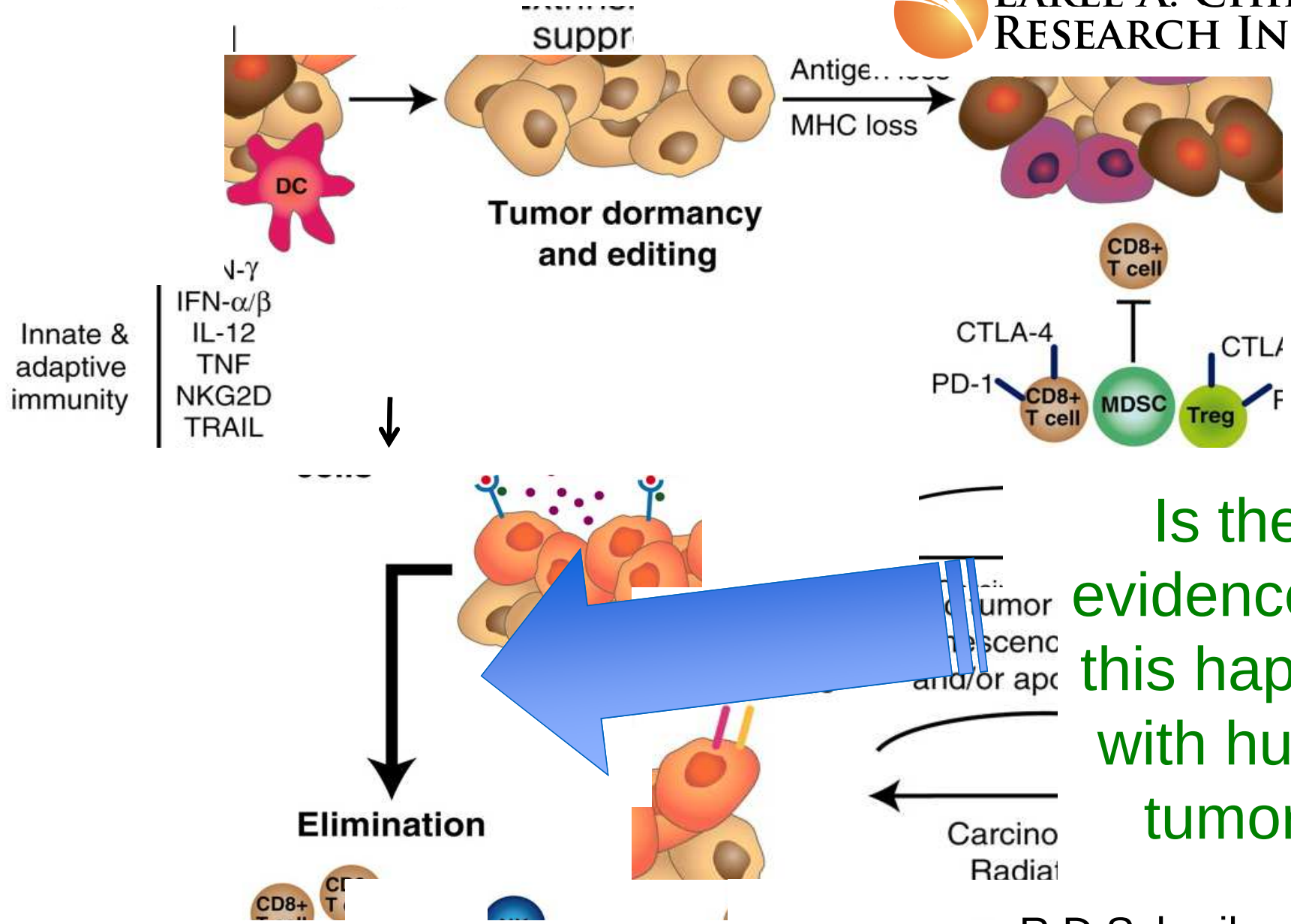

Is there evidence that this happens with human tumors?

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

Immune cells are present within the tumor

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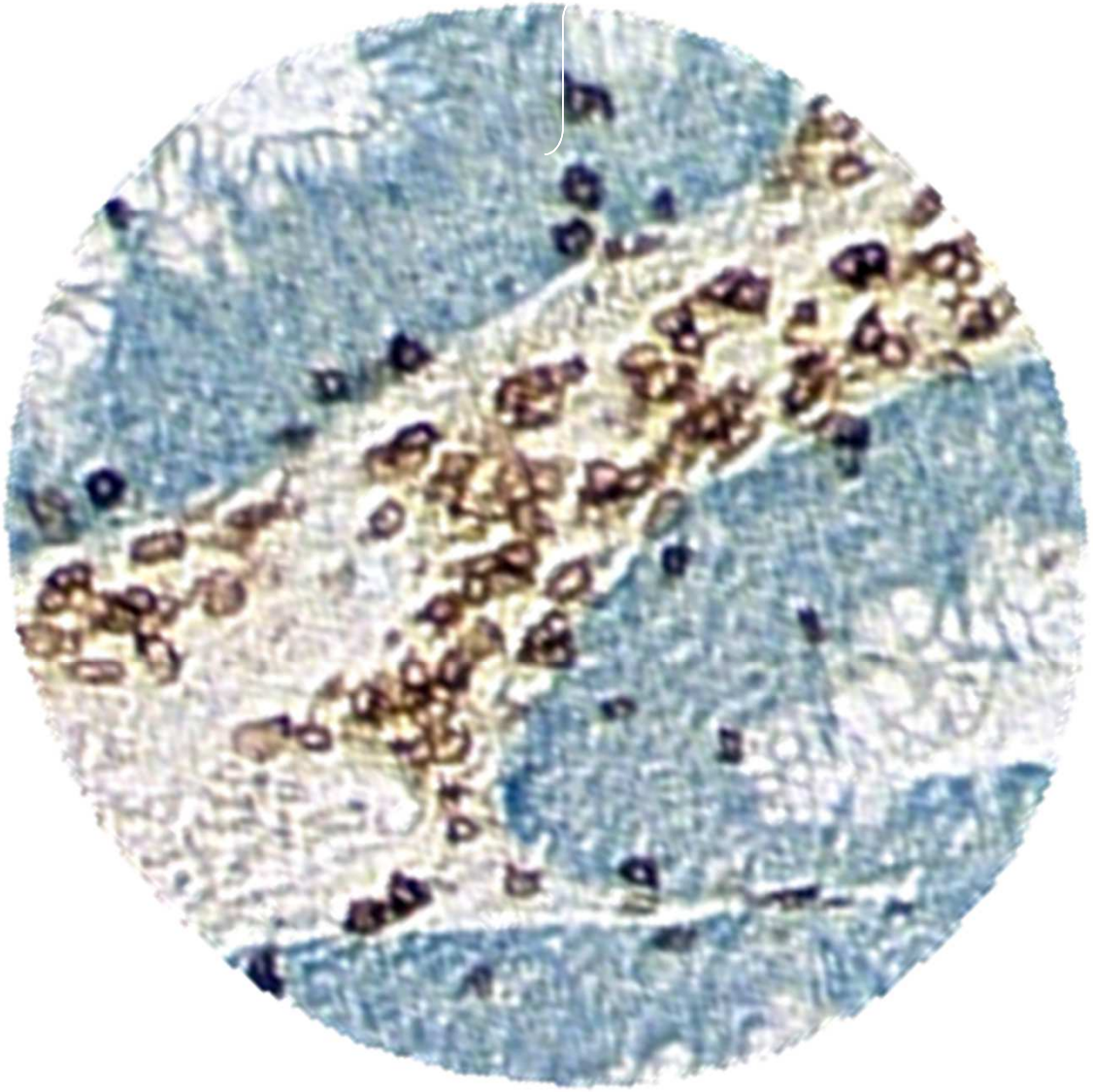

Tumor (blue)

CD3 T cells (brown)

Colon Cancer DFS by Stage: UICC - TNM

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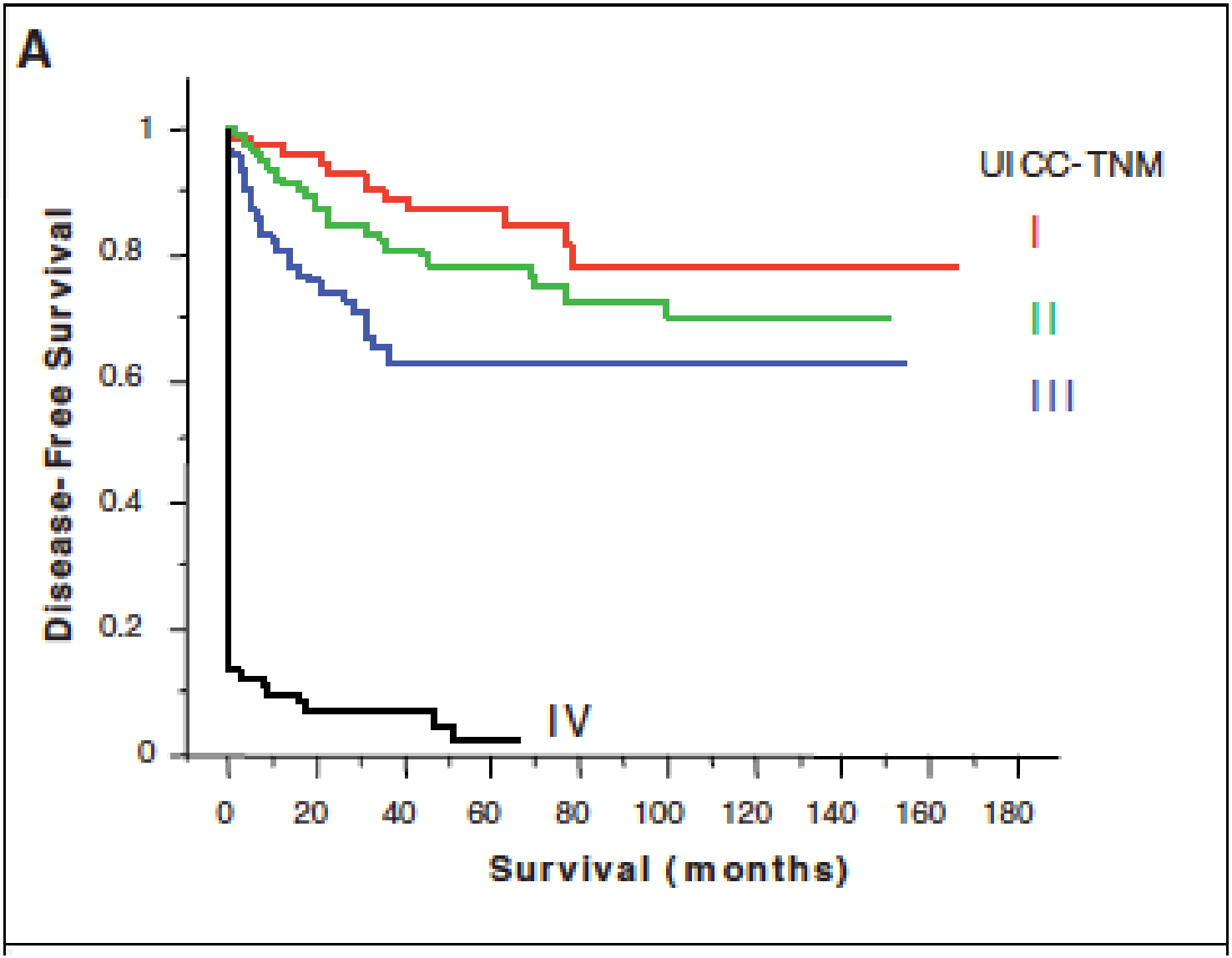

