Normalizing the Tumor Microenvironment to Improve Cancer Immunotherapy: Bench to Bedside

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LUDWIG CANCER RESEARCH
Harvard

VE RI TAS

Disclosure Information

- Board of Trustees - Tekla Healthcare Investors, Tekla Life Sciences Investors, Tekla Healthcare Opportunities Funds, and Tekla World Healthcare Fund
- SAB/Consultant - Accurius, Elpis, Innocoll, SPARC, SynDevRx and Twentyeight-Seven
- Equity - Accurius, Enlight, and SynDevRx
- Grant - Böhringer-Ingelheim
- I'll discuss off-label use of losartan

May 3, 2019

Estimation of the Percentage of US Patients With Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs

Alyson Haslam, PhD[1]; Vinay Prasad, MD, MPH[2,3,4,5]

» Author Affiliations | Article Information

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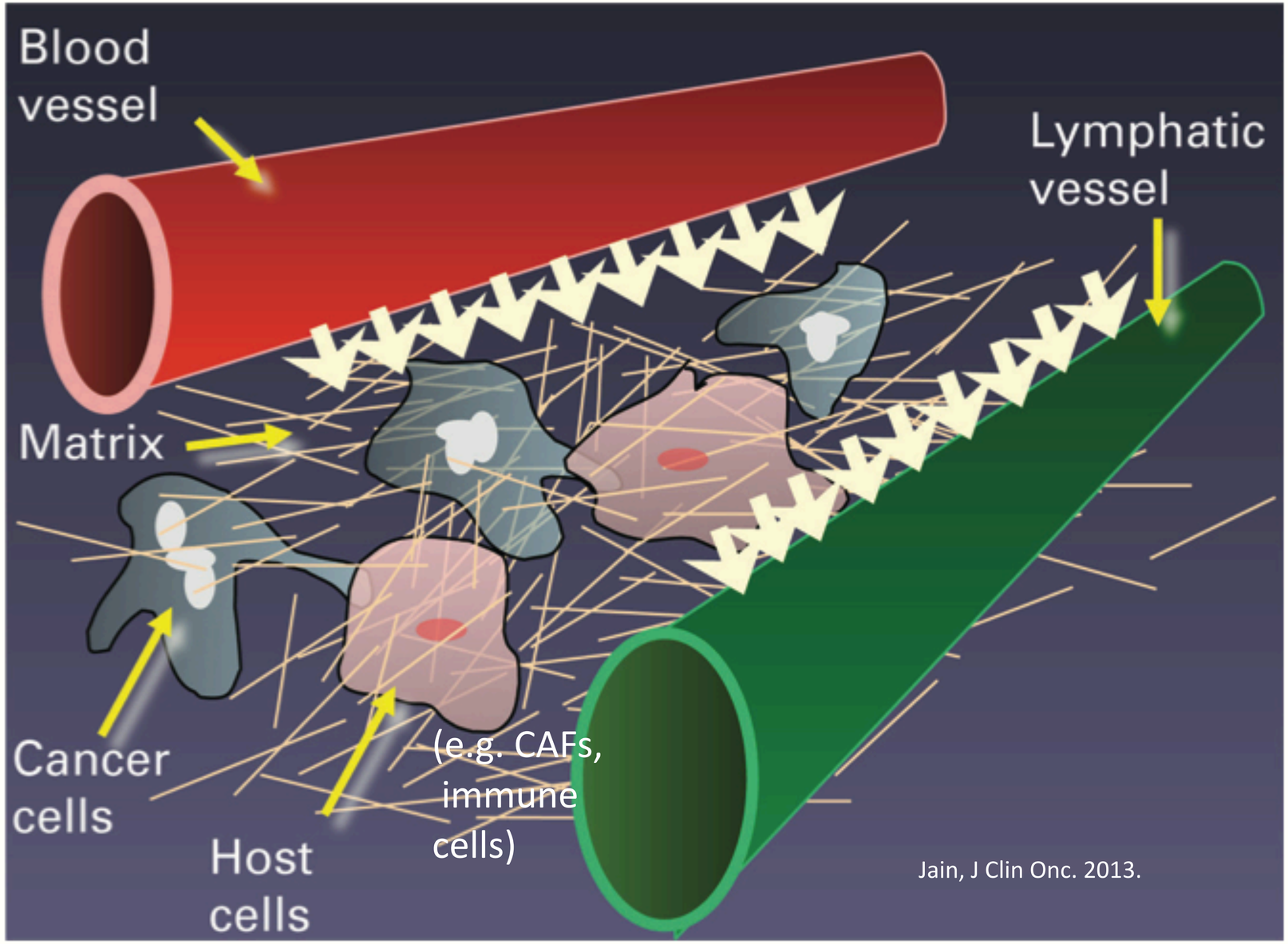
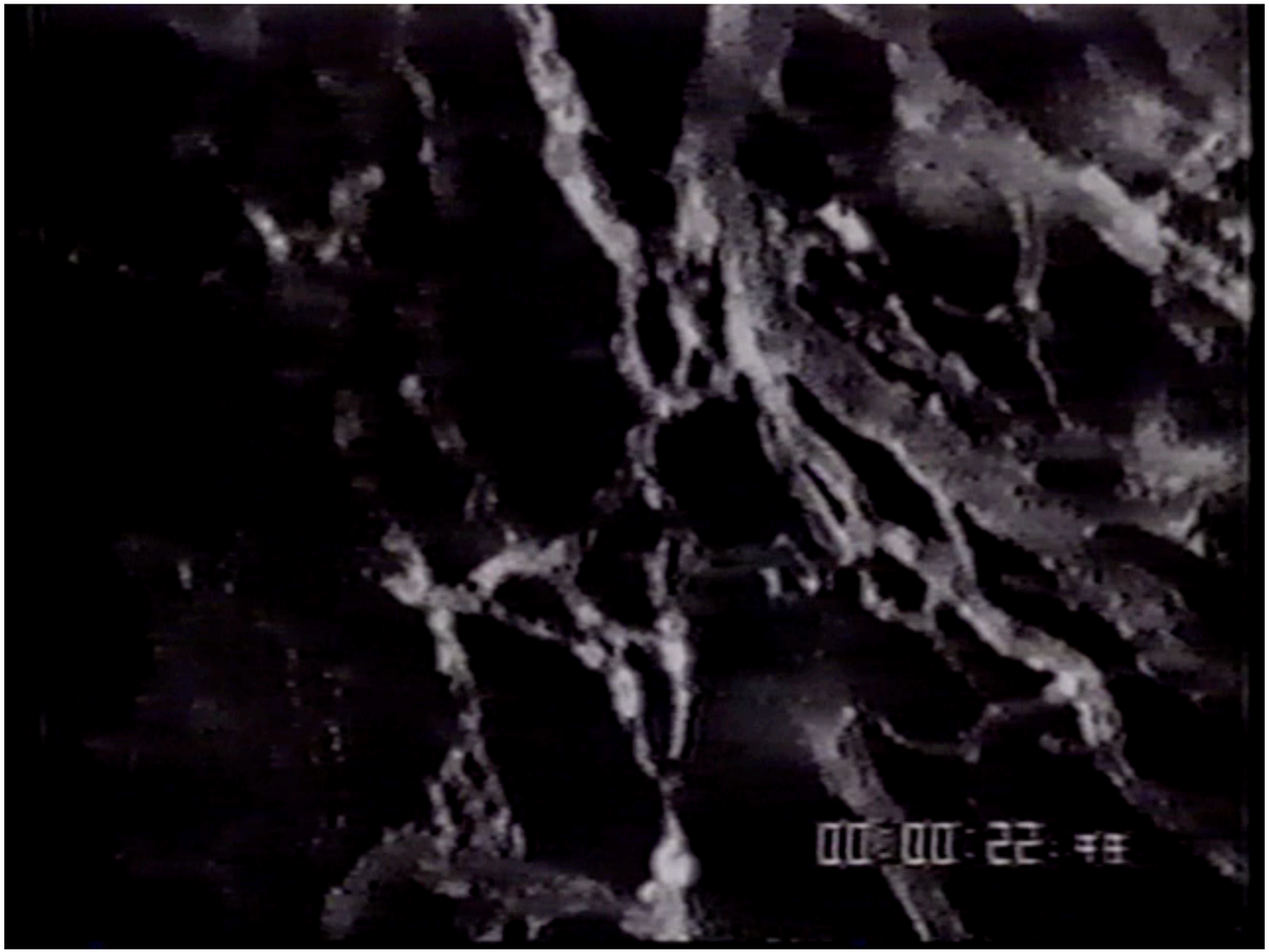
- Cancer patients eligible for checkpoint inhibitors increased from 1.54% in 2011 to 43.63% in 2018.

- Patients who respond to checkpoint inhibitors increased from 0.14% in 2011 to 12.46% in 2018.

Tumor Microenvironment

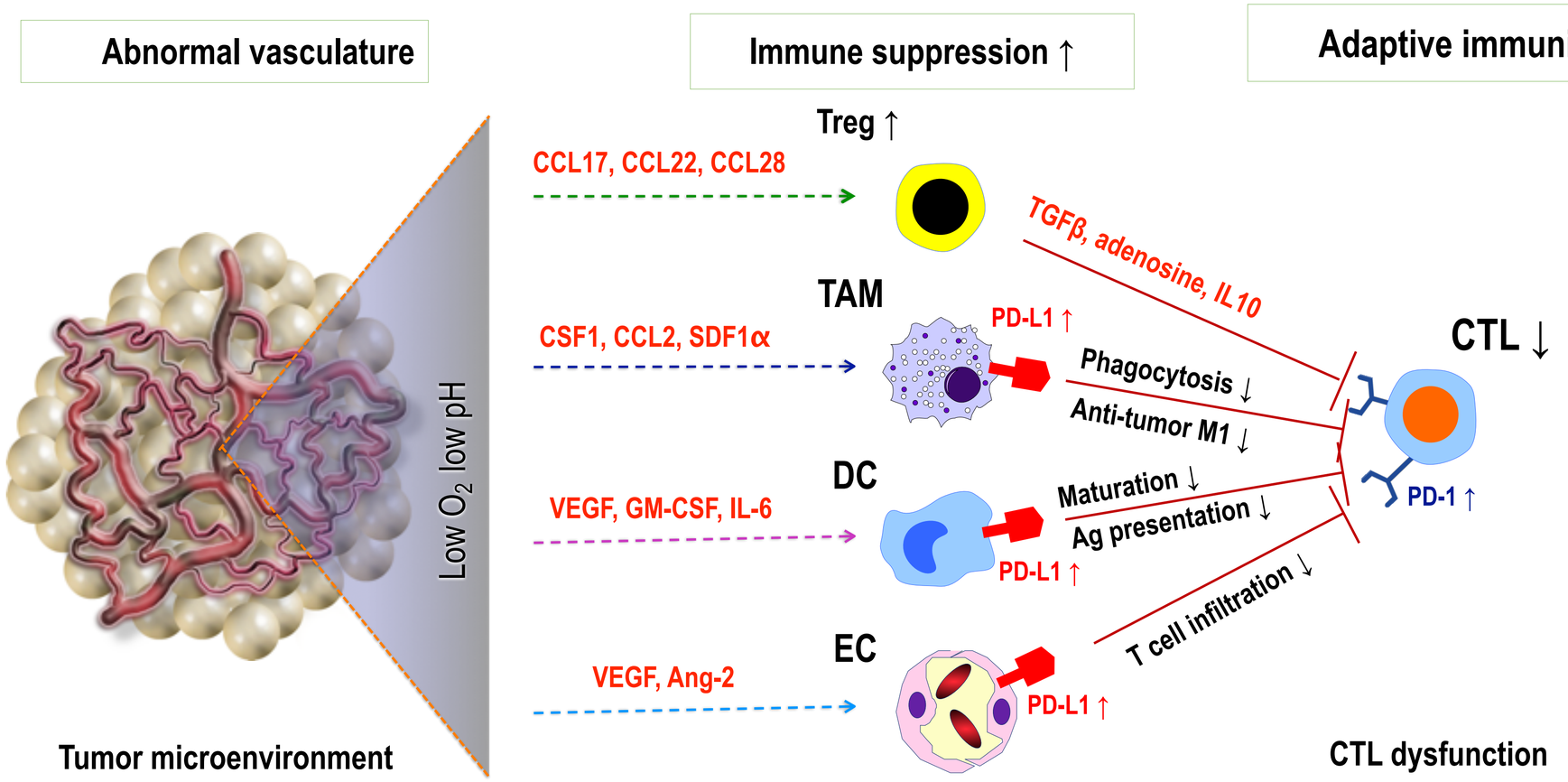


Abnormal blood vessels lead to impaired blood flow, resulting in hypoxia & low pH and poor delivery of molecules and cells



Jain, Cancer Cell (2014)

Hypoxia and low pH contribute to immuno-suppressive tumor microenvironment



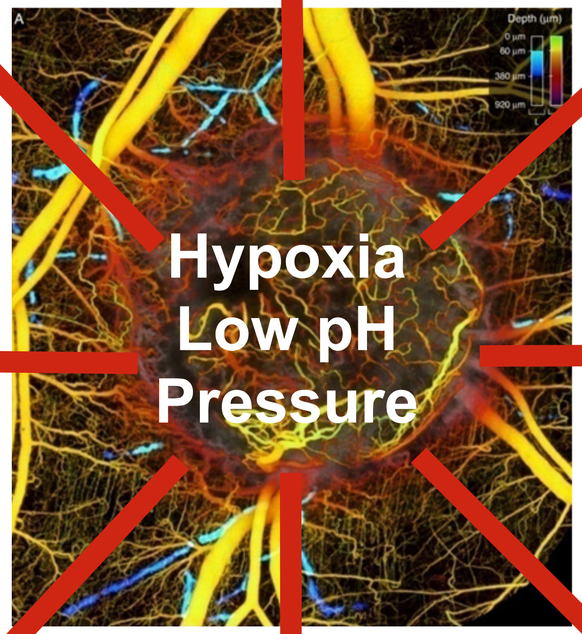
Fukumura, Kloepper, Amoozgar, Duda and Jain, *Nature Reviews Clinical Oncology* (2018)

