Tumor Microenvironment and Tumor Immunology

Robert Schwabe, MD

Date: 11/05/2025

CANCER CELL BIOLOGY COURSE COLUMBIA UNIVERSITY MEDICAL CENTER, FALL 2025

Today's lecture

Part I: Tumor microenvironment:

1. Components and organization of the TME
2. Functions of the TME and role of specific cell types
3. Diversity in the TME

Literature: *The Biology of Cancer (Weinberg, 3rd ed, 2023) Chapter 13; as well as select papers mentioned in various slides*

Part II: Tumor immunology

1. Immunosurveillance and immunoediting
2. Key cell types contributing to anti-tumor immunity
3. Immune checkpoints, exhaustion and mechanisms of immunosuppression.
4. "Hot" versus "cold" tumors
5. Anti-tumor therapy

(more on that topic also in the lecture by **Dr. Benjamin Izar**)

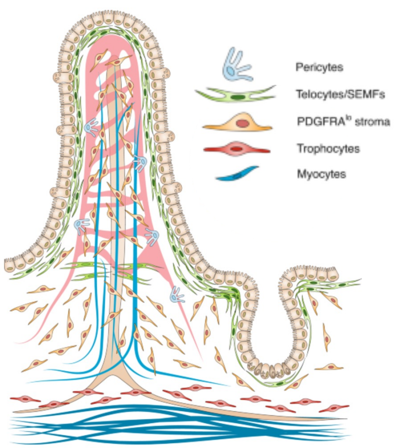
Literature: *The Biology of Cancer (Weinberg, 3rd ed, 2023) Chapters 15+16; as well as select papers mentioned in various slides*

- **Part 1: The Tumor Microenvironment**
- **Questions**

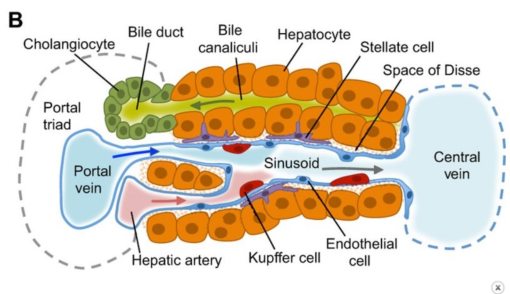
- Part 2: Part 2: Tumor Immunology
- Questions

Complex and organ-specific architecture and cell-cell communication in normal tissues

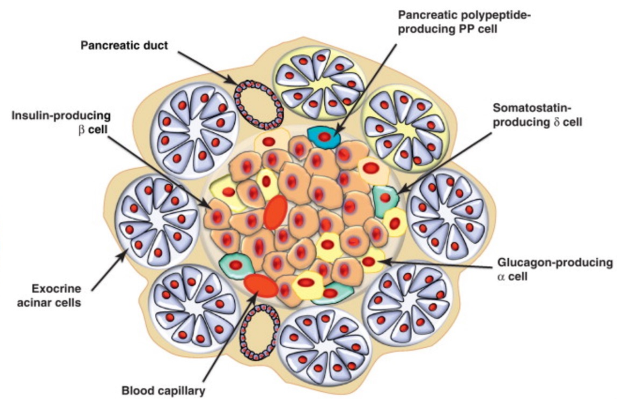
Intestine



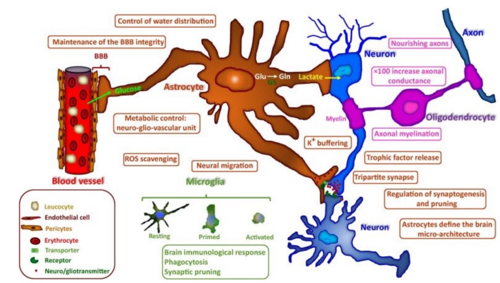
Liver



Pancreas



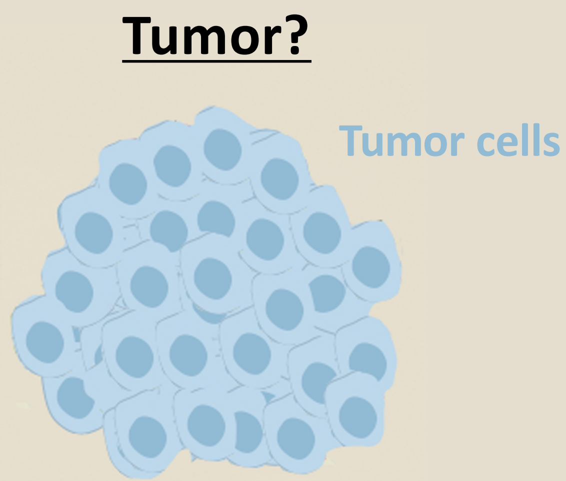
Brain

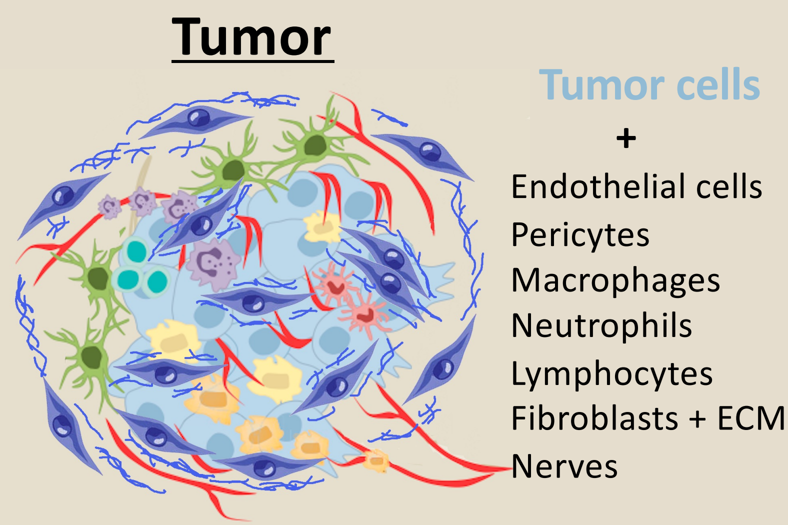


Multiple cell types required to maintain epithelial cell (the source of most tumors) function and communication

Vast differences between organs in organization and cell-cell communication, but conserved patterns

What does a tumor look like?



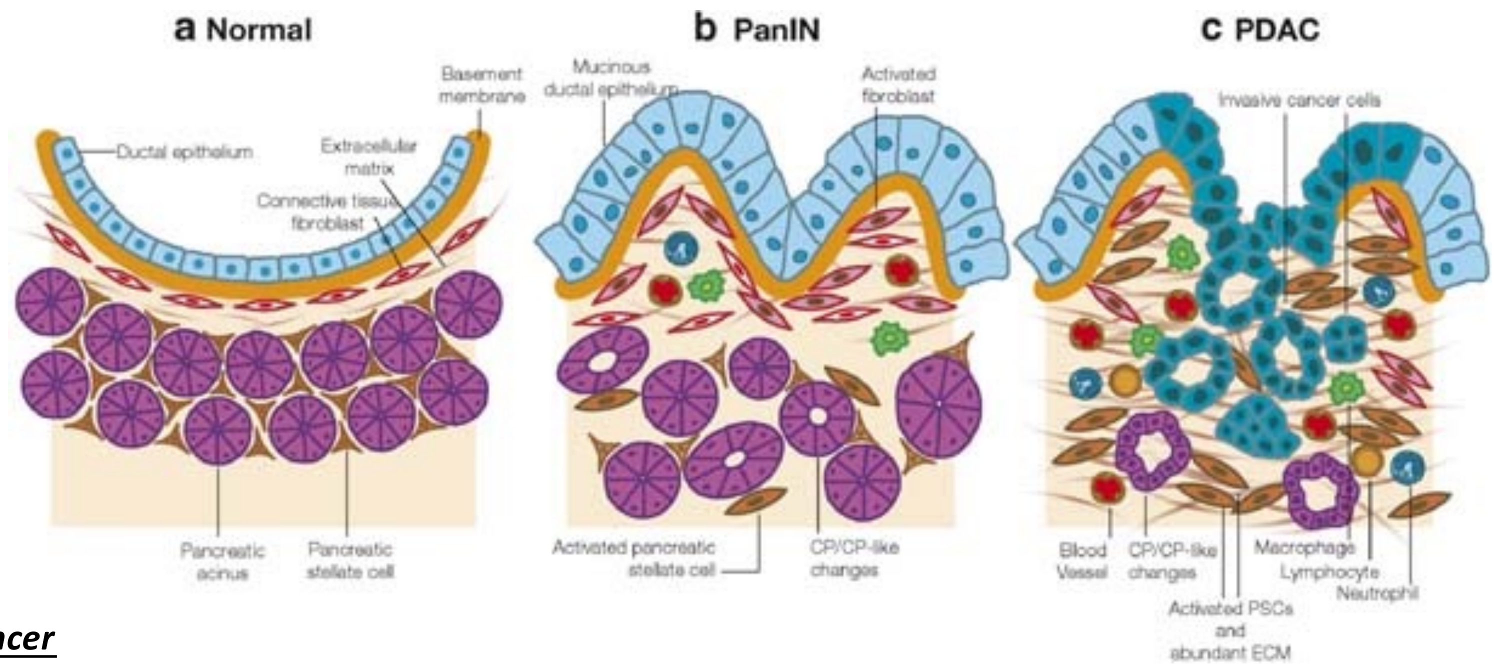


1. The tumor-microenvironment (TME) and cell-cell communication with the TME have **organ-specific characteristics.** In some tumors, cells from the TME can constitute >80% of tumor mass (e.g. pancreatic cancer).
2. **The TME co-evolves with the tumor.** The tumor requires other cells to grow – however, not all cells in the TME are ”pro-tumor”. The immune system may eliminate tumor cells; cancer-associated fibroblasts (CAF) may encapsulate tumors to inhibit their grow. Over time, tumors, co-opt the TME and turn restriction into promotion.
3. Advanced/dedifferentiated/metastatic tumors **may lose this organ-specific TME** and/or requirement for it (e.g. allowing to metastize/grow in different environments)

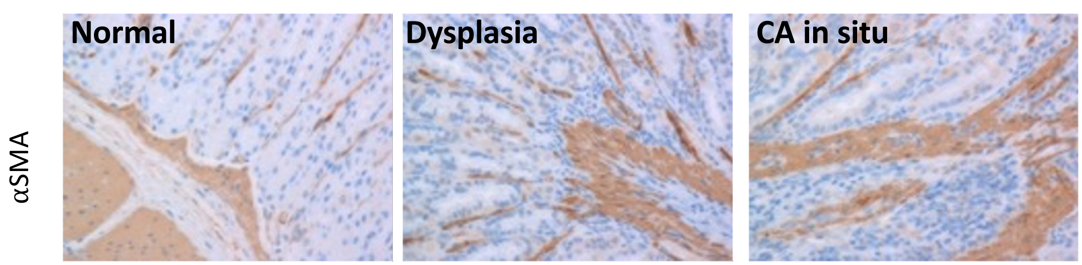
Stromal changes can already occur in premalignant stages

Pancreatic cancer

Intraepithelial neoplasia



Gastric cancer

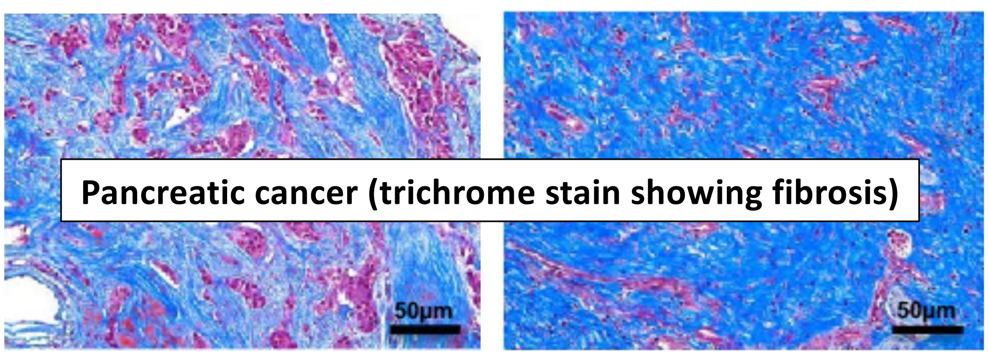


Chu et al., Journal of Cellular Biochemistry 101:887–907 (2007)

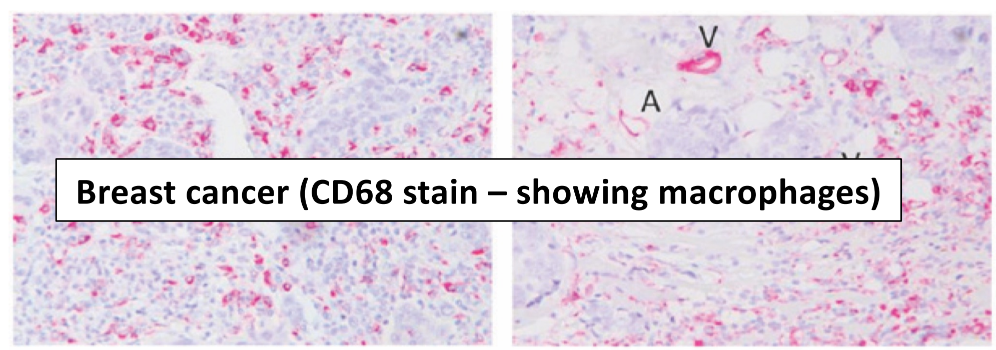
The stroma can constitute >50% of the tumor mass in some tumor types

	Estimated % stroma
Esophagus (mostly SCC)	50-82%
Gastric	34%
Liver	50%
Pancreas	**83%**
Colon	**34%**
Breast	**41-66%**
Prostate	40%
Renal	10%
Glioblastoma	10%

Most abundant cell types in stroma-rich tumors are CAF and macrophages



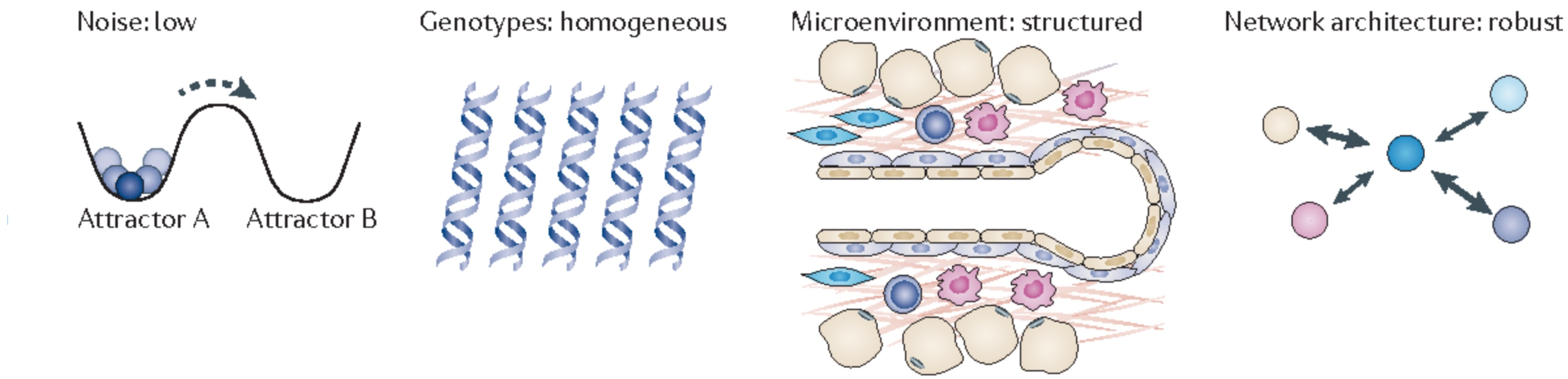
Pancreatic cancer (trichrome stain showing fibrosis)



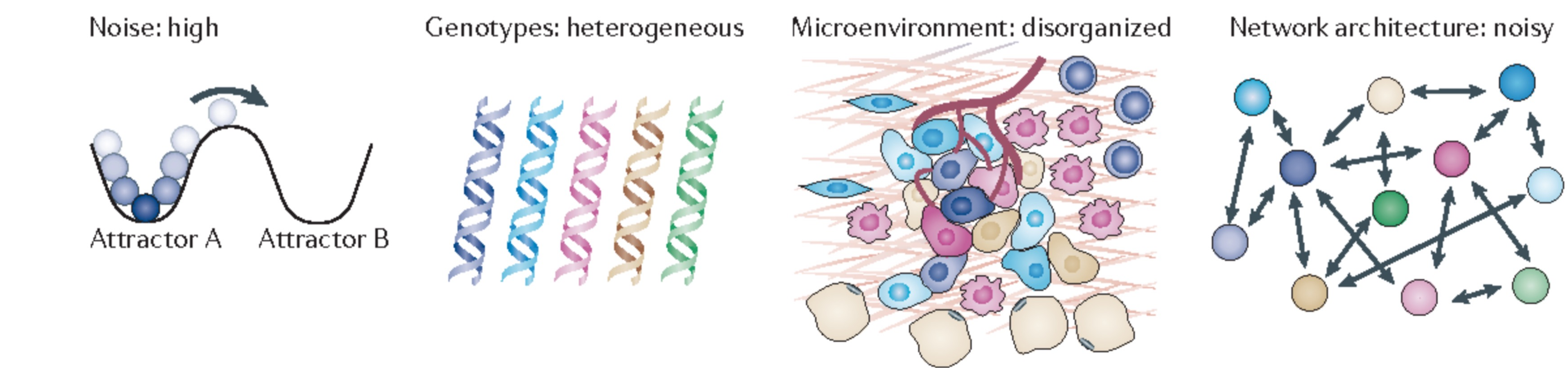
Breast cancer (CD68 stain – showing macrophages)

Differences between the normal and tumor microenvironemnt

Normal tissue: Structured organization and robust network/interactions



Tumor tissue: High heterogeneity, chaotic organization/high “entropy”, reorganized interactions/network



Many cell culture models of cancer ignore the TME

Standard 2D tumor cell culture models (usually monocultures)

