Society for Immunotherapy of Cancer

Direction of the Field: The Future of Cancer Immunotherapy

February 24, 2021

SITC Winter School

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Disclosures

- Nektar Therapeutics – Advisory Board/Honorarium
- By virtue of discussing the future, I will be discussing non-FDA approved indications during my presentation.

Diagnostics

Therapeutics

Improvements in Staging and Immunotherapy Biomarkers

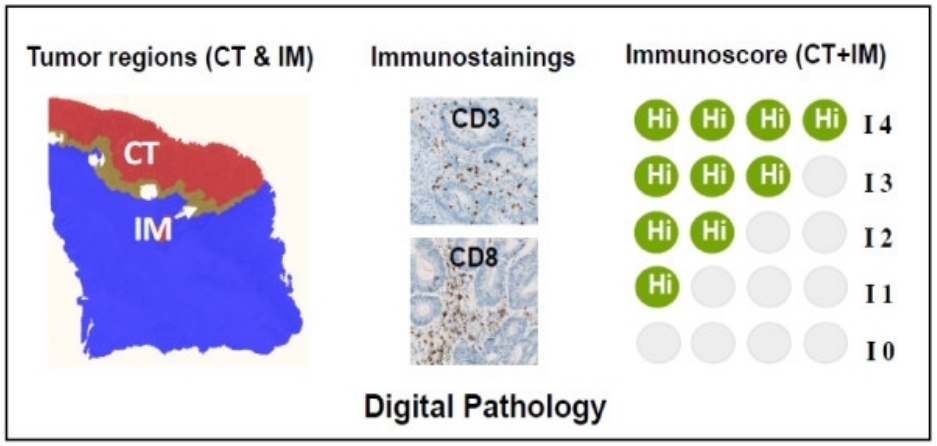
- Immunoscore
  - CD3, CD8, T cell memory
  - PD-L1, TMB, GEP and others
- Next generation sequencing
  - MSI-high, MMR defects, etc.
- Gut microbiome
- Tumor microenvironment/metabolomics

Current standard diagnostics

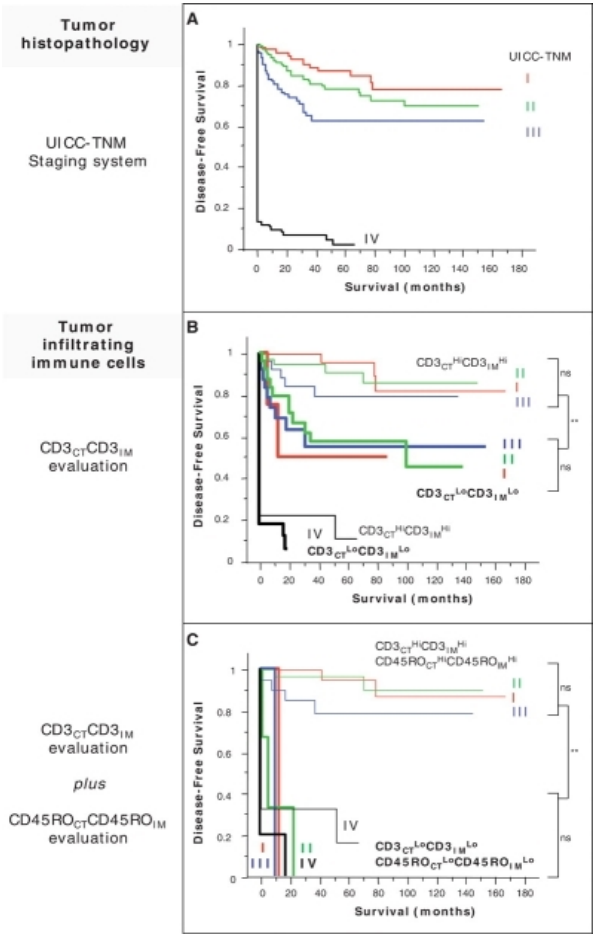
- Histopathology
- Flow cytometry
- Immunohistochemistry
- Cytogenetics
- Molecular studies: RT-PCR/FISH

- Next generation sequencing (NGS) panels
  - Identify fusions without having to know fusion partners
  - Identify pathways for targeting by FDA-approved drugs, on- or off-label

Immunoscore will become part of standard pathologic reports for all tumors, used as a biomarker for responses and correlate with survival



CT = center of tumor; IM = invasive margin; Galon et al. 2012 J Transl Med



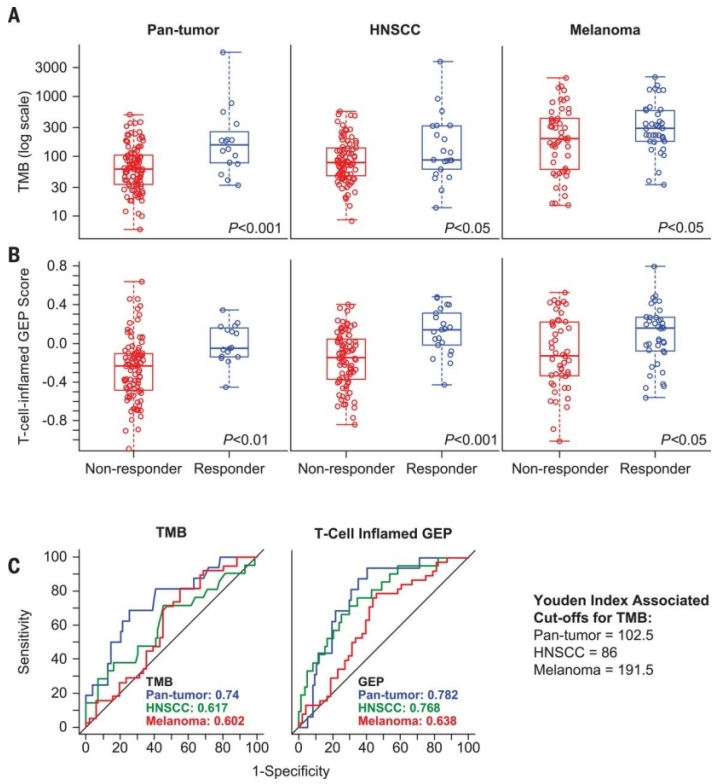
Galon et al. 2006 Science

Cancers where immunoscore correlates with outcome	
Adult tumors	Hepatocellular carcinoma
Colorectal cancer	Breast cancer
Melanoma	Ovarian cancer
Renal cell carcinoma	Spinal chordoma
Non-small cell lung cancer	Cholangiocarcinoma
Head and neck cancer	**Pediatric tumors**
Esophageal/Gastric cancer	Neuroblastoma
Bladder cancer	Osteosarcoma`

Using assays together increases positive predictive value of responding to anti-PD(L)1 therapy

- PD-L1 immunohistochemistry
- Tumor mutation burden (TMB)
- Gene expression profiling (GEP)
- Multiplex immunohistochemistry/immunofluorescence (mIHC/IF)

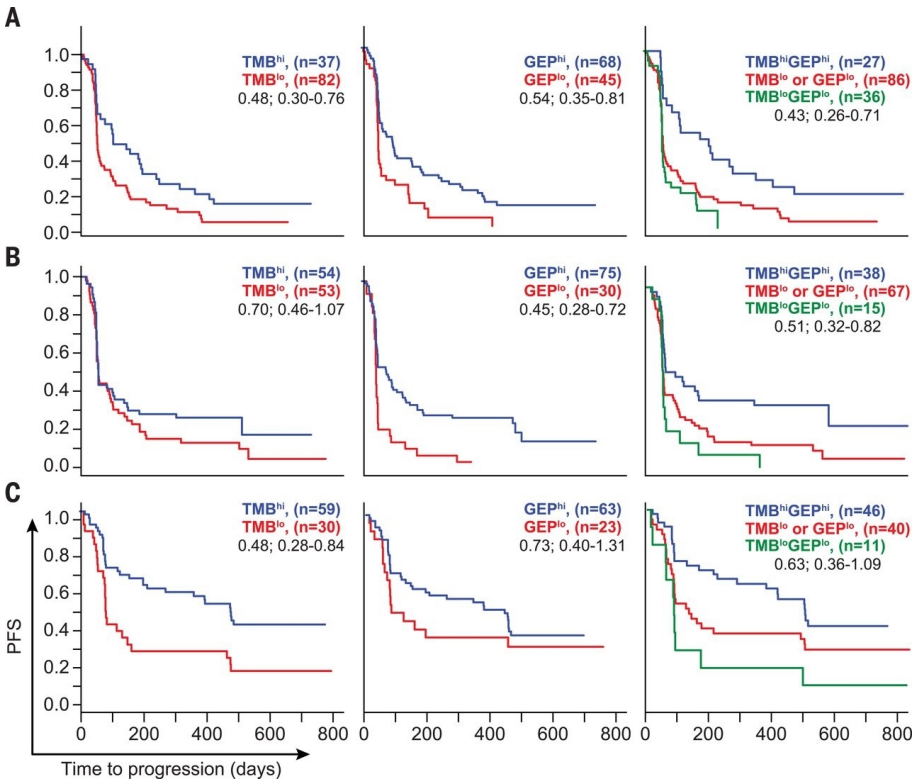
Individual association of TMB or T cell–inflamed GEP with anti–PD-1 response across multiple patient cohorts



