What's Next for Cancer Immunotherapy?

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Bernard A. Fox, PhD – COI Disclosures

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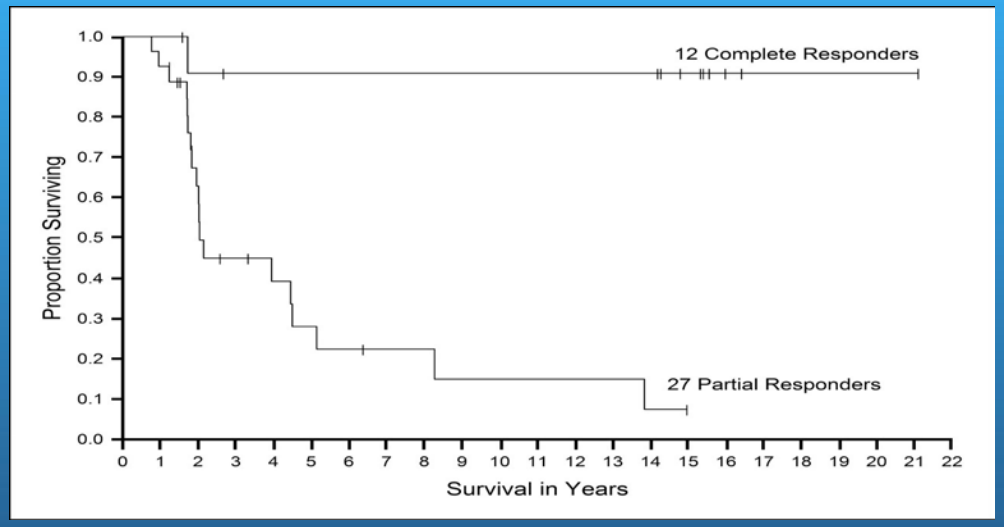
- Contracted Research: Macrogenics, OncoSec, BMS, Akoya, Nanostring, Incyte, Shimadzu, Viralytics/Merck
- Ownership interest *greater* than 5%: UbiVac

April 2021

Earle A. Chiles Research Institute

Immunotherapy can Cure Patients of Their Cancer!



Smith F O et al. Clin Cancer Res 2008;14:5610-5618

NCI's Dr. Steven Rosenberg reunites with former patient Linda Taylor, whose cancer vanished 29 years ago. She was interviewed for a PBS series.

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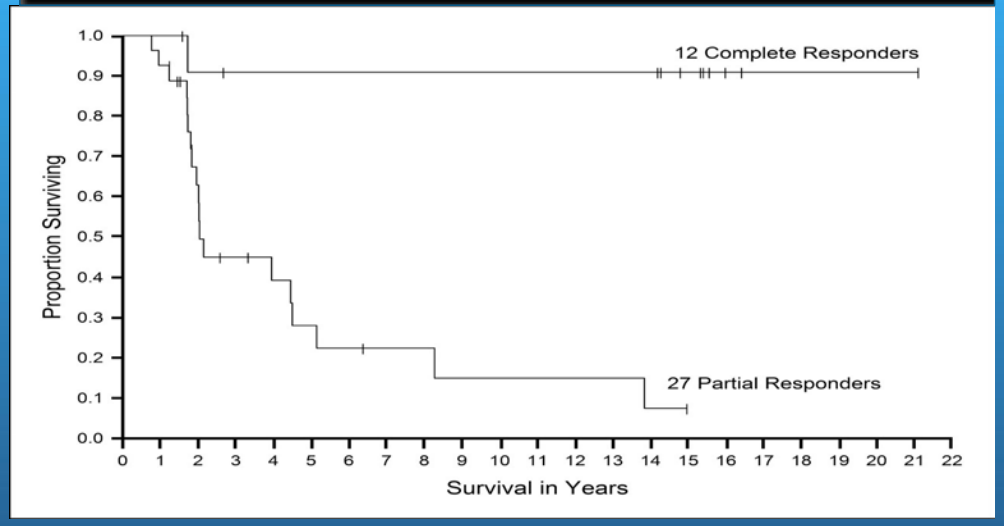
Immunotherapy can Cure Patients of Their Cancer!

- Certainly IL-2 can "Cure"



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In 2021 we still do not know:

- Why these patients were "cured"
- If other immunotherapies will cure

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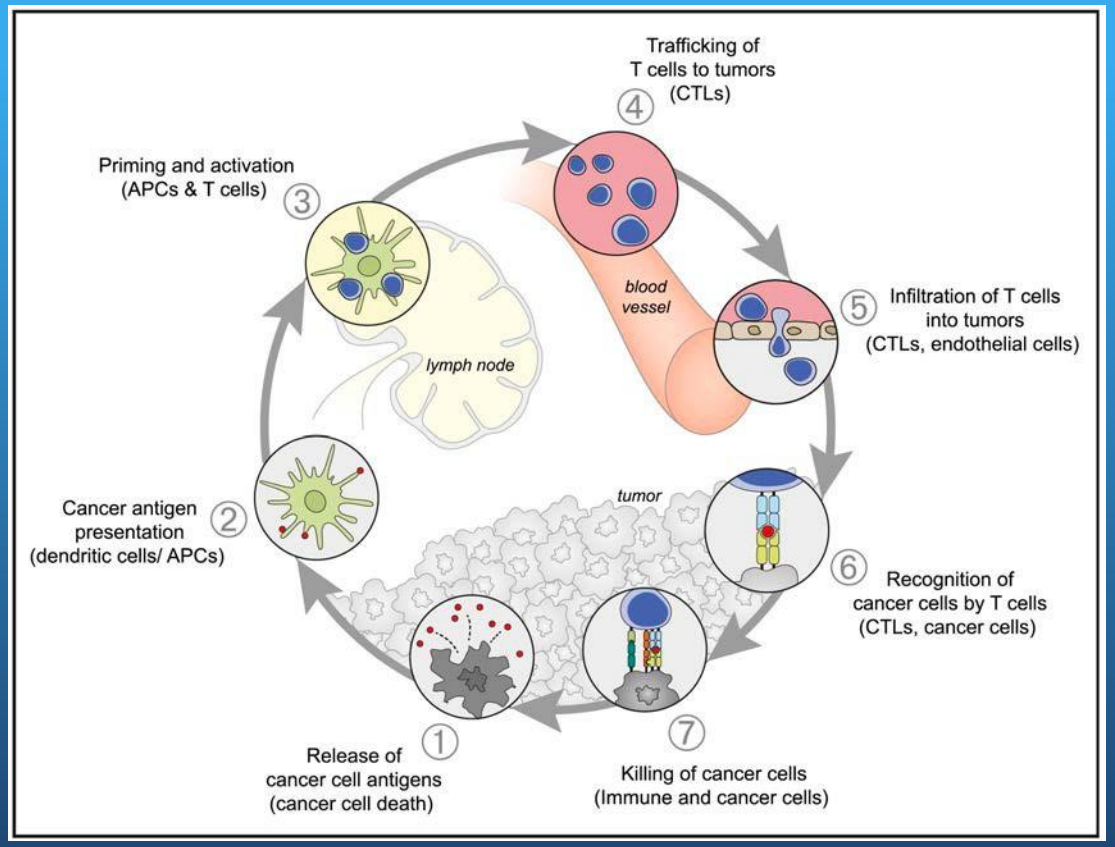
Cancer Immunity Cycle



Daniel S. Chen[1,3] and Ira Mellman[2,3,*]

Immunity *39*, July 25, 2013

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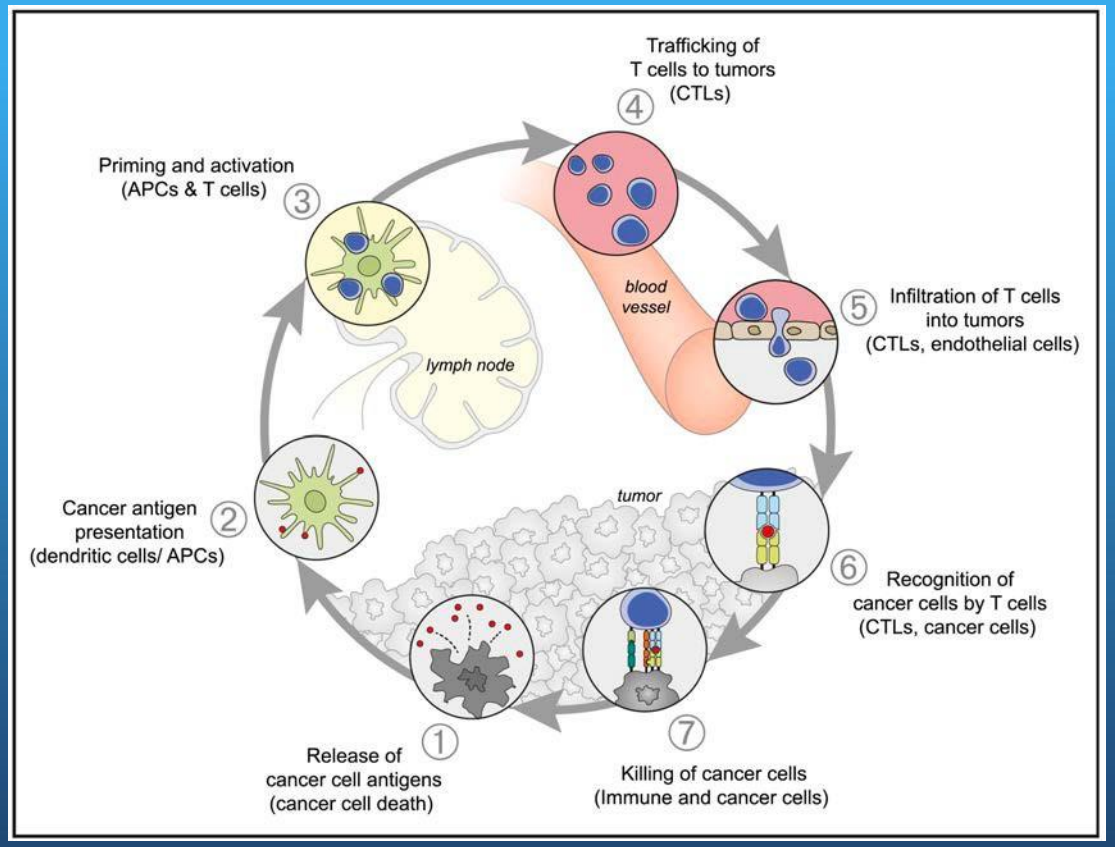
Hypothesis:

T cell immune responses that effectively recognize all cancer cells will **CURE** patients of cancer

T Cell Centric View



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NK cells?
B cells?
Innate effectors?

Cancer immunology

B cells to the forefront of immunotherapy

Tullia C. Bruno

Nature | Vol 577 | 23 January 2020

Three studies reveal that the presence in tumours of two key immune components — B cells and tertiary lymphoid structures — is associated with favourable outcomes when individuals undergo immunotherapy. See p.549, p.556 & p.561

Biomarkers:

- Prognostic significance
- Marker of immune response

Article

B cells and tertiary lymphoid structures promote immunotherapy response

https://doi.org/10.1038/s41586-019-1922-8
Received: 5 February 2019
Accepted: 4 December 2019
Published online: 15 January 2020

Beth A. Helmink[1,24*], Sangeetha M. Reddy[2,24], Jianjun Gao[3,24], Shaojun Zhang[4,24], Rafet Basar[5,24], Rohit Thakur[1], Keren Yizhak[6], Moshe Sade-Feldman[6,7], Jorge Blando[8], Guangchun Han[4], Vancheswaran Gopalakrishnan[1], Yuanxin Xi[9], Hao Zhao[8], Rodabe N. Amaria[10], Hussein A. Tawbi[10], Alex P. Cogdill[1], Wenbin Liu[8], Valerie S. LeBleu[11], Fernanda G. Kugeratski[11], Sapna Patel[10], Michael A. Davies[10], Patrick Hwu[10], Jeffrey E. Lee[1], Jeffrey E. Gershenwald[1], Anthony Lucci[1], Reetakshi Arora[4], Scott Woodman[10], Emily Z. Keung[1], Pierre-Olivier Gaudreau[1], Alexandre Reuben[12], Christine N. Spencer[13], Elizabeth M. Burton[1], Lauren E. Haydu[1], Alexander J. Lazar[4,14,15], Roberta Zapassodi[16], Courtney W. Hudgens[14], Deborah A. Ledesma[14], SuFey Ong[17], Michael Bailey[17], Sarah Warren[17], Disha Rao[18], Oscar Krijgsman[18], Elisa A. Rozeman[18], Daniel Peeper[18], Christian U. Blank[18], Ton N. Schumacher[18], Lisa H. Butterfield[19], Monika A. Zelazowska[20], Kevin M. McBride[20], Raghu Kalluri[11], James Allison[8], Florent Petitprez[21,22,23], Wolf Herman Fridman[21,22], Catherine Sautès-Fridman[21,22], Nir Hacohen[6,7], Katayoun Rezvani[5,25], Padmanee Sharma[3,8,25], Michael T. Tetzlaff[14,15,25], Linghua Wang[4,25] & Jennifer A. Wargo[1,4,25*]

Article

Tertiary lymphoid structures improve immunotherapy and survival in melanoma

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Rita Cabrita[1,12], Martin Lauss[1,12], Adriana Sanna[1], Marco Donia[2], Mathilde Skaarup Larsen[3], Shamik Mitra[1], Iva Johansson[1], Bengt Phung[1], Katja Harbst[1], Johan Vallon-Christersson[1], Alison van Scholack[4], Kristina Lövgren[1], Sarah Warren[4], Karin Jirström[1], Håkan Olsson[1], Kristian Pietras[5], Christian Ingvar[6], Karolin Isaksson[6], Dirk Schadendorf[7], Henrik Schmidt[8], Lars Bastholt[9], Ana Carneiro[1,10], Jennifer A. Wargo[11], Inge Marie Svane[2] & Göran Jönsson[1*]