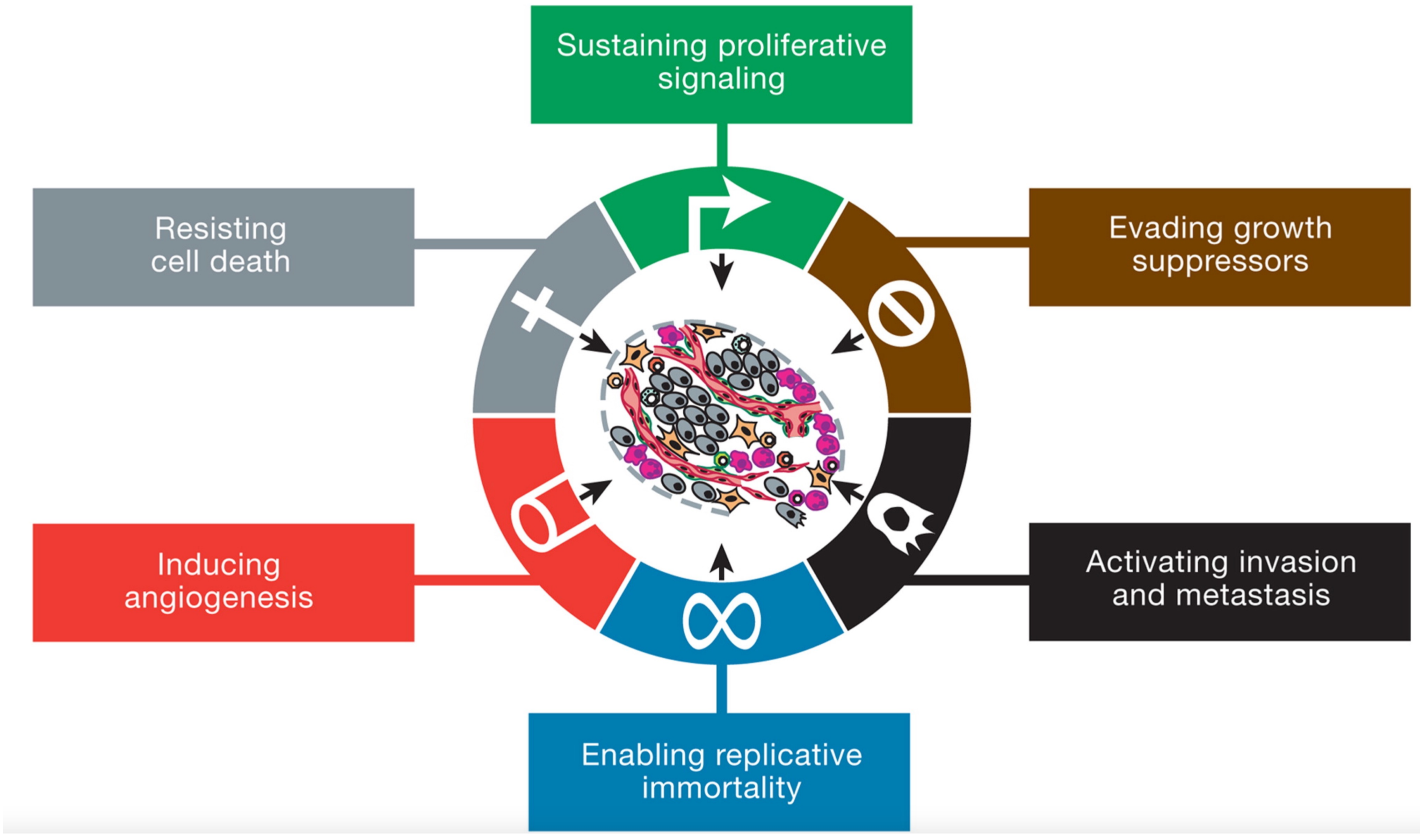
- Absence of cells from the TME such as CAF, inflammatory cells, nerves, vessels
- Absence of tumor-typical ECM; instead plastic surfaces that are over 1000-fold stiffer than tumors
- Most cell lines are selected for these specific cell culture conditions and may therefore differ from tumor cells *in vivo* (many tumors taken out of mice or people will not easily grow in dishes)

3D models/organoids address some concerns – increasing use of multicellular model

Ok to work with cell lines but have to know what they are useful for and the limitations

2. Functional impact of the TME

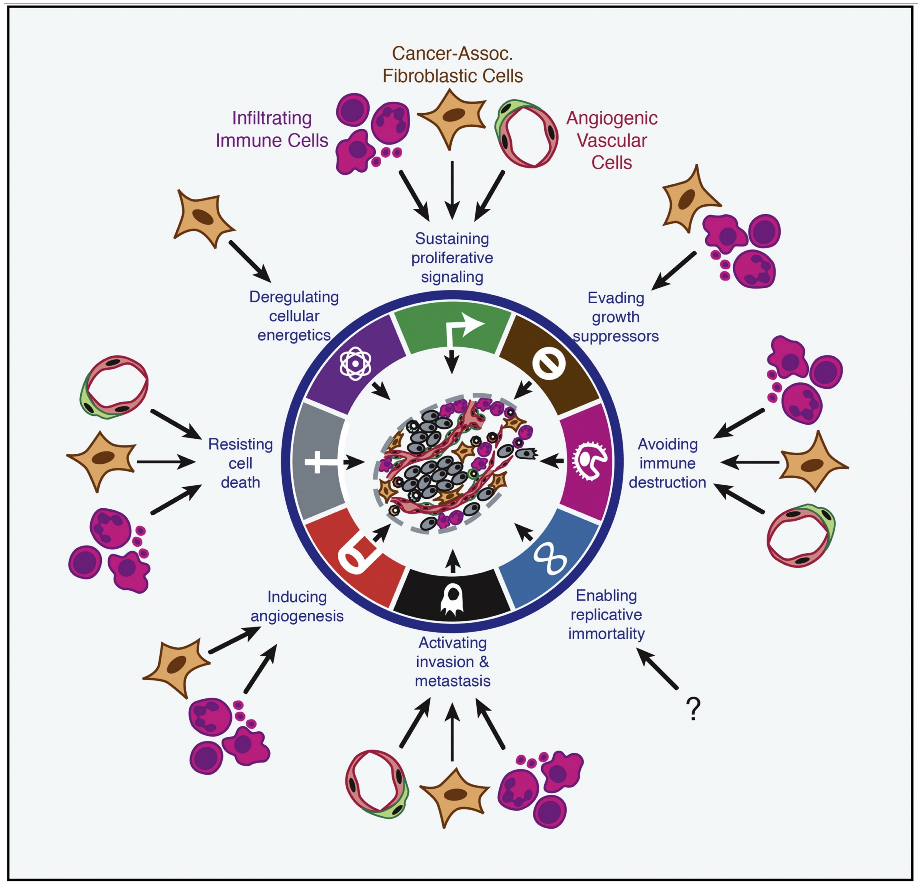
Hallmarks of cancer



Hanahan and Weinberg. Hallmarks of cancer: the next generation. **Cell**. 2011 Mar 4;144(5):646-74.

How does the tumor microenvironment fit into the Hallmark concept/cancer biology?

Cells in the TME: "Accessories to the crime"



Hanahan and Coussens. Accessories to the crime: functions of cells recruited to the tumor microenvironment. **Cancer Cell** . 2012 Mar 20;21(3):309-22.

Tumor-promoting and tumor-restricting effects of cell in the TME

Tumor restricting

- Immune recognition + destruction
- Growth restriction/encapsulation by ECM

Tumor promoting

- Immunosuppression by MDSC/CAF, ECM
- Tumor-promoting inflammation
- Tumor-promoting angiogenesis
- Tumor-promoting metabolism
- Tumor-promoting fibrosis and stiffness
- Tumor-promoting nerve signals

Caveats:
- The role of the stroma is often tumor-, context- and stage-specific
- In the long run, tumors reprogram the stroma to become tumor promoting

Fibroblasts and cancer-associated fibroblasts (CAF)

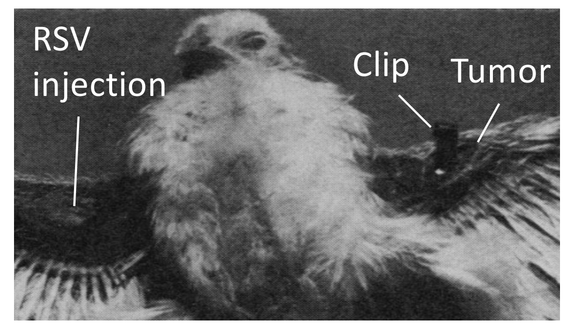
Tumors: "Wounds that do not heal"

"Tumors: Wounds that do not heal" (Dvorak, HF, *N Engl J Med* 1986)

- In many aspects, tumors resemble wounds with influx of inflammatory cells; fibroblast activation; necrosis and ensuing wound healing responses; activation of the coagulation cascade; angiogenesis
- Tumors employ many aspects of this wound healing response to (i) reorganize the environment and (ii) utilize the growth/regeneration-promoting aspects of wound healing for their own growth

Wounding promotes cancer development in experimental models.

Wounding promotes tumor formation induced by Rous sarcoma virus (Dolberg et al, *Science* 1985)



Oncogenic event
+
Injury/inflammation/wound healing → **Cancer**

Normal fibroblasts can be tumor suppressive

J. Cell Sci. 1, 297–310 (1966)
Printed in Great Britain

GROWTH INHIBITION OF POLYOMA-TRANSFORMED CELLS BY CONTACT WITH STATIC NORMAL FIBROBLASTS

M. G. P. STOKER, MOIRA SHEARER AND C. O'NEILL
Medical Research Council Experimental Virus Research Unit, Institute of Virology, University of Glasgow

17188–17193 | PNAS | December 2, 2014 | vol. 111 | no. 48

Inhibition of tumor cell proliferation and motility by fibroblasts is both contact and soluble factor dependent

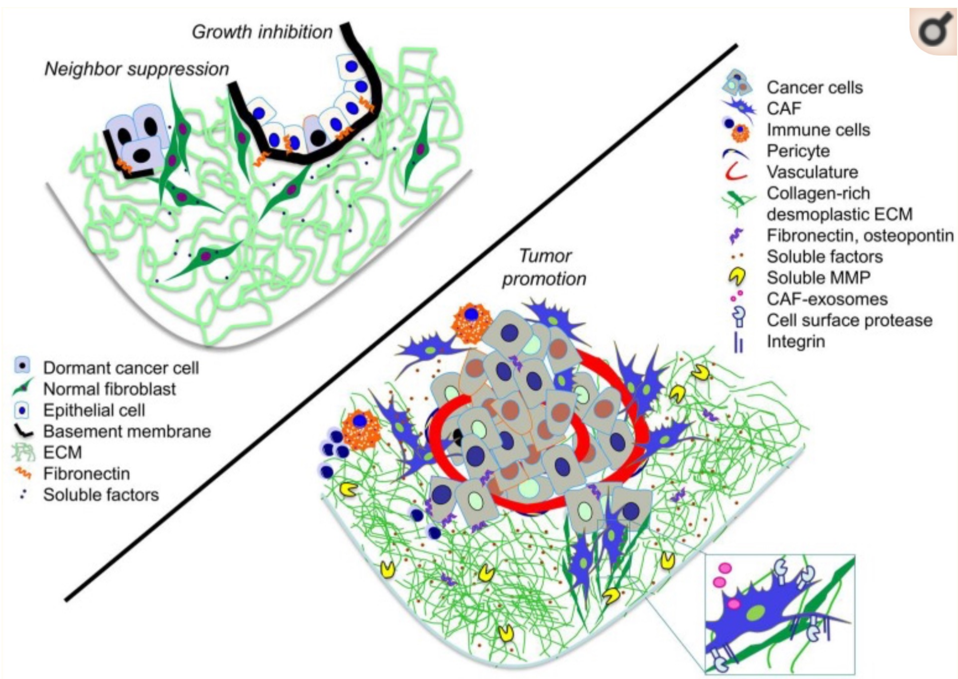
Twana Alkasalias[a,b], Emilie Flaberg[a], Vladimir Kashuba[a,c], Andrey Alexeyenko[a,d], Tatiana Pavlova[a], Andrii Savchenko[a], Laszlo Szekely[a], George Klein[a,1,2], and Hayrettin Guven[a,1]

Article

Opposing roles of hepatic stellate cell subpopulations in hepatocarcinogenesis

Aveline Filliol[1], Yoshinobu Saito[1,19], Ajay Nair[1,2,19], Dianne H. Dapito[1,19], Le-Xing Yu[1,19], Aashreya Ravichandra[1,14], Sonakshi Bhattacharjee[1], Silvia Affo[1,15], Naoto Fujiwara[3], Hua Su[4], Qiuyan Sun[1], Thomas M. Savage[5], John R. Wilson-Kanamori[6], Jorge M. Caviglia[1,16], LiKang Chin[7,17], Dongning Chen[7], Xiaobo Wang[1], Stefano Caruso[8], Jin Ku Kang[1,9], Amit Dipak Amin[1], Sebastian Wallace[6], Ross Dobie[6], Deqi Yin[1], Oscar M. Rodriguez-Fiallos[1], Chuan Yin[1,18], Adam Mehal[1], Benjamin Izar[1], Richard A. Friedman[10], Rebecca G. Wells[7], Utpal B. Pajvani[1,9], Yujin Hoshida[3], Helen E. Remotti[11], Nicholas Arpaia[5], Jessica Zucman-Rossi[8], Michael Karin[4], Neil C. Henderson[6,12], Ira Tabas[1,9,11,13] & Robert F. Schwabe[1,9]

356 | Nature | Vol 610 | 13 October 2022



Multiple mechanisms of suppression:

- Contact and soluble factors involved
- Likely organ-specific mechansims

Activated fibroblasts can be tumor-promoting

TGF-β Signaling in Fibroblasts Modulates the Oncogenic Potential of Adjacent Epithelia

Neil A. Bhowmick,[1,4] Anna Chytil,[1] David Plieth,[2] Agnieszka E. Gorska,[1,4] Nancy Dumont,[2,4] Scott Shappell,[3,4] M. Kay Washington,[3,4] Eric G. Neilson,[2,4] Harold L. Moses[1,3,4]*

Approach:
FSP1-Cre x Tgfbr2 $^{fl/fl}$ to delete Tgfbr2 in fibroblasts

Development of PIN

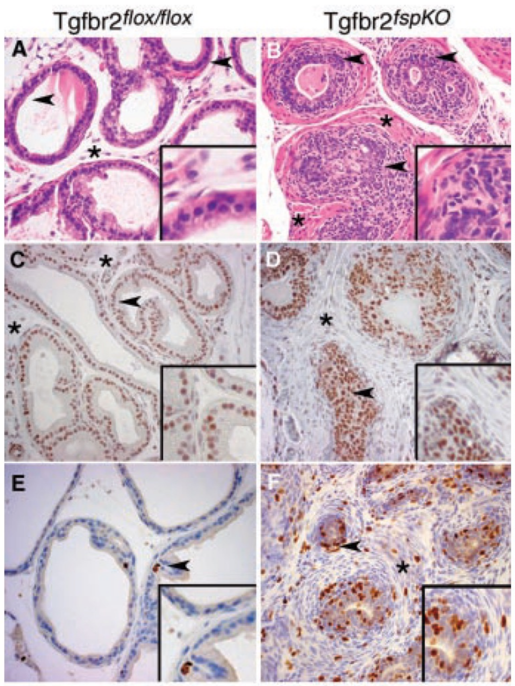


Fig. 1. Loss of TβRII expression in fibroblasts results in prostate intraepithelial neoplasia (PIN).

Development of squamous cell carcinoma

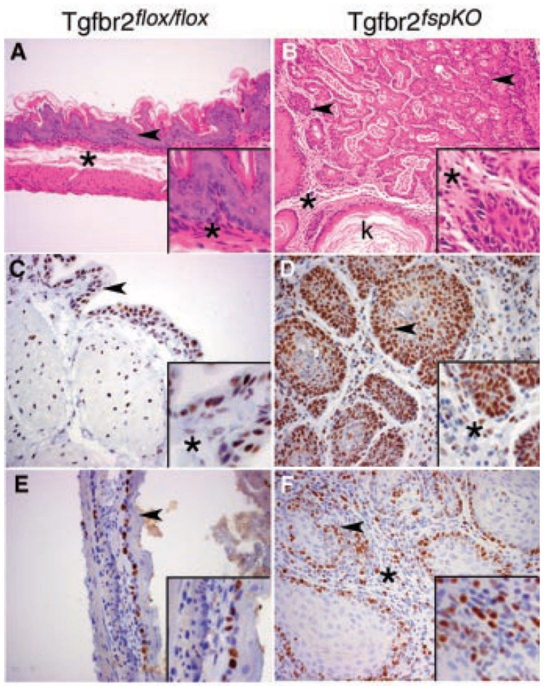


Fig. 2. Squamous cell carcinoma develops in the forestomachs of Tgfbr2^{fspKO} mice.

Suggestive of strong effects of altered fibroblasts on neighboring epithelial cells

- Is FSP1-Cre specific to fibroblasts or was there recombination in epithelial cells?
- Is this related to developmental issues as Cre expression may have be turned on early in development?

