Tumor Microenvironment and Tumor Immunology

Robert Schwabe, MD

11/16/2020

CANCER CELL BIOLOGY COURSE COLUMBIA UNIVERSITY MEDICAL CENTER, FALL 2020

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 – incl. examplesfrom the Schwabe lab on CAF/ECM in the liver

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

Part II: Tumor immunology

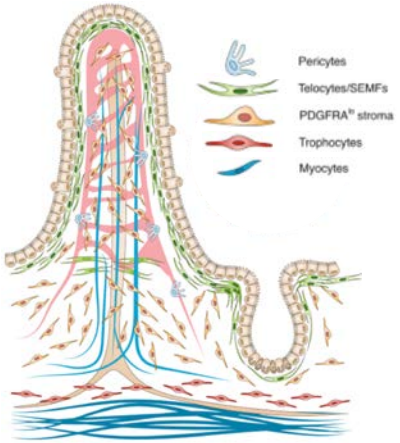
1. Immunosurveillance and immunoediting
2. Key cell types contributing to anti-tumor immunity
3. Immune checkpoints, exhaustion and mechanisms of immunosuppression.
4. "Hot" versus "cold" tumors
5. Anti-tumor therapy

Literature: *The Biology of Cancer (Weinberg) Chapter 15; as well as select papers mentioned in various slides*

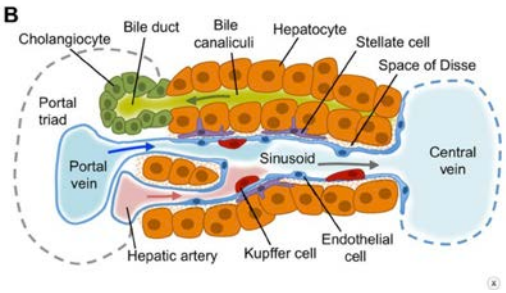
Part 1: The Tumor Microenvironment

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

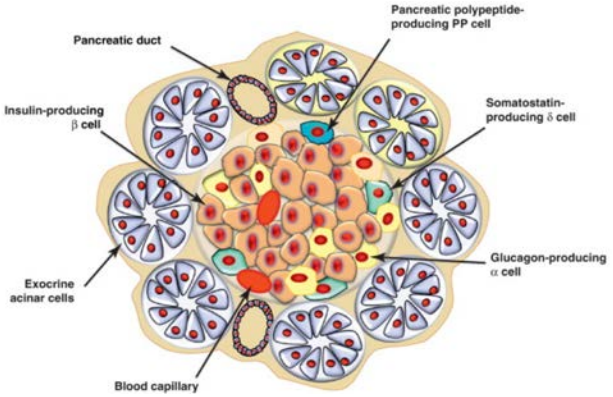
Intestine



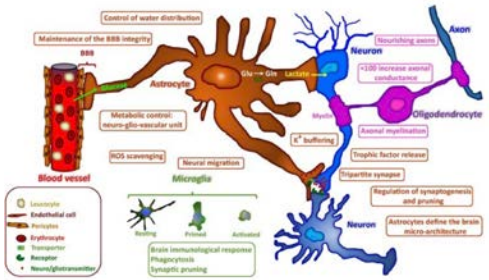
Liver



Pancreas



Brain

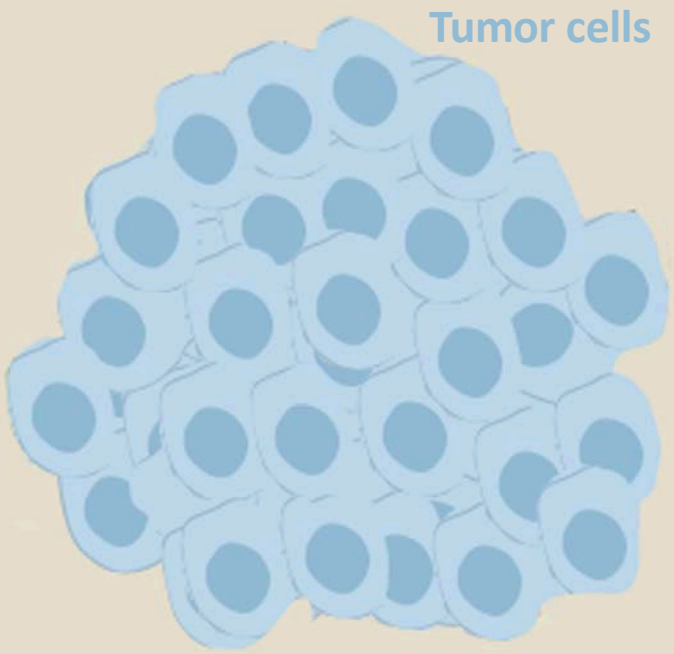


Multiple cell types required to maintain epithelial cell (the source of most tumors) function and communication

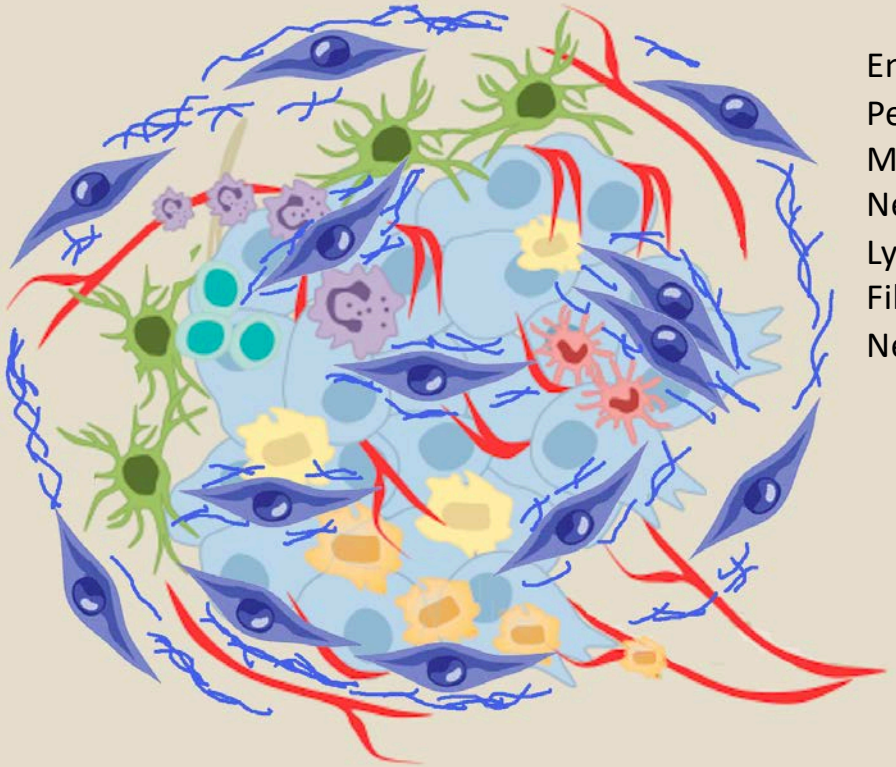
Vast differences between organs in organization and cell-cell communication, but conserved patterns

What does a tumor look like?

Tumor?



Tumor



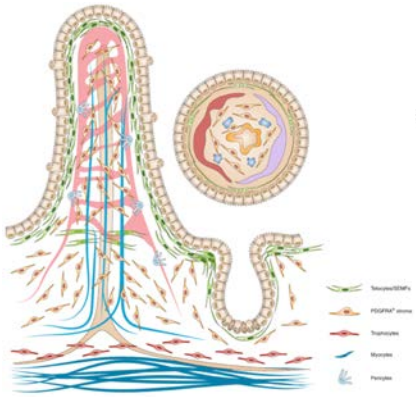
Tumor cells

+

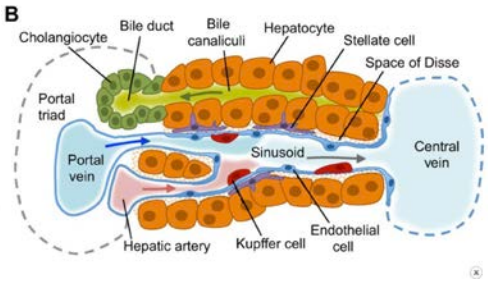
Endothelial cells
Pericytes
Macrophages
Neutrophils
Lymphocytes
Fibroblasts + ECM
Nerves

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

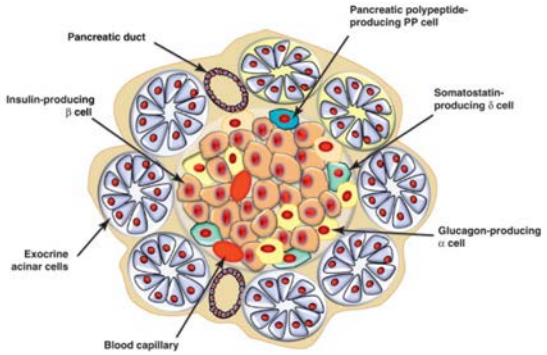
Intestine



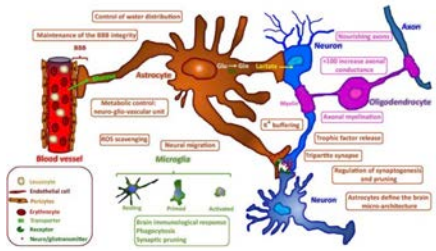
Liver



Pancreas



Brain



=

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).

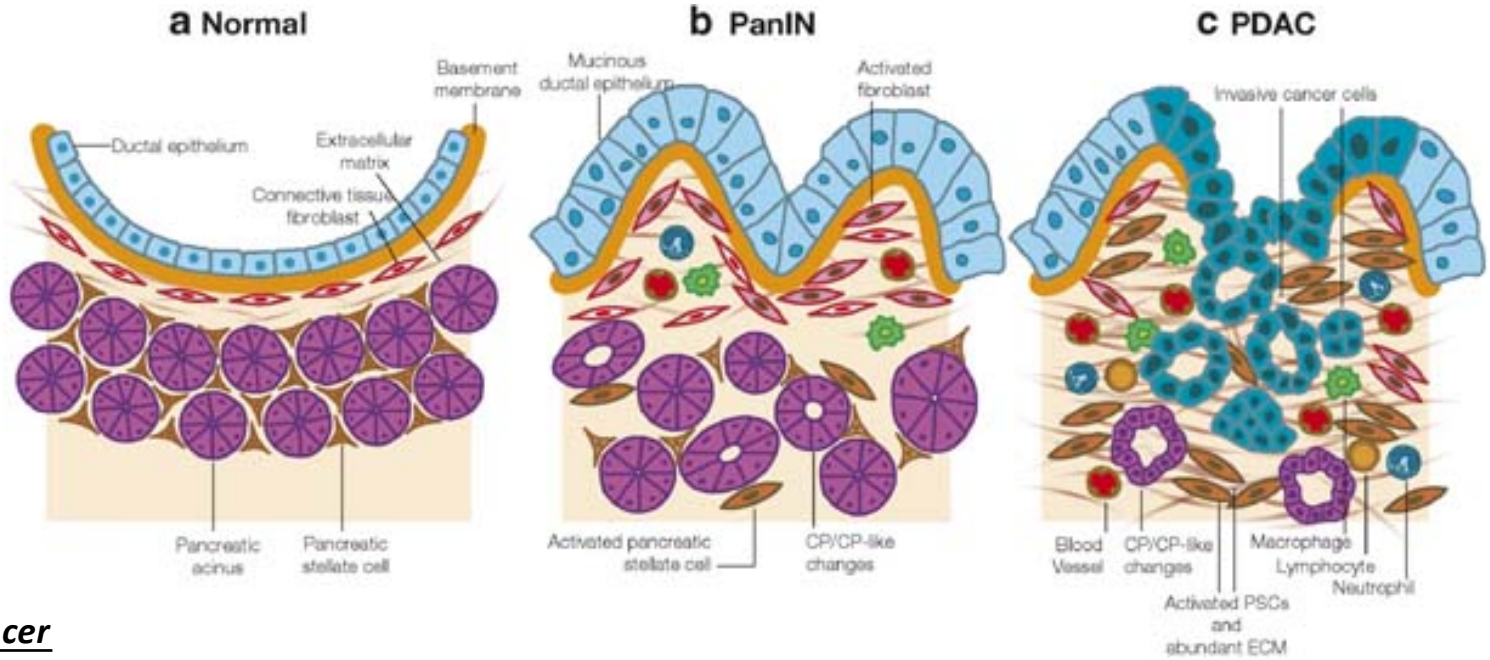
2. **The TME co-evolves with the tumor.** The tumor requires other cells to grow – however, not all cells in the TME are ”pro-tumor”. The immune system may eliminate tumor cells; cancer-associated fibroblasts (CAF) may encapsulate tumors to inhibit their grow. Over time, tumors, co-opt the TME and turn restriction into promotion.