B cells are associated with survival and immunotherapy response in sarcoma

Florent Petitprez, Aurélien de Reyniès, Emily Z. Keung, Tom Wei-Wu Chen, Cheng-Ming Sun, Julien Calderaro, Yung-Ming Jeng, Li-Ping Hsiao, Laetitia Lacroix, Antoine Bougoüin, Marco Moreira, Guillaume Lacroix, Ivo Natario, Julien Adam, Carlo Lucchesi, Yec'han Laizet, Maud Toulmonde, Melissa A. Burgess, Vanessa Bolejack, Denise Reinke, Khalid M. Wani, Wei-Lien Wang, Alexander J. Lazar, Christina L. Roland, Jennifer A. Wargo, Antoine Italiano, Catherine Sautès-Fridman, Hussein A. Tawbi ✉ & Wolf H. Fridman ✉

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Cancer immunology

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Biomarkers:

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B Cell Effector Functions *and Suppressive Functions*

Article

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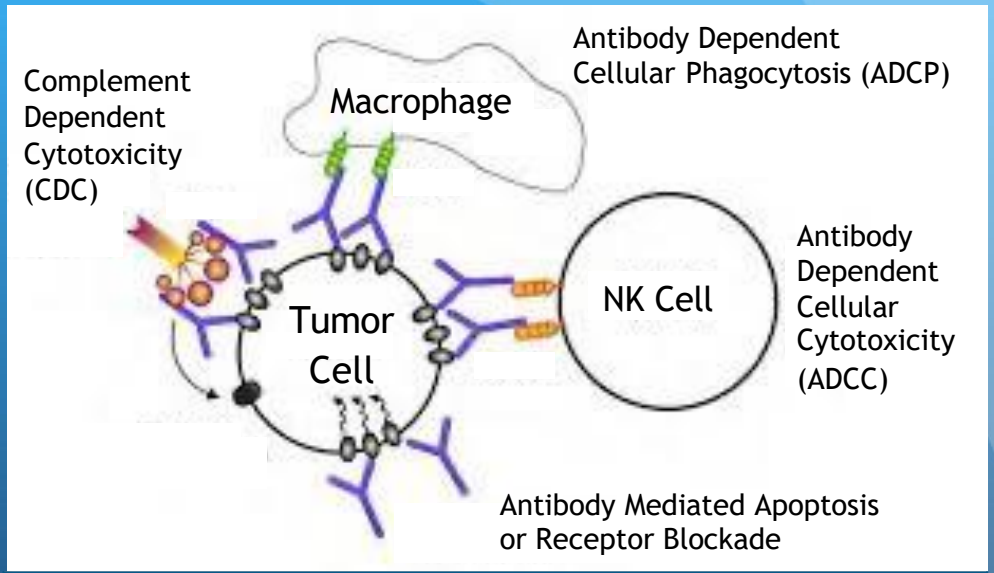
B Cell Effector Mechanisms Exist!

B Cell Effector Mechanisms

- ✕ CDC
- ✕ ADCC
  - ✕ Macrophages
  - ✕ NK cells
- ✕ Signaling
  - ✕ Apoptosis
  - ✕ Blocking (Herceptin)
- ✕ Killer B cells (Fas-FasL)

Other Functions

- ✕ Augment APC function



- Tao H, Eur J. Immunol 2015 45(4): 999-1009
- Li Q, J. Immunol 2009 183(5): 3195-3203
- Xu G, BBRC 2013 437 (2):287-291
- Neuberger M, JITC 2013 (Supp1 1) : P271

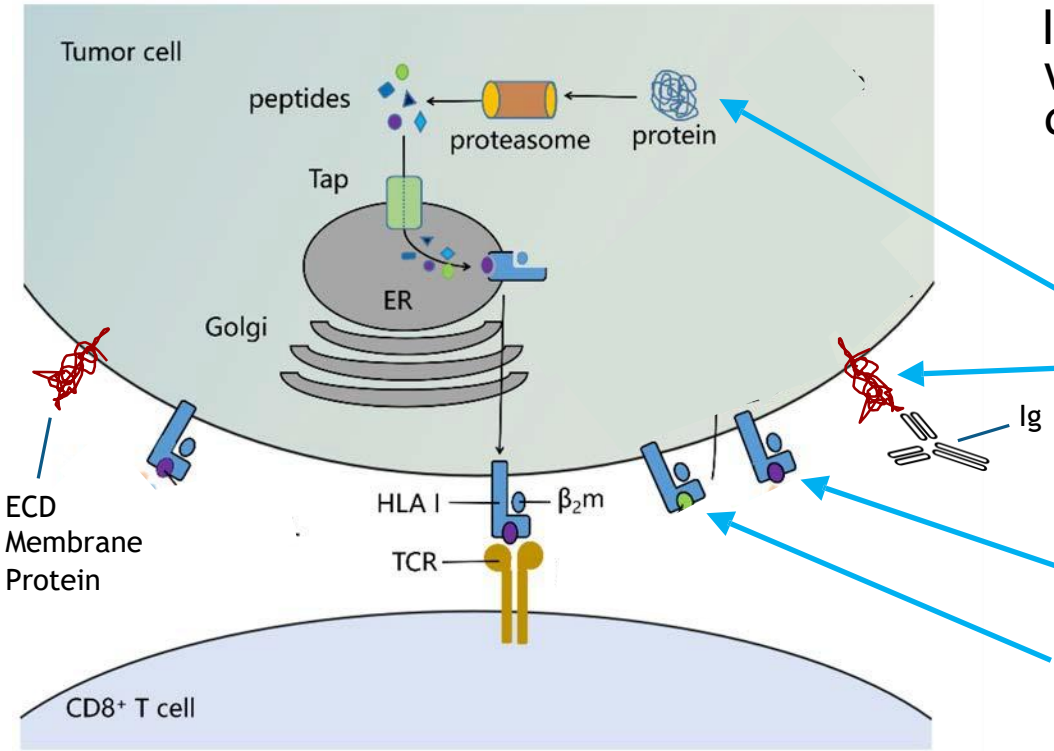
B Cell Antibody Responses MAY Play a Critical Role in Anti-Cancer Immunity in Humans

We Don't Know Because we haven't carefully looked using robust technology

Can also be a double-edged sword

- APC and Effector functions
- Suppressive functions

Immune responses against cancer "Surfaceome" - Natural and Synthetic Immunity



Immune responses to proteins whose genes are over-expressed or differentially expressed by cancer

Antibody responses

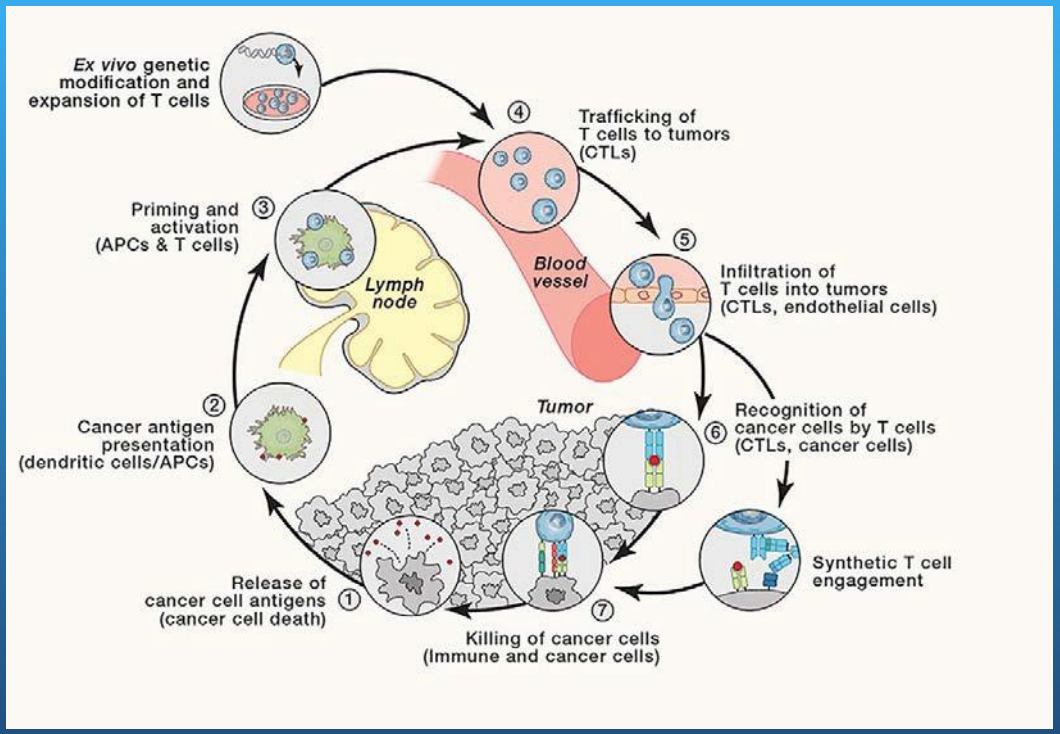
- Intracellular proteins
- ECD of transmembrane proteins

T cell responses - Peptidome

- Non-mutated shared antigens
- Mutated epitopes

Modified Image from *Int J. Sci 2019 20, 3912*

Synthetic Immunology

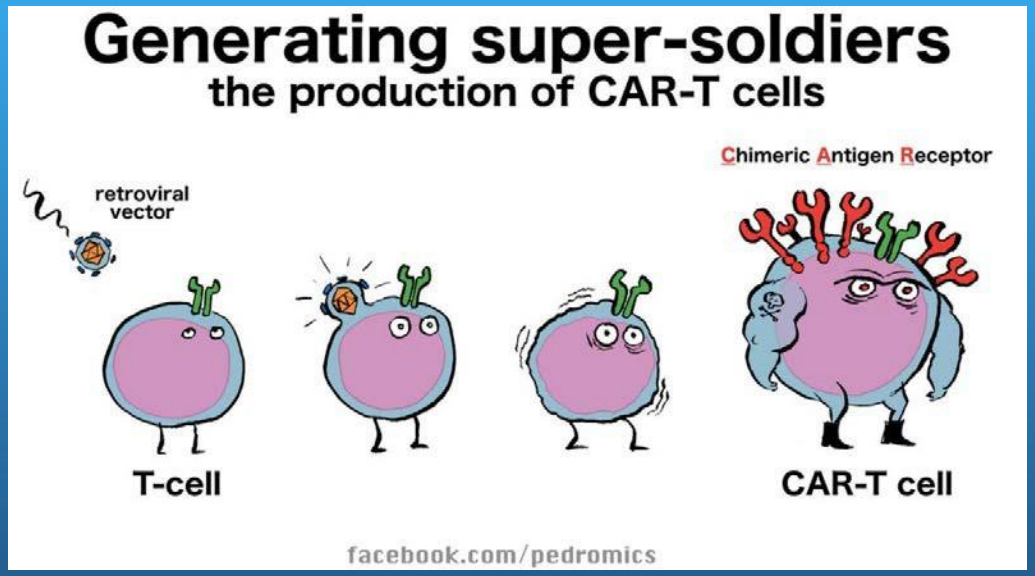


Immunity 52, January 14, 2020

Identification of surfasome targets:

- New Chimeric Ag receptors (T, NK, other)
- More strategies to target immune cells to cancer
  - DARTs / BiTEs
- Fully synthetic constructs / drugs
  - ADC

Synthetic Immunology
- Genetically Engineered Cells



- New Chimeric Ag and TCR receptor constructs
  - T & NK / autol & allo
- Augmented effector functions
- Shielded from inhibitory molecules
- Engineered to sense and be protected from low O2 and pH

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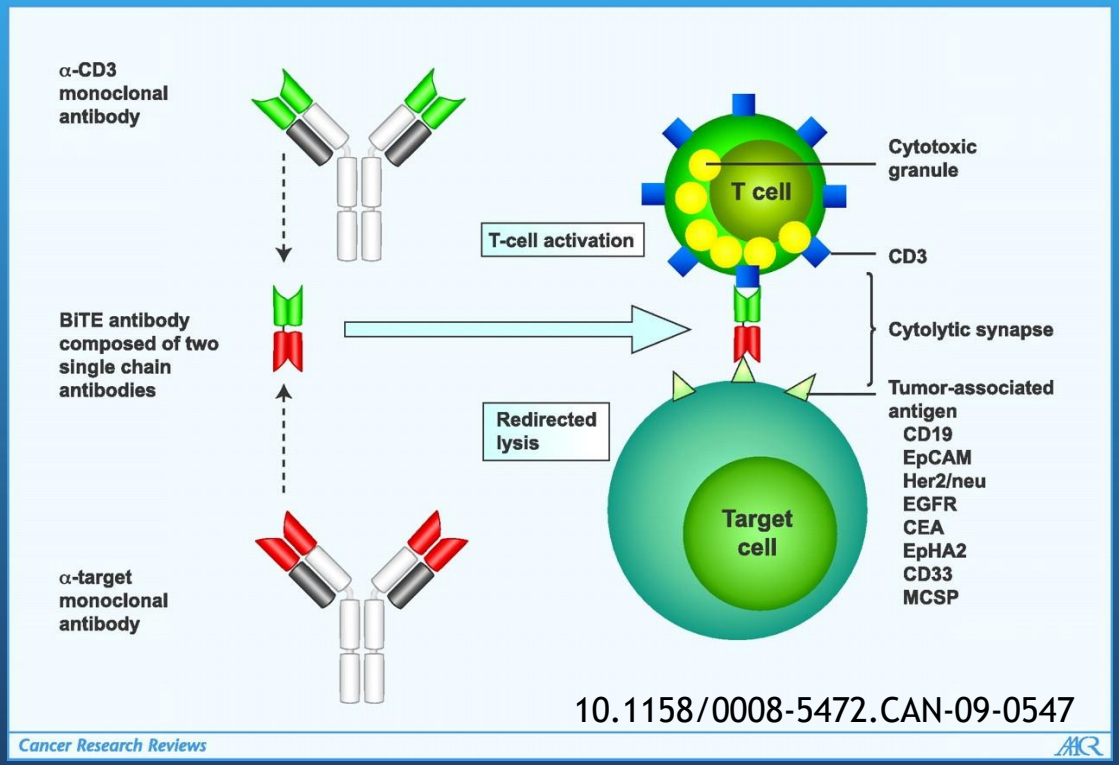
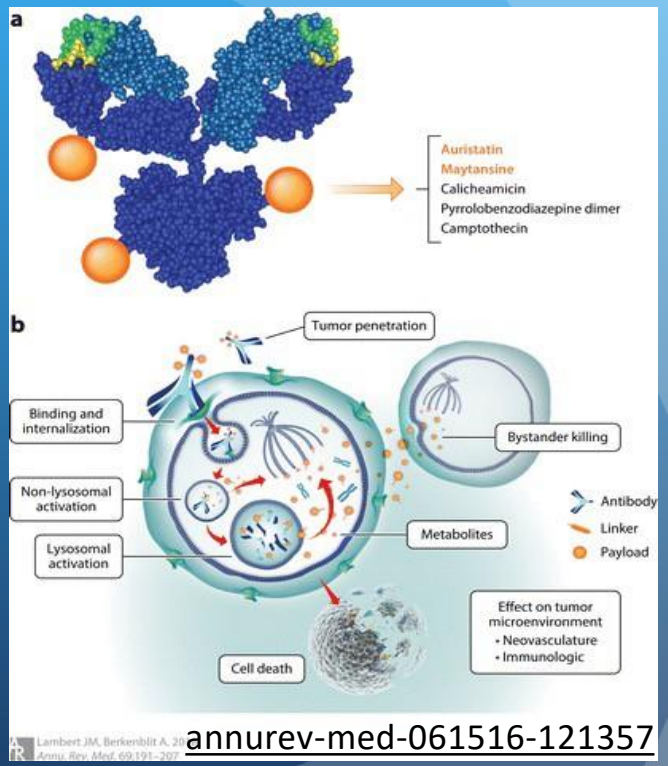
Synthetic Immunology
- Targets Immunity or Drug without Gene Therapy