Galon J. et al, Science 2006

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

The role of the adaptive immune response in controlling the growth and recurrence of human tumors has been controversial. We characterized the tumor-infiltrating immune cells in large cohorts of human colorectal cancers by gene expression profiling and in situ immunohistochemical staining. Collectively, the immunological data (the type, density, and location of immune cells within the tumor samples) were found to be a better predictor of patient survival than the histopathological methods currently used to stage colorectal cancer. The results were validated in two additional patient populations. These data support the hypothesis that the adaptive immune response influences the behavior of human tumors. In situ analysis of tumor-infiltrating immune cells may therefore be a valuable prognostic tool in the treatment of colorectal cancer and possibly other malignancies.

Landmark Article

-> **Top 0.1%** most frequently cited research article in all disciplines (ESI, Essential Science Indicators)

29 SEPTEMBER 2006 VOL 313 SCIENCE

Jerome Galon and Franck Pagès used digital imaging and objectively assessed immune infiltrates – IM vs Tumor (Science 2006).

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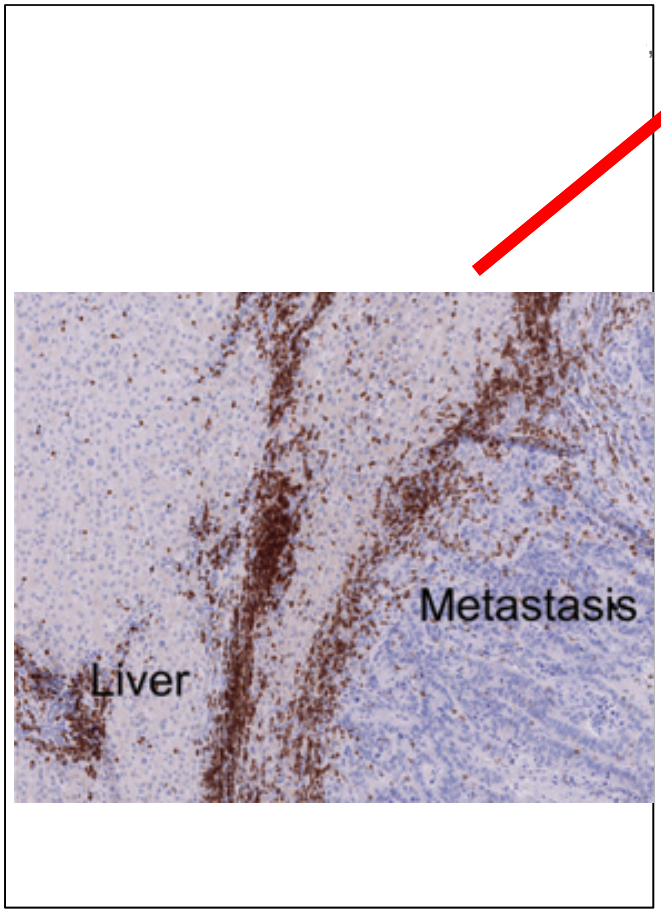
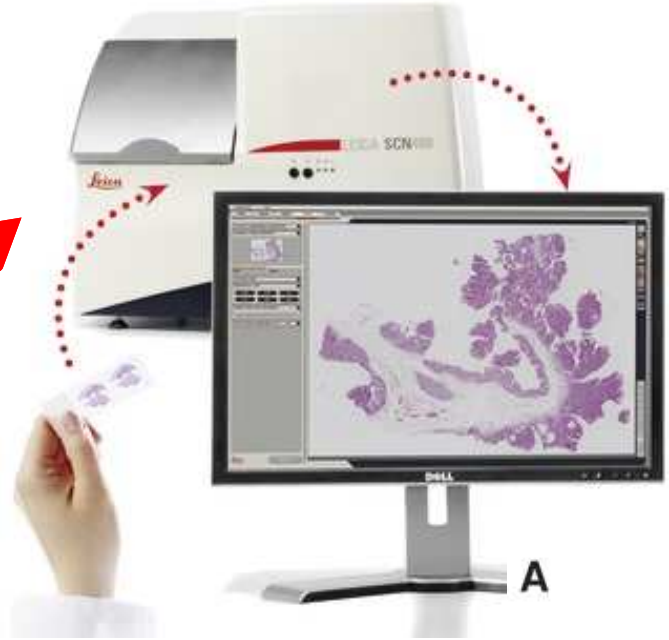
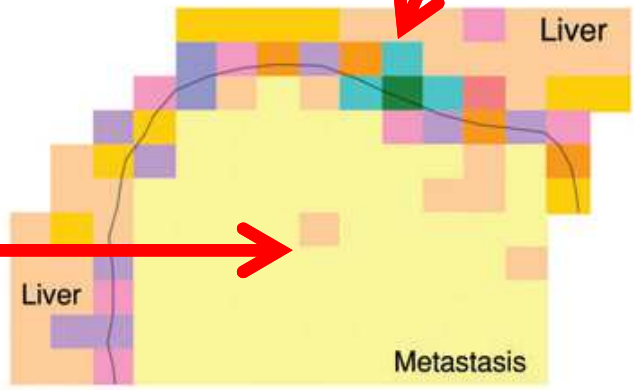