Hypoxia and low pH also cause…

Genomic instability,
Hypermethylation &
Unfolded protein response

Abnormal
Angiogenesis

Inflammation, Immunosuppression
& fibrosis



Switch to anaerobic
metabolism

Resistance to
radiotherapy,
chemotherapy
and immunotherapy

Resistance to
apoptosis/autophagy

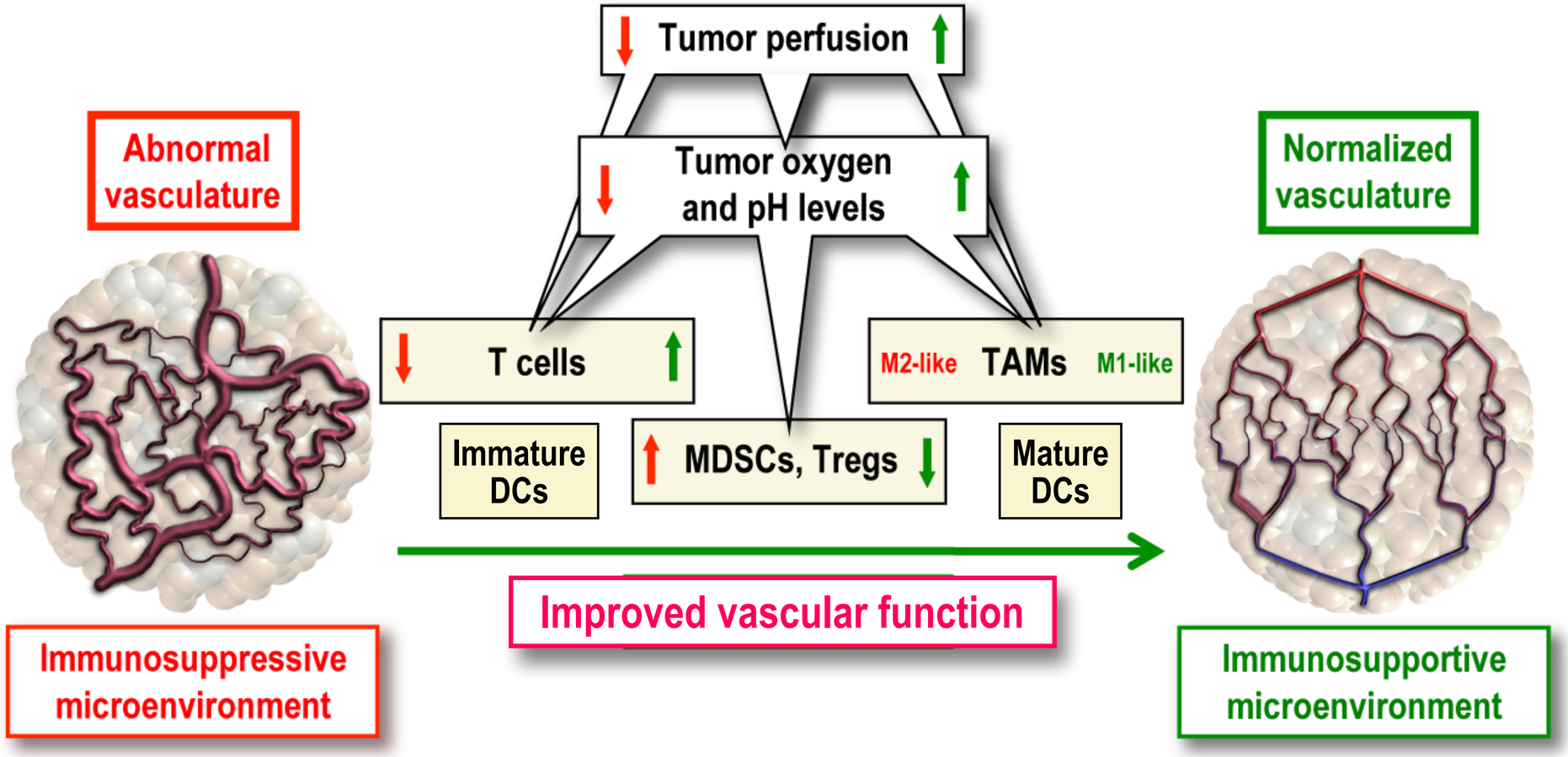
EMT, Invasion &
Metastasis

Induction of
cancer “stem cell”
phenotype

Jain, Cancer Cell (2014)

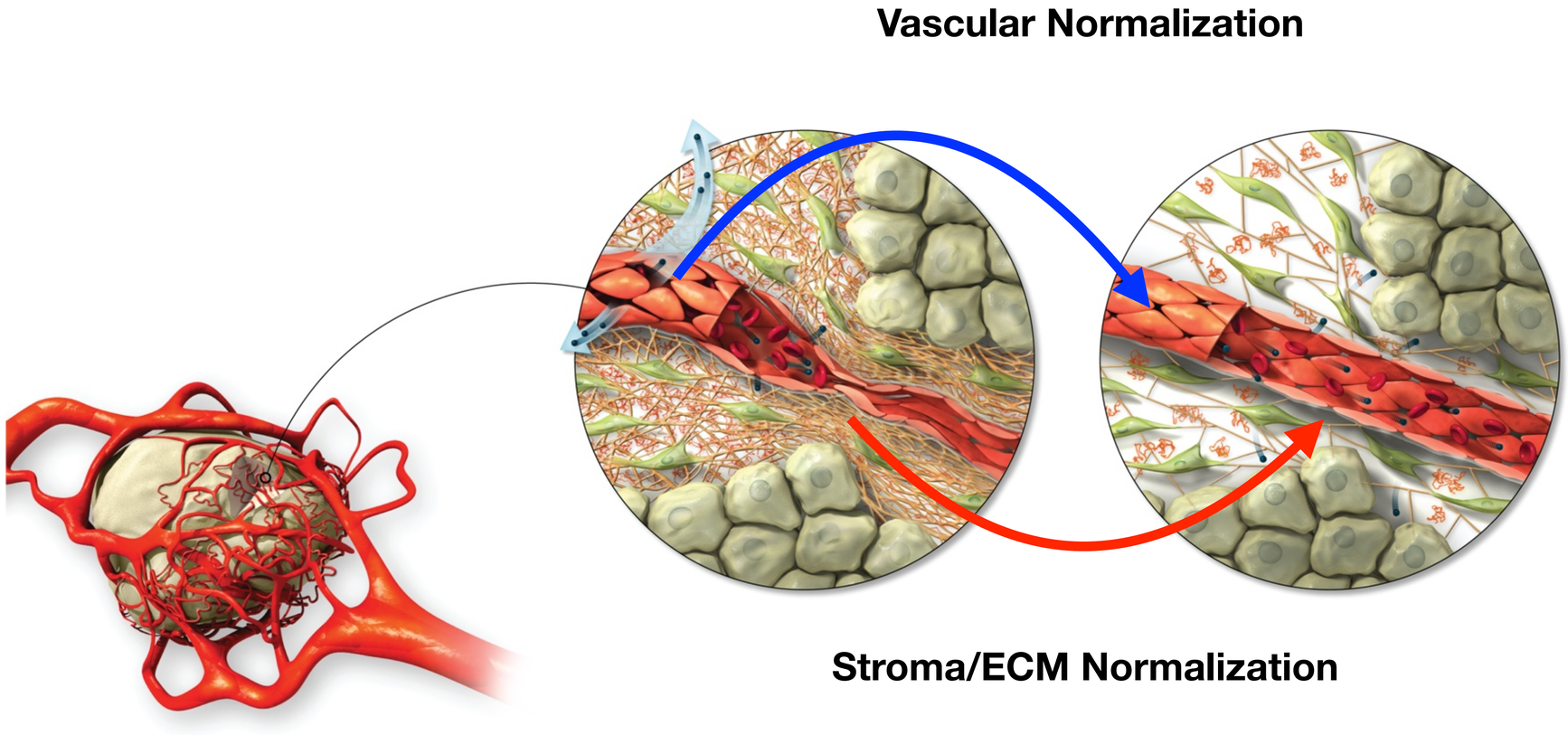
HYPOTHESIS:

Improving vascular function can reprogram the TME into an immunosupportive milieu



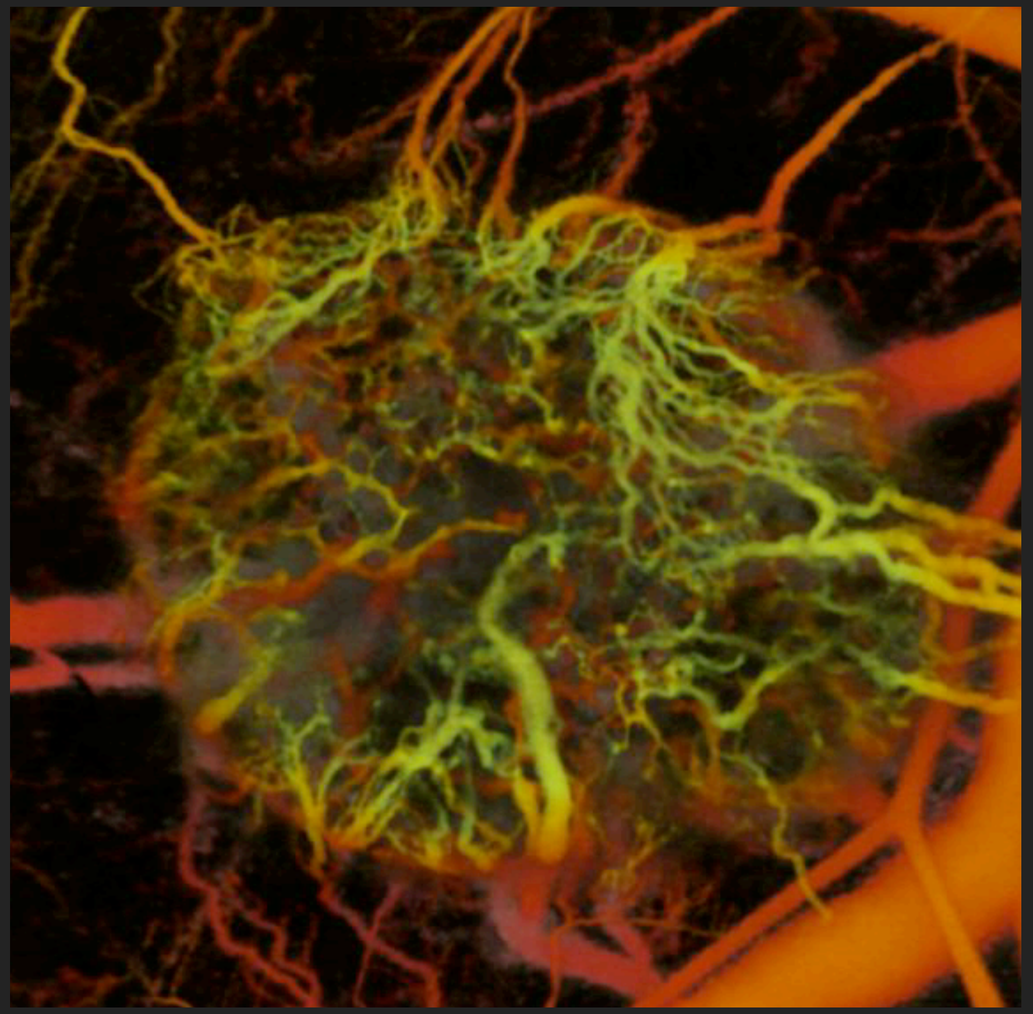
Jain, *Cancer Cell* (2014)

Two strategies to improve function of tumor blood vessels



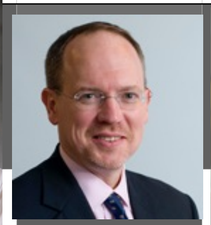
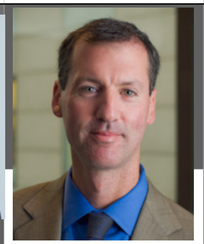
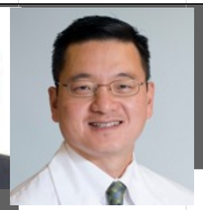
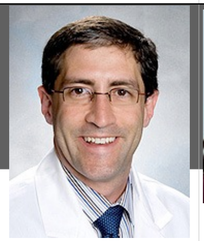
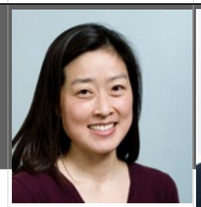
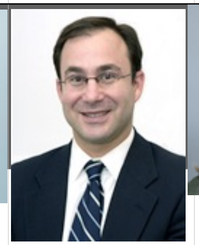
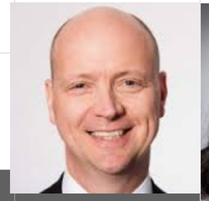
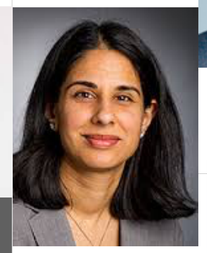
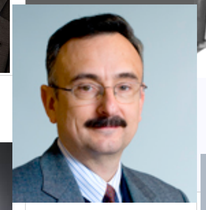
Jain, *Nature Medicine* (2001); *Science* (2005, 2019)

Normalization of Vessels in Response to Antiangiogenic Therapy



Vakoc, Lanning et al, Nature Medicine (2009)

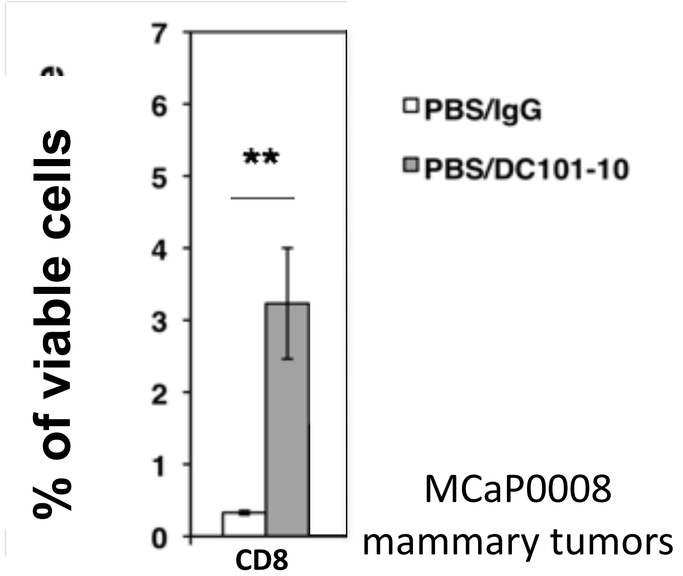
MGH/DF Clinical Collaborators and Patients

Agent / Cancer Type	Rectal Cancer	Brain tumors	Breast Cancer	Upper GI Ca	Sarcoma	Ovarian Cancer	Lung Cancer	Schwannoma	Pediatric brain tumors
Bevacizumab (Genentech)	 Willett	 Batchelor	 Krop	 Zhu	 Yoon	 Horowitz	 Heist	 Plotkin	 Yock
Cediranib (AstraZeneca)									
Sunitinib (Pfizer)	 Clark	 Loeffler	 Winer	 Ryan	 Eder	 Penson	 Sahani		 Ebb
Sorafenib (Bayer/Onyx)									
Ramucirumab (ImClone)	 Meyerhardt	 Sorensen	 Tolaney	 Fernandez del-Castillo	 Hornichek				
Vatalanib (Novartis)									
Vandetanib (AstraZeneca)				 Hong					
Plerixafor (Genzyme)	 Lauwers	 Wen				 Spriggs			
Losartan/Chemo/ Proton Therapy									

