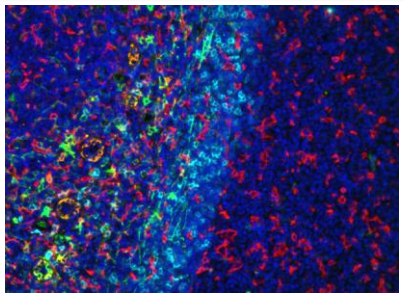
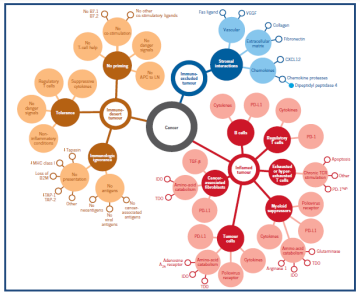
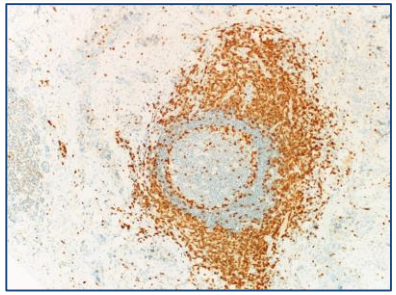
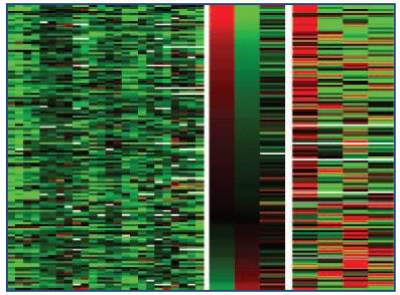
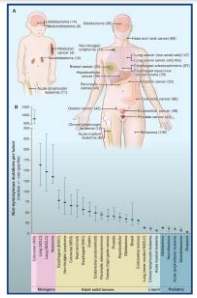
5th Masterclass OF SARCOMA AND RARE CANCERS

DECEMBER 9-10 2022 Acropolis museum venue *"Dimitrios Pantermalis"* ATHENS

16.15-17.30 **Session 5: Immunotherapy in sarcomas**

Moderators: **J-M. Broto, R. Jones**

16.15-16.35	Tissue microenvironment and immunotherapy in sarcomas	**P. Foukas**
16.35-16.55	Immunotherapy for patients with sarcoma: pathological or biological driven choice	**A. Italiano**
16.55-17.15	Perspectives in Cell Therapy and Immunotherapy of sarcomas	**G. Demetri**
17.15-17.30	Discussion	

Periklis G. FOUKAS
2nd Department of Pathology,
Attikon University Hospital,
National and Kapodistrian University of Athens,
Athens, Greece

LUDWIG CANCER RESEARCH

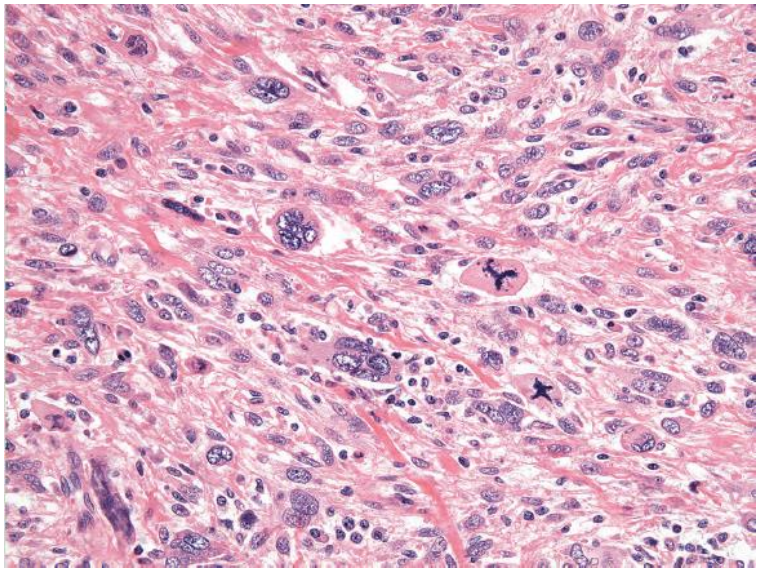
UNIL | Université de Lausanne

CHUV

No conflict of interest to declare

Outline

- Tumor Immune Microenvironment (TIME)
- Tumor infiltrating lymphocytes landscape
    - T cells
    - B cells
- Turning-up the heat



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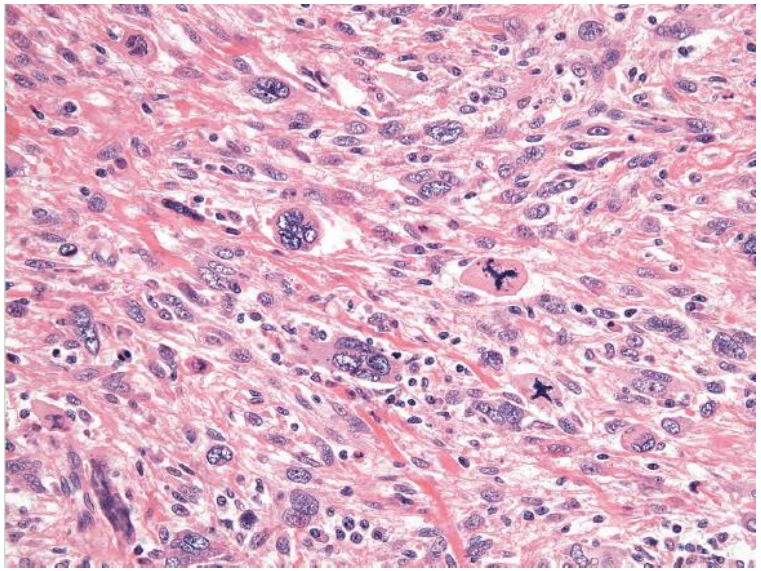
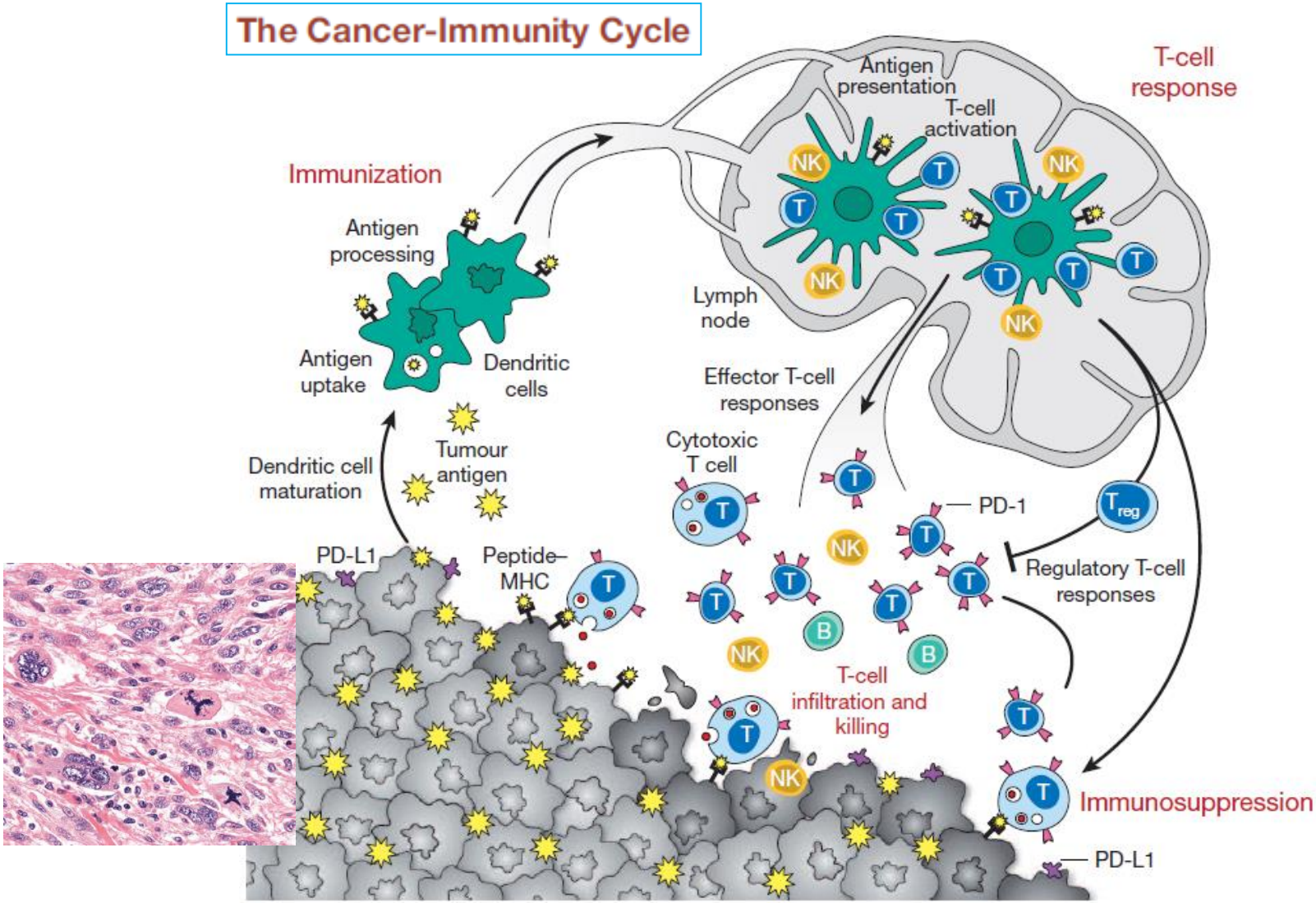


Cancer immunotherapy comes of age

Ira Mellman[1], George Coukos[2] & Glenn Dranoff[3]



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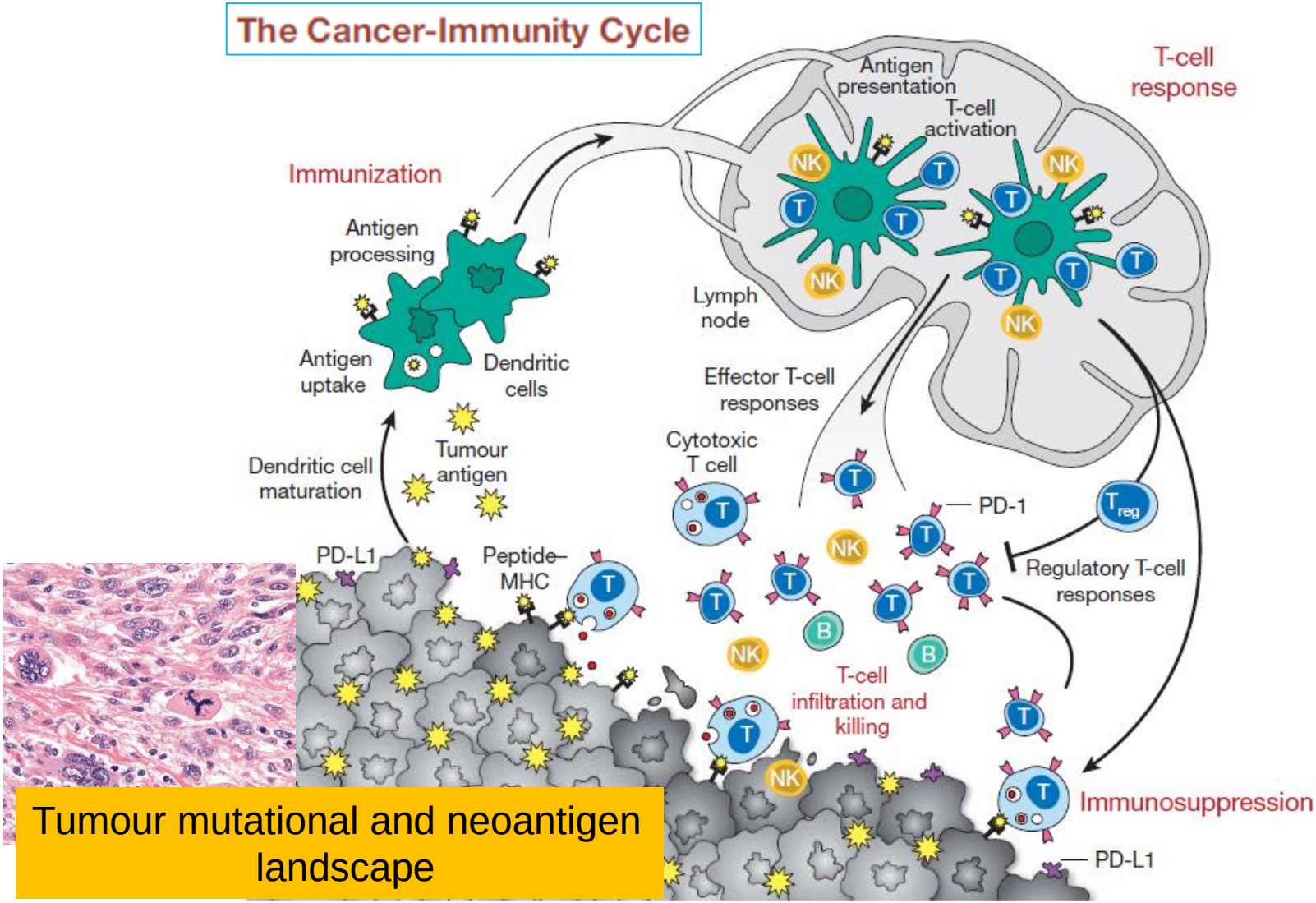

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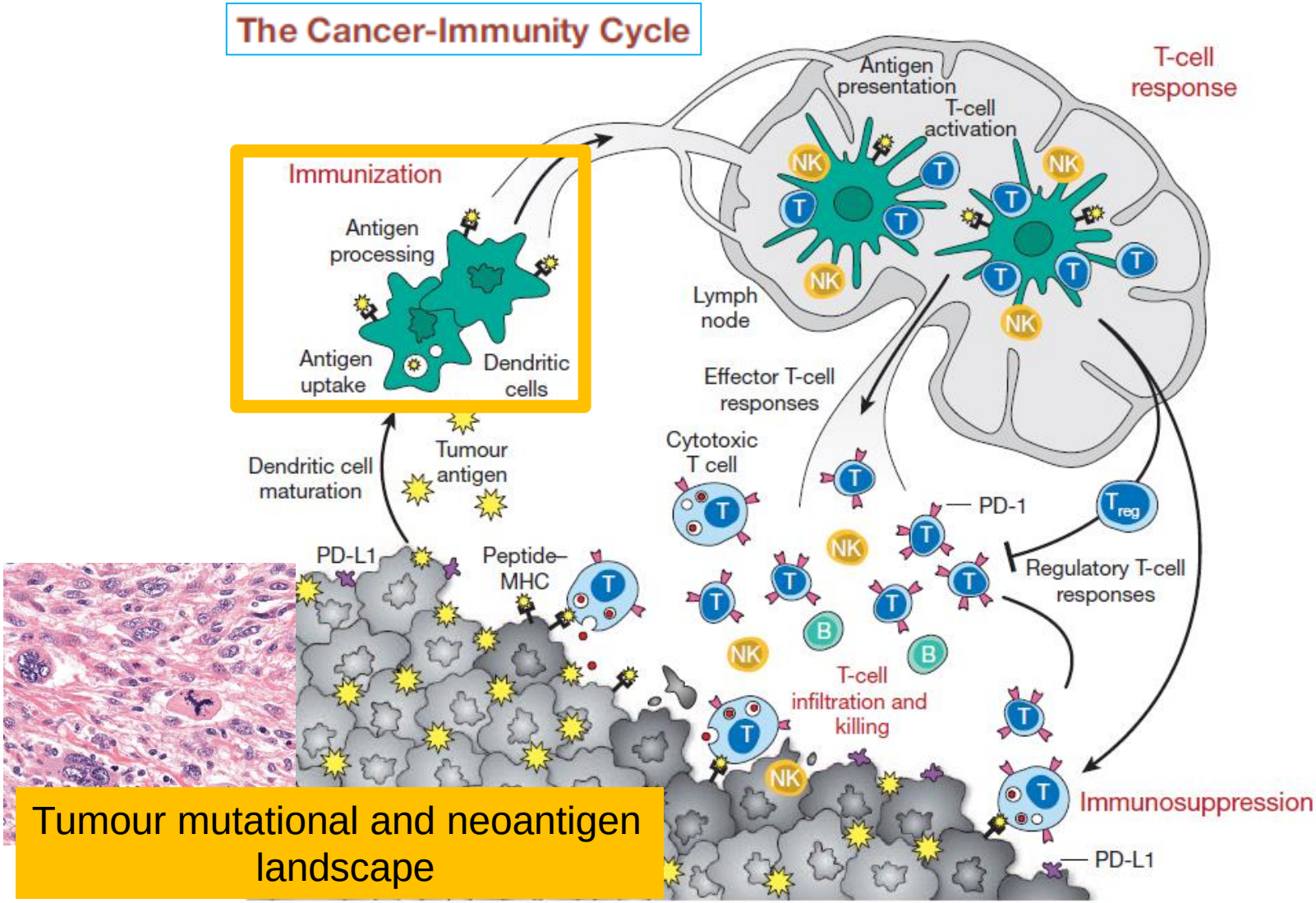

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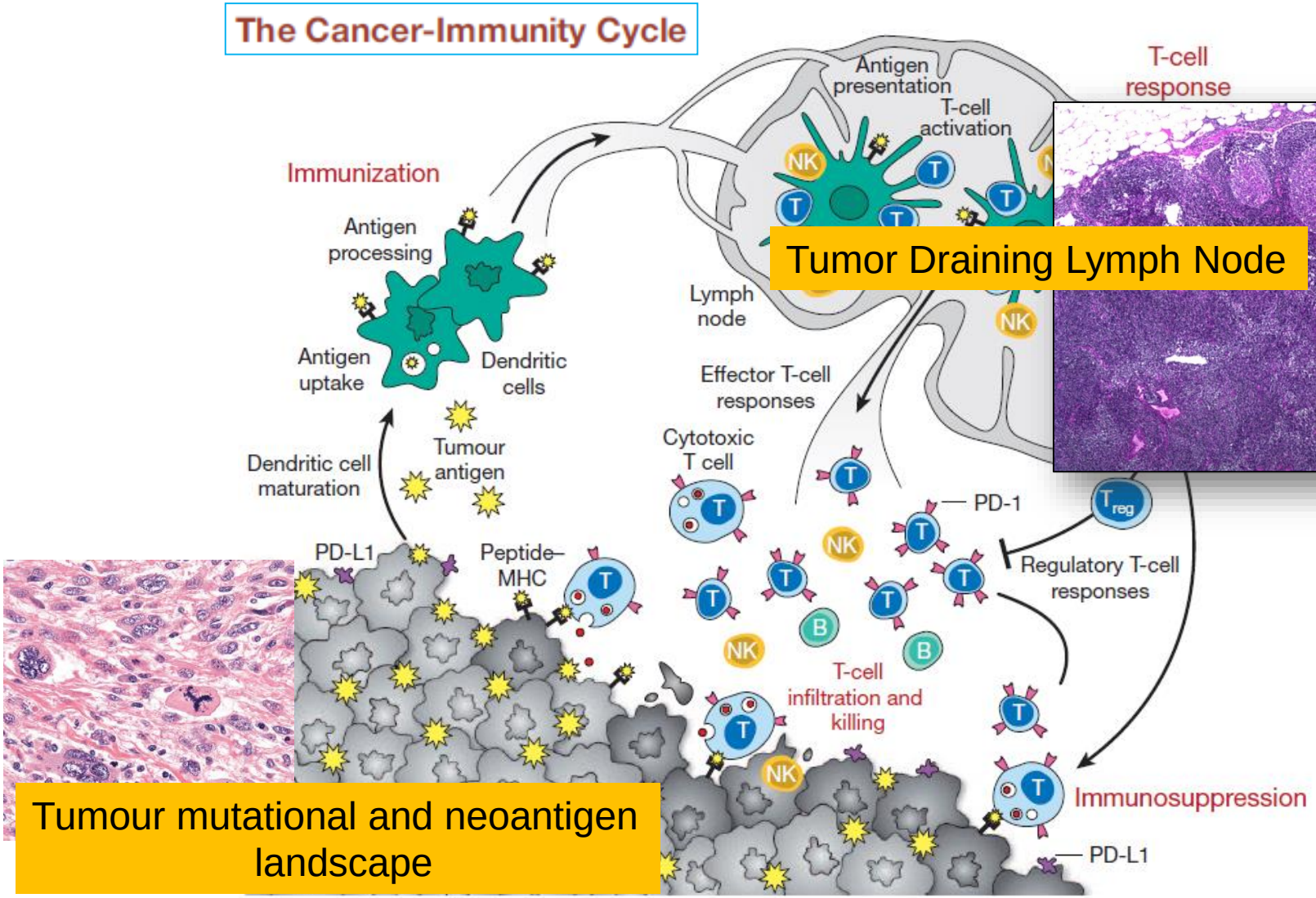

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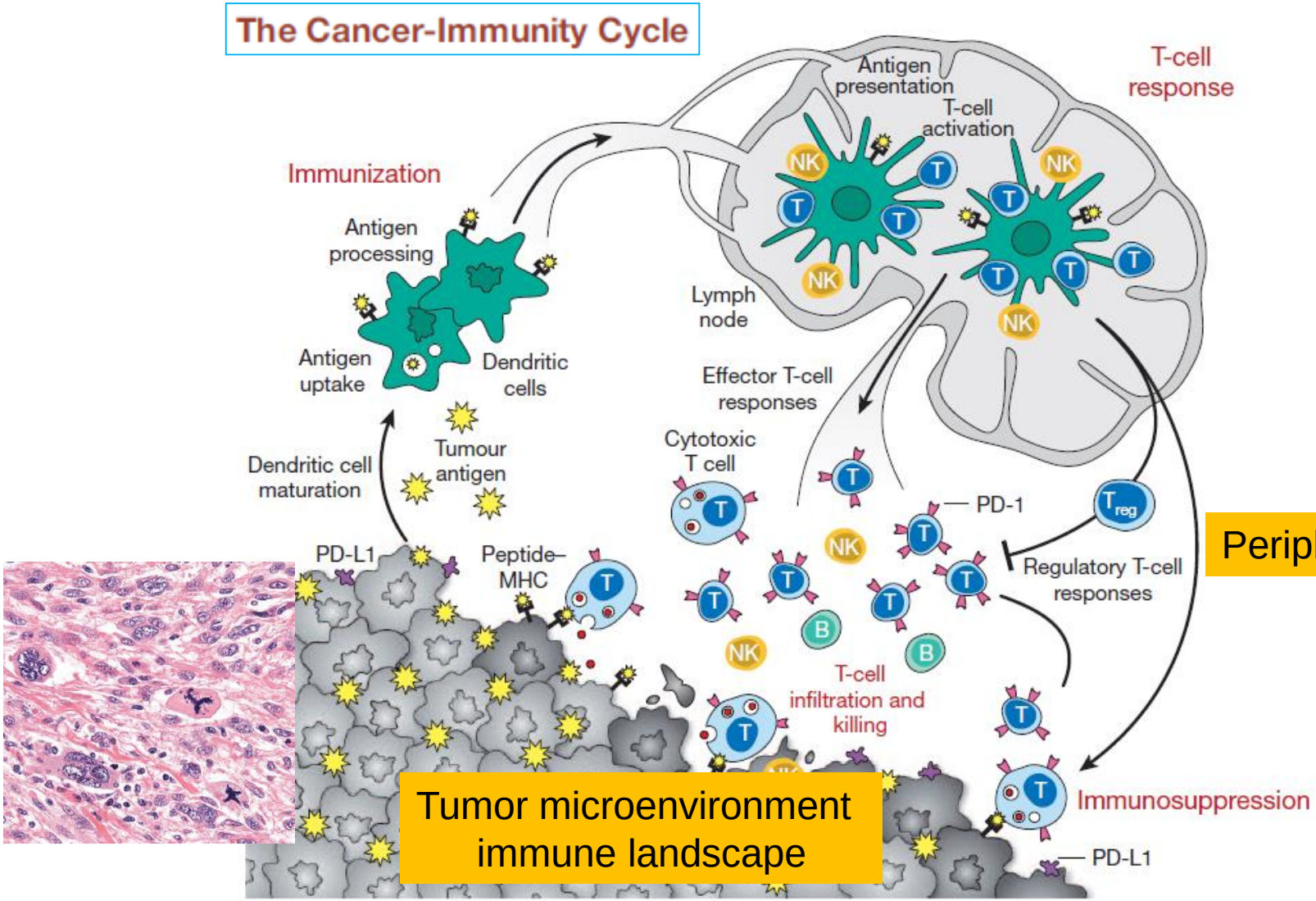