Activated fibroblasts can be tumor-promoting

[CANCER RESEARCH 60, 1254–1260, March 1, 2000]

Irradiated Mammary Gland Stroma Promotes the Expression of Tumorigenic Potential by Unirradiated Epithelial Cells[1]

Mary Helen Barcellos-Hoff[2] and Shraddha A. Ravani

Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, California 94720

CellPress Cancer Cell

Article

Promotion of cholangiocarcinoma growth by diverse cancer-associated fibroblast subpopulations

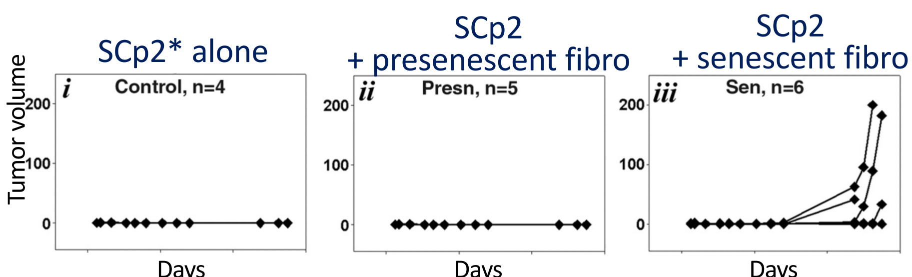
Silvia Affo,[1] Ajay Nair,[2,25] Francesco Brundu,[2,25] Aashreya Ravichandra,[1,25] Sonakshi Bhattacharjee,[1] Michitaka Matsuda,[3] LiKang Chin,[4] Aveline Filliol,[1] Wen Wen,[1] Xinhua Song,[5] Aubrianna Decker,[6] Jeremy Worley,[2] Jorge Matias Caviglia,[1] Lexing Yu,[1] Deqi Yin,[1] Yoshinobu Saito,[1] Thomas Savage,[7] Rebecca G. Wells,[4] Matthias Mack,[8] Lars Zender,[9,10,11] Nicholas Arpaia,[7,12] Helen E. Remotti,[13] Raul Rabadan,[2] Peter Sims,[14] Anne-Laure Leblond,[15] Achim Weber,[15] Marc-Oliver Riener,[15] Brent R. Stockwell,[6,16] Jellert Gaublomme,[6] Josep M. Llovet,[17,18,19] Raghu Kalluri,[20] George K. Michalopoulos,[21] Ekihiro Seki,[3] Daniela Sia,[18] Xin Chen,[5] Andrea Califano,[1,2,12,14,22,23] and Robert F. Schwabe[1,12,24,26,*]

866 Cancer Cell *39*, 866–882, June 14, 2021

12072–12077 | PNAS | October 9, 2001 | vol. 98 | no. 21

Senescent fibroblasts promote epithelial cell growth and tumorigenesis: A link between cancer and aging

Ana Krtolica*, Simona Parrinello*, Stephen Lockett*[†], Pierre-Yves Desprez[‡], and Judith Campisi*[§]



*immortal but non-tumor forming mammary epithelial cells

Article

Opposing roles of hepatic stellate cell subpopulations in hepatocarcinogenesis

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356 | Nature | Vol 610 | 13 October 2022

Activated fibroblasts can be tumor-restraining

In most tumors, CAF seem to be tumor promoting. But a different picture in some studies on pancreatic cancer:

Cancer Cell
Article
CellPress

Stromal Elements Act to Restrain, Rather Than Support, Pancreatic Ductal Adenocarcinoma

Andrew D. Rhim,[1,2,8] Paul E. Oberstein,[3,8] Dafydd H. Thomas,[4,5,8] Emily T. Mirek,[2] Carmine F. Palermo,[4,5] Stephen A. Sastra,[4,5] Erin N. Dekleva,[2] Tyler Saunders,[6] Claudia P. Becerra,[5] Ian W. Tattersall,[5] C. Benedikt Westphalen,[4] Jan Kitajewski,[5] Maite G. Fernandez-Barrena,[7] Martin E. Fernandez-Zapico,[7] Christine Iacobuzio-Donahue,[6] Kenneth P. Olive,[4,5,*] and Ben Z. Stanger[2,*]

Cancer Cell
Article
CellPress

Depletion of Carcinoma-Associated Fibroblasts and Fibrosis Induces Immunosuppression and Accelerates Pancreas Cancer with Reduced Survival

Berna C. Özdemir,[1,2] Tsvetelina Pentcheva-Hoang,[3] Julienne L. Carstens,[1] Xiaofeng Zheng,[1] Chia-Chin Wu,[4] Tyler R. Simpson,[3] Hanane Laklai,[5] Hikaru Sugimoto,[1,2] Christoph Kahlert,[1,2] Sergey V. Novitskiy,[6] Ana De Jesus-Acosta,[7] Padmanee Sharma,[3] Pedram Heidari,[8] Umar Mahmood,[8] Lynda Chin,[4] Harold L. Moses,[6] Valerie M. Weaver,[5] Anirban Maitra,[9] James P. Allison,[3] Valerie S. LeBleu,[1,2] and Raghu Kalluri[1,2,*]

CellPress
Cancer Cell
Article

Type I collagen deletion in αSMA$^+$ myofibroblasts augments immune suppression and accelerates progression of pancreatic cancer

Yang Chen,[1] Jiha Kim,[1] Sujuan Yang,[1] Huamin Wang,[2] Chang-Jiun Wu,[3] Hikaru Sugimoto,[1] Valerie S. LeBleu,[1] and Raghu Kalluri[1,4,*]

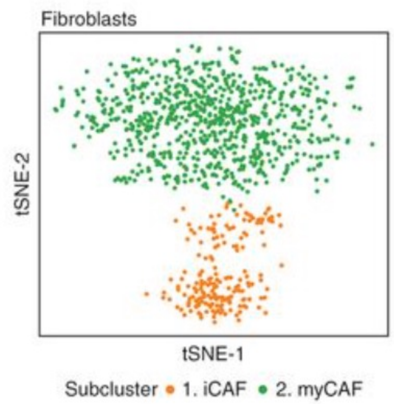
Possibility of tumor-promoting and tumor-restricting CAF subpopulations in PDAC and other tumors.

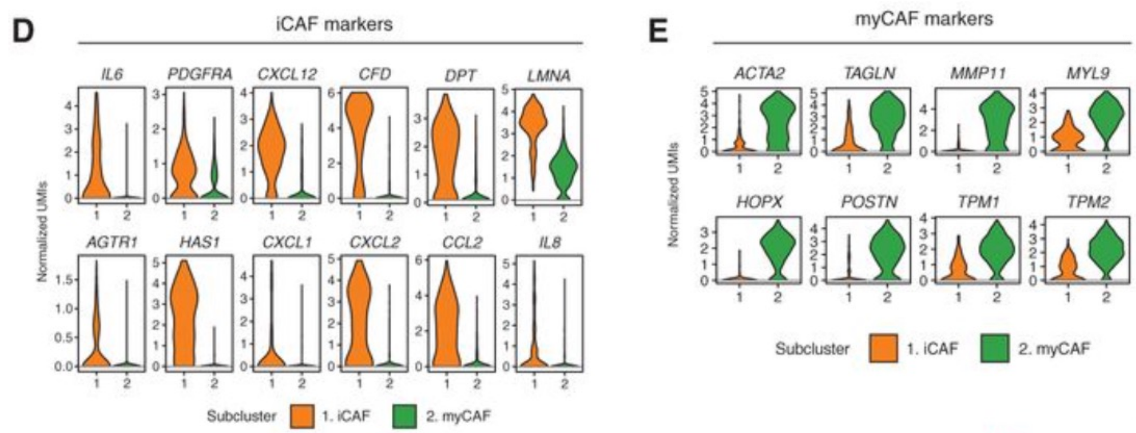
CAF diversity: Inflammatory, antigen-presenting and myofibroblastic CAF

Cross-Species Single-Cell Analysis of Pancreatic Ductal Adenocarcinoma Reveals Antigen-Presenting Cancer-Associated Fibroblasts

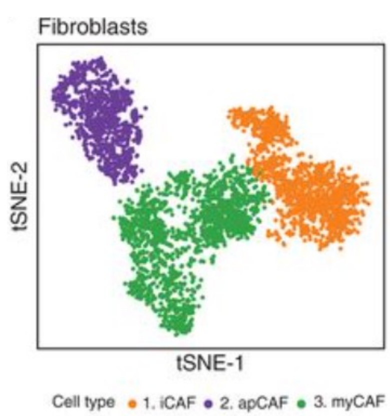
Ela Elyada[1,2], Mohan Bolisetty[3,4], Pasquale Laise[5], William F. Flynn[3], Elise T. Courtois[3], Richard A. Burkhart[6], Jonathan A. Teinor[6], Pascal Belleau[1], Giulia Biffi[1,2], Matthew S. Lucito[1,2], Santhosh Sivajothi[3], Todd D. Armstrong[6], Dannielle D. Engle[1,2,7], Kenneth H. Yu[8], Yuan Hao[1], Christopher L. Wolfgang[6], Youngkyu Park[1,2], Jonathan Preall[1], Elizabeth M. Jaffee[6], Andrea Califano[5,9,10,11,12], Paul Robson[3,13], and David A. Tuveson[1,2]

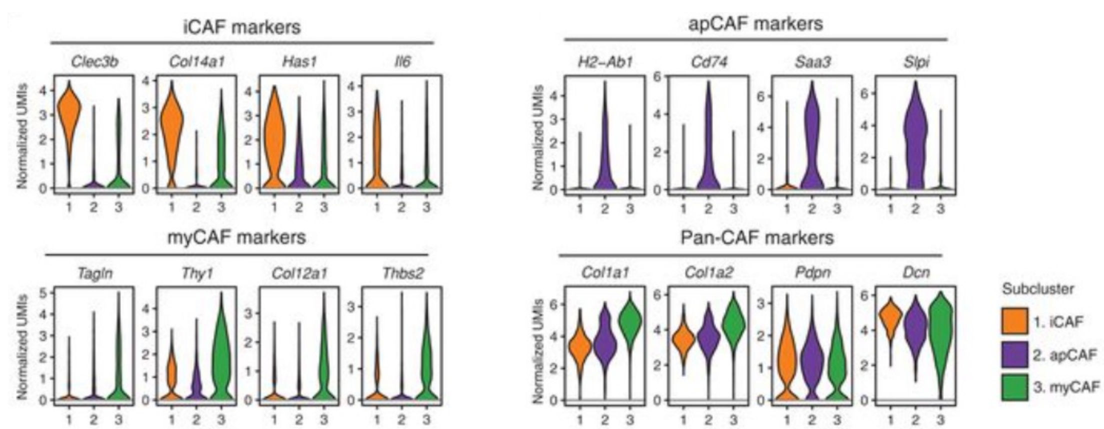
Mice





Patients





CAF can promote resistance to tumor therapy

- Desmoplastic CAF-rich tumors are often highly resistant to therapy (e.g PDAC, cholangiocarcinoma)

- CAF can mediate resistance to multiple forms of therapy (chemo- and radiotherapy, targeted therapy....)
  (Chen et al, Nat Rev Drug Discov 2019;18(2):99-115; Feng et al, Cancer Cell Int. 2022 9;22:166)

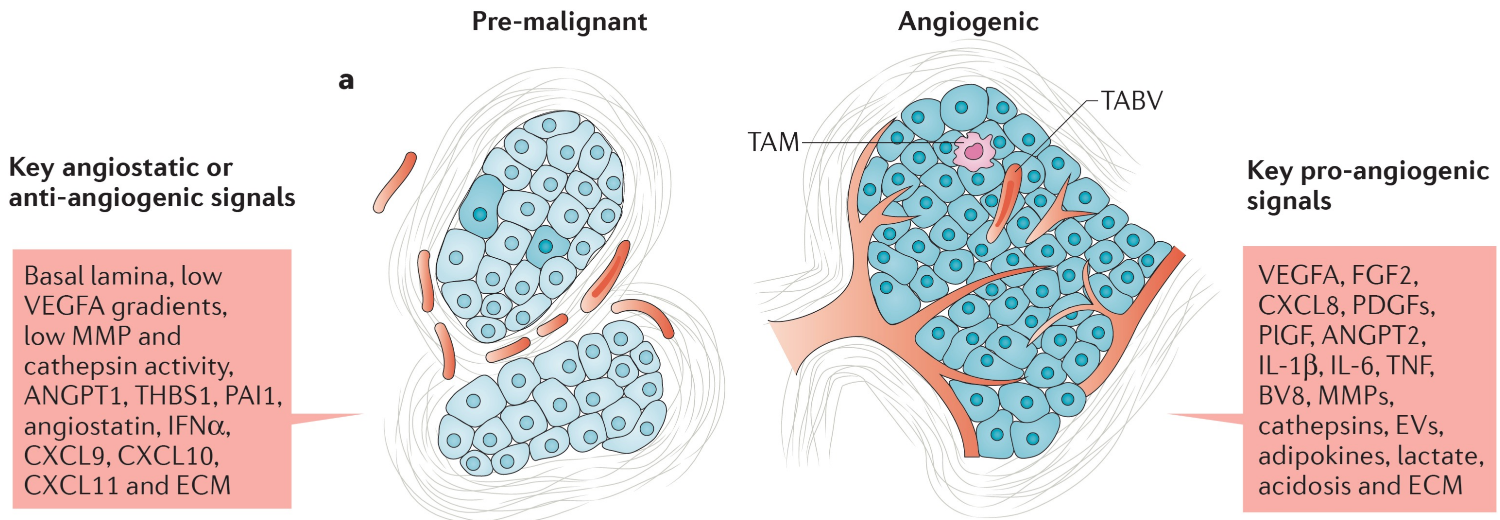
- These effects can be mediated by soluble factors (e.g. CAF-produced HGF), immune mechanisms, ECM....

Endothelial cells/angiogenesis

How is tumor angiogenesis induced and maintained in the TME?

- The main stimulus for tumor angiogenesis is tumor cell **hypoxia**, which induces secretion of angiogenic factors such as **VEGF** from tumor cells. VEGF acts on endothelial cells, promoting motility of EC ("tip cells") resulting in new vascular sprouts towards the VEGF gradient.

- Tumor vascularization typical for established tumors - but not premalignant stages due to smaller size, intact basement membrane and **angiostatic signals**



Microenvironmental regulation of tumour angiogenesis. De Palma M, Biziato D, Petrova TV. Nat Rev Cancer. 2017 Aug;17(8):457-474.

"Angiogenesis" lecture by Dr. Minah Kim

Crosstalk in the TME maintains angiogenesis

Role of myeloid cells

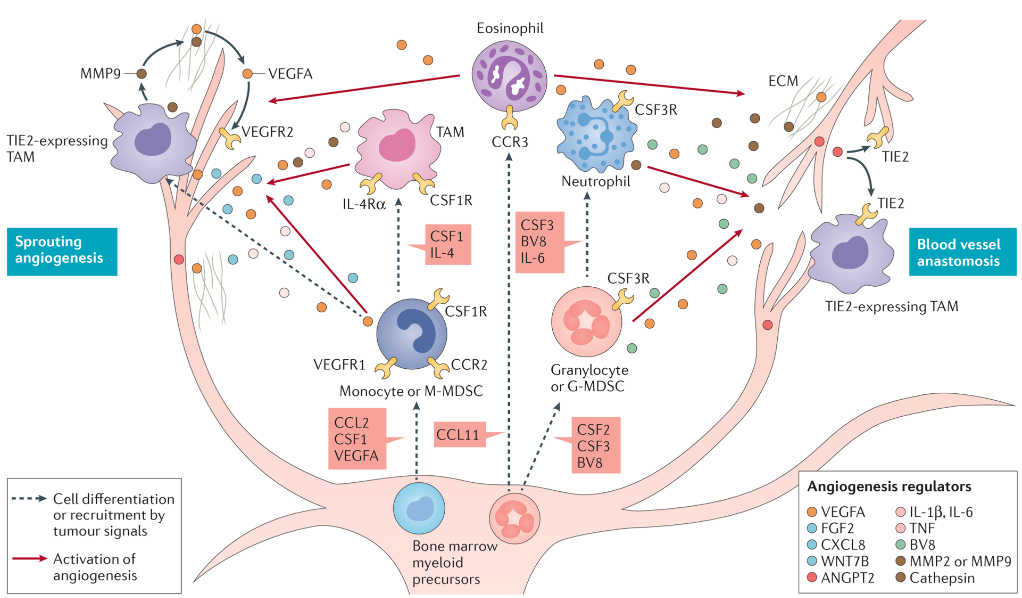


Figure 2 | **Myeloid cell regulation of tumour angiogenesis.** Various tumour-derived myeloid-cell chemoattractants — such

Role of CAF

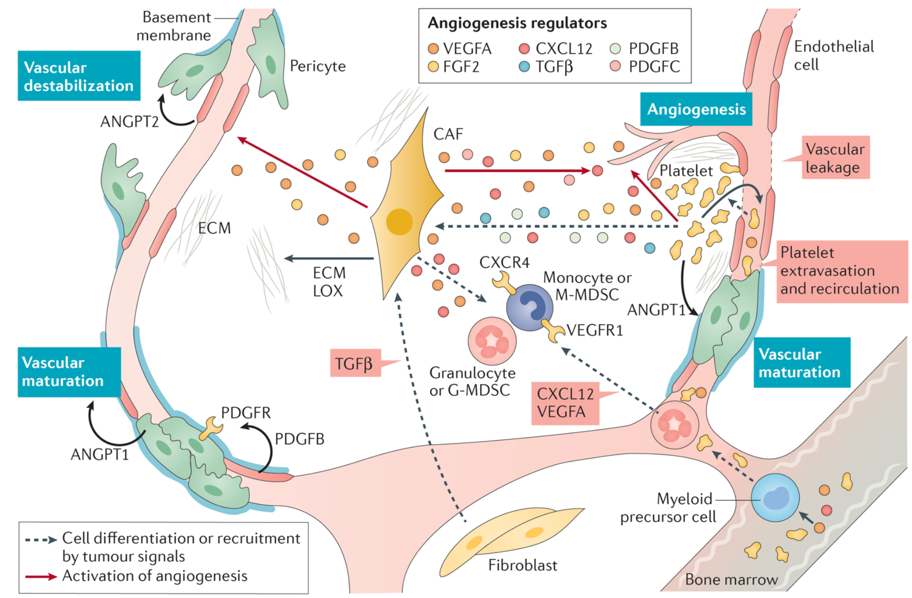


Figure 4 | **Chronic wound-healing response promotes tumour angiogenesis.** Under the influence of transforming growth

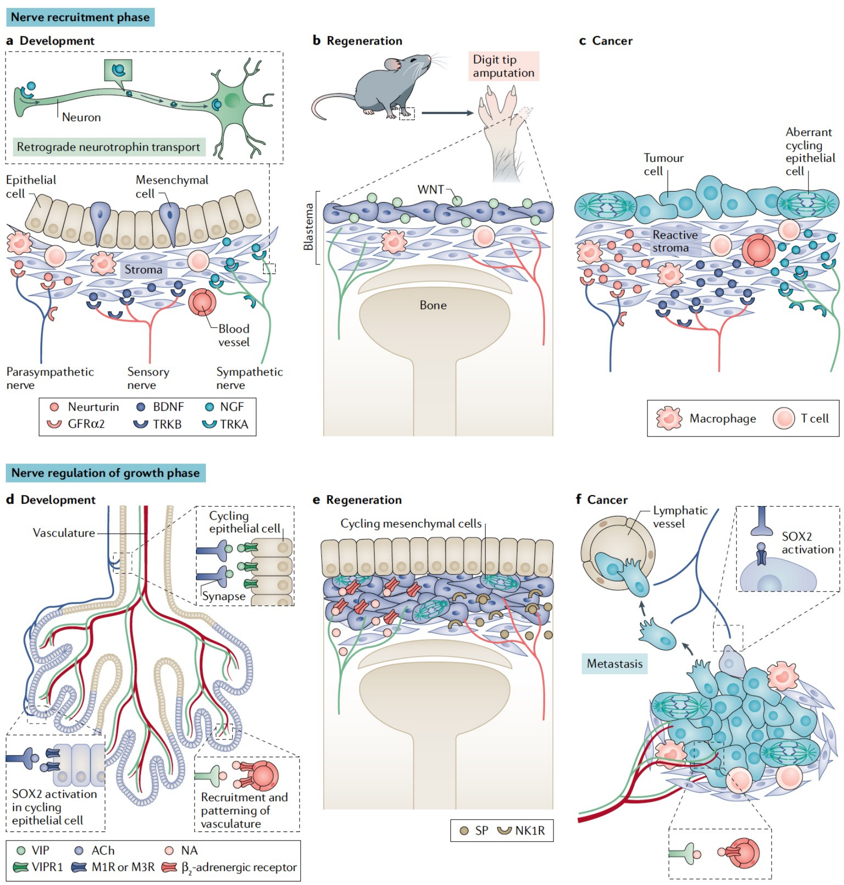
Microenvironmental regulation of tumour angiogenesis. De Palma M, Biziato D, Petrova TV. Nat Rev Cancer. 2017 Aug;17(8):457-474.