10.1158/0008-5472.CAN-09-0547



annurev-med-061516-121357

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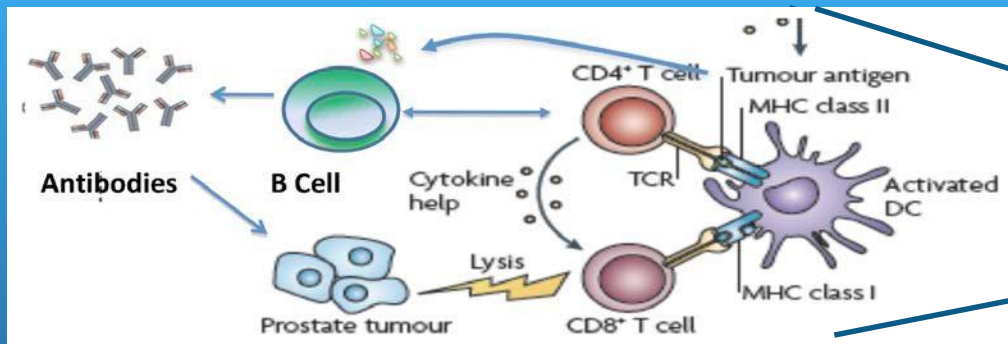
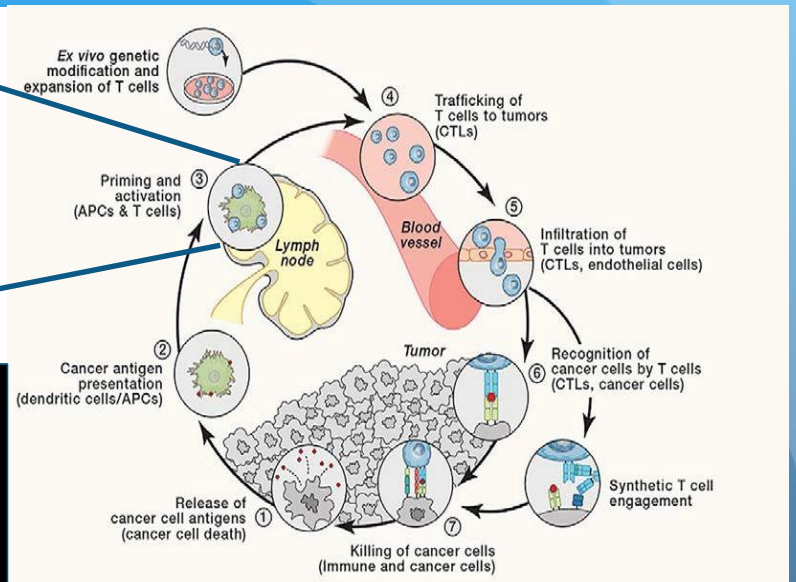
B Cell Response Reveals Antigens Recognized by CTL





Priti S. Hedge and Daniel S. Chen

Immunity 52, January 14, 2020

Coordinated T & B immune response to cancer:

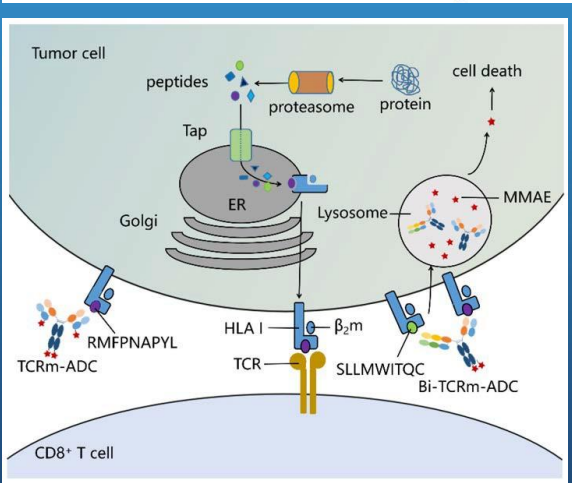
- *Kwek S, et al, J Immunol 2012*
- *Tripathi SC, et al, PNAS 2016*
- *Hulett T, et al, J ImmunoTher Cancer 2018*

Modified from: Drake C, Nat Rev Immunol, 2010
Goodnow, Nat. Immunol. 2010

Characterized the IgG Profile of Newly Diagnosed Patients with NSCLC – What Were IgG Against?

Immunoproteasome deficiency is a feature of non-small cell lung cancer with a mesenchymal phenotype and is associated with a poor outcome

Satyendra C. Tripathi[a], Haley L. Peters[b], Ayumu Taguchi[c], Hiroyuki Katayama[a], Hong Wang[a], Amin Momin[a], Mohit Kumar Jolly[d], Muge Celiktas[a], Jaime Rodriguez-Canales[c], Hui Liu[c], Carmen Behrens[c], Ignacio I. Wistuba[c], Eshel Ben-Jacob[d,1], Herbert Levine[d,2], Jeffrey J. Molldrem[b], Samir M. Hanash[a], and Edwin J. Ostrin[e,2]



Int. J. Mol. Sci. **2019**, *20*, 3912

Newly diagnosed NSCLC patients have IgG Ab to proteins whose peptides are being presented by HLA on surface of lung cancer cell lines

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PNAS | Published online February 29, 2016 | E1557

Newly Diagnosed NSCLC Patients have a Coordinated B and T cell Response to Shared Cancer Antigens

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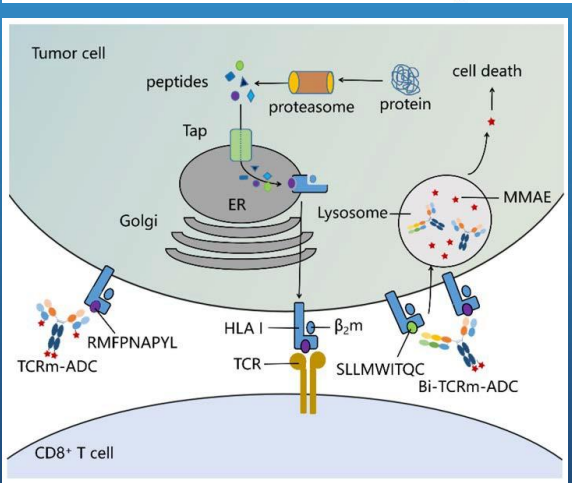

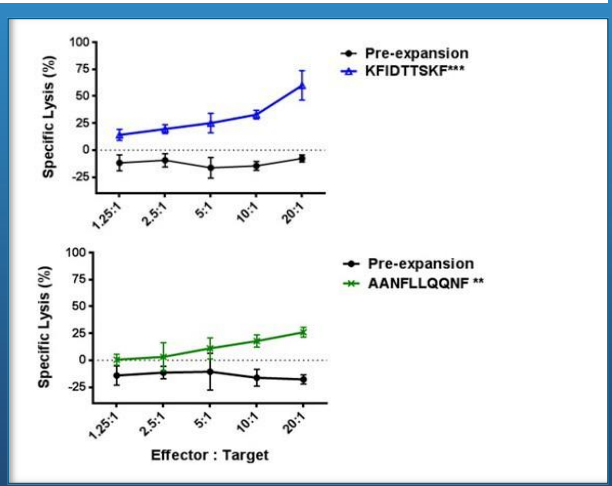

Patients have T cells that can be activated by peptide (IVS) to become CTL

Int. J. Mol. Sci. **2019**, *20*, 3912

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PNAS | Published online February 29, 2016 | E1557

TIL Recognize Shared Melanoma Antigens

Recognition of Shared Melanoma Antigens in Association With Major HLA-A Alleles by Tumor Infiltrating T Lymphocytes From 123 Patients With Melanoma

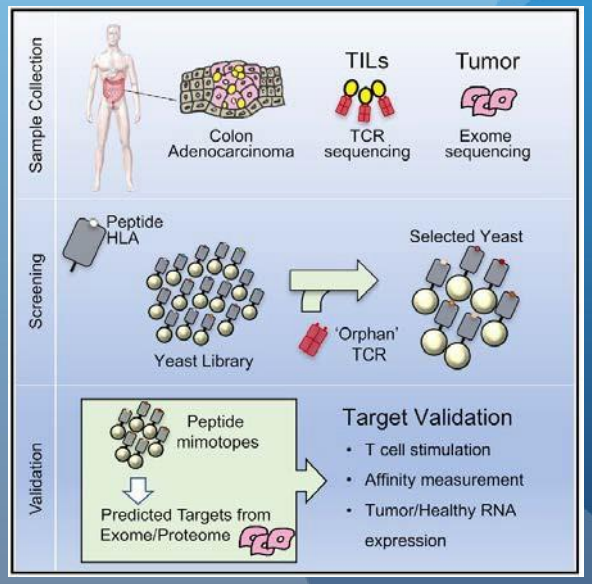
Yutaka Kawakami;Nita Dang;Xiang Wang;Janis Tupesis;Paul Robbins;Rong-Fu Wang;John Wunderlich;John Yannelli;Steven Rosenberg;

- Screened for recognition of shared melanoma antigens
  - tyrosinase, MART-1/melan-A, gp100, TRP1, TRP2
  - peptides derived from MAGE-1 and MAGE-3.
- Majority of HLA-A2 TIL recognized shared melanoma antigens
- Recognition of gp100 by HLA-A2 restricted TIL significantly correlated with clinical response to adoptive immunotherapy with TIL in 21 HLA-A2 melanoma patients ($p = 0.024$).

Journal of Immunotherapy. 23(1):17-27, JANUARY 2000

Antigen Identification for Orphan T Cell Receptors Expressed on Tumor-Infiltrating Lymphocytes

Marvin H. Gee,[1,2,11] Arnold Han,[3,4,11] Shane M. Lofgren,[3,5] John F. Beausang,[6] Juan L. Mendoza,[2] Michael E. Birnbaum,[1,2] Michael T. Bethune,[7] Suzanne Fischer,[2] Xinbo Yang,[2] Raquel Gomez-Eerland,[8] David B. Bingham,[5] Leah V. Sibener,[1,2] Ricardo A. Fernandes,[2] Andrew Velasco,[2] David Baltimore,[7] Ton N. Schumacher,[8] Purvesh Khatri,[3,5] Stephen R. Quake,[6,9] Mark M. Davis,[3,4,10] and K. Christopher Garcia[2,10,12,*]



- 3 of 4 TCRs characterized recognized non-mutated peptide that is overexpressed in colon cancer and other cancers
- Identification of a shared non-mutated tumor antigen between two patients (same TCR α)
  - U2AF2 overexpressed in many cancers incl. COAD, NSCLC, Breast and lymphoma

Gee et al., 2018, Cell *172*, 1–15

Earle A. Chiles Research Institute

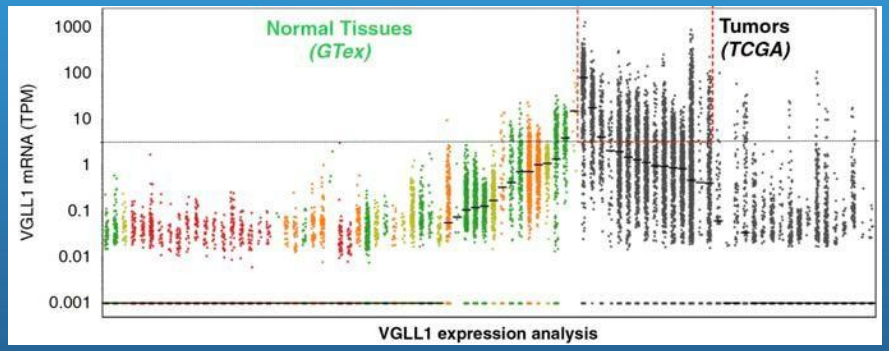
CTL recognize VGLL1 & Kill Pancreatic, Breast, Ovarian, Bladder, Gastric & Lung Cancer / But not Normal Cells

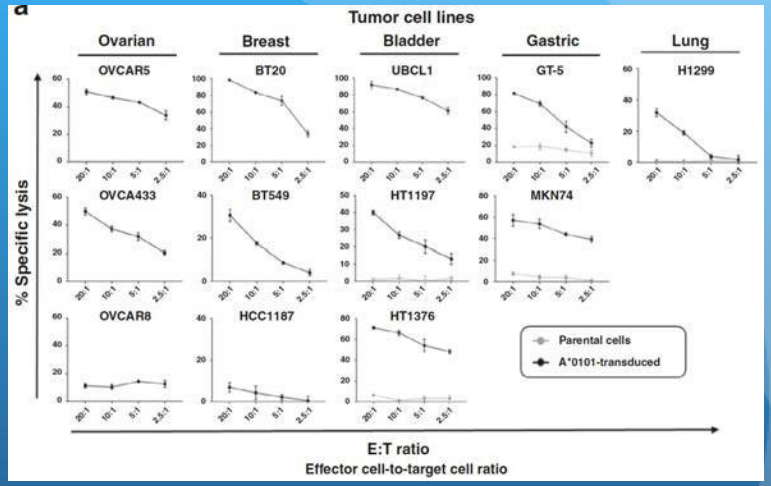
Vestigial-like 1 is a shared targetable cancer-placenta antigen expressed by pancreatic and basal-like breast cancers