REVIEW Open Access

Novel technologies and emerging biomarkers for personalized cancer immunotherapy

Jianda Yuan[1*], Priti S. Hegde[2], Raphael Clynes[3], Periklis G. Foukas[4,5], Alexandre Harari[4], Thomas O. Kleen[6], Pia Kvistborg[7], Cristina Maccalli[8], Holden T. Maecker[9], David B. Page[10], Harlan Robins[11], Wenru Song[12], Edward C. Stack[13], Ena Wang[14], Theresa L. Whiteside[15], Yingdong Zhao[16], Heinz Zwierzina[17], Lisa H. Butterfield[18] and Bernard A. Fox[10*]

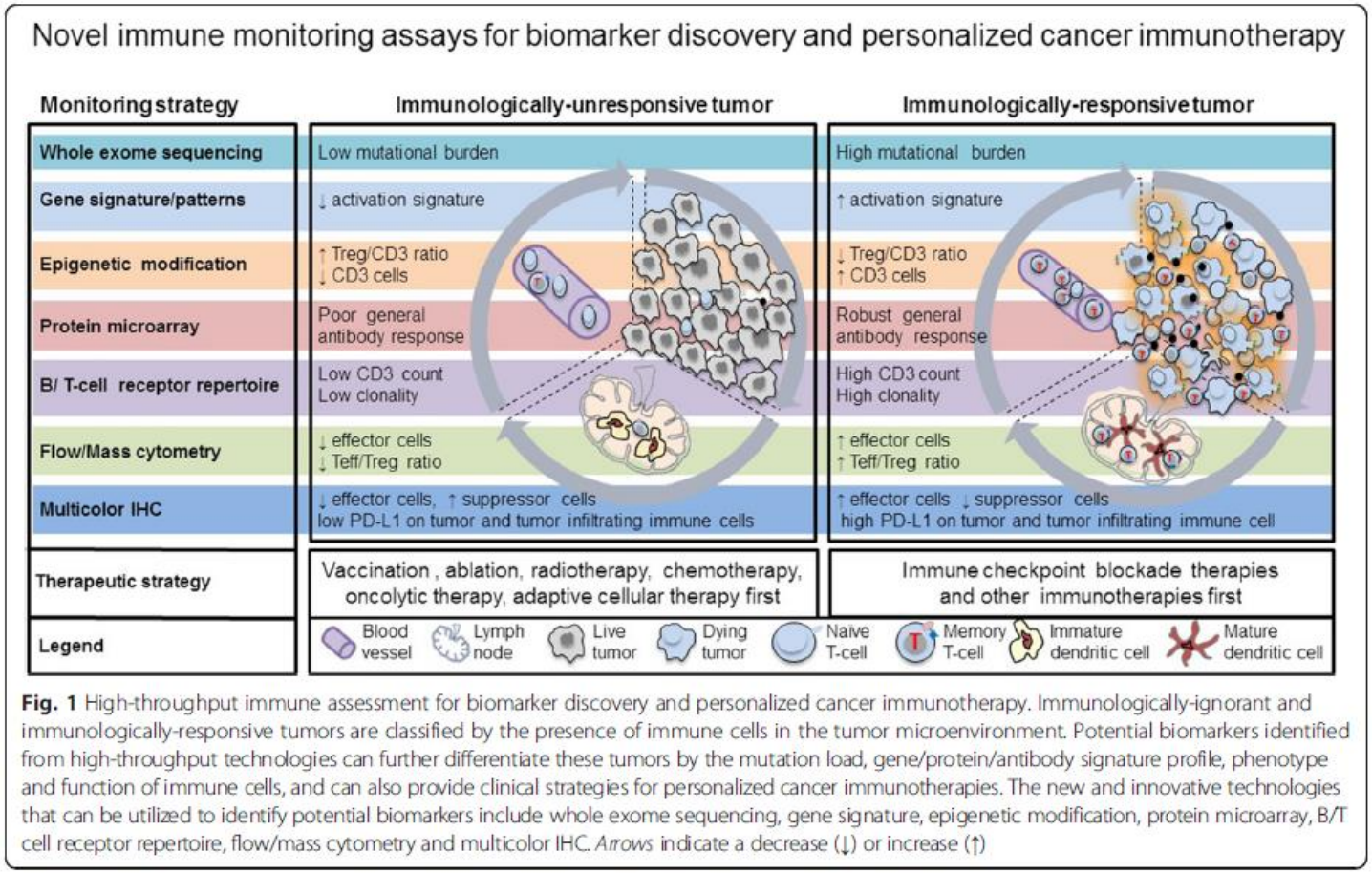

Fig. 1 High-throughput immune assessment for biomarker discovery and personalized cancer immunotherapy. Immunologically-ignorant and immunologically-responsive tumors are classified by the presence of immune cells in the tumor microenvironment. Potential biomarkers identified from high-throughput technologies can further differentiate these tumors by the mutation load, gene/protein/antibody signature profile, phenotype and function of immune cells, and can also provide clinical strategies for personalized cancer immunotherapies. The new and innovative technologies that can be utilized to identify potential biomarkers include whole exome sequencing, gene signature, epigenetic modification, protein microarray, B/T cell receptor repertoire, flow/mass cytometry and multicolor IHC. *Arrows* indicate a decrease (↓) or increase (↑)

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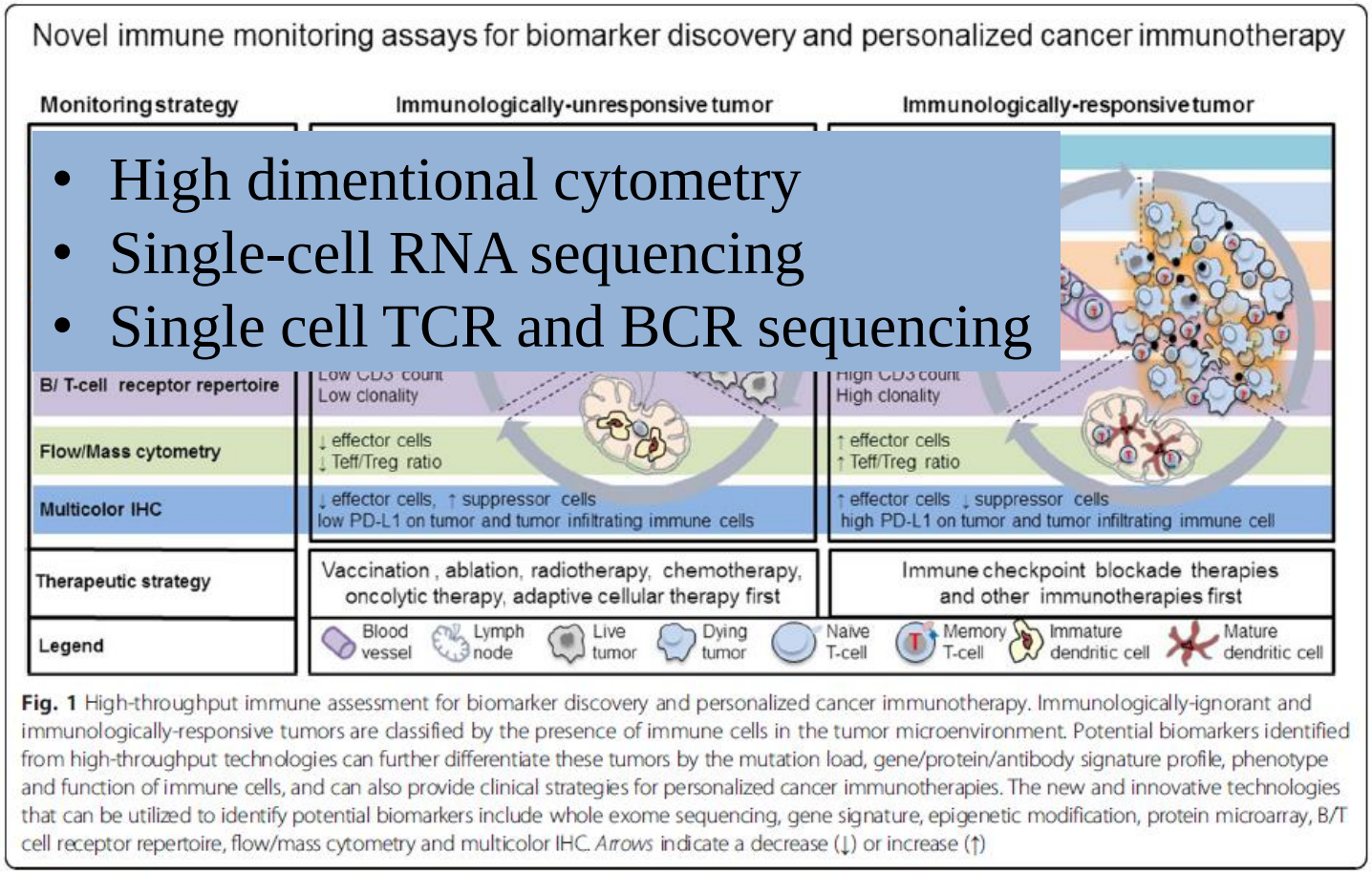

- High dimentional cytometry
- Single-cell RNA sequencing
- Single cell TCR and BCR sequencing

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Elements of cancer immunity and the cancer–immune set point

Daniel S. Chen[1] & Ira Mellman[1]

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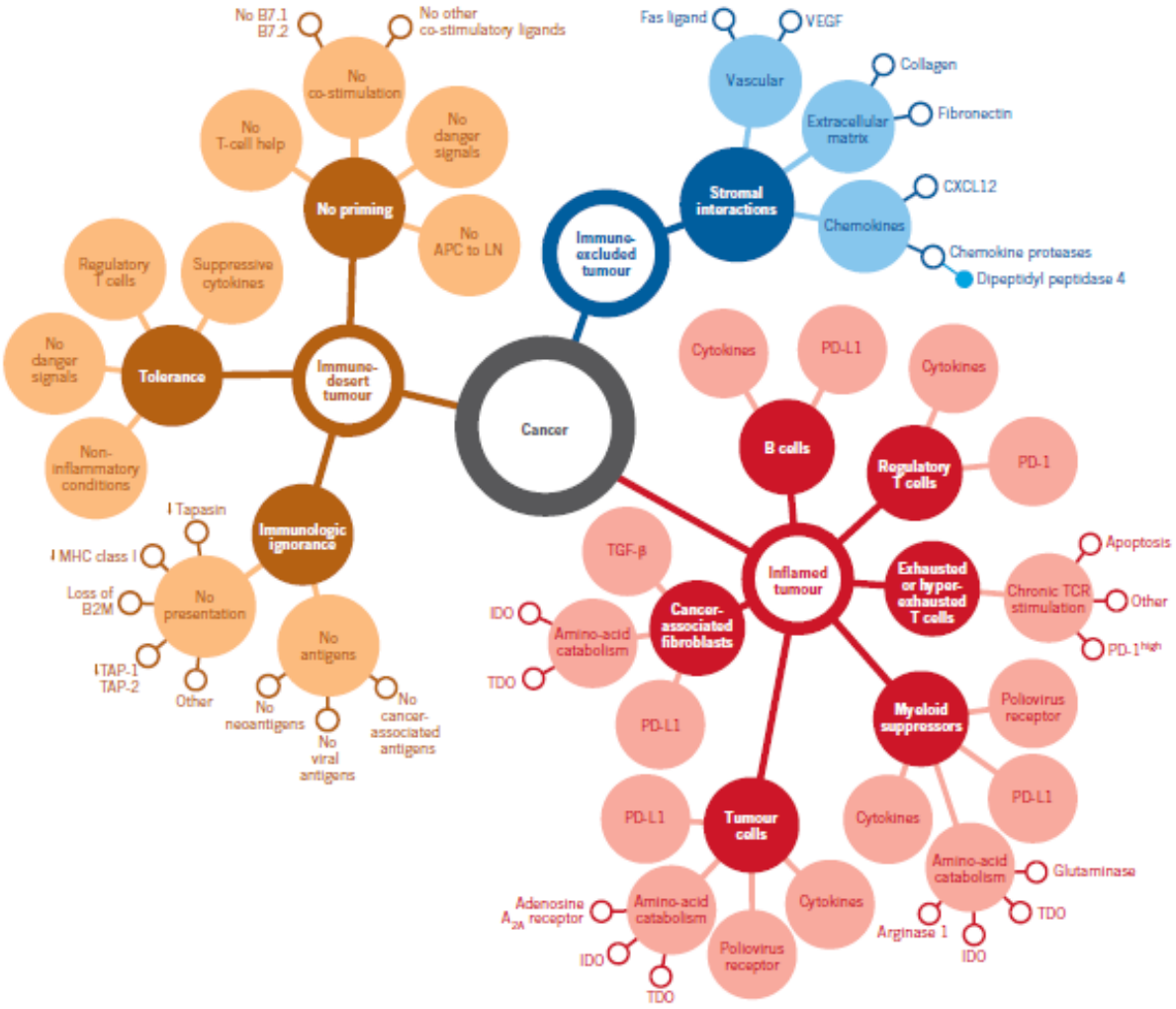

Figure 3 | Cancer-immune phenotypes. Anticancer immunity in humans can be segregated into three main phenotypes: the immune-desert phenotype (brown), the immune–excluded phenotype (blue) and the inflamed phenotype (red). Each is associated with specific underlying biological mechanisms that may prevent the host's immune response from eradicating the cancer. A tumour that is characterized as an immune desert can be the result of immunological ignorance, the induction of tolerance or a lack of appropriate T-cell priming or activation. Immune-excluded tumours may reflect a specific chemokine state, the presence of particular vascular factors or barriers, or specific stromal-based inhibition. Inflamed tumours can demonstrate infiltration by a number of subtypes of immune cells, including immune-inhibitory regulatory T cells, myeloid-derived suppressor cells, suppressor B cells and cancer-associated fibroblasts. Tumour-infiltrating lymphocytes that express CD8 may also demonstrate a dysfunctional state such as hyperexhaustion. Tumour cells in inflamed tumours can also express inhibitory factors, downregulating MHC class I molecule expression or other pathways that de-sensitize them to anticancer immunity. APC, antigen-presenting cell; B2M, β-2-microglobulin; IDO, indoleamine 2,3-dioxygenase; LN, lymph node; TAP, transporter associated with antigen processing; TDO, tryptophan 2,3-dioxygenase; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

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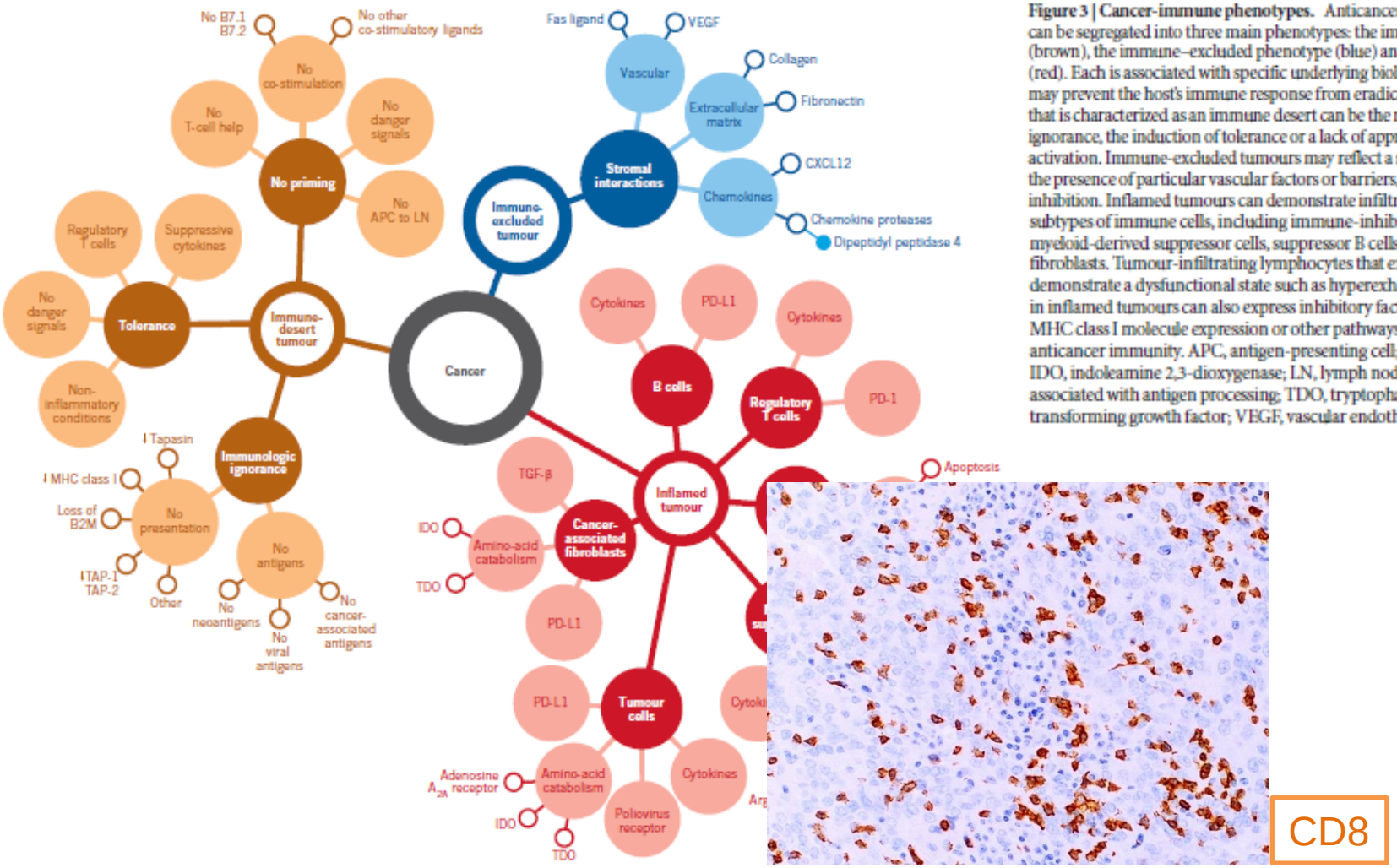

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CD8

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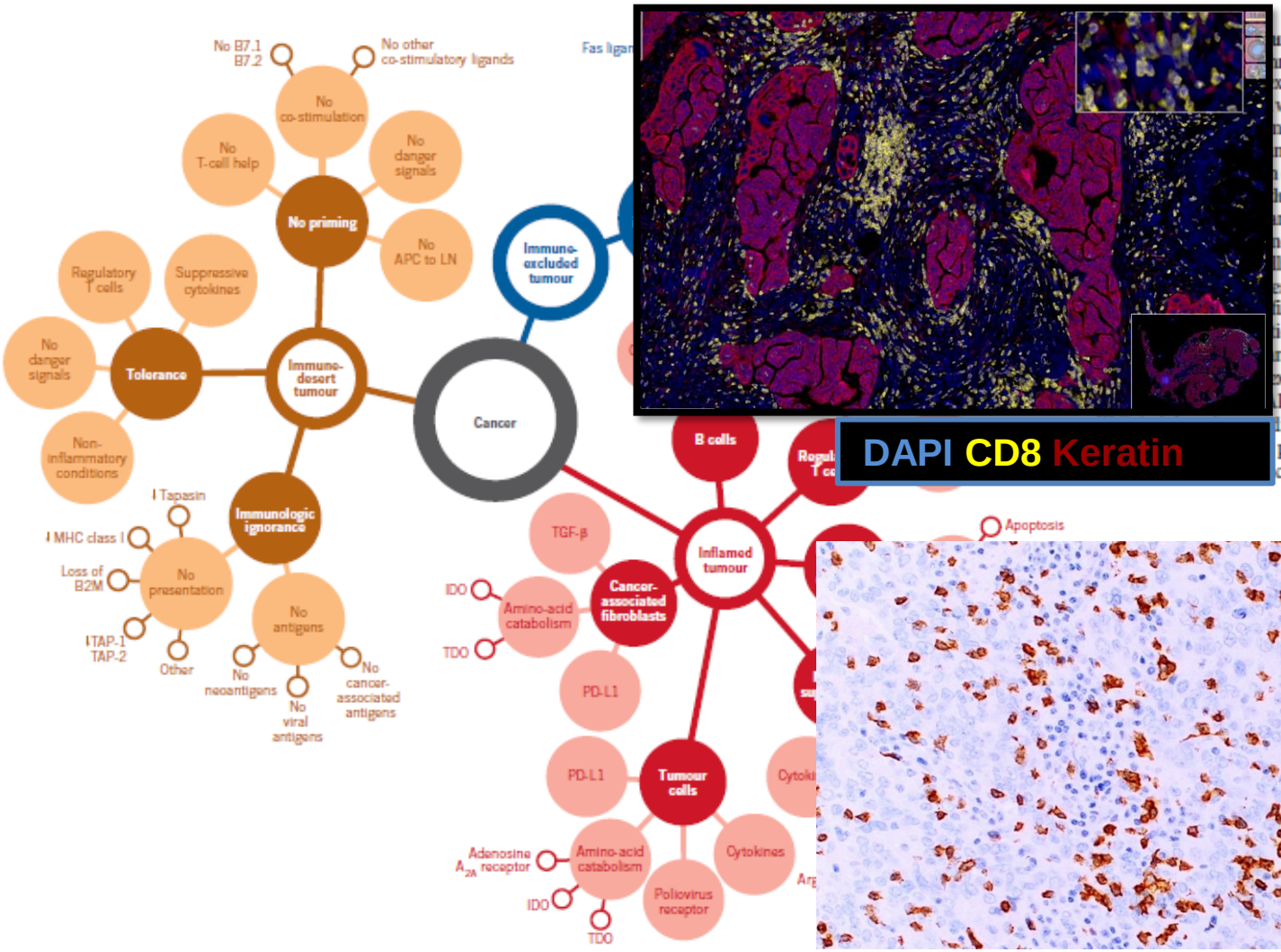

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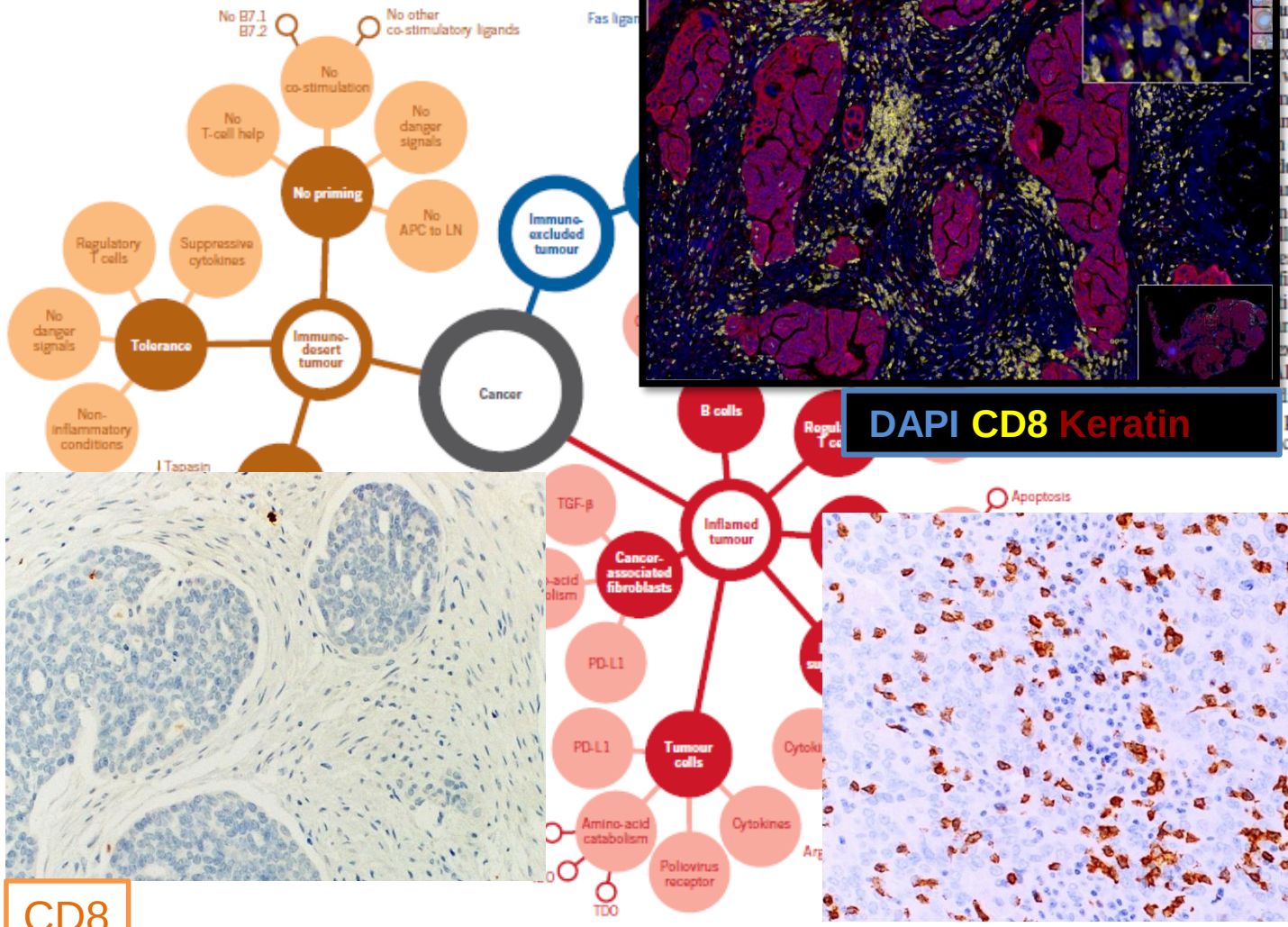