Pan-tumor

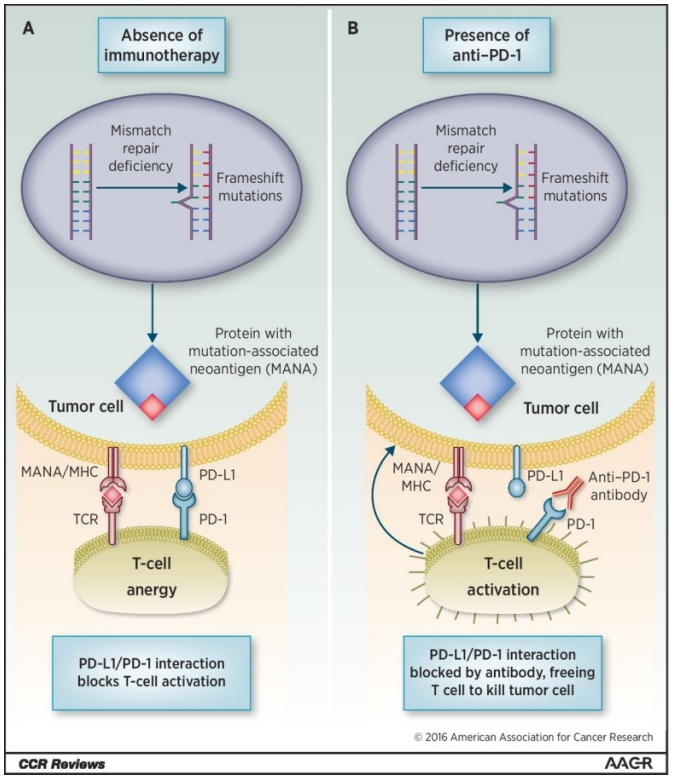
HNSCC

Melanoma



Razvan Cristescu et al. Science 2018;362:eaar3593

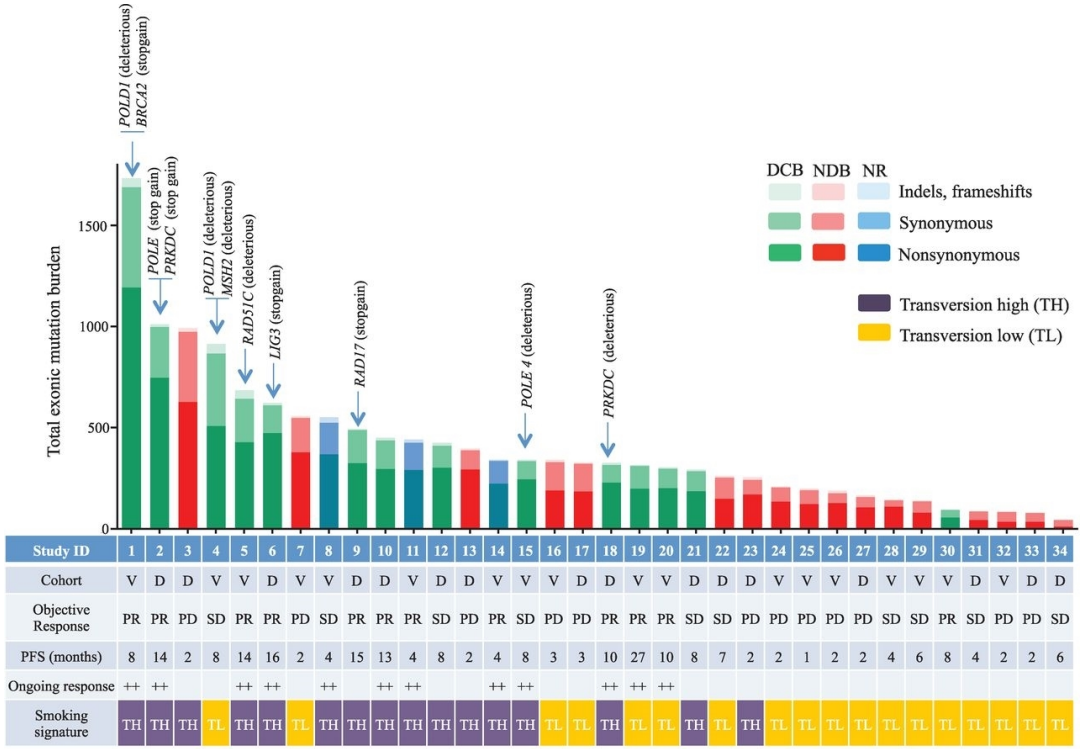
Relationship between MSI status and immunologic response.



Jonathan C. Dudley et al. Clin Cancer Res 2016;22:813-820

Better intersection of NGS with predicting immunotherapy responses

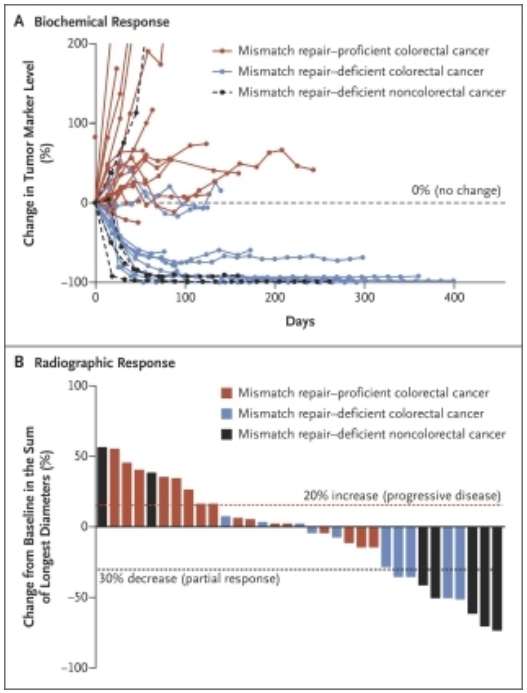
Tumor mutational burden



Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Cohort	V	D	D	V	V	D	V	V	D	D	V	D	D	V	V	V	D	D	V	V	D	D	D	V	V	V	D	V	V	V	D	V	D	D
Objective Response	PR	PR	PD	SD	PR	PR	PD	SD	PR	PR	PR	SD	PD	PR	SD	PD	PD	PR	PR	PR	SD	SD	PD	PD	PD	PD	PD	SD	SD	PR	SD	PD	PD	SD
PFS (months)	8	14	2	8	14	16	2	4	15	13	4	8	2	4	8	3	3	10	27	10	8	7	2	2	1	2	2	4	6	8	4	2	2	6
Ongoing response	++	++			++	++		++		++	++			++	++			++	++	++														
Smoking signature	TH	TH	TH	TL	TH	TH	TL	TH	TH	TH	TH	TH	TH	TH	TH	TL	TL	TH	TL	TL	TH	TL	TH	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL

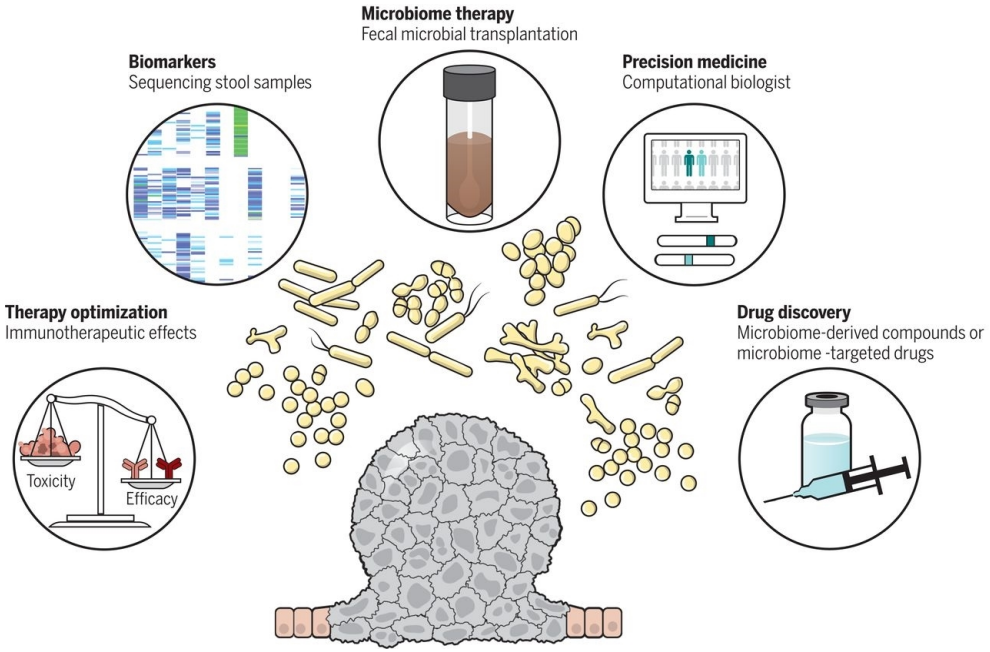
Rizvi et al. 2016 Science

Mismatch repair defects

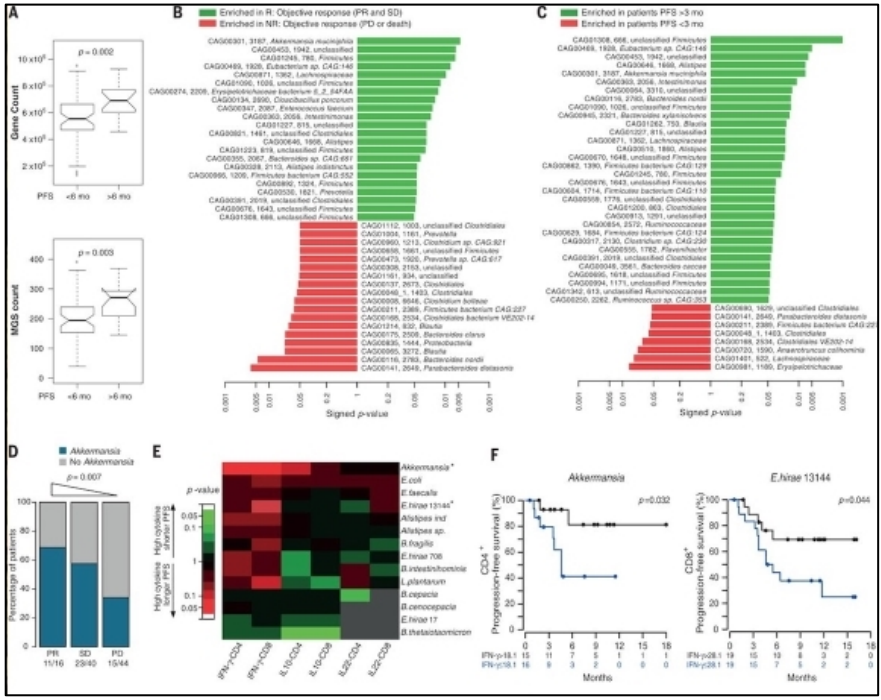


Le et al. 2015 New Engl J Med

Query and modulate the gut microbiome to improve responses to immunotherapy

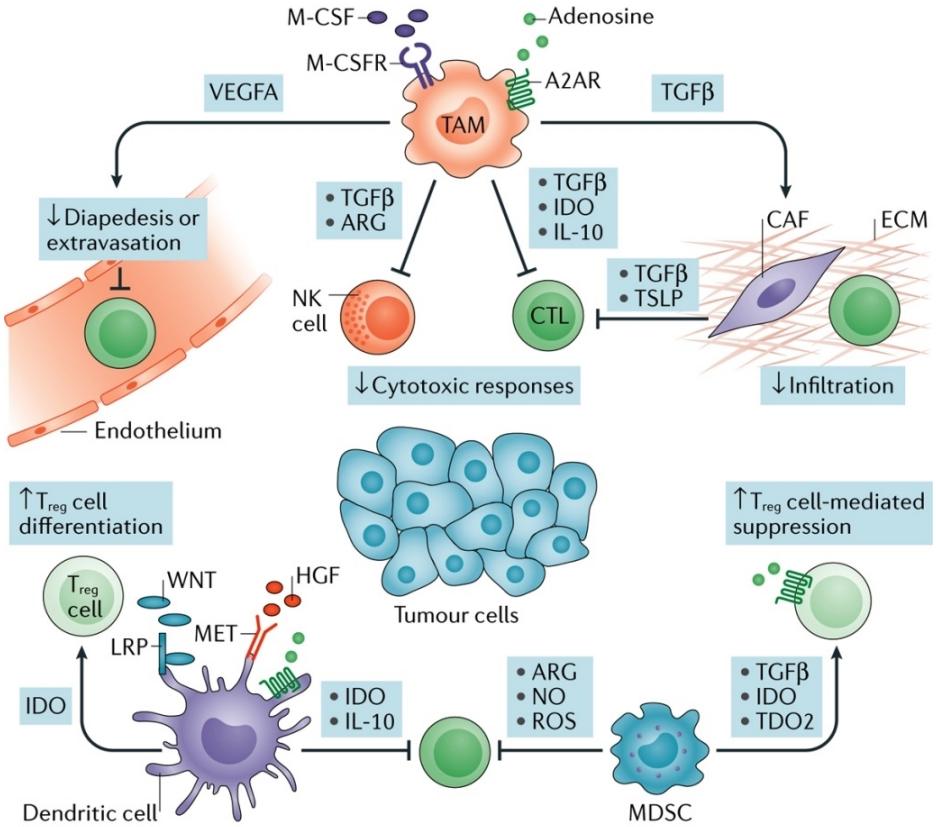


Zitvogel et al. 2018 Science



Routy et al. 2018 Science

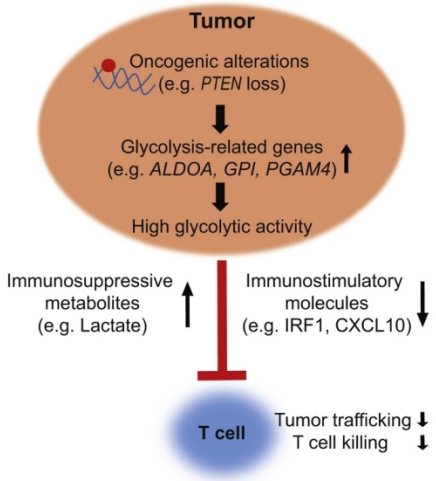
Tumor microenvironment is immuno-suppressive due to multiple cells and cytokines



Nature Reviews | Cancer

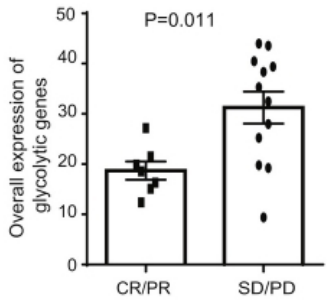
Gotwals et al. 2017

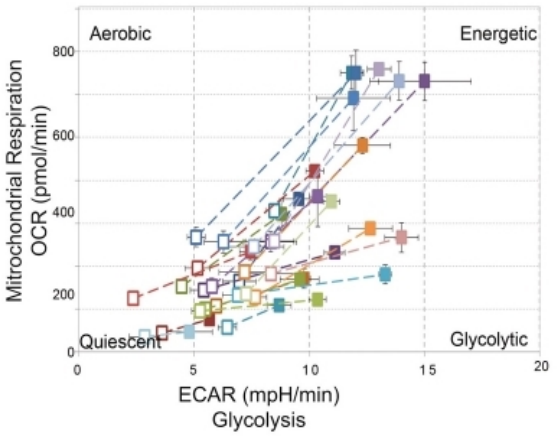
Manipulate the tumor metabolic environment to enhance immunotherapy responses



A

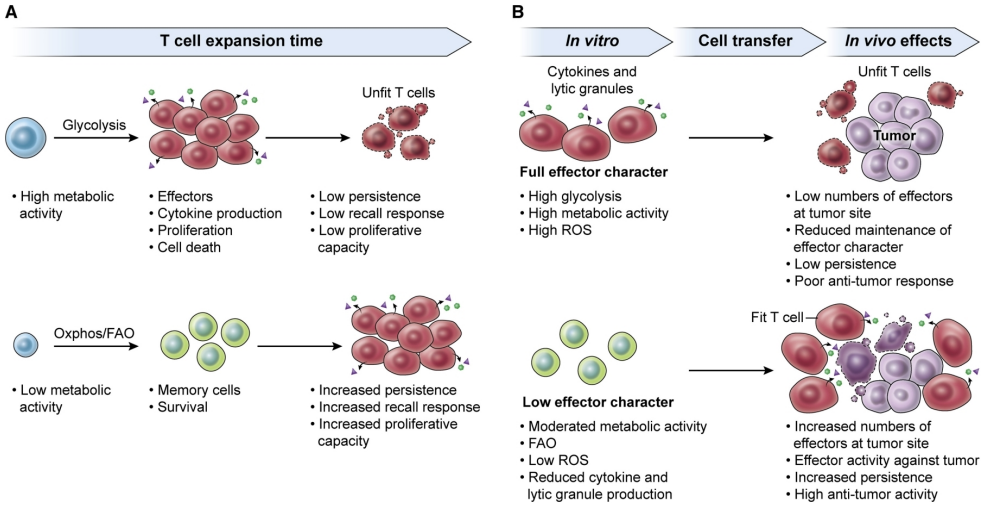
GENE	FC (N/R)	P value
ALDOA	1.697746	0.136385
ALDOC	1.758665	0.186307
ENO2	1.257908	0.685237
ENO3	2.365525	0.205193
GAPDH	1.733471	0.143722
GPI	1.700951	0.015443
LDHA	1.429014	0.302088
LDHB	1.511258	0.152462
PFKM	1.152264	0.57808
PFKP	1.232823	0.463708
PGAM1	1.421356	0.108866
PGAM4	1.5305	0.033143
PGK1	1.636341	0.087465





Cascone et al. 2018 Cell Metab

Will also change T cell metabolism to enhance immunotherapy responses



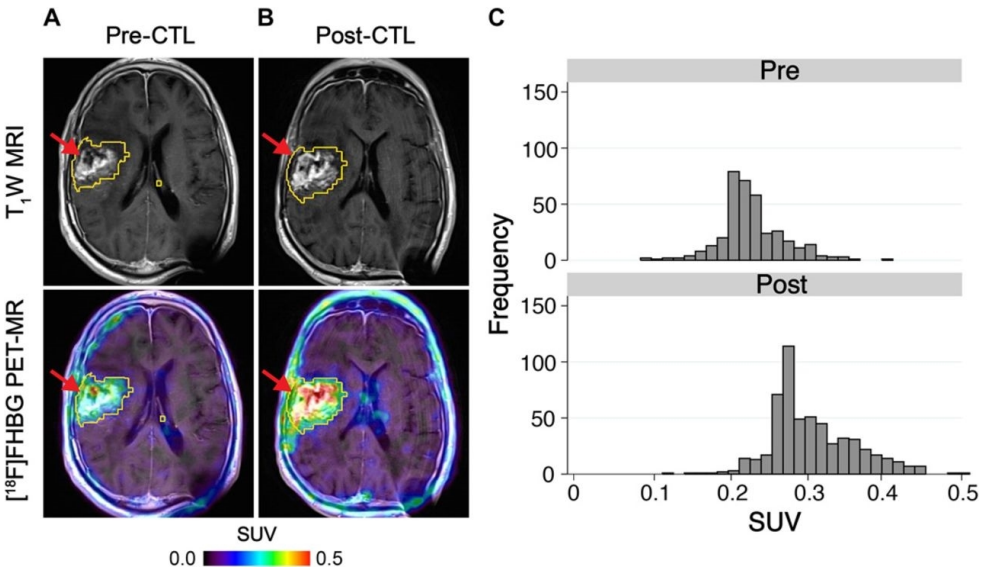
Kishton et al. 2017 Cell Metab

Molecule	Target	Metabolic outcome	Clinical (C), pre-clinical (P)
2-DG	Hexokinase	↓Glycolysis	P
Mdivi-1	Drp-1	↓Mitochondrial fission	P
JQ1	c-Myc	↓Glycolysis	P
STF-31	GLUT1	↓Glycolysis	P
WZB117	GLUT1	↓Glycolysis	P
Rapamycin	mTOR	↓Glutamine metabolism	C
Metformin	AMPK, ETC	↑FAO, others	C
Fenofibrate	PPARα	↑Fatty acid catabolism	P

Dugnani et al. 2017 Cancer Lett

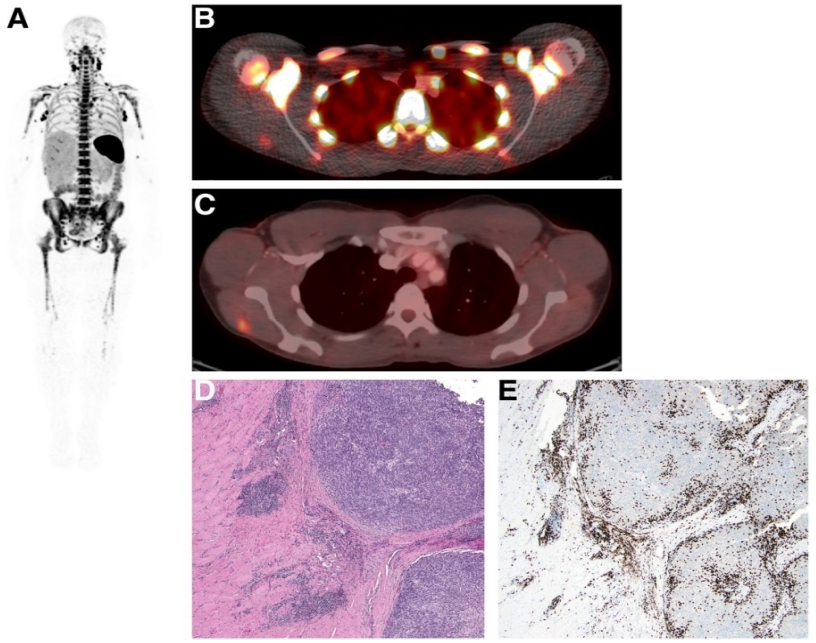
Will see improvements in use of imaging modalities to track immune response