3. Advanced/dedifferentiated/metastatic tumors **may lose this organ-specific TME** and/or requirement for it (allowing to metastize/grow in different environments

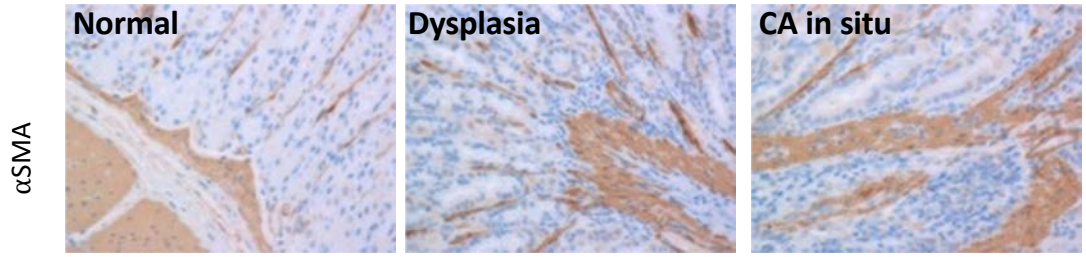
Stromal changes can already occur in premalignant stages

Pancreatic cancer

Intraepithelial neoplasis



Gastric cancer

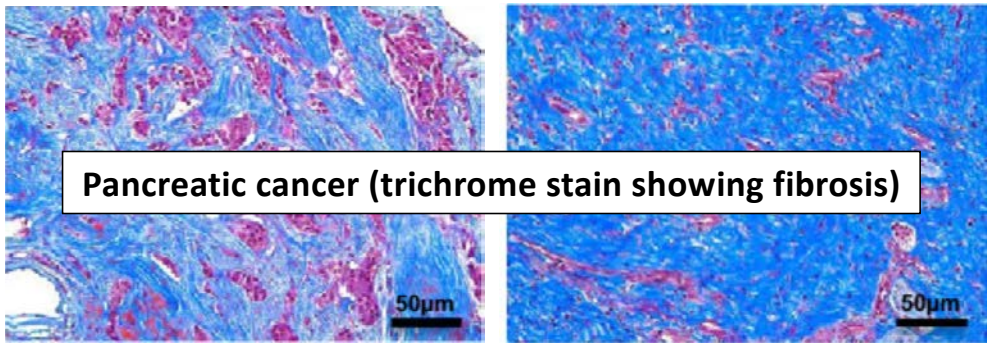


Chu et al., Journal of Cellular Biochemistry 101:887–907 (2007)

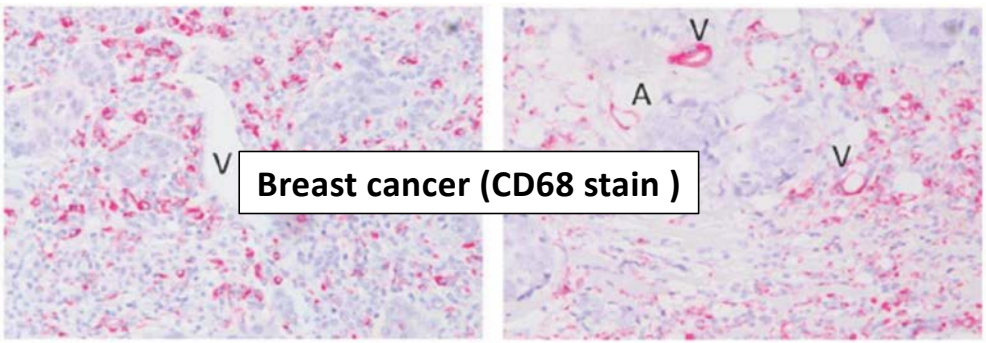
The stroma can constitute >50% of the tumor mass in some tumor types

	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)

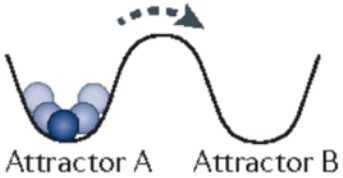


Breast cancer (CD68 stain)

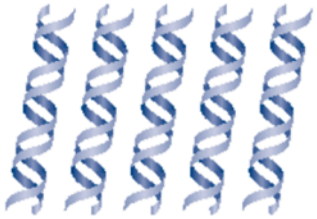
Differences between the normal and tumor microenvironemnt

Normal tissue: Structured organization and robust network/interactions

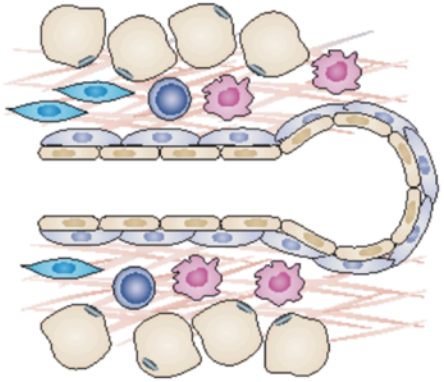
Noise: low



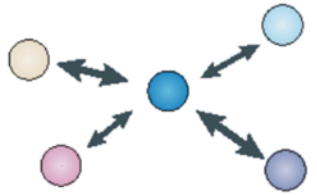
Genotypes: homogeneous



Microenvironment: structured

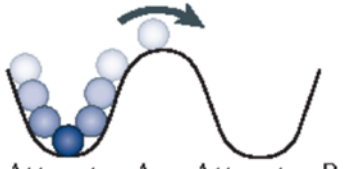


Network architecture: robust

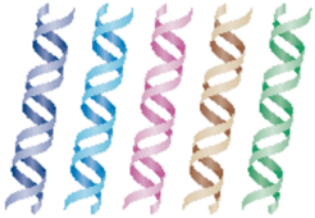


Tumor tissue: High heterogeneity, chaotic organization/high "entropy", reorganized interactions/network

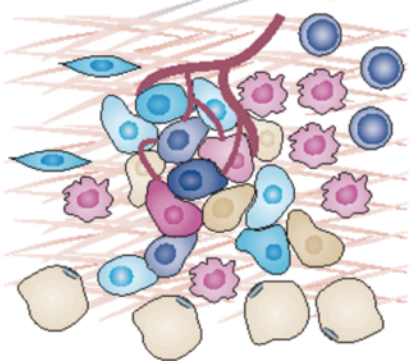
Noise: high



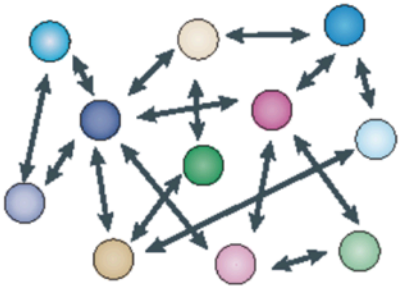
Genotypes: heterogeneous



Microenvironment: disorganized



Network architecture: noisy



Most 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)

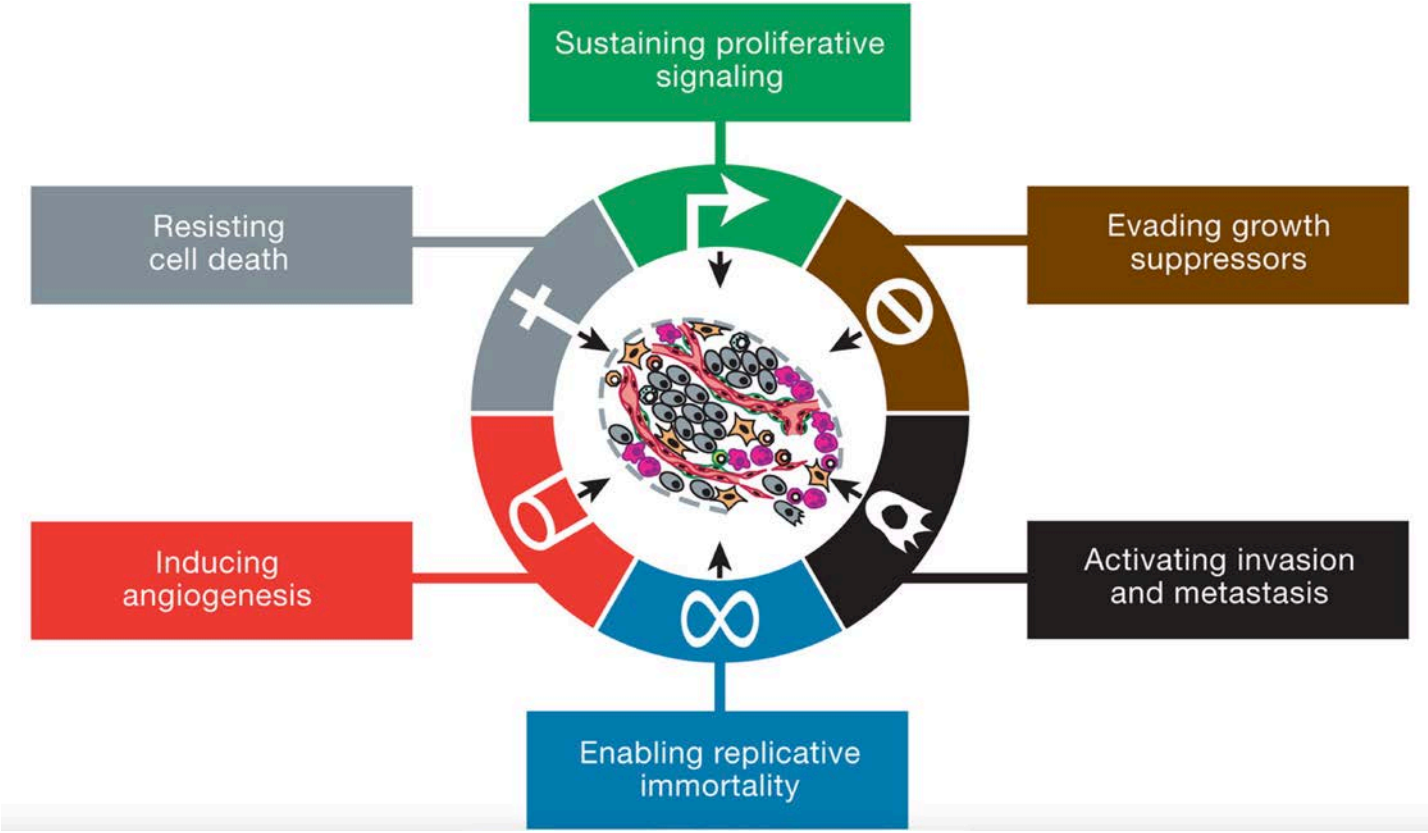
3D models/organoids address some concerns, but also lack stromal cells

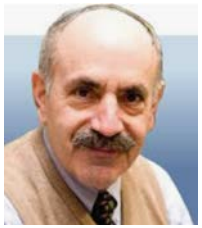
Organotypic 3D models that incorporate multiple cell types are most similar to *in vivo* tumors

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

2. Functional impact of the TME

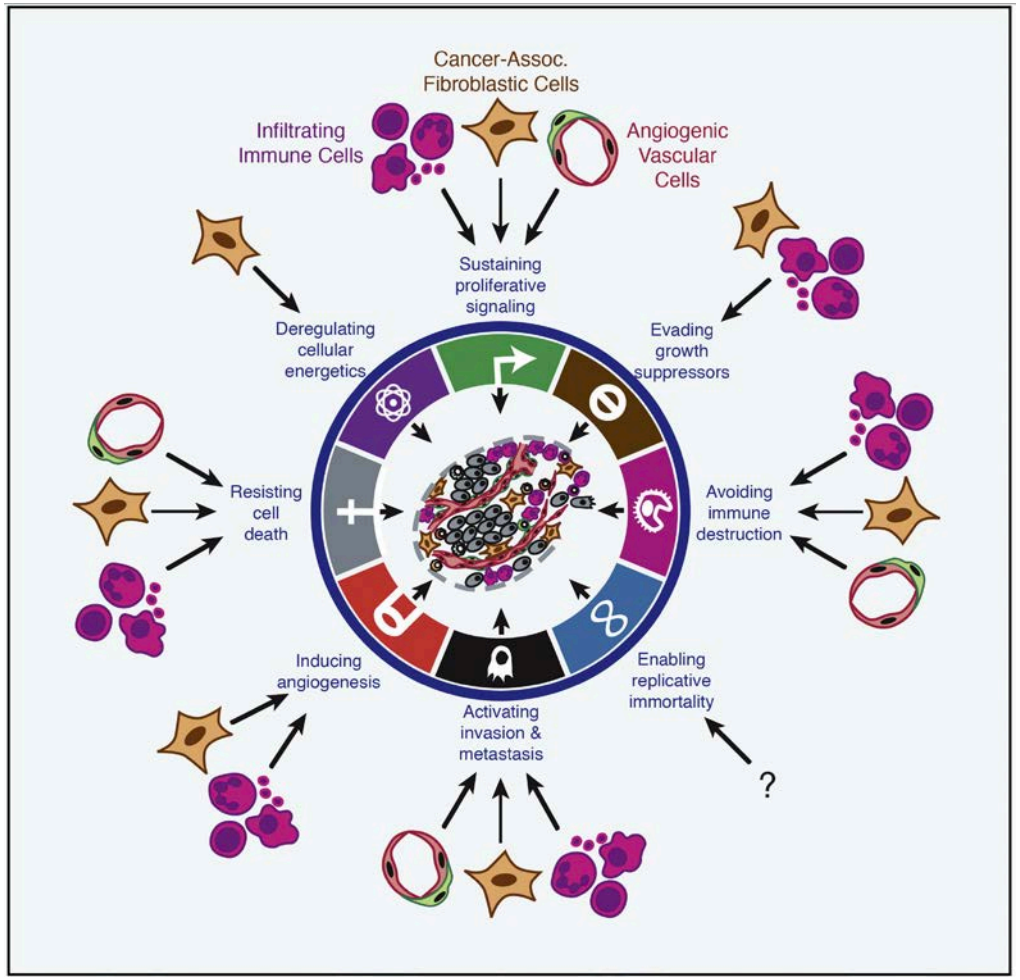
Hallmarks of cancer





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?