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Turning up the heat on non-immunoreactive tumours: opportunities for clinical development

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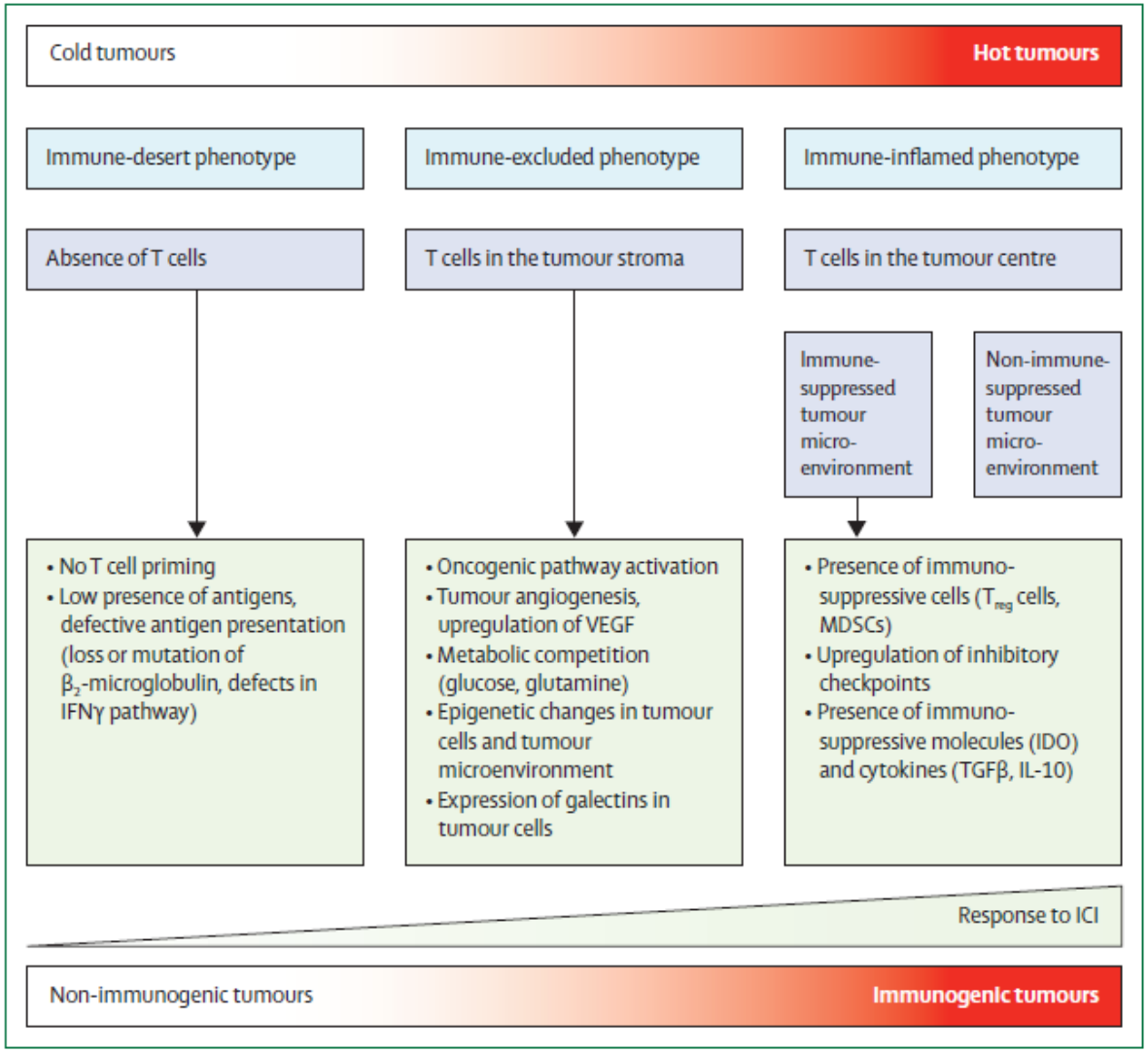

Figure 1: **Immune phenotypes and their underlying mechanisms**

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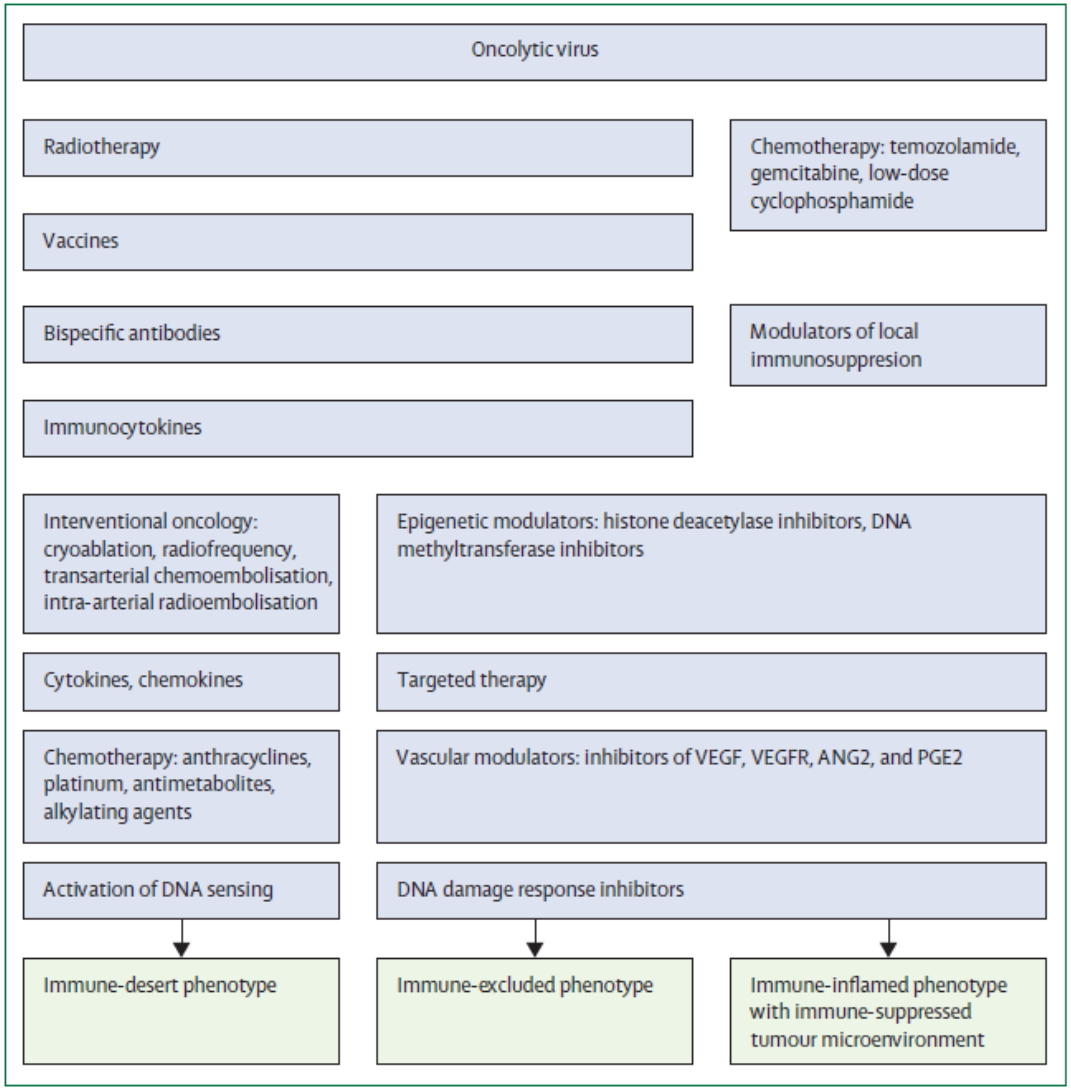
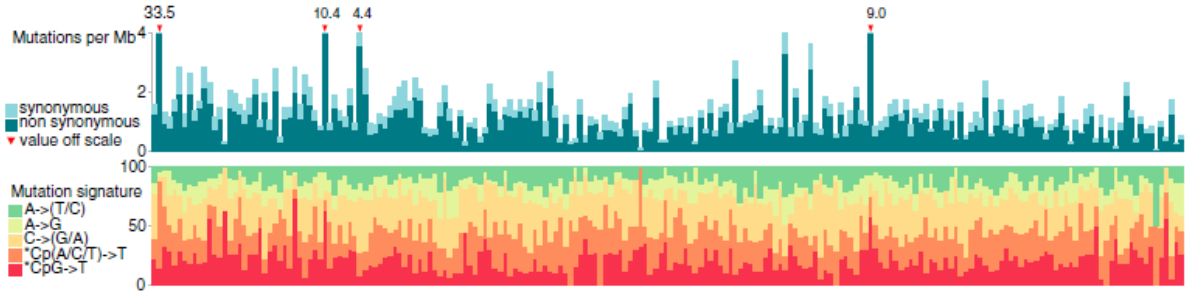


Figure 2: **Proposal of therapeutic strategies according to immune phenotype**
ANG2=angiopoietin 2. PGE2=prostaglandin E_2. VEGFR=VEGF receptor.

Comprehensive and Integrated Genomic Characterization of Adult Soft Tissue Sarcomas

The Cancer Genome Atlas Research Network[1,2,*]
[1]Cancer Genome Atlas Program Office, National Cancer Institute at NIH, 31 Center Drive, Bldg. 31, Suite 3A20, Bethesda, MD 20892, USA
[2]Lead Contact (Alexander J. Lazar)
*Correspondence: elizabeth.demicco@sinaihealthsystem.ca (Elizabeth G. Demicco), lding@wustl.edu (Li Ding), ladanyim@mskcc.org (Marc Ladanyi), alazar@mdanderson.org (Alexander J. Lazar), singers@mskcc.org (Samuel Singer)
https://doi.org/10.1016/j.cell.2017.10.014

Cell *171*, 950–965, November 2, 2017



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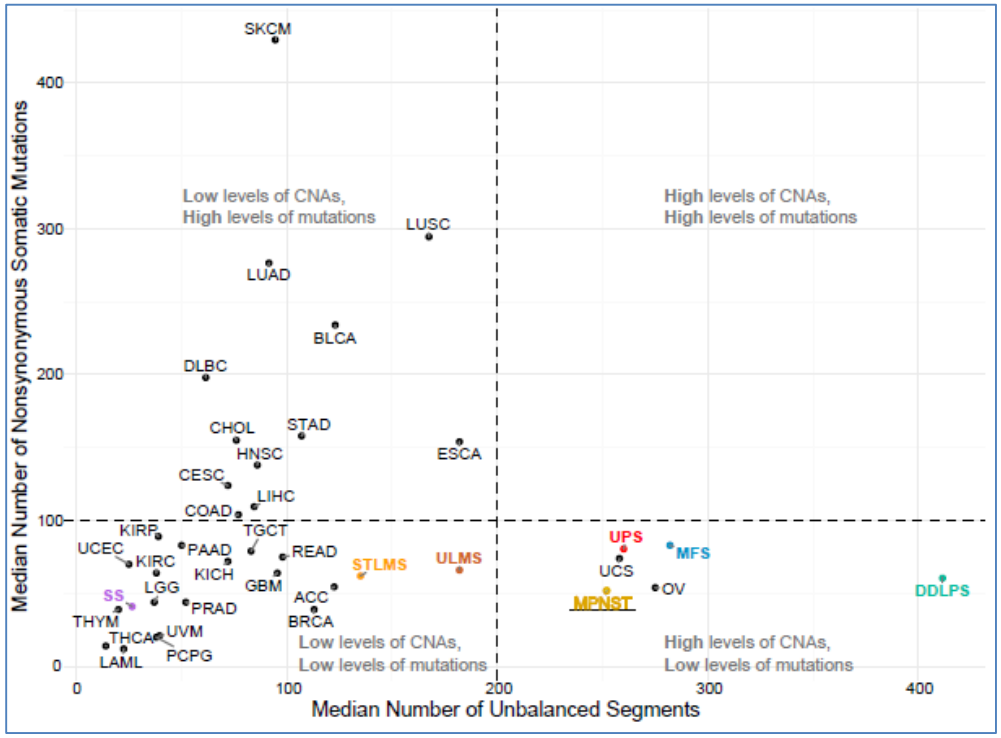

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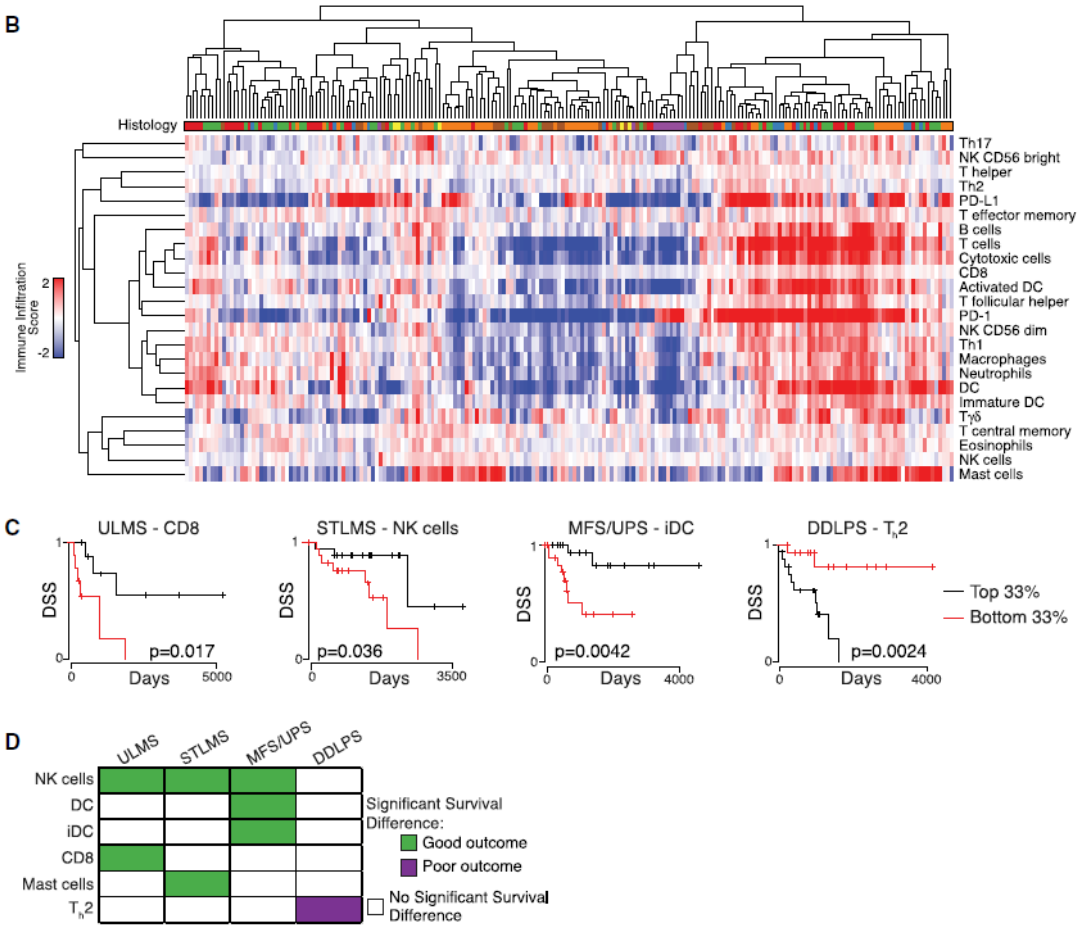

Figure 7. Specific Types of Immune Infiltration Show Associations with Survival Outcomes

(A) Clusters identified by unsupervised clustering of the 2,038 most variably expressed genes across 206 samples. Heatmap shows expression; the gray wedge marks 203 genes with immune-related and inflammatory-related GO terms. The bar graph (right) shows the Benjamini-Hochberg adjusted p values for enrichment for the specific ontologies listed, as defined by the DAVID algorithm.

(B) Unsupervised cluster analysis of tumors by calculated immune infiltration scores. The analysis defines a subset of DDLPS, LMS, MFS, and UPS with high immune infiltrates (right).

(C) Selected Kaplan-Meier curves for DSS by histology and immune class. The graphs show the patients in the top third versus bottom third for the immune scores indicated.

(D) Significant DSS associations ($p < 0.05$) for high immune score by histology.

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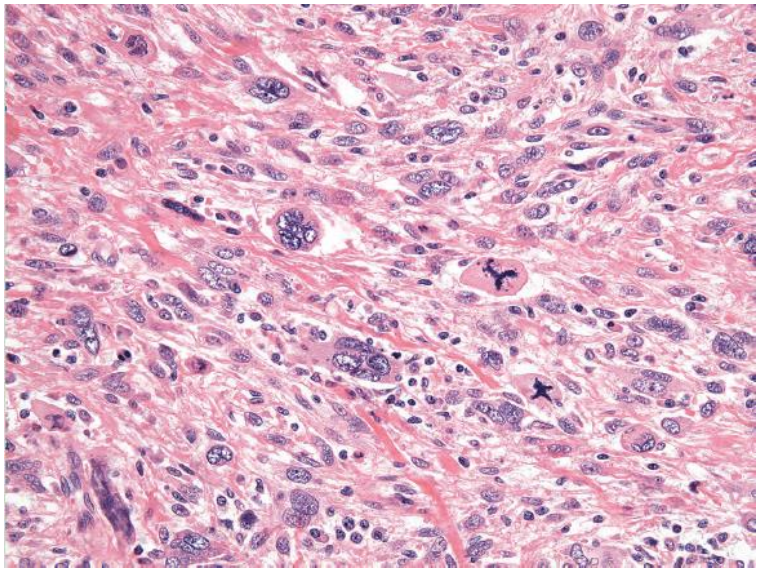

Tumor Immunology and Tumor Evolution: Intertwined Histories

Jérôme Galon[1,*] and Daniela Bruni[1]

Immunity *52*, January 14, 2020

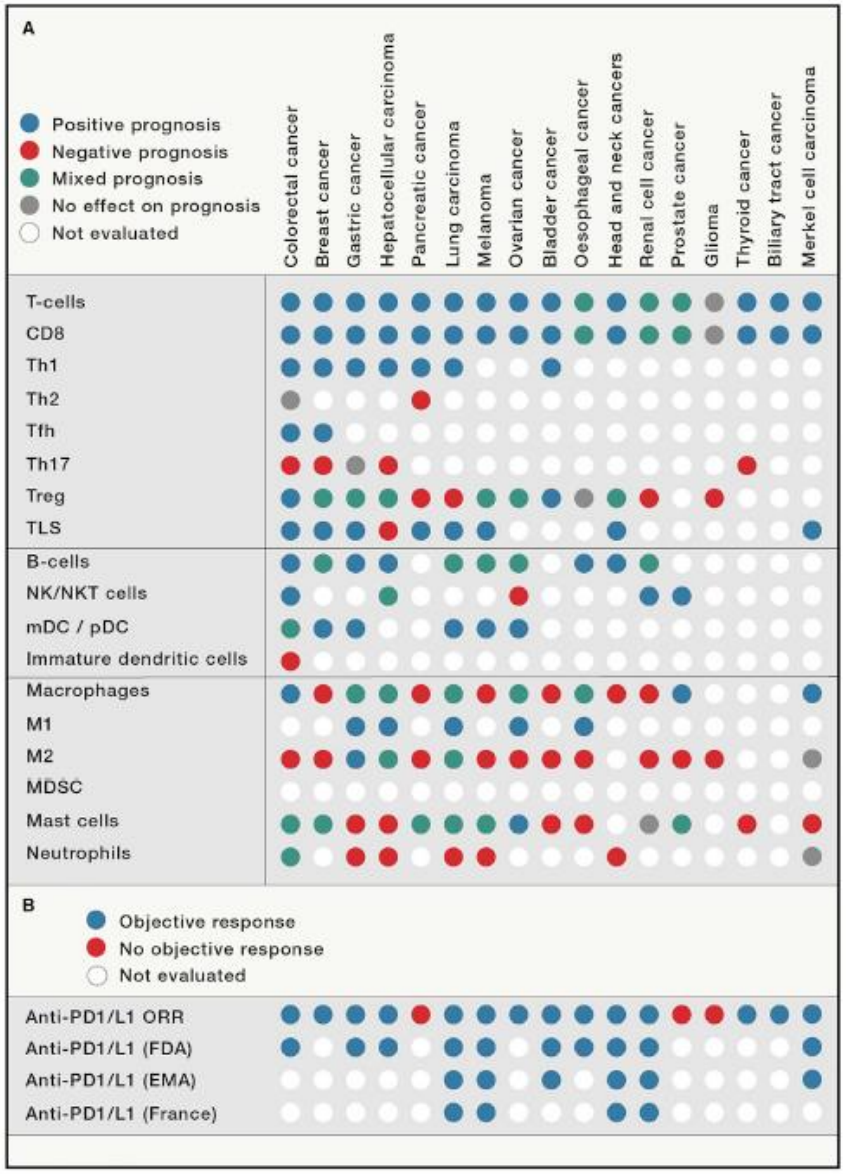

Figure 3. Prognostic Effect of Immune Cells in Solid Cancer

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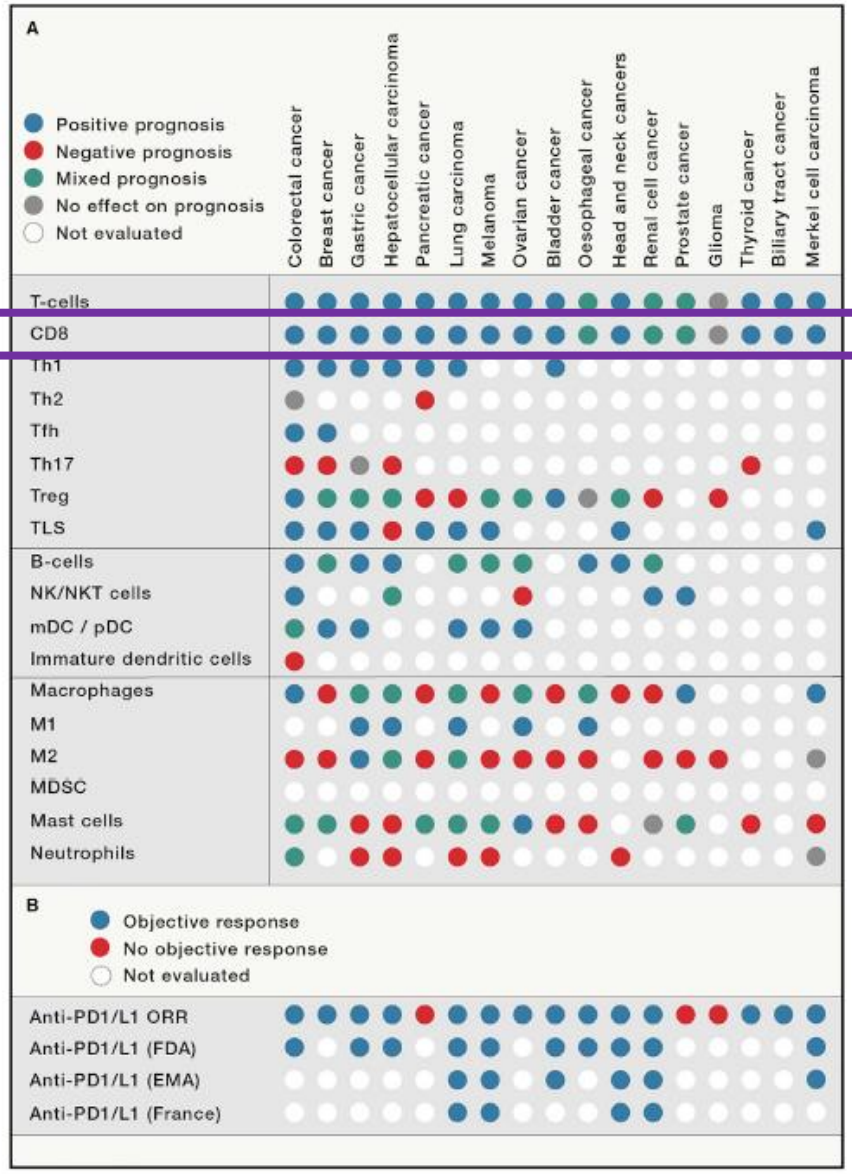
Immunity *52*, January 14, 2020