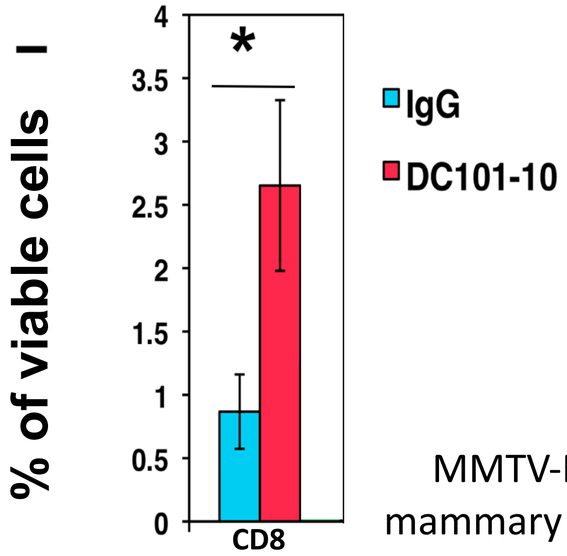
Increase in tumor blood perfusion or oxygenation correlates with better outcome after anti-VEGF therapy

Cancer type	Agent(s)	Imaging parameter	Outcome measure	Reference
Recurrent GBM	Cediranib	↑ Blood flow (MRI)	↑ PFS, OS	Sorensen *et al.*, *Cancer Res* 2012
Newly diagnosed GBM	Cediranib with chemoradiotherapy	↑ Blood flow (MRI)	↑ PFS, OS	Batchelor *et al.*, *PNAS* 2013
Advanced non-small cell lung cancer (NSCLC)	Bevacizumab alone and then with chemotherapy	↑ Blood flow (dCT after bev alone)	↑ ORR	Heist *et al.*, *PNAS* 2015
Chemo-naive breast cancer	Neoadjuvant bevacizumab alone and then with chemotherapy	↑ Oxygenation (FMISO-PET after bev alone)	↑ ORR	Garcia-Foncillas *et al.*, *ASCO* 2012
Triple negative breast cancer	Neoadjuvant bevacizumab alone and then with chemotherapy	Vessel density & pericyte coverage ↑ (IHC in serial biopsies after bev alone)	Path response (Miller-Payne score)	Tolaney *et al.*, *PNAS* 2015

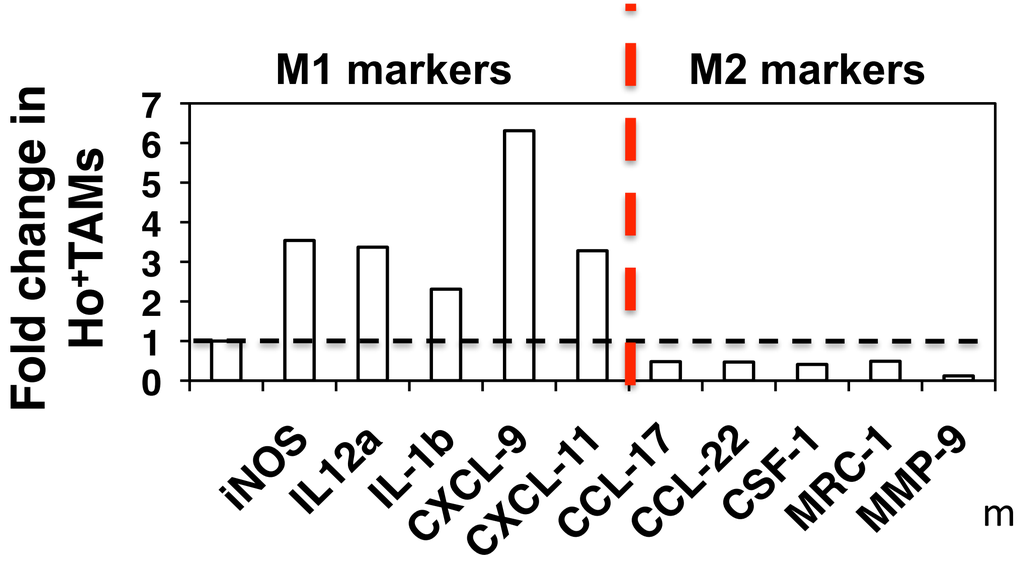
Vascular normalization reprograms the tumor immune microenvironment



MCaP0008
mammary tumors



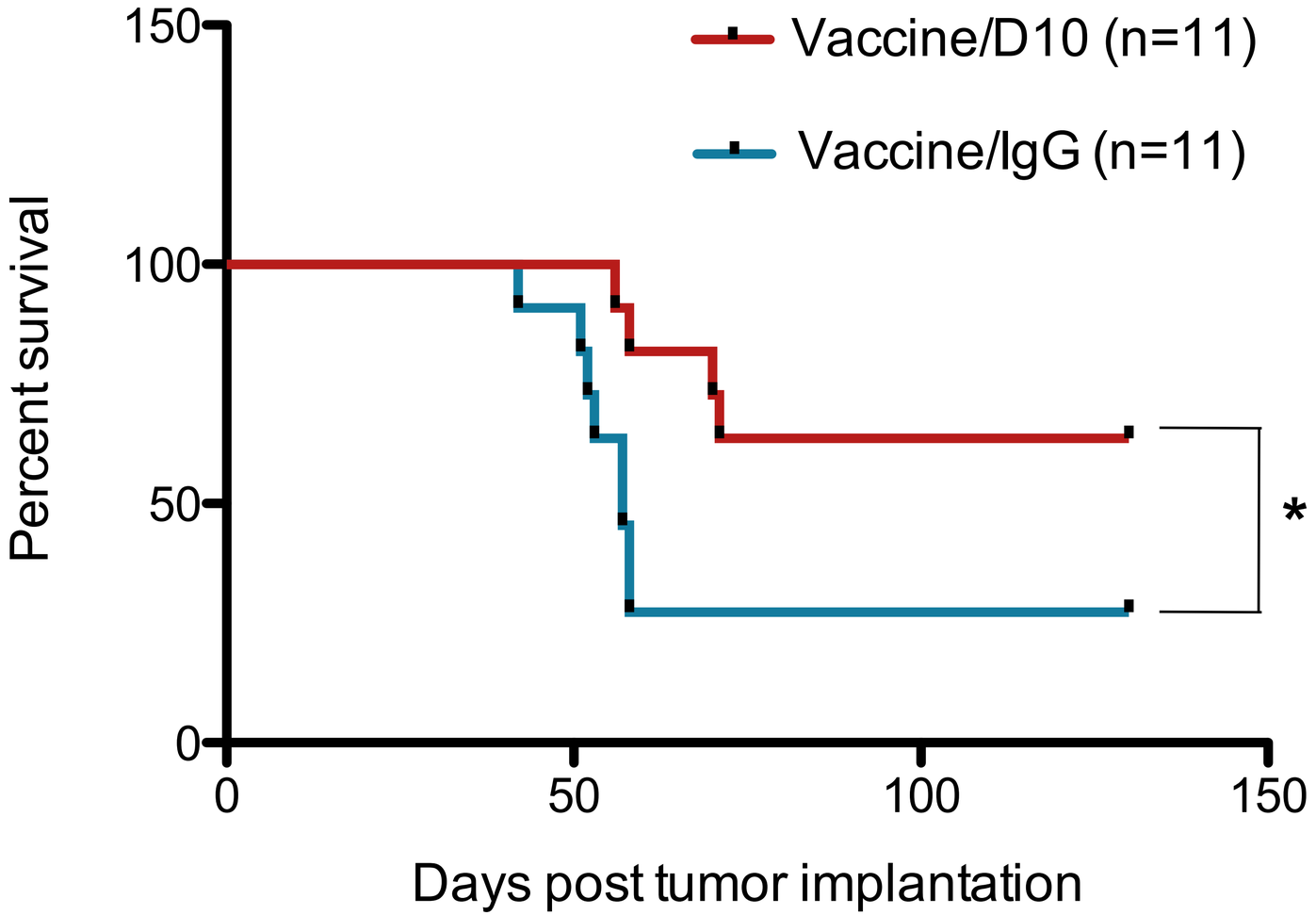
MMTV-PyVT
mammary tumors



MCaP0008
mammary tumors

Huang et al, *PNAS*, 2012

Anti-VEGFR2 treatment (D10) combined with immunotherapy doubled survival

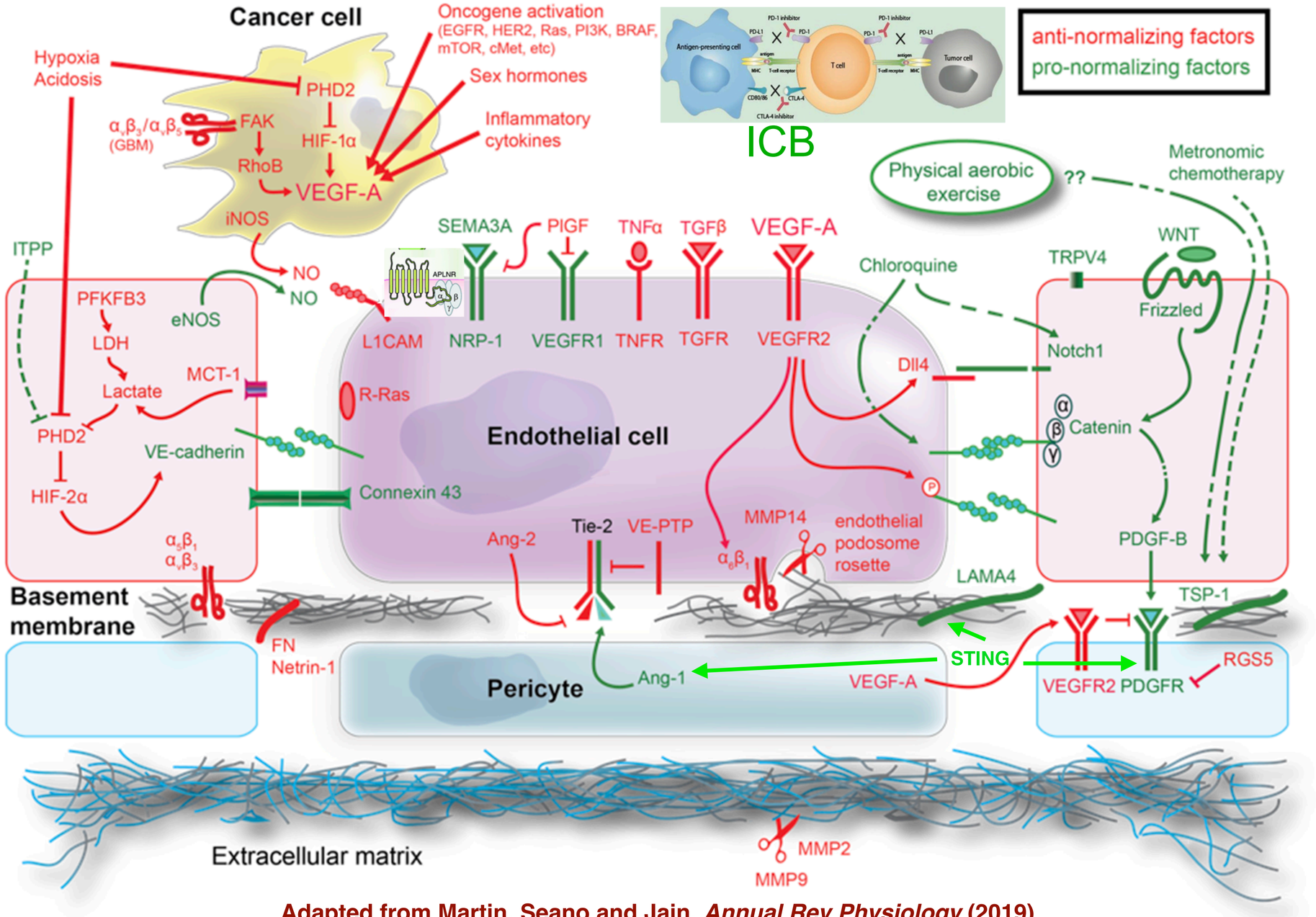


Huang et al, *PNAS*, 2012

FDA-Approvals of drugs targeting the VEGF/VEGFR and PD-1/PD-L1 pathways

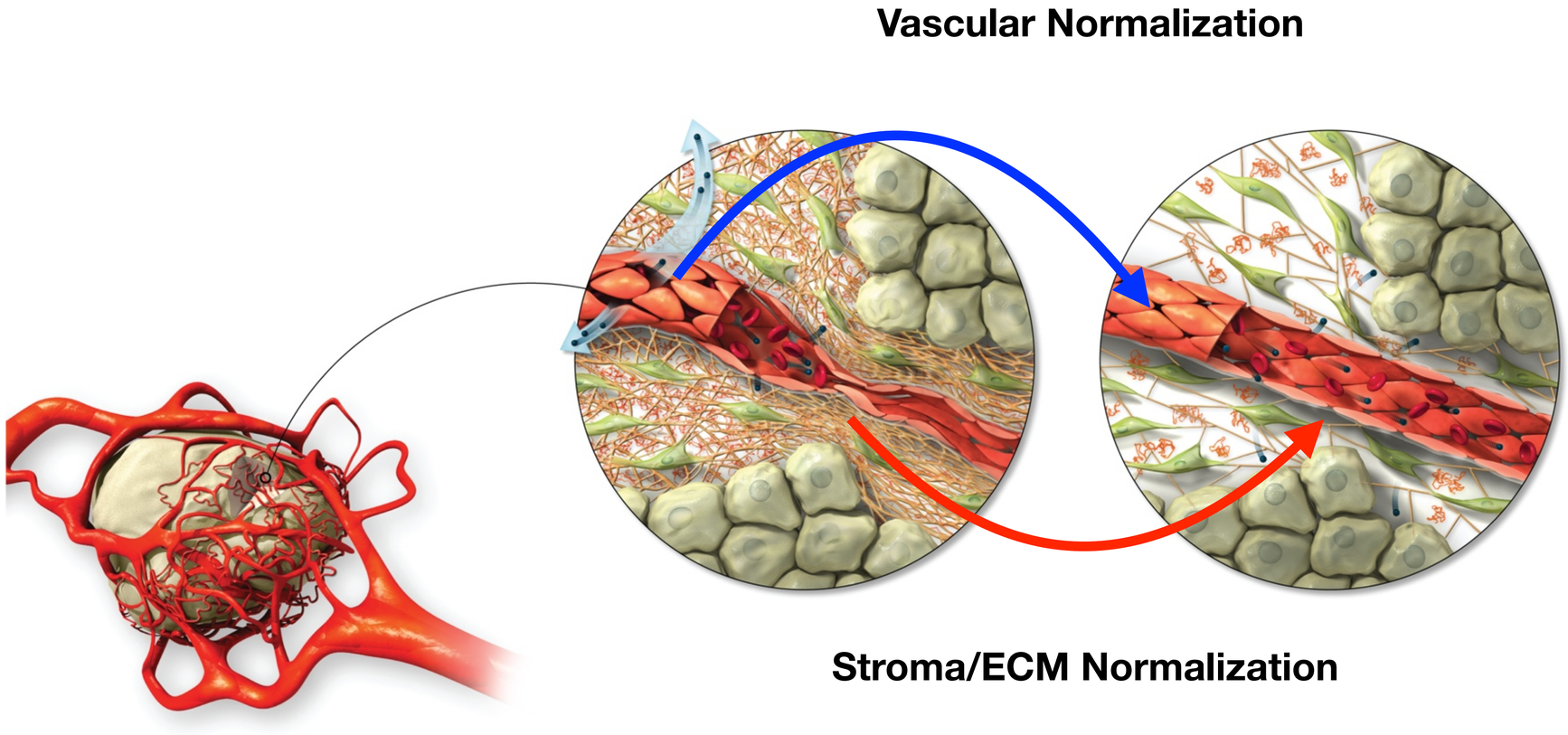
Combination	Disease	ORR	PFS	OS	Ref.	FDA approval date
Bevacizumab/ Atezolizumab/ Chemotherapy	NSCLC	55% vs. 42% (bev + chemo)	8.3 m vs. 6.8 m (bev + chemo)	19.2 m vs. 14.7 m (bev + chemo)	Socinski et al., *N Engl J Med* 2018	Dec 7, 2018
Axitinib/ Pembrolizumab	RCC	59.3% vs. 35.7% (sunitinib)	15.1 m vs. 11.1 m (sunitinib)	Not reached (NR)	Rini et al., *N Engl J Med* 2019	Apr 30, 2019
Axitinib/ Avelumab	RCC	51.4% vs. 25.7% (sunitinib)	13.8 m vs. 8.4 m (sunitinib)	NR	Motzer et al., *N Engl J Med* 2019	May 14, 2019
Bevacizumab/ Atezolizumab	HCC	27% vs. 12% (sorafenib)	6.8 m vs. 4.5 m (sorafenib)	19.2 m vs. 13.2 m (sorafenib)	Finn et al., *N Engl J Med* 2020	May 29, 2020
Cabozantinib/ Nivolumab	RCC	55.7% vs. 27.1% (sunitinib)	16.6 m vs. 8.3 m (sunitinib)	NR	Choueiri et al., *ESMO* 2020 (Abstract 696O_PR)	Jan 22, 2021
Lenvatinib/ Pembrolizumab	Endometrial Cancer (not MSI-H or dMMR)	30% vs. 15% (chemo)	6.6 m vs. 3.8 m (chemo)	17.4 m vs. 12.0 m (chemo)	Makker et al., *SGO* 2021 (Abstract 11512)	July 21, 2021
Lenvatinib/ Pembrolizumab	RCC	71% vs. 36% (sunitinib)	29.9 m vs. 9.2 m (sunitinib)	NR	Motzer et al., *N Engl J Med* 2021	Aug 10, 2021