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 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 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

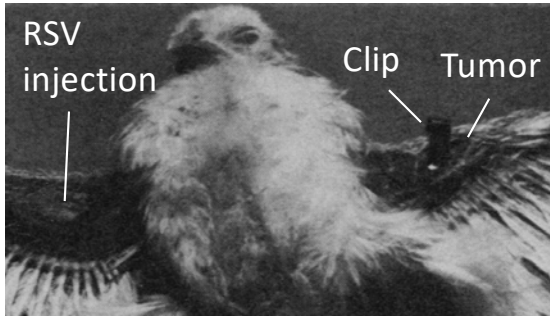
Tumors: “Wounds that do not heal”

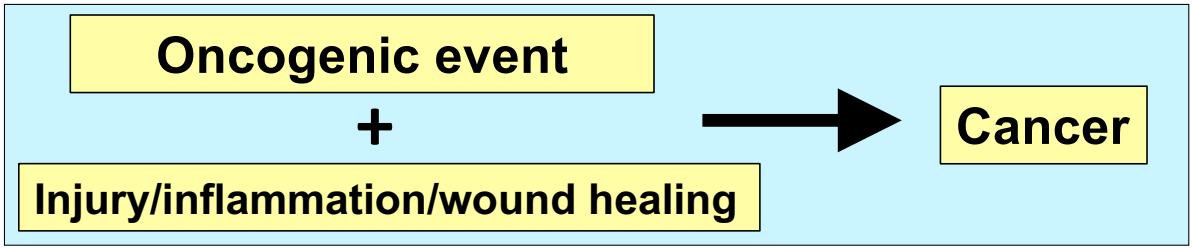
“Tumors: Wounds that do not heal” (Dvorak, HF, *N Engl J Med* 1986)

- 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)





Normal fibroblasts can be tumor suppressive

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

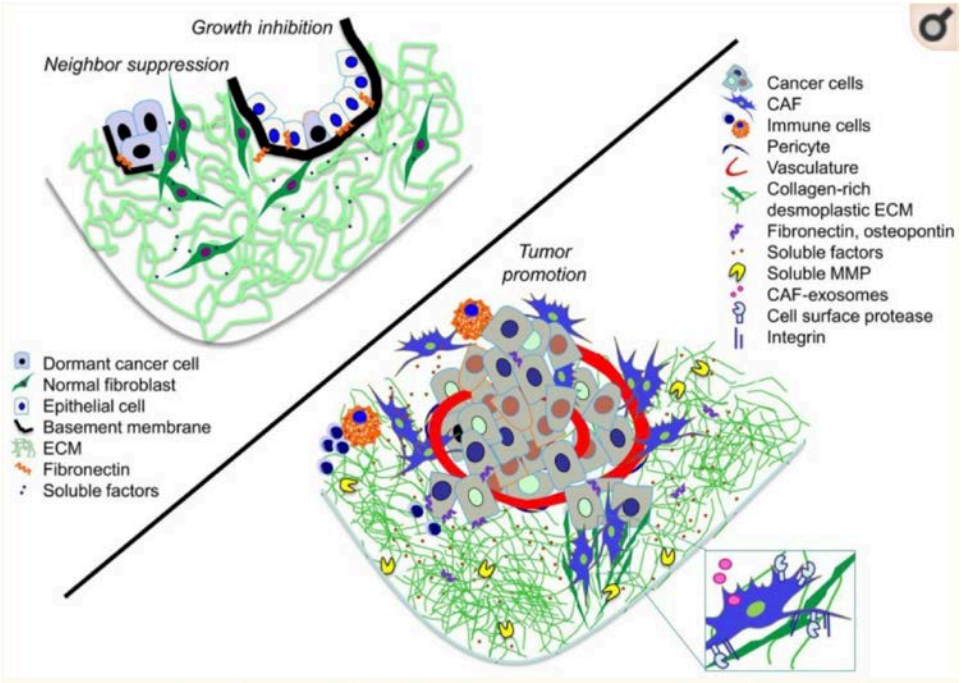
GROWTH INHIBITION OF POLYOMA-TRANSFORMED CELLS BY CONTACT WITH STATIC NORMAL FIBROBLASTS

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]



Multiple mechanisms:

- Contact required

- Soluble factor seem to amplify this

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

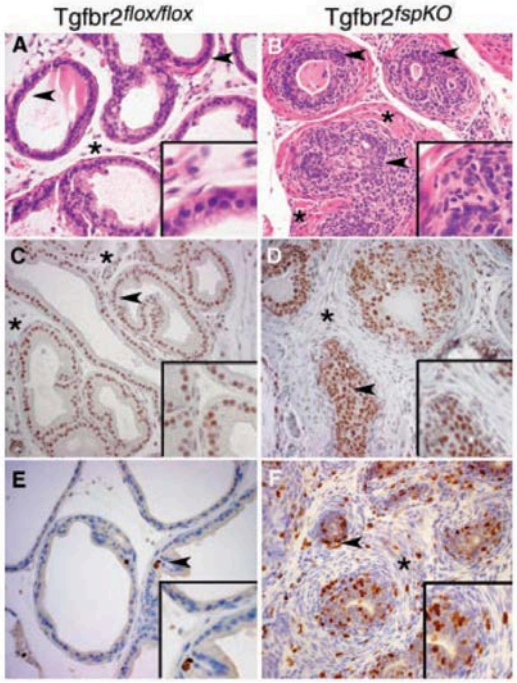


Fig. 1. Loss of TβRII expression in fibroblasts results in prostate intraepithelial neoplasia (PIN).

Development of squamous cell carcinoma

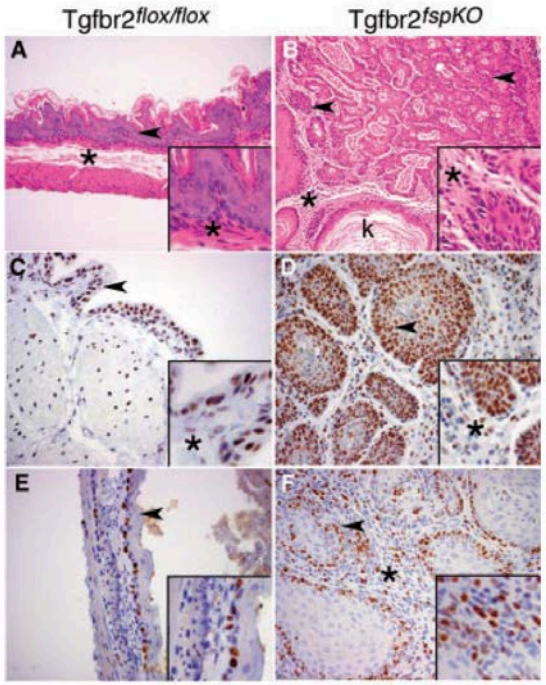


Fig. 2. Squamous cell carcinoma develops in the forestomachs of Tgfbr2^{fspKO} mice.

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

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

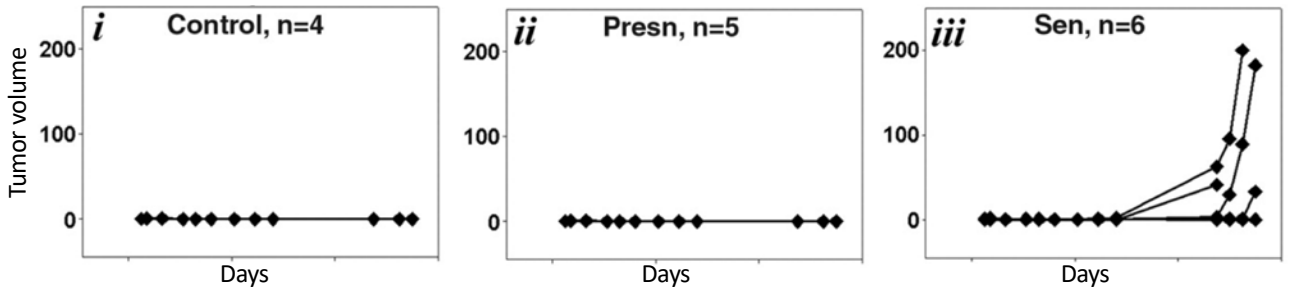
Senescent fibroblasts promote epithelial cell growth and tumorigenesis: A link between cancer and aging

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

SCp2* alone

SCp2 + presenescent fibro

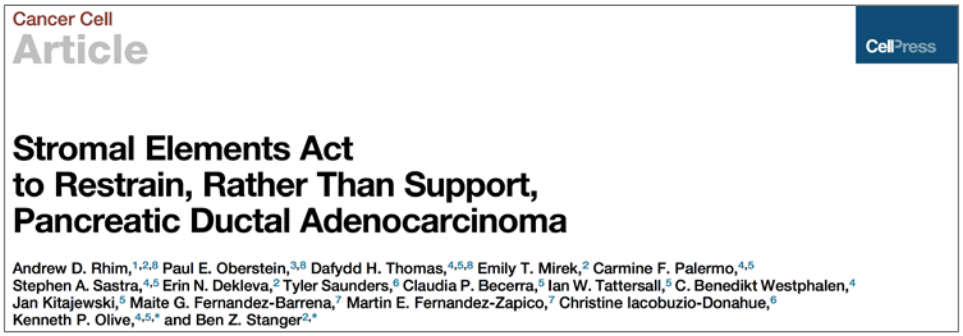
SCp2 + senescent fibro



*immortal but non-tumor forming mammary epithelial cells

Activated fibroblasts can be tumor-restrictaining

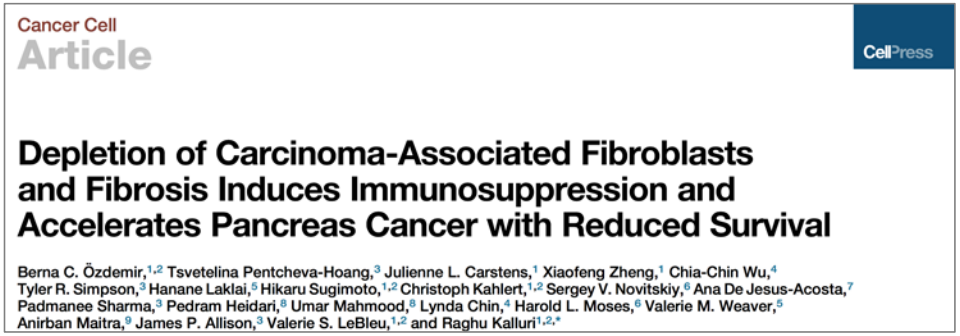
In most tumors, CAF seem to be tumor promoting. But a different picture in some studies on pancreatic cancer”


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,[6] 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,*]

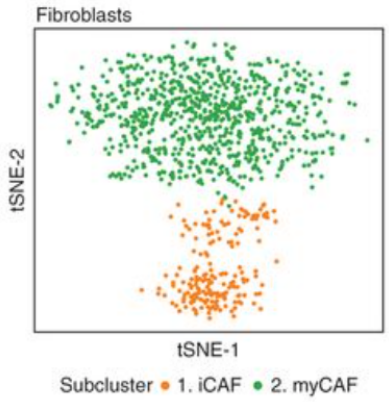
Possibility of tumor-promoting and tumor-restricting CAF subpopulations in PDAC and other tumors.

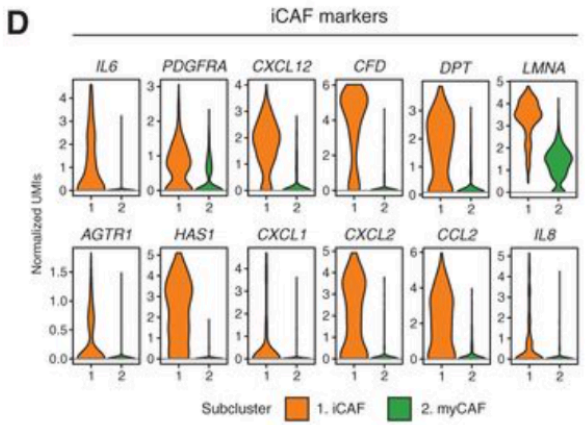
CAF diversity – inflammatory CAF and myofibroblastic CAF

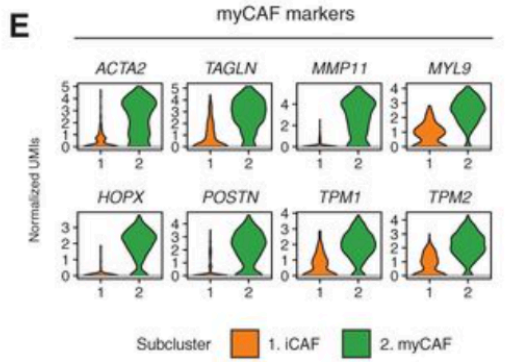
Cross-Species Single-Cell Analysis of Pancreatic Ductal Adenocarcinoma Reveals Antigen-Presenting Cancer-Associated Fibroblasts

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]