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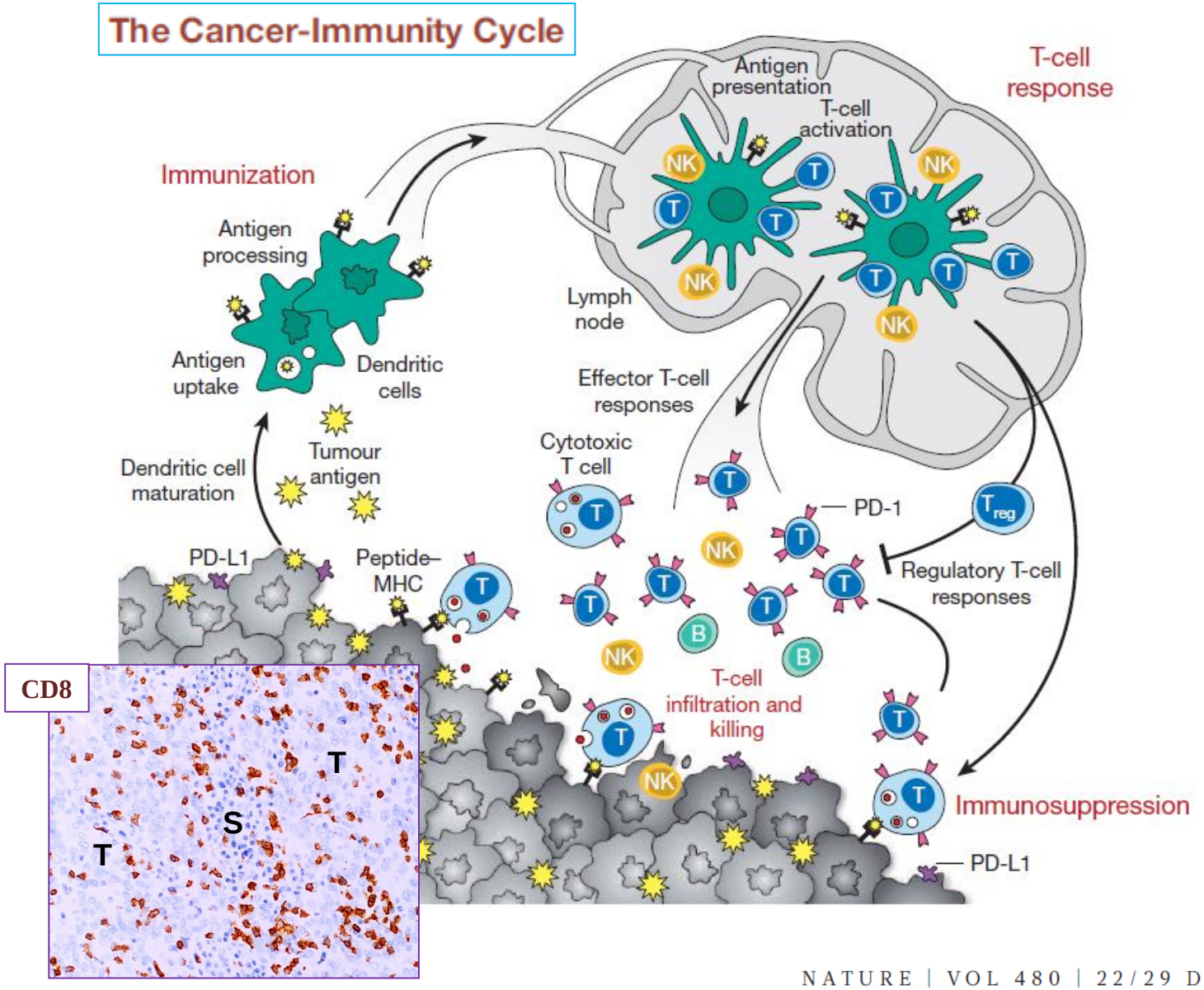

CD8+ T cell states in human cancer: insights from single-cell analysis

*Anne M. van der Leun, Daniela S. Thommen and Ton N. Schumacher **

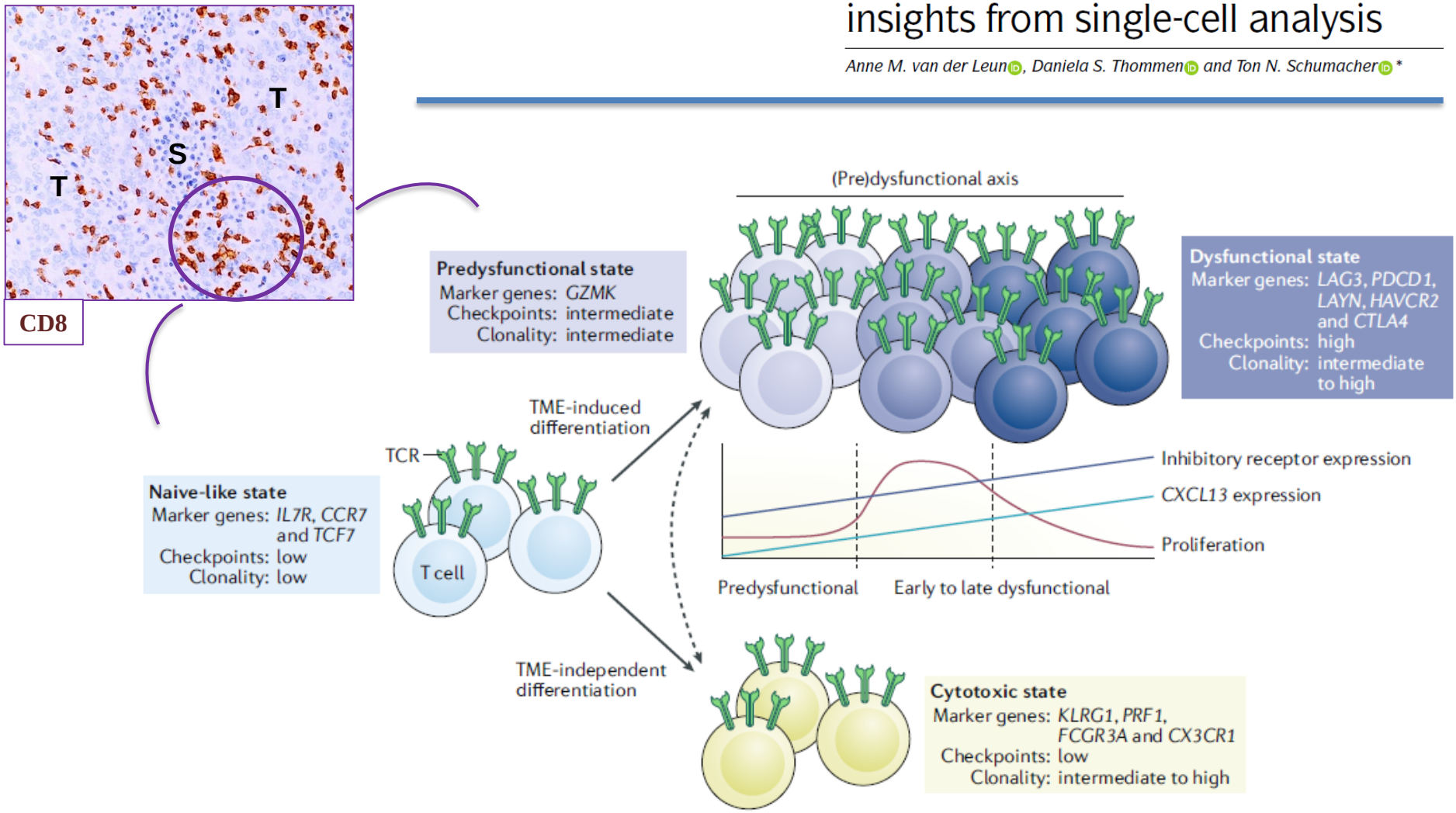

Fig. 1 | **Model of intratumoural CD8+ T cell states.**

CD8⁺ T cell states in human cancer: insights from single-cell analysis

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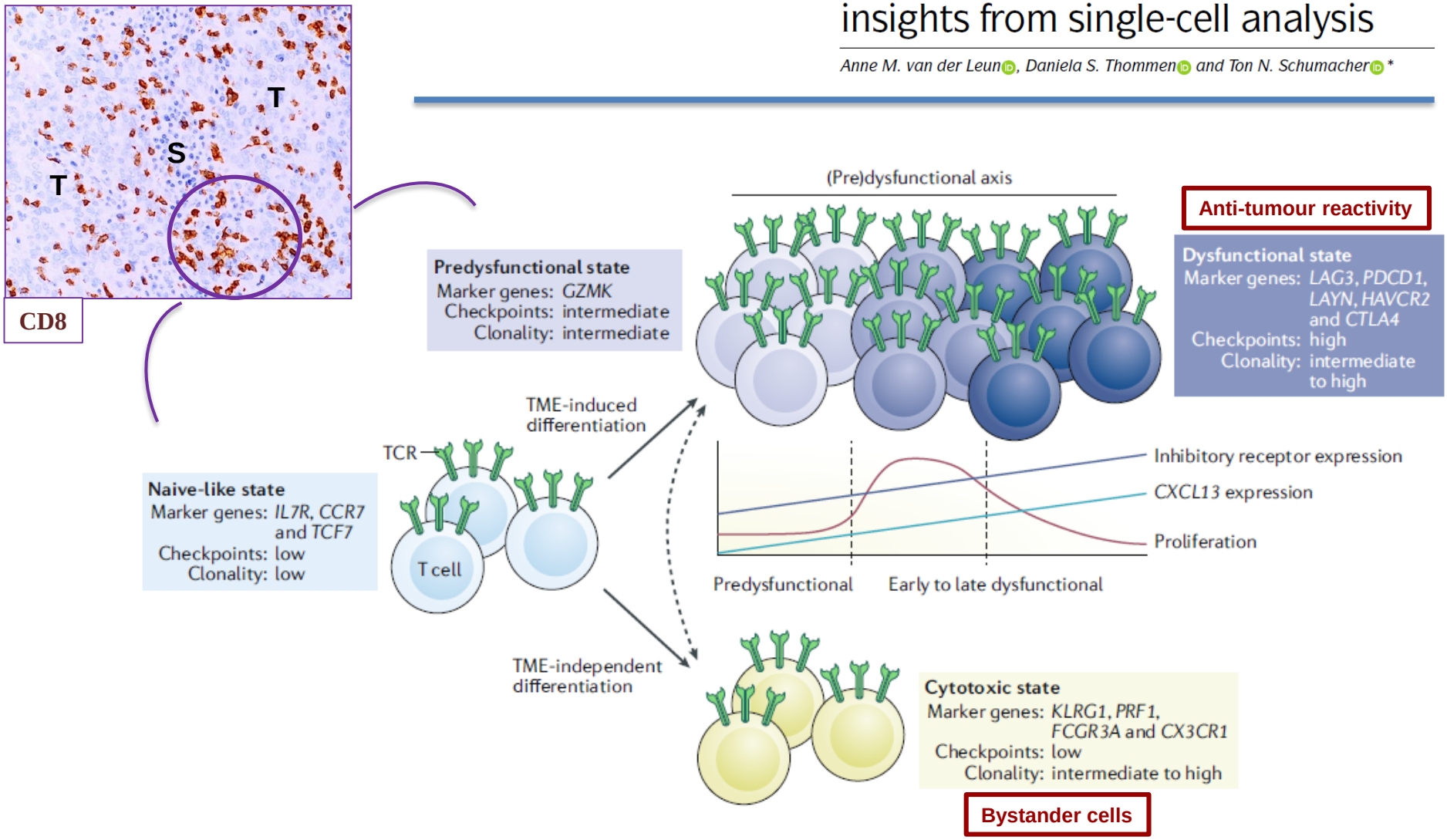

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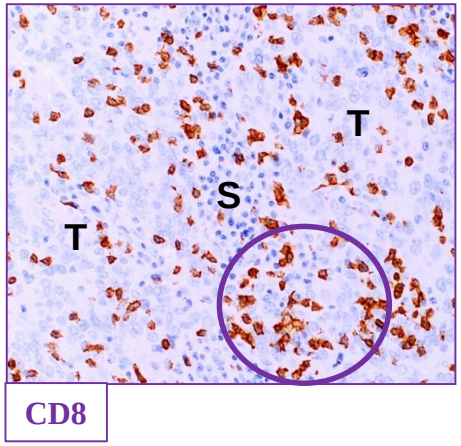


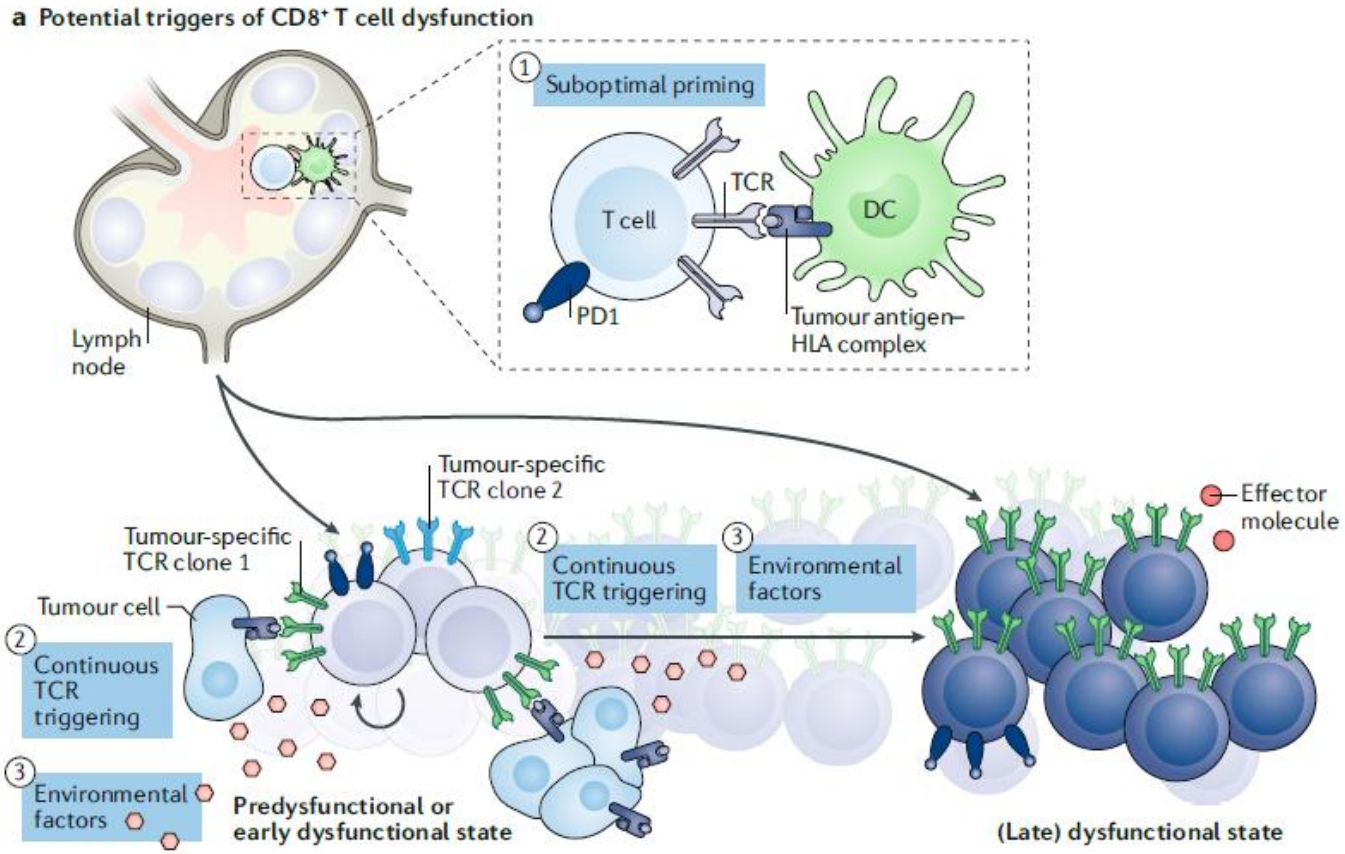
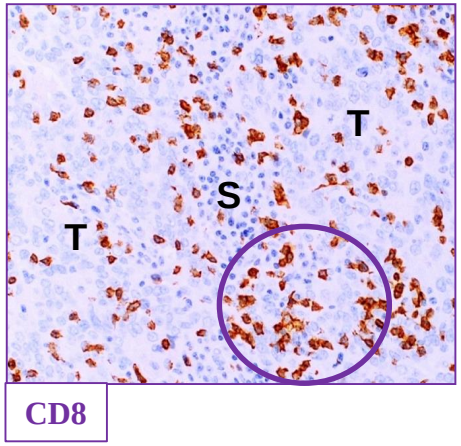


Fig. 2 | **Model for the development of CD8⁺ T cell dysfunction and the effect of PD1 blockade.**

CD8⁺ T cell states in human cancer: insights from single-cell analysis

*Anne M. van der Leun, Daniela S. Thommen and Ton N. Schumacher **



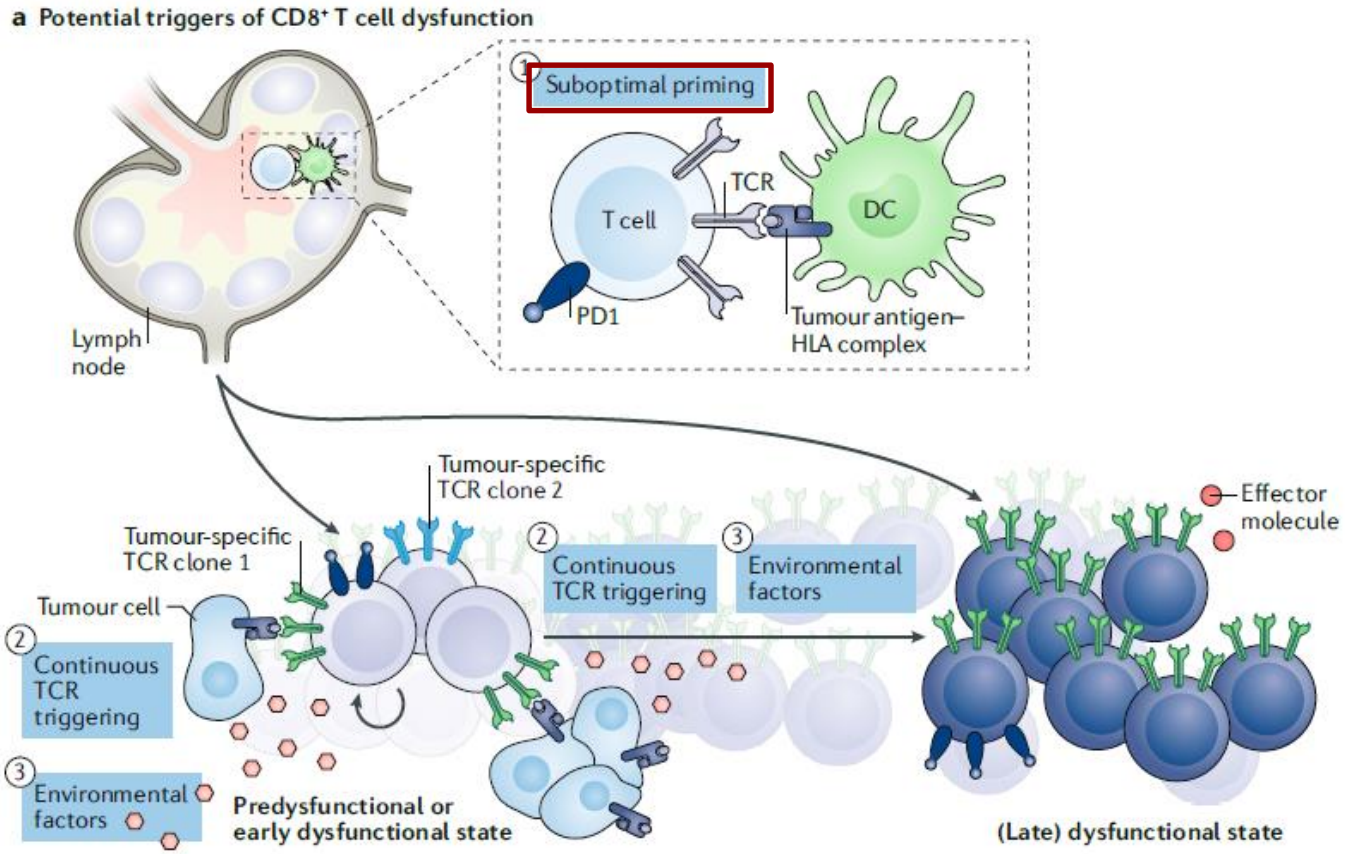


Fig. 2 | **Model for the development of CD8⁺ T cell dysfunction and the effect of PD1 blockade.**

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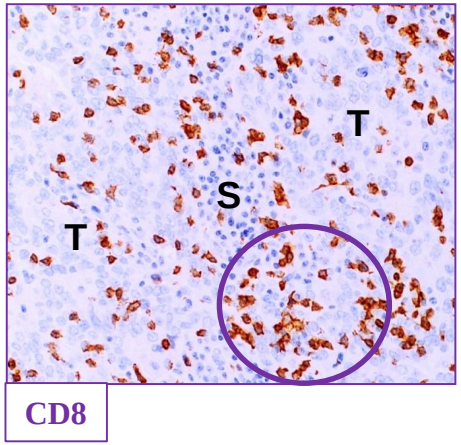