Invasive Margin

Tumor

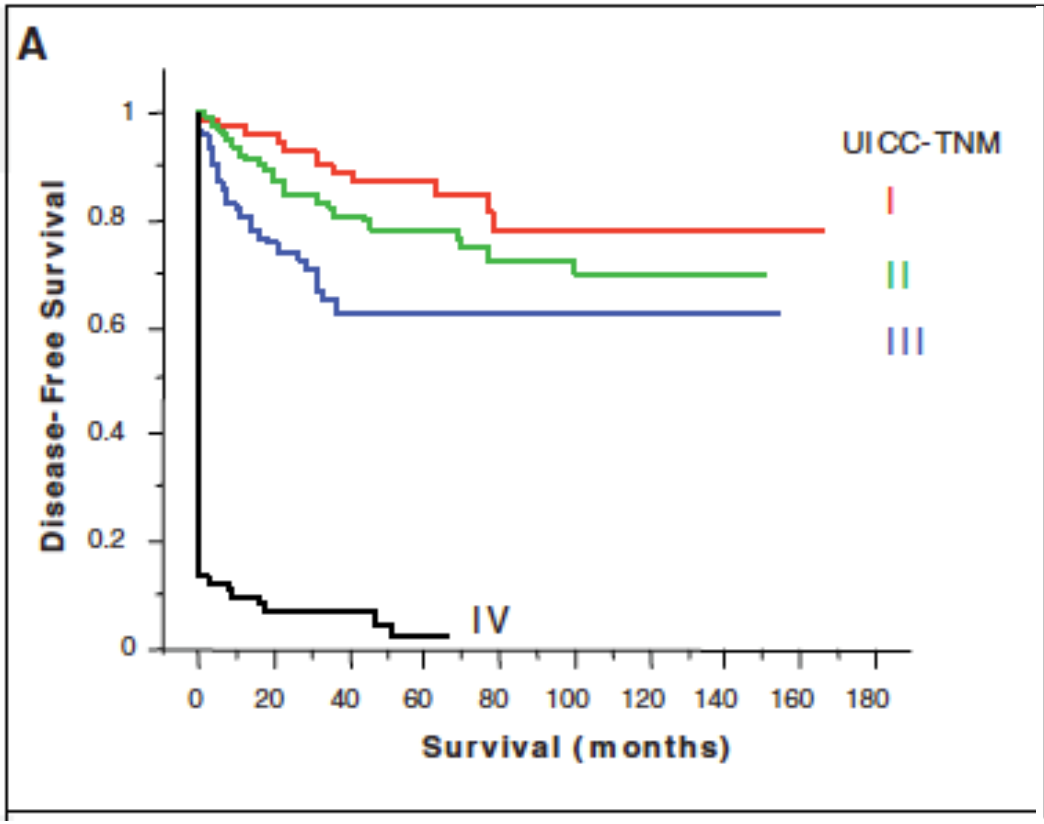


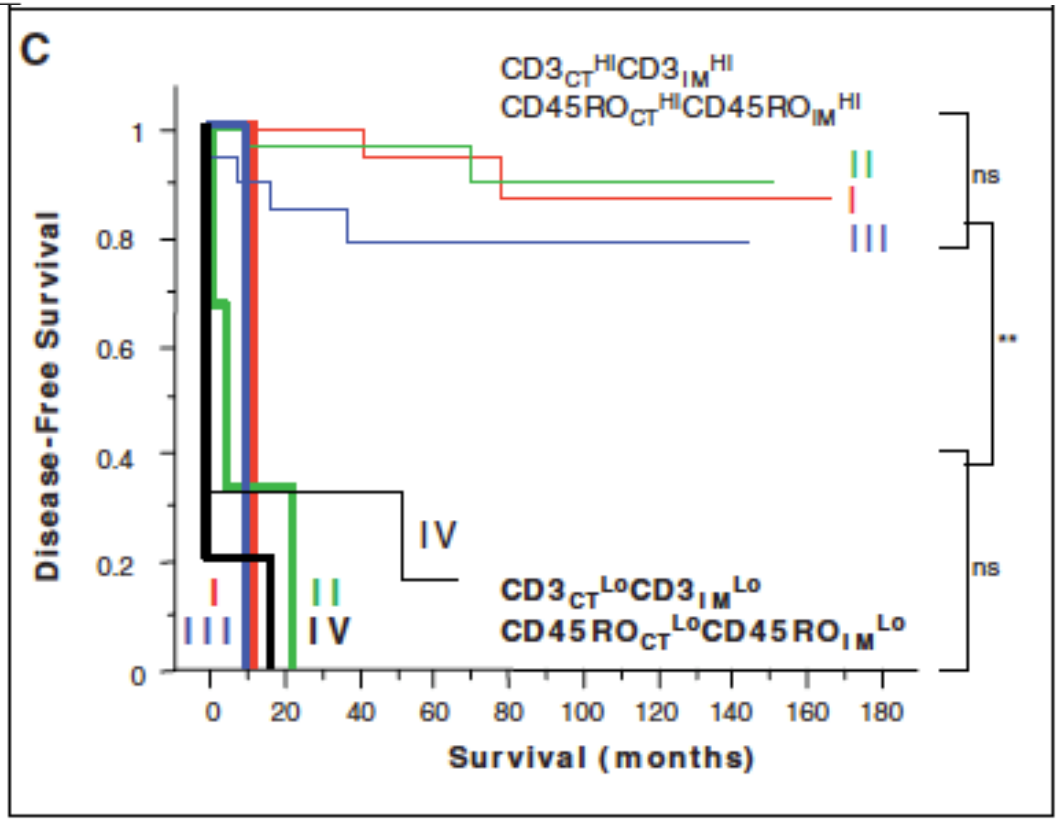
Halama N, et al. Can Res 71:5670 2011

Coordinated adaptive immune response more than tumor invasion predicts outcome.

UICC-TNM Staging system

$CD3_{CT}CD3_{IM}$ evaluation ± $CD45RO_{CT}CD45RO_{IM}$ evaluation





29 SEPTEMBER 2006 VOL 313 SCIENCE

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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.

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

VOLUME 29 · NUMBER 6 · FEBRUARY 20 2011

JOURNAL OF CLINICAL ONCOLOGY

EDITORIALS

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*

SITC Immunoscore Taskforce

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

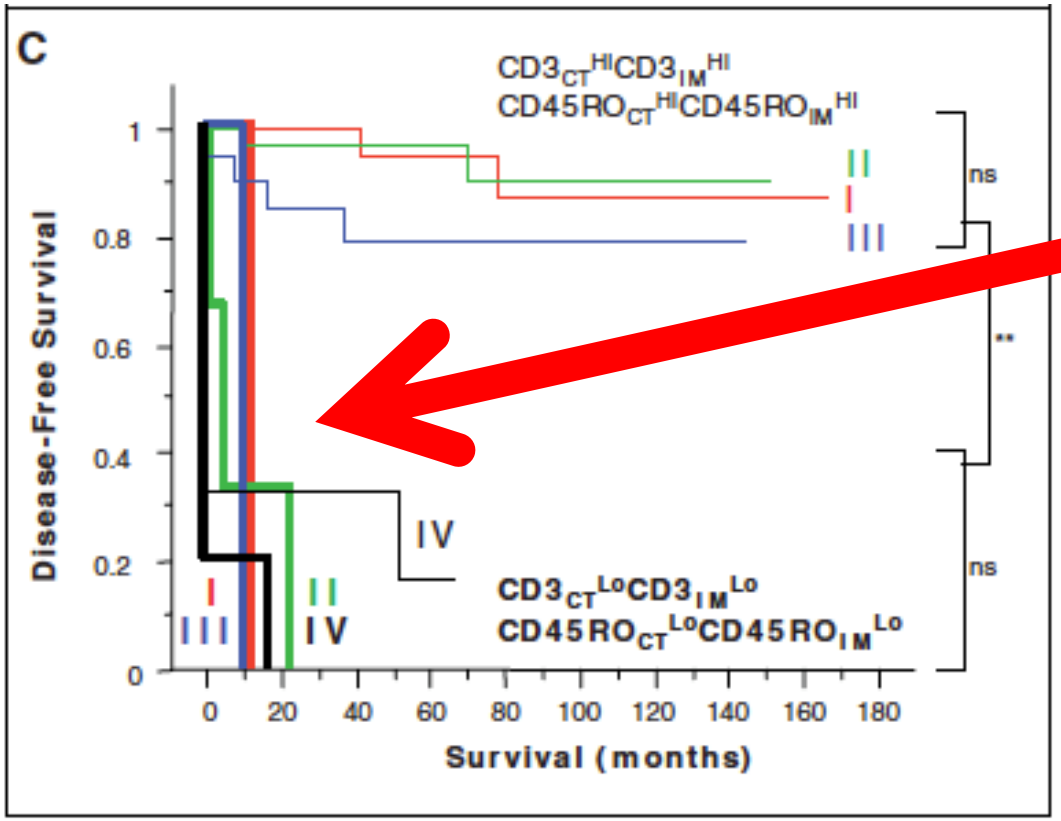
JOURNAL OF TRANSLATIONAL MEDICINE

EDITORIAL **Open Access**

The Immune Score as a New Possible Approach for the Classification of Cancer

Jérôme Galon[1,2,3,4,5*], Franck Pagès[1,2,3,4], Francesco M Marincola[5,6], Magdalena Thurin[7], Giorgio Trinchieri[8], Bernard A Fox[5,9,10], Thomas F Gajewski[5,11] and Paolo A Ascierto[12,13]

Stratify stage I or II patients for adjuvant trials.



-
- **Can we use this to identify patients at high risk of recurrence for HNSCC?**

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

Cells	$CD8^+CD45RO^+$ T cells	T_H1 cells	T_H2 cells	T_H17 cells	T_{Reg} cells
Melanoma	Good[103–106]				• None[23,25] • Poor[107,108]
Head and neck cancers	Good[30,109,110]			None[29]	Good[29,30]
Breast cancer	Good[111–114]	• Good[115,116] • None[117]	• Good[42] • None[117]		• None[26] • Poor[17,18]
Bladder cancer	Good[118,119]				Good[38]
Ovarian cancer	Good[120–122]	Good[123,124]	Poor[123]	Good[125]	• Good[33,61] • Poor[16]
Oesophageal cancer	Good[126,127]	Good[128]		Good[129]	
Colorectal cancer	Good[5,6,28,35,36,63,79,130–148]	Good[5,36,79]	None[36]	Poor[36,149]	• Good[32,34–36] • None[28]
Renal cell carcinoma	• Good[15] • Poor[15]	Good[71]			Poor[150]
Prostatic adenocarcinoma	Good[151–153]				
Lung carcinoma	• Good[13,154–157] • None[158]	Good[13]		Poor[159]	Poor[160–162]
Pancreatic cancer	Good[163]		Poor[164,165]		Poor[155]
Cervical cancer		Good[166]			
Anal squamous cell carcinoma					None[21]
Brain cancer					None[22,24]
Hepatocellular carcinoma	• Good[167,168] • Poor[20]	Good[169]		Poor[170]	Poor[19,20]
Gastric cancer		Good[171]	Poor[171]	Good[172]	
Medulloblastoma		Good[173]			
Merkel cell carcinoma	Good[174]				
Urothelial cell carcinoma	Good[119]				
Follicular lymphoma and Hodgkin's lymphoma			Good[43]		• Good[31,37] • None[27] • Poor[43]

T_H, T helper; T_{Reg} cell, regulatory T cell.

Wolf H. Fridman et al, Nature Reviews Cancer, 2012

SITC Immunoscore Taskforce

sitc

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. 2014 [Epub ahead of print]

FOR THE ONCOLOGY SPECIALIST

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V.15 / N.2 / 2.14

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New Paradigms Emerge for Translating Immunotherapy Into Broad Clinical Use

Adverse Events Report
A snapshot of findings from recent reports, articles, and abstracts

Discovery Dilemma: Narrow "Superiority" Standard Is an Inferior Way to Evaluate Novel Therapies
By Maurie Markman, MD

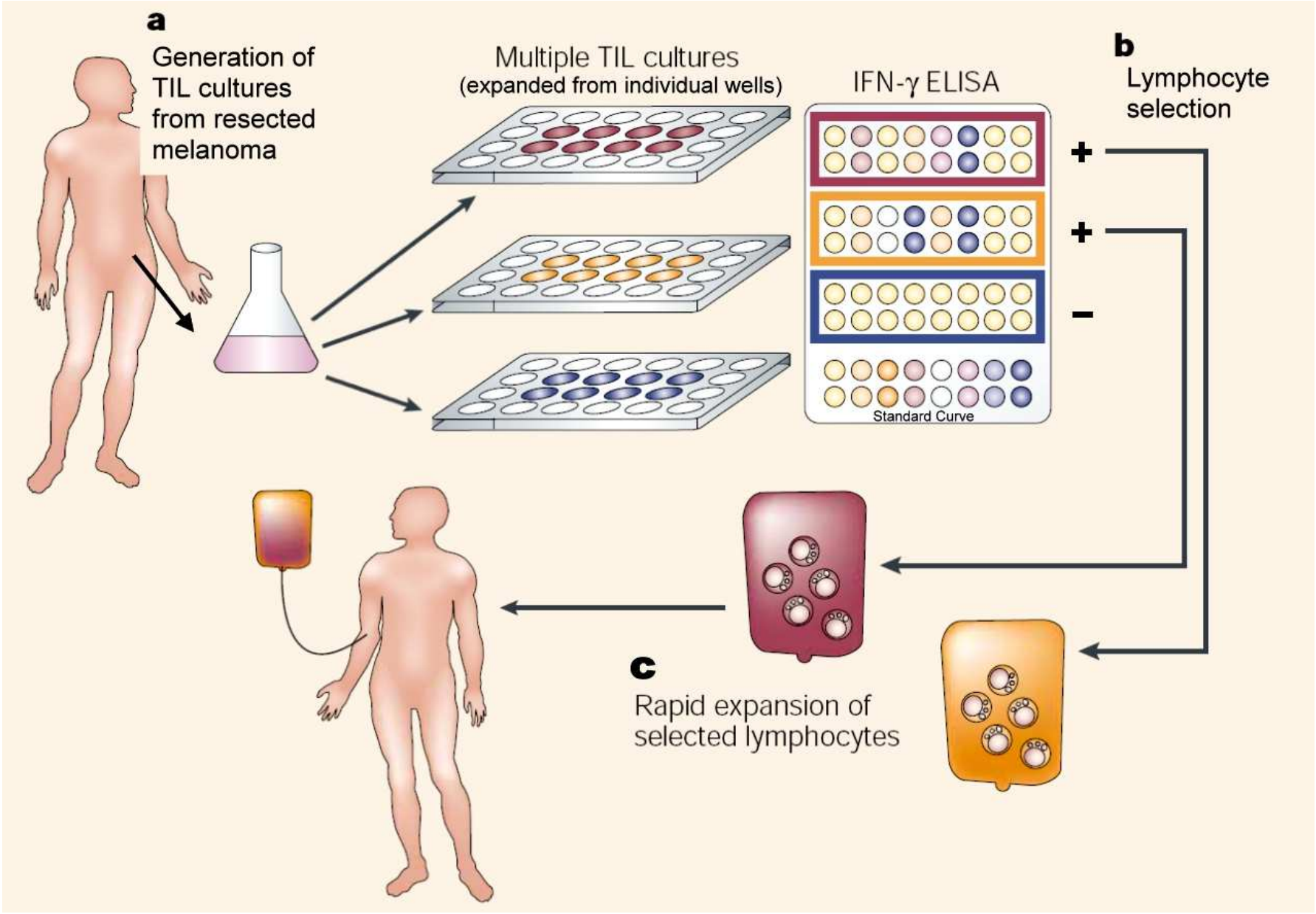
Failed Studies Provide Clues in Renal Cell Carcinoma