^{18}F-FHBG-CTL



Khun Visith Keu et al., Sci Transl Med 2017;9:eaag2196

^{89}Zr-Anti-CD8 minibody



Neeta Pandit-Taskar et al. J Nucl Med 2020;61:512-519

Science Translational Medicine AAAS

JNM The Journal of NUCLEAR MEDICINE

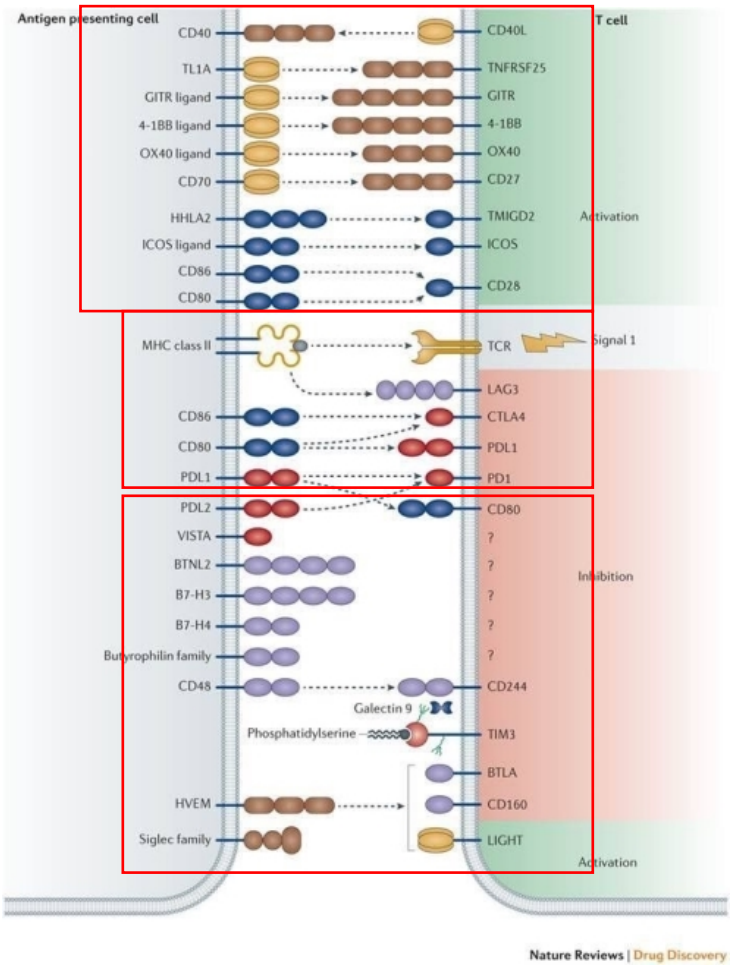
Diagnostics

Therapeutics

Expansion of immunotherapy therapeutics

- Antibody therapy
  - Checkpoint agonists/inhibitors
  - Antibody-drug conjugates
  - Bispecifics
- Oncolytic viral therapy
- Radiotherapy/Immunotherapy
- Cytokine therapy
  - Bempegaldesleukin
  - N-803
- Cellular therapy
  - Vaccines
    - +/- anti-PD1
  - CAR T, CAR NK
    - CAR NKT, CAR CIK cells emerging
  - TCR transduced T cells

The number of checkpoint agonists and antagonists will expand and be used in combination



Mahoney KM et al. 2015 Nat Rev Drug Discovery

Appendix: Immune checkpoint modulators in combination clinical trials (August 2017)

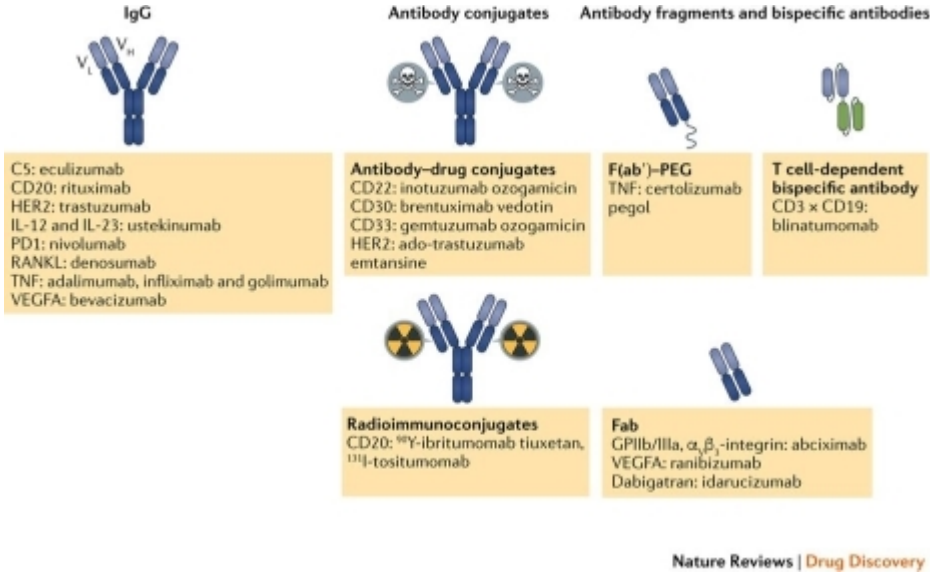
Checkpoint modulator name	Target
PF-05082566 / Utomilumab	4-1BB
Urelumab	4-1BB
AZD4635	ADORA2A
CPI-444	ADORA2A
NIR178	ADORA2A
PBF-509	ADORA2A
Preladenant / MK-3814 / SCH420814	ADORA2A
Enoblituzumab	B7-H3
Varlilumab	CD27
APX005M	CD40
CP-870,893 / RO7009789	CD40
Dacetuzumab	CD40
Lucatumumab	CD40
SEA-CD40	CD40
ISF35 / rAd-CD40L	CD40
MEDI5083	CD-40L
ARGX-110	CD70
Galiximab	CD80
BMS-986218	CTLA-4
Ipilimumab	CTLA-4
MK-1308	CTLA-4
Tremelimumab	CTLA-4
BMS-986156	GITR

Checkpoint modulator name	Target
GWN323	GITR
INCAGN01876	GITR
MK-1248	GITR
MK-4166	GITR
GSK3359609	ICOS
JTX-2011	ICOS
Epacadostat	IDO
Indoximod	IDO
KHK2455	IDO
NLG919 / GDC-0919	IDO
BMS-986205	IDO
Lirilumab	KIR
BMS-986016	LAG-3
LAG525	LAG-3
MK-4280	LAG-3
REGN3767	LAG-3
IMP321	MHC II
Monalizumab	NKG2A
ABBV-368	OX-40
BMS-986178	OX-40
GSK3174998	OX-40
MEDI0562	OX-40
MEDI6383	OX-40
MEDI6469	OX-40

Checkpoint modulator name	Target
MOXR0916	OX-40
PF-04518600	OX-40
AMP-224	PD-1
BGB-A317	PD-1
IBI308	PD-1
JS001	PD-1
MEDI0680	PD-1
Nivolumab	PD-1
PDR001	PD-1
Pembrolizumab	PD-1
PF-06801591	PD-1
REGN2810	PD-1
SHR-1210	PD-1
Atezolizumab	PD-L1
Avelumab	PD-L1
Durvalumab	PD-L1
FAZ053	PD-L1
LY3300054	PD-L1
CX-072	PD-L1
BMS-986207	TIGIT
MTIG7192A	TIGIT
LY3321367	TIM-3
MBG453	TIM-3
TSR-022	TIM-3

More development and potential approvals of antibody-drug conjugates

Emerging antibody-drug conjugates	Target cancer
Mirvetuximab canavanine	Ovarian cancer
Oportuzumab monatox	Bladder cancer
Denintuzumab mafodotin	B cell malignancies
Indatuximab ravtansine	Multiple myeloma



Carter and Lazar 2018 Nat Rev Drug Discovery

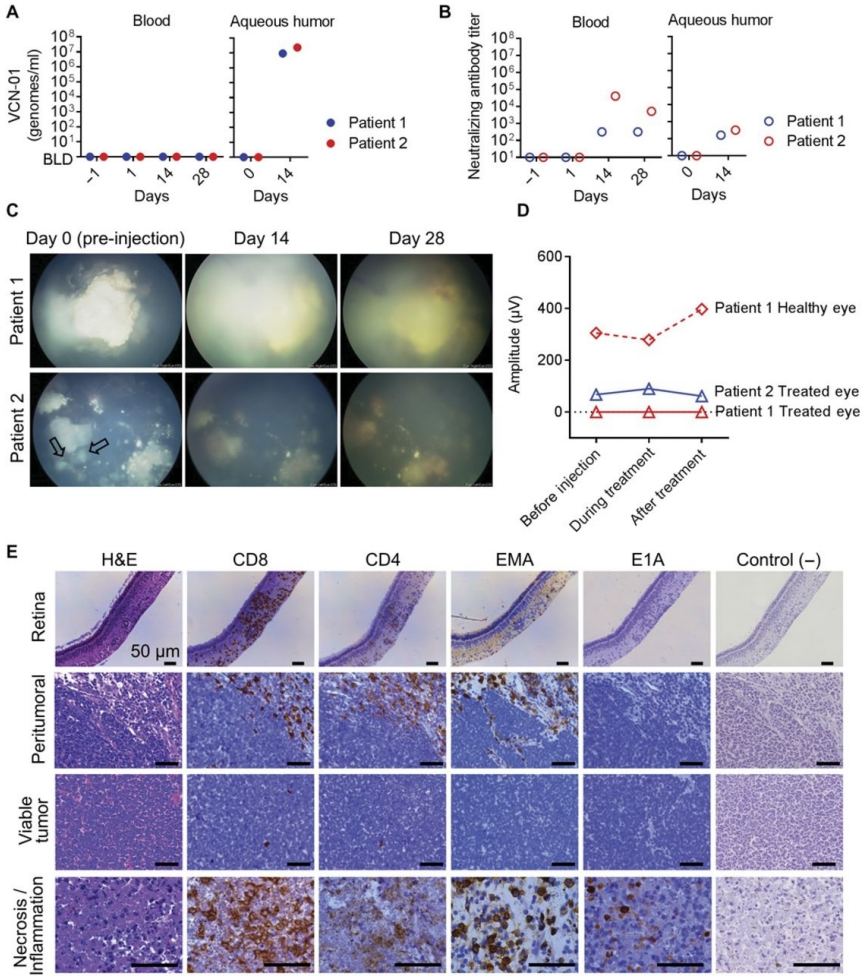
Oncolytic viral therapy will continue to expand viral agents, biologics, and target tumors