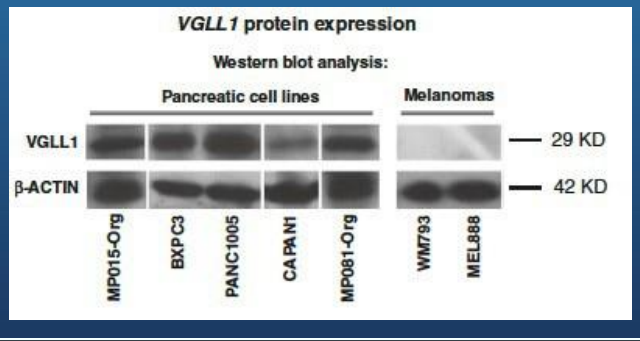
Sherille D. Bradley[1], Amjad H. Talukder[1], Ivy Lai[1], Rebecca Davis[1], Hector Alvarez[2], Herve Tiriac[3], Minying Zhang[1], Yulun Chiu[1], Brenda Melendez[1], Kyle R. Jackson[1], Arjun Katailiha[1], Heather M. Sonnemann[1], Fenge Li[1], Yaan Kang[4], Na Qiao[5], Bih-Fang Pan[6], Philip L. Lorenzi[7], Mark Hurd[8], Elizabeth A. Mittendorf[4], Christine B. Peterson[9], Milind Javle[10], Christopher Bristow[11], Michael Kim[4], David A. Tuveson[3], David Hawke[6], Scott Kopetz[10], Robert A. Wolff[10], Patrick Hwu[1], Anirban Maitra[12], Jason Roszik[1], Cassian Yee[1,13✉] & Gregory Lizée[1,13✉]

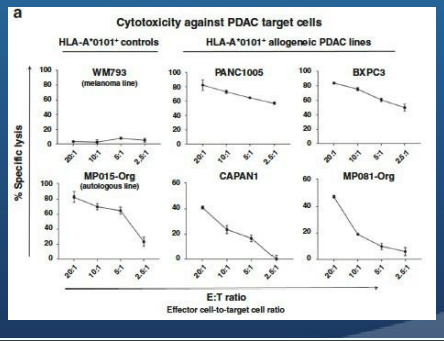
nature COMMUNICATIONS

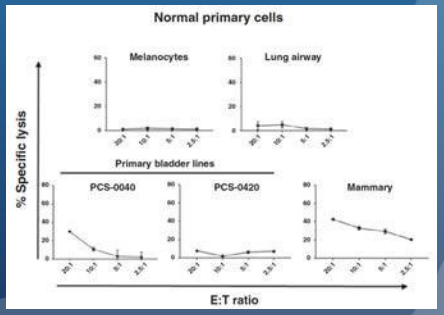
21 October 2020











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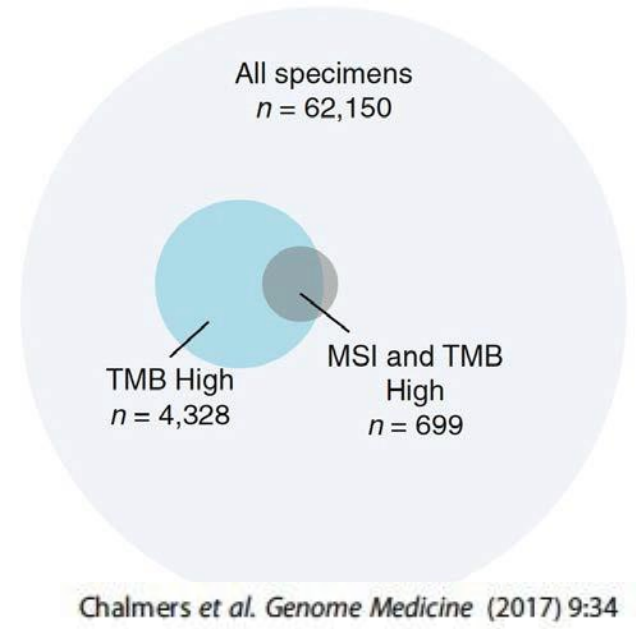
It is Good News that the Immune System can Recognize Non-Mutated Shared Ags



Source of Antigens for Low TMB

× Overexpressed self

× Cancer Testis Ags

× Viral antigens

Shared Non-Mutated Cancer Antigens

ON MEDICINE

The Search for Cancer Treatment Beyond Mutant-Hunting

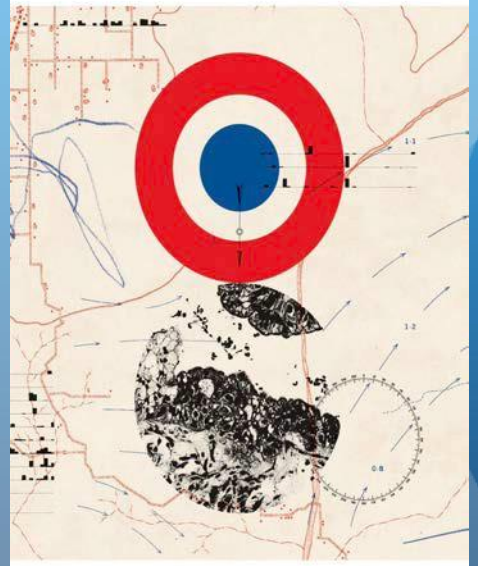


Photo illustration by Cristiana Couceiro. Cells: National Cancer Institute, via Wikipedia.

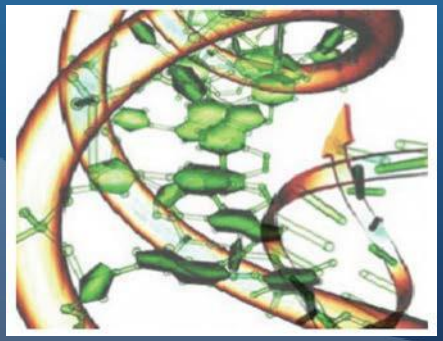
Human Cancer Biology

The Prioritization of Cancer Antigens: A National Cancer Institute Pilot Project for the Acceleration of Translational Research

Martin A. Cheever,[1] James P. Allison,[2] Andrea S. Ferris,[3] Olivera J. Finn,[4] Benjamin M. Hastings,[3] Toby T. Hecht,[5] Ira Mellman,[7] Sheila A. Prindiville,[6] Jaye L. Viner,[6] Louis M. Weiner,[8] and Lynn M. Matrisian[6]

Clin Cancer Res 2009;15:5323-5337

NIH **THE CANCER GENOME ATLAS**
National Cancer Institute
National Human Genome Research Institute



- ID genes in cancer that are upregulated, amplified, mutated compared to normal tissue
- Associations with survival

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How to Tailor Therapy to a Specific Patient?

REVIEW Open Access

Novel technologies and emerging biomarkers for personalized cancer immunotherapy

Journal for ImmunoTherapy of Cancer

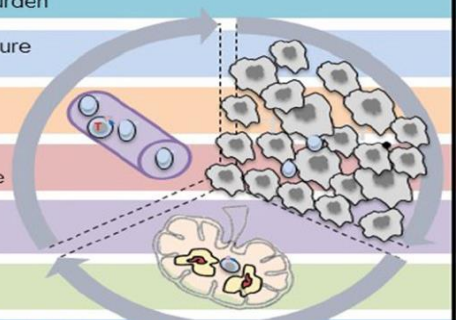
Yuan *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:3
DOI 10.1186/s40425-016-0107-3

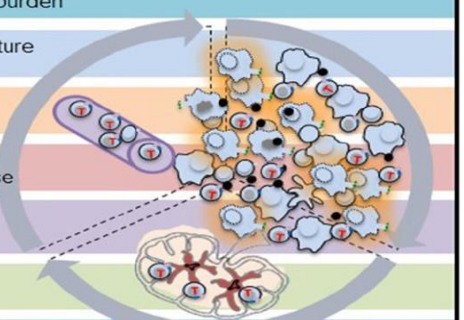
Jianda Yuan[1*], Priti S. Hegde[2], Raphael Clynes[3], Periklis G. Foukas[4,5], Alexandre Harari[4], Thomas O. Kleen[6], Pia Kvistborg[7], Cristina Maccalli[8], Holden T. Maecker[9], David B. Page[10], Harlan Robins[11], Wenru Song[12], Edward C. Stack[13], Ena Wang[14], Theresa L. Whiteside[15], Yingdong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

SITC Immune Biomarkers Task Force

Novel immune monitoring assays for biomarker discovery and personalized cancer immunotherapy

Monitoring strategy	Immunologically-unresponsive tumor	Immunologically-responsive tumor
Whole exome sequencing	Low mutational burden	High mutational burden
Gene signature/patterns	↓ activation signature	↑ activation signature
Epigenetic modification	↑ Treg/CD3 ratio ↓ CD3 cells	↓ Treg/CD3 ratio ↑ CD3 cells
Protein microarray	Poor general antibody response	Robust general antibody response
B/ T-cell receptor repertoire	Low CD3 count Low clonality	High CD3 count High clonality
Flow/Mass cytometry	↓ effector cells ↓ Teff/Treg ratio	↑ effector cells ↑ Teff/Treg ratio
Multicolor IHC	↓ effector cells, ↑ suppressor cells low PD-L1 on tumor and tumor infiltrating immune cells	↑ effector cells ↓ suppressor cells high PD-L1 on tumor and tumor infiltrating immune cell
Therapeutic strategy	Vaccination , ablation, radiotherapy, chemotherapy, oncolytic therapy, adaptive cellular therapy first	Immune checkpoint blockade therapies and other immunotherapies first
Legend	Blood vessel, Lymph node, Live tumor, Dying tumor, Naïve T-cell, Memory T-cell, Immature dendritic cell, Mature dendritic cell	





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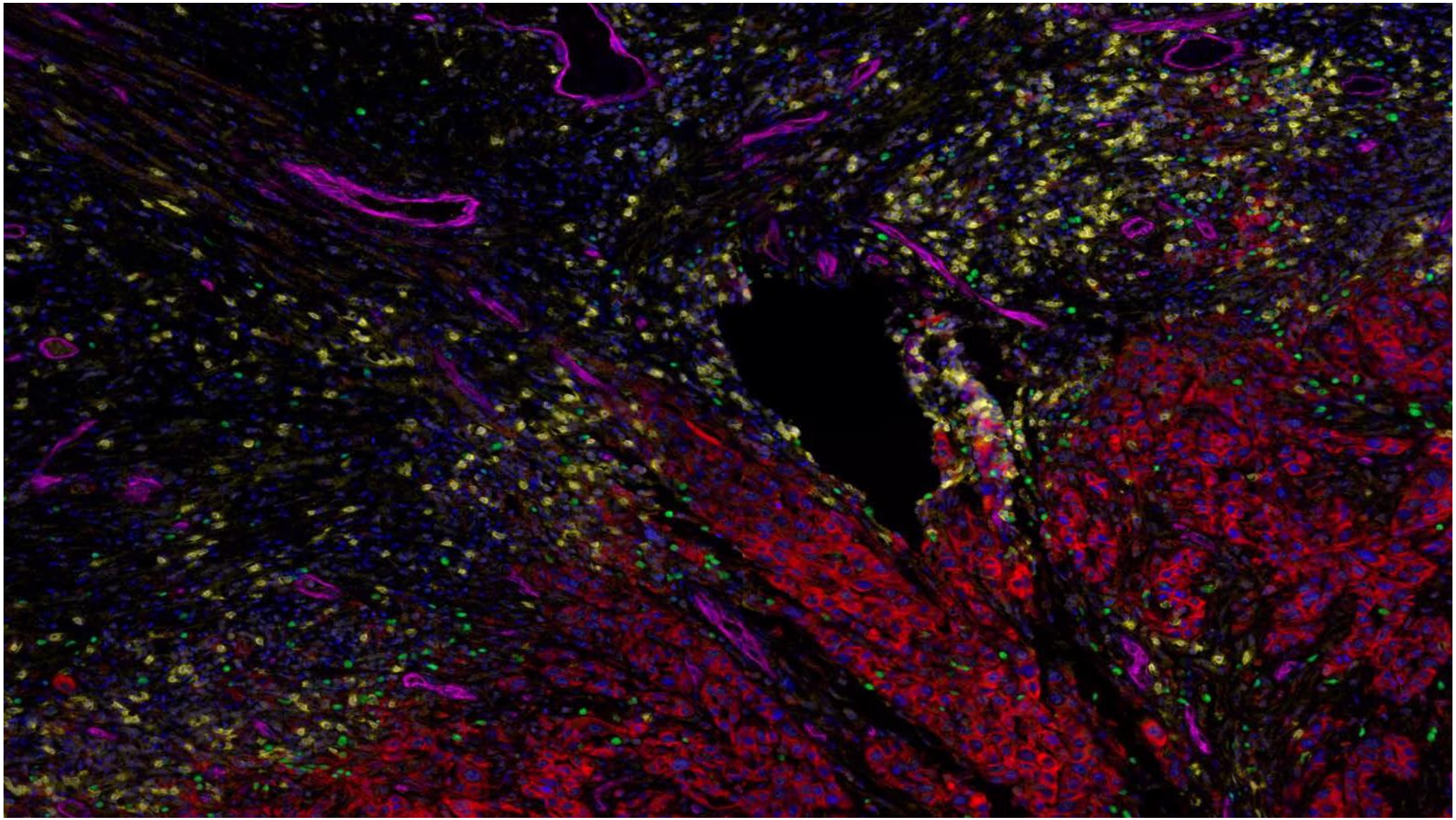