Success of First BTK Inhibitor Opens New Options in B-Cell Malignancies

SABCS Roundup

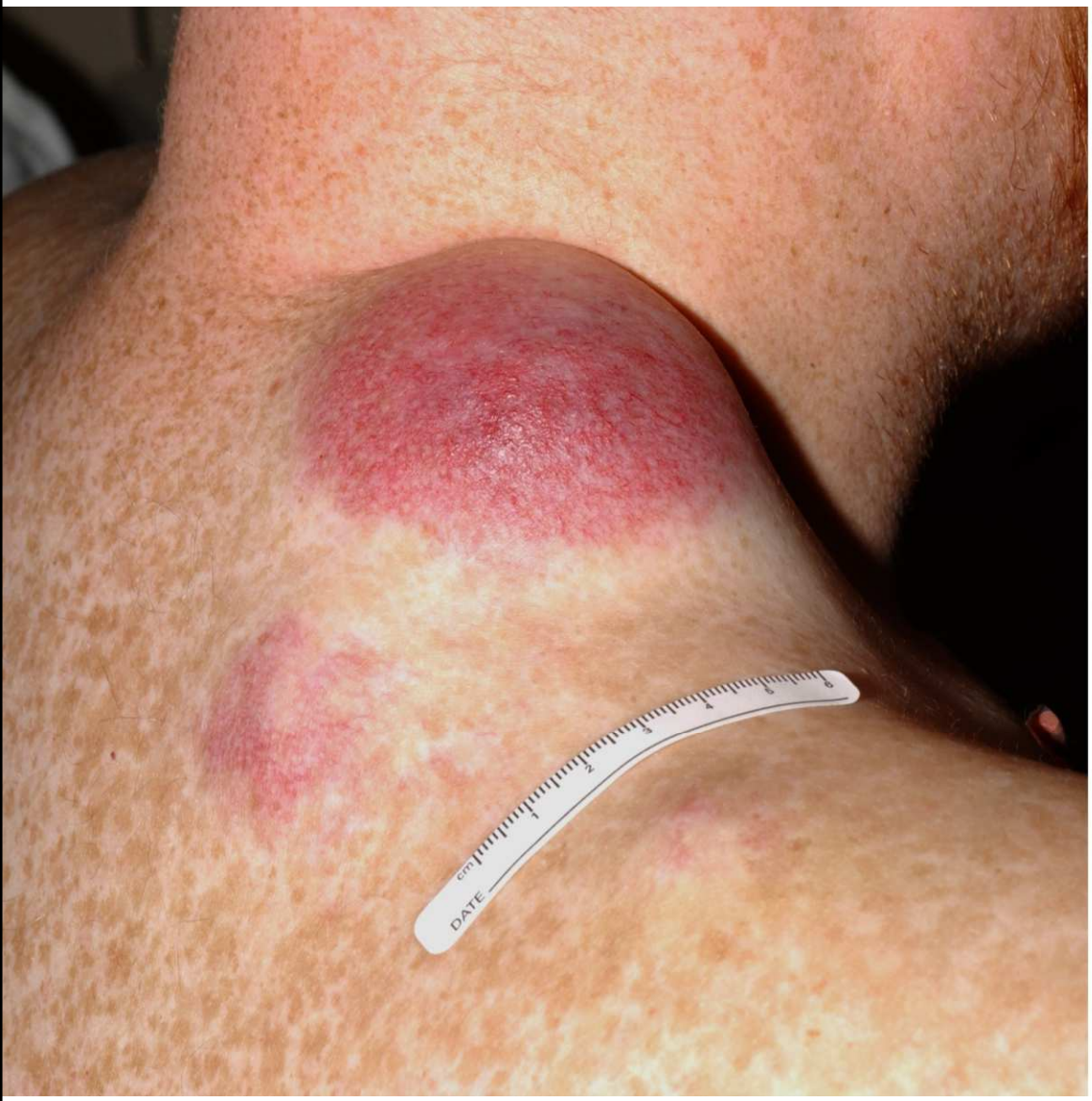
THE NEW YORKER

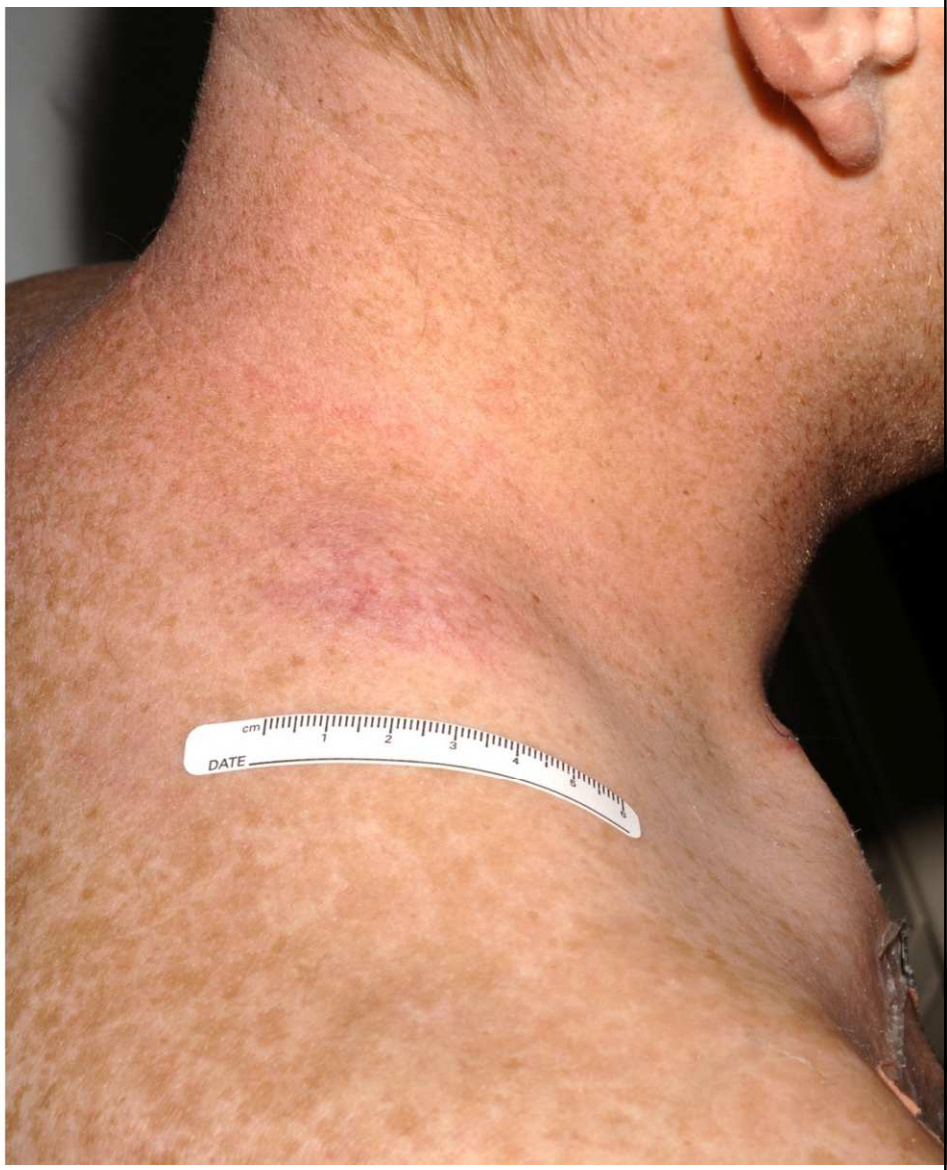
Adoptive Cell Therapy with TIL for Melanoma