	Adenovirus [a]	Herpes simplex virus [b]	Pox virus	Coxsackie virus	Maraba virus	Poliovirus	Measles virus	Newcastle Disease virus
Genome	dsDNA	dsDNA	dsDNA	ssRNA	ss (–) RNA	ss (+) RNA	ss (–) RNA	ss (–) RNA
Genome size	Moderate (32 kb)	Large (152 kb)	Large (130–375 kb)	Small (~8 kb)	Small (11–15 kb)	Small (7.5 kb)	Small (~16 kb)	Small (~15 Kb)
Cell entry mechanism	Endocytosis	Endocytosis; penetration	Membrane penetration and fusion	Micropinocytosis via epithelial tight junctions	Endocytosis; pH-dependent fusion activation	Receptor-mediated endocytosis	Membrane fusion	Endocytosis; pH-independent direct fusion
Cell entry receptors	hCAR; VCAM1; CD46	HVEM; nectin 1; nectin 2	GAGs; EFC	CAR; DAF	Unknown	CD155	CD46; SLAM	Neuraminidase receptor; sialoglyco-conjugates

[a]E1B-55 K/E3B-deleted adenovirus in combination with chemotherapy was approved for the treatment of late-stage refractory nasopharyngeal cancer by the Chinese State Food and Drug Administration in 2005. [b]Herpes simplex virus type 1 (HSV-1) with ICP34.5 deletion and encoding granulocyte–macrophage colony-stimulating factor (GM-CSF) was approved for stage III–IV melanoma treatment by the US Food and Drug Administration in 2015 and by Australia and the European Medicines Agency (EMA) in 2016.

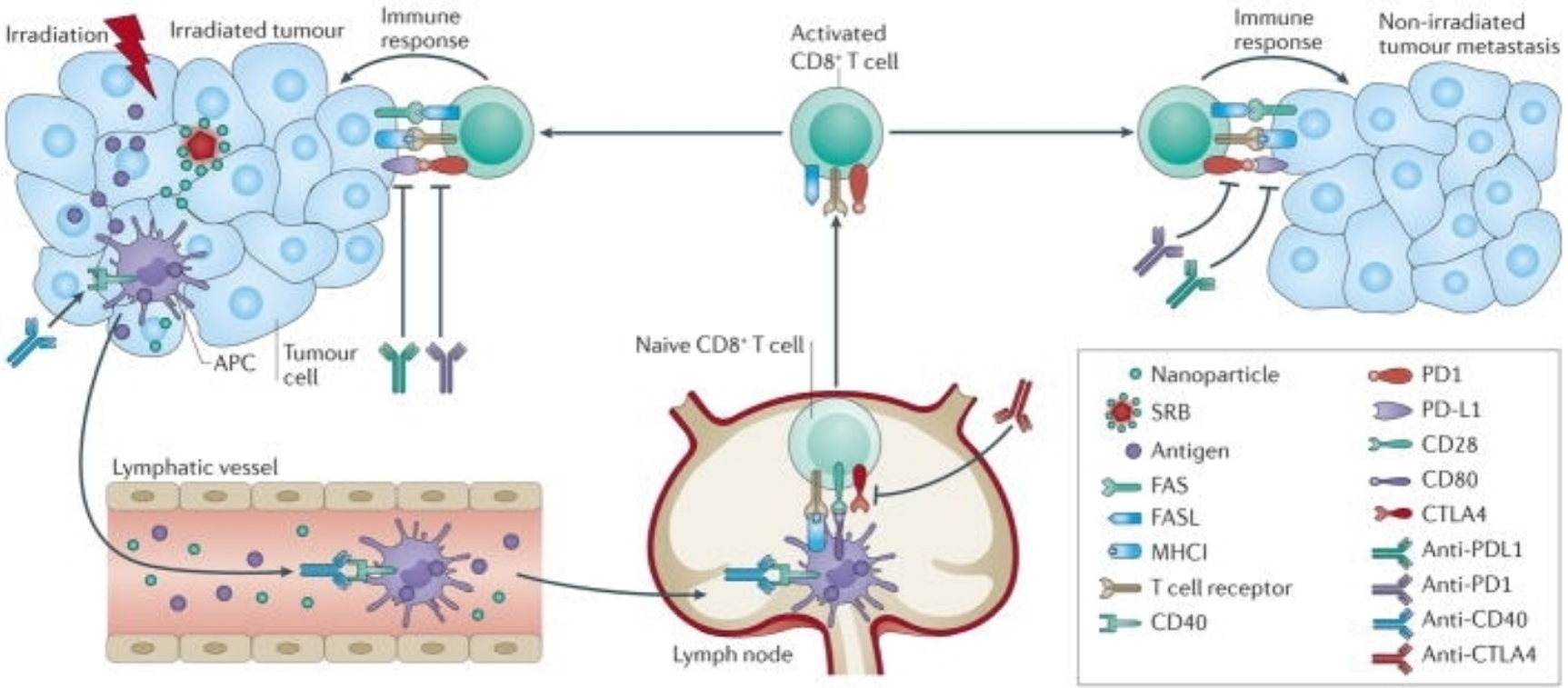
Adapted from Bommareddy et al. 2018 Nat Rev Immunol

Oncolytic viral therapy will continue to expand viral agents, biologics, and target tumors



Guillem Pascual-Pasto et al., Sci Transl Med 2019;11:eaat9321

Radiation therapy is immunogenic and can be safely combined with checkpoint inhibitor



Ngwa et al. 2018 Nat Rev Cancer

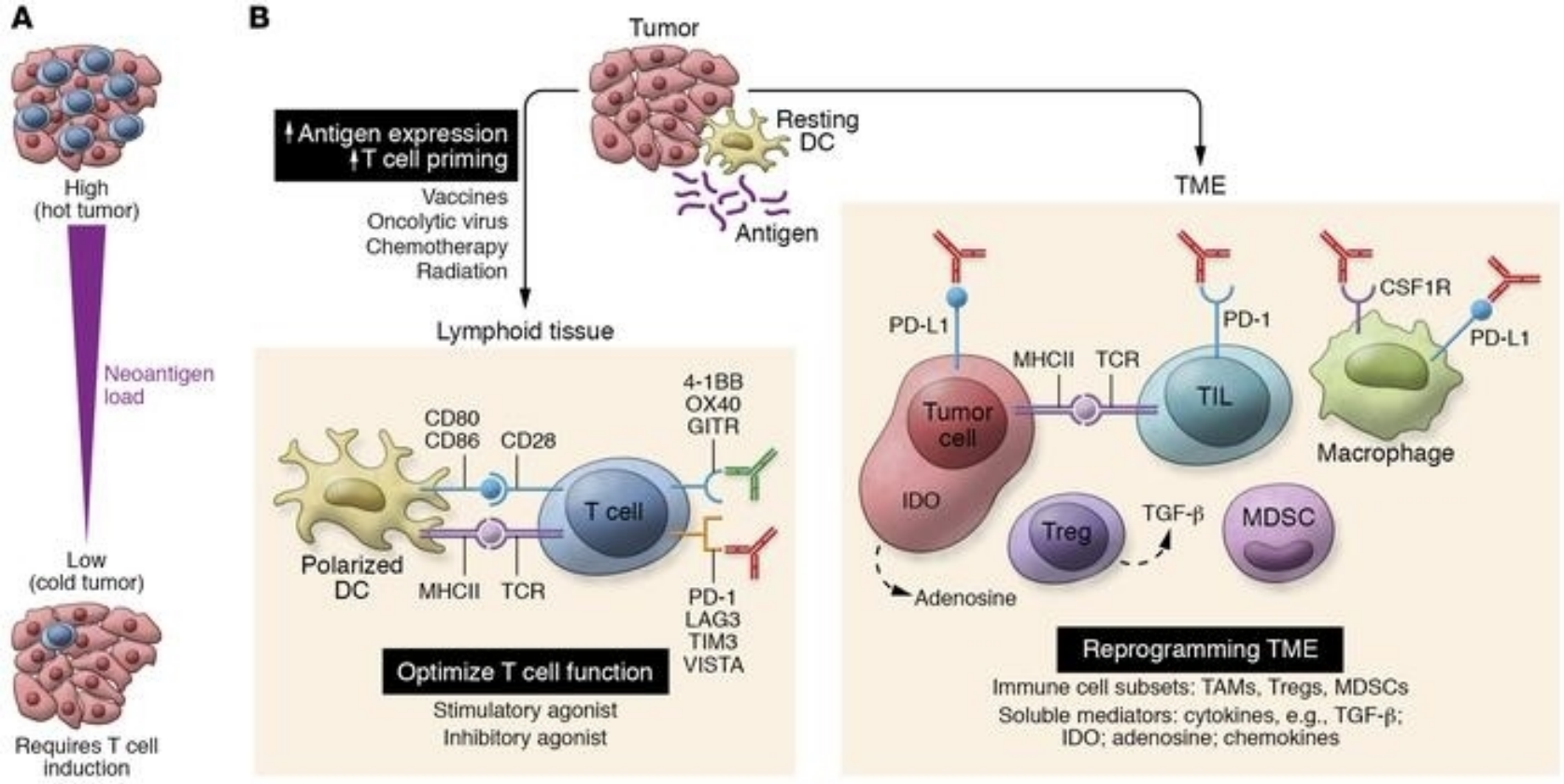
Radiation therapy will be increasingly used as a means of enhancing immunotherapy

Table 1. Summary of main prospective available data related to the efficacy of radiotherapy and ICI combination.