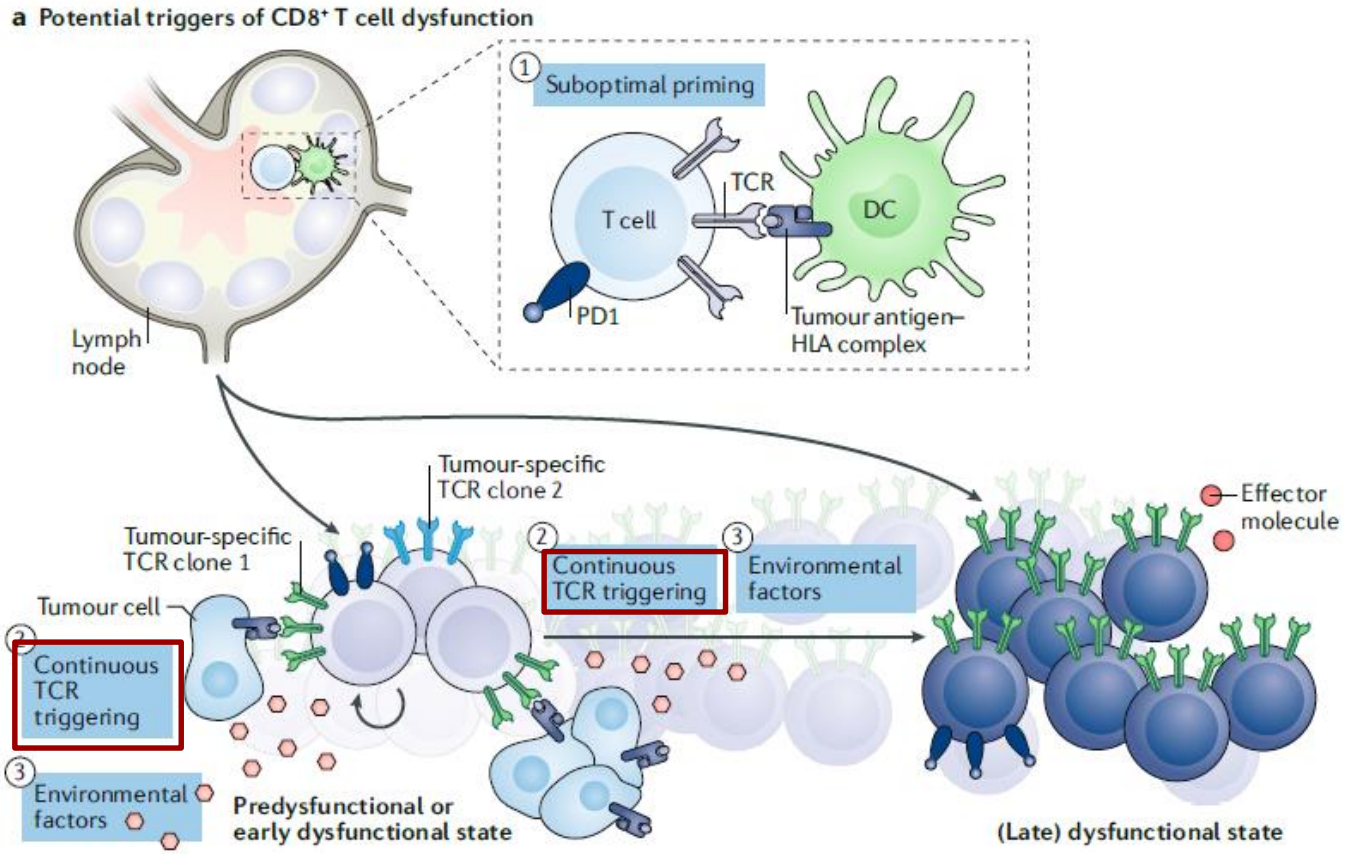

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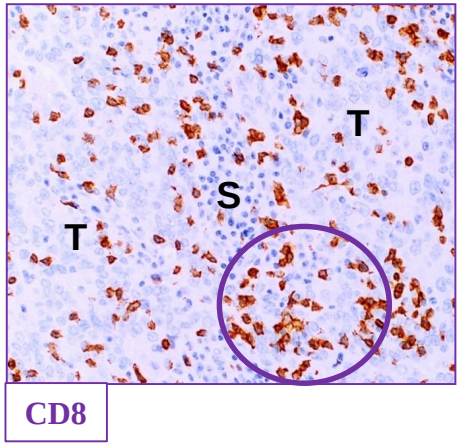

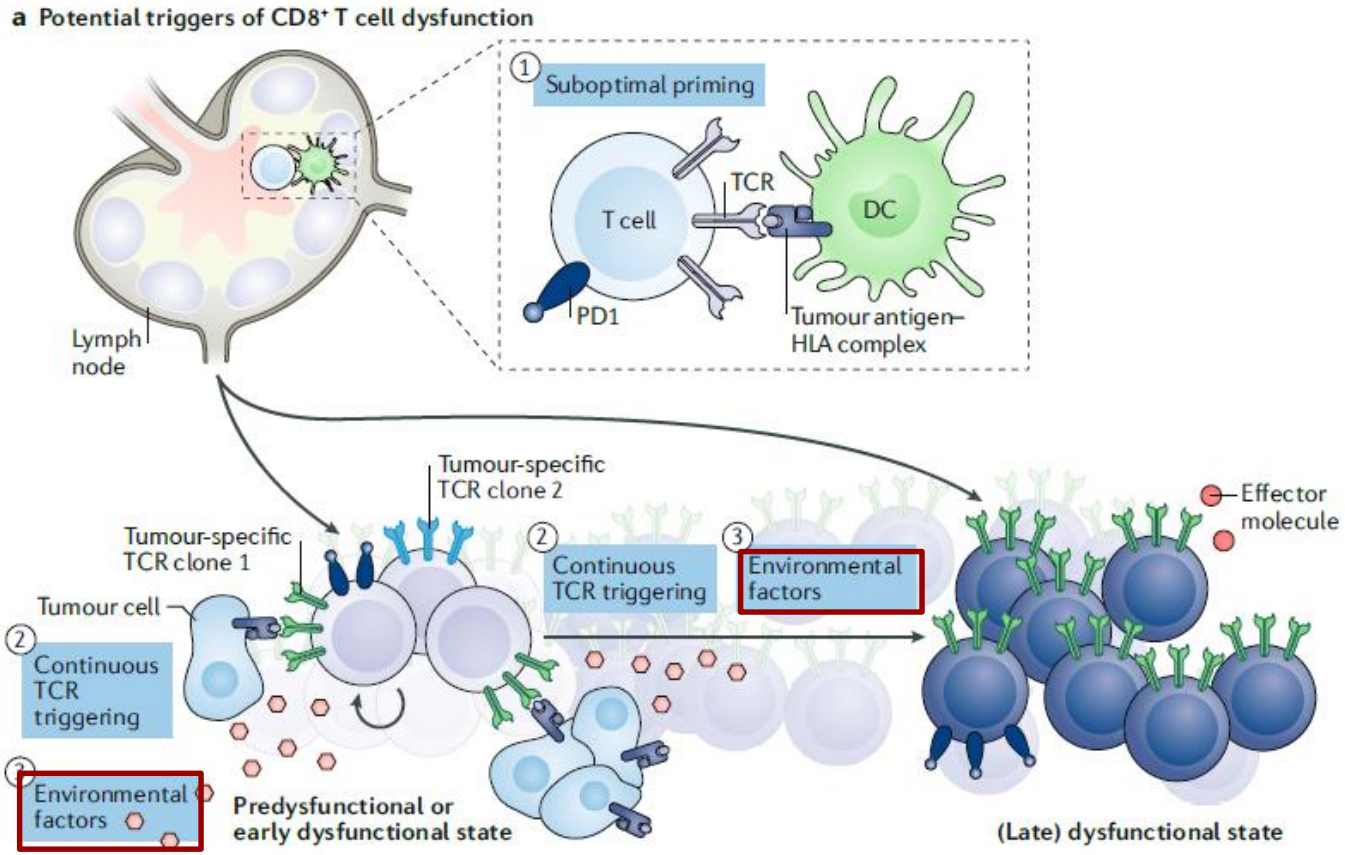

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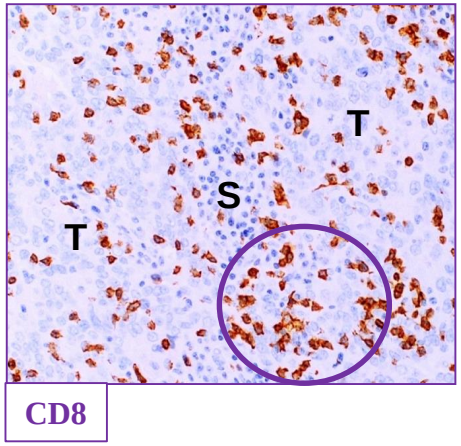


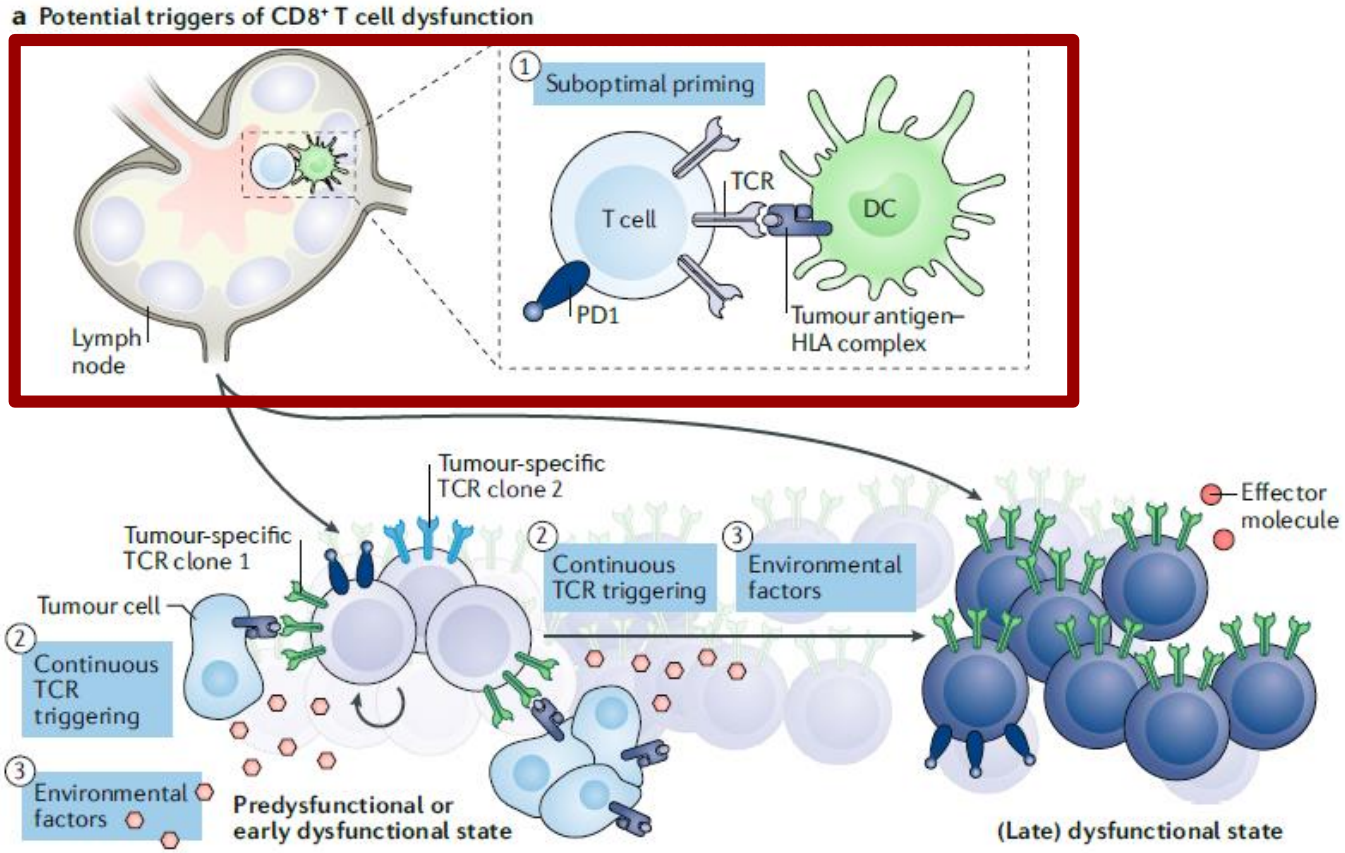


Fig. 2 | **Model for the development of CD8⁺ T cell dysfunction and the effect of PD1 blockade.**

Tumor-draining lymph nodes: At the crossroads of metastasis and immunity

Haley du Bois[1†], Taylor A. Heim[1†], Amanda W. Lund[1,2,3*]

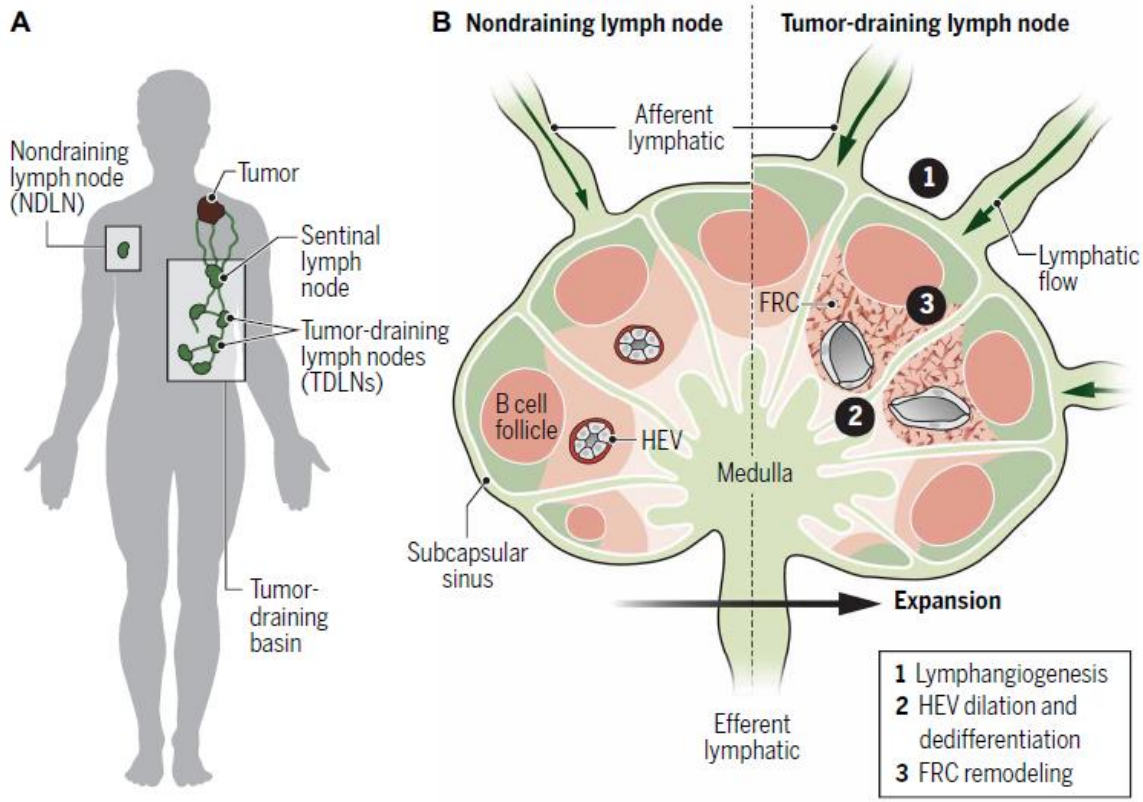
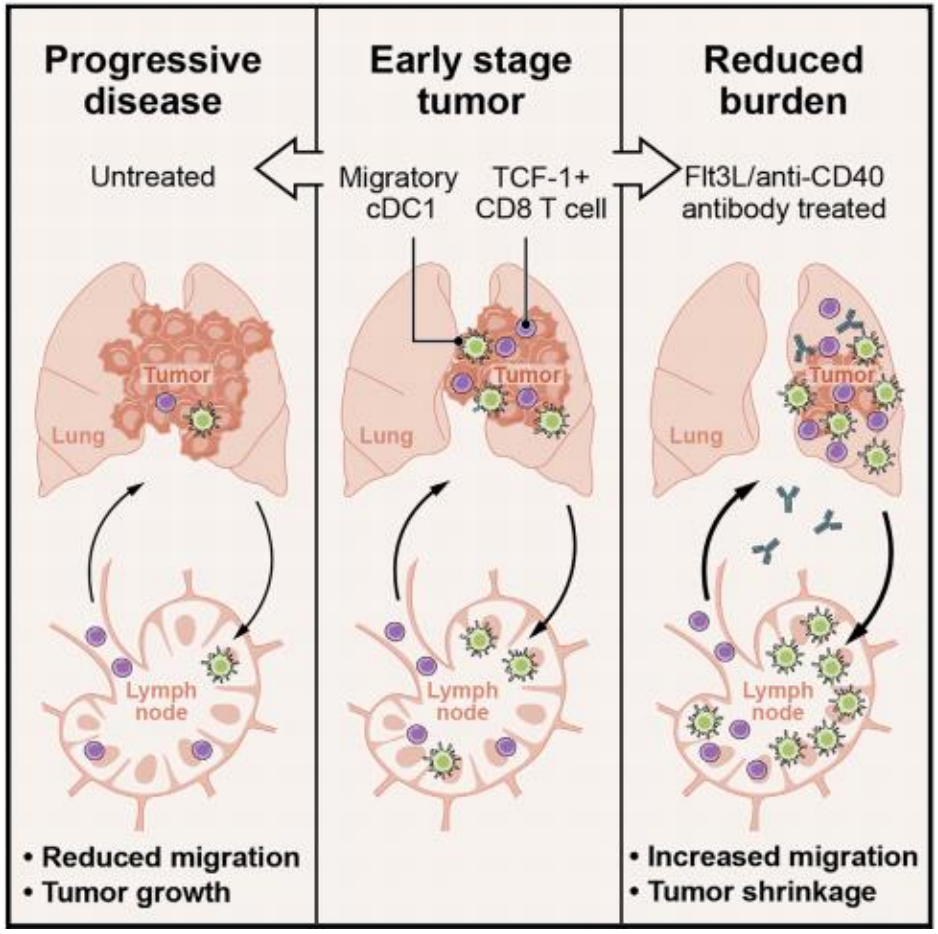


Fig. 1. The LN undergoes structural changes as a function of tumor drainage. (**A**) Solid tumors are connected to LNs through a network of lymphatic vessels that transport fluid, soluble factors, lipids, and cells. The SLN is the first LN draining tumor-associated lymph and is assayed clinically to determine the metastatic potential of a nascent malignant lesion. This SLN sits in a basin of TDLNs that are at risk of metastatic seeding and uniquely affected by a tumor when compared with distant NDLNs. (**B**) Afferent lymph flows from the tumor to the TDLN and delivers tumor-derived material including antigens and extracellular vesicles to the TDLN. TDLNs progressively expand and initiate three major stromal remodeling processes that affect TDLN structure and metastatic potential: (1) The TDLN undergoes extensive lymphangiogenesis, expanding lymphatic sinuses. LN lymphangiogenesis is initiated before tumor seeding and supports initial regional metastatic progression. (2) HEVs initially increase in density but ultimately undergo dilation and dedifferentiation, which may impair lymphocyte recruitment. (3) FRCs proliferate in the TDLN, resulting in widened conduits, altered size exclusion properties of the reticular conduits, and antigen delivery into the LN paracortex.

Conventional type I dendritic cells maintain a reservoir of proliferative tumor-antigen specific TCF-1^{+} CD8^{+} T cells in tumor-draining lymph nodes

Jason M. Schenkel,[1,2,3,15] Rebecca H. Herbst,[3,4,13,15] David Canner,[1,5,14,16] Amy Li,[1,3,5,16] Michelle Hillman,[1] Sean-Luc Shanahan,[1] Grace Gibbons,[1] Olivia C. Smith,[1] Jonathan Y. Kim,[1] Peter Westcott,[1] William L. Hwang,[1,4,6] William A. Freed-Pastor,[1,7] George Eng,[1,8] Michael S. Cuoco,[4] Patricia Rogers,[4] Jin K. Park,[1,3] Megan L. Burger,[1] Orit Rozenblatt-Rosen,[4] Le Cong,[9] Kristen E. Pauken,[10,11] Aviv Regev,[1,4,5,12,17,*] and Tyler Jacks[1,5,17,18,*]

Immunity *54*, 1–16, October 12, 2021

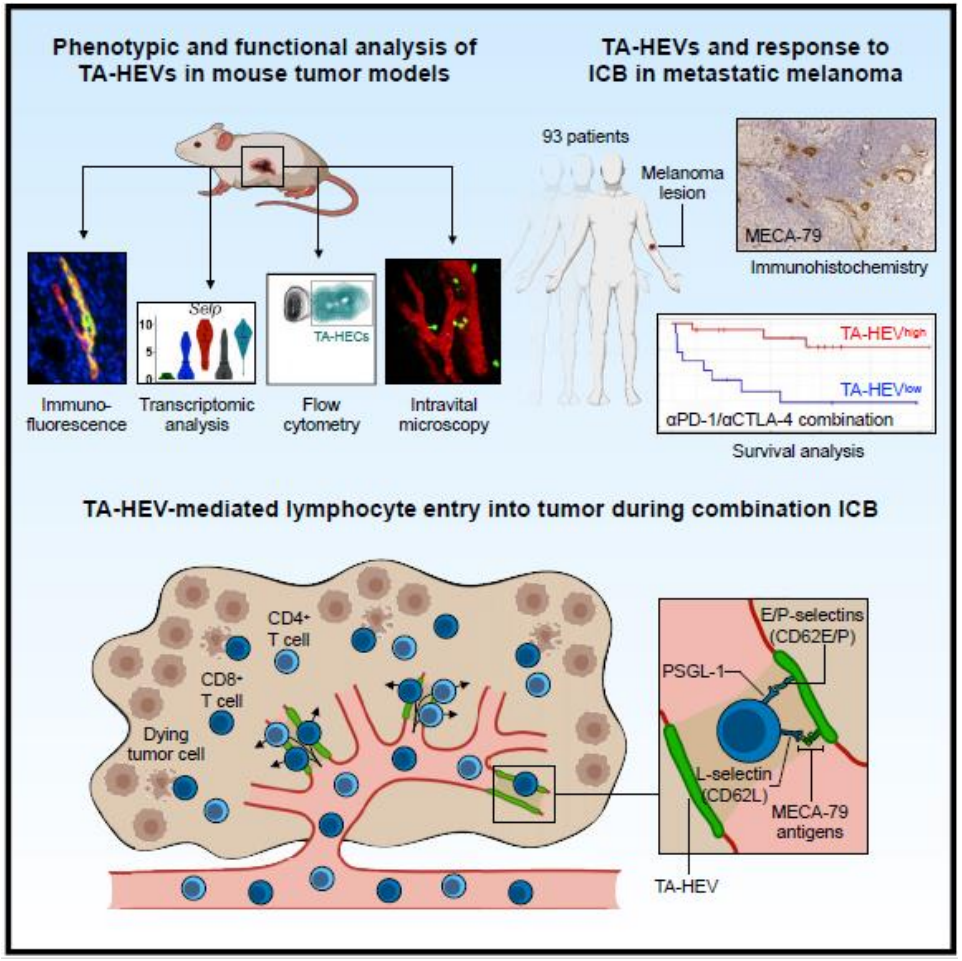


- In lung adenocarcinoma while intratumoral **TCF-1+ CD8+ T cells** acquired dysfunctional features and decreased in number as tumors progressed, a reservoir of TCF-1+ CD8+ T cells in the tumor draining LN (dLN) remained stable by conventional type I dendritic cells
- Decrease of these cDC1 as the tumor progresses contributes to failed anti tumor immunity
- Flt3L+CD40 boosts cDC1, increases TCF-1+ CD8+ T cell frequencies, decreases tumor burden

Tumor-associated high endothelial venules mediate lymphocyte entry into tumors and predict response to PD-1 plus CTLA-4 combination immunotherapy

Assia Asrir,[1,9] Claire Tardiveau,[1,9] Juliette Coudert,[1,9] Robin Laffont,[1,9] Lucas Blanchard,[1,9] Elisabeth Bellard,[1] Krystle Veerman,[1] Sarah Bettini,[1] Fanny Lafouresse,[1] Estefania Vina,[1] Dorian Tarroux,[1] Severine Roy,[2,3] Isabelle Girault,[2,3] Irma Molinaro,[4] Frédéric Martins,[5,6] Jean-Yves Scoazec,[3,4,7,8] Nathalie Ortega,[1] Caroline Robert,[2,3,7] and Jean-Philippe Girard[1,10,*]