“Angiogenesis” lecture by Dr. Minah Kim

Nerves in the TME

Role of nerves in tumor growth

Nerves are recruited in development, regeneration and cancer and regulate growth



Nerves influence the TME

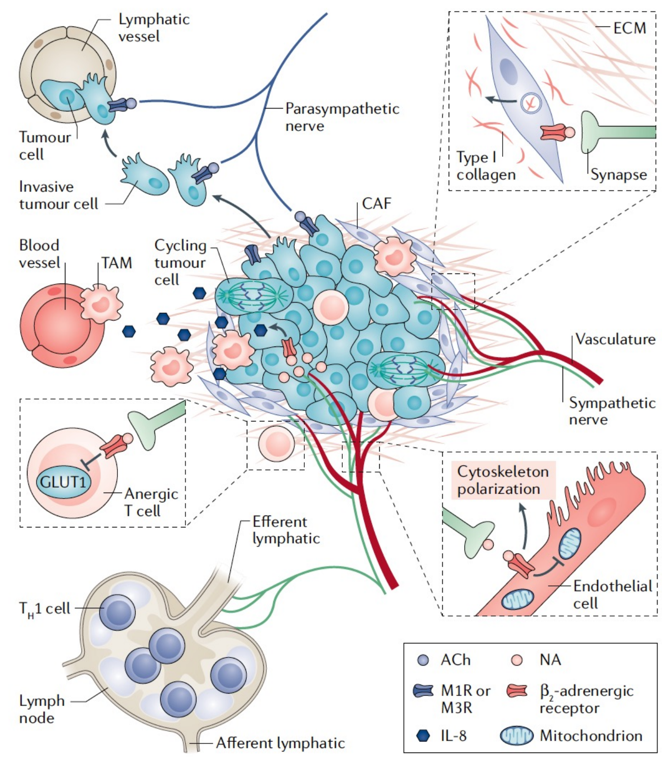


Fig. 3 | **Neural regulation of the tumour microenvironment.** Nerves interact with

Ali H Zahalka and Paul S Frenette.. Nerves in cancer. **Nat Rev Cancer** 2020 Mar;20(3):143-157.

Examples of the tumor-promoting effects of nerves

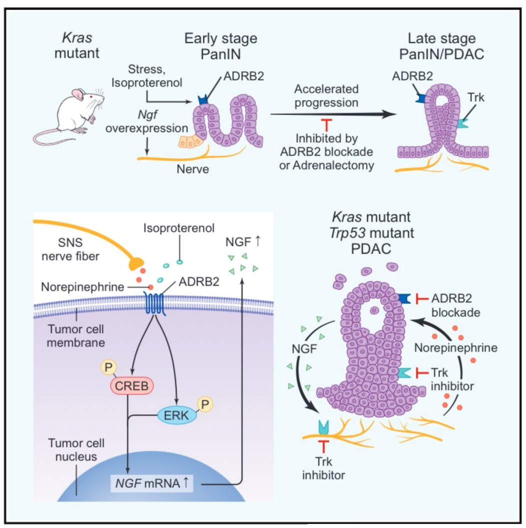
Cancer Cell
Article

β2 Adrenergic-Neurotrophin Feedforward Loop Promotes Pancreatic Cancer

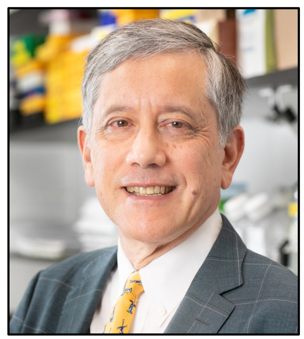
Bernhard W. Renz,[1,2,14] Ryota Takahashi,[2,14] Takayuki Tanaka,[2] Marina Macchini,[2,3] Yoku Hayakawa,[2,4] Zahra Dantes,[5] H. Carlo Maurer,[2] Xiaowei Chen,[2,15] Zhengyu Jiang,[2] C. Benedikt Westphalen,[2,6] Matthias Ilmer,[1] Giovanni Valenti,[2] Sarajo K. Mohanta,[7] Andreas J.R. Habenicht,[7] Moritz Middelhoff,[2] Timothy Chu,[2] Karan Nagar,[2] Yagnesh Tailor,[2] Riccardo Casadei,[8] Mariacristina Di Marco,[9] Axel Kleespies,[1] Richard A. Friedman,[10] Helen Remotti,[11] Maximilian Reichert,[5] Daniel L. Worthley,[2,12] Jens Neumann,[13] Jens Werner,[1] Alina C. Iuga,[11] Kenneth P. Olive,[2,11] and Timothy C. Wang[2,16,*]

Highlights

- Neuropsychological stress accelerates PDAC development
- ADRB2-signaling upregulates NGF and BDNF, thereby increasing nerve density
- Blockade of the ADRB2 and NGF/Trk pathways prolongs survival in KPC mice
- ADRB2 and NGF-BDNF/Trk pathways may be promising targets in PDAC treatment



Cancer Cell 33, 75–90, January 8, 2018



Timothy Wang, MD

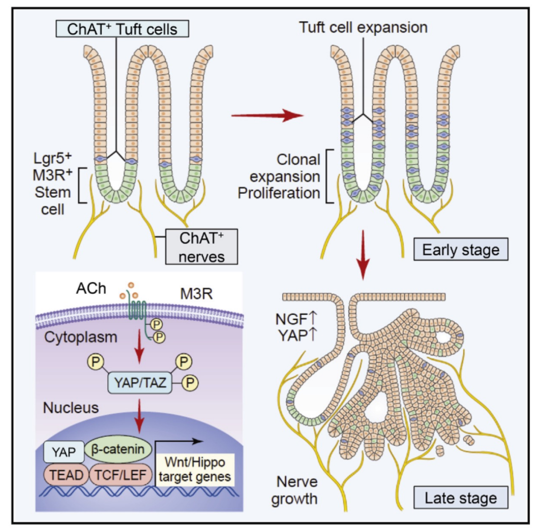
Cancer Cell
Article

Nerve Growth Factor Promotes Gastric Tumorigenesis through Aberrant Cholinergic Signaling

Yoku Hayakawa,[1,2,12] Kosuke Sakitani,[1,12] Mitsuru Konishi,[2] Samuel Asfaha,[1,3] Ryota Niikura,[2] Hiroyuki Tomita,[4] Bernhard W. Renz,[1,5] Yagnesh Tailor,[1] Marina Macchini,[1] Moritz Middelhoff,[1] Zhengyu Jiang,[1] Takayuki Tanaka,[1] Zinaida A. Dubeykovskaya,[1] Woosook Kim,[1] Xiaowei Chen,[1] Aleksandra M. Urbanska,[1] Karan Nagar,[1] Christoph B. Westphalen,[1,6] Michael Quante,[7] Chyuan-Sheng Lin,[8,9] Michael D. Gershon,[8] Akira Hara,[4] Chun-Mei Zhao,[10] Duan Chen,[10] Daniel L. Worthley,[1,11] Kazuhiko Koike,[2] and Timothy C. Wang[1,13,*]

Highlights

- NGF expression is induced in gastric cancer by ACh from nerves and tuft cells
- NGF promotes innervation and proliferation in gastric epithelium
- Blockade of NGF or ablation of cholinergic tuft cells inhibits tumor development
- Cholinergic signaling activates YAP signaling that is essential for Wnt activation

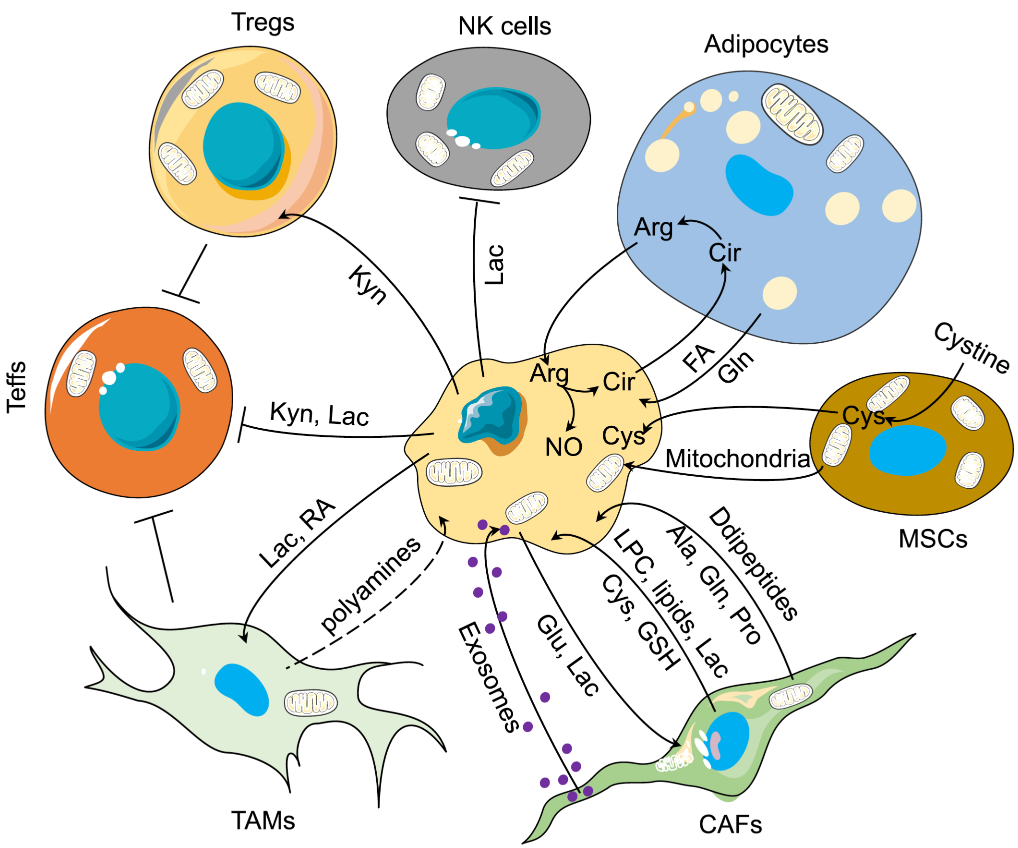


Cancer Cell 31, 21–34, January 9, 2017

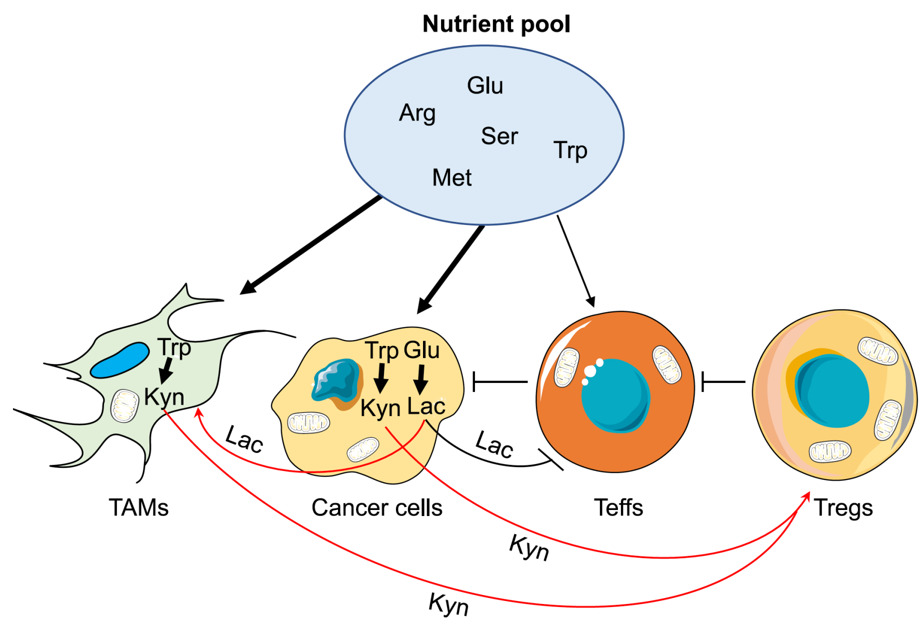
TME: Metabolism affects tumor cells and immune responses

The TME has an important role in tumor metabolism

Extensive metabolic communication in the TME



Nutrient competition leading to **increased Tregs** (via kynurenine production in Tu and Mo) and **TAM polarization** (via lactate from tumor cells)



Fuming Li , M Celeste Simon. Cancer Cells Don't Live Alone: Metabolic Communication within Tumor Microenvironments. ***Dev Cell*** 2020 Jul 20;54(2):183-195.

Take home messages on the TME

- Tumor cells grow in a complex microenvironment like other cells in our body
- The TME can be **tumor-promoting** and **tumor-restricting**. Tumors often reprogram the TME to their favor.
- The **healthy environment can be tumor-restricting** and the loss of this restriction is a mechanisms of tumor promotion
- Major roles of **CAFs**, **angiogenesis**, **nerves** and **immune cells**.
- **Metabolism/metabolites** recognized as important in the TME crosstalk and tumor progression.
- **High diversity in the TME**; many subclasses of tumor-suppressing and tumor-promoting immune cells; increasing evidence that there is high CAF diversity with sometimes opposing functions

Questions?

- Part 1: The Tumor Microenvironment (22 slides)
- Questions

- **Part 2: Part 2: Tumor Immunology**
- **Questions**

The birth and rebirth of tumor immunology

The concept of immune surveillance

"It is by no means inconceivable that small accumulations of tumor cells may develop and, because of their possession of new antigenic potentialities, provoke and effective immunological reaction with regression offer tomorrow and no clinical hint of its existence"

Marfarlane Burnet, Immunologist, 1957

The birth and rebirth of tumor immunology

- Tumor transplantation studies in different strains appeared to show that the immune system eradicates tumors. However, this proved to turn out as **allograft rejection** that was not tumor-specific.

- After recognizing this, the focus was on tumor development in immunocompromised Nude mice. There were no drastic differences in tumor development. Tumor surveillance by the immune system was for some time considered less elevant. In the 1980s, it was recognized that cells such as Nk cells, still present in Nude mice, were important for anti-tumor immunity. Tumor surveillance was reconsidered.

- A series of studies demonstrated immunoediting of tumors by the immune system – changes of antigen profile and functional consequences of this (unedited tumors were recognized and destroyed when given to the same mouse; edited tumors grew)

- Mice deficient in IFNy signaling displayed profoundly increased tumors when subjected to carcinogens (Kaplan, D. H. et al. Demonstration of an interferon γ-dependent tumor surveillance system in immunocompetent mice. Proc. Natl Acad. Sci. USA 1998. 95, 7556–7561).

letters to nature

IFNγ and lymphocytes prevent primary tumour development and shape tumour immunogenicity

NATURE | VOL 410 | 26 APRIL 2001 | www.nature.com

Vijay Shankaran*, Hiroaki Ikeda*, Allen T. Bruce*, J. Michael White*, Paul E. Swanson*, Lloyd J. Old† & Robert D. Schreiber*

Figure 1: Lymphocyte-deficient mice are highly susceptible susceptible to MCA-induced tumour development.

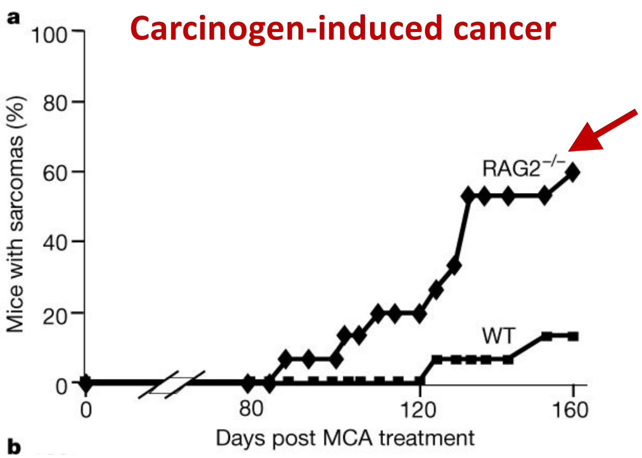


Figure 2: Increased development of spontaneous neoplastic disease in immunodeficient mice.