Population	Reference	Phase	Intervention	Results
Locally advanced NSCLC	[31]	I	Pembrolizumab + chemoradiotherapy	6-mo PFS rate = 81% 12-mo PFS rate = 69.7% Median PFS = 18.7 mo
Locally advanced NSCLC	PACIFIC [32–34]	III	Durvalumab (12 mo) as consolidation therapy vs. placebo (12 mo)	ORR = 28.4% vs. 16.0% ($p < 0.001$) Median PFS = 16.8 mo vs. 5.6 ($p < 0.001$) 36 months OS = 55.3% vs. 43.5%
Locally advanced NSCLC	[35]	II	Chemoradiation + pembrolizumab (12 mo) as consolidation therapy	Time to metastatic disease = 30.7 mo PFS = 18.7 mo OS = 35.8 mo
1–4 metastatic sites NSCLC	[36]	II	Pembrolizumab within 4–12 weeks after locally ablative therapy	Median PFS from the start of locally ablative therapy = 19.1 mo
Locally advanced HNSCC	[37]	I	Cisplatin-based chemoradiotherapy + pembrolizumab (concurrently + as maintenance)	CR (HPV+) = 85.3% CR (HPV−) = 78%
Locally advanced HNSCC	JAVELIN H&N 100 [38]	III	Avelumab + chemoradiotherapy + avelumab maintenance vs. Placebo + chemoradiotherapy + placebo maintenance	At the time of the interim analysis: no significant improvement in PFS or OS
Locally advanced HNSCC (cisplatin-unfit patients)	PembroRad [39]	II	Once-daily RT up to 69.9 Gy associated with: Cetuximab vs. pembrolizumab	Loco-regional-control at 15 mo = 59% vs. 50% ($p = 0.91$) 24-mo PFS = 40% vs. 42% ($p = 0.41$) 24-mo OS = 55% vs. 62% ($p = 0.5$)
Stage III/IV RCC	RADVAX RCC [40]	II	Nivolumab + ipilimumab + SBRT (40–50 Gy in 5 fractions)	PR = 56% SD = 24% PD = 16% 12-mo PFS rate = 36%
2nd or 3rd line RCC	NIVES [41]	II	Nivolumab + SBRT (10 Gy × 3 fractions 7 days after the 1st infusion of nivolumab)	ORR = 17.4% 12-mo median OS = 73.4%
Metastatic Melanoma	[42]	I	RT (6–8 Gy, 2–3 times) followed by ipilimumab injections	PR = 18% SD = 18%
Metastatic Melanoma	[43]	I	Ipilimumab + RT (between 18–50 Gy, in 1–15 fractions)	Clinical benefit = 50% PR = 15% CR = 15%
Metastatic Melanoma	[44]	I	Nivolumab + ipilimumab + extracranial RT (30 Gy in 10 fractions or 27 Gy in 3 fractions)	PR outside of the irradiated volume: 6/19 No progression of irradiated metastases

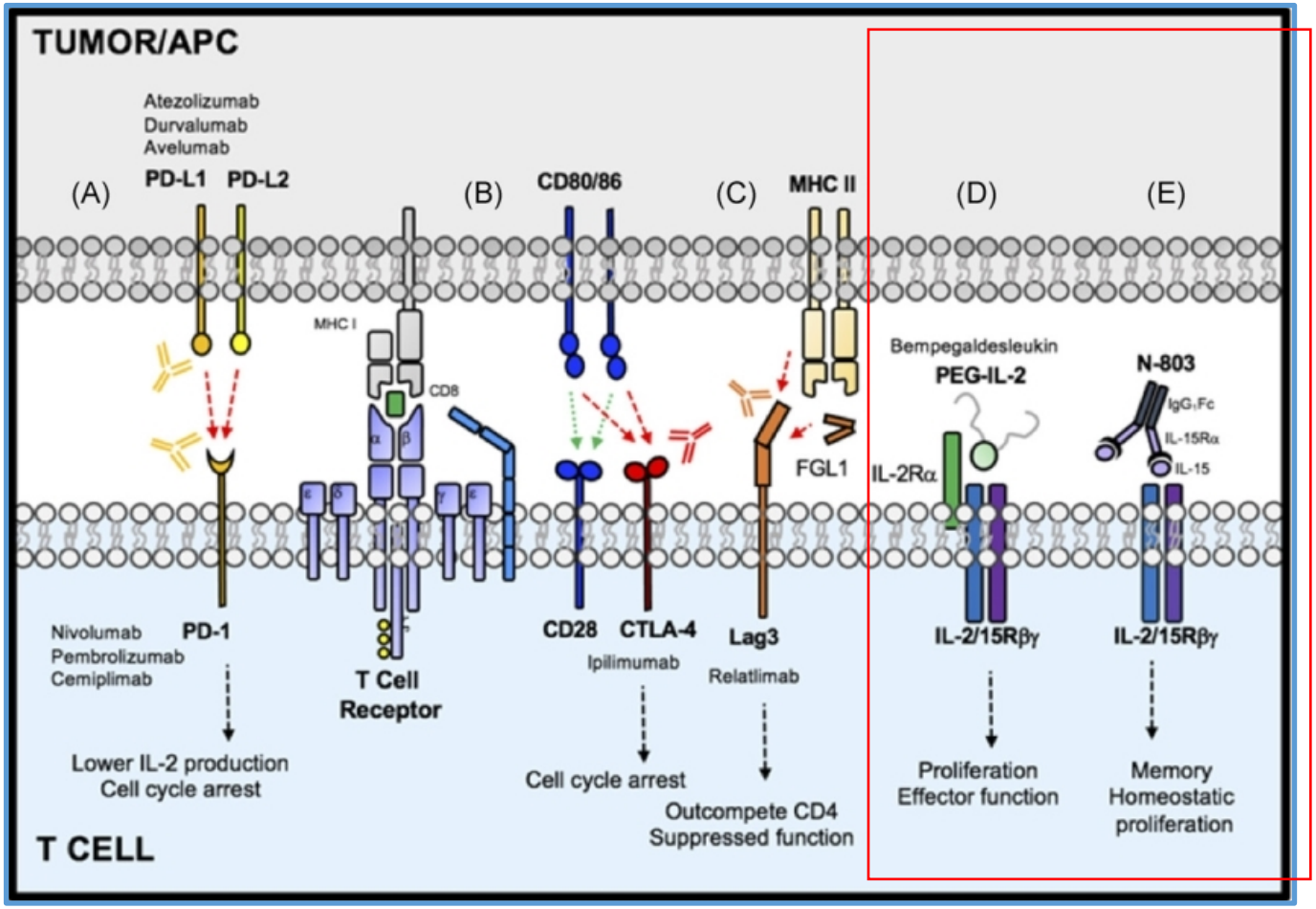
Procureur et al 2021 Cancers

Emerging strategies for combination checkpoint modulators in cancer immunotherapy



Popovic et al. 2019 J Clin Invest

Cytokine “superagonists” will emerge as adjuvants for combination immunotherapy



Keilson et al 2021 J Surgical Oncol

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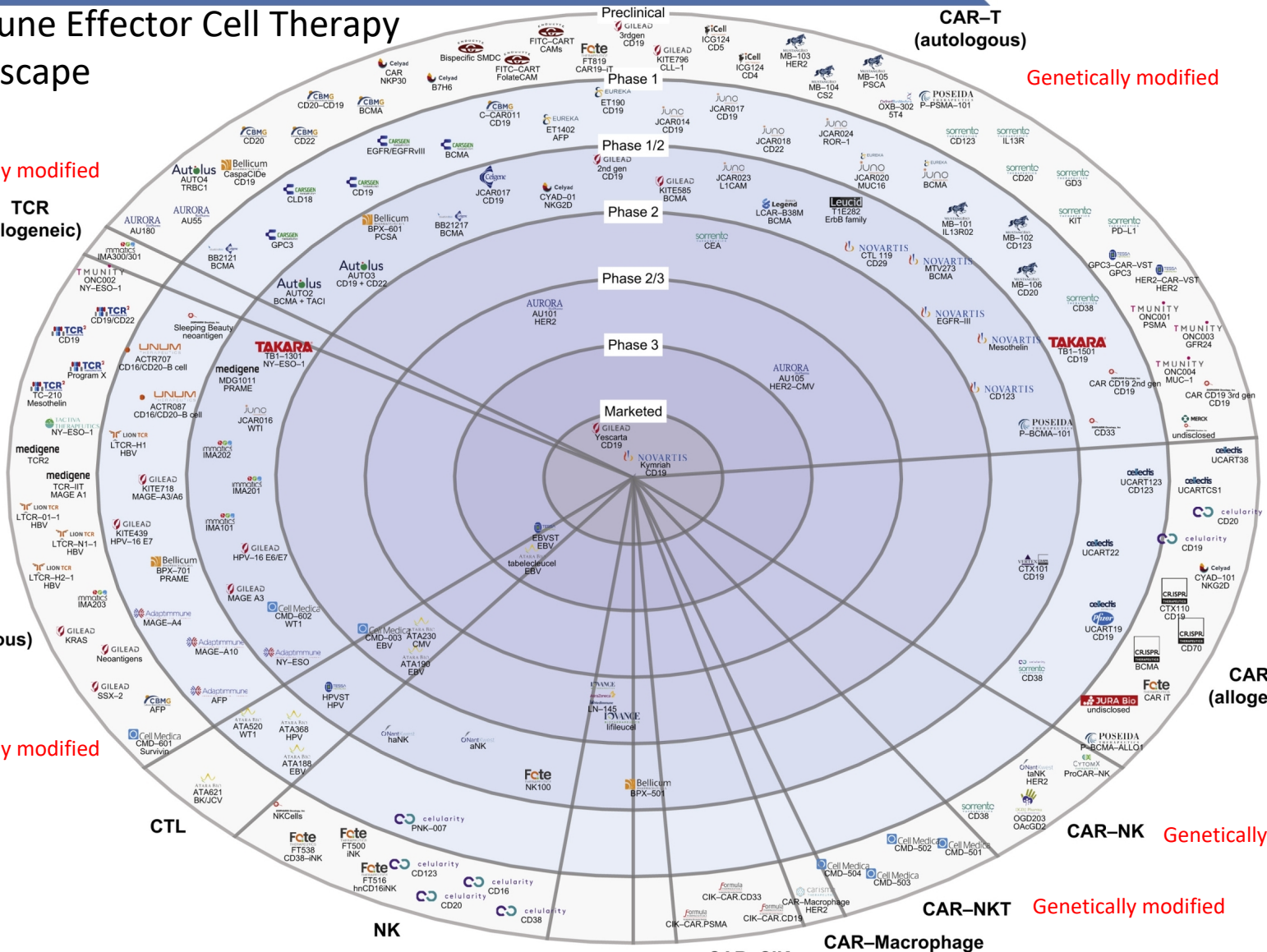
Tumor vaccines will re-emerge and become part of standard of care