Cancer Cell *40*, 318–334, March 14, 2022

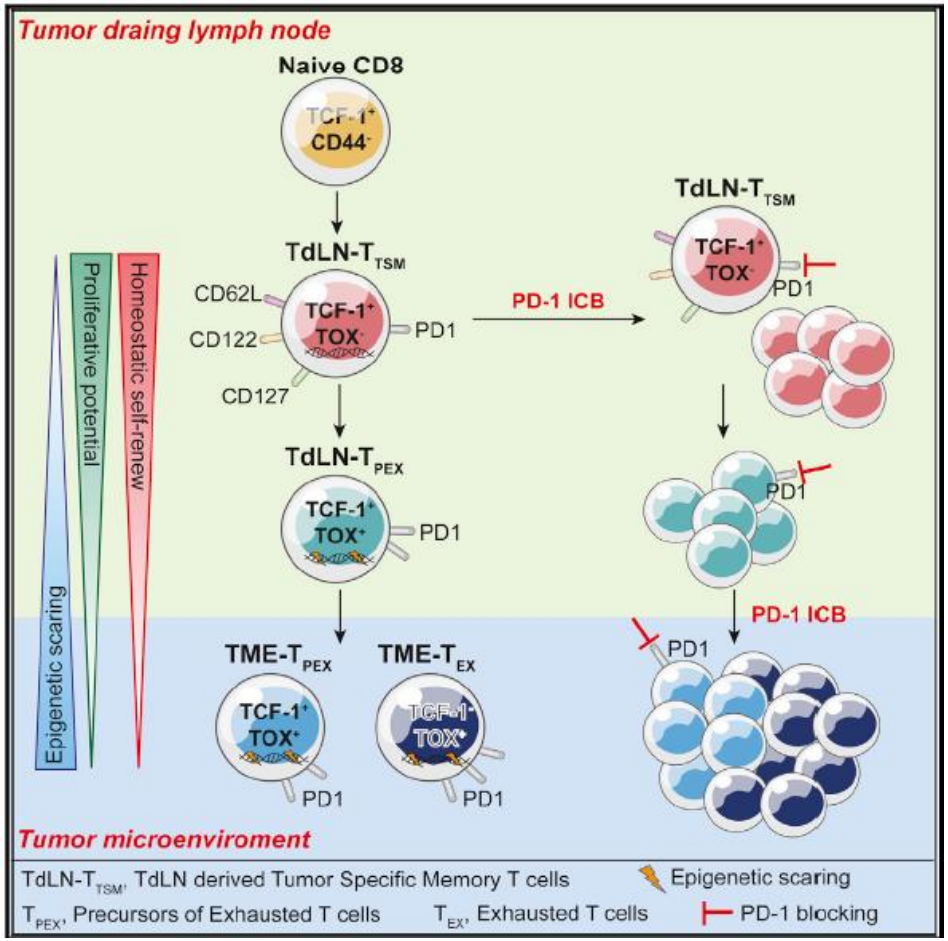


- TA-HEVs are main sites of lymphocyte extravasation Into PD-1/aCTLA-4-treated tumors
- Increasing TA-HEC differentiation increases the proportion of stem-like CD8+ T cells
- TA-HEVs predict response and survival of melanoma patients treated with aPD-1/aCTLA-4

The primordial differentiation of tumor-specific memory CD8$^+$ T cells as bona fide responders to PD-1/PD-L1 blockade in draining lymph nodes

Qizhao Huang,[1,7,8] Xia Wu,[2,8] Zhiming Wang,[3,8] Xiangyu Chen,[1,8] Lisha Wang,[3] Yijun Lu,[4] Dan Xiong,[2] Qiao Liu,[3] Yuhan Tian,[2] Huayu Lin,[3] Junyi Guo,[5] Shuqiong Wen,[5] Wei Dong,[2] Xiaofan Yang,[1] Yuchen Yuan,[2] Zhengliang Yue,[3] Shun Lei,[3] Qing Wu,[3] Ling Ran,[3] Luoyingzi Xie,[3] Yifei Wang,[1] Leiqiong Gao,[1] Qin Tian,[3] Xinyuan Zhou,[3] Beicheng Sun,[4,6,*] Lifan Xu,[3,*] Zhonghui Tang,[2,*] and Lilin Ye[3,7,9,*]

Cell *185*, 1–18, October 27, 2022



Highlights

- TdLN-T_{TSM} cells are bona fide memory T cells
- Exhaustion-associated epigenetic scaring marks T_{PEX} but not TdLN-T_{TSM} cells
- Adoptive transfer of TdLN-T_{TSM} represents a promising immunotherapy strategy
- TdLN-T_{TSM} cells are primary responders to PD-1/PD-L1 ICB

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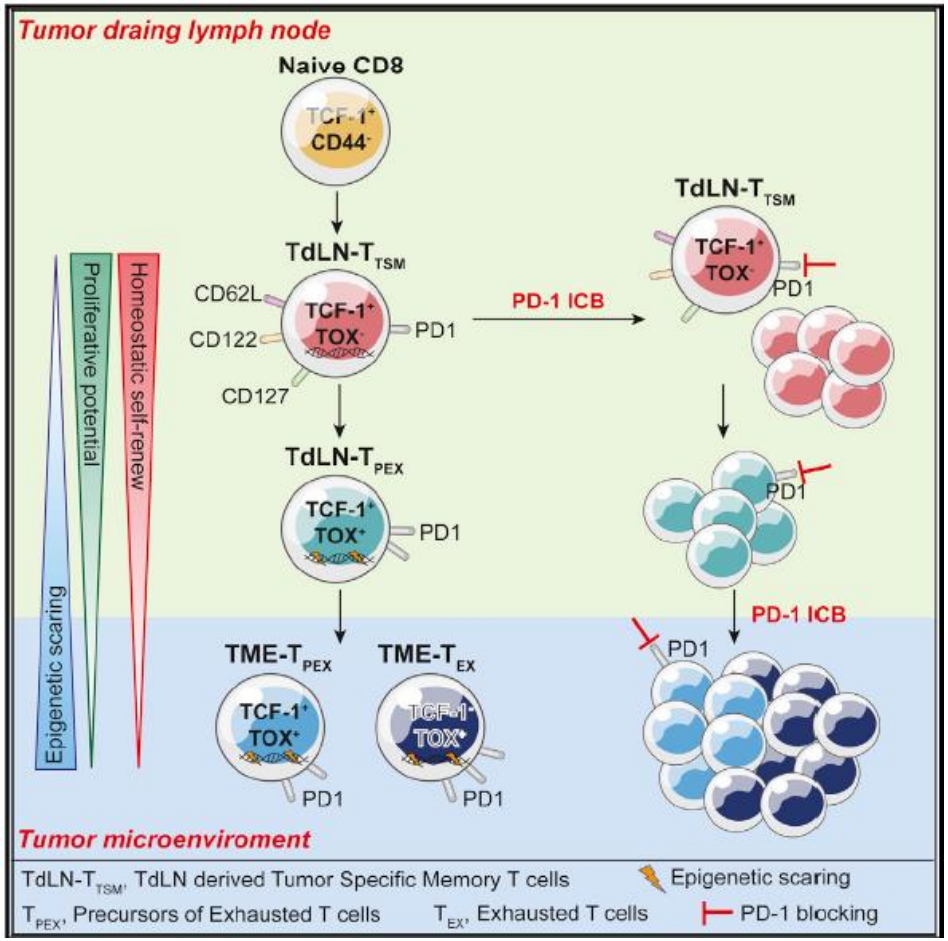
Cell *185*, 1–18, October 27, 2022



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- TdLN-T_{TSM} cells are primary responders to PD-1/PD-L1 ICB

Importantly**, lymphadenectomy** abrogated the tumor-suppressive effects of PDL1 ICB, while the **adoptive transfer of TdLN-T_{TSM} cells,** but not TdLN-T_{PEX} cells, efficiently rectified PD-L1 ICB mediated anti-tumor efficacy in tumor-bearing mice with lymphadenectomy

Tumor Immunology and Tumor Evolution: Intertwined Histories

Jérôme Galon[1,*] and Daniela Bruni[1]

Immunity *52*, January 14, 2020

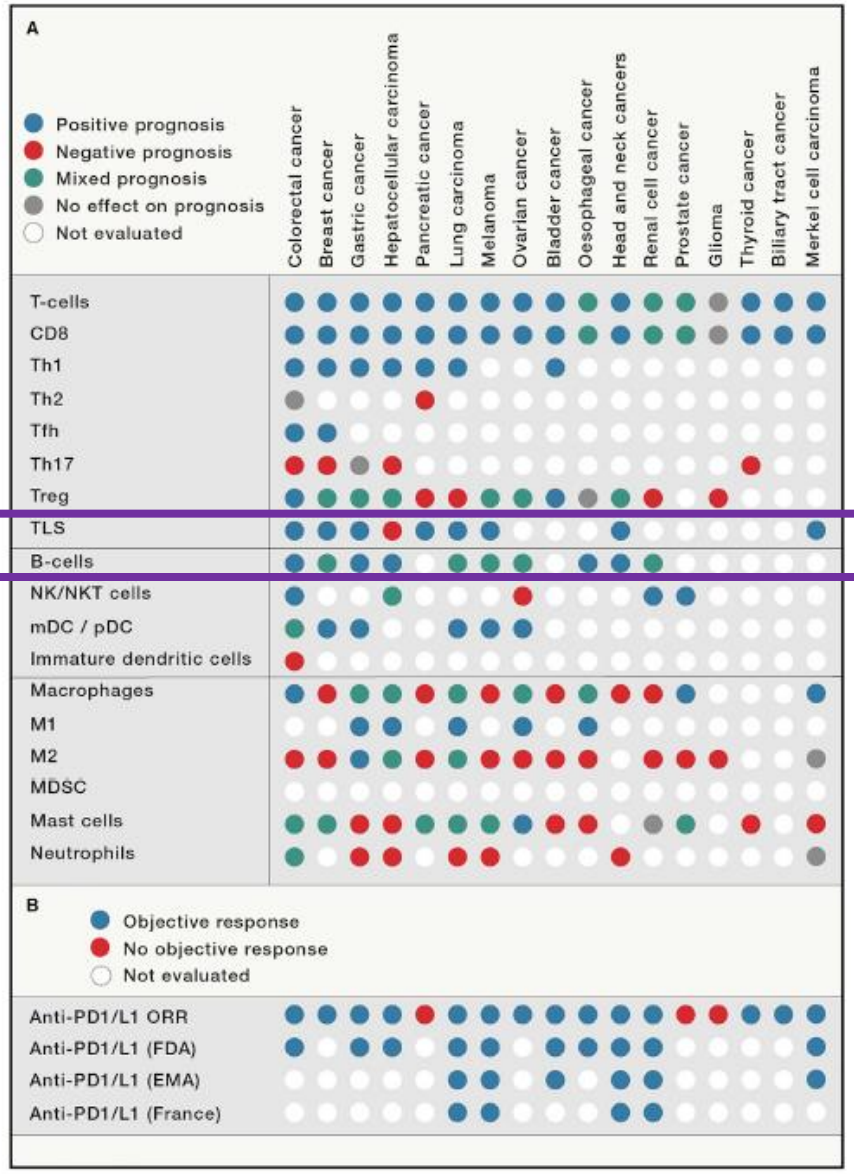

Figure 3. Prognostic Effect of Immune Cells in Solid Cancer

B cells are associated with survival and immunotherapy response in sarcoma

Florent Petitprez[1,2,3,4], Aurélien de Reyniès[4,24], Emily Z. Keung[5,24], Tom Wei-Wu Chen[6,7,8,9], Cheng-Ming Sun[1,2,3], Julien Calderaro[1,10,11], Yung-Ming Jeng[9,12], Li-Ping Hsiao[7], Laetitia Lacroix[1,2,3], Antoine Bougouin[1,2,3], Marco Moreira[1,2,3], Guillaume Lacroix[1,2,3], Ivo Natario[1,2,3], Julien Adam[13], Carlo Lucchesi[14,15], Yec'han Laizet[14,15], Maud Toulmonde[14,16], Melissa A. Burgess[17], Vanessa Bolejack[18], Denise Reinke[19], Khalid M. Wani[20], Wei-Lien Wang[20], Alexander J. Lazar[20,21], Christina L. Roland[5], Jennifer A. Wargo[5,21], Antoine Italiano[14,16,22], Catherine Sautès-Fridman[1,2,3], Hussein A. Tawbi[23]* & Wolf H. Fridman[1,2,3]*

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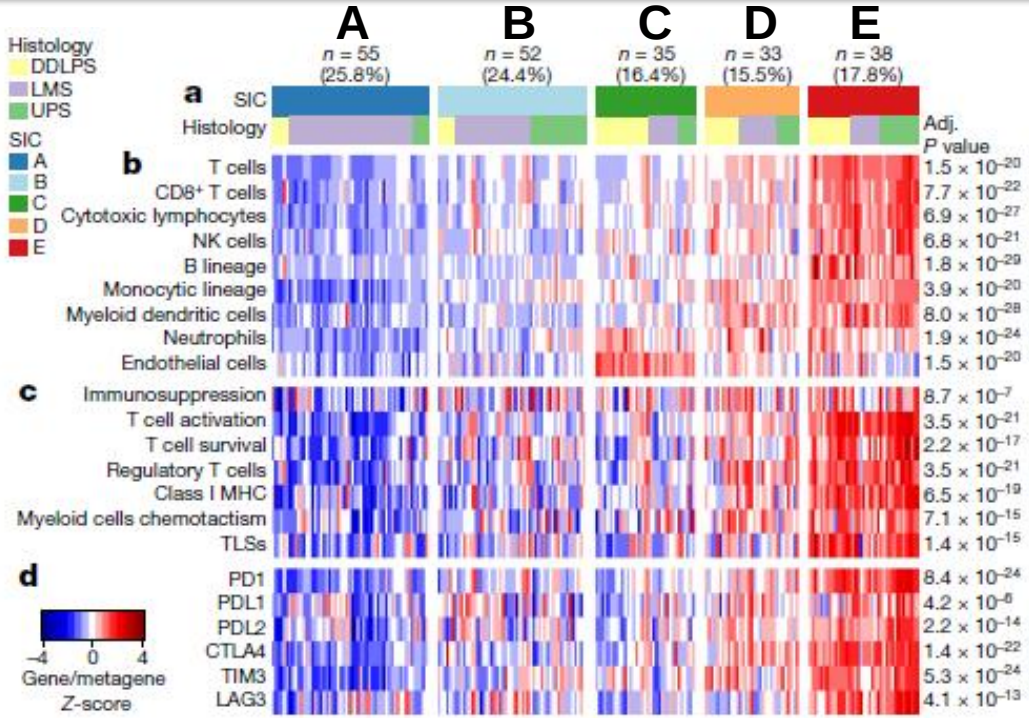

Fig. 1 | The SICs exhibit strongly different TMEs. This figure refers to the TCGA SARC cohort ($n = 213$). **a**, Composition of the TCGA SARC cohort by SIC, and histology. **b**, Composition of the TME by SIC as defined by the MCP-counter *Z*-scores. NK cells, natural killer cells. **c**, Expression of gene signatures related to the functional orientation of the immune TME by SIC. **d**, Expression of genes related to immune checkpoints by SIC. Adjusted *P* values are obtained from Benjamini–Hochberg correction of two-sided Kruskal–Wallis tests *P* values.

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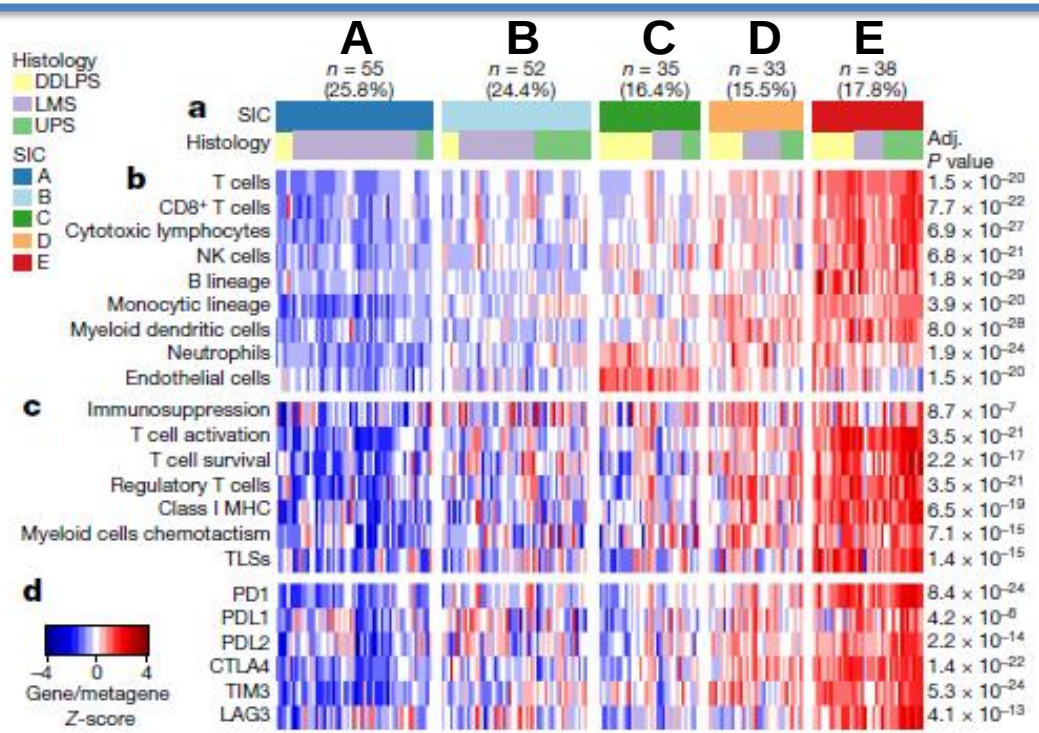

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A= immune desert
B= heterogenous, immune-low
C= vascularized
D= heterogenous, immune-high
E= immune and TLS high

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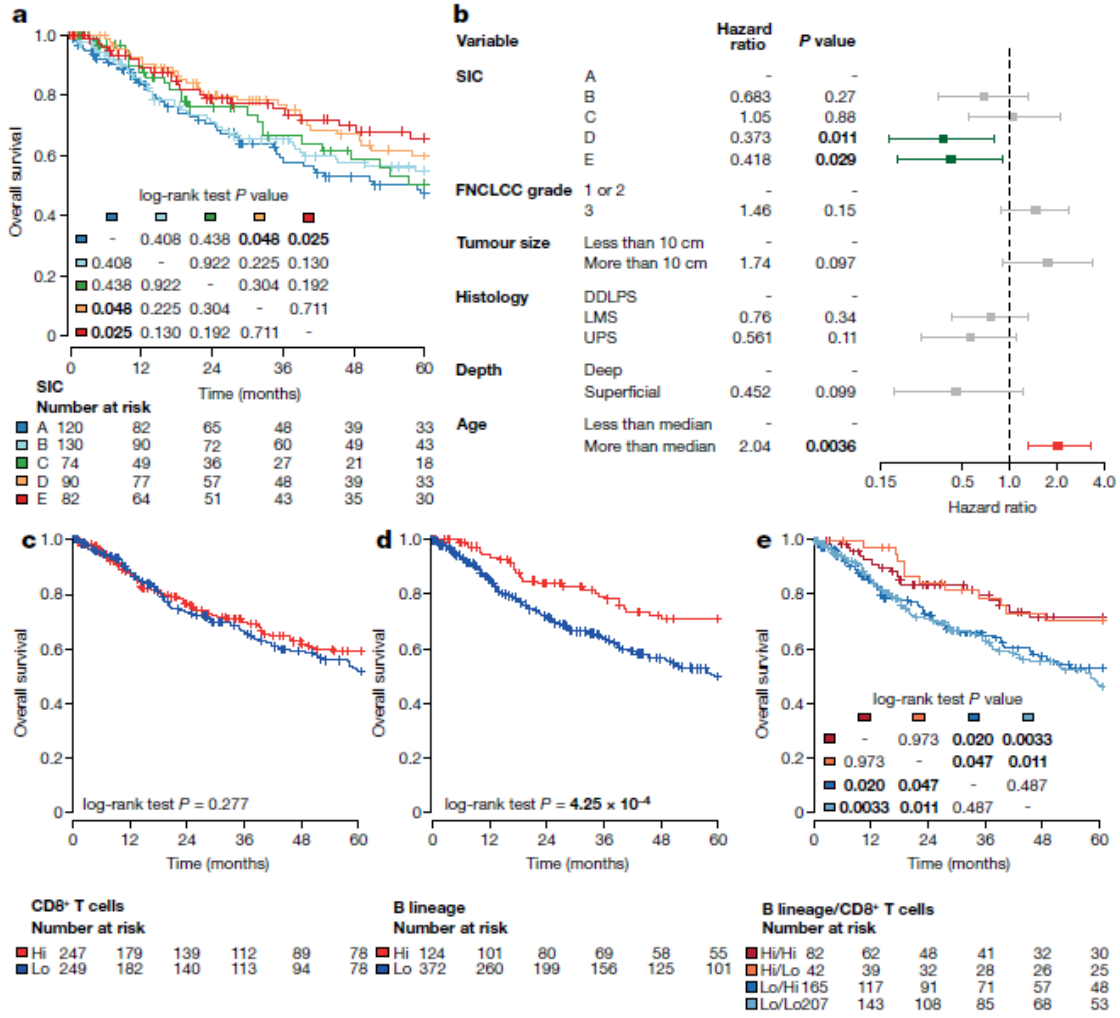

Fig. 2 | SICs and B cells are predictive of the survival of patients with STS. This figure refers to TCGA SARC and GSE21050 pooled cohorts ($n = 496$). **a**, Overall survival of patients with STS by the SIC of their tumour. **b**, Multivariate Cox proportional regression outcome, with all included variables represented. For each variable, the reference level is the first one. A grey bar indicates $P > 0.05$; and variables indicated by green and red bars are positively and negatively, respectively, significantly associated with prognosis in this multivariate model. Error bars represent the 95% confidence interval. FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer. **c**, **d**, Overall survival of patients with STS according to MCP-counter scores for $CD8^+$ T cells (**c**) or B lineage cells (**d**). **e**, Overall survival of patients based on the tumour-infiltrating B lineage cells and $CD8^+$ T cells. Analyses were performed with Kaplan–Meier estimates and two-sided log-rank tests. In each cohort, tumours were considered high (Hi) for $CD8^+$ T cells if their score was above the median, and high for cytotoxic lymphocytes and B lineage if their score was above the third quartile.

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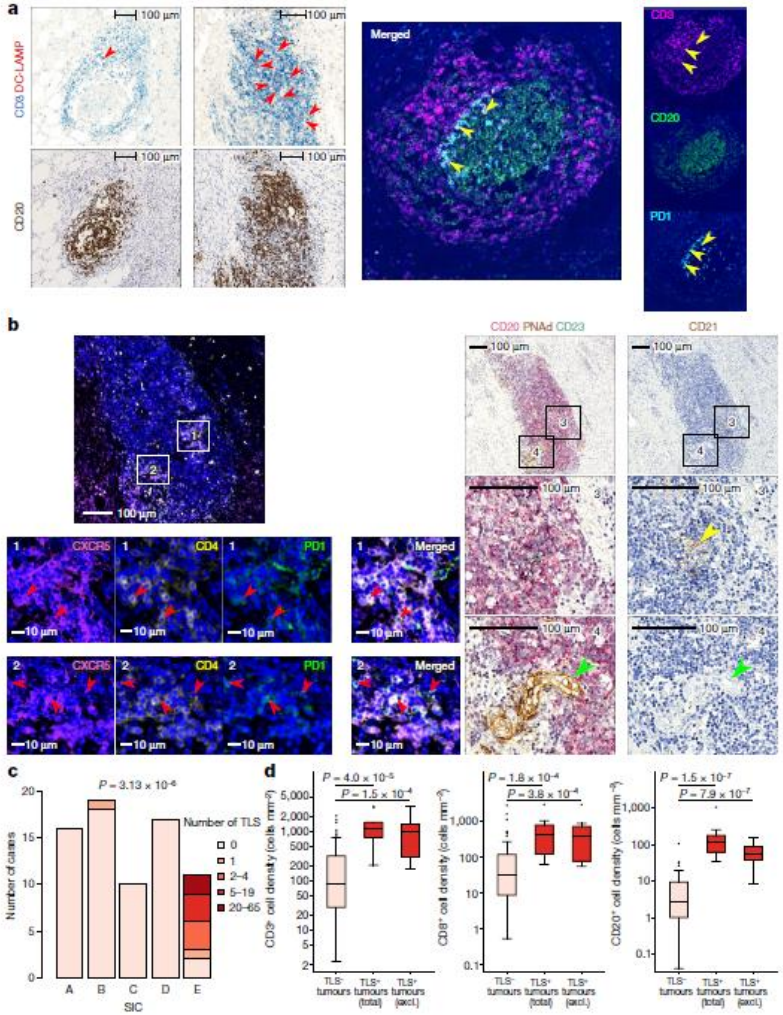

Fig. 3 | TLSs are a distinguishing feature of the immune-high class of STS. This figure refers to the NTUH cohort ($n = 93$). **a**, Populational characterization of TLSs. Left, examples of two tertiary lymphoid structures by immunohistochemistry, identified as CD3$^+$ T cell (blue) aggregates containing DC-LAMP$^+$ mature dendritic cells (red, red arrows) and juxtaposing CD20$^+$ B cell aggregates (brown). Right, representative immunofluorescence staining of a TLS for CD3 (magenta), CD20 (green) and PD1 (cyan). DAPI staining is shown in blue. The multispectral image shows CD3$^+$PD1$^+$ double-positive cells (yellow arrows). **b**, Functionality of TLSs. Left, CXCR5$^+$ (magenta), CD4$^+$ (yellow) and PD1$^+$ (green) cells in zones 1 and 2 of the same TLS. Multispectral fluorescence images of zones 1 and 2 show CXCR5$^+$CD4$^+$PD1$^+$ triple positive cells (red arrows) characteristic of T follicular helper cells. Right, CD20$^+$ cells stained in pink (left) on consecutive sections of a TLS. CD23 (green on left) and CD21 (brown on right) positive cells with reticular morphology characteristic of follicular dendritic cells (yellow arrow, zone 3). PNAd$^+$ structures (brown, green arrow) with high endothelial venule morphology are also detectable nearby (zone 4). **c**, Number of TLS among 5 SICs of 73 tumours of NTUH cohort ($n = 73$). **d**, Characterization of the immune infiltrate in tumours according to TLS presence (TLS$^-$ $n = 82$, TLS$^+$ $n = 11$, total $n = 93$). Densities of CD3$^+$ (left), CD8$^+$ (centre) and CD20$^+$ (right) cells in tumours lacking or containing TLSs; densities including (total) or excluding (excl) TLS are indicated for the TLS$^+$ tumours. Box plots represent median (larger bar) and interquartile range (IQR). Upper whisker extends to whichever is minimal, maximum or third quartile plus 1.5× IQR. Lower whisker extends to whichever is maximal, minimum or first quartile minus 1.5× IQR. *P* values were determined by chi-squared test (**c**) or two-sided Mann–Whitney tests (**d**).