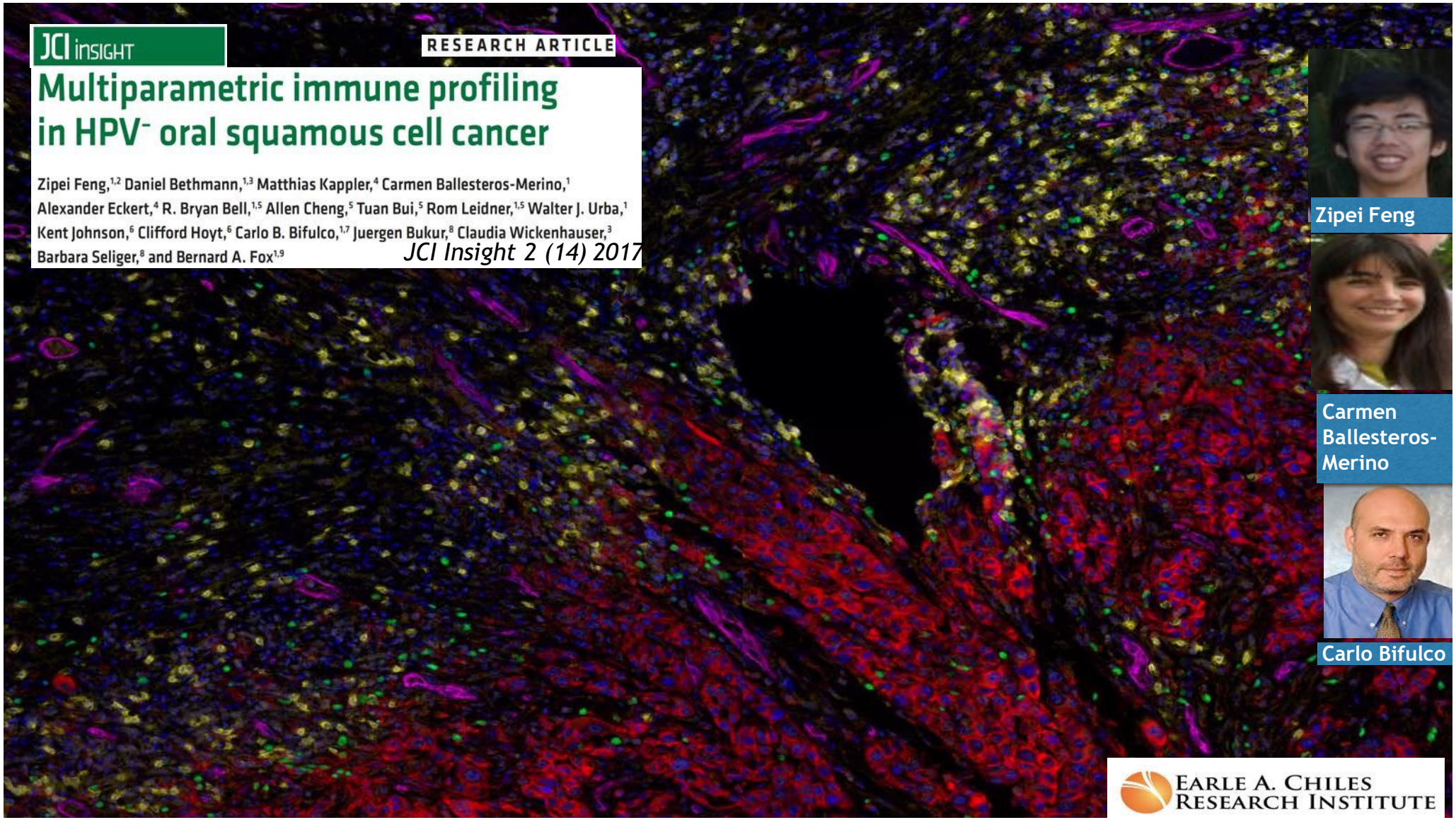
JCI insight
RESEARCH ARTICLE
Multiparametric immune profiling in HPV⁻ oral squamous cell cancer
Zipei Feng,[1,2] Daniel Bethmann,[1,3] Matthias Kappler,[4] Carmen Ballesteros-Merino,[1] Alexander Eckert,[4] R. Bryan Bell,[1,5] Allen Cheng,[5] Tuan Bui,[5] Rom Leidner,[1,5] Walter J. Urba,[1] Kent Johnson,[6] Clifford Hoyt,[6] Carlo B. Bifulco,[1,7] Juergen Bukur,[8] Claudia Wickenhauser,[3] Barbara Seliger,[8] and Bernard A. Fox[1,9]
JCI Insight 2 (14) 2017
Zipei Feng
Carmen Ballesteros-Merino
Carlo Bifulco
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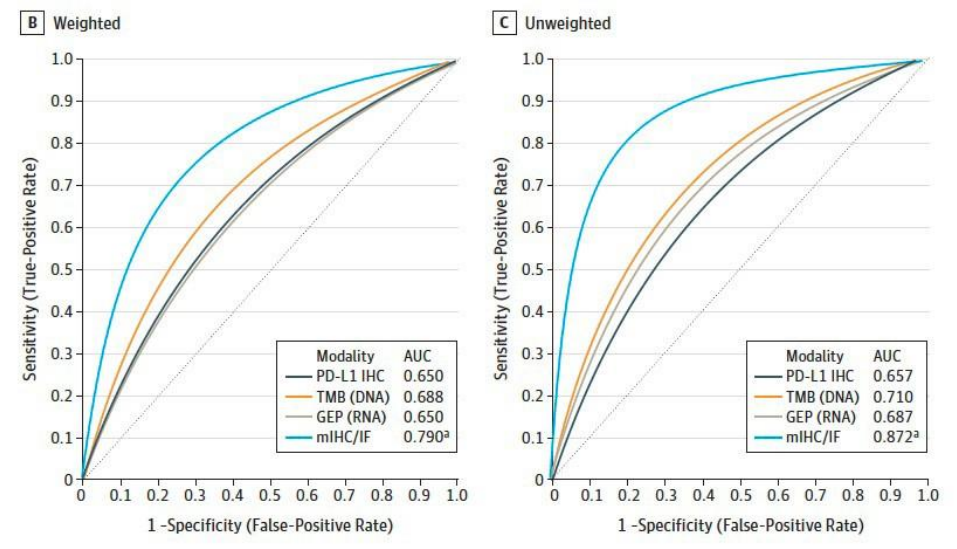
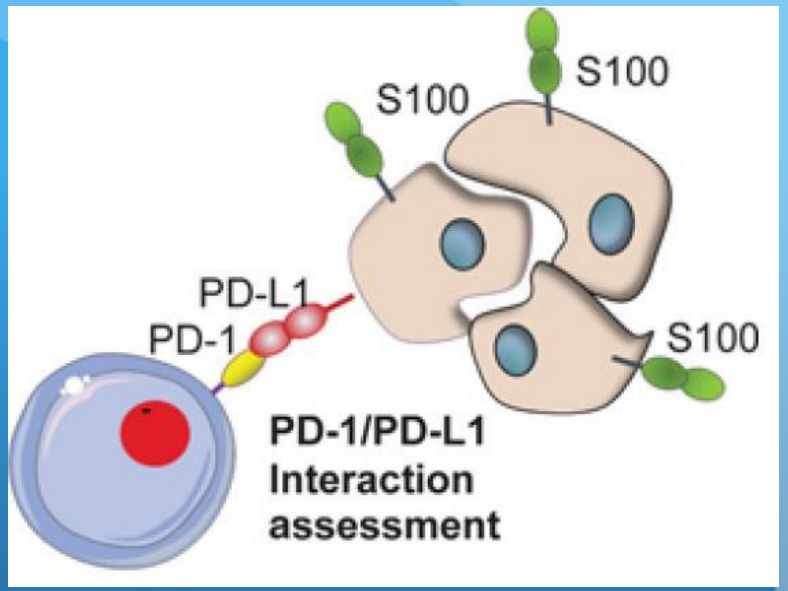
Multiplex IHC

JAMA Oncology | Original Investigation

Comparison of Biomarker Modalities for Predicting Response to PD-1/PD-L1 Checkpoint Blockade
A Systematic Review and Meta-analysis

Steve Lu; Julie E. Stein, MD; David L. Rimm, MD, PhD; Daphne W. Wang, MS; J. Michael Bell; Douglas B. Johnson, MD; Jeffrey A. Sosman, MD; Kurt A. Schalper, MD, PhD; Robert A. Anders, MD, PhD; Hao Wang, PhD; Clifford Hoyt, MS; Drew M. Pardoll, MD, PhD; Ludmila Danilova, PhD; Janis M. Taube, MD





Future: These assays will be standardized/approved & enrich for patients likely to respond to CPI & ID pts who need clinical trials

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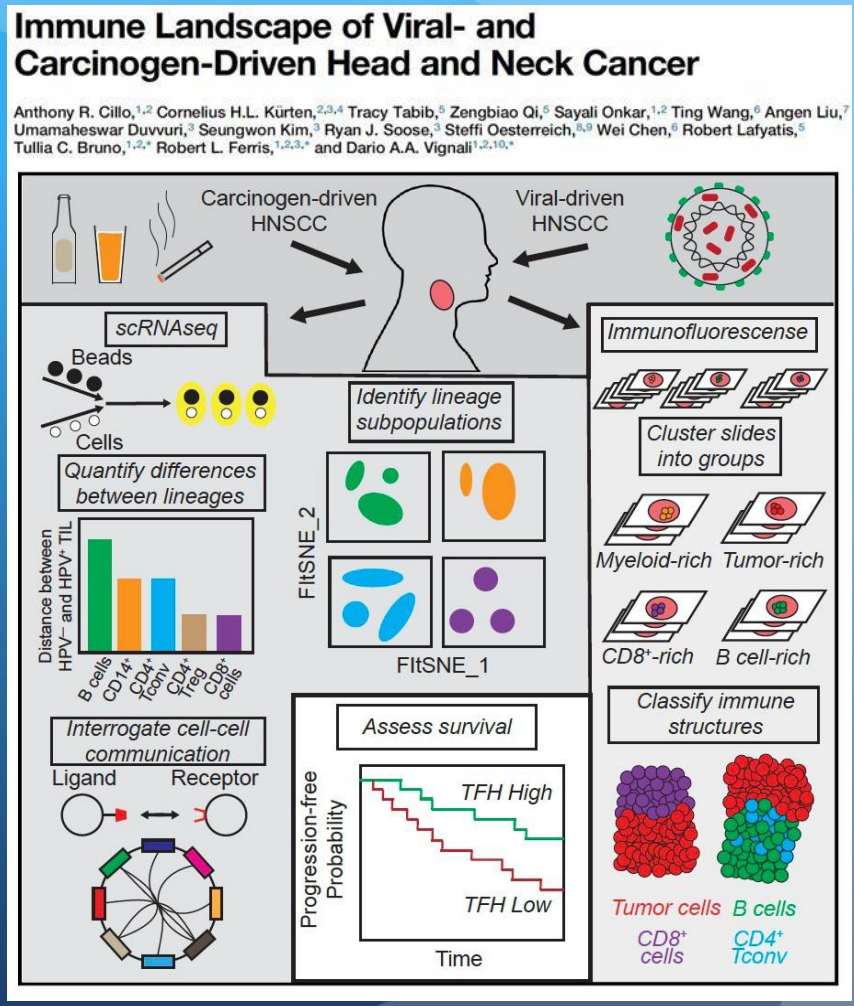
Single cell sequencing & Digital Spatial Profiling (DSP)

Single Cell Seq:

Provides assessment of the status of all the cells in a tumor

DSP:

Allows and assessment of the cells that are interacting with each other in a specific spot



Immunity 52, 183–199, January 14, 2020

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Observation:

- Patients with **Melanoma, Pancreatic, Breast, Ovarian, Bladder, Gastric, Colon & Lung Cancer** have immunity **to non-mutated cancer epitopes**
- Once "**re-activated**" with Ag and cytokine – T cells can kill cancer cells

Observation:

- Many patients with **Melanoma, Pancreatic, Breast, Ovarian, Bladder, Gastric, Colon & Lung Cancer** have immunity **to non-mutated cancer epitopes**
- Once "**re-activated**" with Ag and cytokine – T cells can kill cancer cells

Challenge:

- Identify approaches that re-activate and expand tumor-reactive T cells

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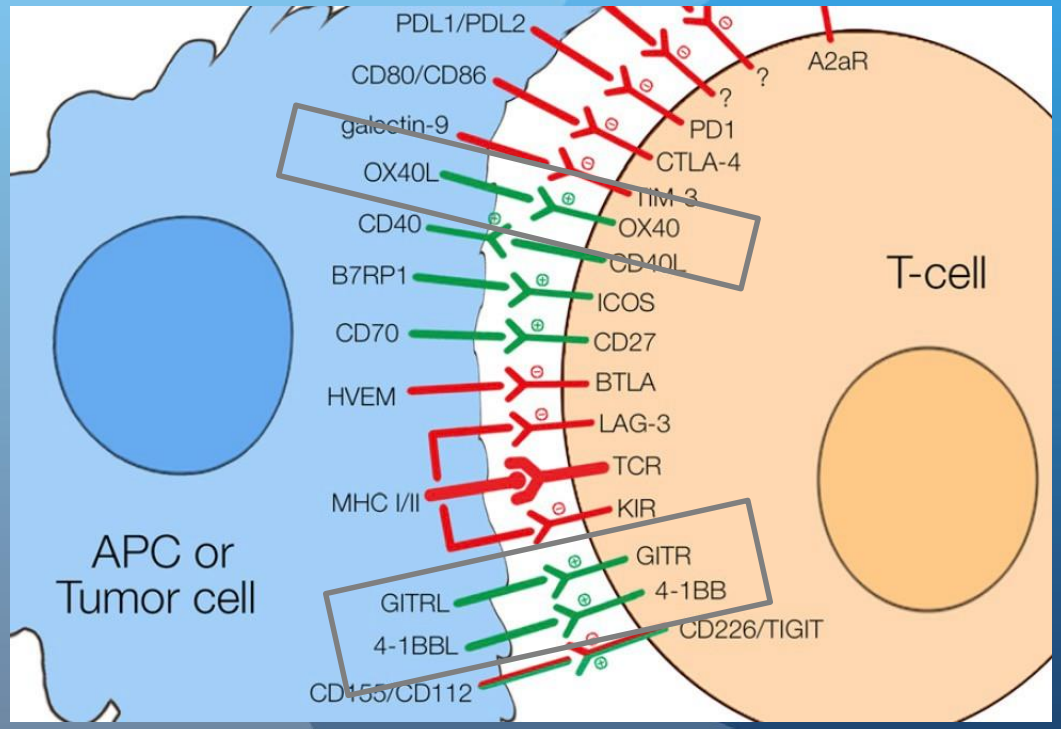
Costimulation Augments T cell Function OX40, GITR and 4-1BB