Vascular Normalization Pathways



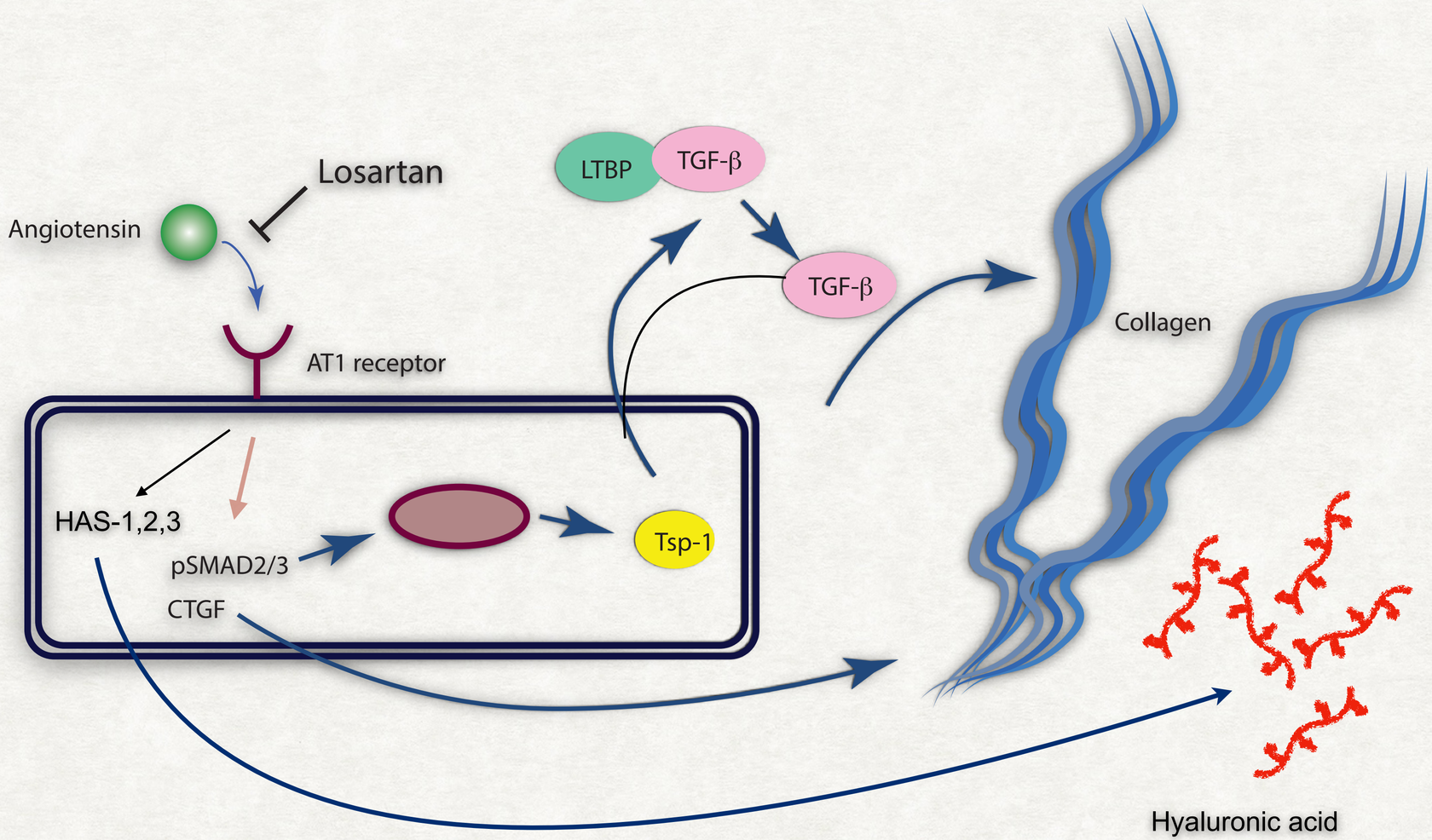
Adapted from Martin, Seano and Jain, *Annual Rev Physiology* (2019)

Two strategies to improve function of tumor blood vessels



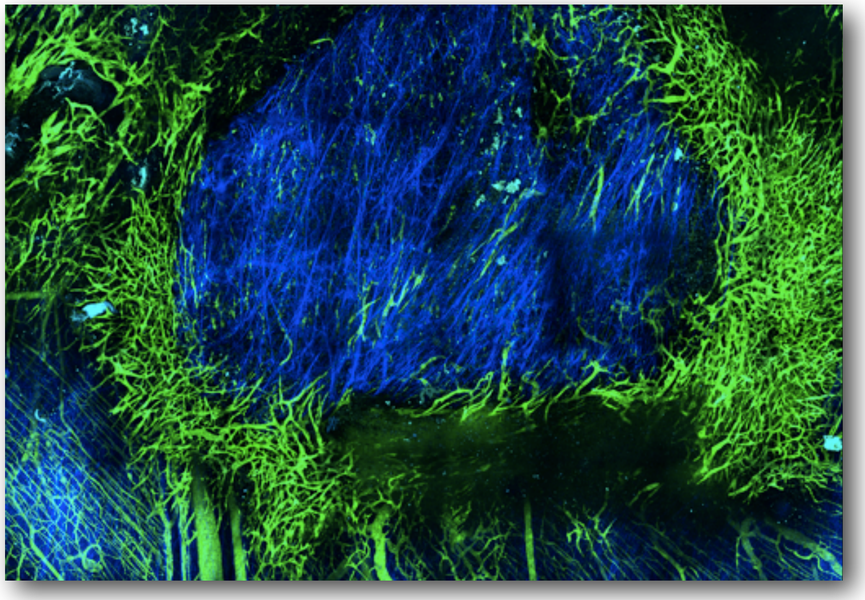
Jain, *Nature Medicine* (2001); *Science* (2005, 2019)

Losartan:
Angiotensin II receptor type I blocker

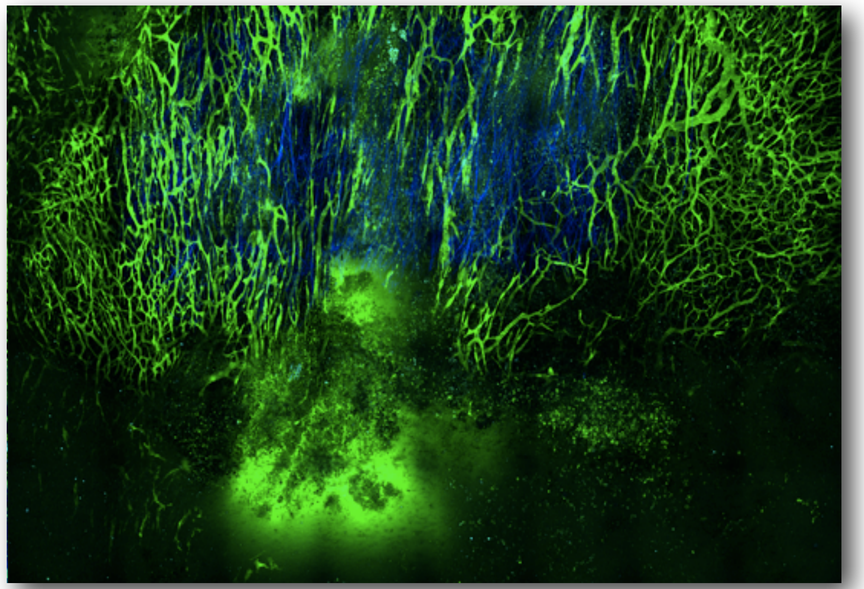


Chauhan, Martin *et al*, *Nature Comm* (2013)

Decreasing matrix increases tumor blood flow



Pre-Losartan



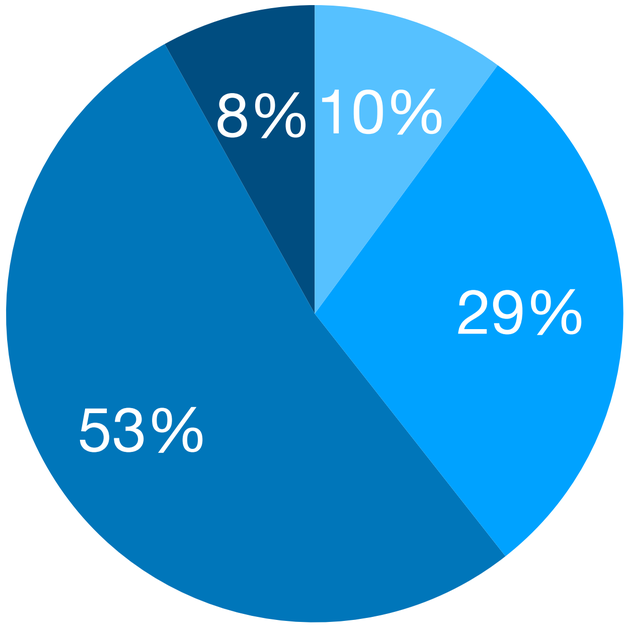
Post-Losartan

vessels matrix

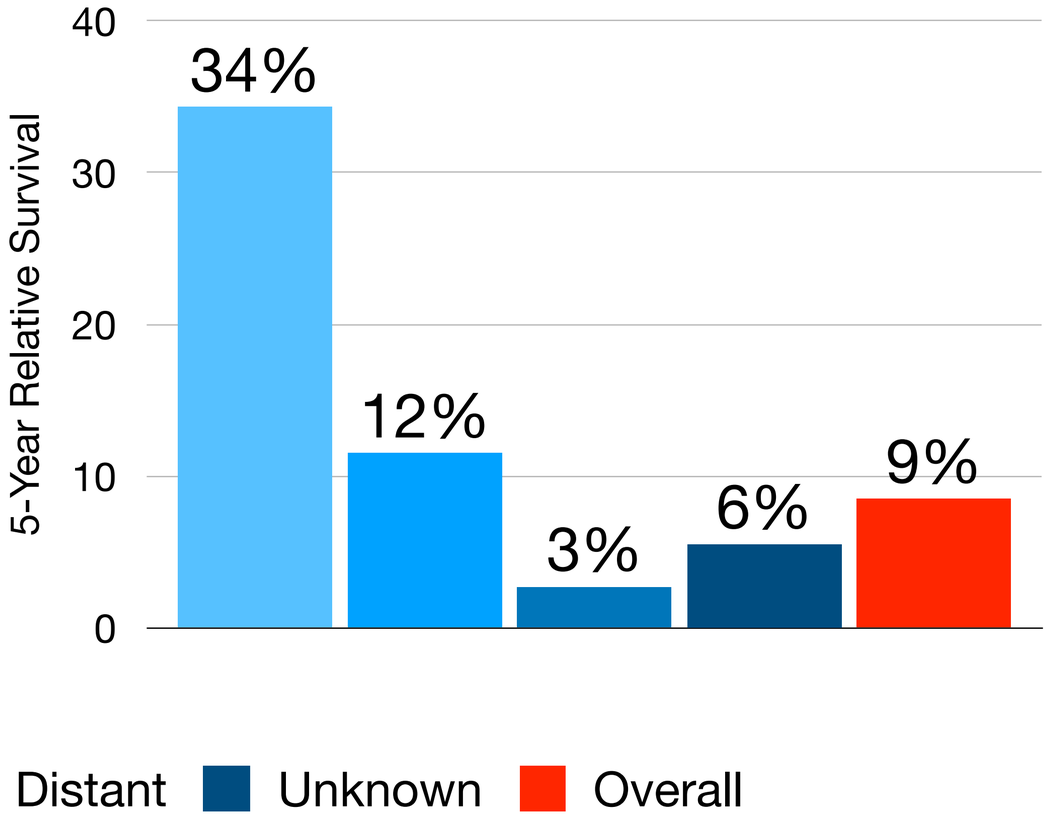
Chauhan, Martin *et al*, *Nature Comm* (2013)

Pancreatic Ductal Adenocarcinoma (PDAC)

% Cases by Stage

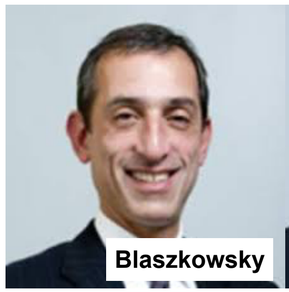


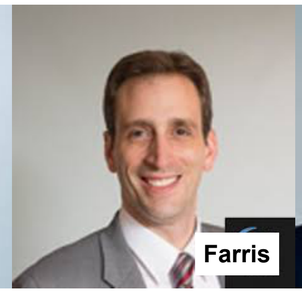
5-Year Survival Rates

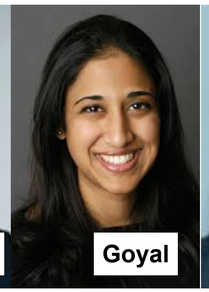


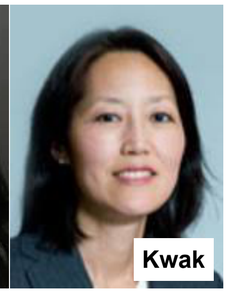
Reference: SEER 18 2008-2014, All Races, Both Sexes by SEER Summary Stage 2000