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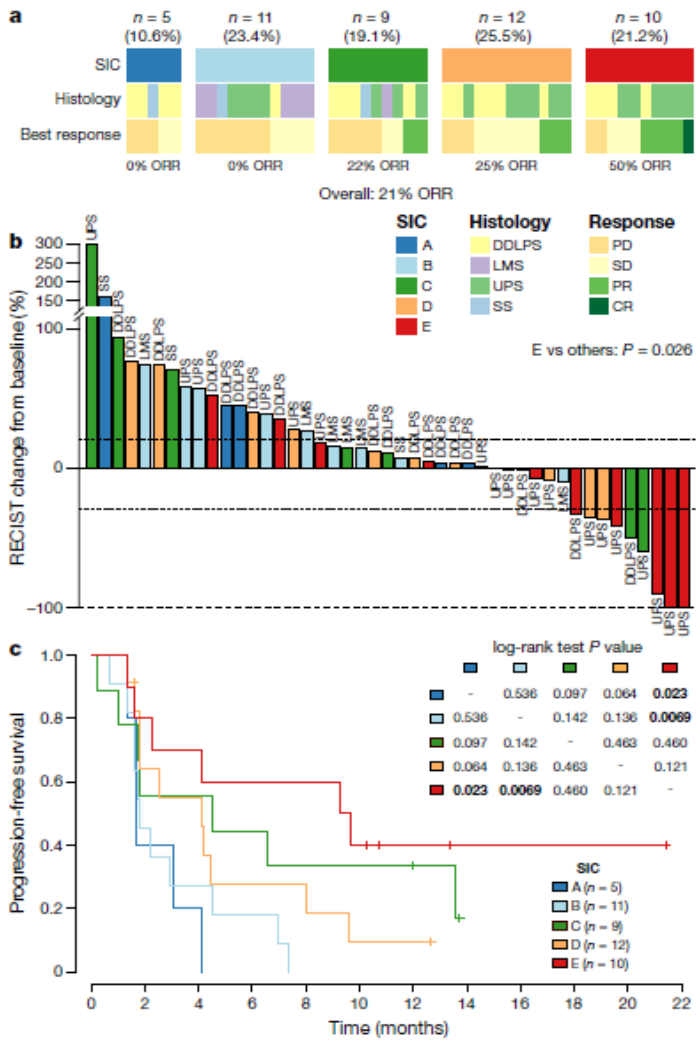
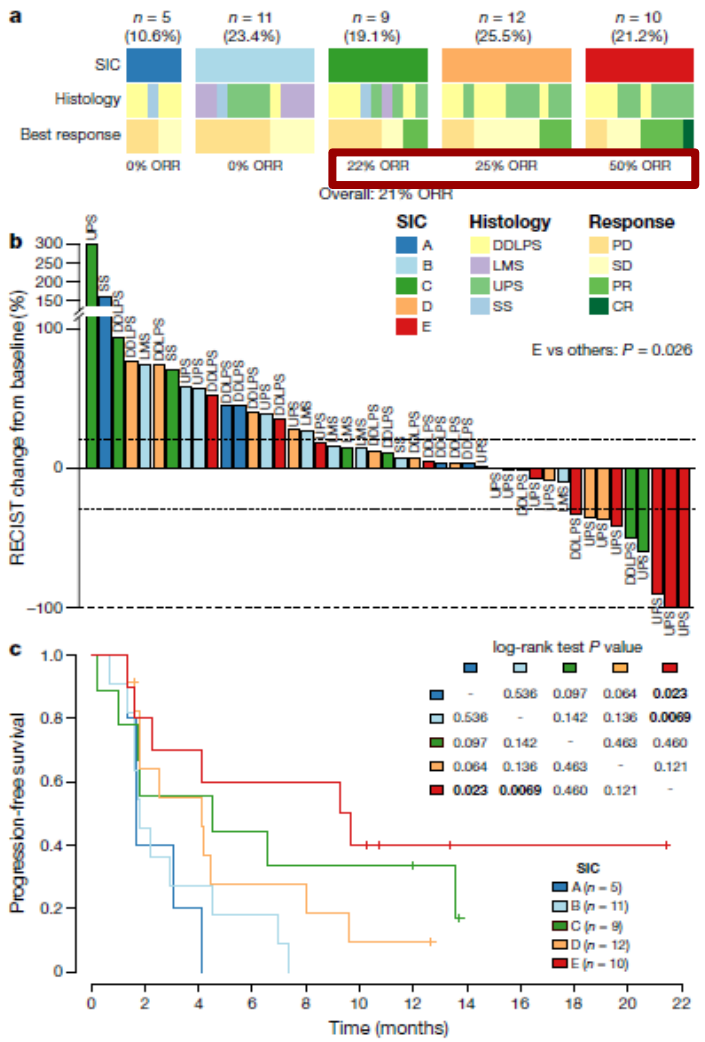


Fig. 4 | SICs are strongly associated with STS response to PD1 blockade therapy. This figure refers to the SARC028 cohort ($n = 47$). **a**, Relationship between SIC, histology and response to treatment in the SARC028 cohort. **b**, Waterfall plot showing the best response to pembrolizumab as a percentage change in the size of target lesions from baseline ($n = 45$). Tumour sizes were calculated as the sum of target lesion diameters. Colours indicate the SIC to which each tumour was assigned. Dashed lines indicate +20%, −30% and −100% change from baseline levels. SIC E versus other comparison was performed using a two-sided Mann–Whitney test. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; SS, synovial sarcoma. **c**, Progression-free survival of patients by tumour SIC ($n = 47$).

B cells are associated with survival and immunotherapy response in sarcoma

Florent Petitprez[1,2,3,4], Aurélien de Reyniès[4,24], Emily Z. Keung[5,24], Tom Wei-Wu Chen[6,7,8,9], Cheng-Ming Sun[1,2,3], Julien Calderaro[1,10,11], Yung-Ming Jeng[9,12], Li-Ping Hsiao[7], Laetitia Lacroix[1,2,3], Antoine Bougoüin[1,2,3], Marco Moreira[1,2,3], Guillaume Lacroix[1,2,3], Ivo Natario[1,2,3], Julien Adam[13], Carlo Lucchesi[14,15], Yec'han Laizet[14,15], Maud Toulmonde[14,16], Melissa A. Burgess[17], Vanessa Bolejack[18], Denise Reinke[19], Khalid M. Wani[20], Wei-Lien Wang[20], Alexander J. Lazar[20,21], Christina L. Roland[5], Jennifer A. Wargo[5,21], Antoine Italiano[14,16,22], Catherine Sautès-Fridman[1,2,3], Hussein A. Tawbi[23]* & Wolf H. Fridman[1,2,3]*

Nature | Vol 577 | 23 January 2020



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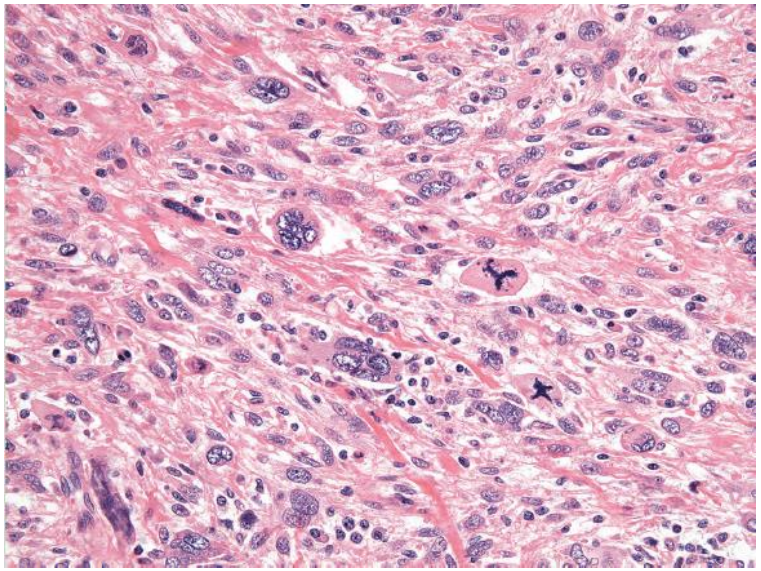
Outline

- Tumor Immune Microenvironment (TIME)
- Tumor infiltrating lymphocytes landscape
    - T cells
    - B cells
- Turning-up the heat



Q: Can low dose radiation reprogramme the tumor microenvironment of tumors with scarce immune infiltration and together with immunotherapy induce mobilization of (innate and/or adaptive) immunity?

Cancer Discov 2022;12:1-26

Low-Dose Radiotherapy Reverses Tumor Immune Desertification and Resistance to Immunotherapy

Fernanda G. Herrera[1,23], Catherine Ronet[1], Maria Ochoa de Olza[1,3], David Barras[1], Isaac Crespo[1], Massimo Andreatta[1], Jesus Corria-Osorio[1], Aodrenn Spill[1], Fabrizio Benedetti[1], Raphael Genolet[1], Angela Orcurto[3], Martina Imbimbo[3], Eleonora Ghisoni[3], Blanca Navarro Rodrigo[3], Dominik R. Berthold[4], Apostolos Sarivalasis[4], Khalil Zaman[4], Rafael Duran[5], Clarisse Dromain[5], John Prior[6], Niklaus Schaefer[6], Jean Bourhis[2], Georgia Dimopoulou[11], Zoi Tsourti[11], Marius Messemaker[8], Thomas Smith[9], Sarah E. Warren[9], Periklis Foukas[10], Sylvie Rusakiewicz[1], Mikaël J. Pittet[8,12], Stefan Zimmermann[3], Christine Sempoux[7], Urania Dafni[11], Alexandre Harari[1], Lana E. Kandalaft[1,13], Santiago J. Carmona[1], Denarda Dangaj Laniti[1], Melita Irving[1], and George Coukos[1,3]

- orthotopic intraperitoneal (i.p.) murine ID8 ovarian cancer model

Cancer Discov 2022;12:1–26

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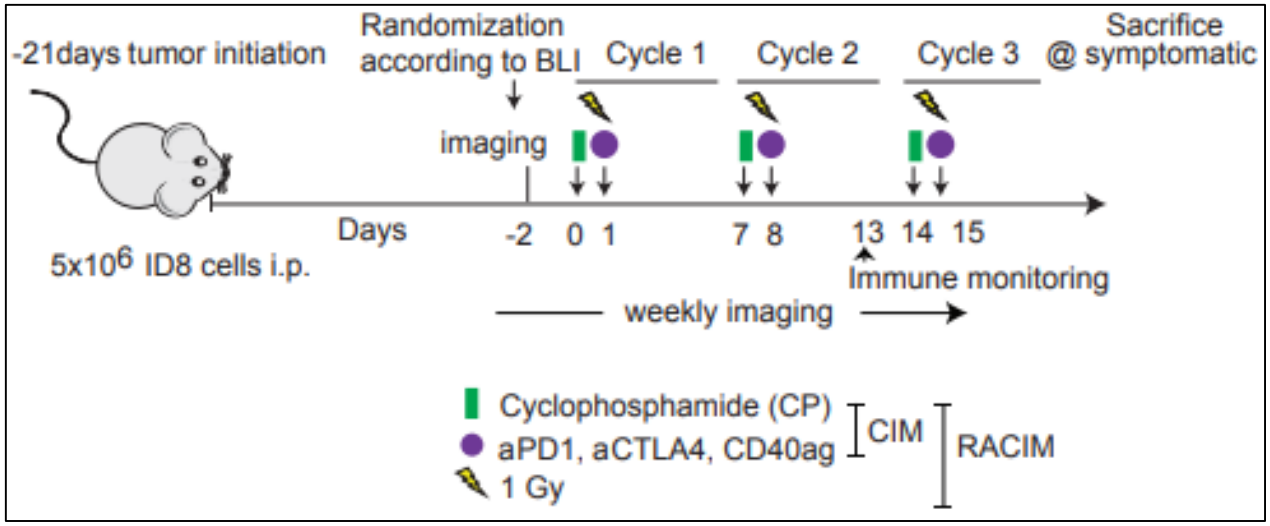

Cancer Discov 2022;12:1-26

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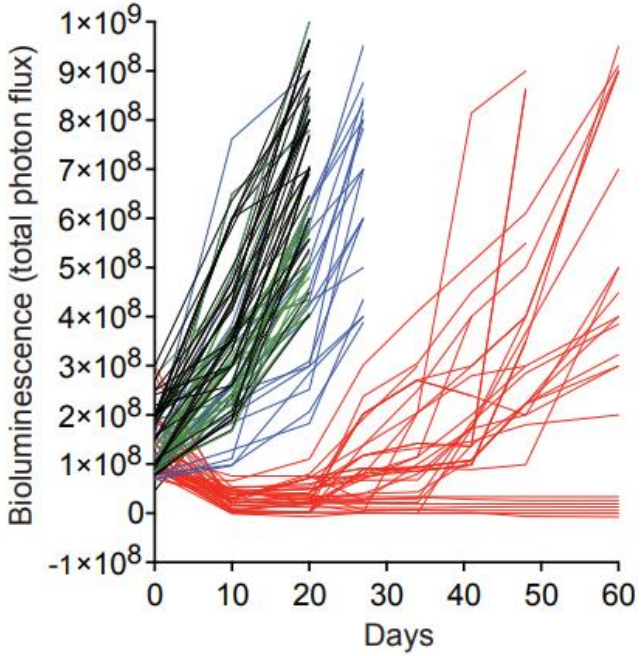
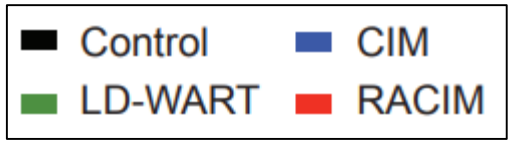
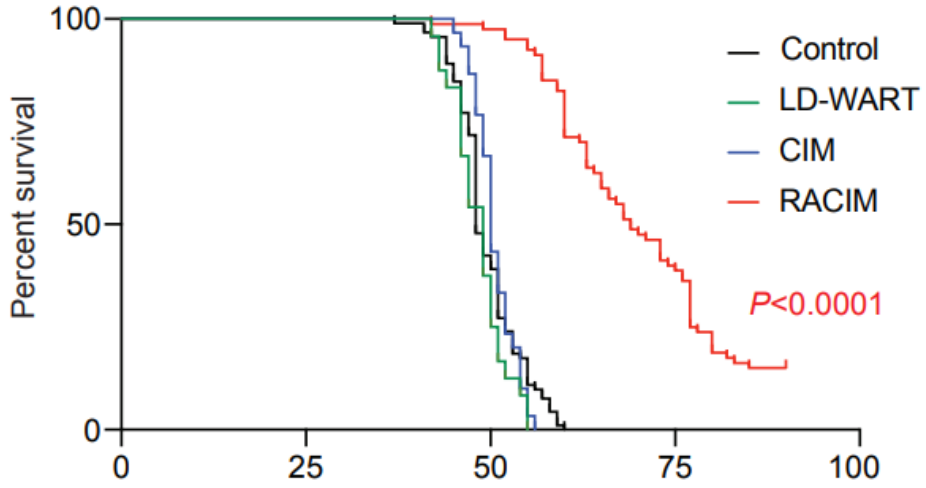
Cancer Discov 2022;12:1–26

Low-Dose Radiotherapy Reverses Tumor Immune Desertification and Resistance to Immunotherapy





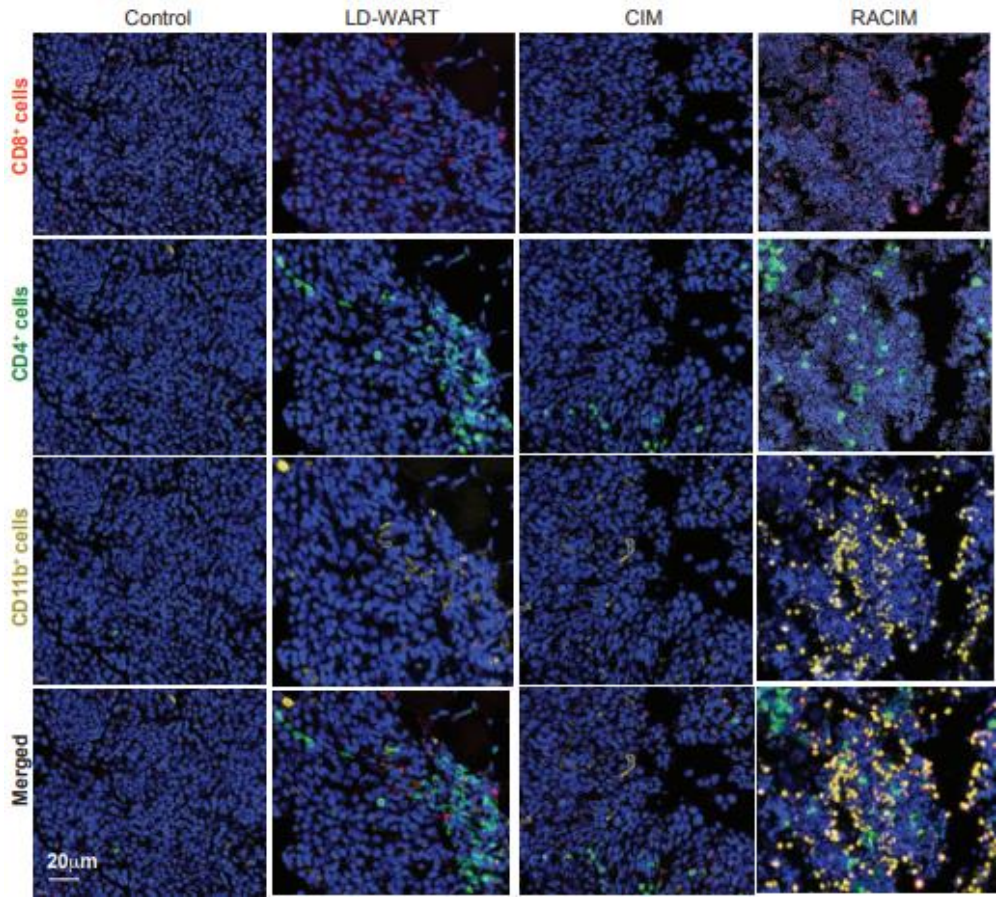


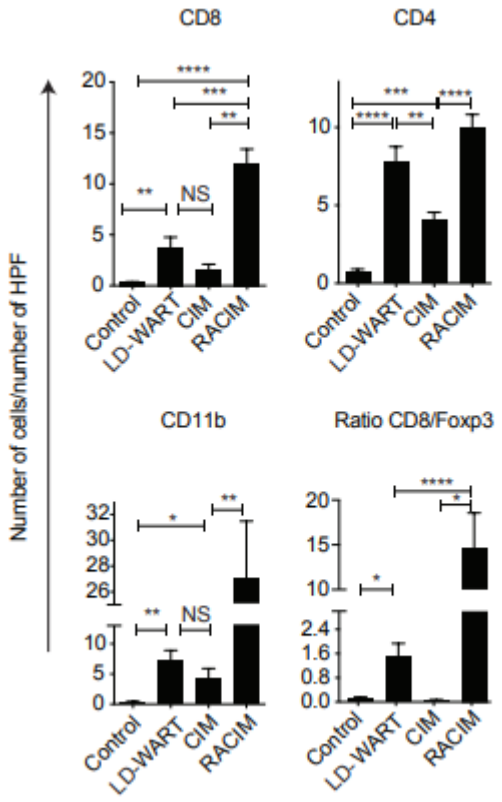
No. at Risk					
Control	92	92	39	0	0
LD-WART	24	24	9	0	0
CIM	30	30	20	0	0
RACIM	80	80	79	32	12

Cancer Discov 2022;12:1–26

Low-Dose Radiotherapy Reverses Tumor Immune Desertification and Resistance to Immunotherapy

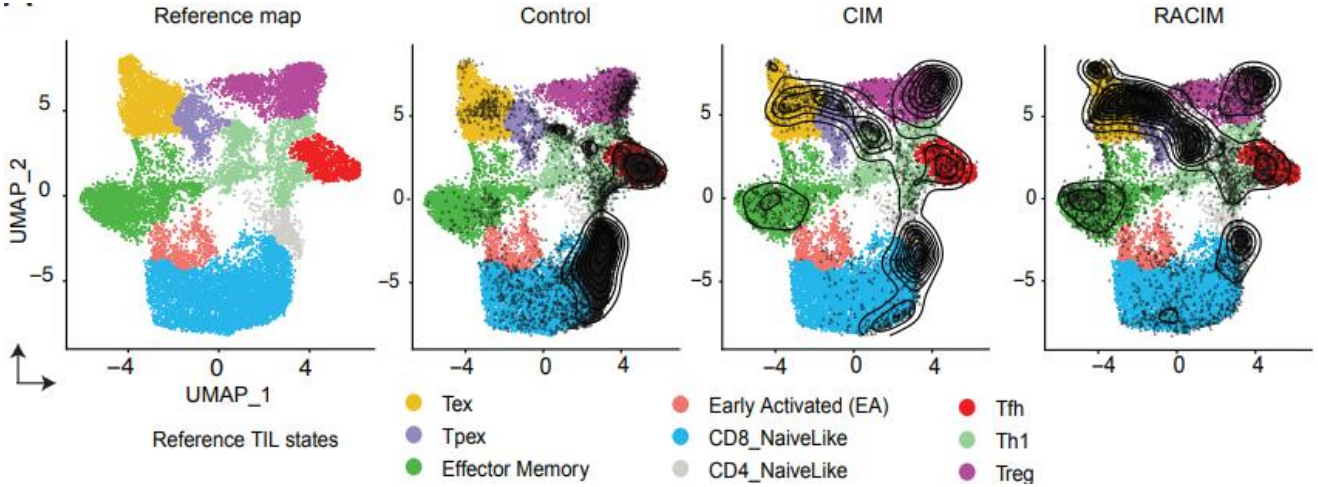
IHC

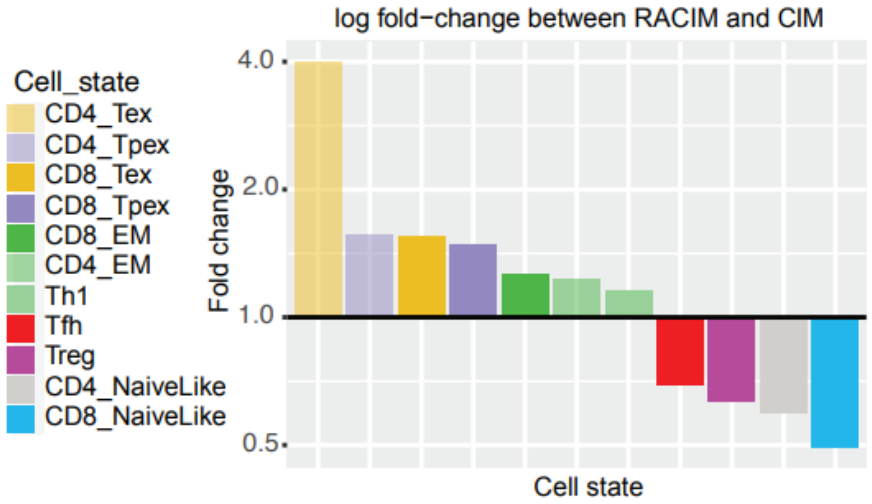




Cancer Discov 2022;12:1-26

Low-Dose Radiotherapy Reverses Tumor Immune Desertification and Resistance to Immunotherapy