Table 3 Select ongoing phase 3 studies evaluating cancer vaccines

Vaccine platform type	Product name	Antigen(s)	Identifier (phase, name)	Patient population	Enrollment	Regimens	Primary outcome measures
Cell-based (trivalent DC)	–	Autologous tumor stem cells, survivin, and hTERT	NCT03548571 (phase 2/3, DEN-STEM)	Glioblastoma IDH wild-type, with unmethylated MGMT-gene promotor	60	Trivalent DC immunization vs. radiotherapy with concomitant and adjuvant temozolomide	PFS
Peptide	GP96 heat shock protein-peptide complex	–	NCT04206254 (phase 2/3)	Liver cancer	80	GP96 vaccination after surgery vs. no treatment after surgery	2-year recurrence-free survival rate
Adenoviral vector containing the herpes simplex virus thymidine kinase gene	ProstAtak® (AdV-tk) + valacyclovir	–	NCT01436968 (phase 3)	Localized prostate cancer (intermediate risk or one NCCN high-risk feature) due to undergo standard prostate-only EBRT	711	ProstAtak® (AdV-tk) + valacyclovir + radiation therapy ± androgen deprivation therapy vs. placebo + valacyclovir + radiation therapy ± androgen deprivation therapy	DFS
Cell-based (bacterial)	BCG Tokyo-172 strain solution	–	NCT03091660 (phase 3)	Stage 0/0is/1 urothelial carcinoma	969	Tokyo-172 strain BCG (arm 2) vs. Tokyo-172 strain BCG solution with priming (arm 3) vs. TICE® BCG (arm 1)	Time to high-grade recurrence for arm 1 vs. arm 2, and arm 2 vs. arm 3
Cell-based (DCs)	DCs plus autologous tumor RNA	–	NCT01983748 (phase 3)	Stage T2, T3, or T4 melanoma of the uvea	200	Autologous DCs loaded with autologous tumor RNA vs. SOC	Prolongation of OS
Cell-based (tumor cell)	OncoVAX®	–	NCT02448173 (phase 3)	Stage II colon cancer	550	OncoVAX® and surgery vs. surgery	DFS
Oral vaccine (tablet) derived from pooled blood	Hepcortespenlisimut-L (Hepko-V5)	–	NCT02232490 (phase 3, Hepko-V5)	Advanced hepatocellular carcinoma	120	Hepcortespenlisimut-L vs. placebo	Changes in plasma AFP
Cell-based (bacterial)	BCG	–	NCT04165317 (phase 3)	High-risk non-muscle-invasive transitional cell carcinoma of the urothelium and complete resection of all Ta/T1 papillary disease	999	PF-06801591 + BCG induction and maintenance (arm A) vs. PF-06801591 + BCG induction only (arm B) vs. BCG induction and maintenance (arm C)	EFS (arm A vs. arm C and arm B vs. arm C)

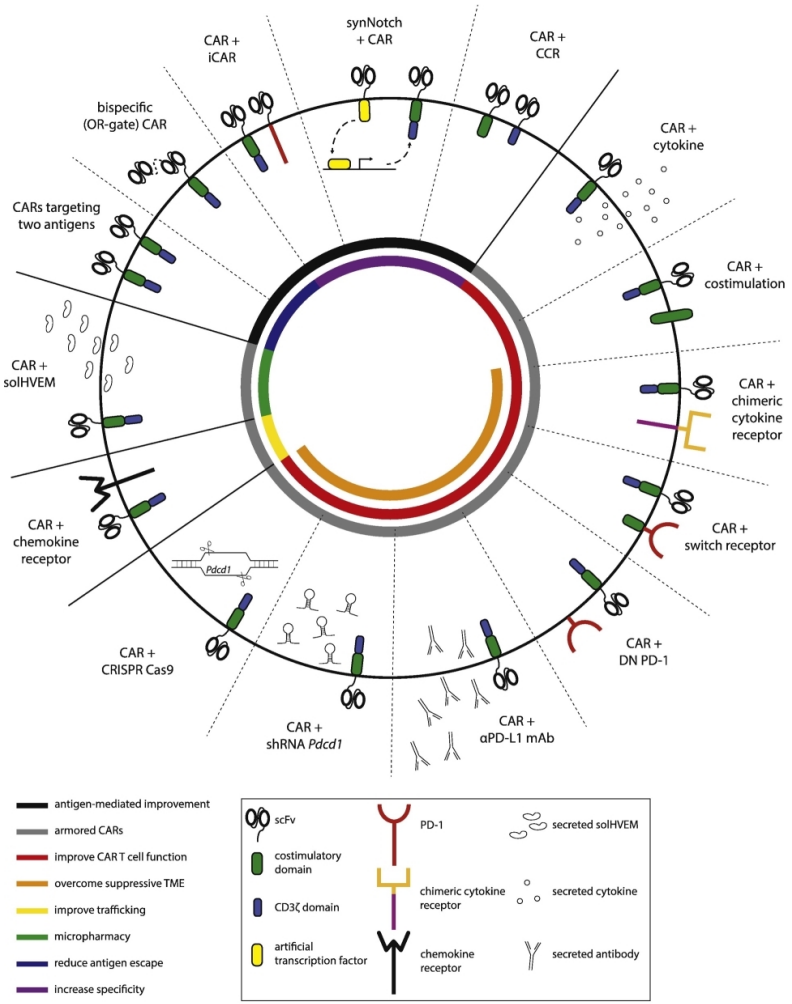
Morse et al. 2021 Target Oncol

Immune Effector Cell Therapy Landscape

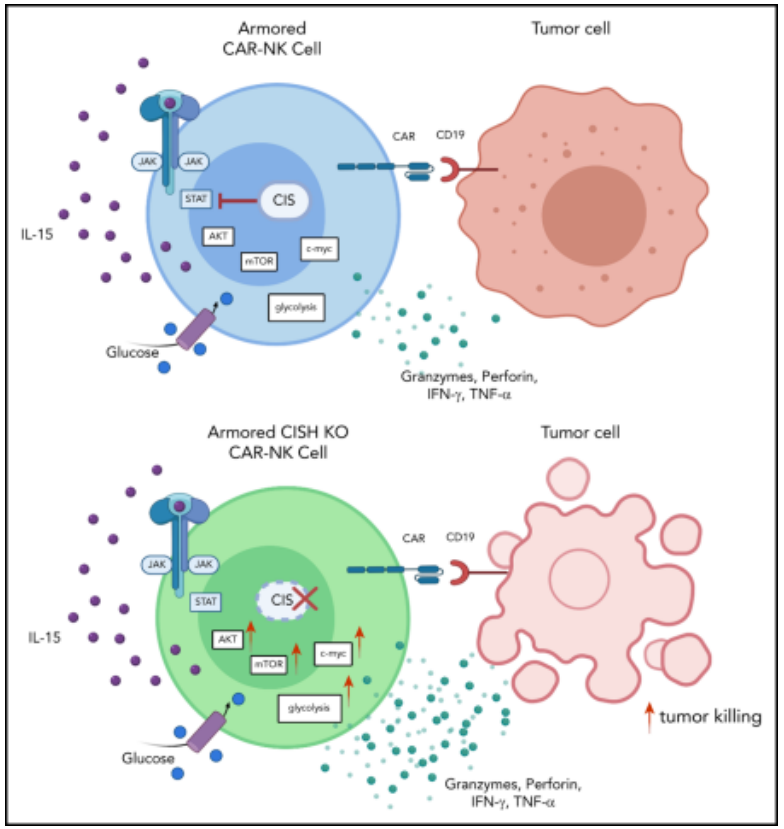


Cauchon et al. 2019 *J Pharm Sciences*

Enhanced engineering of CAR T and CAR NK will help reduce side effects while improving efficacy



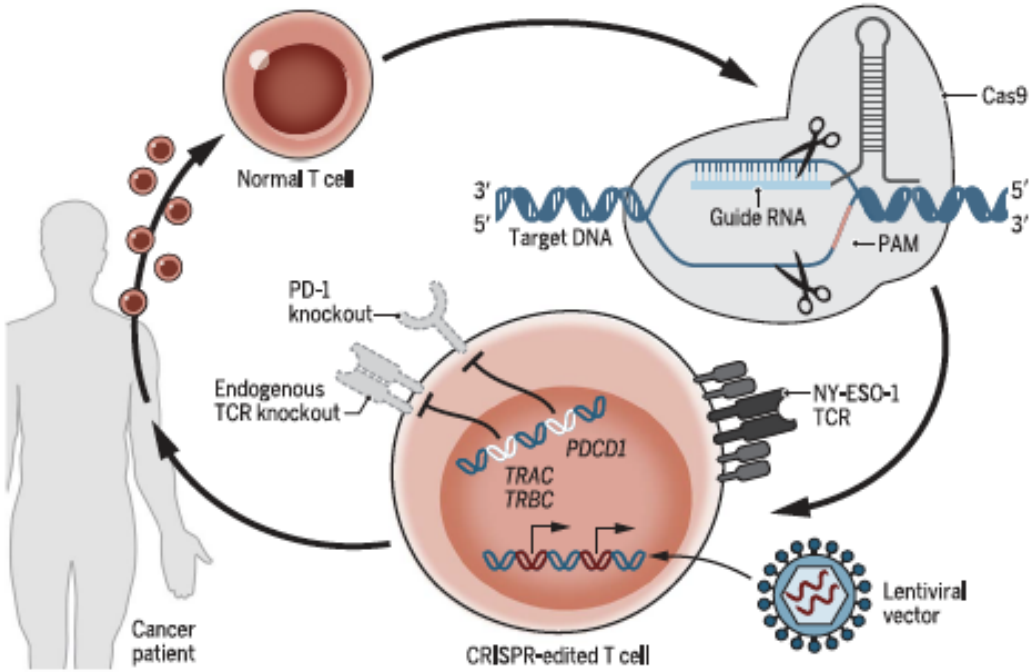
Jaspers and Brentjens 2017 Pharmacol Ther

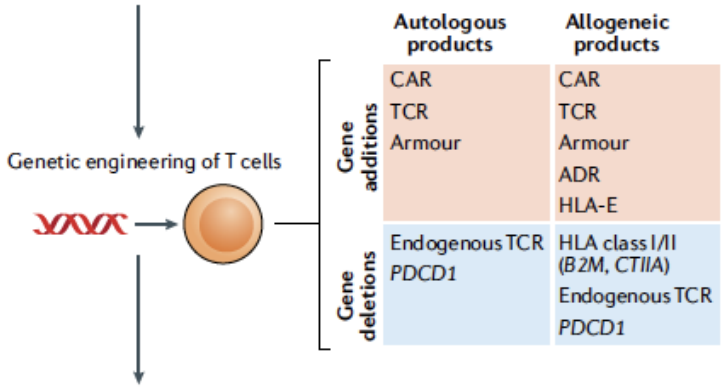


American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Daher et al Blood 2021