Dudley et al, Nat Rev Ca, 2003

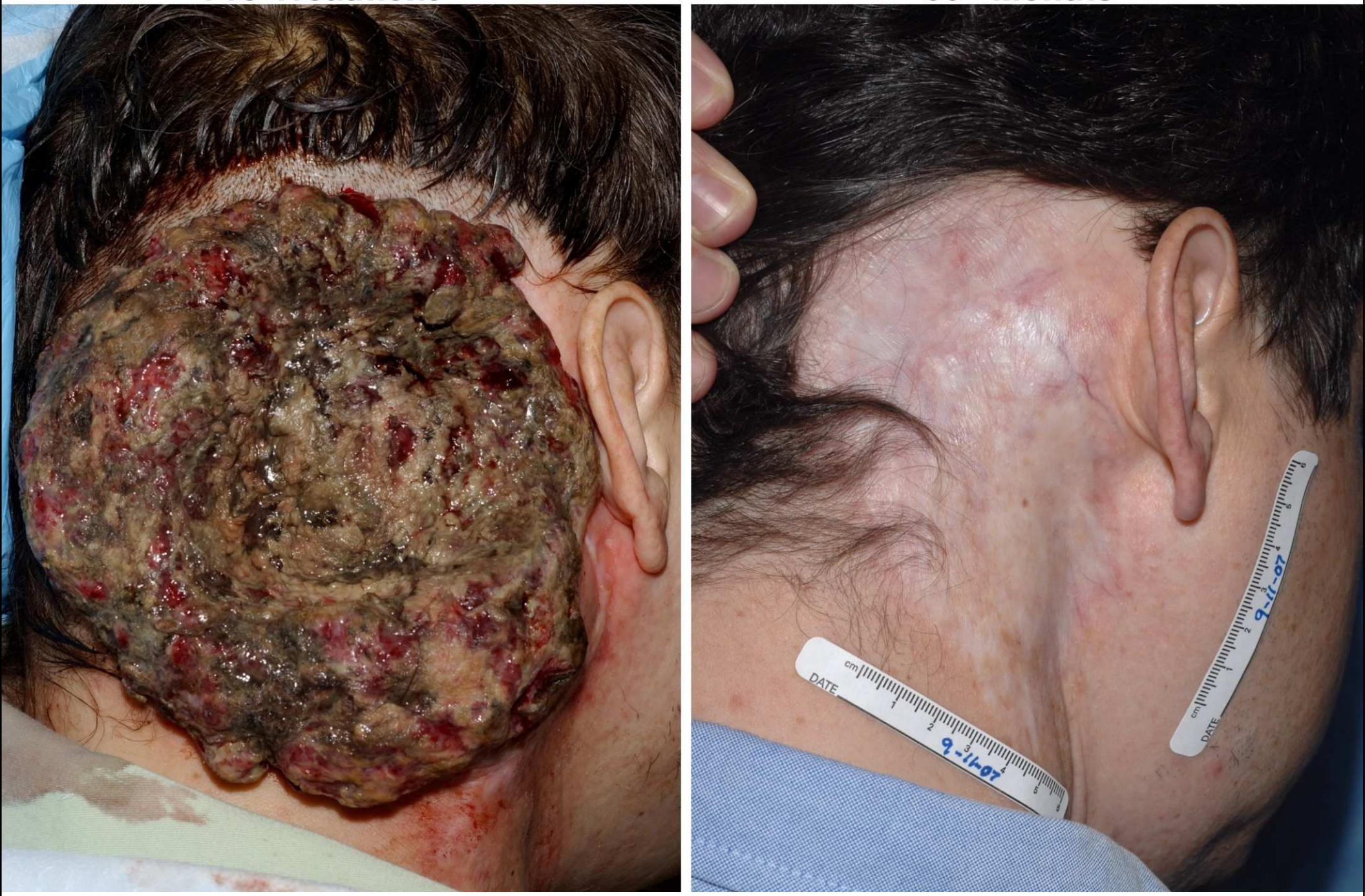
C.K. (200cGy) **Pre** **12 days**

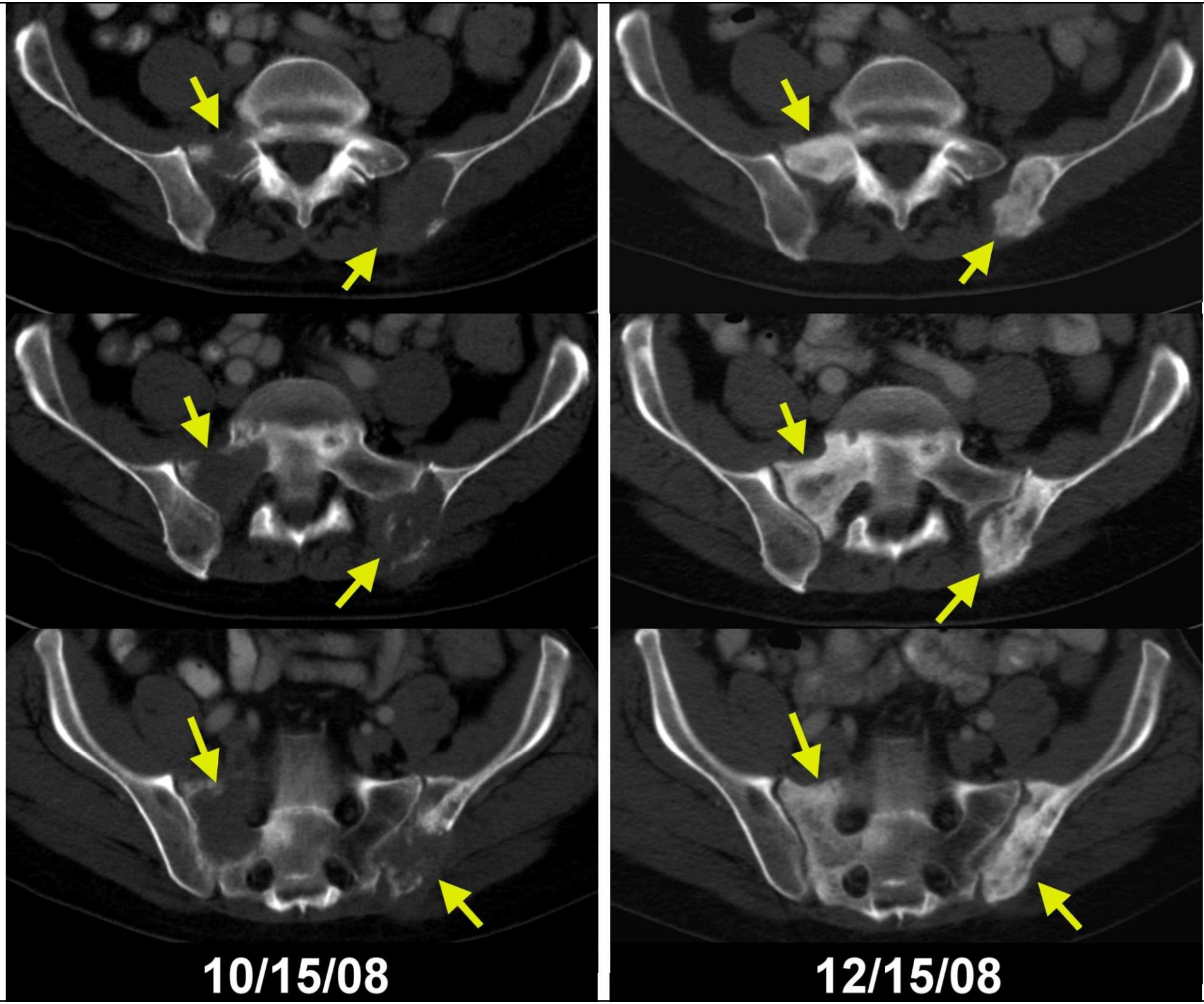




Pre-Treatment

30+ Months




10/15/08
12/15/08

Proof of Concept

Adoptive Immunotherapy with TIL has provided a proof of concept that tumor-specific T cells were present at the tumor site and could be isolated and used for effective treatment (50% patients).

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Tailoring Therapy

What should “we” be doing?

For every trial:

- Require cancer slides or blocks.
- Biopsy: pre, mid or post tx.

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Tailoring Therapy

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For every trial:

- Require cancer slides or blocks.
- Biopsy: pre, mid or post tx.

WHY?

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Tailoring Therapy

Most Cancer therapies are:

“One Size Fits All”

- That’s like treating all patients with a targeted agent, whether they have the mutation or not.

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Tailoring Therapy

For colon cancer the answer may be as simple as Immunoscore (CD3 and CD8).

- Similar for other cancers?
- Or more complex?

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Tailoring Therapy

For colon cancer the answer may be as simple as Immunoscore (CD3 and CD8).

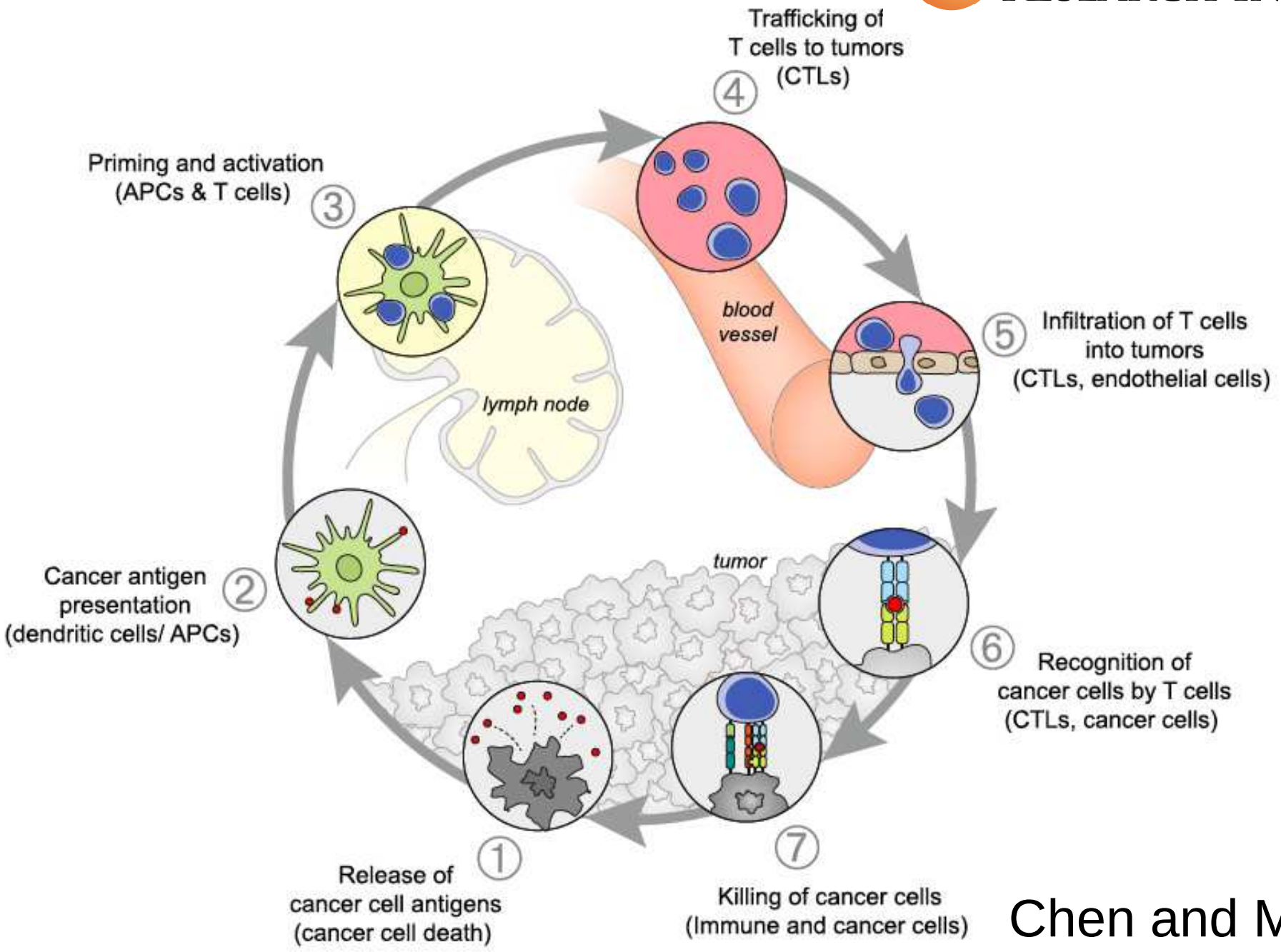
- Similar for other cancers?
- Or more complex?