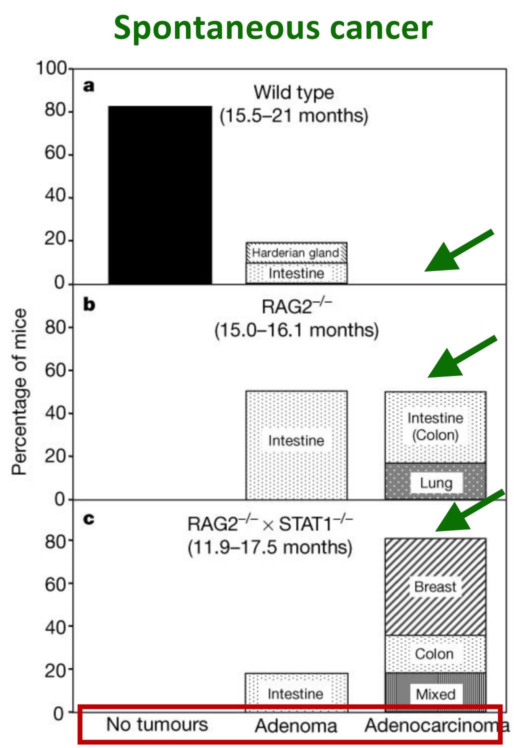
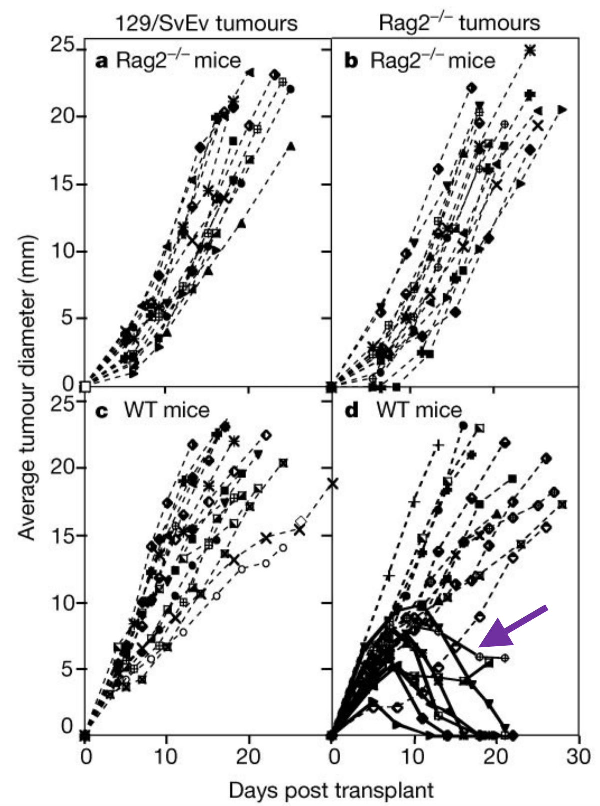


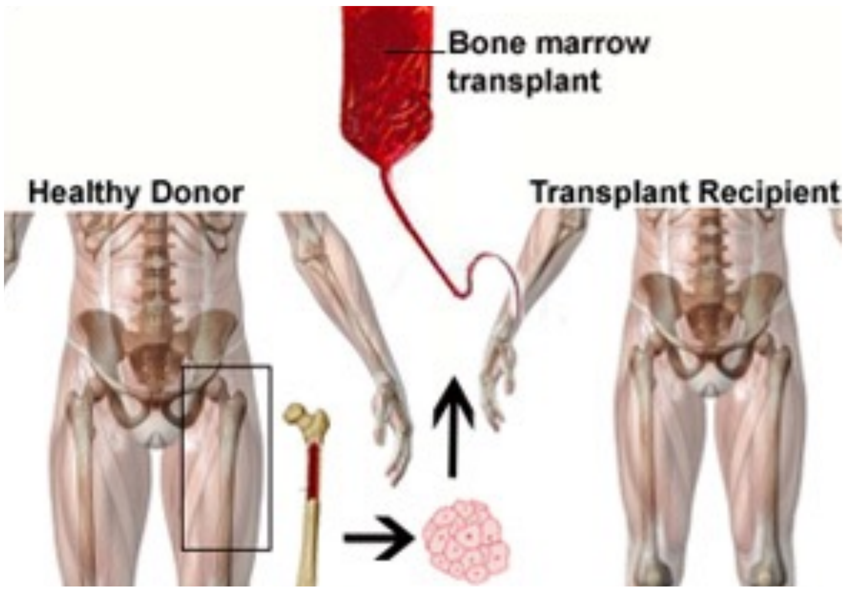
Figure 3: Increased immunogenicity of tumours derived from MCA-treated RAG2−/− mice.



Increased cancer development in immunosuppressed patients

- Renal transplant patients have a 2.7-fold increased risk of overall cancer development
- Renal transplant patients have a 200-fold risk of non-melanoma skin cancer (Moloney, Br. J. Dermatol. 154: 498–504)
- Heart transplant patients have a 22.7-fold increase in non-Hodgkin's lymphoma (Jiang et al, Am. J. Transplant. 10: 637–45)
- Heart transplant patients have a 2-25-fold increase in lung cancer (Jian et al; Am.J.Transplant.10: 637–45; Pham et al, Ann.Thorac.Surg. 60:1623–26)

Graft-versus-host reactions can eliminate tumors



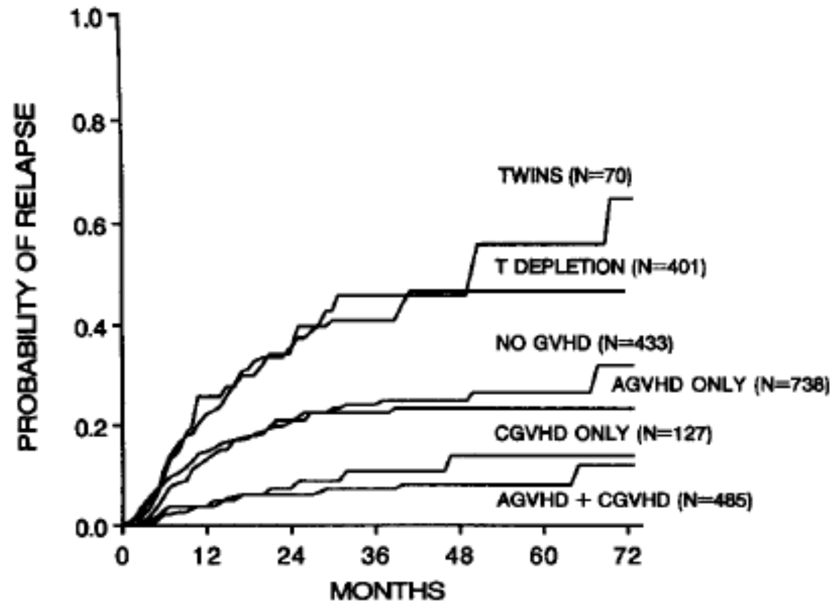
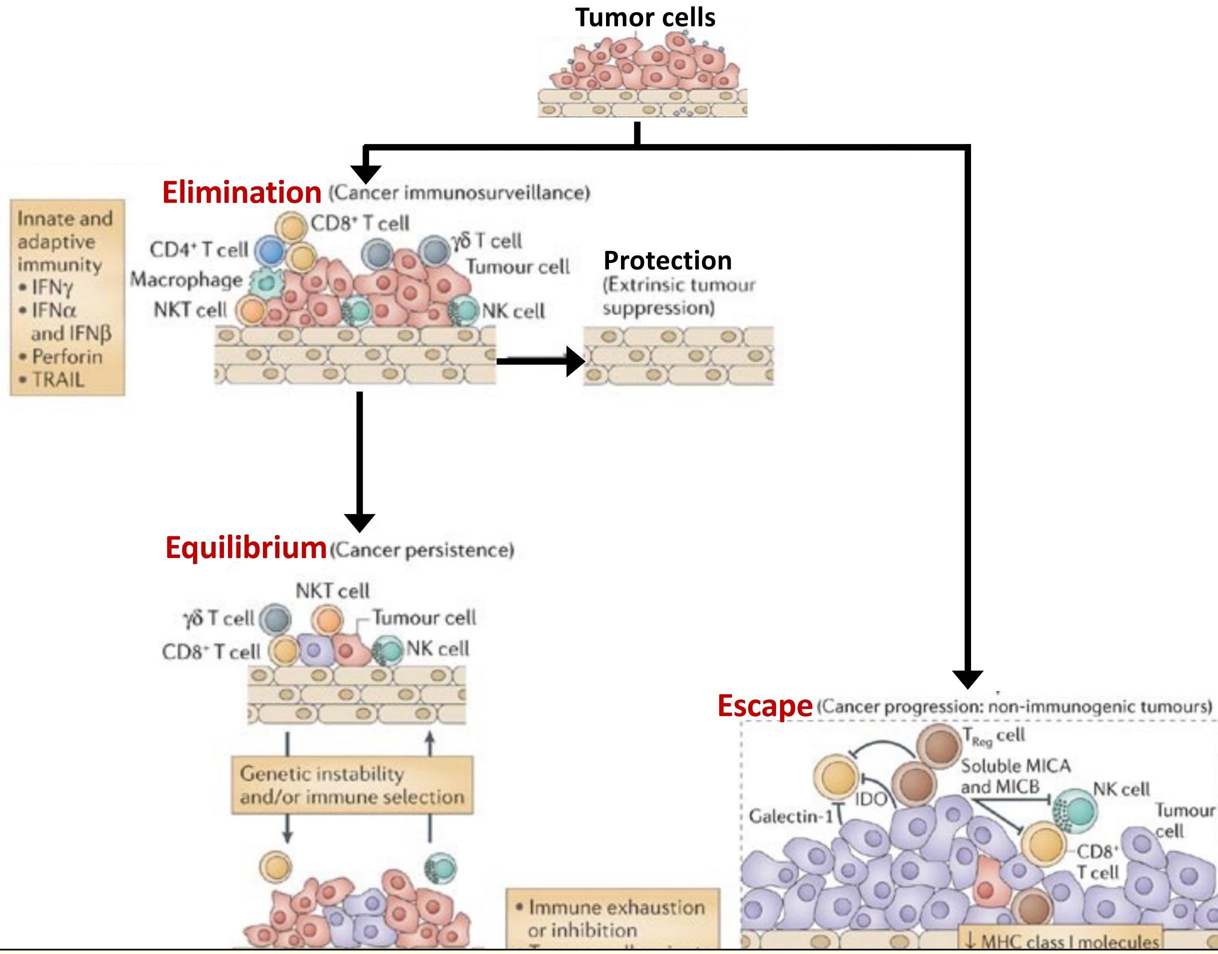


Fig 1. Actuarial probability of relapse after bone marrow transplantation for early leukemia according to type of graft and development of GVHD.

High immune reactivity = less relapse; lowest immune reactivity (twins, T cell depletion) = highest relapse

Immunoediting: Elimination, Equilibrium, Escape



Immunoediting seen in many/most tumors; but it can fail for many reasons including active interference by tumors

Gavin P. Dunn, Catherine M. Koebel & Robert D. Schreiber Interferons, immunity and cancer immunoediting. ***Nature Reviews Immunology*** 6, 836–848(2006)

Key mediators of anti-tumor immunity

Adaptive

CD8+ T cells

Classically kill tumor cells via secreted IFNy and granzyme B (Tc1)

Different subsets:

Tc1: IFNy, perforin, granzymeB
Tc2: type II cytokines IL-4, IL-5, IL-13

High cytotoxicity

Tc9: IL-9
Tc17: IL-17, IL-22

Low cytotoxicity

CD4+ T cells

Enhance CTL and antibody responses

(B cells)

Exert immuno-suppressive functions but also promote anti-tumor immunity

Innate

NK cells

Kill cells with low MHC I expression as absence of MHC I reduces Expression of ”Killer cell immunoglobulin receptors (KIR)

Type I NKT cells

Recognize lipid antigens presented via CD1d

Direct killing and immunomodulatory effects on other immune cells

γδ T cells

non-MHC-restricted innate-like T-cell population

Direct killing of tumor cells via perforin, granzymes and high IFNy secretion

M1 macro

M1 tumor-suppressive, high IL-12, low IL-10

M2 macrophages /TAM immunosuppressive

cDC1

Most efficient Antigen Cross Presenting DC type

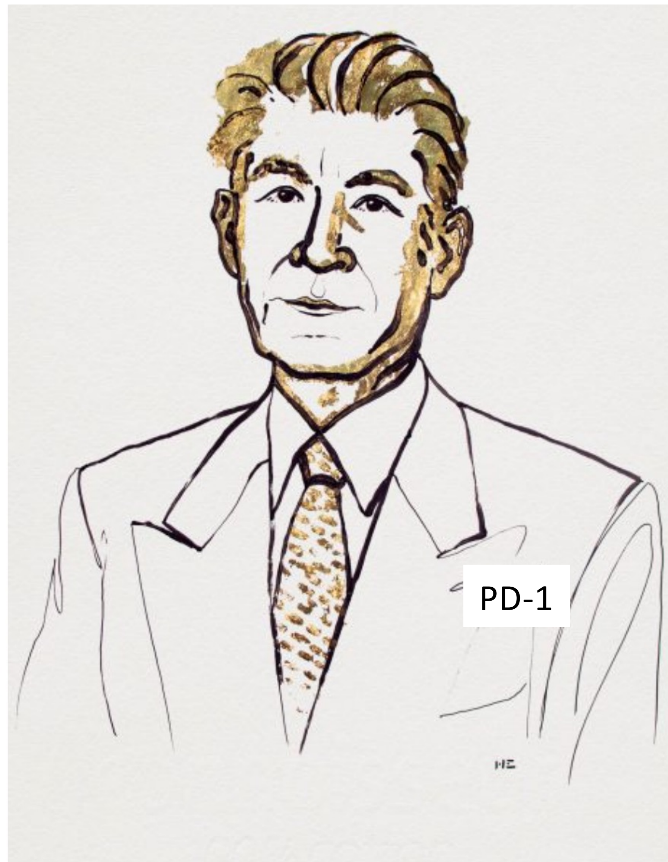
Key suppressors of anti-tumor immunity

Treg	M2 TAM	MDSC	Cancer cells	CAF
FoxP3+ CD4+ T cells that suppress anti-tumor immunity main on effects on **CD8+ CTL** and **CD4+ T** helper cells via CTLA-4.	Express IL-10, arginase, TGFb Inhibit T cell function through expression of PD1 and CTLA4 ligands PD-L1 and B7. Can also promote **Treg differentiation** and survival and **inhibit NK and NKT** cells.	Immature myeloid cells with characteristics of monocytes and/or neutrophils. **PMN-MDSC**s suppress mainly via ROS **M-MDSCs** subtypes suppress via expression of ARG1 and NO	Immunosuppression via expression of **PD-L1** Immunosuppression via **MHC class I downregulation**	Induction of PD-L1 on other cell types Promote **recruitment or expansion of immunosuppressive cells** such as Treg, MDSC, M2 macrophages

Checkpoint inhibition: One of the biggest breakthroughs in cancer therapy

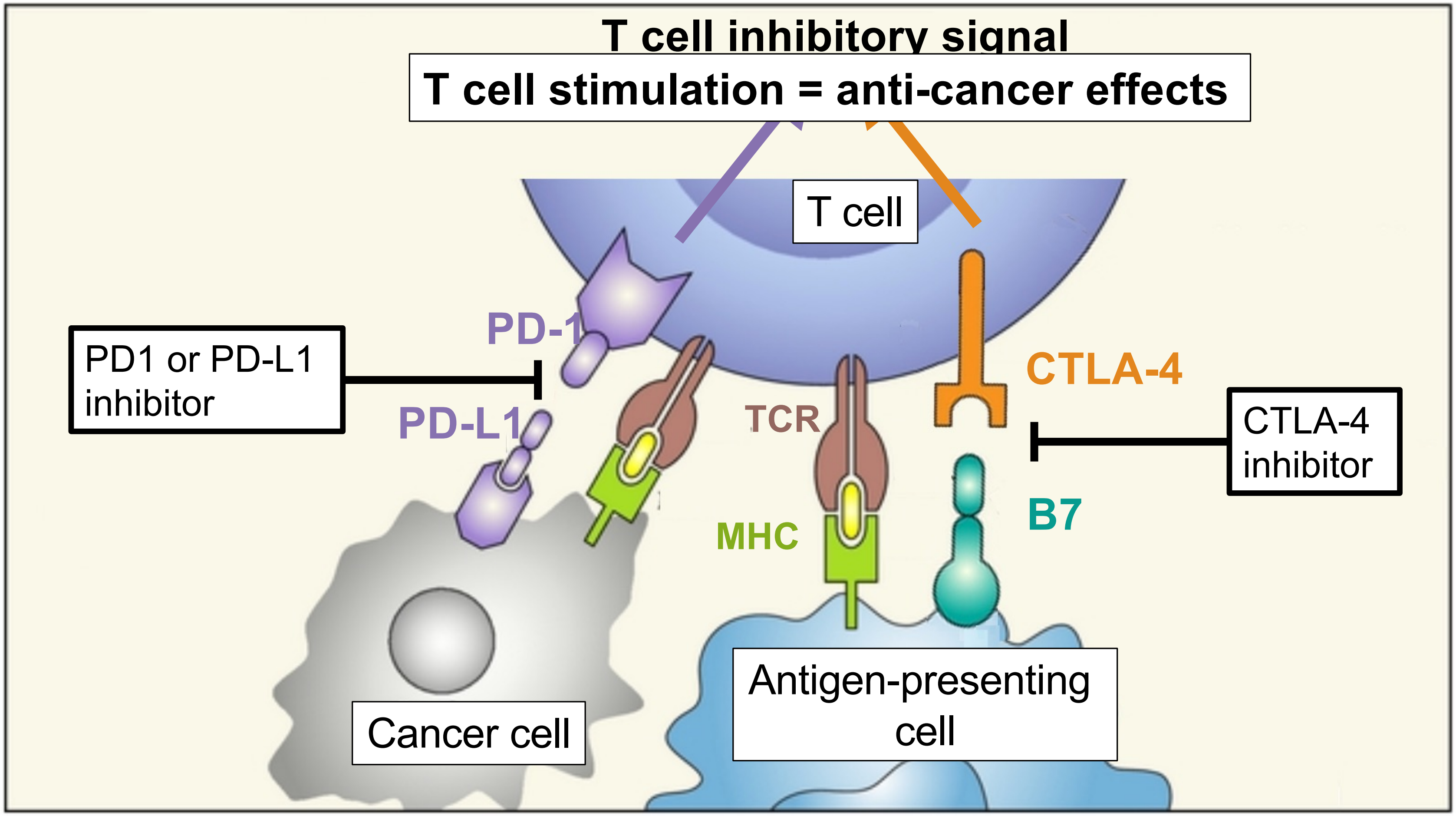
2018 Nobel Prize: Discovery of cancer therapy by inhibition of negative immune regulation.