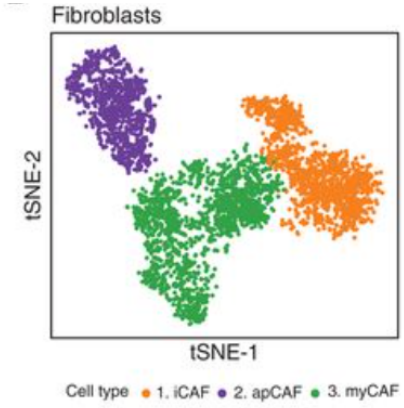
Mice

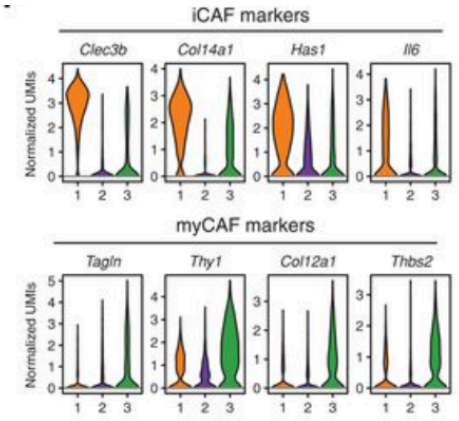


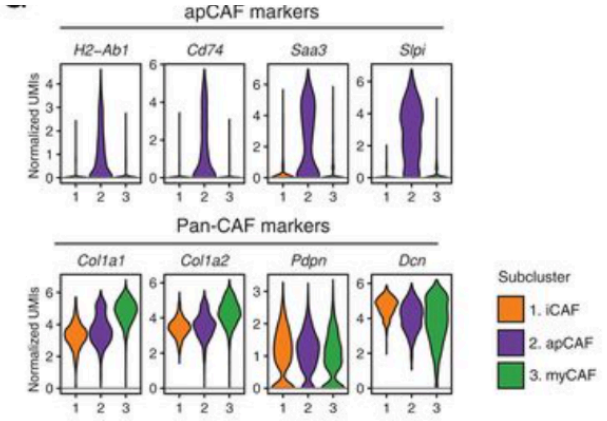




Patients



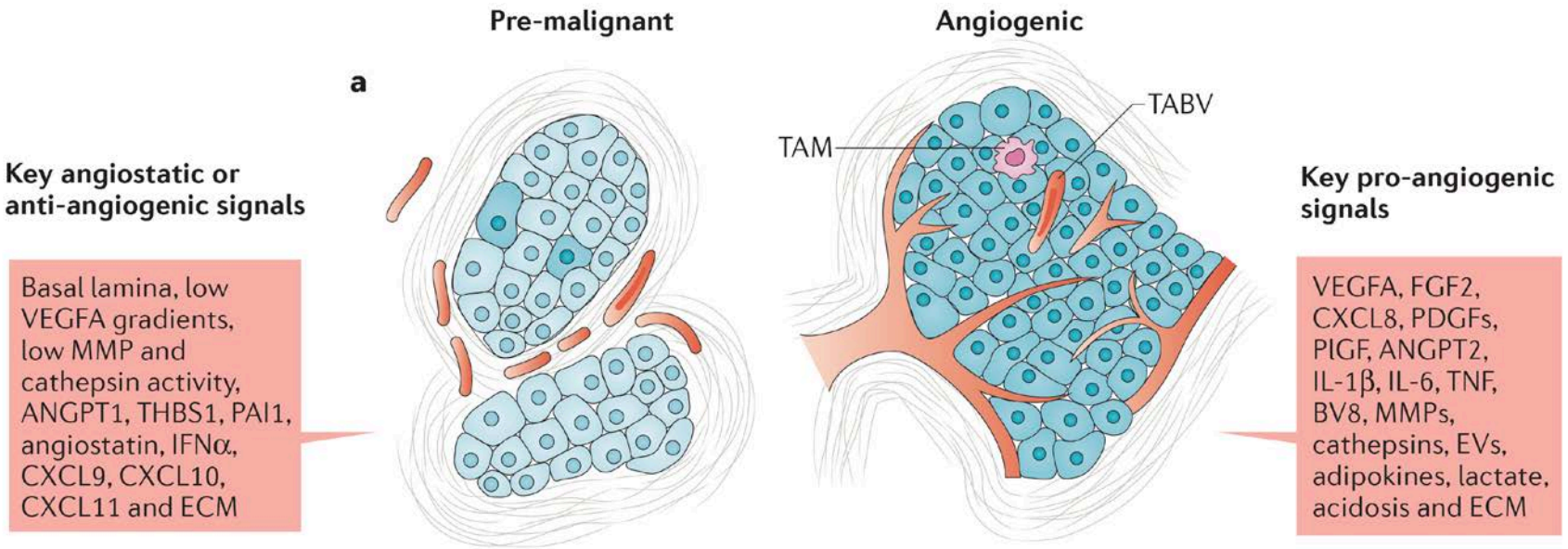




How is tumor angiogenesis induced and maintained in the TME

- 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.

Crosstalk in the TME maintains angiogenesis

Role of myeloid cells

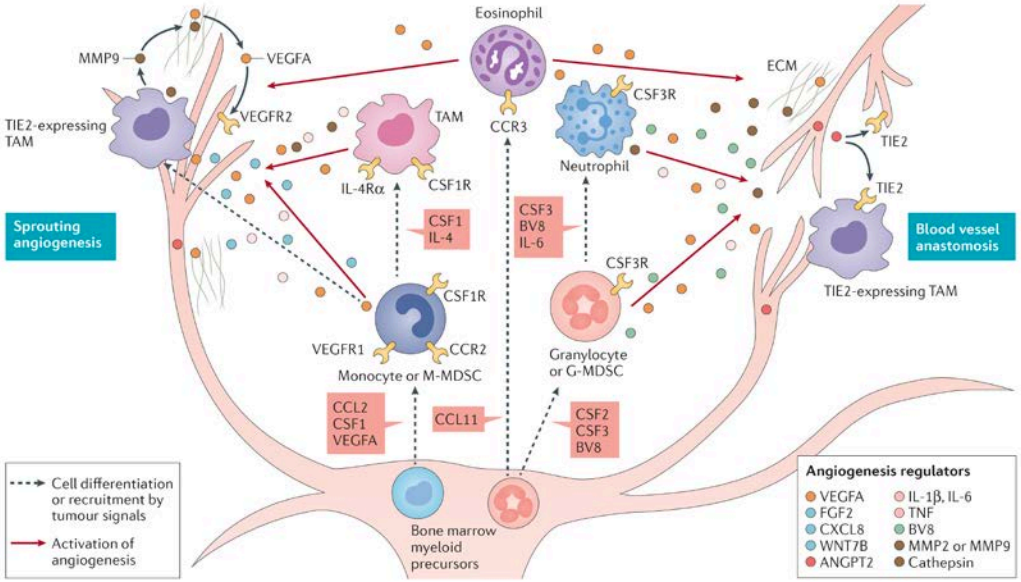


Figure 2 | **Myeloid cell regulation of tumour angiogenesis.**

Role of CAF

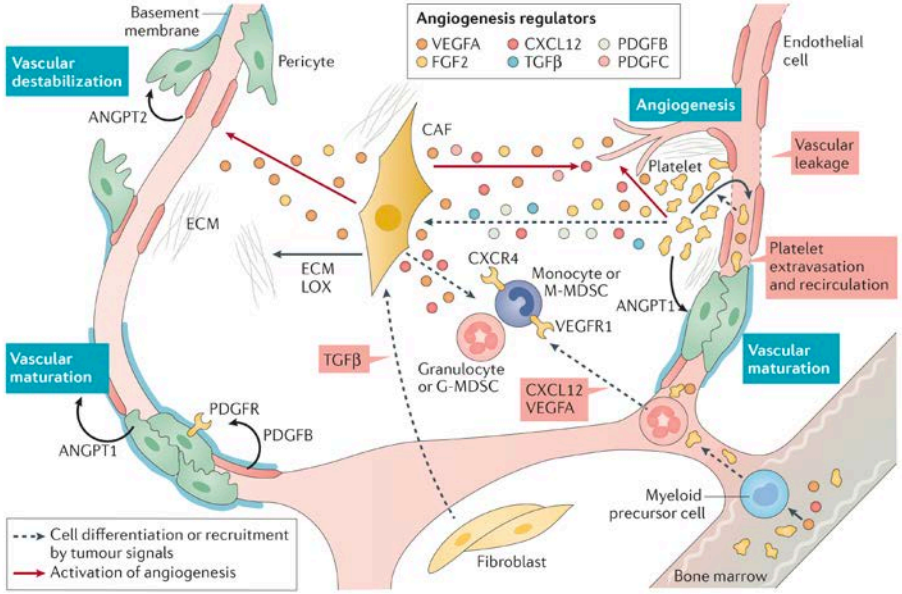
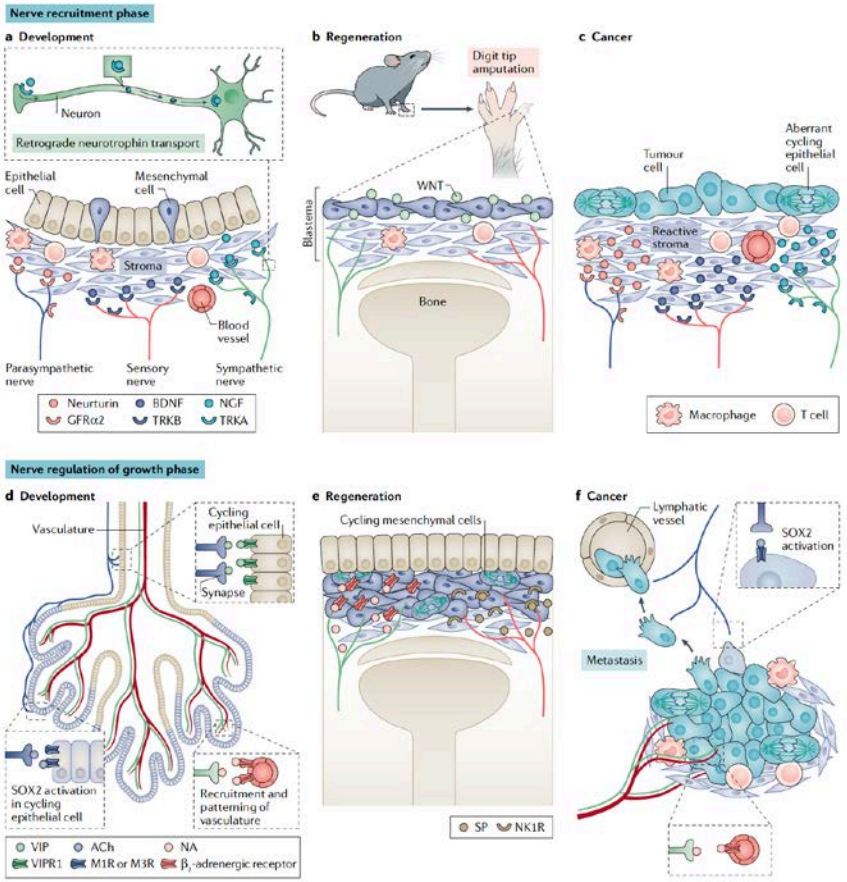


Figure 4 | **Chronic wound-healing response promotes tumour angiogenesis.**

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

Role of nerves in tumor growth

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



Nerves influence the TME

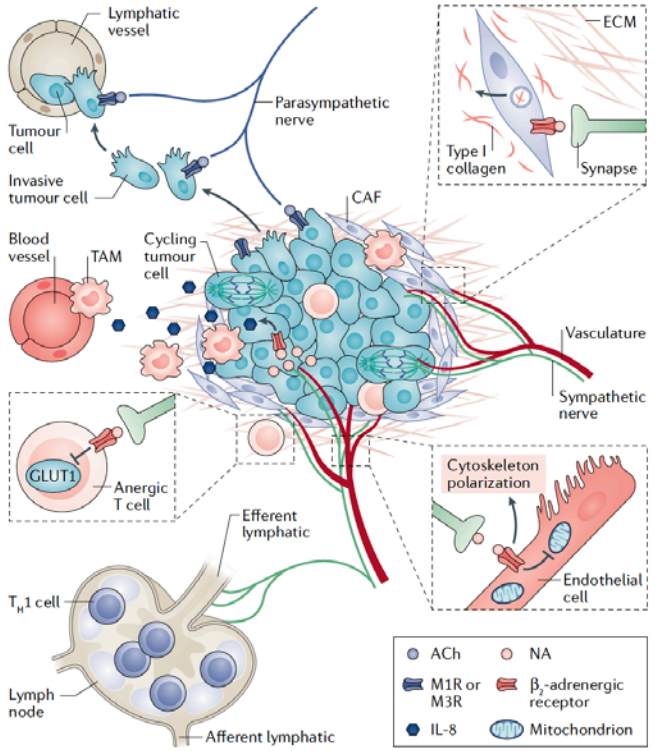


Fig. 3 | **Neural regulation of the tumour microenvironment.** Nerves interact with

