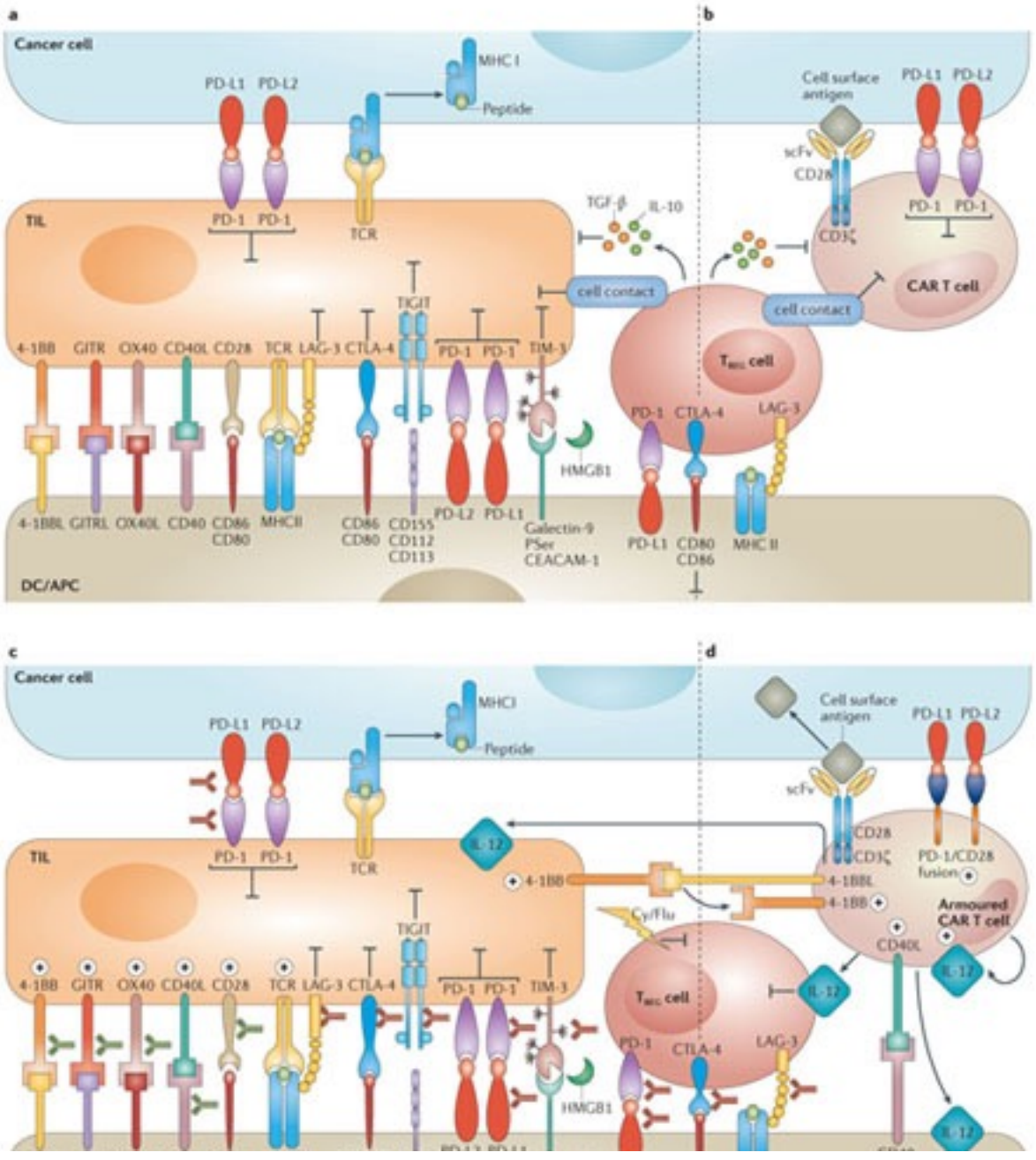
Review of cancer immunotherapy

Key points:

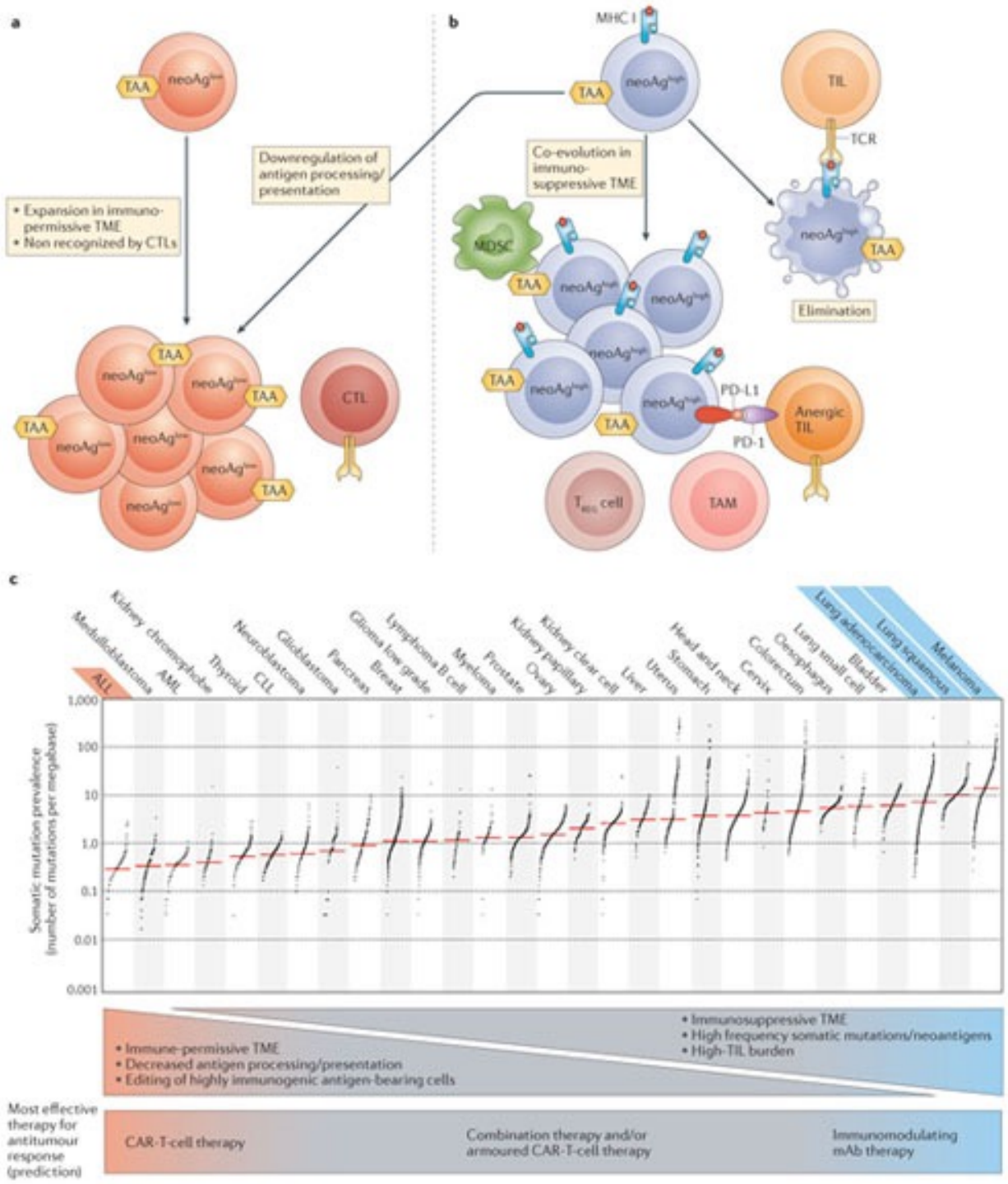
* Cancer immunotherapies have the potential to generate robust anti-tumor responses; th
antibodies or adoptive cellular therapy
* Since 2010, clinical trials using different immunotherapeutic approaches to treat patients
* In contrast with therapies that act on the tumor itself, immunotherapy-dependent anti-tu
* The optimal efficacy of immunotherapy will likely be achieved with designs that include