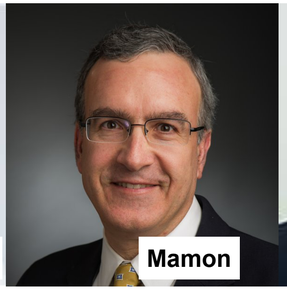
PDAC CLINICAL TEAM: Phase I/II Trial of Losartan, FOLFIRINOX and CRT in Locally Advanced Pancreatic Cancer (LAPC)

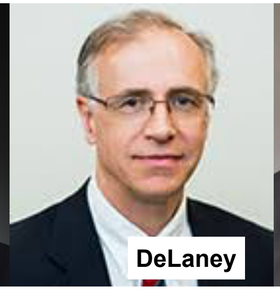


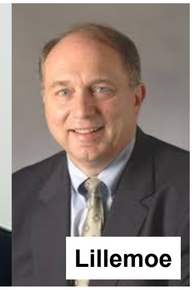




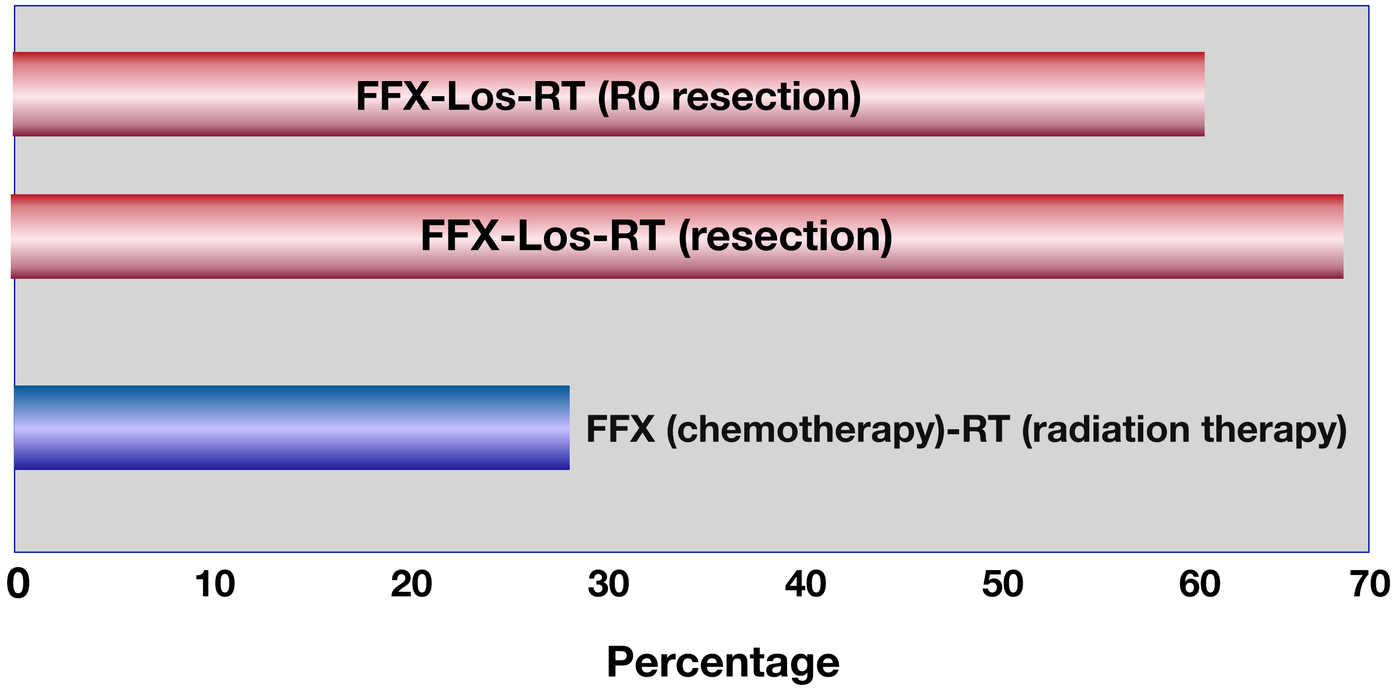


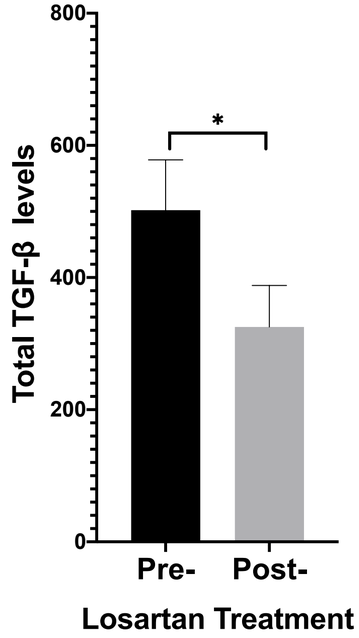






Unprecedented R0 Resection Rates in Locally-Advanced Pancreatic Cancer Patients

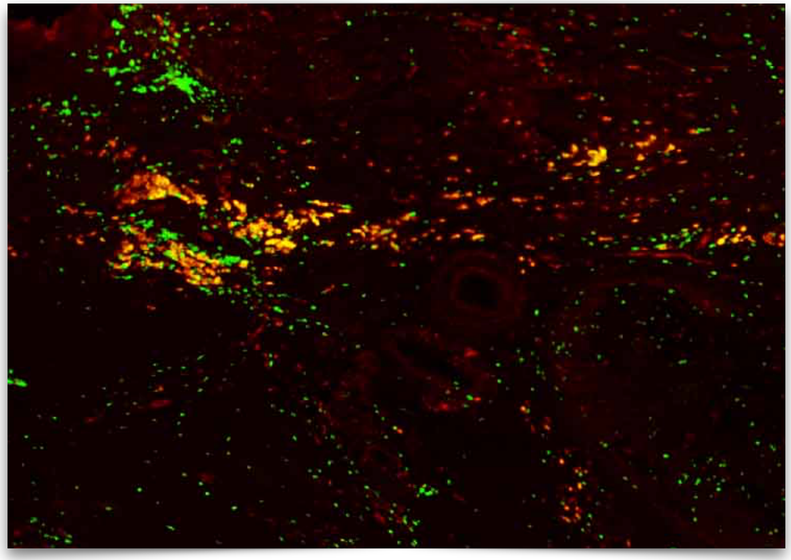




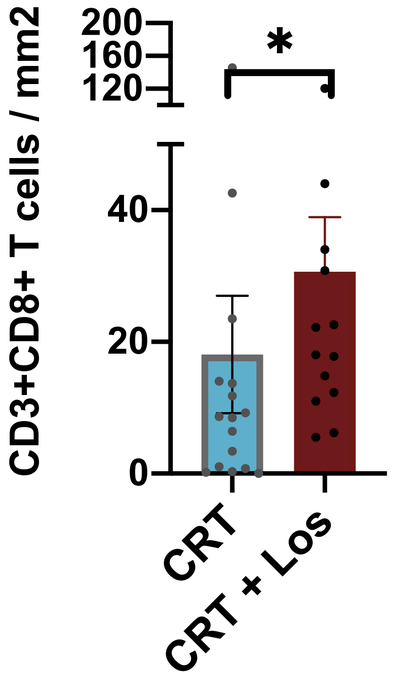
Murphy *et al.*, *JAMA Oncology* 2019

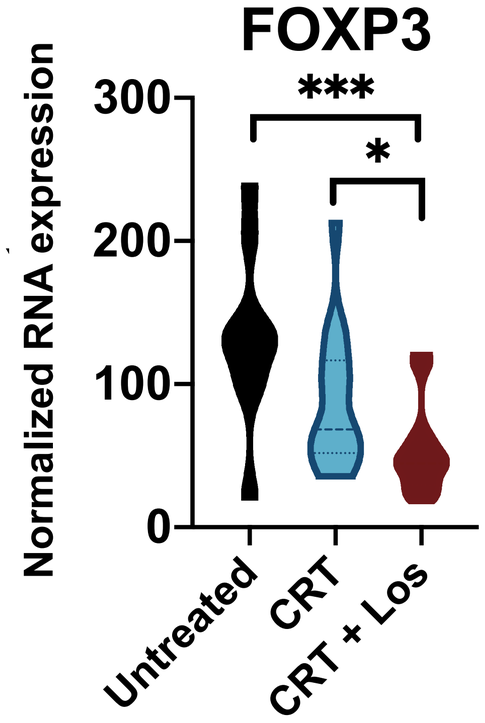
ChemoRadioTherapy (CRT) + losartan (L) increased CD3+CD8+ T cell infiltration and decreased FOXP3 compared to CRT

CRT+Losartan (CRTL)



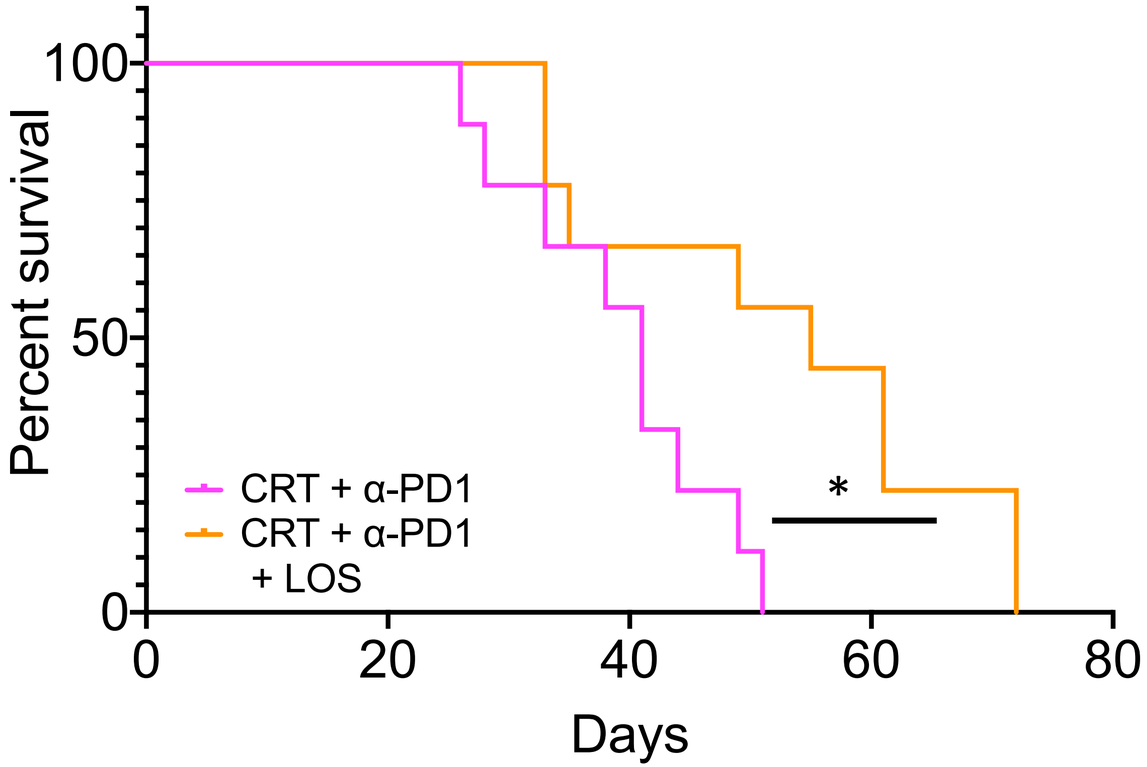
CD3 CD8 CD3CD8

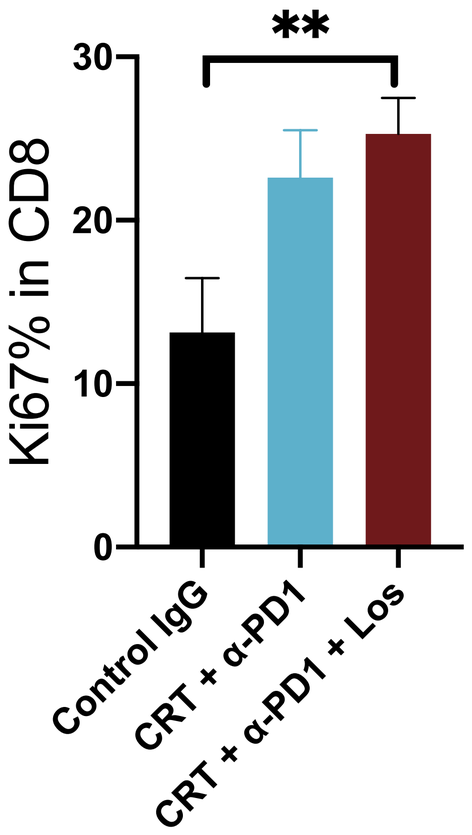




DO NOT POST (unpublished data)

Adding losartan to CRT + aPD1 increased survival and proliferation of CD8+ T cells in murine PDAC

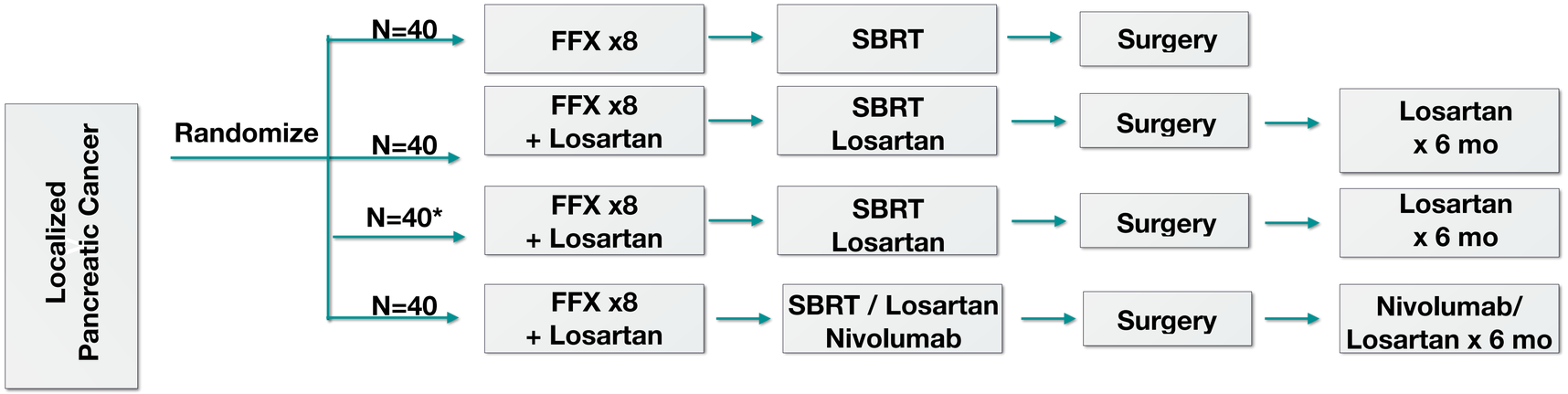




PDAC: KPC001; n = 8 animals/arm; Rx started on day 10 after implantation (tumors ~ 5 mm)