Likey more complex and variable!

So what should you do?

Immunity
Review

Earle A. Chiles Research Institute



Chen and Mellman

Immunity 39, July 25, 2013

Immunity
Review

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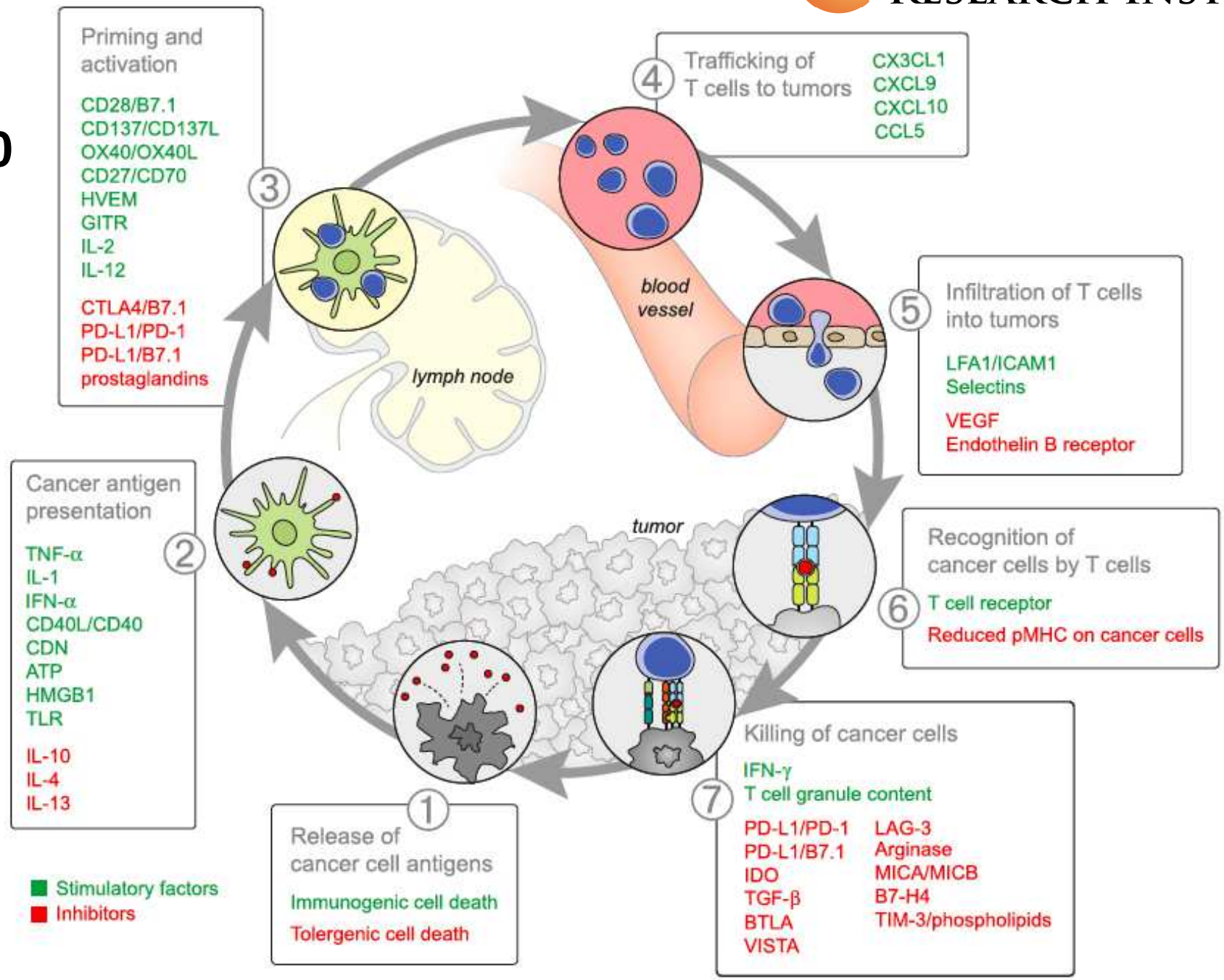
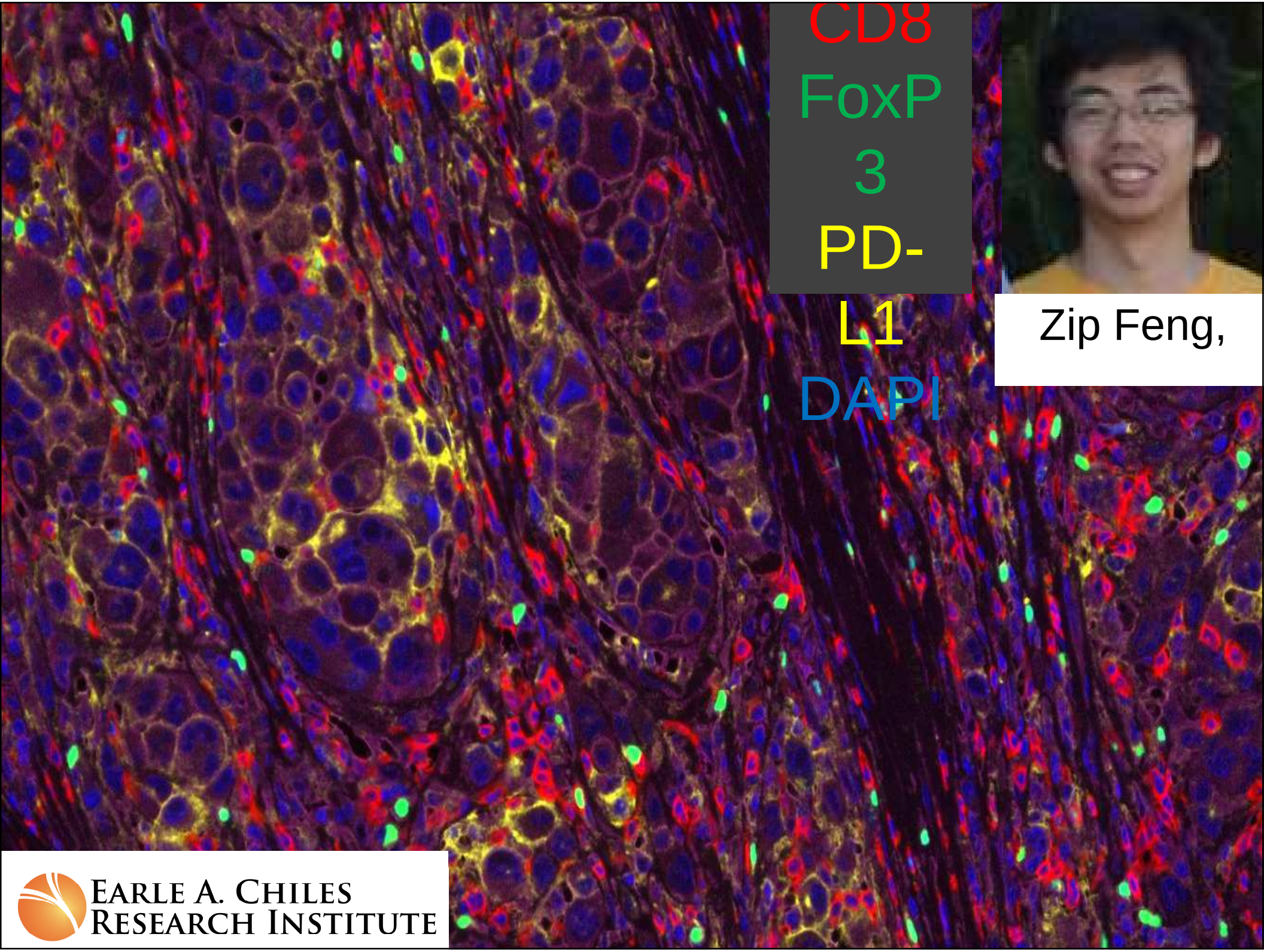
OX40