CRISPR-based editing of immune effector cells





Science AAAS

Edward A. Stadtmauer et al. Science 2020;367:eaba7365

Ellis et al. 2021 Nat Reviews Genetics

CARs in development for hematologic malignancies

- **CD20** (B cell cancers)
- **CD22** (B cell cancers)
- **CD23** (B cell cancers)
- **CD30** (B cell cancers)
- **CD37** (B and T cell cancers)

- **ROR1** (lymphoid cancers)
- **CD133** (lymphoid and myeloid cancers)
- **TSLPR** (lymphoid cancers)

- **BCMA** (multiple myeloma)
- **CS1** (multiple myeloma)
- **CD138** (multiple myeloma)

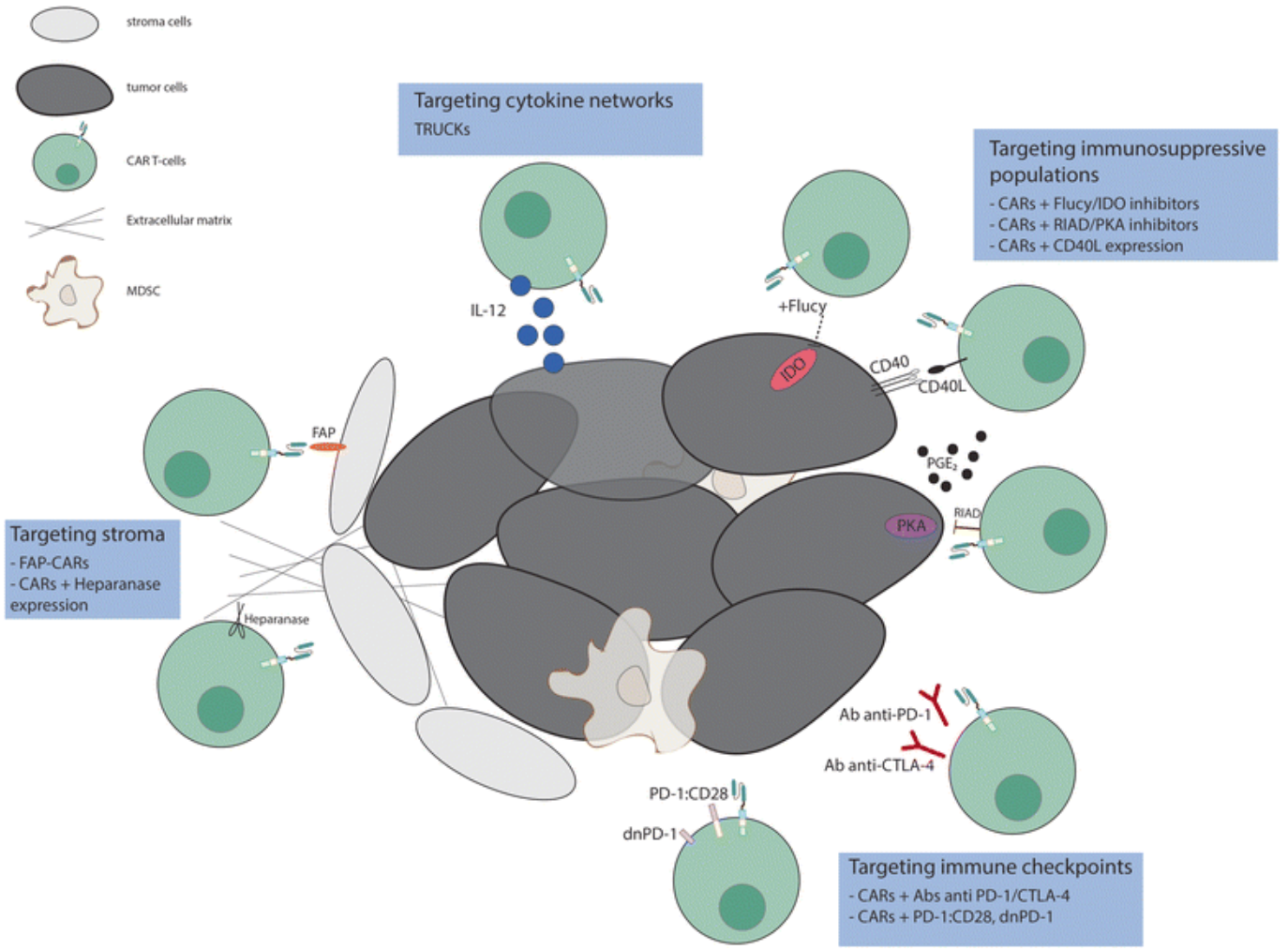
- **CD5** (T cell cancers)
- **CCR4** (T cell cancers)
- **CD7** (T cell and myeloid cancers)

- **CD33** (myeloid cancers)
- **CD123** (myeloid cancers)
- **Lewis-Y** (myeloid cancers)
- **CD44v6** (myeloid cancers)
- **CLL-1** (myeloid cancers)
- **Folate receptor beta** (myeloid cancers)
- **FLT3** (myeloid cancers)
- **NKG2D** (myeloid cancers)

CARs in development for solid tumors

- **AFP** (liver cancer)
- **ALK** (neuroblastoma)
- **Carbonic anhydrase IX** (kidney cancer)
- **CD24** (ovarian cancer)
- **CD70** (kidney cancer)
- **CD133** (liver, brain, breast cancer)
- **CD171** (neuroblastoma)
- **CD276** (multiple histologies)
- **CEA** (lung, colorectal, gastric, pancreatic cancers and liver metastases)
- **cMet** (breast cancer)
- **CSFR1** (tumor-associated macrophages)
- **EGFR** (lung, colorectal, ovary, pancreatic cancer)
- **EGFRvIII** (gliomas, glioblastoma)
- **EpCAM** (liver, stomach and colon cancer)
- **EphA2** (glioma)
- **Fibroblast activation protein** (mesotheiloma)
- **Folate receptor alpha** (breast, ovarian cancer)
- **GD2** (neuroblastoma, sarcomas and melanoma)
- **Glypican-3** (liver, lung cancer)
- **HER2** (breast cancer, glioblastoma, ovarian, lung, pancreatic, sarcoma and medulloblastoma)
- **IL-13Rα** (gliomas)
- **Lewis-Y** (breast cancer)
- **Mesothelin** (pancreatic, ovarian, mesothelioma, breast cancer)
- **MG7** (liver metastases)
- **MUC-1** (breast, liver, lung, pancreatic, glioma, colorectal, gastric cancer)
- **NKG2D** (multiple histologies)
- **PSCA** (pancreatic cancer)
- **PSMA** (prostate cancer)
- **TEM8/ANTRX1** (breast cancer)
- **VEGFR2** (multiple histologies)

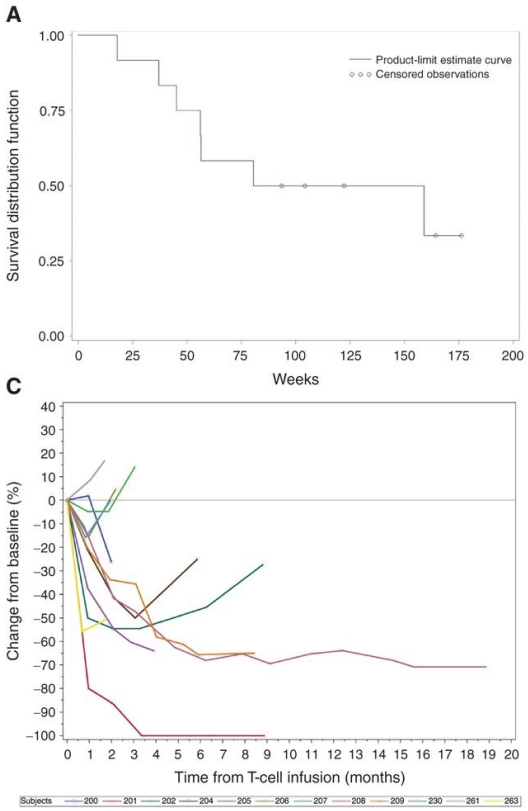
Combination strategies to improve CAR efficacy will be used for solid tumors



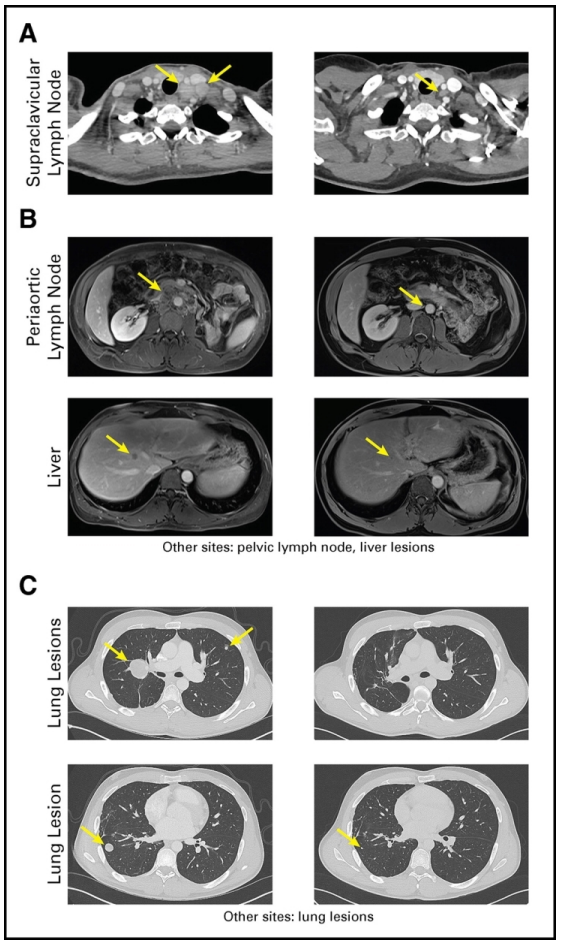
Scarfo and Maus 2017 J Immunother Cancer

TCR transduced T cells will provide durable responses in solid tumors

NY-ESO-1



MAGE-A3



29 months

18 months

4 months

D'Angelo et al. 2018 Cancer Discov

Lu et al. 2017 J Clin Oncol

Conclusions

- The future of cancer immunotherapy is bright, with advances occurring in both diagnostics and therapeutics at a rapid pace

- We will see improvements in our ability to distinguish immunologically “hot” vs. “cold” tumors, and potentially be able to convert “cold” into “hot” tumors

- Advances in genetic engineering and biomanufacturing will permit development of “next generation” antibodies, viruses, targeted radiotherapies and cellular therapies for cancer.