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

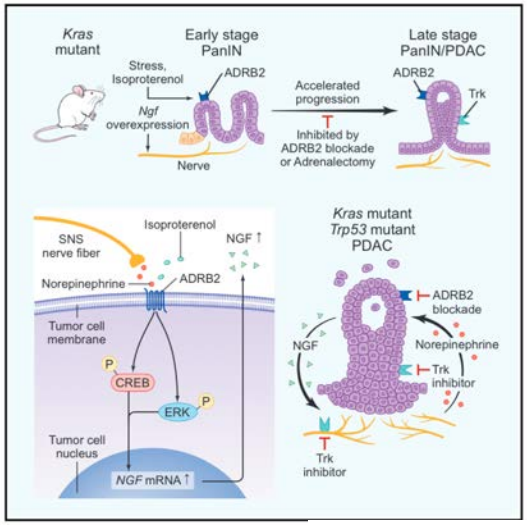
Cancer Cell
Article

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

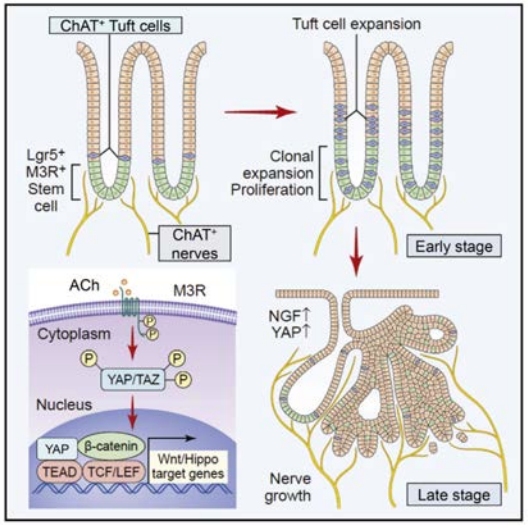
Cancer Cell
Article

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

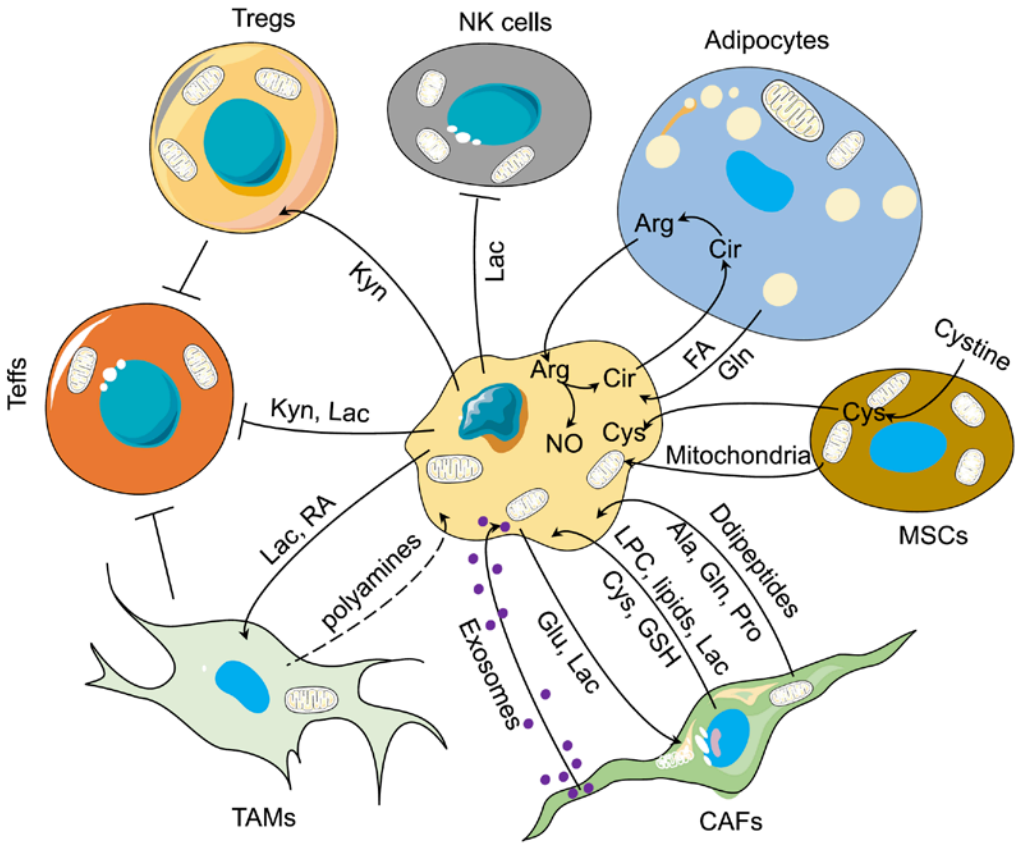
- NGF expression is induced in gastric cancer by ACh from nerves and tuft cells
- NGF promotes innervation and proliferation in gastric epithelium
- Blockade of NGF or ablation of cholinergic tuft cells inhibits tumor development
- Cholinergic signaling activates YAP signaling that is essential for Wnt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



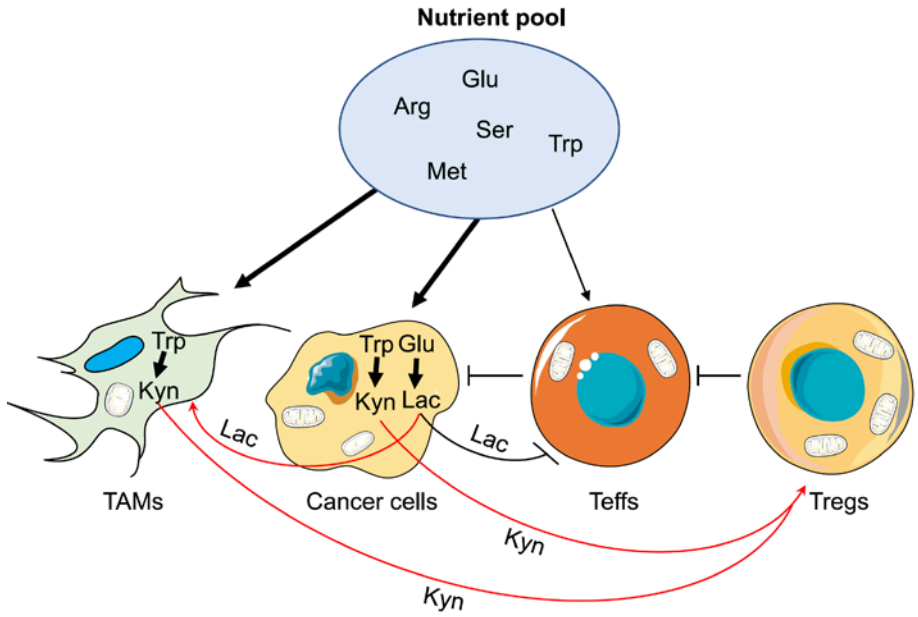
Cancer Cell 31, 21–34, January 9, 2017

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

- Tumors 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/metaobolites 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 as well with possibly opposing functions (e.g. iCAF – myCAF in some settings)

Part 2: Tumor Immunology

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 was no apparent difference in tumor development. Tumor surveillance by the immune system was considered irrelevant.
- 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
- Mice deficient in IFNγ 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).
- Allogeneic bone marrow transplantation showed that a mismatch in the setting of cancer conferred anti-tumor immunity.

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.

Carcinogen-induced cancer

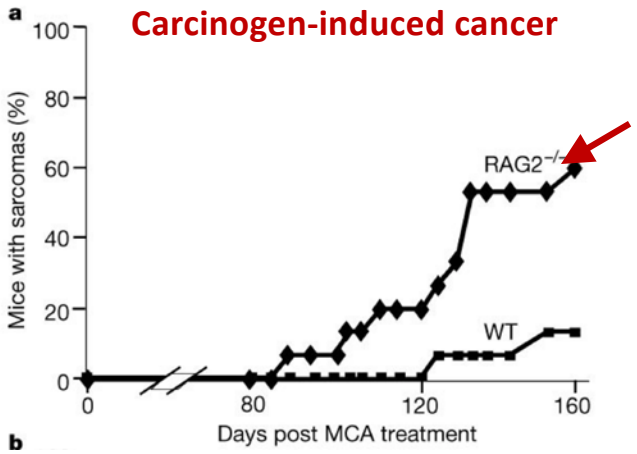


Figure 2: Increased development of spontaneous neoplastic disease in immunodeficient mice.

Spontaneous cancer

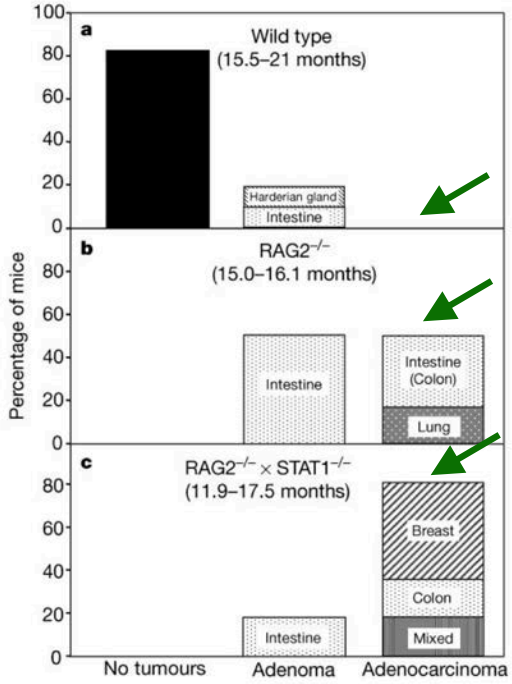
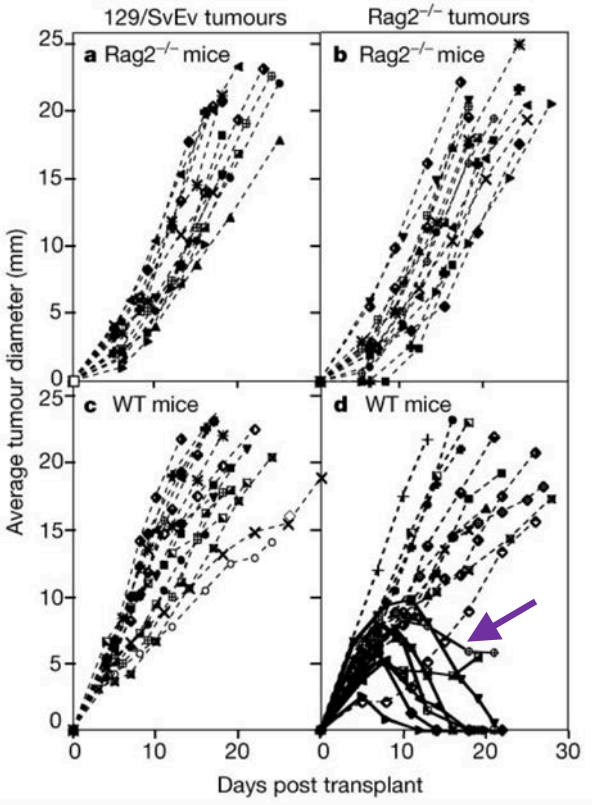


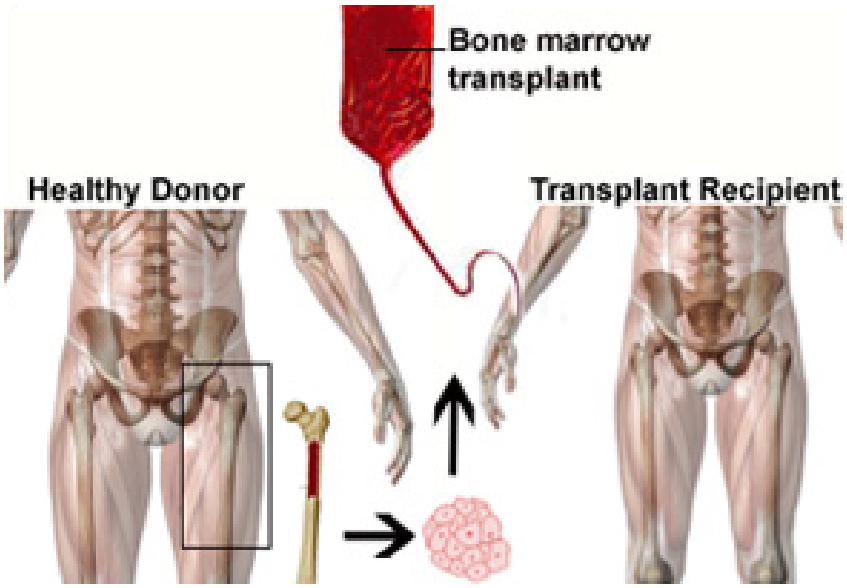
Figure 3: Increased immunogenicity of tumours derived from MCA-treated RAG2$^{-/-}$ mice.



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



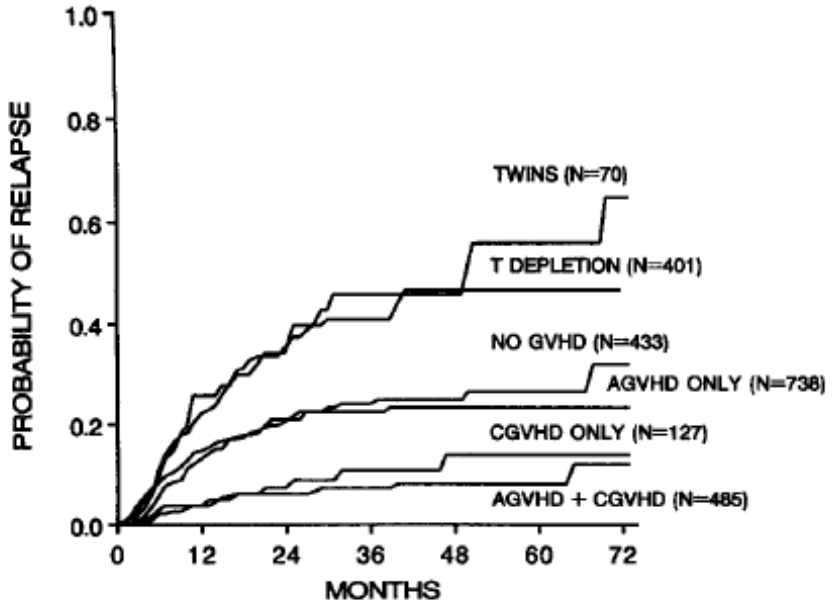
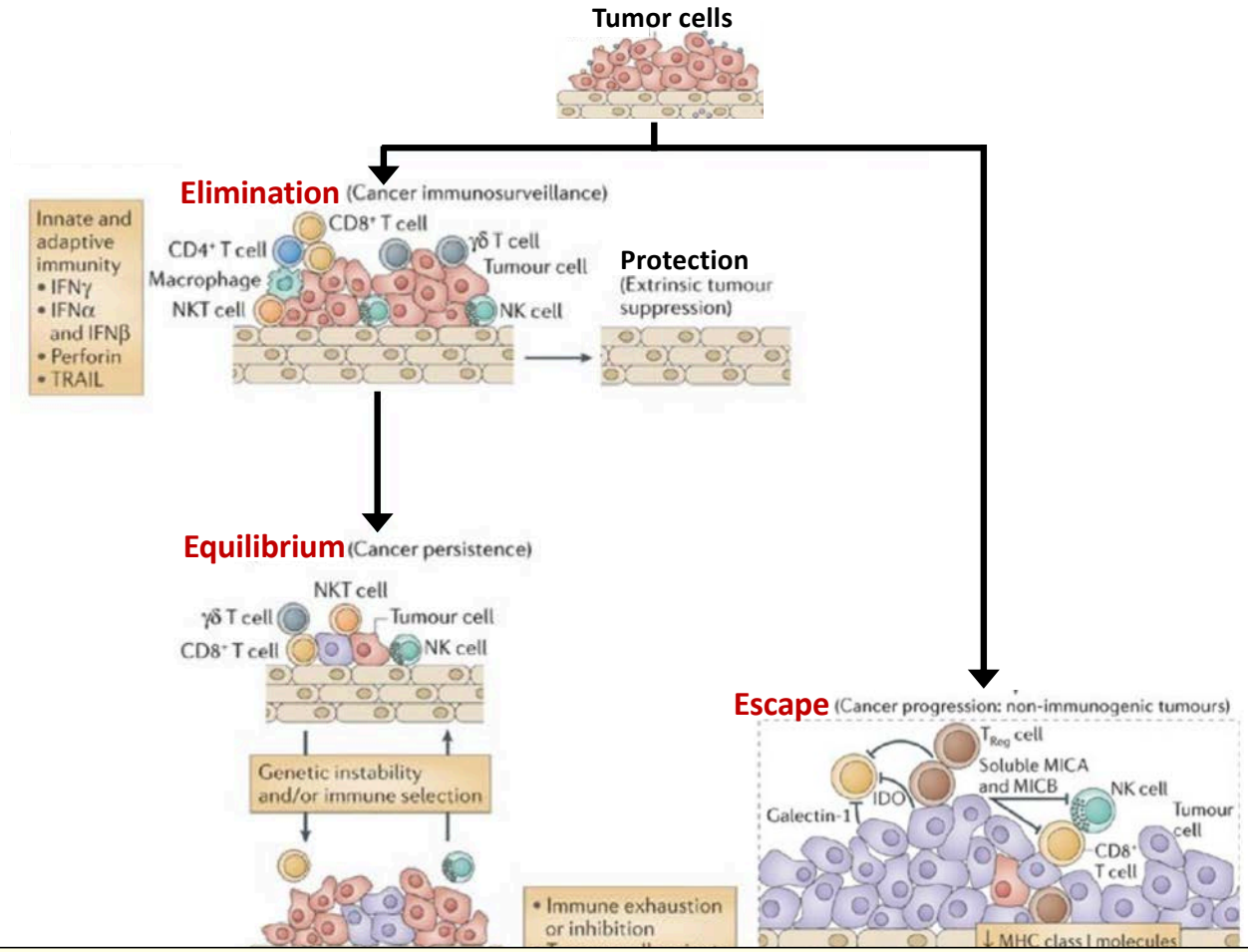


Fig 1. Actuarial probability of relapse after bone marrow transplantation for early leukemia according to type of graft and development of GVHD.