DO NOT POST (unpublished data)

Stand-Up-2-Cancer multi-institutional randomized clinical trial of losartan (160 Patients)



Stratify:
-borderline resectable
-locally advanced

(NCT03563248)
PI: Ted Hong

MGH 1811 · NWH · Dana-Farber Cancer Institute · The University of Texas MD Anderson Cancer Center, Making Cancer History® · NYU Langone Medical Center · Johns Hopkins University · Beth Israel Deaconess Medical Center · University of Colorado Cancer Center

RETROSPECTIVE ANALYSIS of ~11,000 MGB PATIENTS TREATED WITH ICBs

Patients treated with immune checkpoint inhibitor therapy at Mass General Brigham
22/7/2010 - 8/9/2020
N = 10,903

Excluded due to missing data on baseline medications
(n = 570)

N = 10,333

Were on any antihypertensive medication at baseline
(ACE, ARB, Beta Blockers, Calcium Channel Blockers, Alphaadrenergics, Alphablocker, Vasodilator, Thiazide diuretics)
N = 5,910

CASES
Were on a RAAS inhibitor at baseline
N = 3,426

CONTROLS
Were on a non RAAS inhibitor anti-hypertensive at baseline
N = 2,484

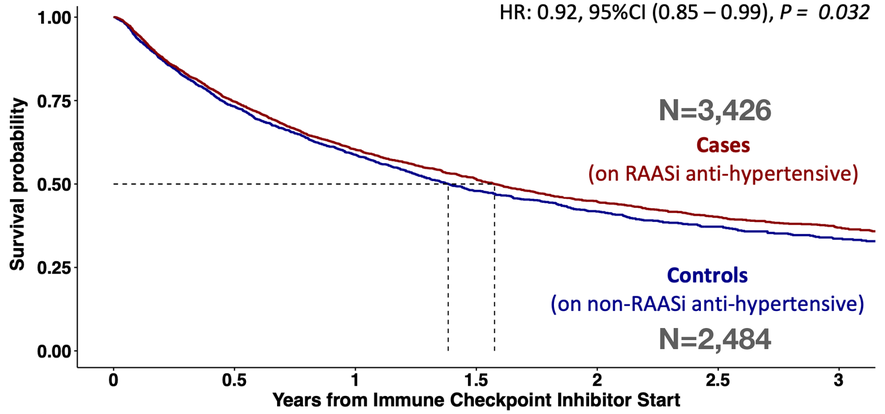
Were on *ARB* at baseline
N = 1,095

Were on *ACEI* at baseline
N = 2,331

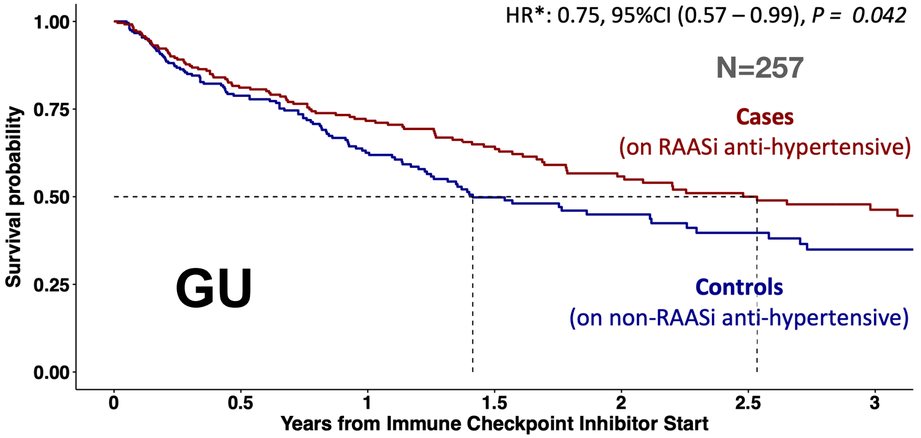
Cancer types	Median OS (months)	
	ARB/ACE-I Hypertensive	Non-ARB/ACE-I Hypertensive
GI	11.9	7.9
GU	28.2	17.0

Drobni et al, Europ J Cancer (2021)

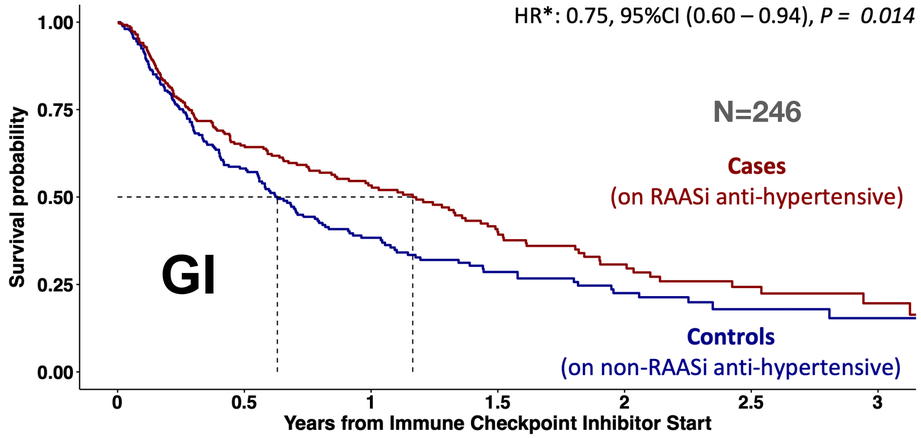
All cancer types



Genitourinary cancer



Gastrointestinal cancer



Critical Importance of Using Orthotopic Tumors in Immunology Studies

(*Ho et al, PNAS* 2021)

Examples of publications using ectopic (subcutaneous) tumors for immunotherapy studies

Authors	Immunotherapy	Models	Journal	Year	Citation
Banta KL, … Chiang Y, Mellman I.	ICB (PD-[L]1 and TIGIT)	CT26 / s.c.	***Immunity***	2022	55: 512–526
Spencer CN, … Trinchieri G, Daniel CR, Wargo JA.	ICB (PD-L1)	MC38 (BP*) / s.c.	***Science***	2021	374: 1632-1640
Wang Y, … Piva M, Moriceau G, Lo RS.	ICB (PD-[L]1, CTLA-4)	CT26, KP4662, melanomas / s.c.	***Cancer Cell***	2021	39: 11375-87
Hong A, … Lo RS.	ICB (PD-L1)	CT26, KPC	***Cancer Discovery***	2021	11: 715-35
Das K, … Derouazi M, Wollmann G.	Oncolytic vaccine	MC38 (E.G7#, B16) / s.c.	***Nature Communications***	2021	12: 5195
Wang Y, … Hastings WD, Goldoni S.	ICB (PD-1)	MC38 (CT26, 4T1) / s.c.	***Scientific Report***	2021	11: 1399
Baharom F, … Seder RS.	SNP vaccine	MC38 / s.c.	***Nature Immunology***	2021	22: 41-52
Jiao S, ... Sharma P.	ICB (PD-1, CTLA-4)	Myc-CaP / s.c., bone	***Cell***	2019	179: 1177-90
Lau J, … Kim M, Schmidt M.	PD-L1 deficiency	MC38 (CT26) / s.c.	***Nature Communications***	2017	8: 14572
Iida N, … Trinchieri G, Goldszmid RS.	CpG-oligonucleotide immunotherapy	MC38 (EL4) / s.c.	***Science***	2013	342: 967-70

**BP, BRAF^{V600E}/PTEN$^{-/-}$; #Lymphoma*

MEK inhibitor + aPDL1 effective in SQ model of CRC but failed in a phase III trial

Immunity
Article

MAP Kinase Inhibition Promotes T Cell and Anti-tumor Activity in Combination with PD-L1 Checkpoint Blockade

Peter J.R. Ebert,[1] Jeanne Cheung,[1] Yagai Yang,[1] Erin McNamara,[1] Rebecca Hong,[1] Marina Moskalenko,[1] Stephen E. Gould,[1] Heather Maecker,[1,2] Bryan A. Irving,[1,3] Jeong M. Kim,[1] Marcia Belvin,[1] and Ira Mellman[1,*]
[1]Genentech, 1 DNA Way, South San Francisco, CA 94080, USA
[2]Present address: Gilead, Foster City, CA 94404, USA
[3]Present address: Cytomics Therapeutics, South San Francisco, CA 94080, USA
*Correspondence: mellman.ira@gene.com
http://dx.doi.org/10.1016/j.immuni.2016.01.024

Highlights

- Pharmacologic inhibition of MEK potentiates rather than hinders anti-tumor T cells
- MEK inhibitors nonetheless suppress anti-tumor priming in lymph nodes in vivo
- MEK inhibitors potentiate anti-tumor T cells by impairing TCR-driven apoptosis
- MEK inhibition combines with anti-PD-L1 treatment to yield durable tumor regression

Immunity *44*, 609–621, March 15, 2016

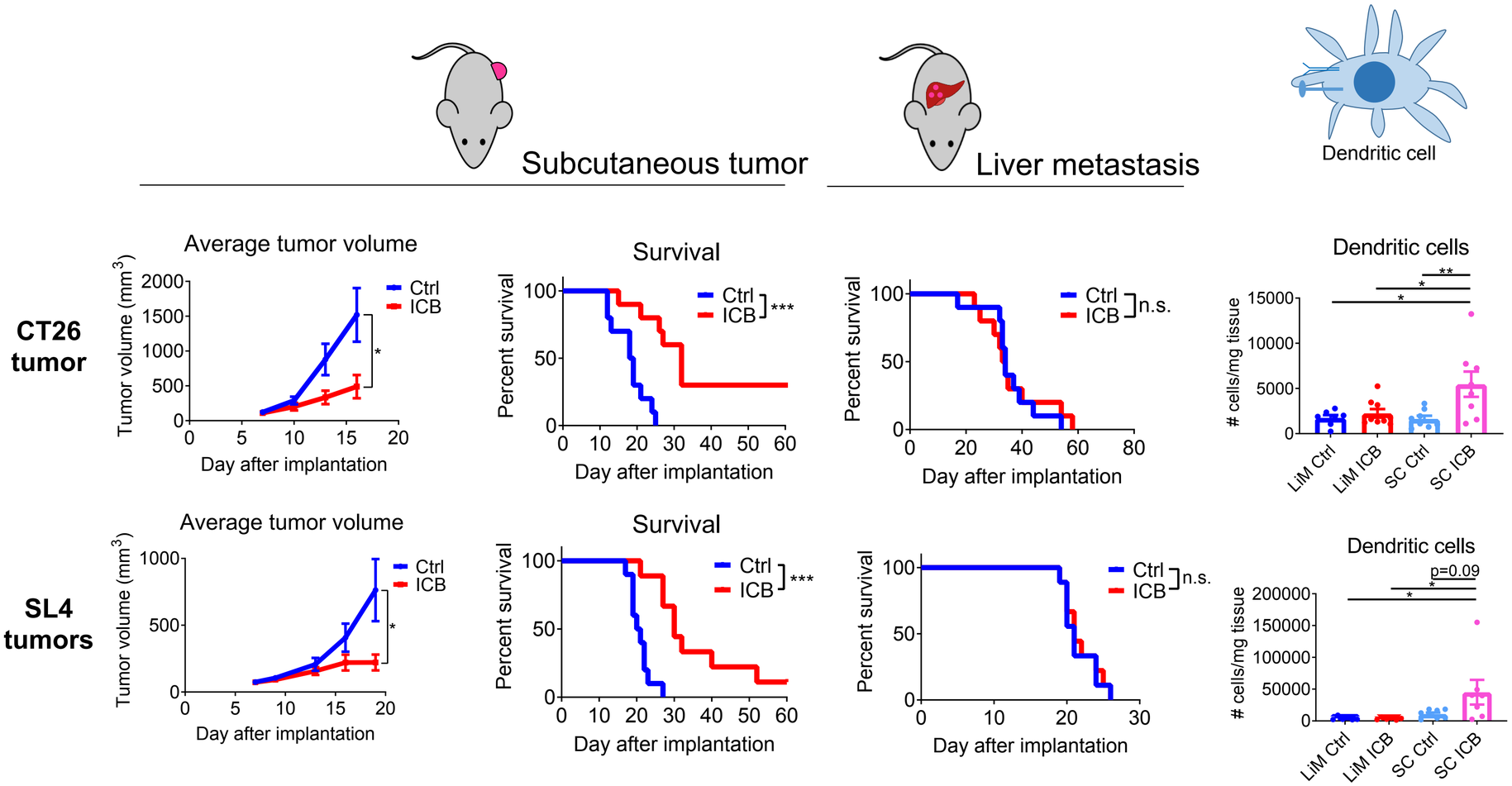
Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial

Cathy Eng [1], Tae Won Kim [2], Johanna Bendell [3], Guillem Argilés [4], Niall C Tebbutt [5], Maria Di Bartolomeo [6], Alfredo Falcone [7], Marwan Fakih [8], Mark Kozloff [9], Neil H Segal [10], Alberto Sobrero [11], Yibing Yan [12], Ilsung Chang [12], Anne Uyei [12], Louise Roberts [12], Fortunato Ciardiello [13], IMblaze370 Investigators

Conclusions: IMblaze370 did not meet its primary endpoint; atezolizumab+cobimetinib and atezolizumab monotherapy did not demonstrate statistically significant prolonged OS benefit vs regorafenib in the ITT population. PFS and ORR were similar across treatment arms. No new safety signals were observed and the safety profiles of atezolizumab+cobimetinib combination and atezolizumab monotherapy were consistent with previous findings.