Immunity 39, July 25, 2013



Zip Feng,

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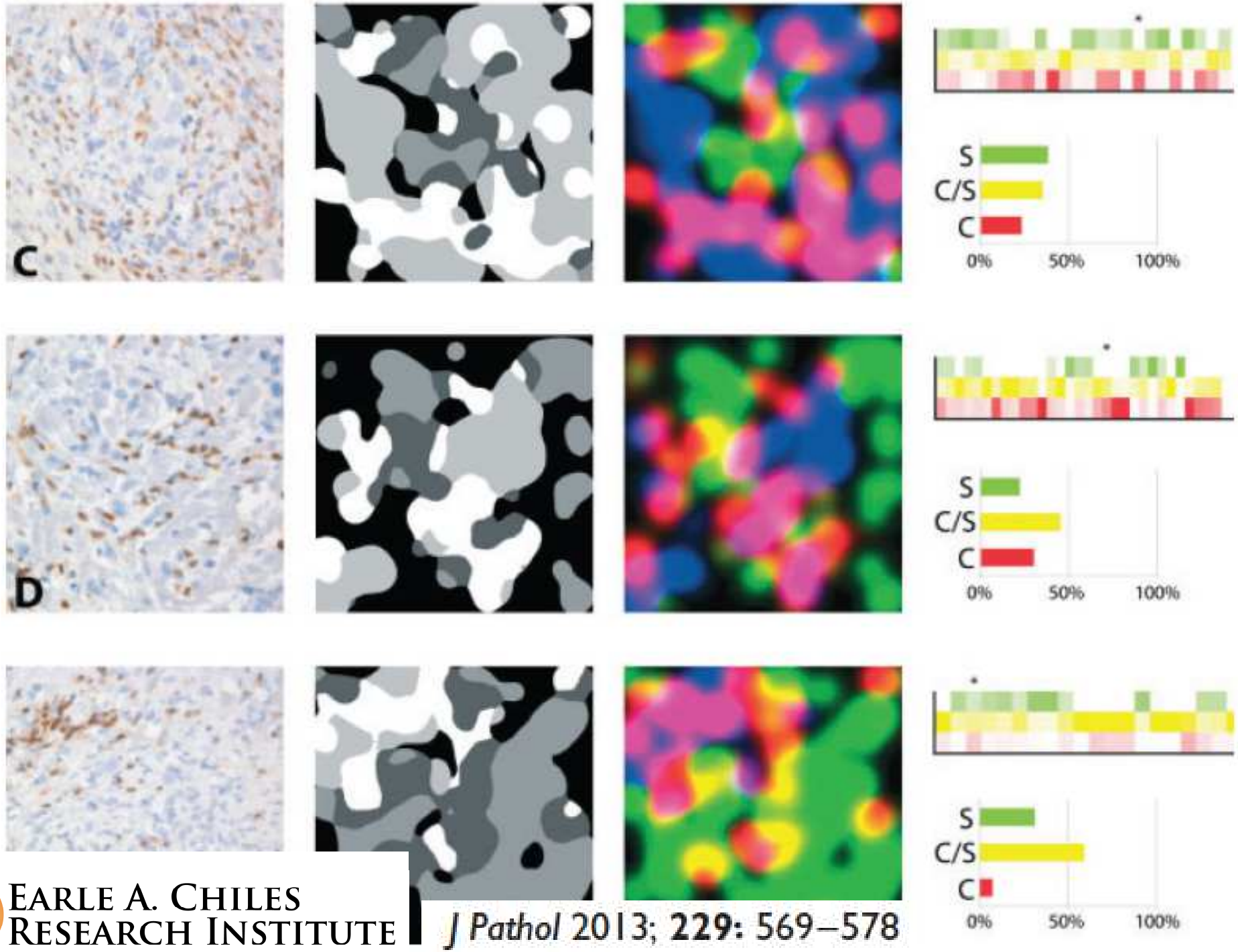
Collaboration



J Pathol 2013; **229**: 569–578

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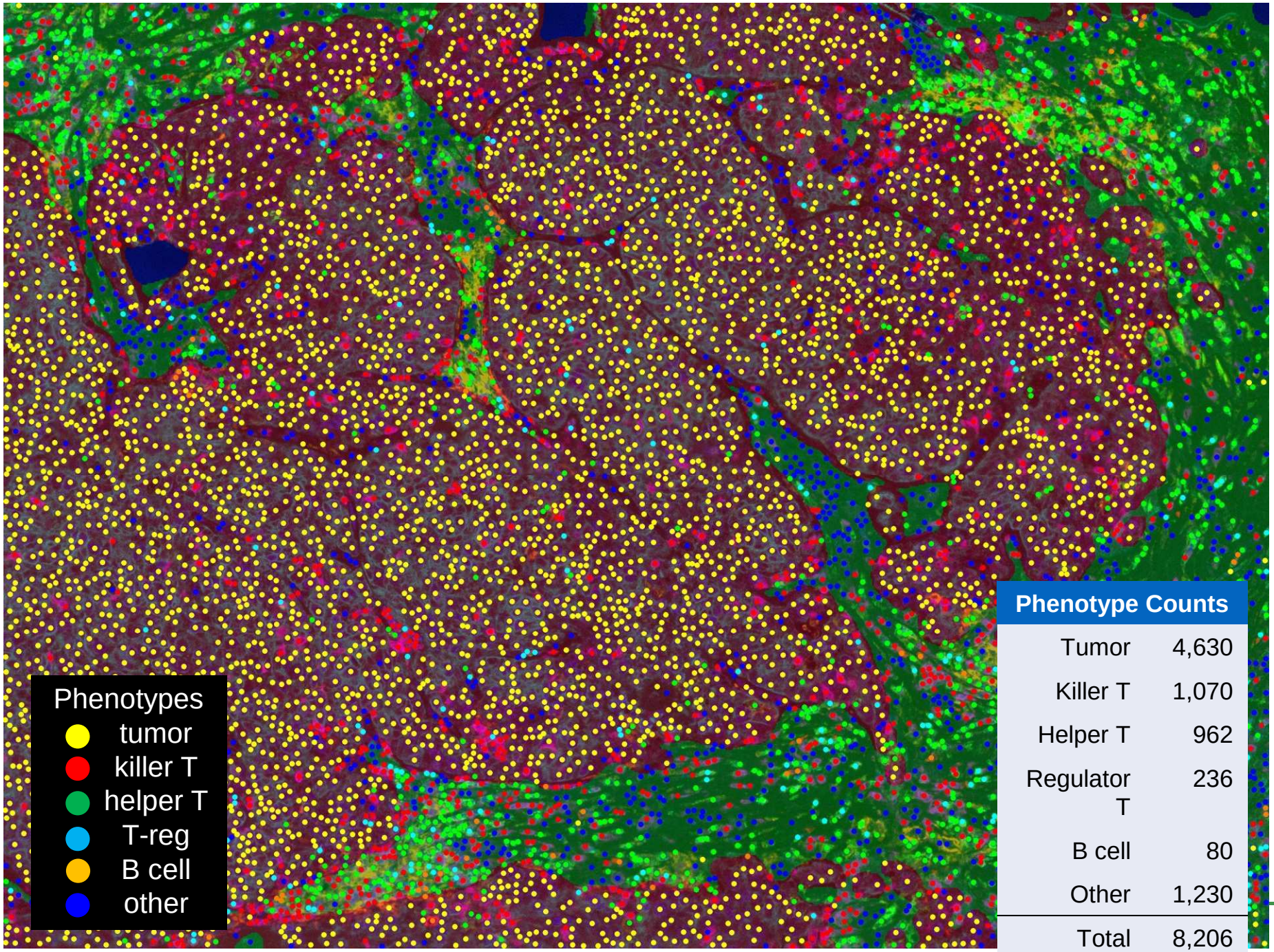
Case #3 – with tumor / stroma map and cell phenotypes



Phenotype Counts	
Tumor	4,630
Killer T	1,070
Helper T	962
Regulator T	236
B cell	80
Other	1,230
Total	8,206

Question:

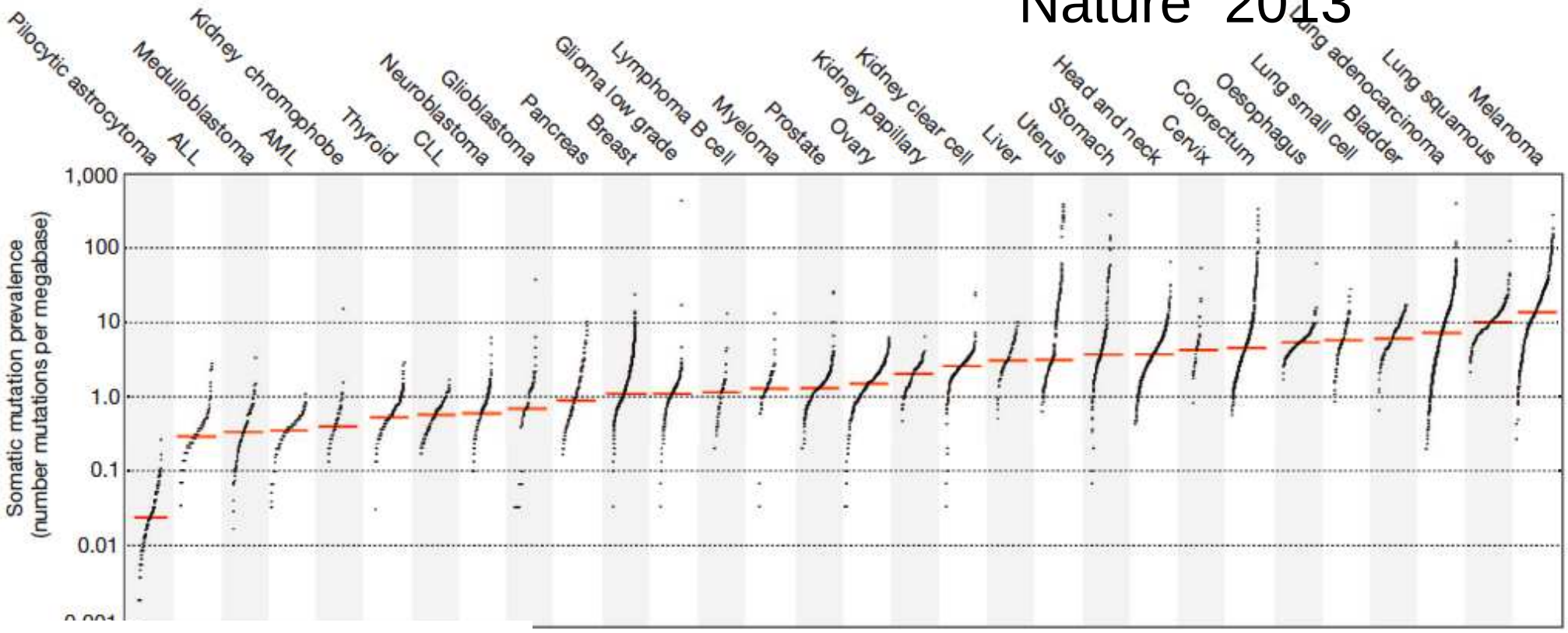
Why are patients immunoscore positive?