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

FoxP3+ CD4+ T cells that suppress anti-tumor immunity main on effects on CD8+ CTL and CD4+ T helper cells via CTLA-4.

PD1 inhibition appears to enhance suppressive effects of Treg.

M2 TAM

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.

MDSC

Immature myeloid cells with characteristics of monocytes and/or neutrophils.

PMN-MDSCs suppress mainly via ROS

M-MDSCs subtypes suppress via expression of ARG1 and NO

Cancer cells

Immunosuppression via expression of PD-L1

Immunosuppression via MHC class I downregulation

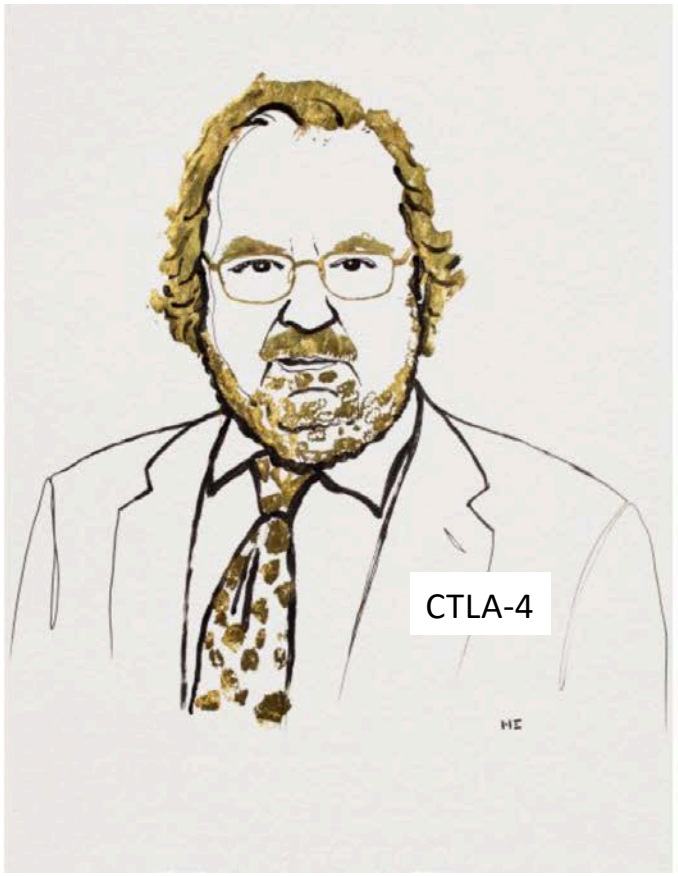
CAF

Induction of PD-L1 on other cell types

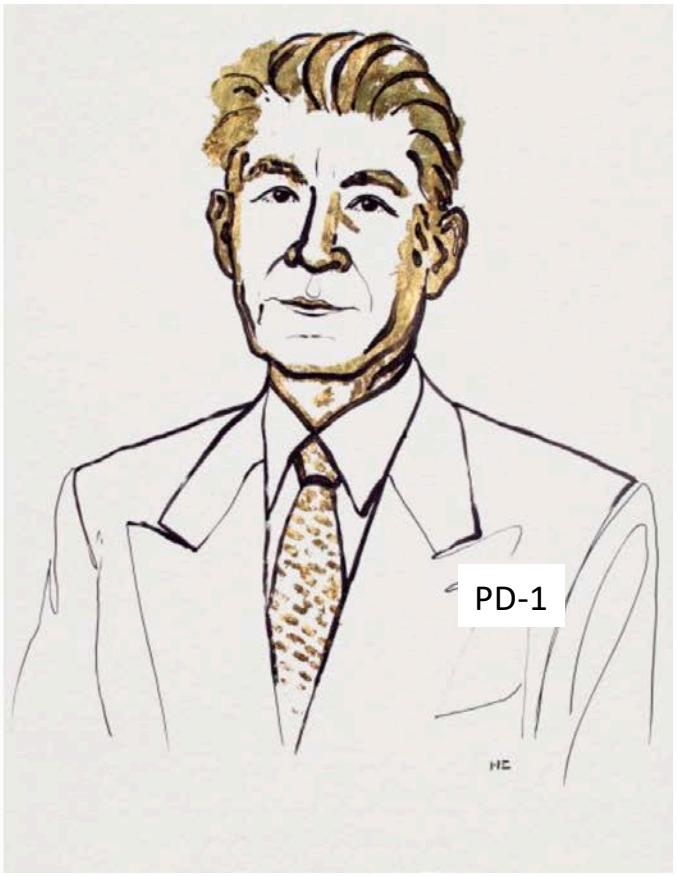
Promote recrutiemnt or expansion of immunosuppressive cells such as Treg, MDSC, M2 macrophages

Checkpoint inhibition: One of the biggest breakthroughs in cancer therapy

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

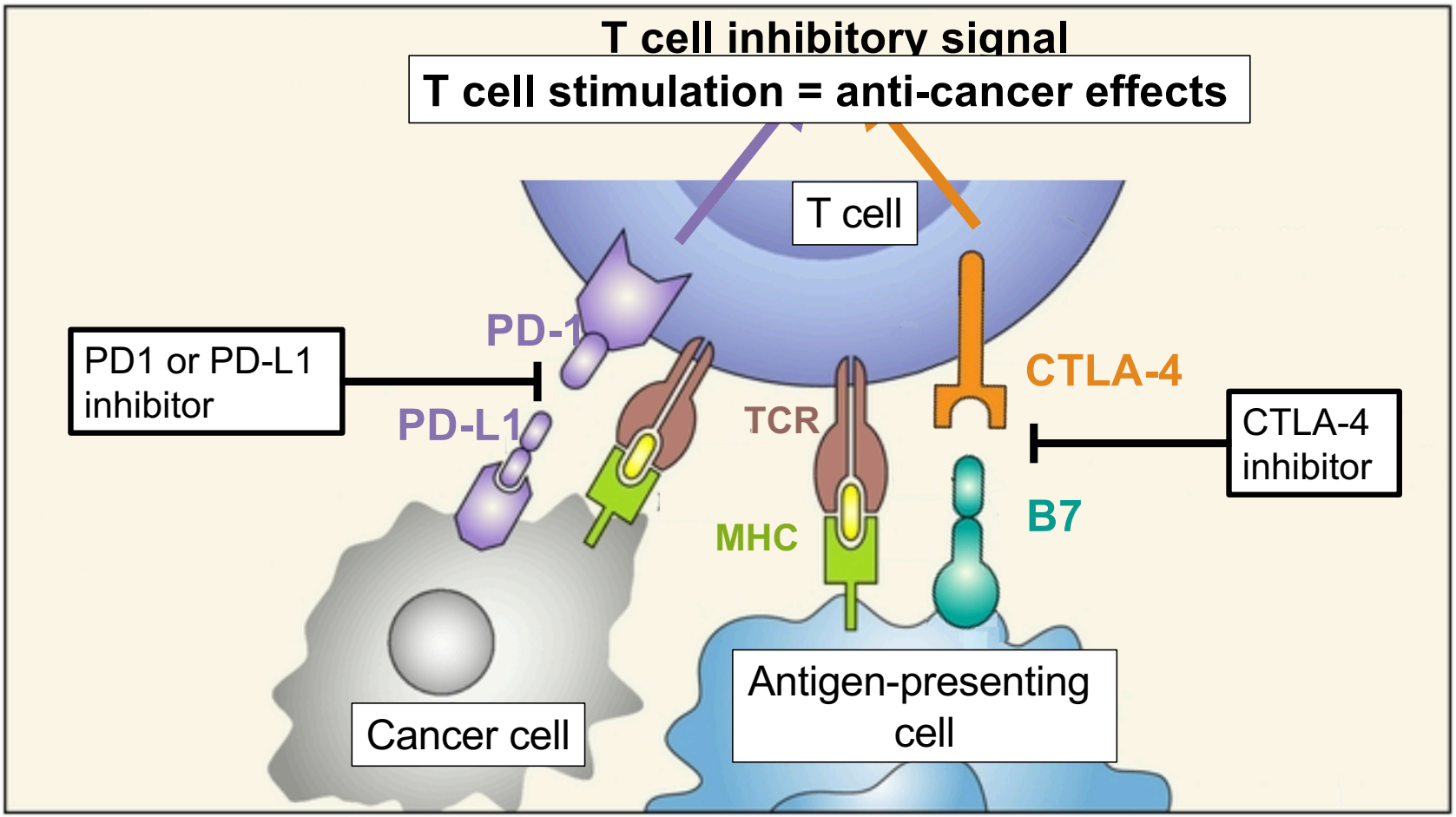


James P. Allison



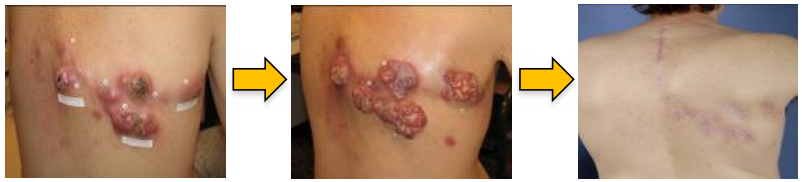
Tasuku Honjo

Releasing the brake on anti-tumor responses



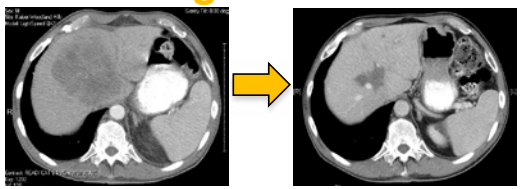
The era of immunotherapy: Responses that were never thought possible