James P. Allison



Tasuku Honjo

Releasing the brake on anti-tumor responses



The era of immunotherapy: Responses that were never thought possible

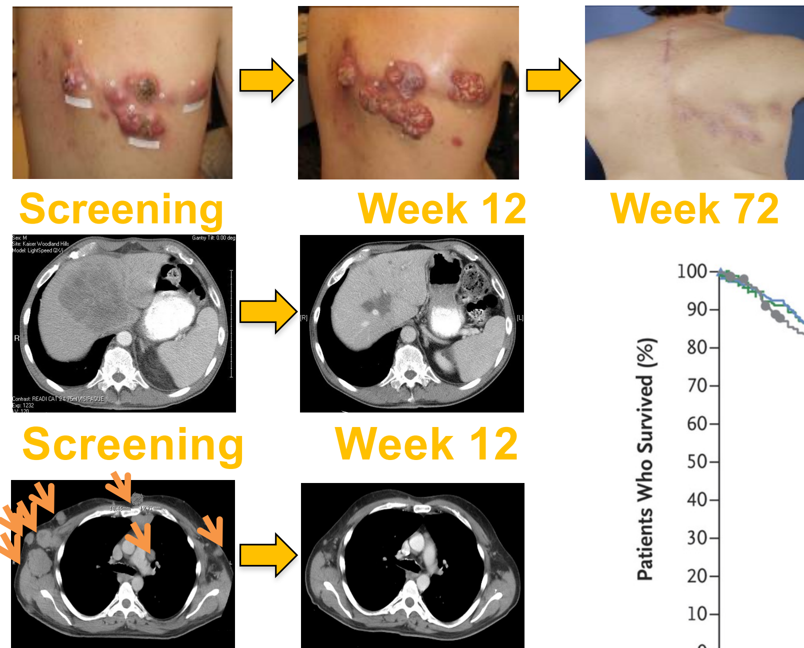
anti-CTLA4

Screening | Week 12 | Week 72

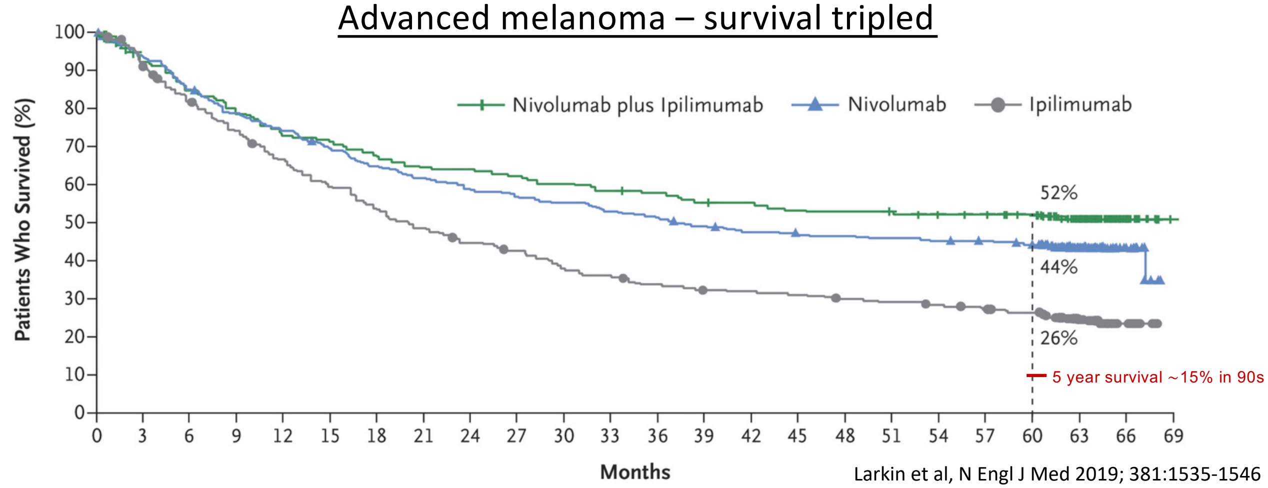
anti-PD-1

Screening | Week 12

CTLA4 + PD-1



Advanced melanoma – survival tripled

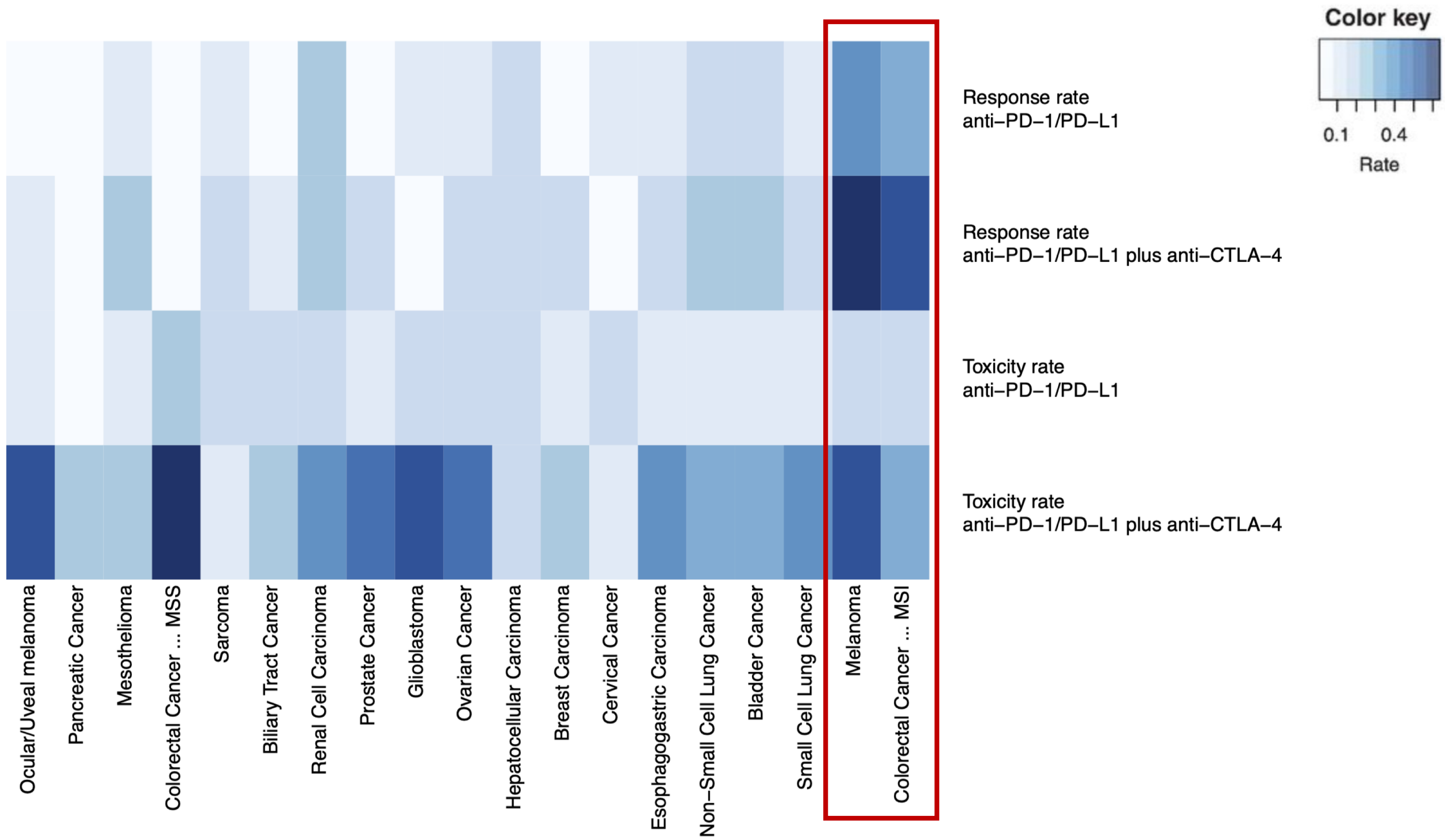


Larkin et al, N Engl J Med 2019; 381:1535-1546

Even cure appears possible in advanced melanoma patients treated with checkpoint inhibitors (up to 20%).

Only good news?

Not all tumors respond equally to checkpoint inhibition

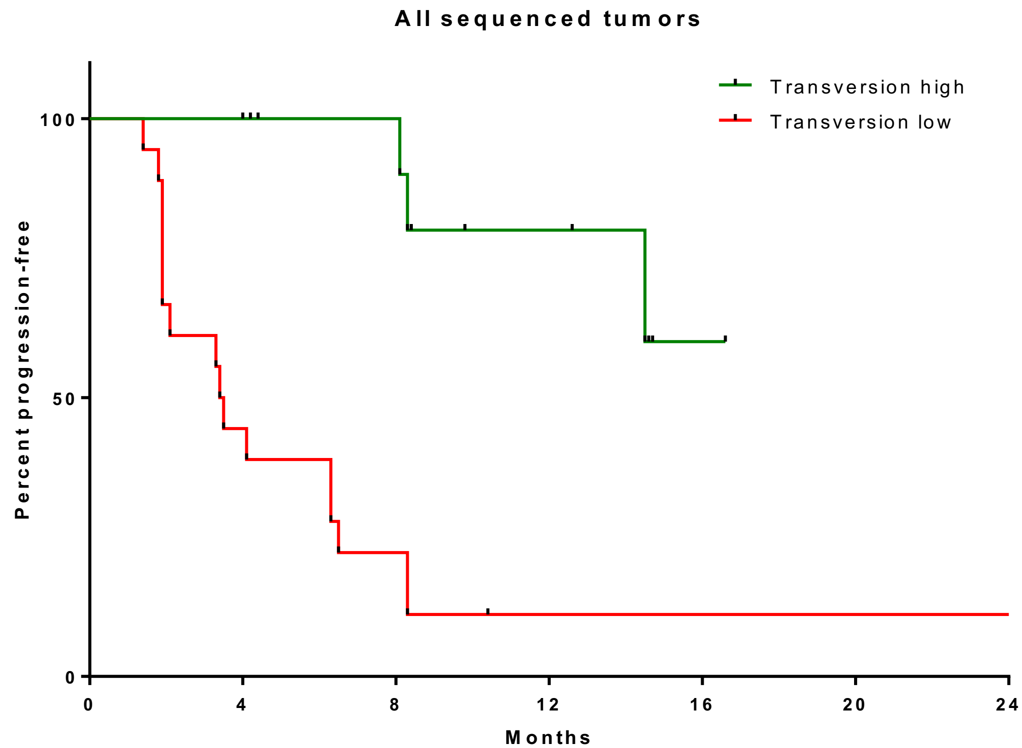


Osipov et al, Clin Cancer Res. 2020 Sep 15;26(18):4842-4851

Tumor mutational burden a main determinant of response rates

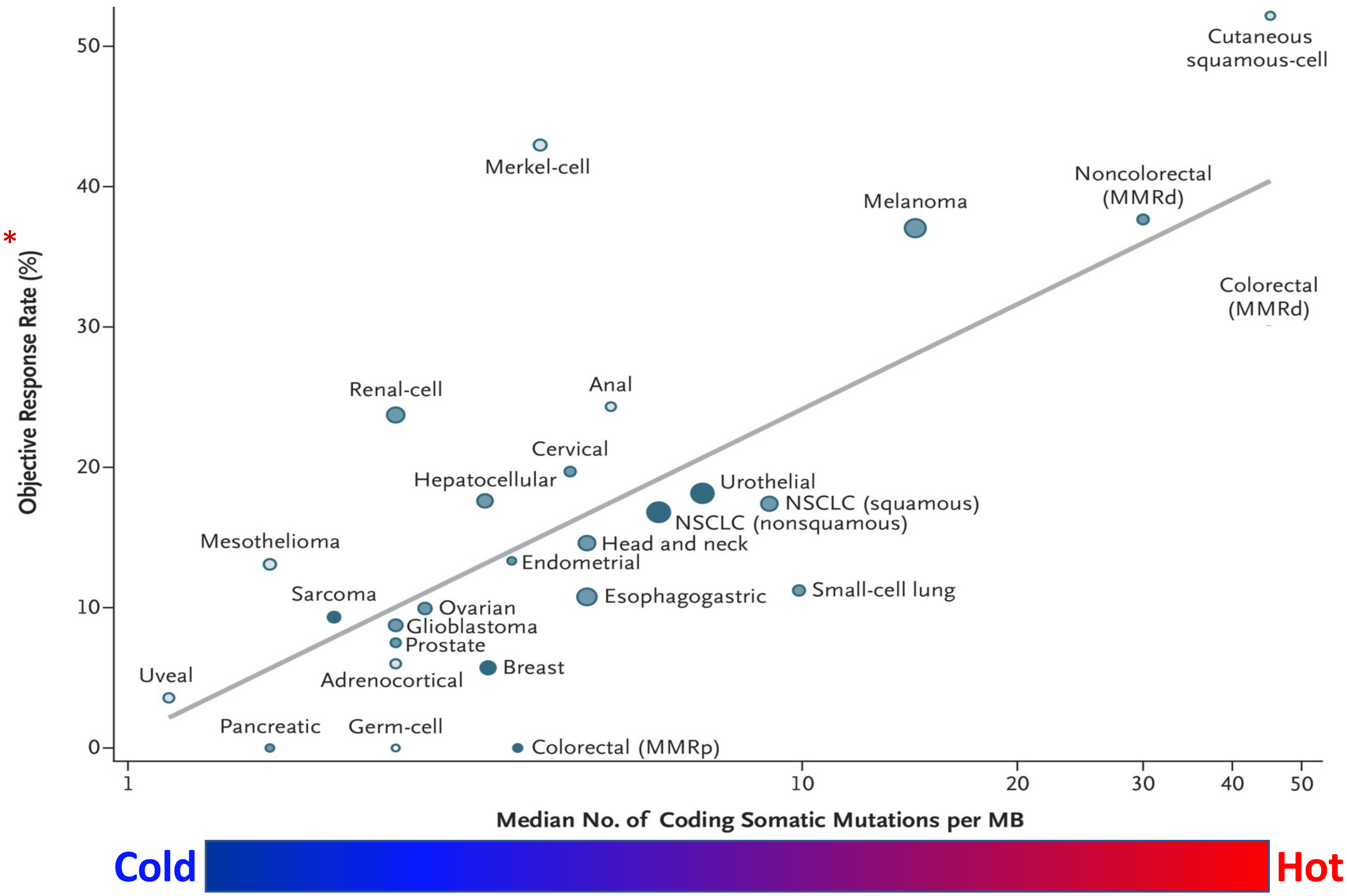
CANCER IMMUNOLOGY

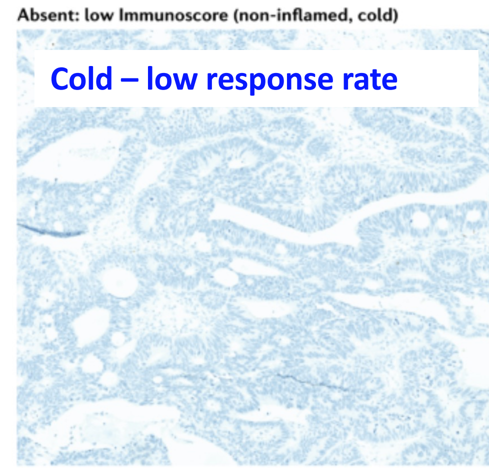
Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

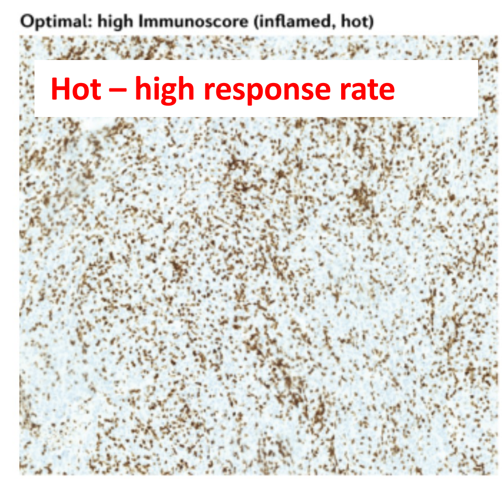


Rizvi NA et al, ***Science*** 2015 Apr 3;348(6230):124-8

Tumor mutational burden a main determinant of response rates
Hot vs cold tumors







*anti-PD or anti-PD-L1 treatment

Yarchoan et al, *N Engl J Med*. 2017 Dec 21;377(25):2500-2501.