ARTICLE

doi:10.1038/nature12477

Signatures of mutational processes in human cancer

Alexandrov L et al.
Nature 2013



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ARTICLE

doi:10.1038/nature12477

Signatures of mutational processes in human cancer

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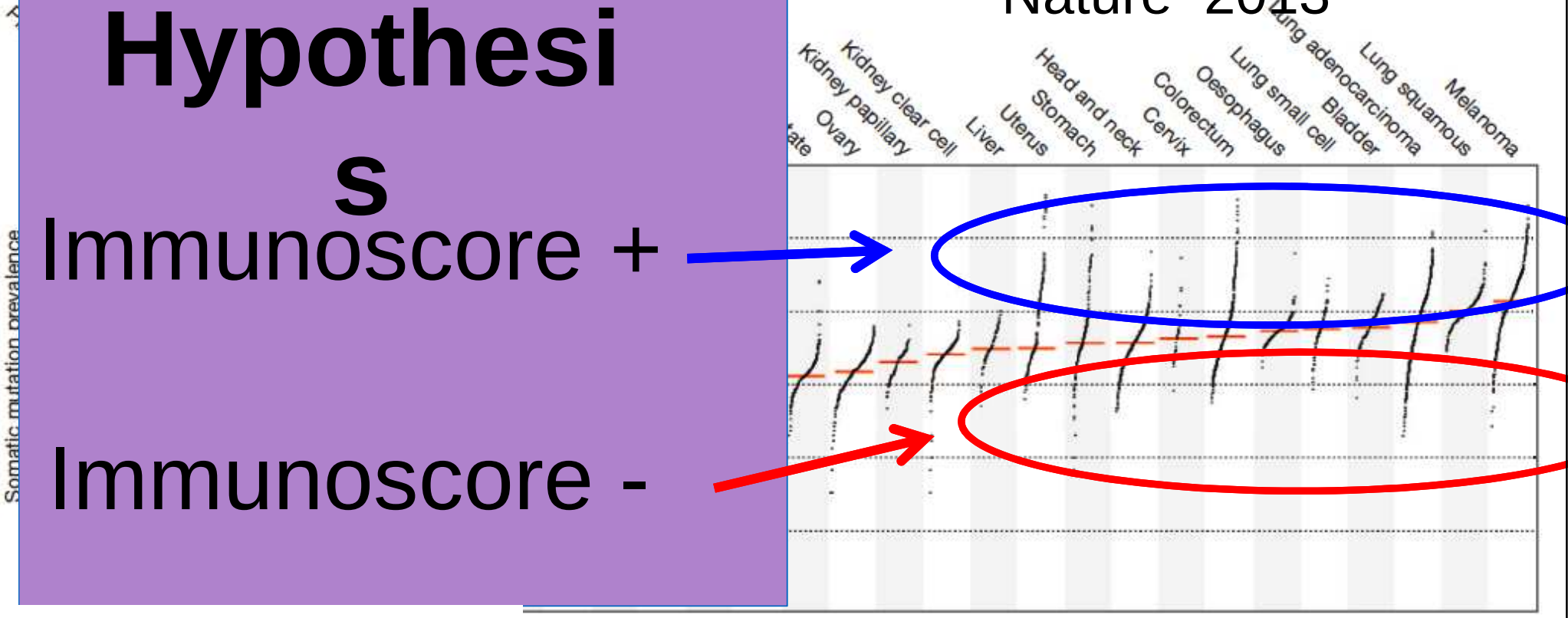
Hypothesis

Immunoscore +

Immunoscore -



ARTICLE

doi:10.1038/nature12477

Signatures of mutational processes in human cancer

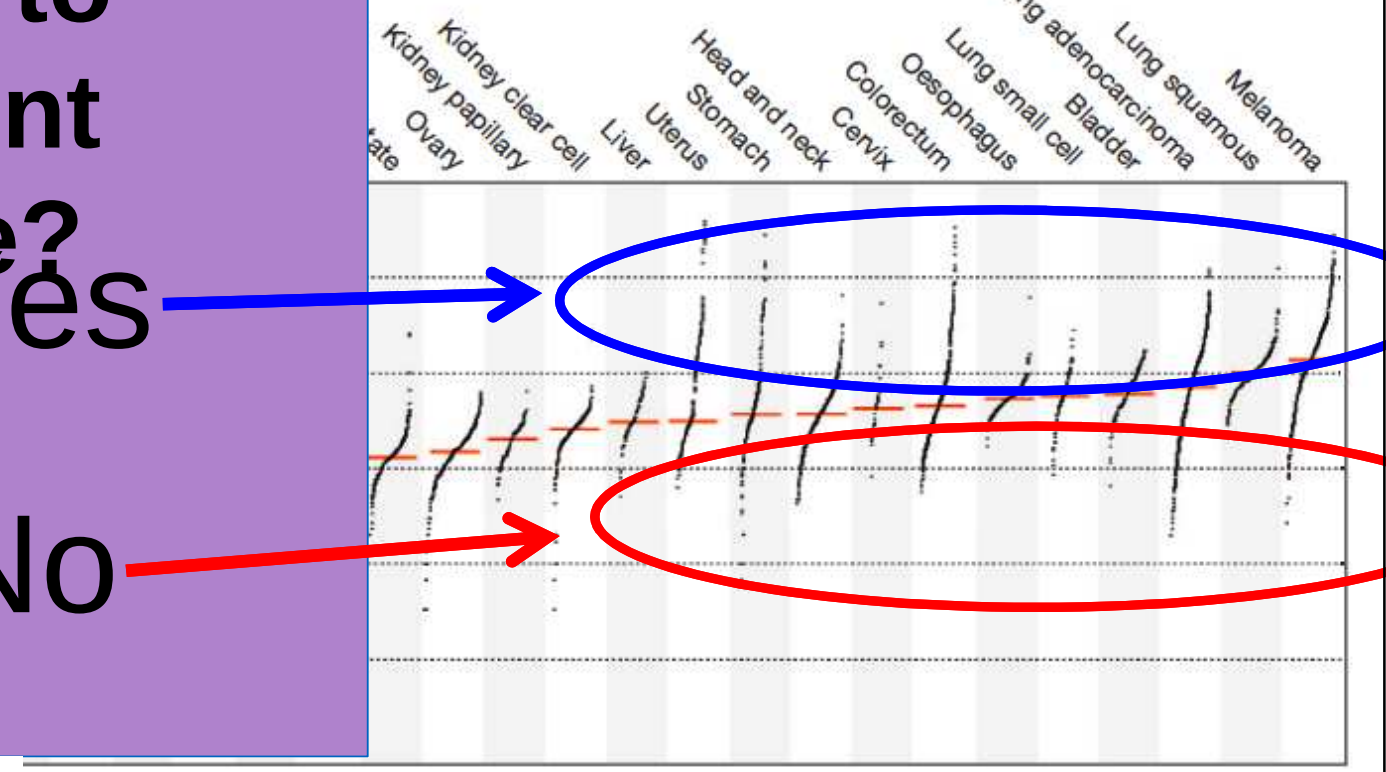
Alexandrov L et al.
Nature 2013

Respond to checkpoint blockade?

Yes

Hypothesis

No



Hypotheses:

1. Only patients with highly mutated tumors are immunoscore positive and contain tumor-specific T cells.

2. Only patients with pre-existing tumor-specific T cells will respond to checkpoint blockade.

What to do for patients who fail checkpoint blockade or are immunoscore negative?

- Combinations of standard anti-cancer therapies (Chemo / rad) – that may release non-mutated over-expressed antigens and help prime tumor-specific T cells.
- Combination immunotherapy with standard cancer vaccines.
- Next Generation vaccines that combine multiple/large numbers of epitopes with TLR agonists and adjuvants.
- Chimeric Antigen Receptor (CAR) T cells
  DARTs, Bi-Specifics

"Never, ever, think outside the box."

THE NEW YORKER

Science
AAAS

The Intestinal Microbiota Modulates the Anticancer Immune Effects of Cyclophosphamide

Sophie Viaud,[1,3] Fabiana Saccheri,[1] Grégoire Mignot,[4,5] Takahiro Yamazaki,[1] Romain Daillère,[1,3] Dalil Hannani,[1] David P. Enot,[7,8] Christina Pfirschke,[9] Camilla Engblom,[9] Mikael J. Pittet,[9] Andreas Schlitzer,[10] Florent Ginhoux,[10] Lionel Apetoh,[4,5] Elisabeth Chachaty,[11] Paul-Louis Woerther,[11] Gérard Eberl,[12] Marion Bérard,[13] Chantal Ecobichon,[14,15] Dominique Clermont,[16] Chantal Bizet,[16] Valérie Gaboriau-Routhiau,[17,18] Nadine Cerf-Bensussan,[17,18] Paule Opolon,[19,20] Nadia Yessaad,[21,22,23,24] Eric Vivier,[21,22,23,24] Bernhard Ryffel,[25] Charles O. Elson,[26] Joël Doré,[17,27] Guido Kroemer,[7,8,28,29,30] Patricia Lepage,[17,27] Ivo Gomperts Boneca,[14,15] François Ghiringhelli,[4,5,6]* Laurence Zitvogel[1,2,3]*†

Commensal Bacteria Control Cancer Response to Therapy by Modulating the Tumor Microenvironment

Noriho Iida,[1]* Amiran Dzutsev,[1,2]* C. Andrew Stewart,[1]* Loretta Smith,[1] Nicolas Bouladoux,[3] Rebecca A. Weingarten,[4] Daniel A. Molina,[5] Rosalba Salcedo,[1] Timothy Back,[1] Sarah Cramer,[1] Ren-Ming Dai,[1,2] Hiu Kiu,[1] Marco Cardone,[1] Shruti Naik,[3] Anil K. Patri,[6] Ena Wang,[7] Francesco M. Marincola,[7,8] Karen M. Frank,[4] Yasmine Belkaid,[3] Giorgio Trinchieri,[1]†‡ Romina S. Goldszmid[1]†‡

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SCIENCE VOL 342 22 NOVEMBER 2013

NEWS&ANALYSIS

SCIENCE VOL 342 22 NOVEMBER 2013

BIOMEDICINE

Cancer Therapies Use a Little Help From Microbial Friends

Nature Reviews Immunology

VOLUME 14 | JANUARY 2014

COMMUNITY CORNER

VOLUME 20 | NUMBER 2 | FEBRUARY 2014 NATURE MEDICINE

Chemotherapy, immunity and microbiota—a new triumvirate?

Questions for the next 5 years:

1) What drives different anti-cancer immune responses in patients that appear otherwise similar for disease stage, age, gender?

    - Tumor landscape (bad actors)?
    - Mutatanome?
    - Microbiome?
    - Other?

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Summary :

1) **Paradigm shift in Oncology**
   - **T cells can cure people**

2) **Identification of good/bad risk factors /**
   - **Immunoprofiling**
   - **tailoring treatment / combinations**

3) **The next five years – How to get to 100%**
   "Thinking outside the box"
   - **3Ms:**
     Multiple / Mutanome / Microbiome

SITC Immunoscore Taskforce

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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]

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