his can be achieved through several methods, such as modulatory

s with several tumor types have yielded unprecedented results
mor responses can be sustained after the treatment has finished
combinations of different immunotherapeutic approaches, or im

munotherapy combined wit



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Immune modulation

Using mAbs to target cancer cells is complicated by the fact that cancer cells are self and vary g
more reliably used to activate or inhibit the action of the patient's immune system. These mA
particularly T-cells, that can then respond to cancer antigens if they are presented to the T-cells
any type of vaccination, they must have primed T-cells that are actively being held in check by t
[Khalil et al., 2016]

Patients with C-reactive protein (a liver protein whose levels rise when inflammation is present
modulation. Patients with high levels of myeloid-derived suppressor cells or high levels of solub
maturation) of T cells), are less likely to respond to immune modulation [Khalil et al., 2016]

PD-1 (programed cell-death protein 1)

Programed cell death (aka apoptosis) is a form of intentional and highly regulated cell death th
Apoptotic cells fragment and 'bleb' into small particles that are then cleaned up by macrophage
PD-1 is a receptor that maintains self-tolerance (prevents the body from attack by its own imm
checkpoint signaling'. Blocking PD-1 with mAbs prevents tumor-targeting T-cells from death an
used against melanoma & non-small-cell lung cancer. [Khalil et al., 2016]

T-cell co-stimulation uses mAbs to stimulate T-cell co-receptors, increasing activation of T-cells

Creation of immune memory against tumors could prevent recurrence and escape of tumors. T
patients who received immunotherapy. [Khalil et al., 2016]

CTLA-4 (cytotoxic T-lymphocyte antigen-4)

T-cells are primed when their T-cell receptor (TCR) binds to a peptide fragment of their antigen
protein on the surface of an antigen presenting cell (APC) such as a dendritic cell. But primed T-
the CD80 or the CD86 protein on the surface of the APC. Without this second signal, primed T-c
autoimmune responses. [Khalil et al., 2016]

In activated T-cells, CTLA-4 moves to the cell surface where it binds to the APCs CD80 or CD86 r
'dampens' T-cell activation and thus restricts the ability of T-cells to kill tumor cells; CTLA-4 con

Regulatory T-cells always express CTLA-4 on their cell membranes and use it to suppress the ac
binding to the CTLA-4 on the primed T-cells and on regulatory T-cells and preventing CTLA-4 fro
antigen presenting cells. [Khalil et al., 2016]

Anti-CTLA-4 mAbs (ipilimumab) allowed patients with advanced melanoma to mount a better im
continued to survive even after mAb treatment stopped. [Khalil et al., 2016]

greatly with the type of cancer and the individual. However, **mAbs can be**
Abs essentially act as adjuvant since they activate the immune system,
s. Since some cancer patients have strong responses to these mAbs without
the cancer; active suppression of a potentially functional immune response.

t) and good lymphocyte levels are most likely to benefit from immune (T-cell)
ble CD25 (soluble interleukin-2 receptor; IL-2 stimulates differentiation (aka

at removes targeted self cells without provoking an immune response to self.
es.
une system) by killing T-cells that target self. This process is called 'immune
d thus allows the immune response to the tumor. Anti-PD-1 mAbs are being

. [Khalil et al., 2016]