Receptor expression is upregulated following T cell activation

Triggering co-stimulates T cells

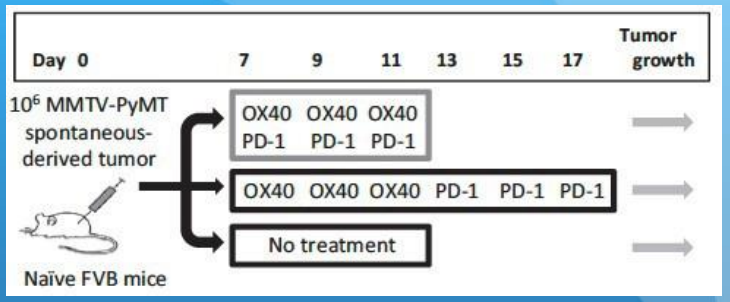
Can augment Anti-Cancer Activity

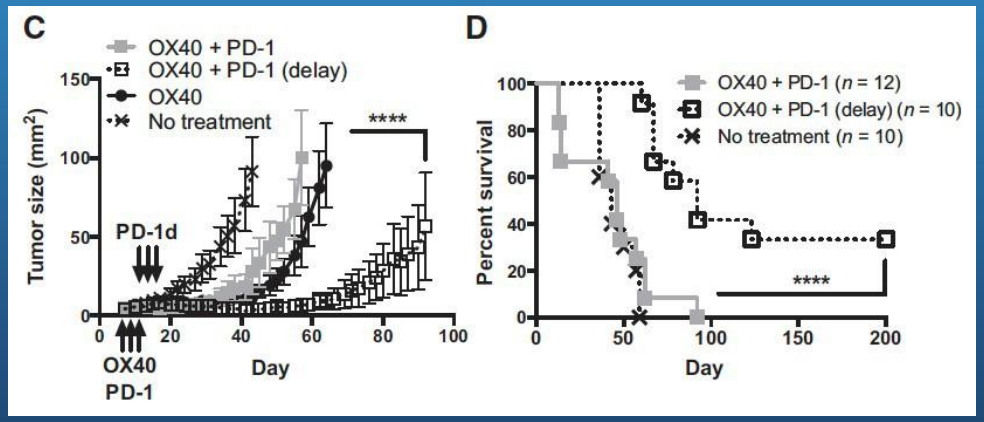
Marin-Acevedo *et al. Journal of Hematology & Oncology* (2018) 11:39

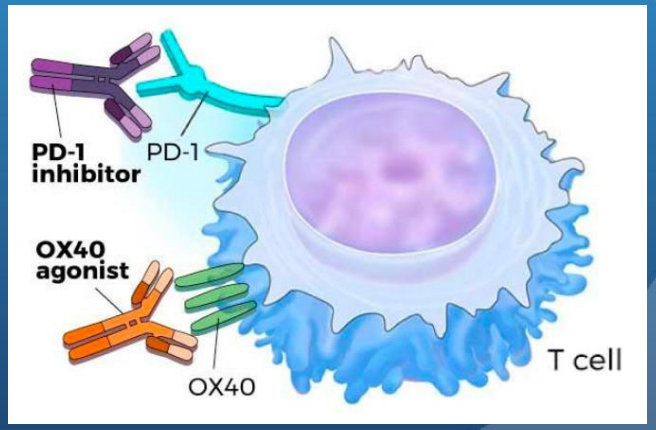
Timing and Sequence Critical for Immunotherapy Combination

Timing of PD-1 Blockade Is Critical to Effective Combination Immunotherapy with Anti-OX40

David J. Messenheimer[1,2], Shawn M. Jensen[1], Michael E. Afentoulis[1], Keith W. Wegmann[1], Zipei Feng[1,3], David J. Friedman[1], Michael J. Gough[1], Walter J. Urba[1], and Bernard A. Fox[1,2,3,4]







Clin Cancer Res; 23(20) October 15, 2017

October 3, 2017, by NCI Staff

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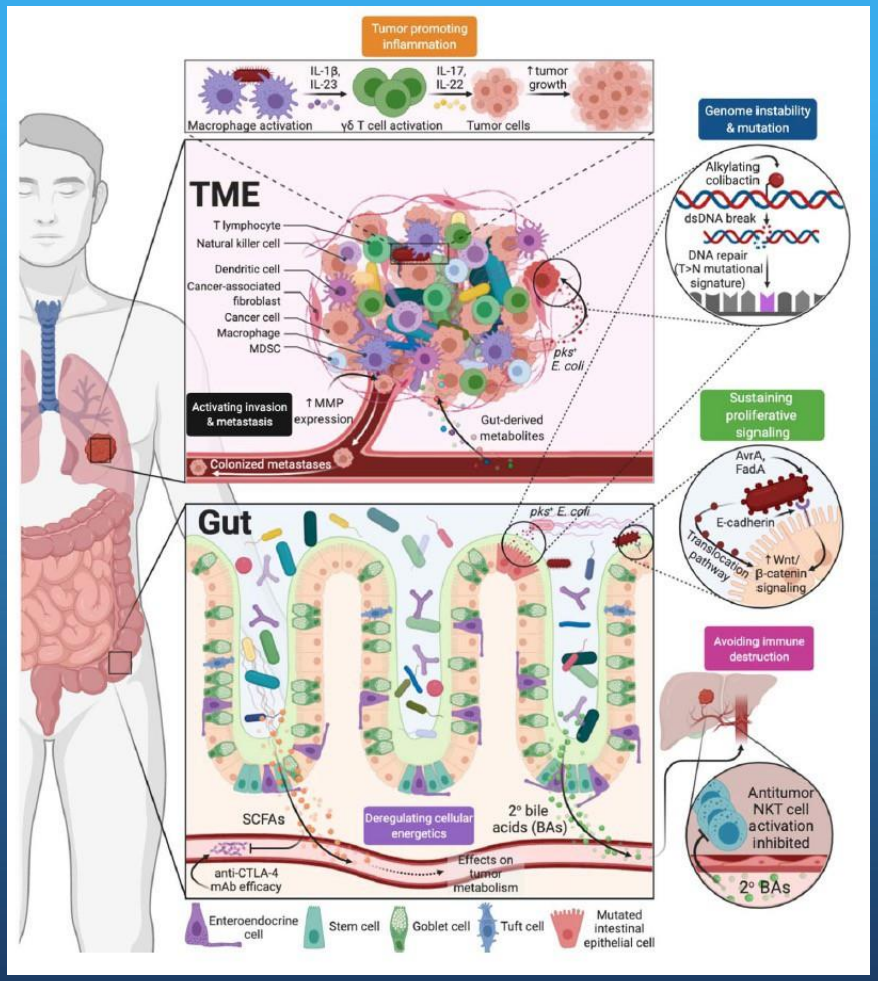
Intersection of microbial mechanisms with cancer hallmarks



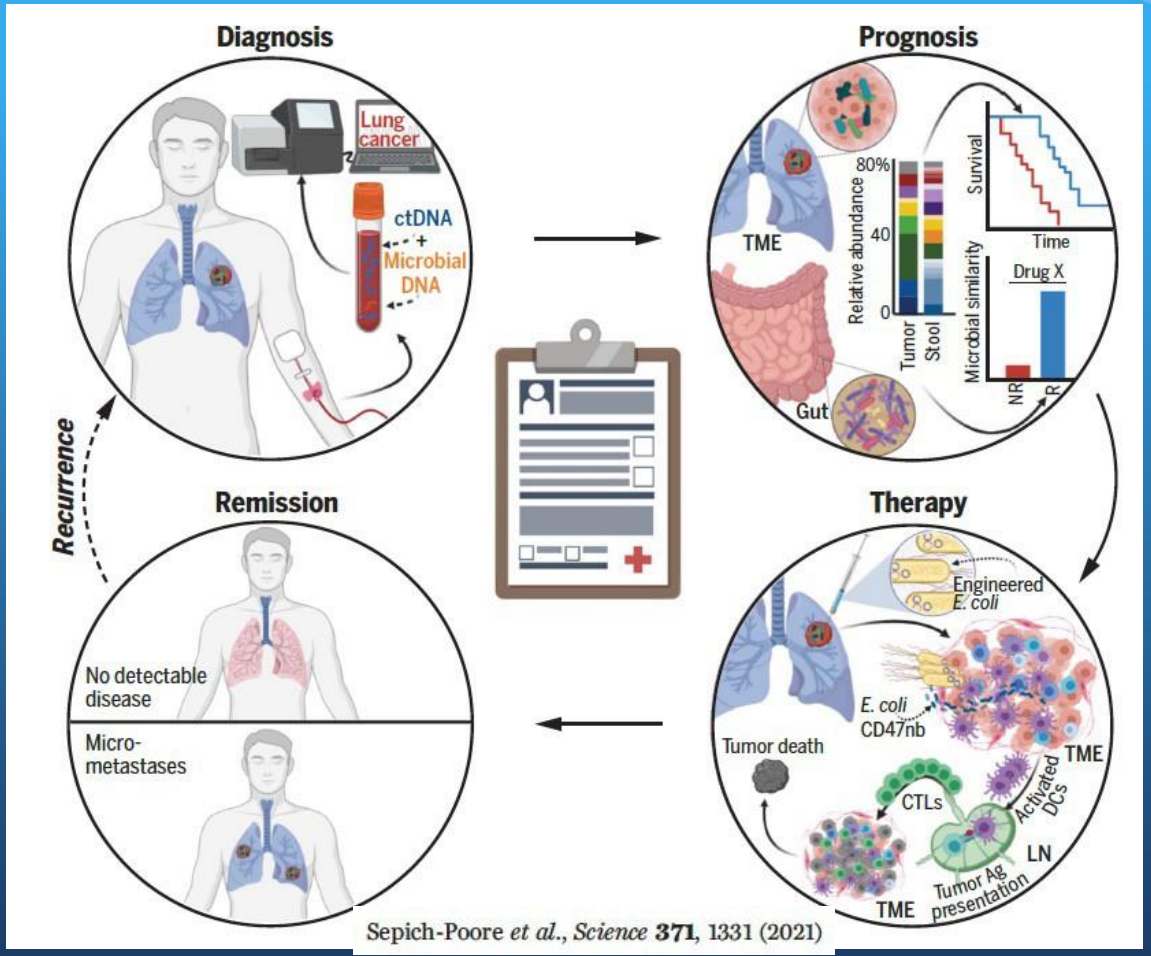
The microbiome and human cancer

Gregory D. Sepich-Poore[1], Laurence Zitvogel[2,3,4,5], Ravid Straussman[6], Jeff Hasty[1,7,8], Jennifer A. Wargo[9,10], Rob Knight[1,11,12]*

Sepich-Poore *et al.*, *Science* **371**, 1331 (2021)

Microbiota-derived metabolites, genotoxins, and antigens influence host antitumor immunity, inflammation, energetics, cellular signaling, and metastasis

Opportunities for Microbes to Affects Cancer Care



Sepich-Poore *et al.*, *Science* **371**, 1331 (2021)

Future:

Understanding the microbiome will impact:

- Diagnosis
- Prognosis
- Therapy

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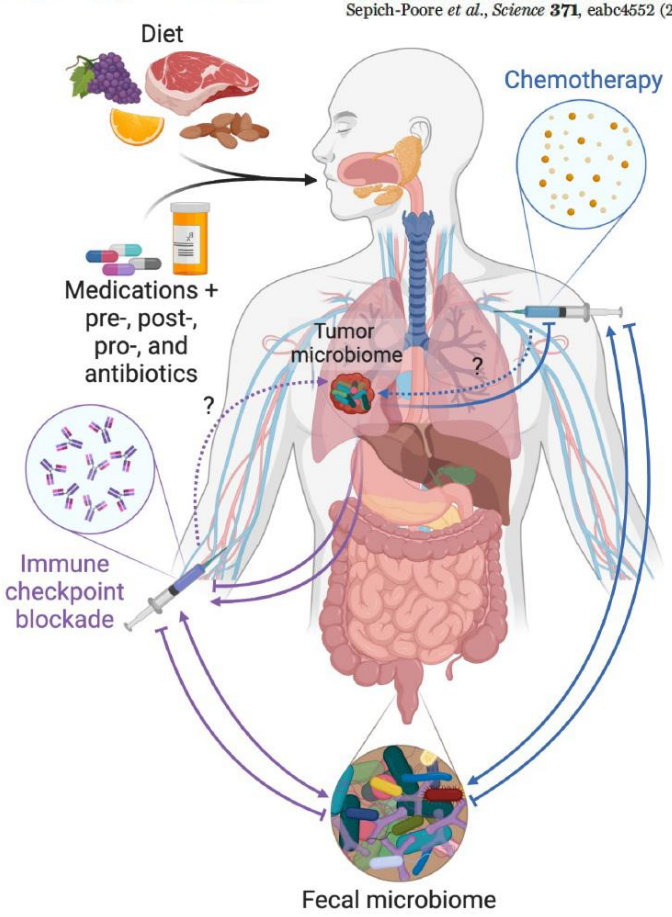
CANCER MICROBIOME

26 March 2021

The microbiome and human cancer

Gregory D. Sepich-Poore[1], Laurence Zitvogel[2,3,4,5], Ravid Straussman[6], Jeff Hasty[1,7,8], Jennifer A. Wargo[9,10], Rob Knight[1,11,12]*

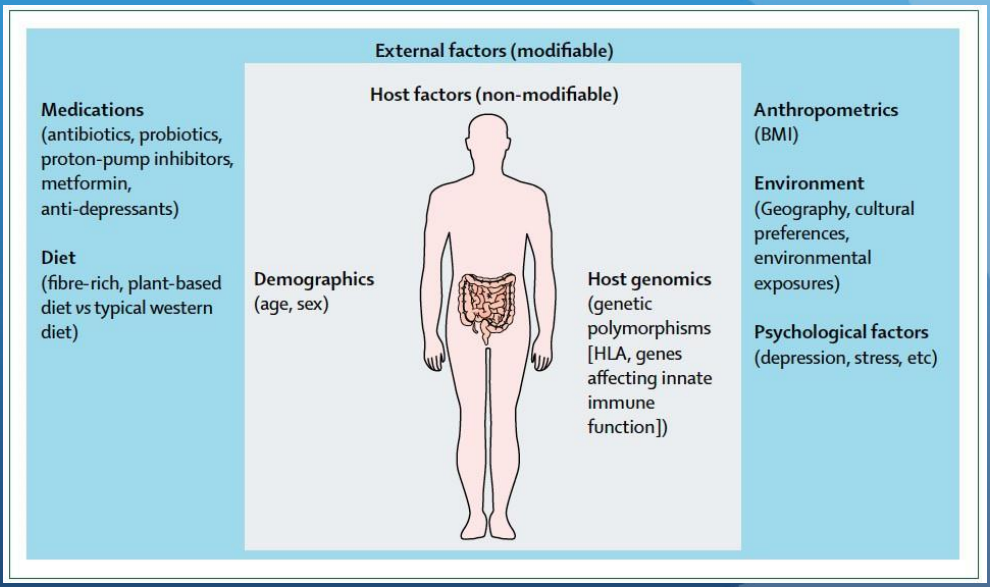
Sepich-Poore *et al.*, *Science* **371**, eabc4552 (2021)