anti-CTLA4



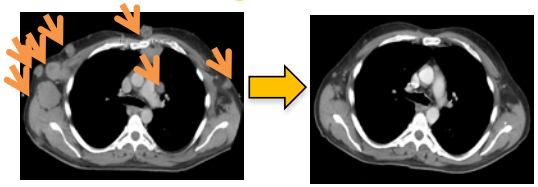
Screening Week 12 Week 72

anti-PD-1

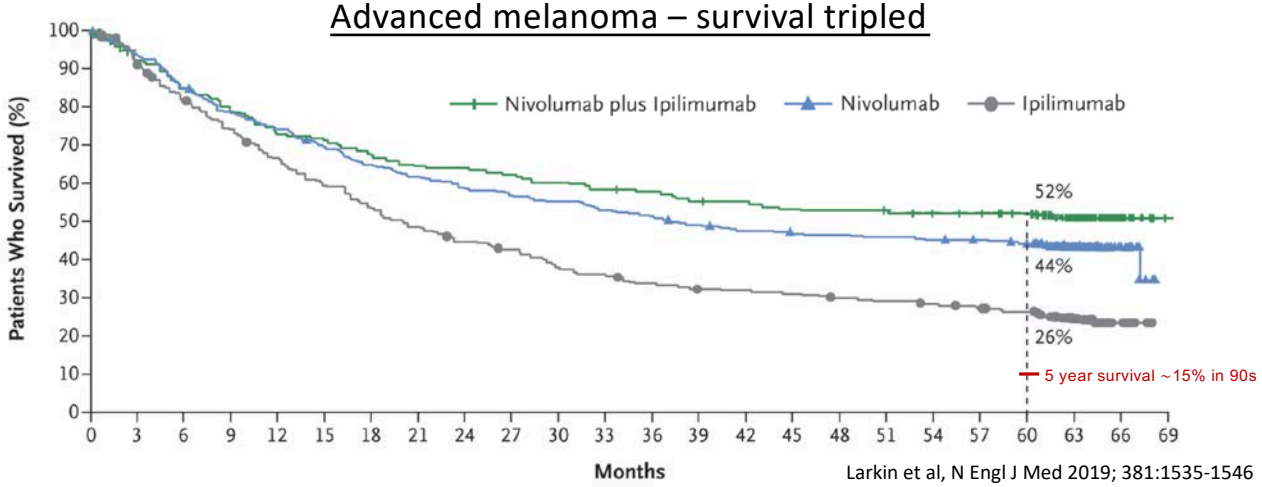


Screening Week 12

CTLA4 + PD-1



Advanced melanoma – survival tripled

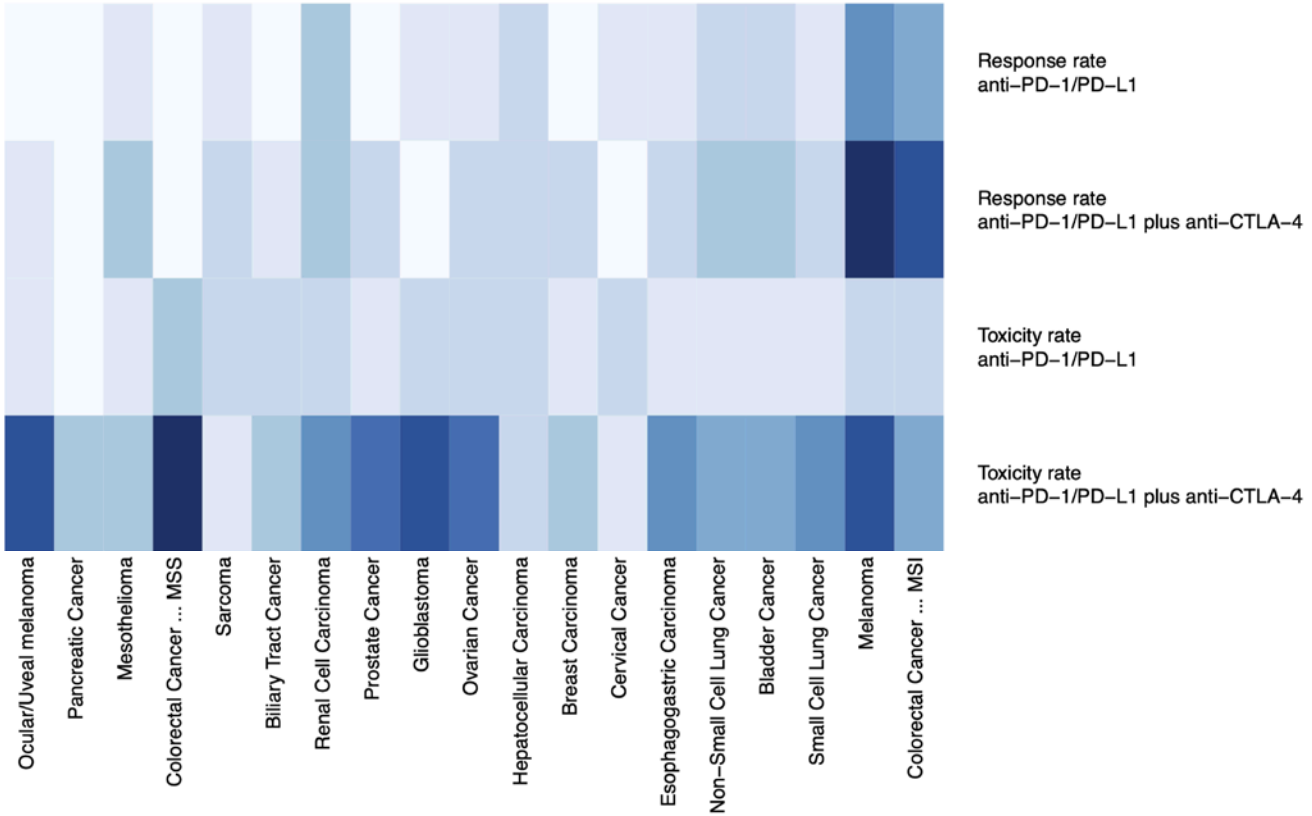


Larkin et al, N Engl J Med 2019; 381:1535-1546

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

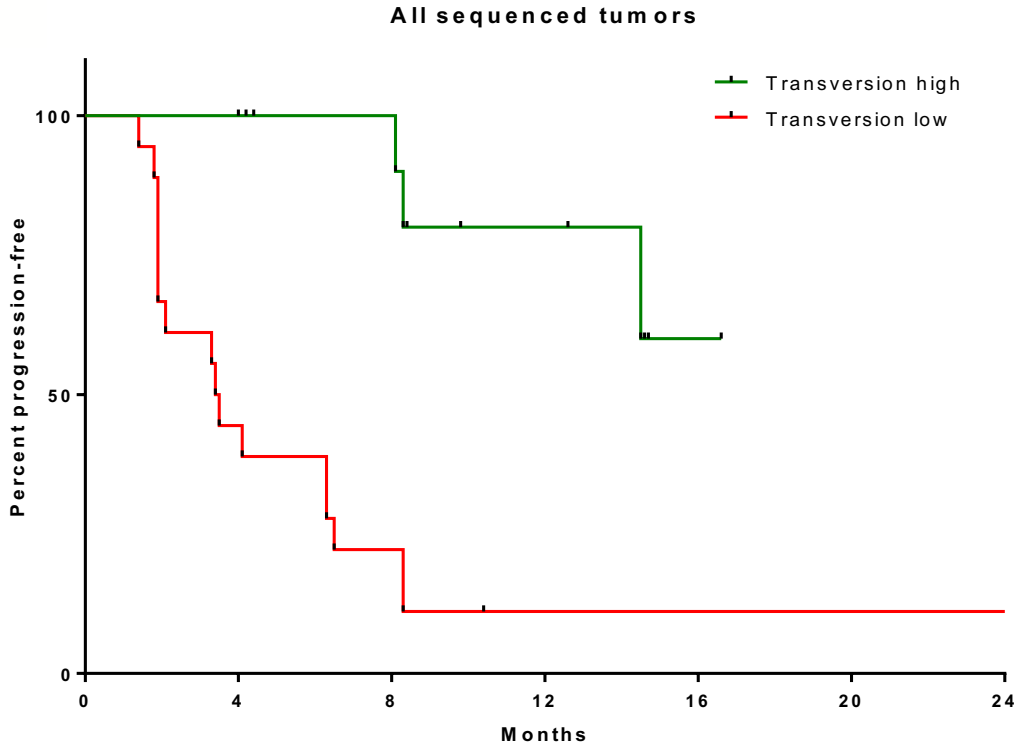


Osipov et al, Clin Cancer Res. 2020 Sep 15;26(18):4842-4851

Tumor mutational burden a main determinant of response rates

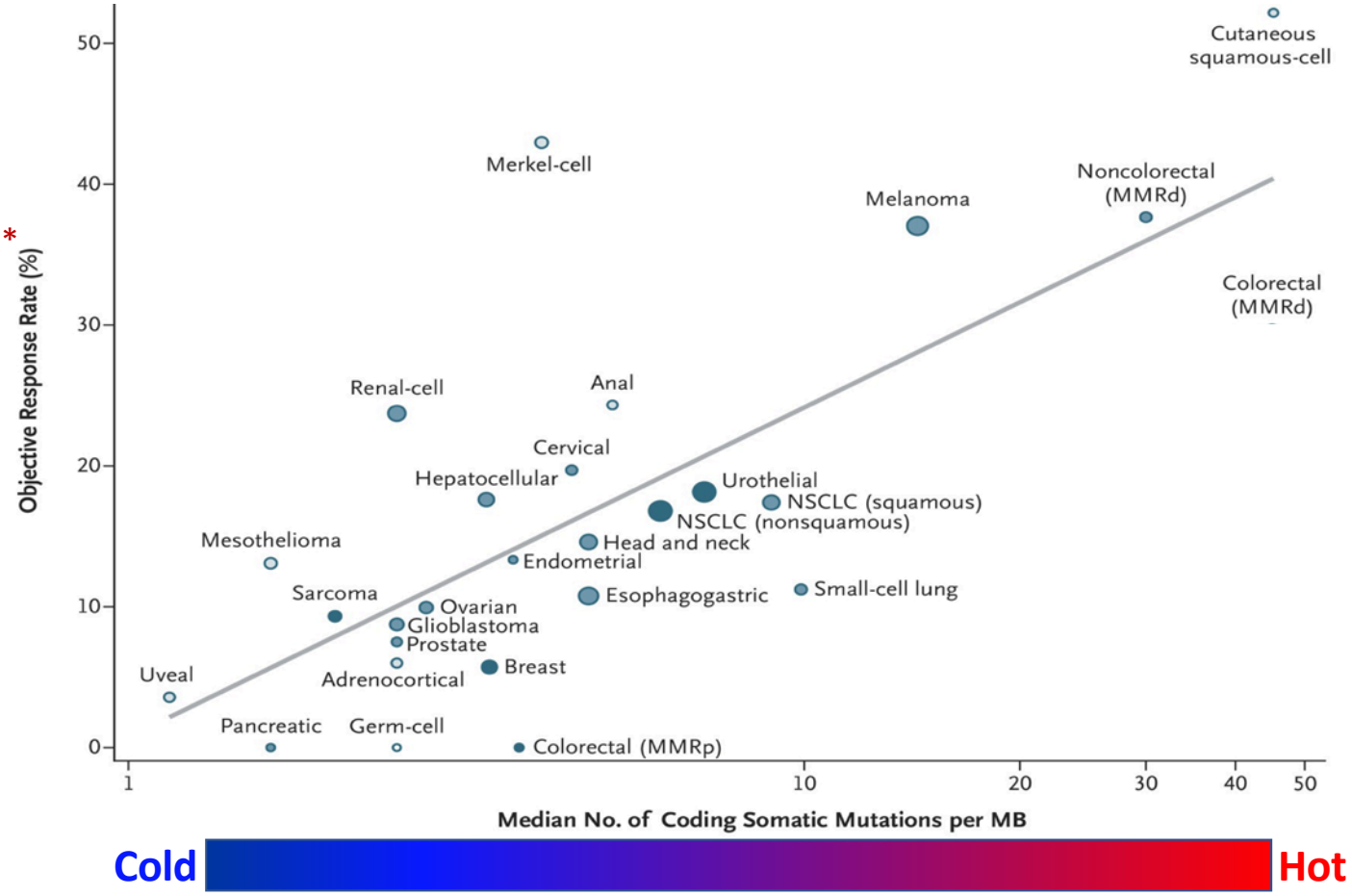
CANCER IMMUNOLOGY

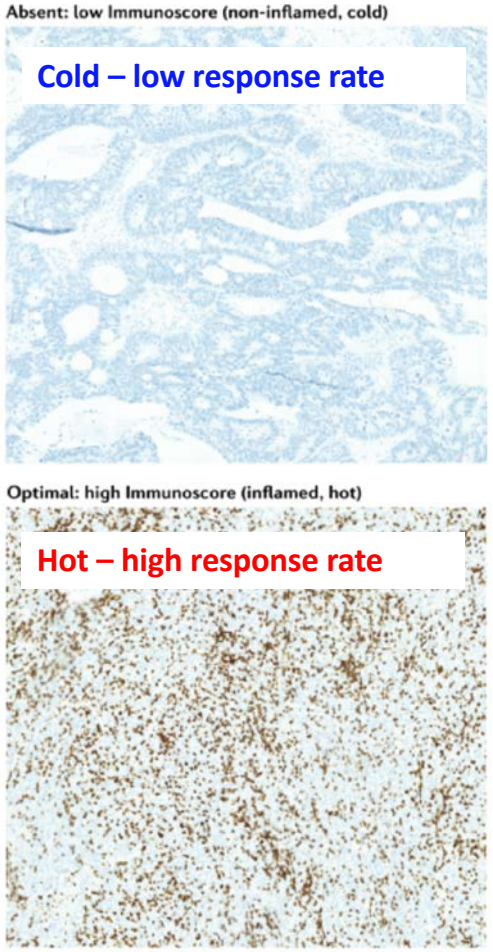
Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer



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,[1,2,5] 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 Zaleman,[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,[6] 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,[4,3] 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

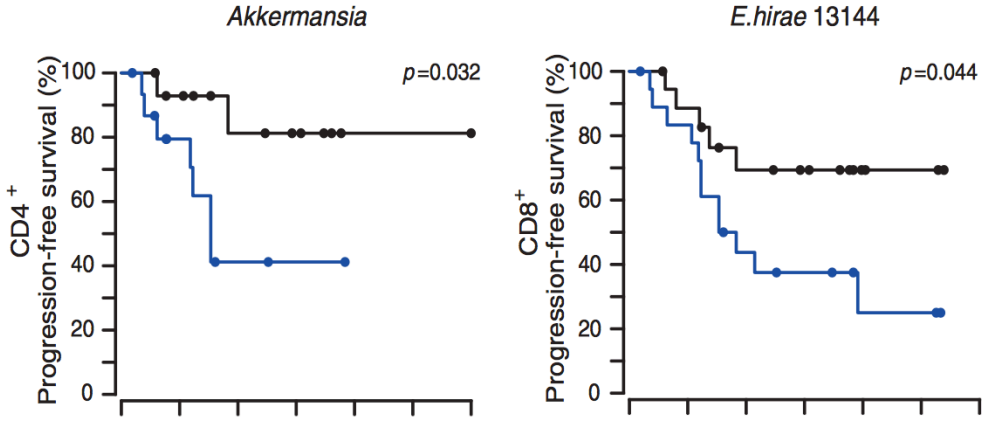
A key role of the microbiome in anti-cancer therapies

CANCER IMMUNOTHERAPY

Science **359**, 91–97 (2018)