A key role of the microbiome in anti-cancer therapies/immunity

1. Microbiome affects chemotherapy in mice

www.sciencemag.org SCIENCE VOL 342 22 NOVEMBER 2013

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]†‡

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*]†

Reduced effects of chemotherapy in Abx-treated or germ-free mice (P815 mastocytoma, MCA205 sarcoma, MC38 colon cancer, Ret melanoma)

2. Microbiome affects immunotherapy in mice

SCIENCE sciencemag.org

CANCER IMMUNOTHERAPY 27 NOVEMBER 2015 • VOL 350 ISSUE 6264 1079

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti–PD-L1 efficacy

Ayelet Sivan,[1*] Leticia Corrales,[1*] Nathaniel Hubert,[2] Jason B. Williams,[1] Keston Aquino-Michaels,[3] Zachary M. Earley,[2] Franco W. Benyamin,[1] Yuk Man Lei,[2] Bana Jabri,[2] Maria-Luisa Alegre,[2] Eugene B. Chang,[2] Thomas F. Gajewski[1,2]†

CANCER IMMUNOTHERAPY

Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota

Marie Vétizou,[1,2,3] Jonathan M. Pitt,[1,2,3] Romain Daillère,[1,2,3] Patricia Lepage,[4] Nadine Waldschmitt,[5] Caroline Flament,[1,2,6] Sylvie Rusakiewicz,[1,2,6] Bertrand Routy,[1,2,3,6] Maria P. Roberti,[1,2,6] Connie P. M. Duong,[1,2,6] Vichnou Poirier-Colame,[1,2,6] Antoine Roux,[1,2,7] Sonia Becharef,[1,2,6] Silvia Formenti,[8] Encouse Golden,[8] Sascha Cording,[9] Gerard Eberl,[9] Andreas Schlitzer,[10] Florent Ginhoux,[10] Sridhar Mani,[11] Takahiro Yamazaki,[1,2,6] Nicolas Jacquelot,[1,2,3] David P. Enot,[1,7,12] Marion Bérard,[13] Jérôme Nigou,[14,15] Paule Opolon,[1] Alexander Eggermont,[1,2,16] Paul-Louis Woerther,[17] Elisabeth Chachaty,[17] Nathalie Chaput,[1,18] Caroline Robert,[1,16,19] Christina Mateus,[1,16] Guido Kroemer,[7,12,20,21,22] Didier Raoult,[23] Ivo Gomperts Boneca,[24,25*] Franck Carbonnel,[3,26*] Mathias Chamaillard,[5*] Laurence Zitvogel[1,2,3,6]†

Reduced effects of anti-PD-L1 and anti-CTLA-4 therapy in Abx-treated or germ-free mice (B16 melanoma, MCA205 sarcoma)

A key role of the microbiome in anti-cancer therapies

Microbiome required for efficient immunotherapy in patients

Science **359**, 91–97 (2018)

CANCER IMMUNOTHERAPY

Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors

Bertrand Routy,[1,2,3] Emmanuelle Le Chatelier,[4] Lisa Derosa,[1,2,3] Connie P. M. Duong,[1,2,5] Maryam Tidjani Alou,[1,2,3] Romain Daillère,[1,2,3] Aurélie Fluckiger,[1,2,5] Meriem Messaoudene,[1,2] Conrad Rauber,[1,2,3] Maria P. Roberti,[1,2,5] Marine Fidelle,[1,3,5] Caroline Flament,[1,2,5] Vichnou Poirier-Colame,[1,2,5] Paule Opolon,[6] Christophe Klein,[7] Kristina Iribarren,[8,9,10,11,12] Laura Mondragón,[8,9,10,11,12] Nicolas Jacquelot,[1,2,3] Bo Qu,[1,2,3] Gladys Ferrere,[1,2,3] Céline Clémenson,[1,13] Laura Mezquita,[1,14] Jordi Remon Masip,[1,14] Charles Naltet,[15] Solenn Brosseau,[15] Coureche Kaderbhai,[16] Corentin Richard,[16] Hira Rizvi,[17] Florence Levenez,[4] Nathalie Galleron,[4] Benoit Quinquis,[4] Nicolas Pons,[4] Bernhard Ryffel,[18] Véronique Minard-Colin,[1,19] Patrick Gonin,[1,20] Jean-Charles Soria,[1,14] Eric Deutsch,[1,13] Yohann Loriot,[1,3,14] François Ghiringhelli,[16] Gérard Zalcman,[15] François Goldwasser,[9,21,22] Bernard Escudier,[1,14,23] Matthew D. Hellmann,[24,25] Alexander Eggermont,[1,2,14] Didier Raoult,[26] Laurence Albiges,[1,3,14] Guido Kroemer,[8,9,10,11,12,27,28]* Laurence Zitvogel[1,2,3,5]*

Science **359**, 97–103 (2018)

CANCER IMMUNOTHERAPY

Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

V. Gopalakrishnan,[1,2]* C. N. Spencer,[2,3]* L. Nezi,[3]* A. Reuben,[1] M. C. Andrews,[1] T. V. Karpinets,[3] P. A. Prieto,[1]† D. Vicente,[1] K. Hoffman,[4] S. C. Wei,[5] A. P. Cogdill,[1,5] L. Zhao,[3] C. W. Hudgens,[6] D. S. Hutchinson,[7] T. Manzo,[3] M. Petaccia de Macedo,[6]‡ T. Cotechini,[8] T. Kumar,[3] W. S. Chen,[9] S. M. Reddy,[10] R. Szczepaniak Sloane,[1] J. Galloway-Pena,[11] H. Jiang,[1] P. L. Chen,[9]§ E. J. Shpall,[12] K. Rezvani,[12] A. M. Alousi,[12] R. F. Chemaly,[11] S. Shelburne,[3,11] L. M. Vence,[5] P. C. Okhuysen,[11] V. B. Jensen,[13] A. G. Swennes,[7] F. McAllister,[14] E. Marcelo Riquelme Sanchez,[14] Y. Zhang,[14] E. Le Chatelier,[15] L. Zitvogel,[16] N. Pons,[15] J. L. Austin-Breneman,[1]|| L. E. Haydu,[1] E. M. Burton,[1] J. M. Gardner,[1] E. Sirmans,[17] J. Hu,[18] A. J. Lazar,[6,9] T. Tsujikawa,[8] A. Diab,[17] H. Tawbi,[17] I. C. Glitza,[17] W. J. Hwu,[17] S. P. Patel,[17] S. E. Woodman,[17] R. N. Amaria,[17] M. A. Davies,[17] J. E. Gershenwald,[1] P. Hwu,[17] J. E. Lee,[1] J. Zhang,[3] L. M. Coussens,[8] Z. A. Cooper,[1,3]¶ P. A. Futreal,[3] C. R. Daniel,[4,2] N. J. Ajami,[7] J. F. Petrosino,[7] M. T. Tetzlaff,[6,9] P. Sharma,[5,19] J. P. Allison,[5] R. R. Jenq,[3]# J. A. Wargo[1,3]#**

Science **359**, 104–108 (2018)

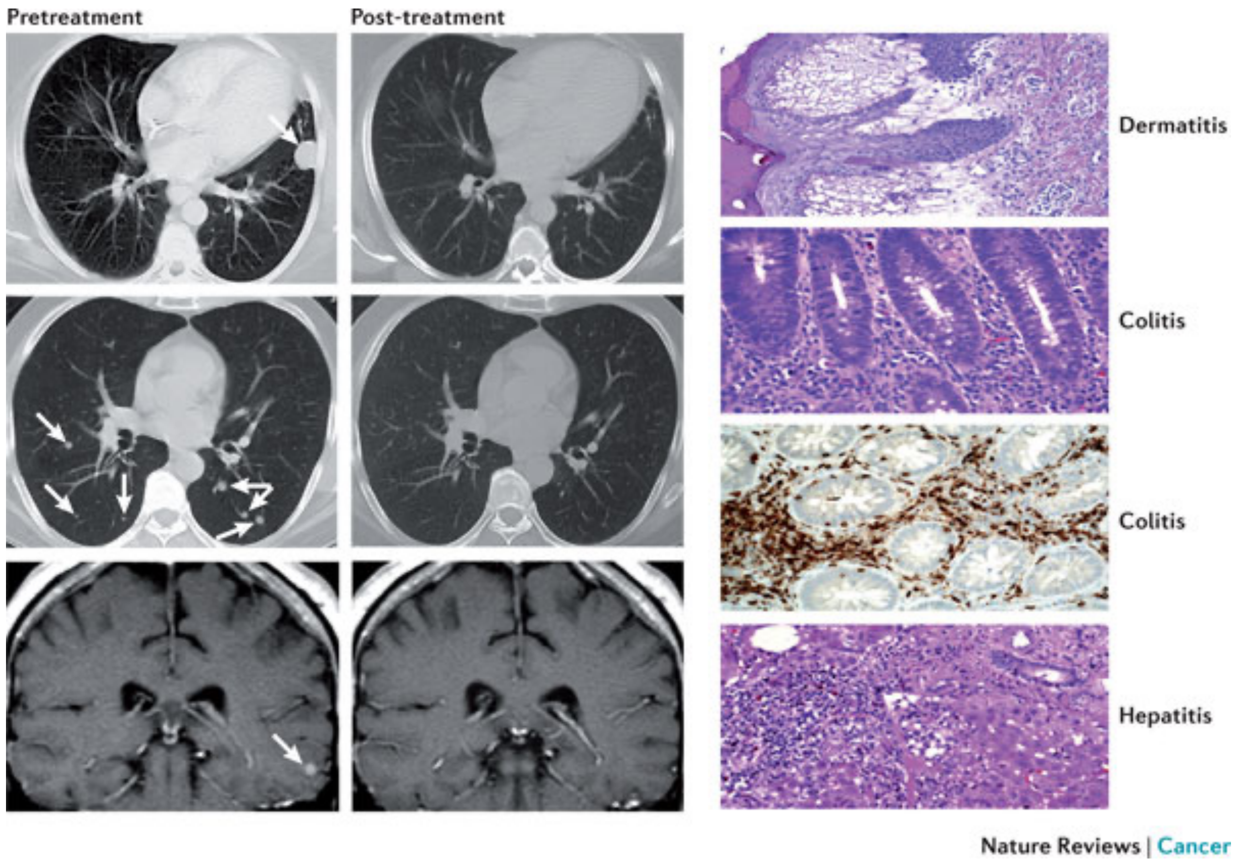
CANCER IMMUNOTHERAPY

The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients

Vyara Matson,[1]* Jessica Fessler,[1]* Riyue Bao,[2,3]* Tara Chongsuwat,[4] Yuanyuan Zha,[4] Maria-Luisa Alegre,[4] Jason J. Luke,[4] Thomas F. Gajewski[1,4]†

Gut microbial profiles modulate immunotherapy in patients

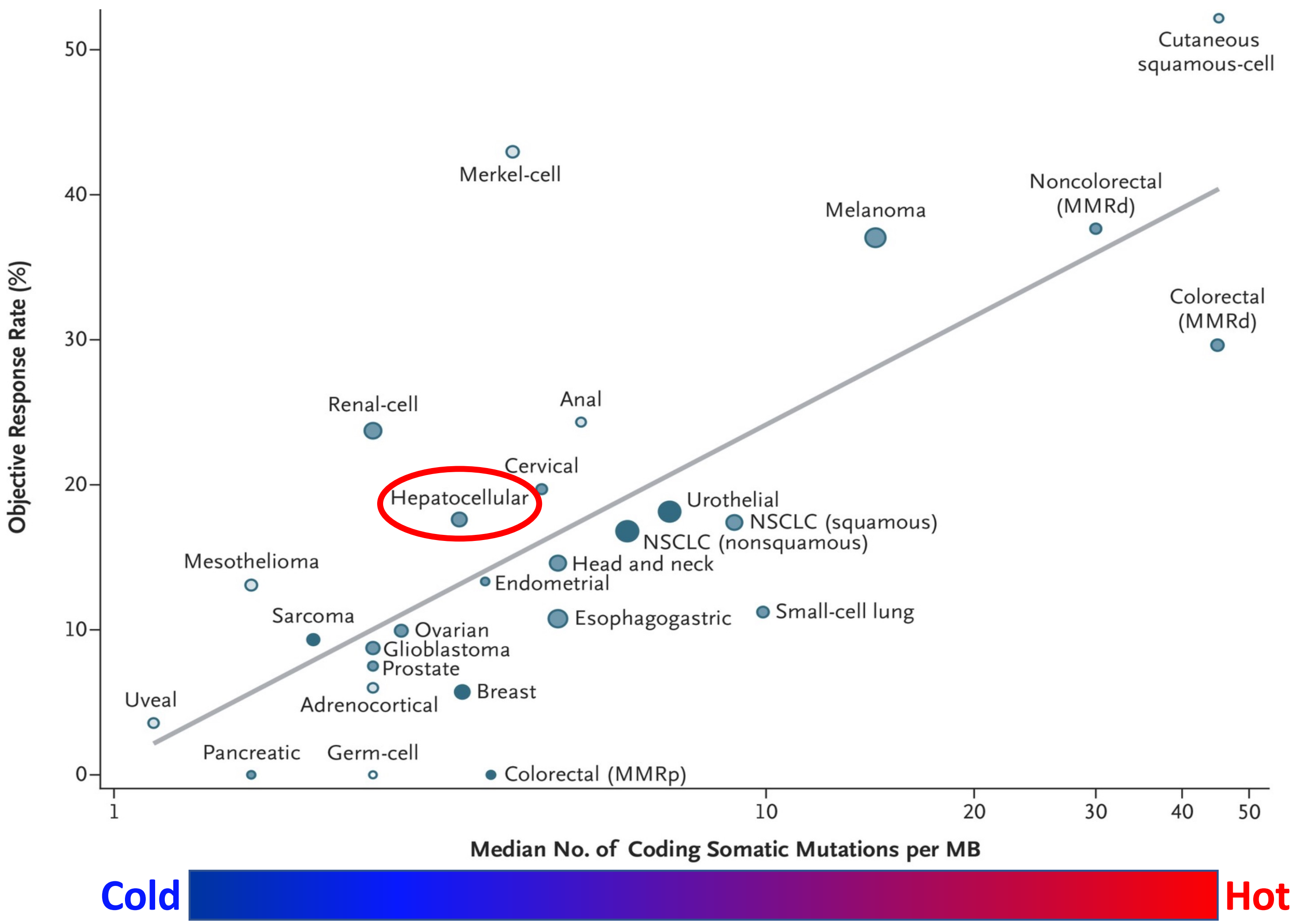
Checkpoint inhibition can be effective but can have severe autoimmune side effects



Side effects can be severe and **life-threatening**; higher in anti-CTLA4-treated patients than anti-PD1/PD-L1

Major impact even in moderately responding tumor types (e.g. HCC)

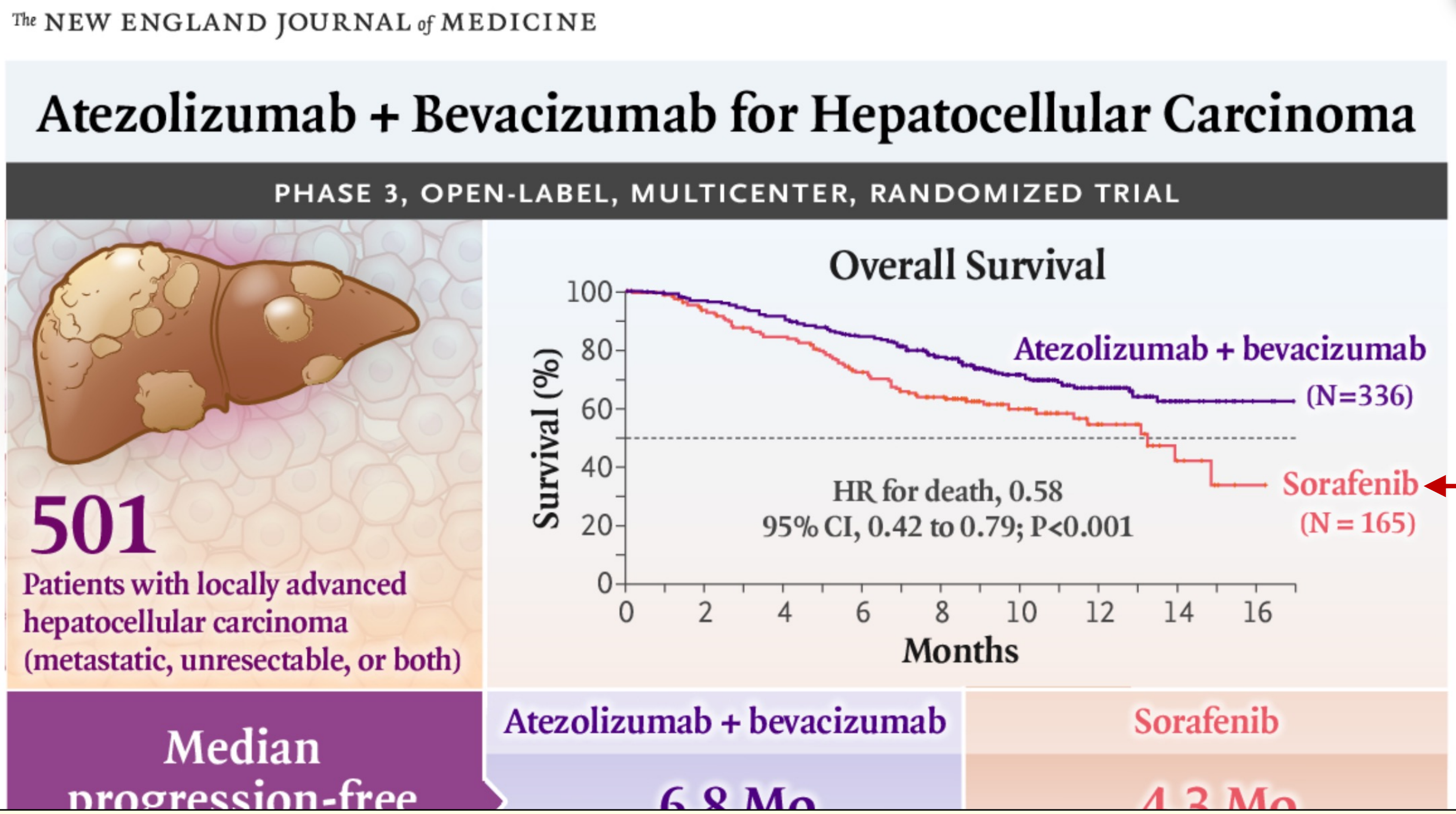
*



*anti-PD or anti-PD-L1 treatment

Yarchoan et al, *N Engl J Med*. 2017 Dec 21;377(25):2500-2501.