Modulating the microbiome to improve therapeutic response in cancer

Jennifer L McQuade, Carrie R Daniel, Beth A Helmink, Jennifer A Wargo

Lancet Oncol 2019; 20: e77–91



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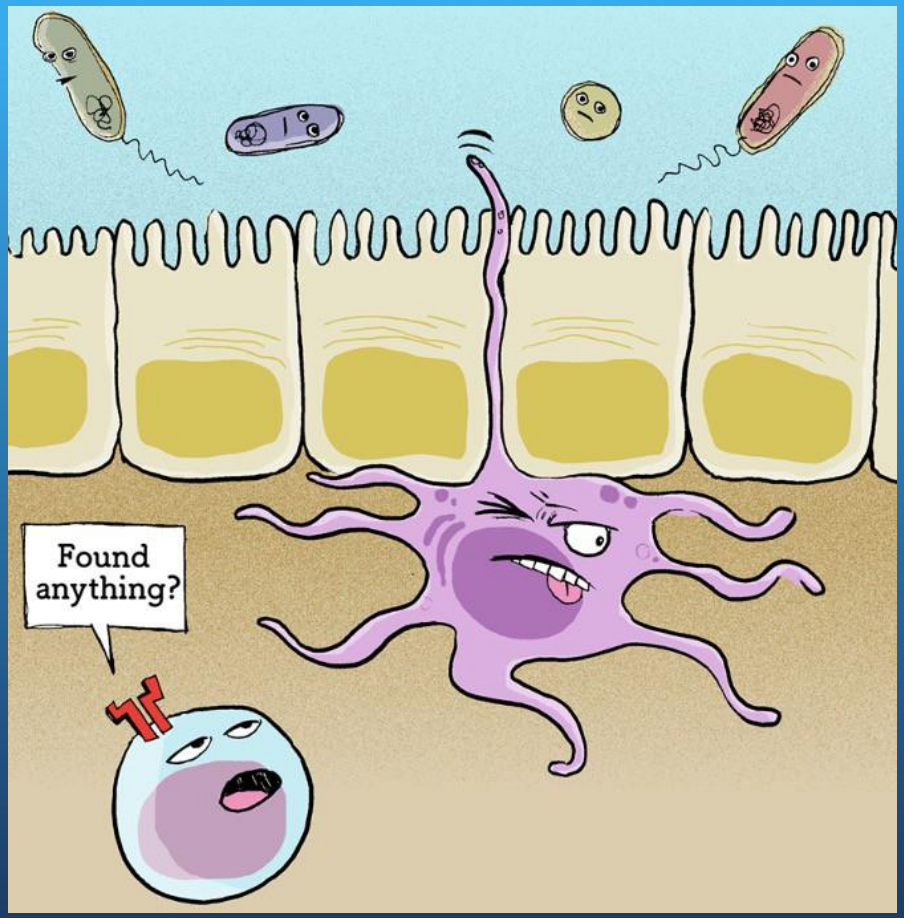
Microbiome Effects on Immune Responsiveness



Clinical Trials.

- Fecal/microbe transplants
- Probiotics
- Diets/prebiotics
- Phage
- Antibiotics / other

Future: Lots of questions?
When to treat and how to assess impact?

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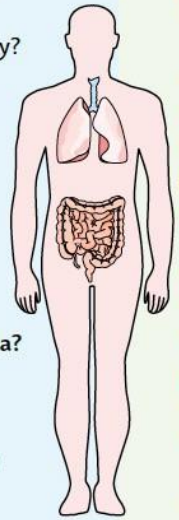
Questions to consider in clinical trial design for microbiome modulation in cancer

Before treatment

Patients
- Which patient population to treat: treatment naive or refractory?
- Should the microbiome be profiled to stratify or select patients?

Pre-conditioning regimen
- Do we need to pre-treat the gut with antibiotics to facilitate engraftment?

How should we optimally modulate the gut microbiota?
- FMT?
- Diet?
- Designer consortia?
- Phage, antibiotics, or other?



During therapy

What therapy should we combine with modulation of the gut microbiome?
- Immune checkpoint blockade anti-PD-1)?
- Other forms of immunotherapy?
- Other therapy?

How do we optimally monitor patients during therapy?
- Microbiome analyses to assess engrafment or function?
- Immune profiling?
- Peripheral blood?
- Tumour?

How can we facilitate stable engraftment?
- Should we recommend dietary changes?
- Any medications to avoid?

Assessing effects

What are appropriate primary endpoints for such studies?
- Safety and tolerability?
- Engraftment?
- Others?

What are appropriate secondary endpoints?
- Response?
  - Radiographic (RECIST or irRC)?
  - Rate of complete responses?
  - Pathological response (on biopsy or after neoadjuvant therapy)?
- Toxicity?
- Novel markers (ctDNA, immunophenotyping)?

Long-term effects

Durability of engraftment
- How durable is engraftment?
- What microbes or functional phenotypes in gut microbiota are associated with responses? Can these microorganisms be used to design consortia?

Overall responses
- What is the effect on overall and disease-specific survival?

Toxicity
- Can we uncouple toxicity and response to immunotherapy?

Other transplanted traits with FMT?
- Obesity?
- Depression?
- Any potentially favourable traits?

Lancet Oncol 2019; 20: e77–91

Identification of bacteria-derived HLA-bound peptides in melanoma

Nature. 2021 Apr;592(7852):138-143.

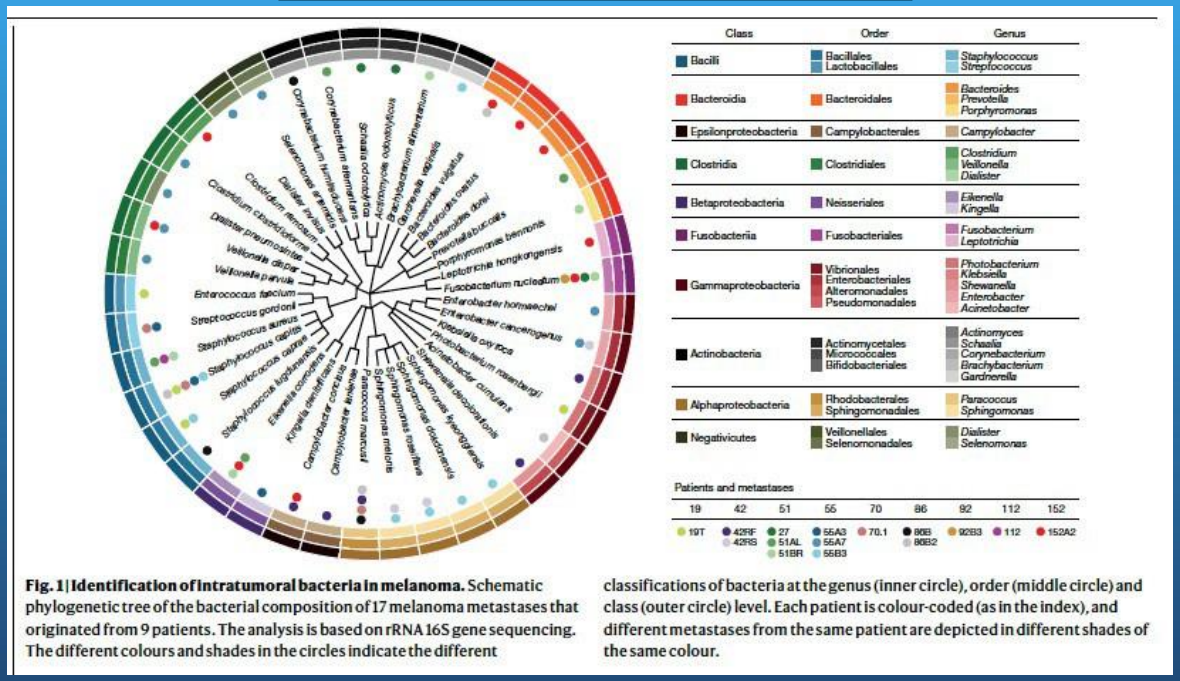


Fig. 1 | Identification of intratumoral bacteria in melanoma. Schematic phylogenetic tree of the bacterial composition of 17 melanoma metastases that originated from 9 patients. The analysis is based on rRNA 16S gene sequencing. The different colours and shades in the circles indicate the different classifications of bacteria at the genus (inner circle), order (middle circle) and class (outer circle) level. Each patient is colour-coded (as in the index), and different metastases from the same patient are depicted in different shades of the same colour.

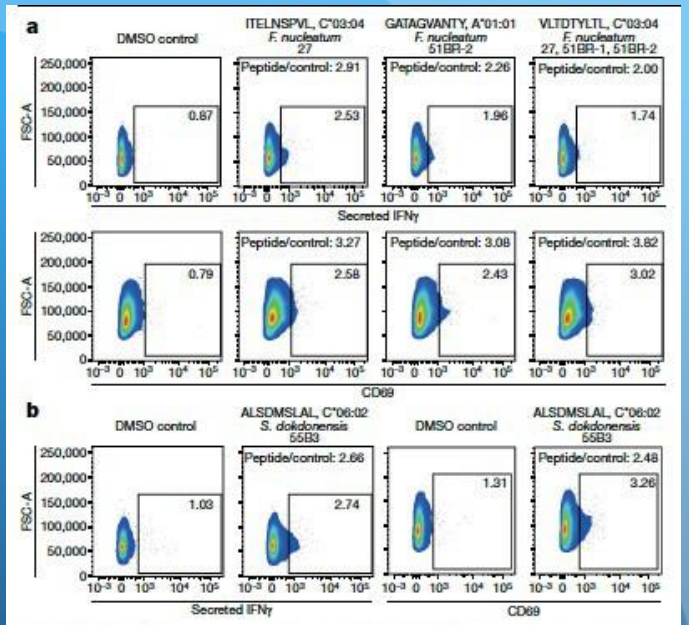


Fig. 4 | TIL reactivity towards bacteria-derived antigens. IFNγ-secreting 51AL and 55A3 TILs were detected after 6 h of coculture with B cells loaded with a bacterial peptide or dimethyl sulfoxide (DMSO) control, using flow cytometry. TILs were also tested for the presence of the CD69 reactivity marker. The image presents 4 representative immunogenic peptides (3 out of 7 immunogenic peptides of patient 51 and 1 out of 1 peptides of patient 55) that showed at least a 2-fold change between the peptide and DMSO control. The percentage of positive IFNγ-secreting or CD69-expressing TILs is an average of three independent experiments (Extended Data Fig. 12, Supplementary Figs. 10, 11). **a**, Patient 51. **b**, Patient 55.

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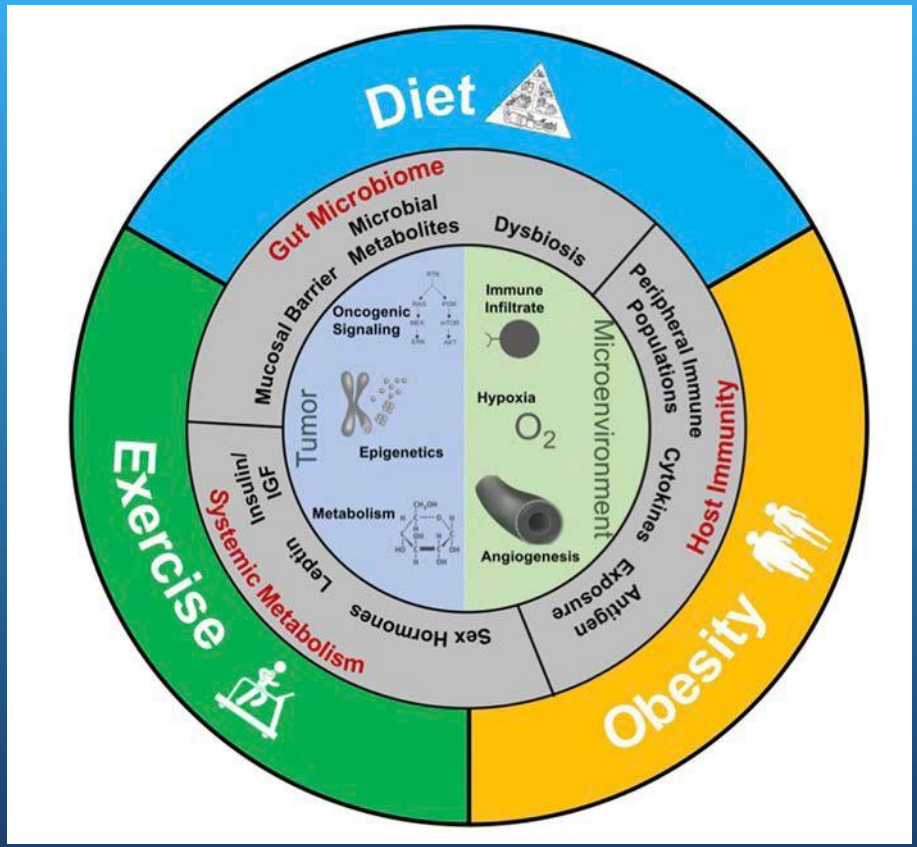
Not Just Diet's Impact on Microbiome -



Curr Oncol Rep. 2019 Jul 1; 21(8): 72.

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Body Weight Affects Cancer Risk

- Being overweight or obese is clearly linked to an overall increased risk of cancer.
  - 8% of all cancers in the United States-
  - 7% of all cancer deaths.