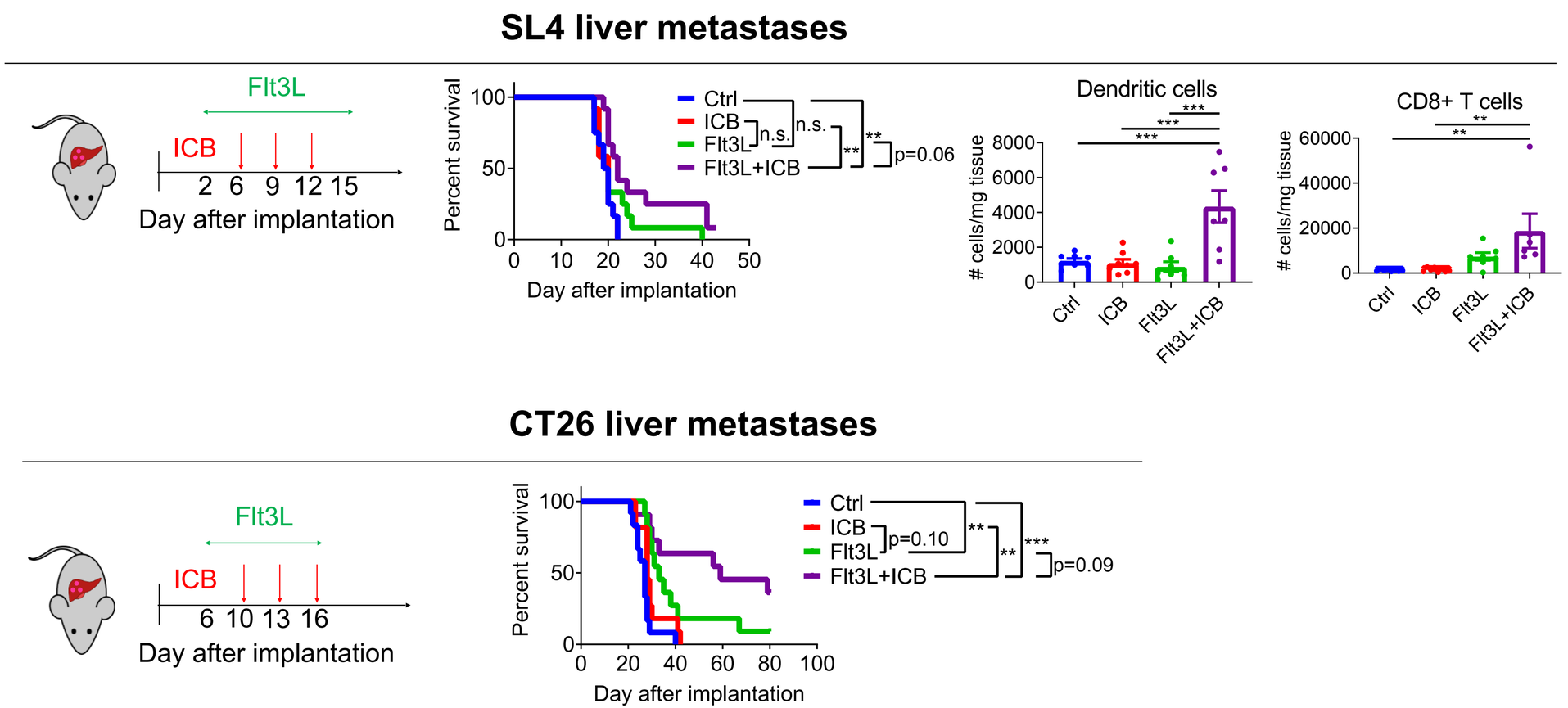
Lancet Oncology Volume 20, Issue 6, June 2019, Pages 849-861

ICB is efficacious in pMMR CRC grown SQ but not in liver mets from CRC



Ho et al., *PNAS (2021)*

Dendritic cell infiltration into pMMR CRC liver mets improves ICB efficacy



Ho et al., *PNAS (2021)*

Normalization strategies can also benefit treatment of a number of diseases characterized by abnormal vessels that afflict 500 million people worldwide

(***Nature Reviews Drug Discovery*** **2011)**

Example #1

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

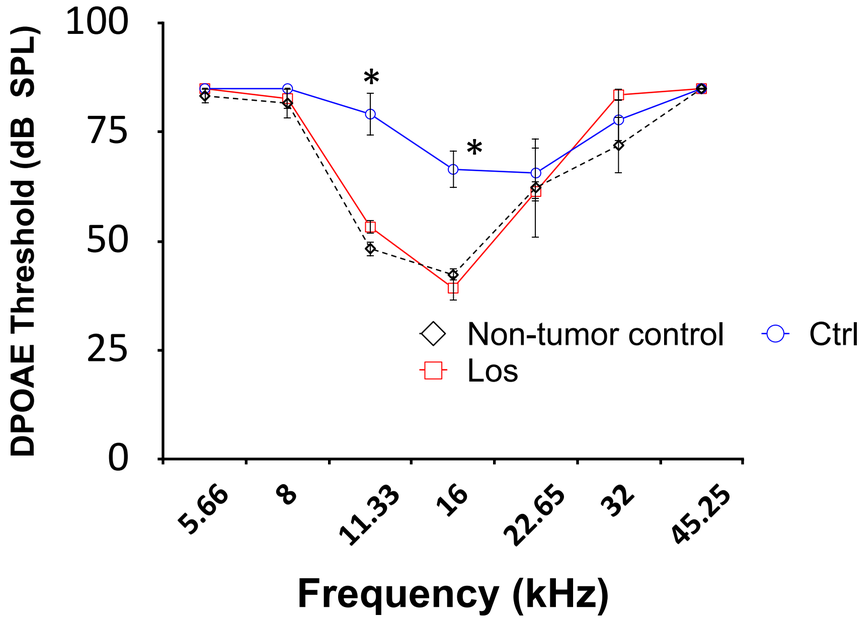
Hearing Improvement after Bevacizumab in Patients with Neurofibromatosis Type 2

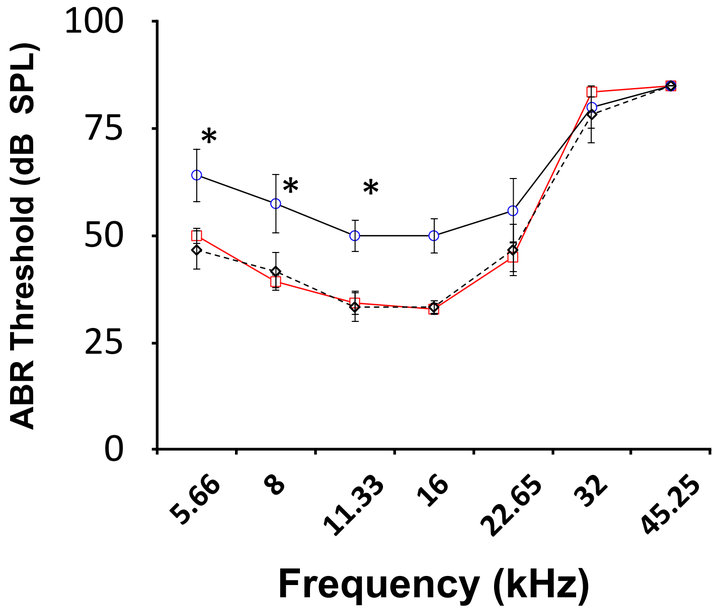
Scott R. Plotkin, M.D., Ph.D., Anat O. Stemmer-Rachamimov, M.D., Fred G. Barker II, M.D., Chris Halpin, Ph.D., Timothy P. Padera, Ph.D., Alex Tyrrell, Ph.D., A. Gregory Sorensen, M.D., Rakesh K. Jain, Ph.D., and Emmanuelle di Tomaso, Ph.D.

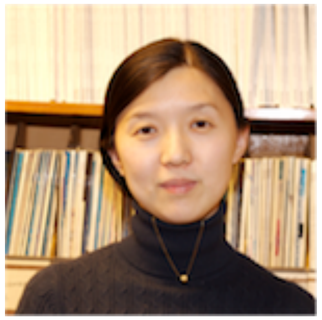
N Engl J Med 2009;361:358-67.

Example #2

NF2 Vestibular Schwannomas:
Losartan treatment restores hearing







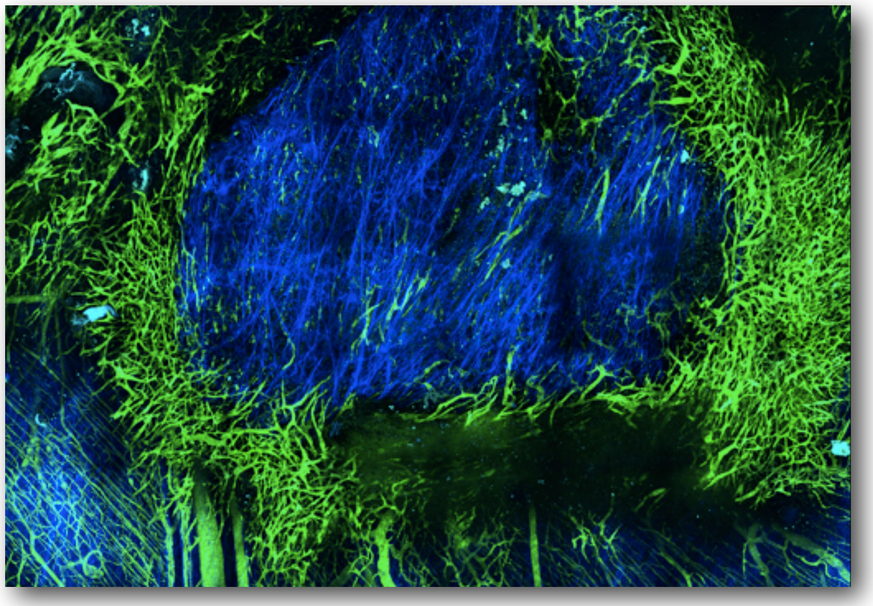
Lei Xu, MD, PhD

(NCT01199978)

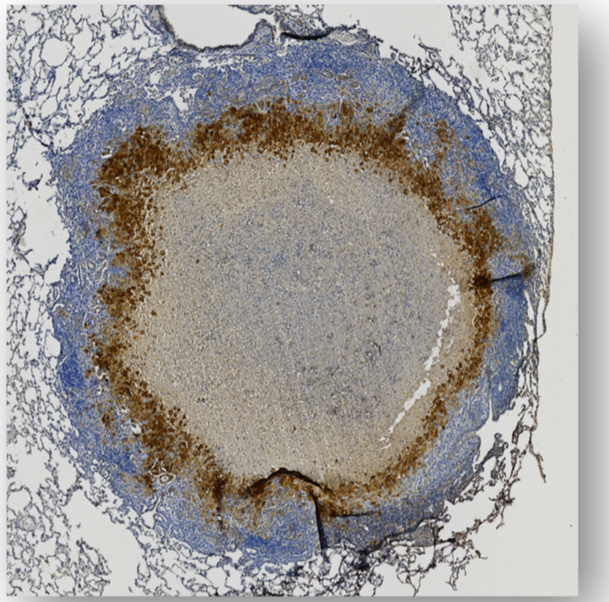
Science Translational Medicine (2021)

Example #2 Losartan increases drug delivery in TB

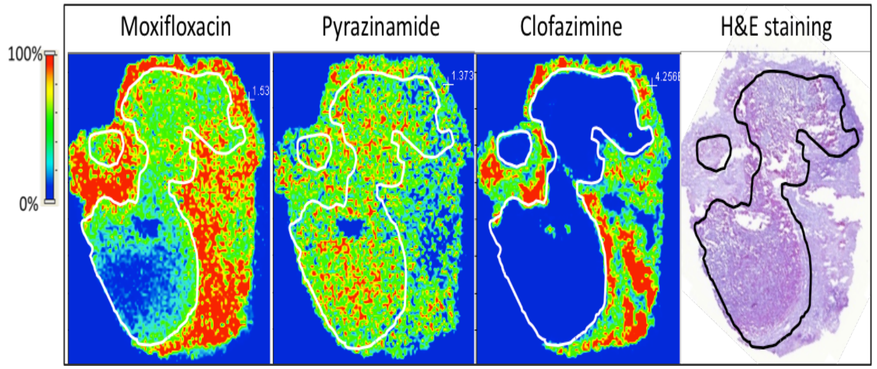
Tumor

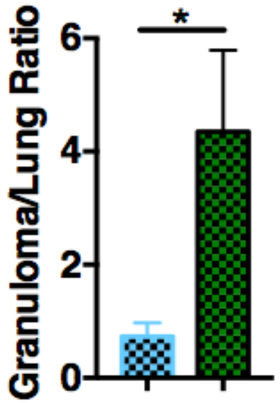


TB Granuloma



Drug delivery





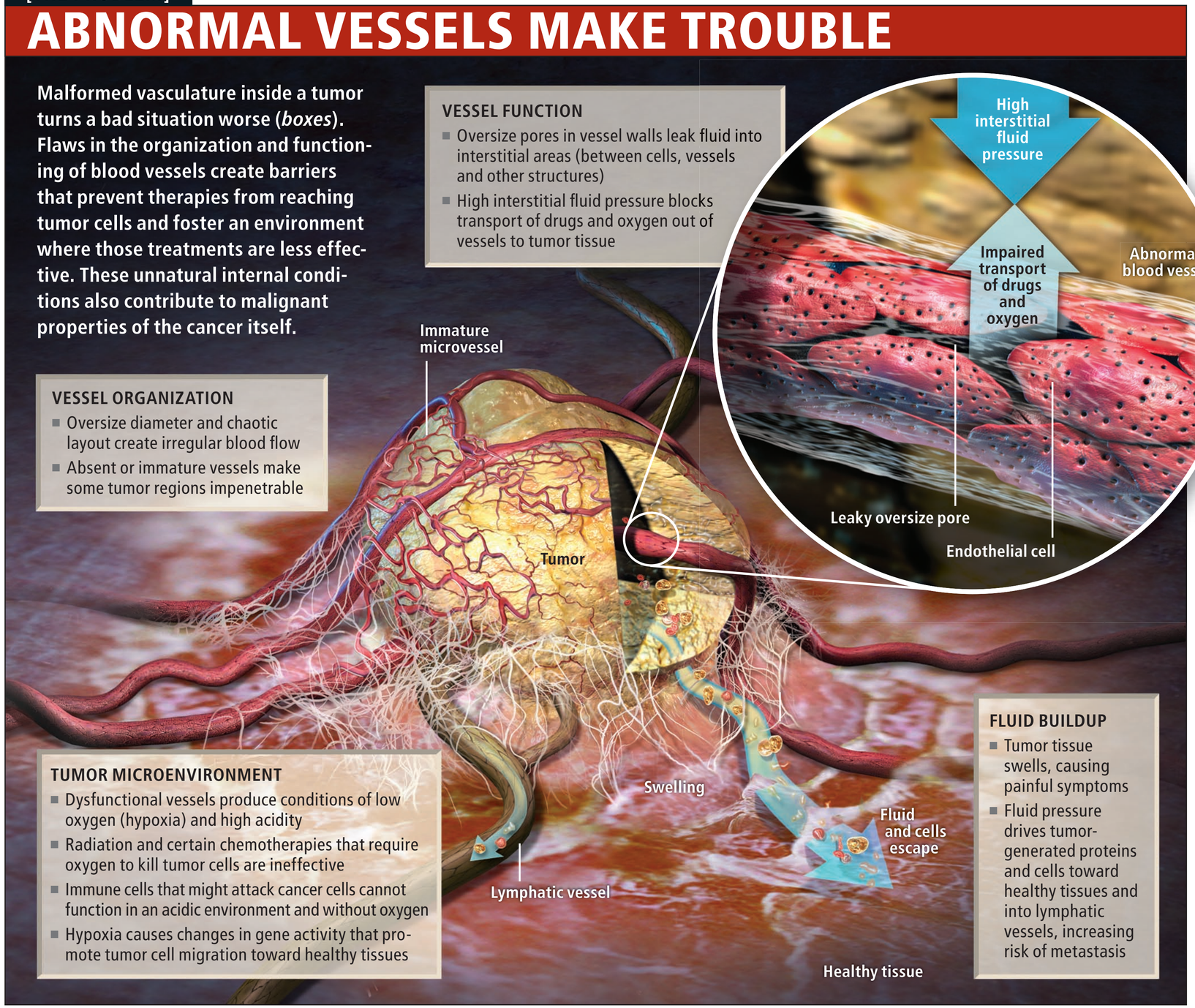
Bedaquiline (BDQ) Delivery

DO NOT POST (unpublished data)