Combination therapies on the horizon – further improvements



Standard of care (extends survival)

Multiple combination therapies tested in clinical trials in various tumors

Additional immunotherapies on the horizon

Targetable co-inhibitory and co-stimulatory receptors (immune checkpoints)

Table 1 | **Examples of targetable co-inhibitory and co-stimulatory receptors**

Receptor and ligands	Mechanism of action	Current status	Examples of agents
Co-inhibitory receptors			
CTLA4 – CD80/86	Limits initial T cell activation and proliferation	FDA-approved	Ipilimumab, tremelimumab
PD1 – PD-L1	Inhibits the activity of effector T cells	FDA-approved	Nivolumab, pembrolizumab, durvalumab, atezolizumab
LAG3 – MHC II	Inhibits the activity of effector T cells via the KIEELE motif, which is functionally linked with T_{reg} cell-mediated immunosuppression	Phase III trial ongoing	Relatlimab
TIM-3 – Galectin-9, CEACAM1	Triggers CD8⁺ T cell apoptosis and/or exhaustion	Phase II trials ongoing	Cobolimab, sabatolimab
TIGIT – CD155, CD112	Downregulation of T cell and NK cell function	Phase II trials ongoing	Tiragolumab
BTLA – HVEM	Suppression of downstream activation of TCR signalling via SH2	Phase I trials ongoing	Icatolimab
Co-stimulatory receptors			
GITR – GITRL	Promotes activation and proliferation of effector T cells and a reduction in T_{reg} cells	Phase II trials ongoing	TRX518, BMS-986156
OX40 – OX40L	Promotes survival, but not priming, of both effector and memory T cells	Phase II trials ongoing	GSK3174998, MEDI6469, PF-04518600
4-1BB – 4-1BBL	Promotes T cell proliferation and mitochondrial function and biogenesis	Phase I trials ongoing	Utomilumab, urelumab
ICOS – ICOSL	Promotes TCR co-stimulation and T_{reg} cell stimulation	Phase I trials ongoing	Vopratelimab, KY1044, GSK3359609

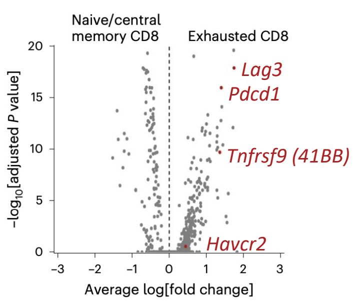
Kraehenbuehl L et al, Nat Rev Clin Onc 2022

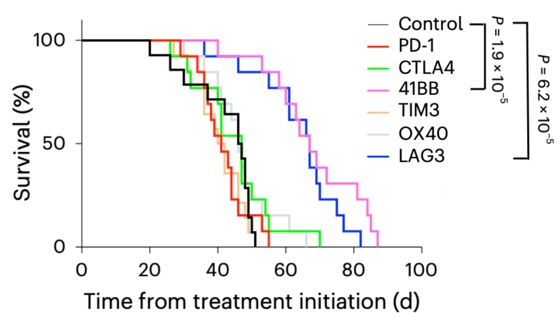
Example for efficient therapy with novel checkpoint inhibitors in PDAC mouse models

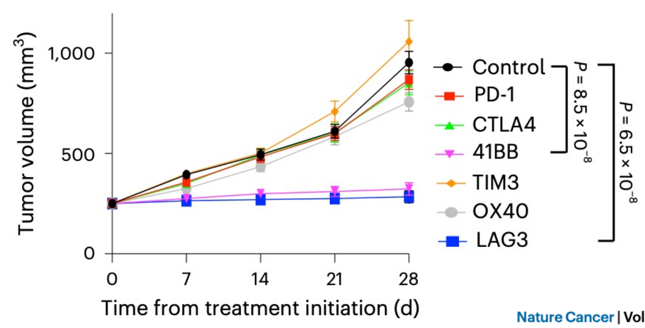
nature cancer
Article
https://doi.org/10.1038/s43018-022-00500-z

Targeting T cell checkpoints 41BB and LAG3 and myeloid cell CXCR1/CXCR2 results in antitumor immunity and durable response in pancreatic cancer

Pat Gulhati[1,2], Aislyn Schalck[3], Shan Jiang[4], Xiaoying Shang[4], Chang-Jiun Wu[5], Pingping Hou[4], Sharia Hernandez Ruiz[6], Luisa Solis Soto[6], Edwin Parra[6], Haoqiang Ying[7], Jincheng Han[4], Prasenjit Dey[8], Jun Li[5], Pingna Deng[4], Emi Sei[3], Dean Y. Maeda[9], John A. Zebala[9], Denise J. Spring[4], Michael Kim[3,10], Huamin Wang[11], Anirban Maitra[11], Dirk Moore[12], Karen Clise-Dwyer[13], Y. Alan Wang[4,14,15,16,17], Nicholas E. Navin[3] & Ronald A. DePinho[4]





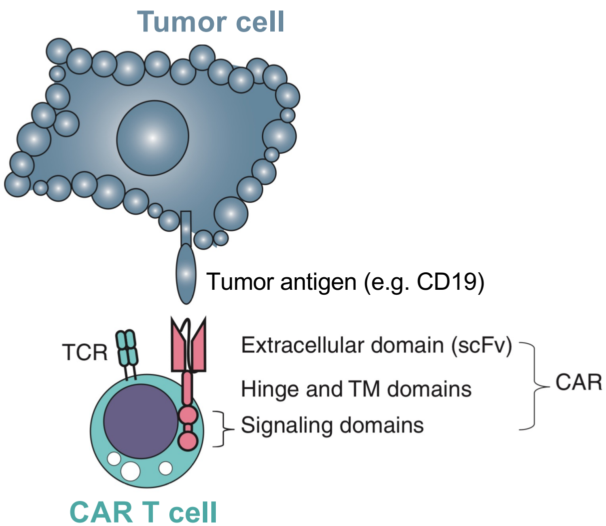


Nature Cancer | Volume 4 | January 2023 | 62–80

Additional immunotherapies on the horizon

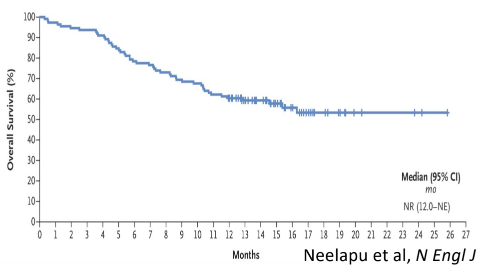
CAR T cells

(Chimeric Antigen Receptor)



Slaney et al, *Cancer Discovery 8(8)*, 924-34 (2018)

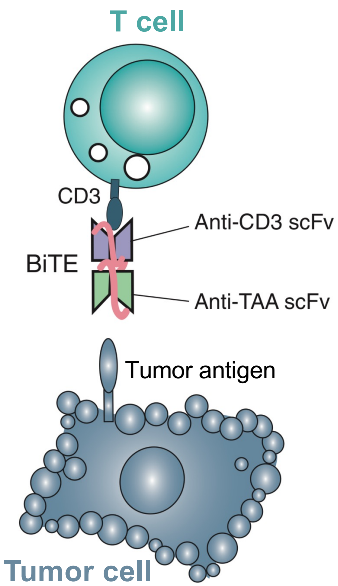
Already approved for CD19 in B cell lymphomas with 80% response rates



Neelapu et al, *N Engl J Med 2017*; 377:2531-2544

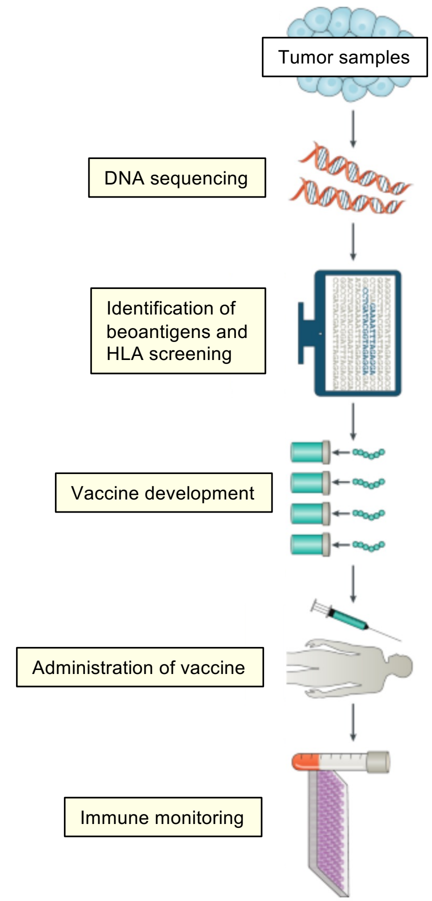
BiTEs

(Bispecific T cell Engager)



Slaney et al, *Cancer Discovery 8(8)*, 924-34 (2018)

Personalized cancer vaccines



Waldman et al, *Nature Reviews Immunology* 20, 651–668(2020)

CAR T cell therapies can be extremely promising

Review/perspective on CAR T cells

nature biotechnology

Perspective

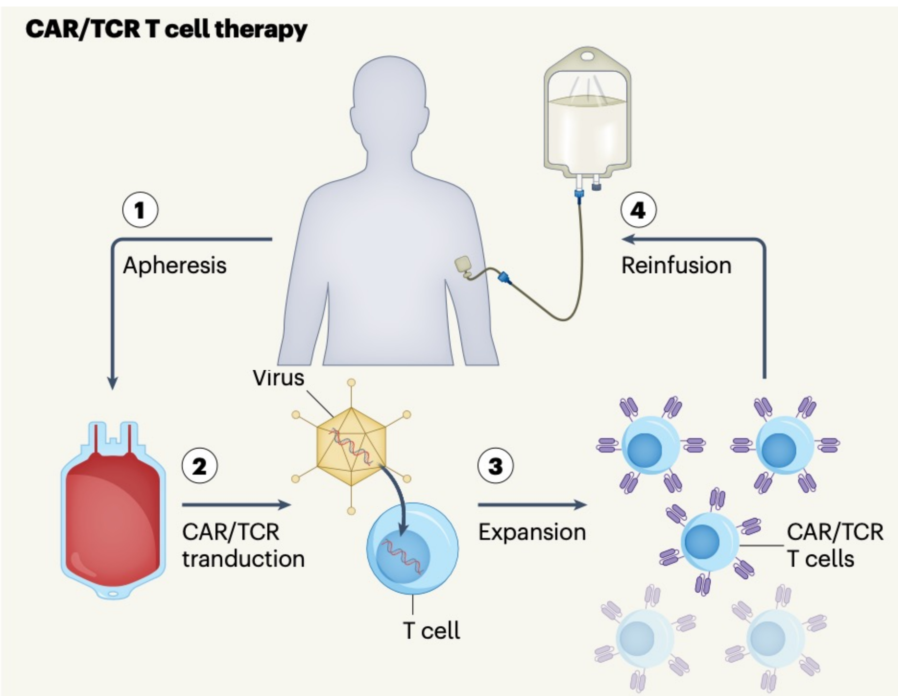
https://doi.org/10.1038/s41587-024-02446-2

Beyond the blood: expanding CAR T cell therapy to solid tumors

Received: 1 June 2024

Accepted: 23 September 2024

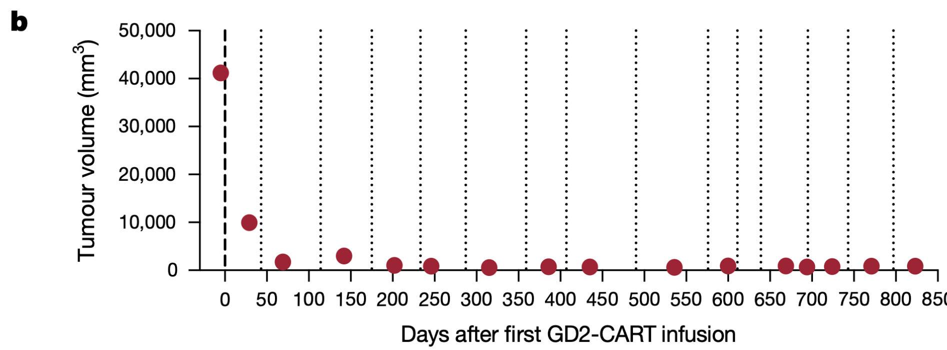
Ugur Uslu[1,2,3] & Carl H. June[1,2,3]



Example of a study with a complete remission for glioma

Article

Intravenous and intracranial GD2-CAR T cells for H3K27M$^+$ diffuse midline gliomas



Nature. 2024 Nov 13. doi: 10.1038/s41586-024-08171-9.

Personalized neoantigen vaccine in PDAC appears promising

Article

Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer

https://doi.org/10.1038/s41586-023-06063-y

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Check for updates

Luis A. Rojas[1,2,18], Zachary Sethna[1,2,18], Kevin C. Soares[2,3], Cristina Olcese[2], Nan Pang[2], Erin Patterson[2], Jayon Lihm[4], Nicholas Ceglia[4], Pablo Guasp[1,2], Alexander Chu[4], Rebecca Yu[1,2], Adrienne Kaya Chandra[1,2], Theresa Waters[1,2], Jennifer Ruan[1,2], Masataka Amisaki[1,2], Abderezak Zebboudj[1,2], Zagaa Odgerel[1,2], George Payne[1,2], Evelyna Derhovanessian[5], Felicitas Müller[5], Ina Rhee[6], Mahesh Yadav[6], Anton Dobrin[7,8], Michel Sadelain[7,8], Marta Łuksza[9], Noah Cohen[10], Laura Tang[11], Olca Basturk[11], Mithat Gönen[12], Seth Katz[13], Richard Kinh Do[13], Andrew S. Epstein[14], Parisa Momtaz[14], Wungki Park[3,14], Ryan Sugarman[14], Anna M. Varghese[14], Elizabeth Won[14], Avni Desai[14], Alice C. Wei[2,3], Michael I. D'Angelica[2,3], T. Peter Kingham[2,3], Ira Mellman[6], Taha Merghoub[15], Jedd D. Wolchok[15], Ugur Sahin[5], Özlem Türeci[5,16], Benjamin D. Greenbaum[4,17] ✉, William R. Jarnagin[2,3], Jeffrey Drebin[2,3], Eileen M. O'Reilly[3,14] & Vinod P. Balachandran[1,2,3] ✉

144 | Nature | Vol 618 | 1 June 2023

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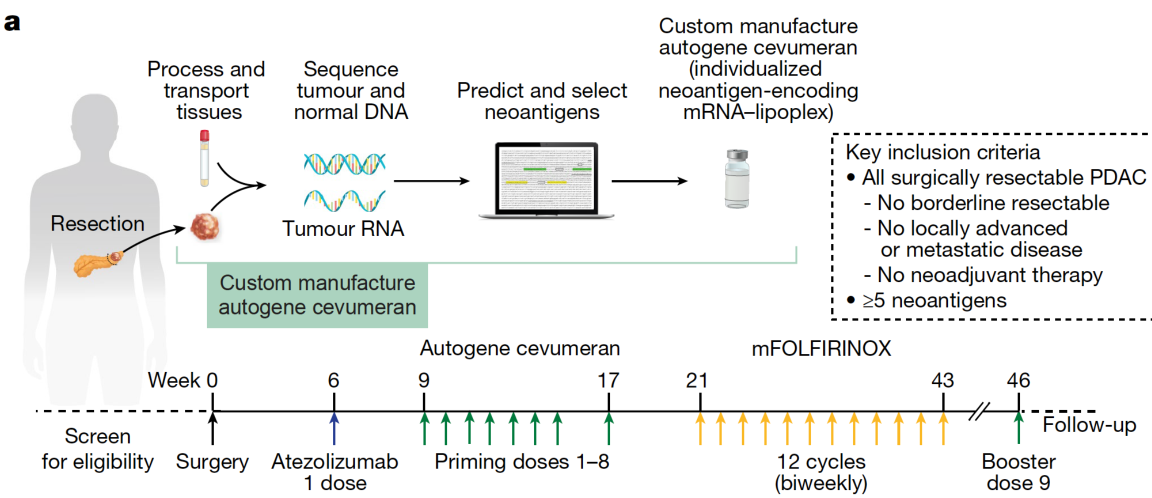

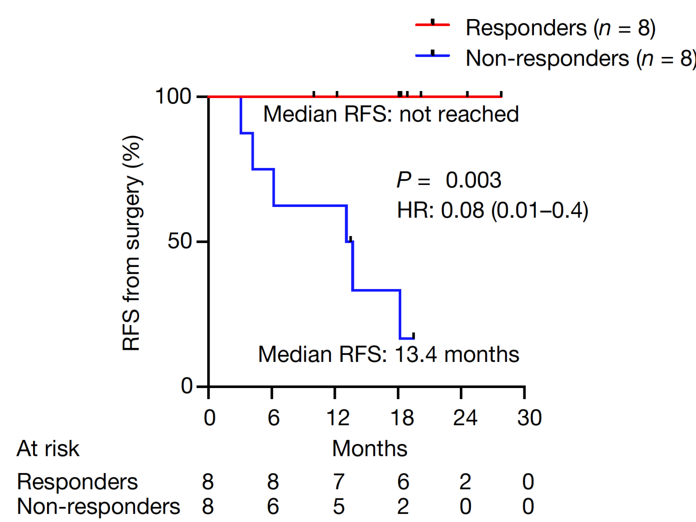

Take home messages on tumor immunity

- There is an active tumor surveillance/immunoediting process that restricts tumor development
- Immune surveillance often fails when tumors grow, e.g. via upregulation of various pathways suppressing immunity
- **PD1/PD-L1** and **CTLA4** are major immune checkpoints that can suppress anti-tumor immunity
- **Immunotherapy** is one of the **most exciting and successful new cancer therapies** from the last decade
- Response rate high for some tumors with high TMB (e.g. melanoma) but **low for many others** (e.g. PDAC, low TMB)
- Further improvements expected via combination therapies; **new checkpoint inhibitors** beyond CTLA4 and PD1/PD-L1
- **Additional immune-based therapies** on the horizon
- Side effects of immunotherapy can be severe/**life-threatening**.

Thank you!