Clearly linked with an increased risk of:

- Breast (in women past menopause)
- Colon and rectum
- Endometrium (lining of the uterus)
- Esophagus
- Kidney
- Pancreas

May raise the risk of:

- Gallbladder
- Liver
- Non-Hodgkin lymphoma
- Multiple myeloma
- Cervix
- Ovary
- Aggressive prostate cancer

https://www.cancer.org/cancer/cancer-causes/diet-physical-activity/body-weight-and-cancer-risk/effects.html

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Future:
Wearables are coming to clinical trials near you!
Here is WHY!

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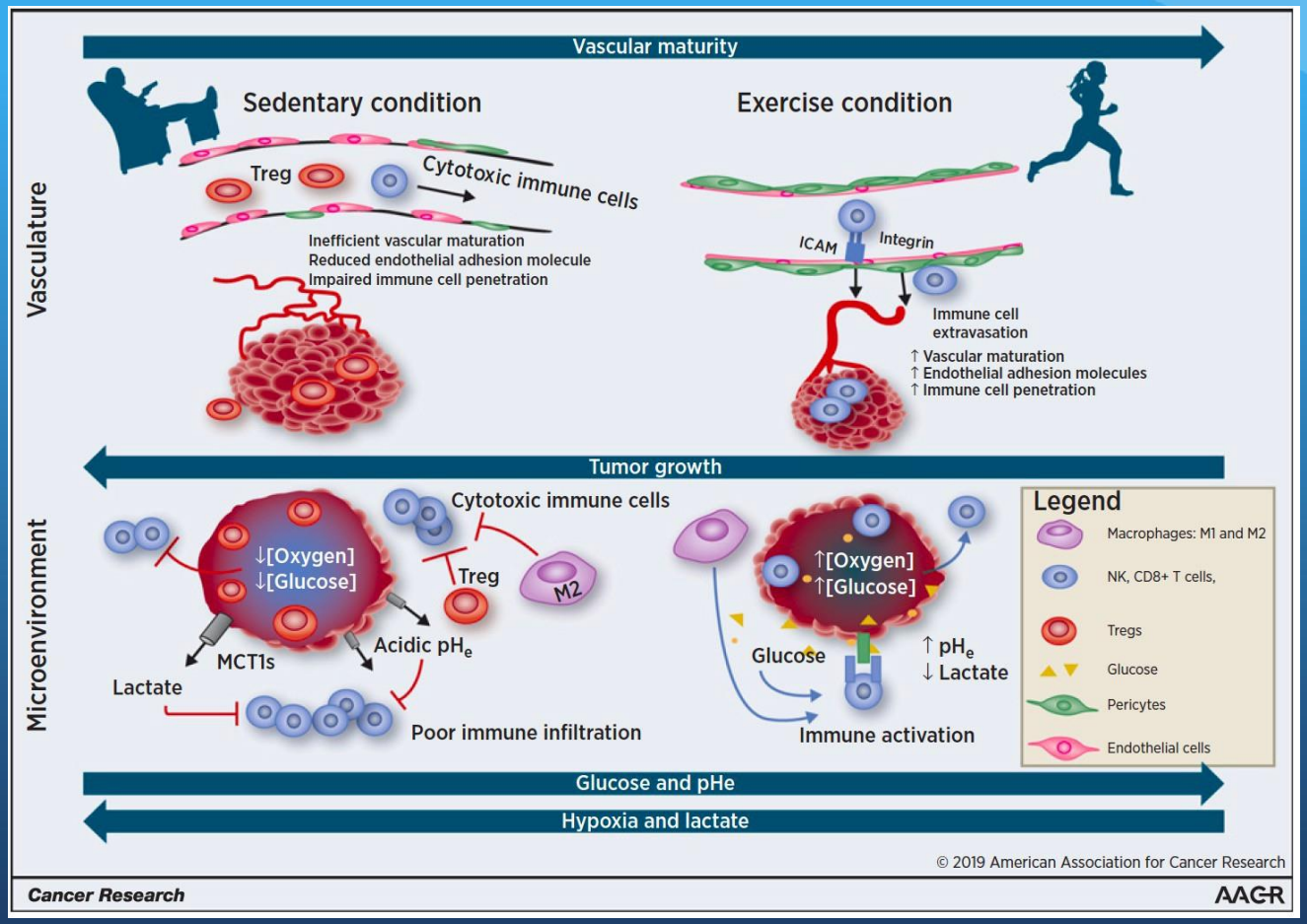
Impact of Exercise



Future:

We will objectively assess activity of patients on clinical trials

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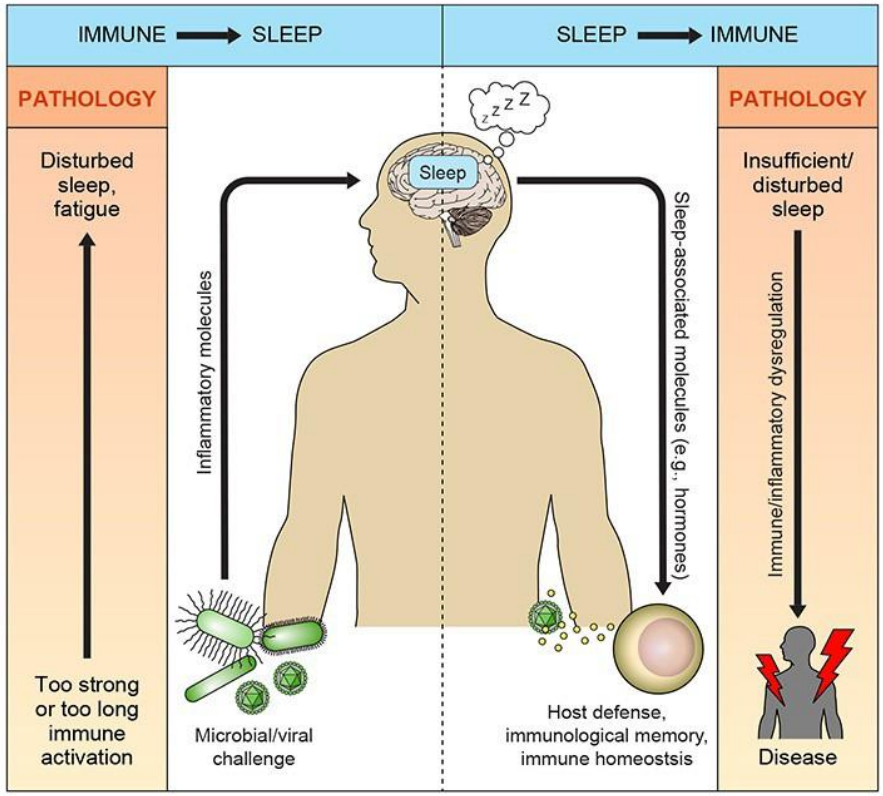
Sleep-Immune Crosstalk in Health and Disease



Future:

Tracking sleep will provide non-invasive strategy to assess "immune response" of patients on clinical trials

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Is Insomnia a Risk Factor for Decreased Influenza Vaccine Response?

Daniel J. Taylor, Kimberly Kelly, Marian L. Kohut & Kai-Sheng Song

Behavioral Sleep Medicine, 00:1–18, 2016

Results indicate insomnia may be a risk factor for lowered immunity to the influenza virus

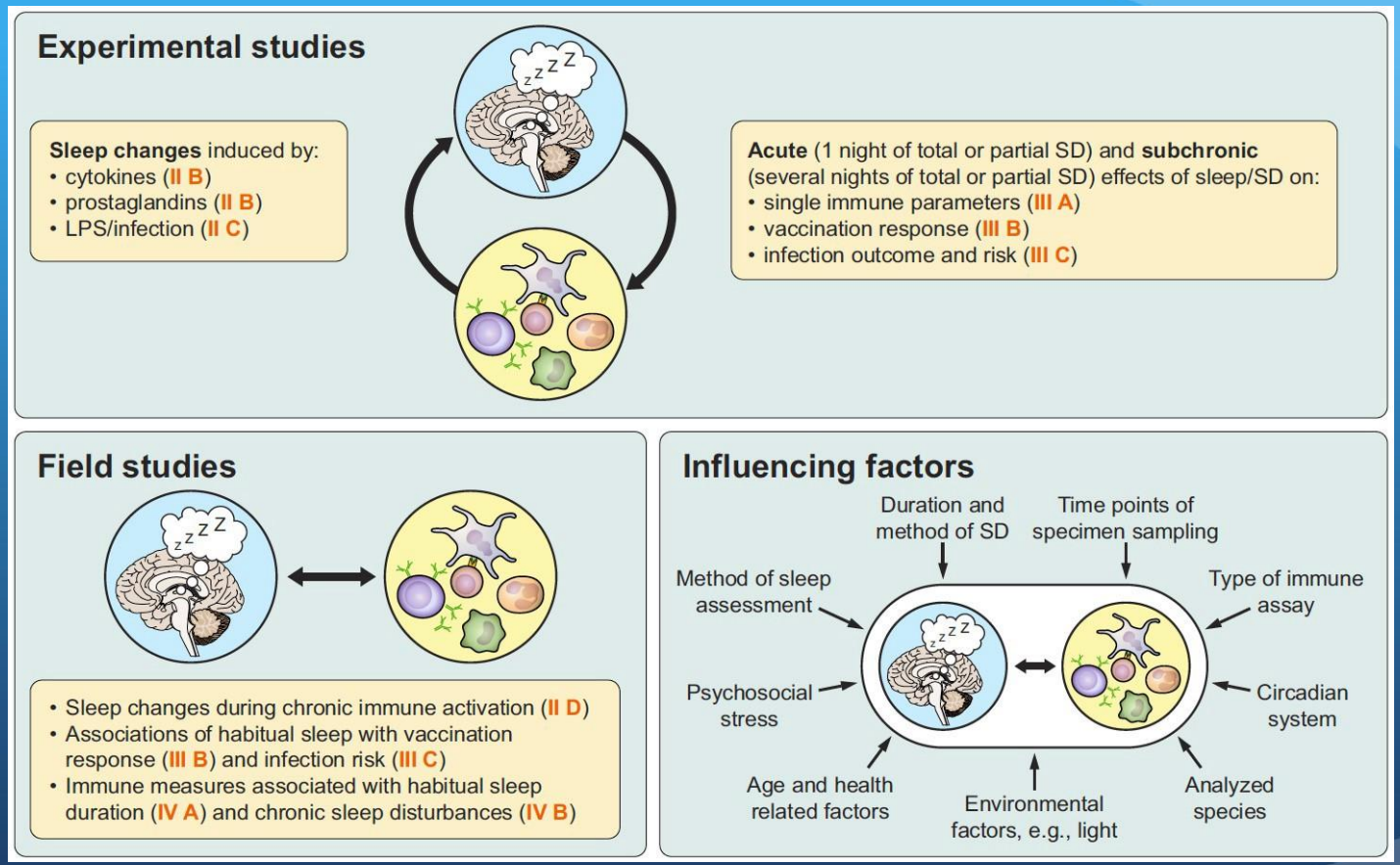
Sleep and Antibody Response to Hepatitis B Vaccination

Aric A. Prather, PhD[1,2]; Martica Hall, PhD[3]; Jacqueline M. Fury, BS[1]; Diana C. Ross, MSN, RN[1]; Matthew F. Muldoon, MD, MPH[4]; Sheldon Cohen, PhD[5]; Anna L. Marsland, PhD, RN[1]

SLEEP 2012;35(8):1063-1069.

Sleep duration was associated with decreased likelihood of clinical protection, which remained significant after adjustment for age, sex, and BMI (OR, 3.53; 95% CI, 1.22-10.27, P = 0.02)

Sleep-Immune Crosstalk in Health and Disease



Physiol Rev 99: 1325–1380, 2019

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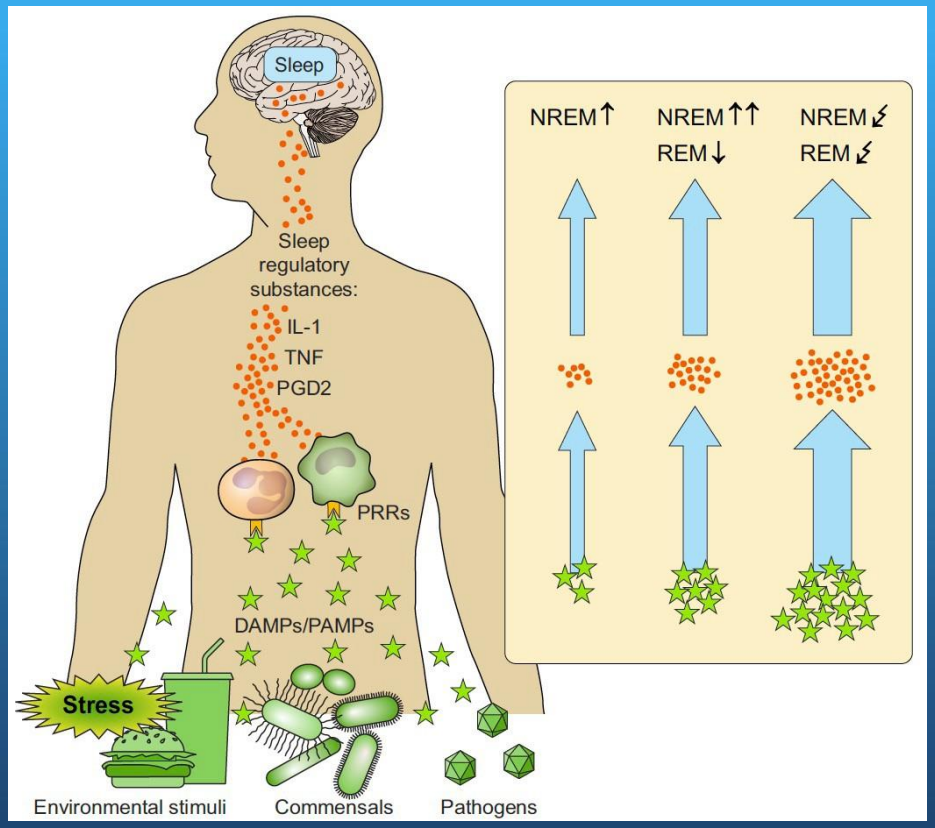
Sleep-Immune Crosstalk in Health and Disease



Physiol Rev 99: 1325–1380, 2019

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Summary:

- The role

Earle A. Chiles Research Institute
Robert W. Franz Cancer Center
Providence Cancer Institute

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