[THE PROBLEM]

ABNORMAL VESSELS MAKE TROUBLE

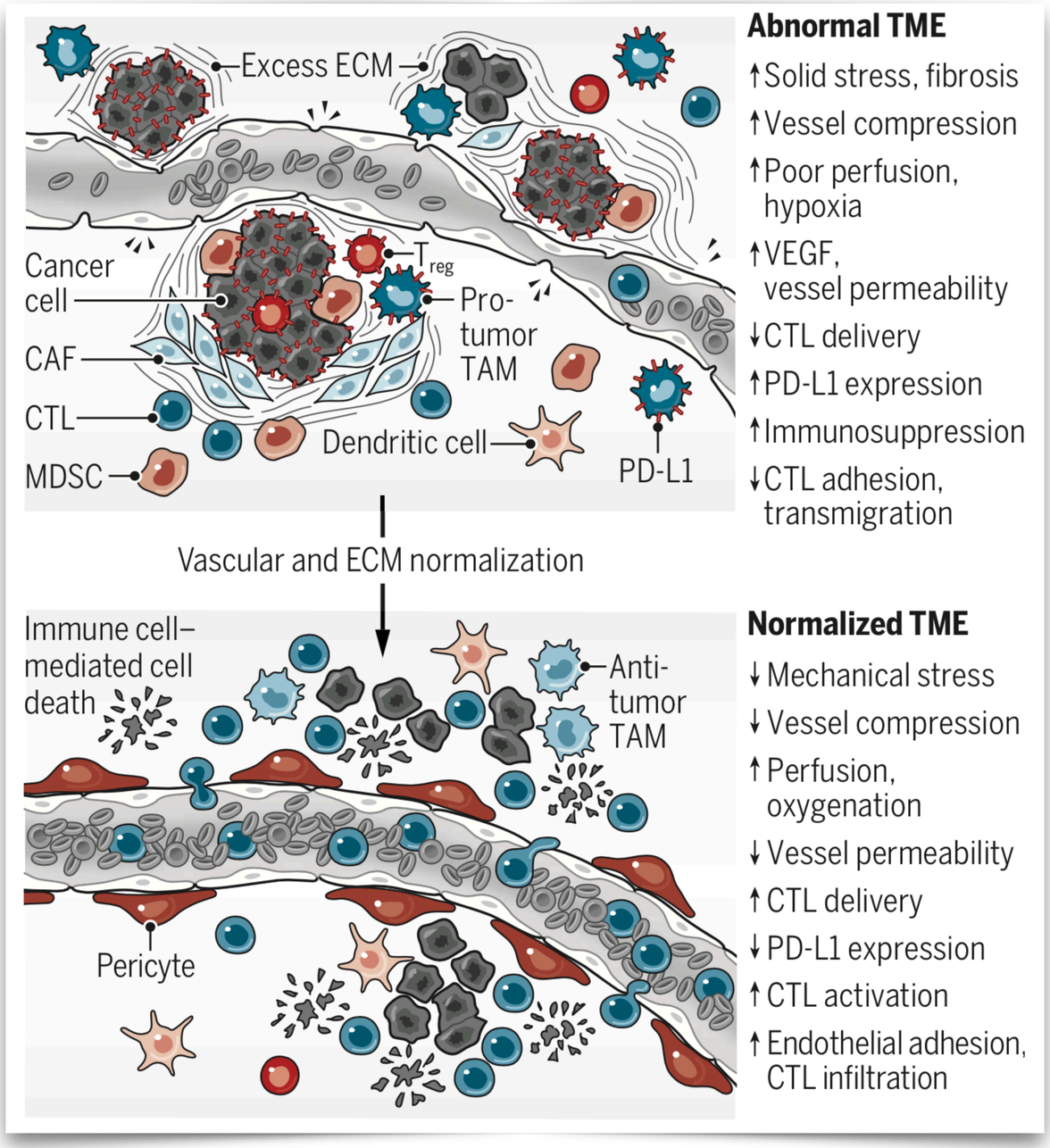
Malformed vasculature inside a tumor turns a bad situation worse (*boxes*). Flaws in the organization and functioning of blood vessels create barriers that prevent therapies from reaching tumor cells and foster an environment where those treatments are less effective. These unnatural internal conditions also contribute to malignant properties of the cancer itself.



Jain, Scientific American, 2008

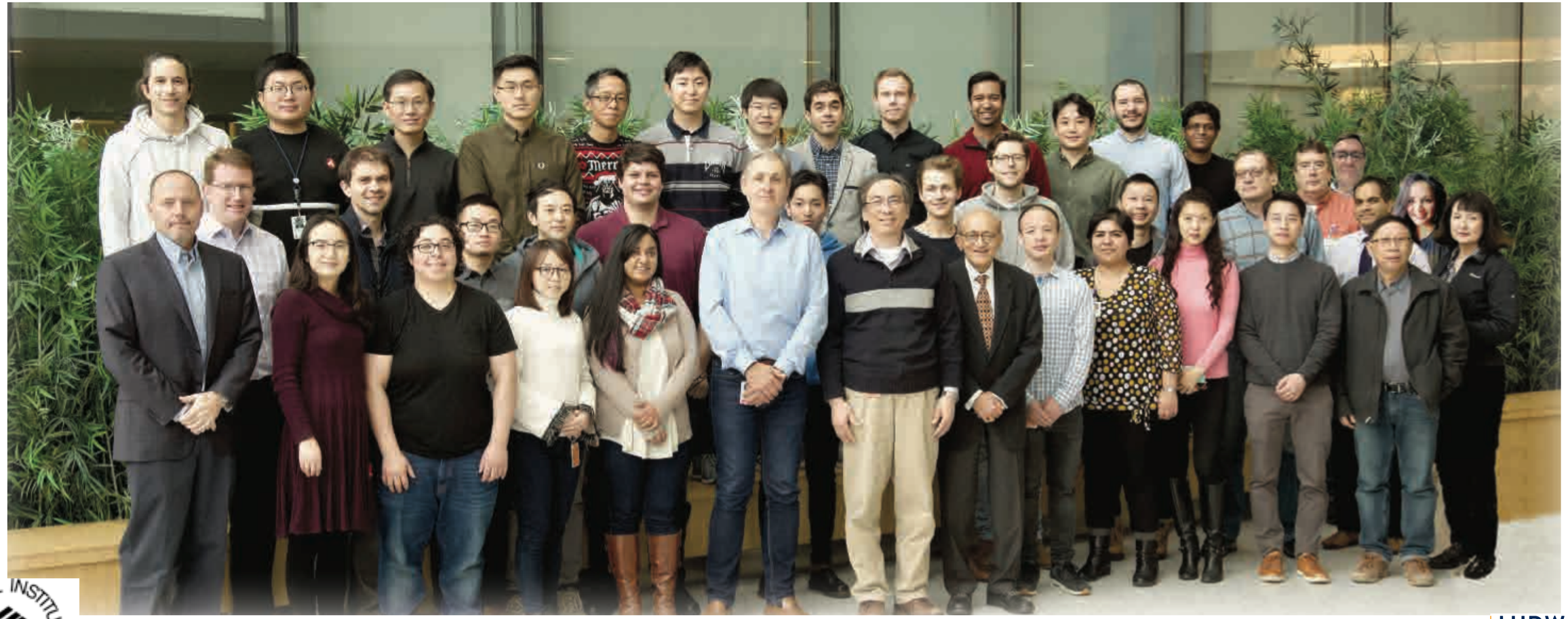
KEITH KASNOT

OUR SOLUTION



Munn and Jain, *Science* (2019)

Acknowledgments



Steele Laboratories: Pre-COVID Days!

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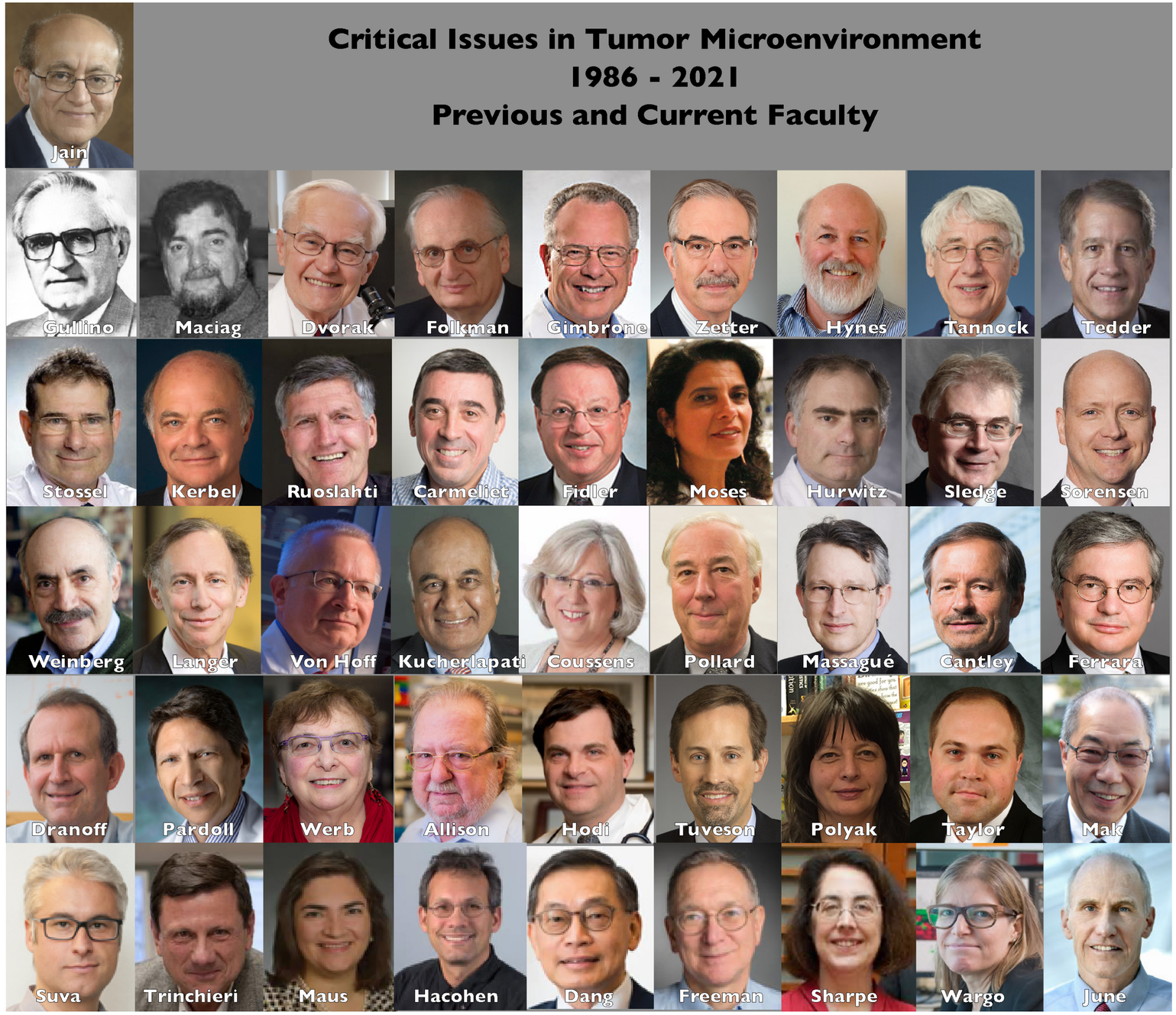
SUSAN G. KOMEN FOR THE CURE

Critical Issues in Tumor Microenvironment
1986 - 2021
Previous and Current Faculty



Critical Issues in Tumor Microenvironment, Angiogenesis, Metastasis & Immunology

October 24– 27, 2022

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George Coukos, M.D., Ph.D
Lisa Coussens, Ph.D.
Nir Hacohen, Ph.D.
Rakesh K. Jain, Ph.D.
Carl June, M.D.
Arlene H. Sharpe, M.D., Ph.D.
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Mario Suva, M.D., Ph.D.
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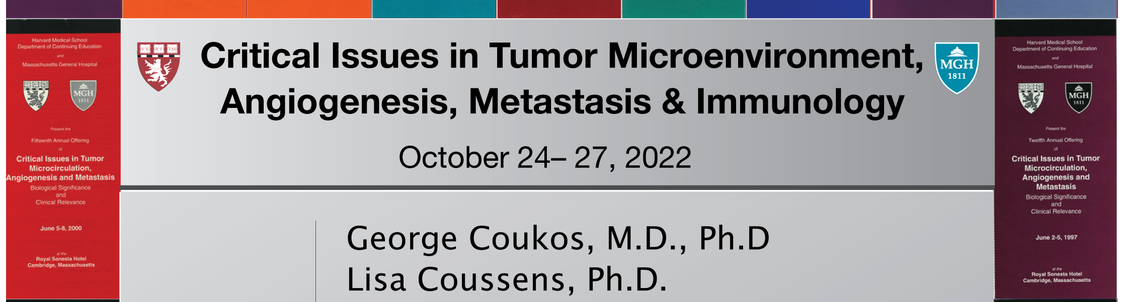
David Tuveson, M.D., Ph.D.
Chi Van Dang, M.D., Ph.D.
Matthew Vander Heiden, M.D., Ph.D.
Jennifer Wargo, M.D.
Robert Weinberg, Ph.D.

http://steele.mgh.harvard.edu/tumorcourse



Postdoctoral Fellows and Junior Faculty

Ager E 2011-13
Alexandrakis G 2001-04
Amoozgar Z 2015-
Andersson P 2017-
Askoxylakis V 2013-16
Babykutty S 2013-15
Badeaux M 2012-
Batista Ana 2010-15
Baxter L 1991-98
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Bhaumik J 2010-11
Bockhorn M 2000-02
Booth M 2003-06
Boucher Y 1988-98
Brown E 1999-05
Burton K 1999-01
Campbell R 1999-02
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Chauhan V 2012-
Chatterjee S 2014-

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Rakesh K. Jain, Ph.D.
Andrew Werk Cook Professor of Radiation Oncology (Tumor Biology)
Director, Edwin L. Steele Laboratories

Postdoctoral Opportunities

TUMOR MICROENVIRONMENT, VASCULAR BIOLOGY, MATRIX BIOLOGY, IMMUNOLOGY, MOLECULAR & CELLULAR BIOLOGY, METABOLISM, INTRAVITAL MICROSCOPY and BIOMEDICAL ENGINEERING

The **JAIN LAB** (https://steelelabs.mgh.harvard.edu/rakesh_jain/pi_bio) in the STEELE LABORATORIES OF TUMOR BIOLOGY (https://steelelabs.mgh.harvard.edu) at MGH/Harvard Medical School invites applications for Postdoctoral Research Fellow positions.

Requirements: A PhD or MD/PhD is required. To apply, please send your CV, a career statement, a summary of your most significant research accomplishments (300 words) and the contact information of three references to: Steele Labs Recruiting jobs@steele.mgh.harvard.edu.