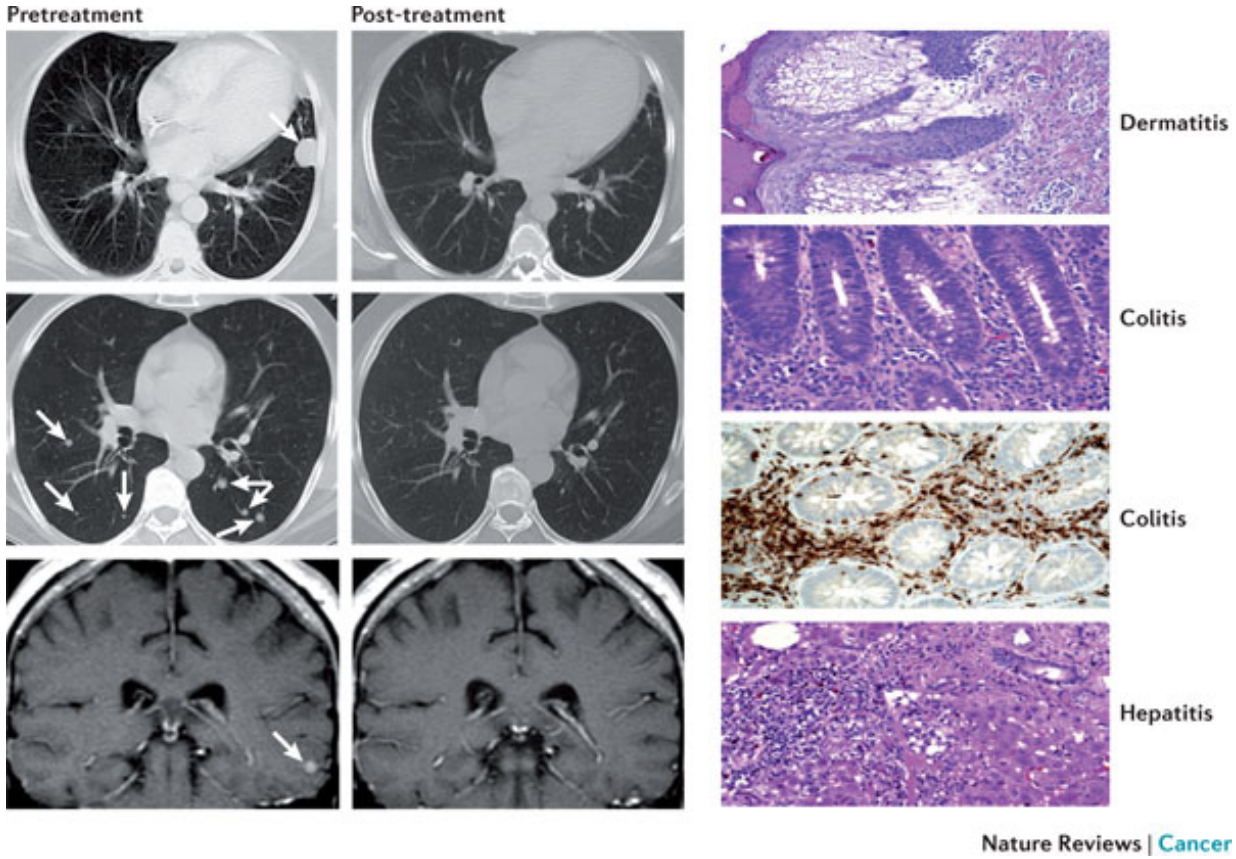
Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors

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]*



Modulation of the gut microbiota could improve responses to immuno- or combination therapy

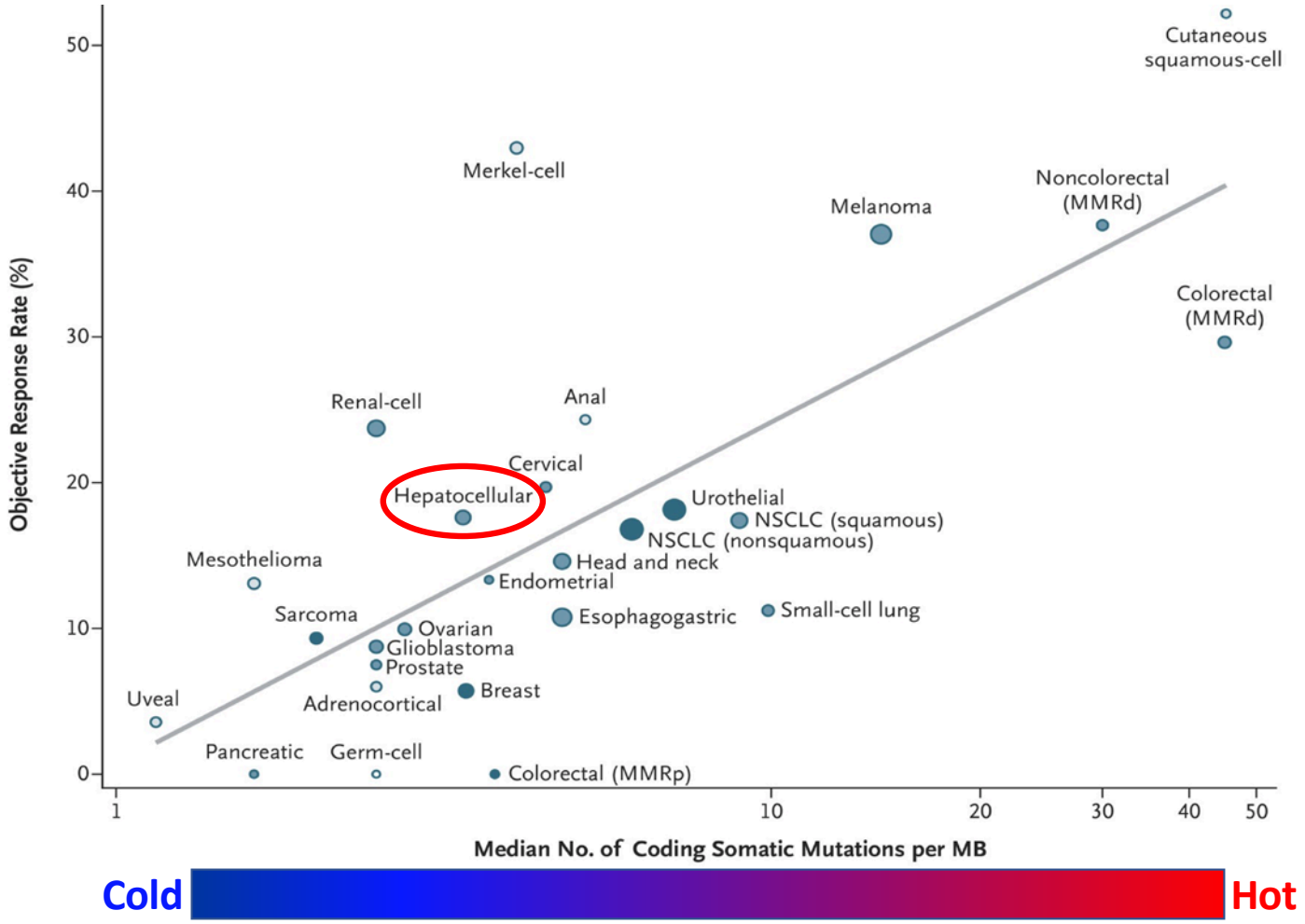
Checkpoint inhibition can be effective but can have severe autoimmune side effects



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)

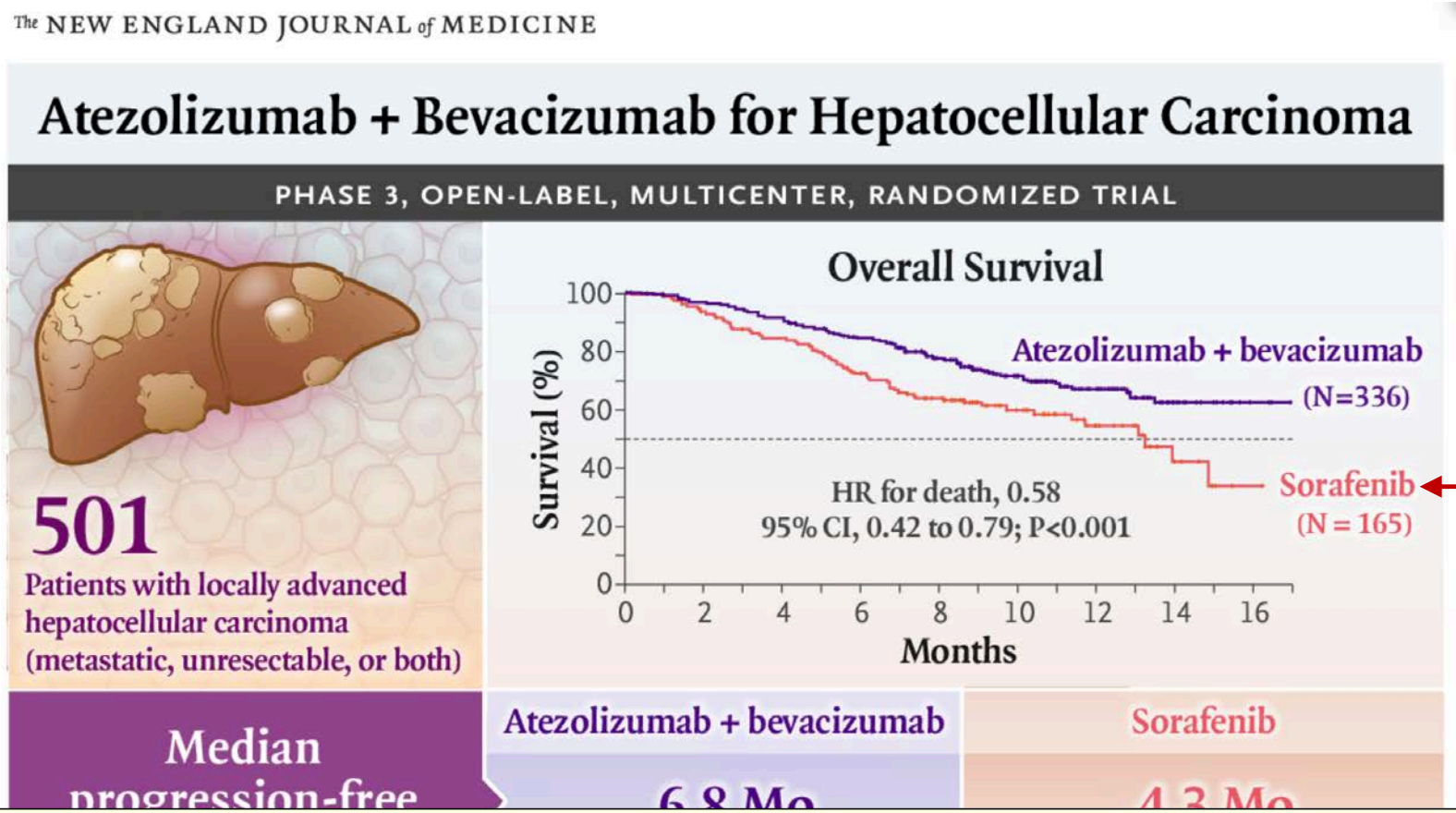
*



*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



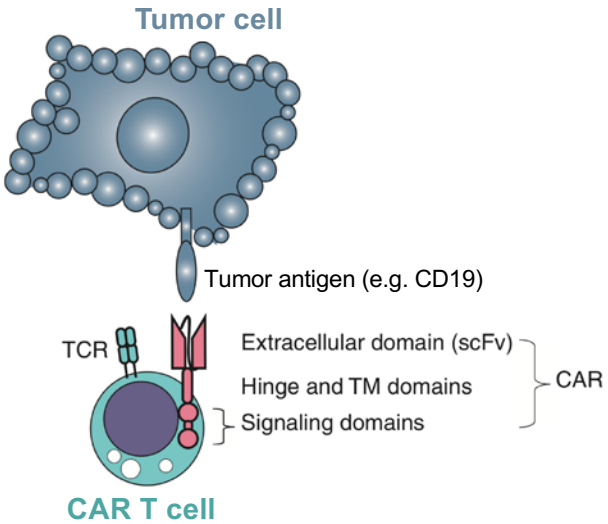
← Standard of care (extends survival)

Multiple combination therapies tested in clinical trials in various tumors

Additional immunotherapies on the horizon

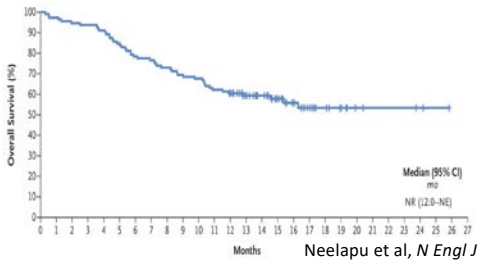
CAR T cells

(Chimeric Antigen Receptor)



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

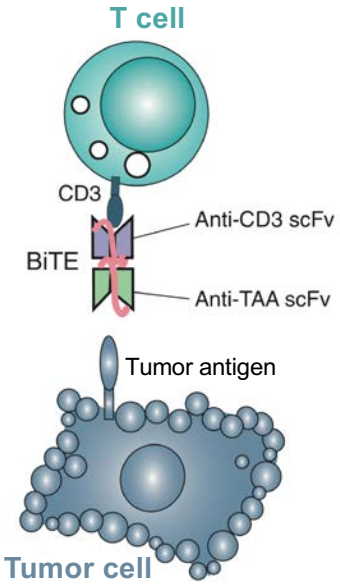
Already approved for CD19 in B cell lymphomas with 80% response rates



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

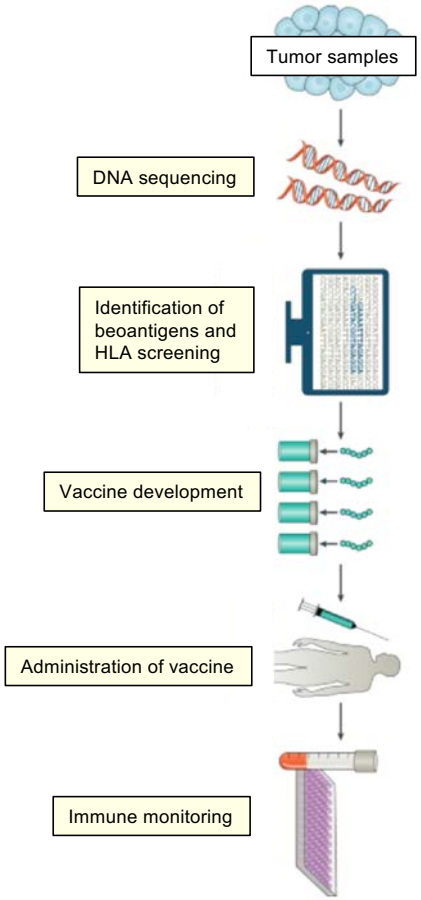
BiTEs

(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)

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!