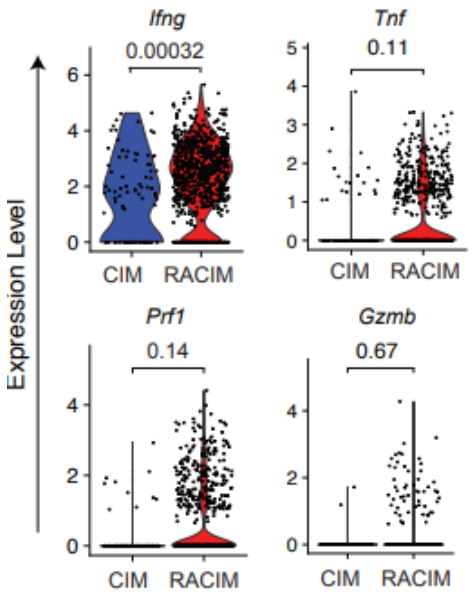


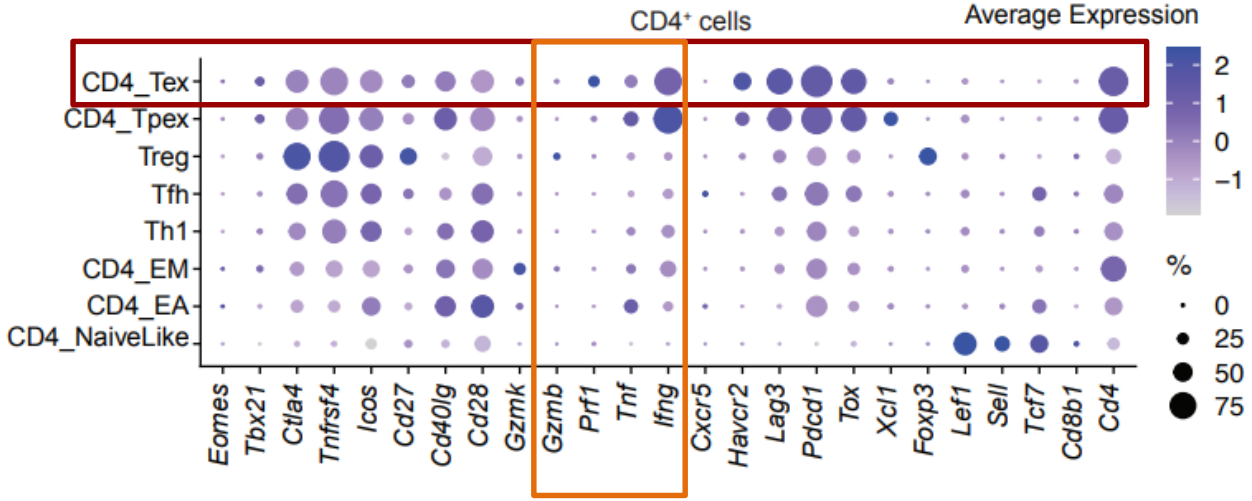


Cancer Discov 2022;12:1-26

RACIM expands tumor-rejecting CD4+ and CD8+ TILs with activation and exhaustion features

CD4 Tex TILs

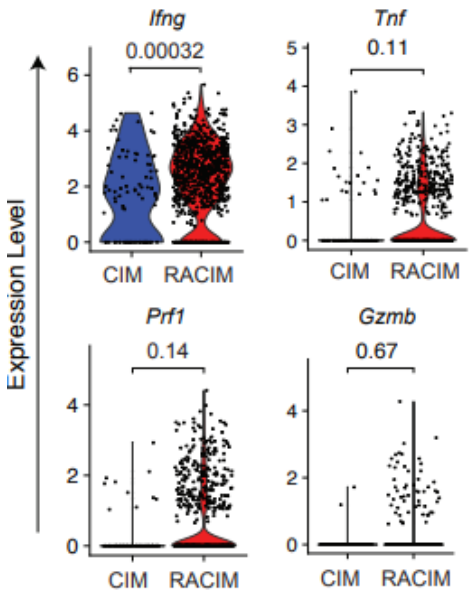


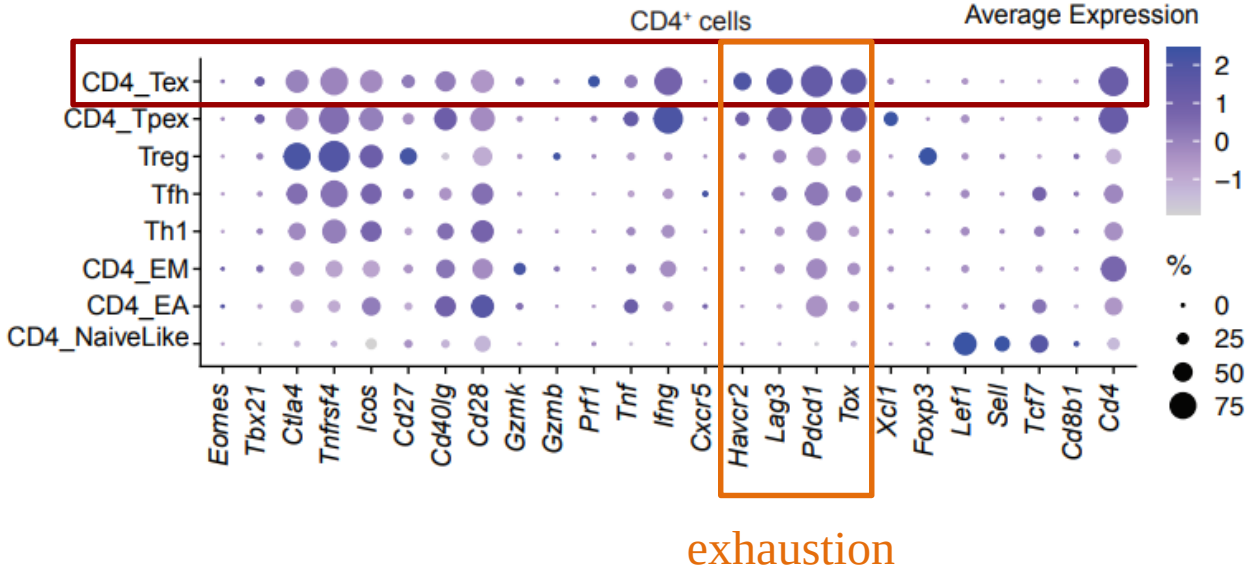


Cancer Discov 2022;12:1–26

RACIM expands tumor-rejecting CD4+ and CD8+ TILs with activation and exhaustion features

CD4 Tex TILs





exhaustion

Cancer Discov 2022;12:1–26

Low-Dose Radiotherapy Reverses Tumor Immune Desertification and Resistance to Immunotherapy

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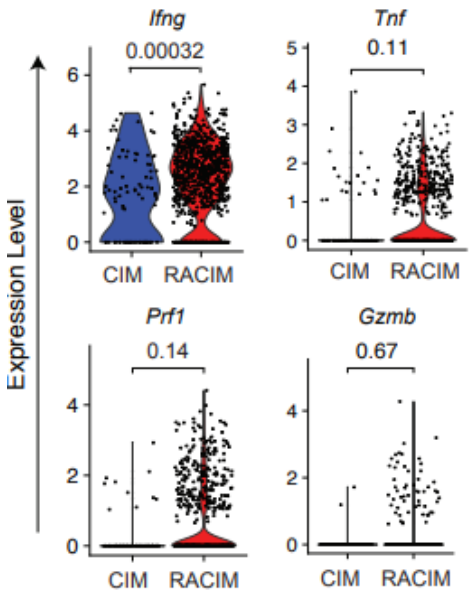
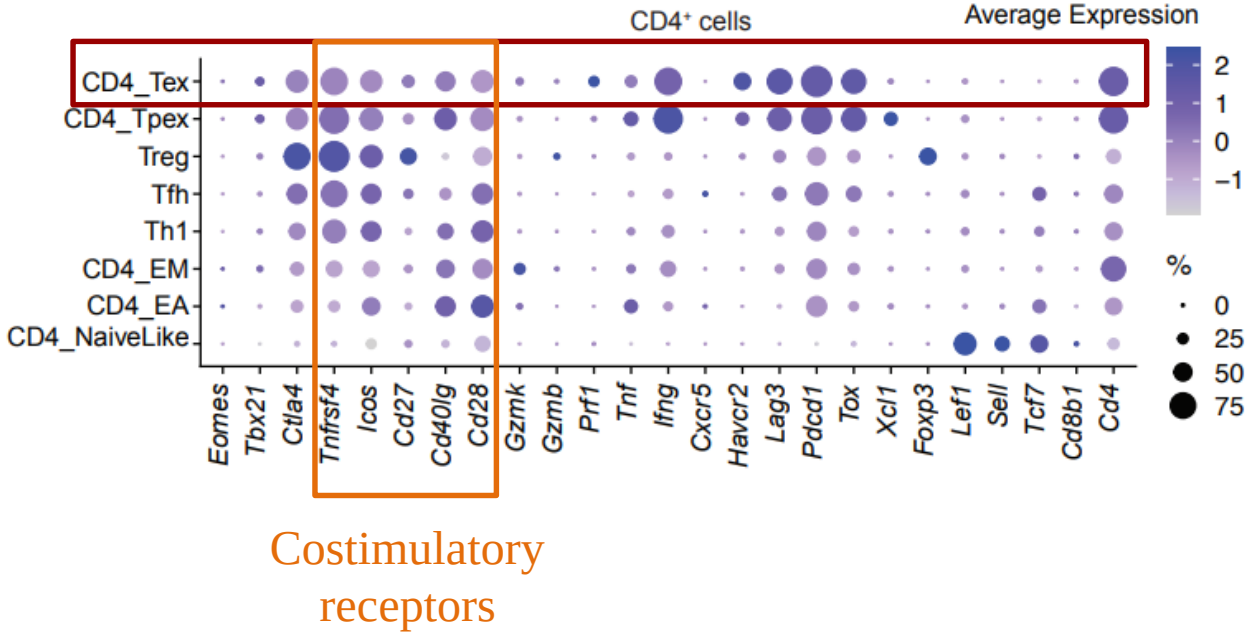
CD4 Tex TILs



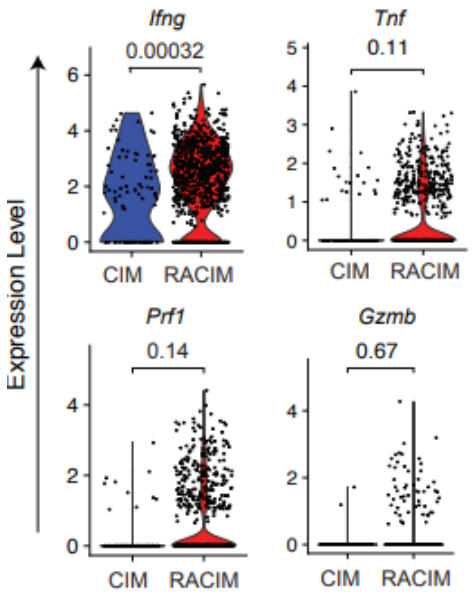


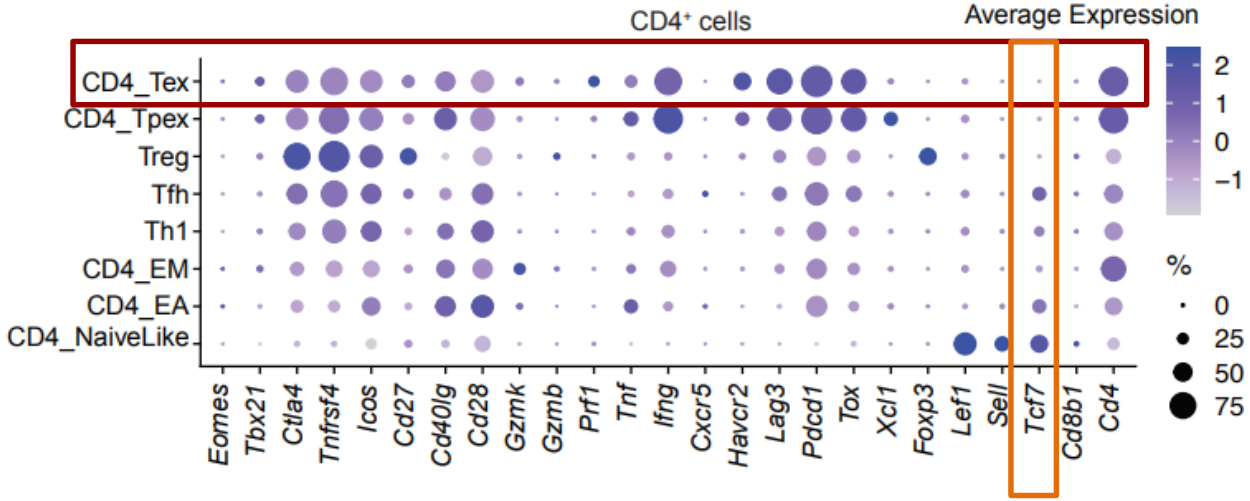
Costimulatory receptors

Cancer Discov 2022;12:1–26

RACIM expands tumor-rejecting CD4+ and CD8+ TILs with activation and exhaustion features

CD4 Tex TILs

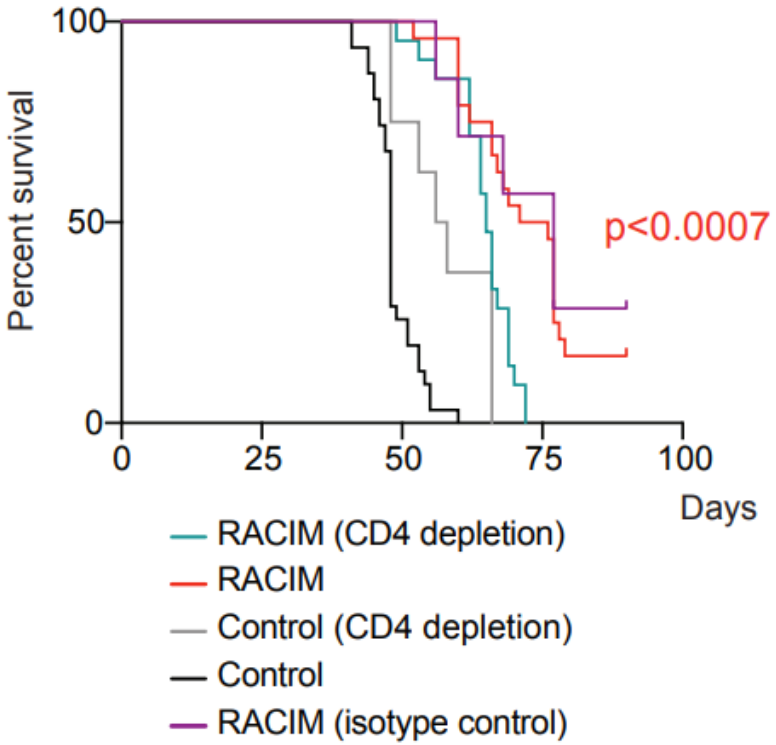


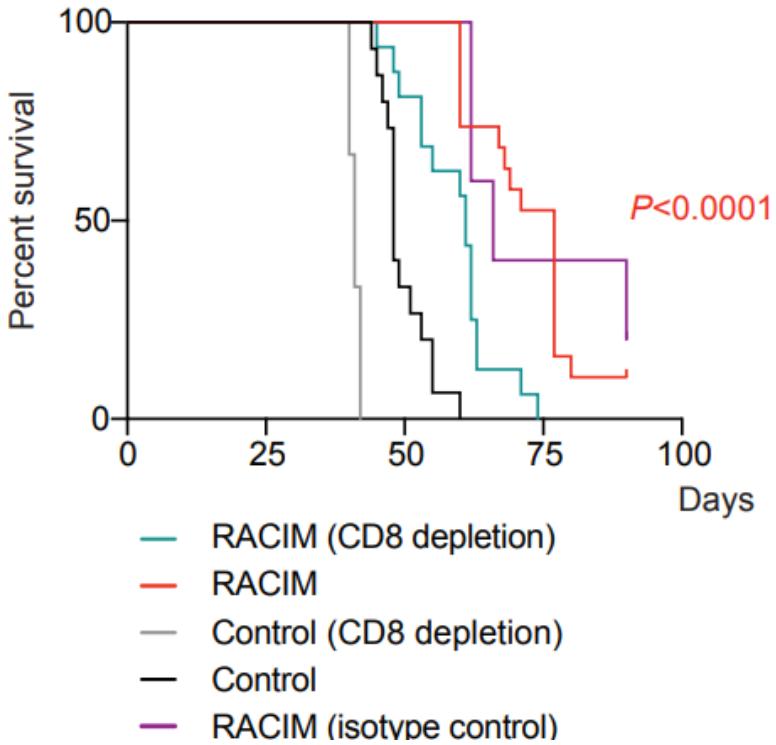


Terminal Tex state

Cancer Discov 2022;12:1-26

RACIM expands tumor-rejecting CD4+ and CD8+ TILs with activation and exhaustion features





Cancer Discov 2022;12:1-26

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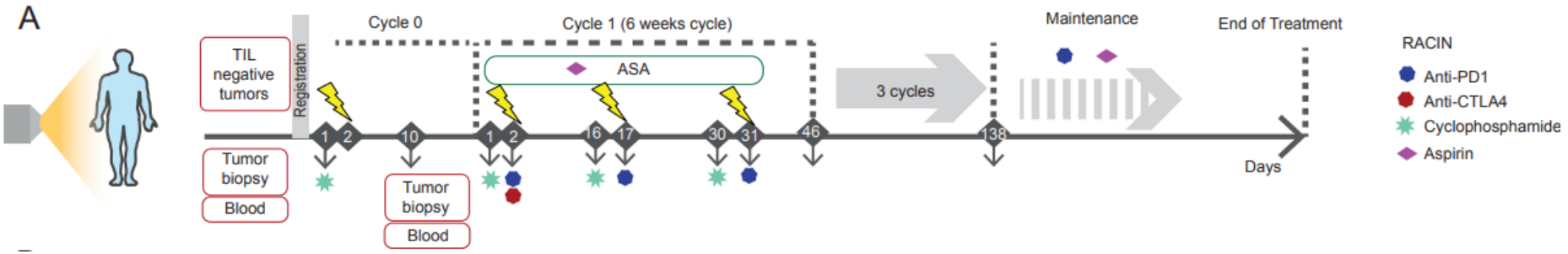
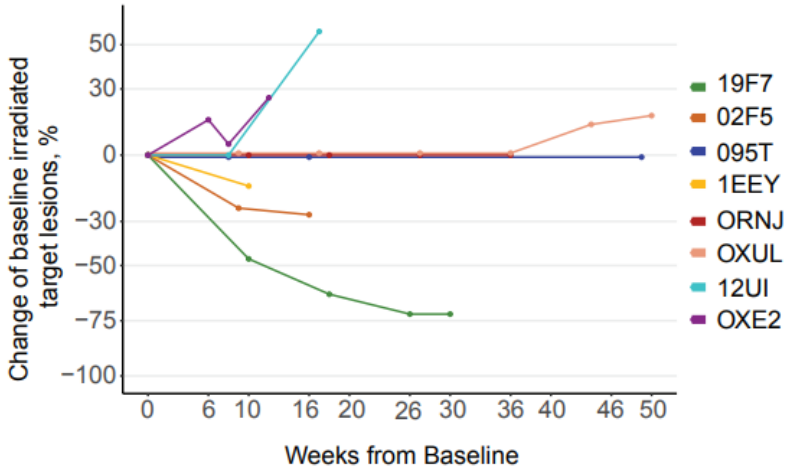
- These findings were translated to a phase I clinical trial administering LDRT, low-dose cyclophosphamide and immune checkpoint blockade to patients with **immune desert tumors**. In responsive patients, the combinatorial treatment triggered T-cell infiltration, predominantly of CD4+ cells with Th1 signatures

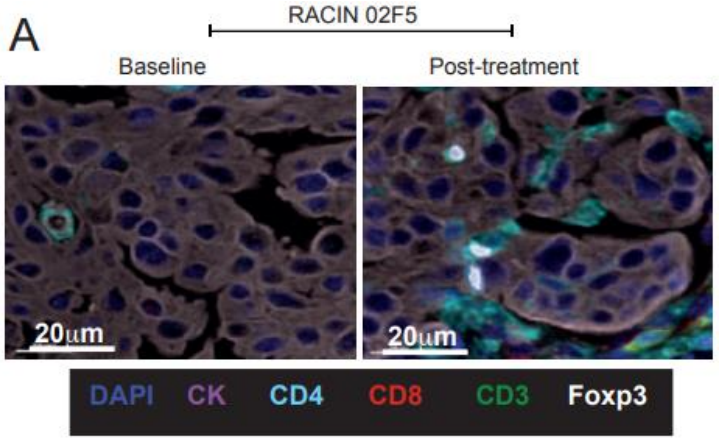
Cancer Discov 2022;12:1-26

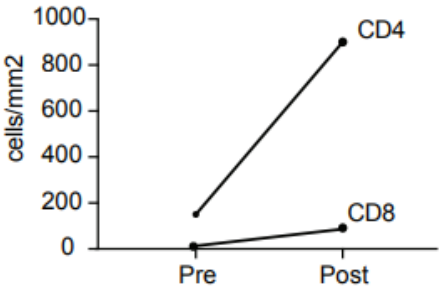
Low-Dose Radiotherapy Reverses Tumor Immune Desertification and Resistance to Immunotherapy

Immune desert tumors in humans are reprogrammed following low-dose radiotherapy









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- **These data support the rational combination of LDRT, that elicits dramatic reprogramming of the TIME, with immunotherapy for the treatment of low-T cell infiltrated tumors**

Cancer Discov 2022;12:1-26

DO_CHUV_Lausanne
Prof. George Coukos, MD, PhD

CTE
Prof. Lana Kandalaft, PhD

Immune monitoring Lab
Alex Harari

Immune Landscape Lab

- ***Sylvie Rusakiewics, PhD***
- ***Esther Danenberg, MSc***
- ***Ekaterina Fortis, MSc***
- ***Pinelopi Chatziemmanuil, MSc***
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Alina Gouloumi
Anny Zaharatou

Aris Spathis
Makis Pouliakis
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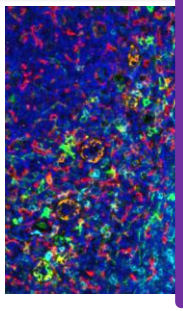
Maria Kelidou,
Katerina Fouledaki,
Pantelis Mantas,
Xristakis Risilia,
Athanasia Koliopanou
Konstantina Gaki
Haritidou Emmanouela
Nasia Nomikariou
Euthimios Souras
Eva Delitzaki

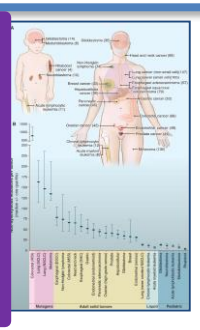
Panagiota Leou
Chara Georgoula

5th Masterclass OF SARCOMA AND RARE CANCERS

DECEMBER 9-10 2022 Acropolis museum venue *"Dimitrios Pantermalis"* ATHENS



THANK YOU



16.15-17.30 **Session 5: Immunotherapy in sarcomas**
Moderators: **J-M. Broto, R. Jones**

16.15-16.35	Tissue microenvironment and immunotherapy in sarcomas	**P. Foukas**
16.35-16.55	Immunotherapy for patients with sarcoma: pathological or biological driven choice	**A. Italiano**
16.55-17.15	Perspectives in Cell Therapy and Immunotherapy of sarcomas	**G. Demetri**
17.15-17.30	Discussion	

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LUDWIG CANCER RESEARCH

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CHUV

Low Dose Radiotherapy Reverses Tumor Immune Desertification and Resistance to Immunotherapy

Along with its direct tumoricidal effects, **hypofractionated (high-dose) radiation therapy** (RT) can mediate important immunomodulatory effects including:

(i) In situ vaccination through release of tumor-associated antigens
(ii) the activation of dendritic cells (DCs)
(iii) the release of danger signals and the upregulation of cytokines and chemokines
(iv) normalization of the tumor vasculature
(v) activate DNA sensing pathways in host and tumor cells, triggering production of type I interferon (IFN) and mobilizing innate and adaptive immunity
(vi) abscopal effect

Cancer Discovery (2021); *DOI: 10.1158/2159-8290.CD-21-0003*