This type of effective memory response has occurred in some melanoma

(a target protein) presented in an MHC (major histocompatibility complex)
-cells do not become active until their CD28 surface protein binds to either
cells become quiet (anergic) or commit suicide (apoptosis); this prevents

more strongly than CD28 does. By competing with TCR activation, CTLA-4
strains T-cell responses. [Khalil et al., 2016]

tivity of other primed T-cells. Anti-CTLA-4 mAbs allow T-cells to be active by
om disrupting the (stimulatory) binding of T-cell CD28 to CD80 & CD86 on

mmune response to their tumors. The 20% of treated patients who survived

Immune-related adverse effects (irAE) can occur after treatment with anti-CTLA-4 mAb when th
maintaining the immune response. And some patients given anti-CTLA-4 mAb have some tumo
al., 2016]

Anti-CTLA-4 mAbs may be most effective in combination with other therapy where the mAb ca
therapy and cryoablation all show better responses with anti-CTLA-4 mAb. [Khalil et al., 2016]

PD-1

PD-1 is also an inhibitory receptor expressed on the surface of T-cells. APCs and cancer cells exp
APCs or tumor cells prevents activation of primed T-cells; effectively supressing the T-cell respo
caused responses in 40% of patients with advanced melanoma, including those who did not res
mAbs is even more effective and is now the treatment of choice. Two anti-PD-1 mAbs, pembro
a number of other cancers. There are also anti-PD-1L mAbs now being used to treat cancer. [Kh

Anti-PD-1 mAbs generally produce fewer irAE side effects than anti-CTLA-4 mAbs, though pulm

Lymphocyte-activation gene 3 (LAG-3) is expressed on the cell surface activated T-cells (??), re
sends an inhibitory signal to T-cells but stimulates the ability of regulatory T-cells to suppress im
'exhausted' and are dysfunctional; this is seen in cases of chronic infection. Soluble LAG-3 is see
LAG-3 can function. Under development and showing promise: soluble LAG-3-Ig fusion proteins

T-cell membrane protein 3 (TIM-3) (aka hepatitis A virus cellular receptor 2) is also seen on exh
of T-cells. Blocking TIM-3 increases proliferation and function of T-cells and increases anti-tumo
& sarcoma, more when combined with blockade of PD-1. [Khalil et al., 2016]

T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is expressed on T-cells and also assoc
anti-tumor activity. [Khalil et al., 2016]

T-cell co-stimulation

This strategy uses agonist (stimulating) mAbs to co-stimulatory molecules on T-cells to activate
factor receptor) family are promising targets. [Khalil et al., 2016]

T-cell antigen 4-1BB homolog (4-1BB) (aka CD137 or TNFR superfamily member 9) is expressed
4-1BBL on the surface of dendritic cells (a potent type of APC) causing T-cell proliferation and in
Anti-4-1BB mAb increases preclinical antitumor responses, especially in combination with block
therapy. The anti-4-1BB mAb urelumab is effective in melanoma patients, but caused severe liv
should increase natural killer cell destruction of tumors. [Khalil et al., 2016]

he 'disinhibited' immune system attacks self. Most irAE can be managed while
or growth before a successful immune response against the tumor. [Khalil et

n potentiate the efficacy of the second treatment. Radiation, oncolytic virus

press PD-1 ligands (PD-L1 and PD-L2). Binding of T-cell PD-1 to its ligands on
onse. Tumors expressing PD-L1 lead to poorer prognosis. Anti-PD-1 mAbs
spond to anti-CLTA-4 mAbs. Treatement with both anti-CLTA-4 and anti-PD-1
olizumab (aka keytruda) and nivolumab, are now used against melanoma and
halil et al., 2016]

honary issues must be watched for and treated. [Khalil et al., 2016]

egulatory T-cells, B cells and dendritic cells. LAG-3 binds to MHC II on APCs and
mmune responses. T-cells that express both LAG-3 and PD-1 are called
en in some breast cancer patients and indicates a better prognosis; soluble
s and LAG-3-blocking mAb.[Khalil et al., 2016]

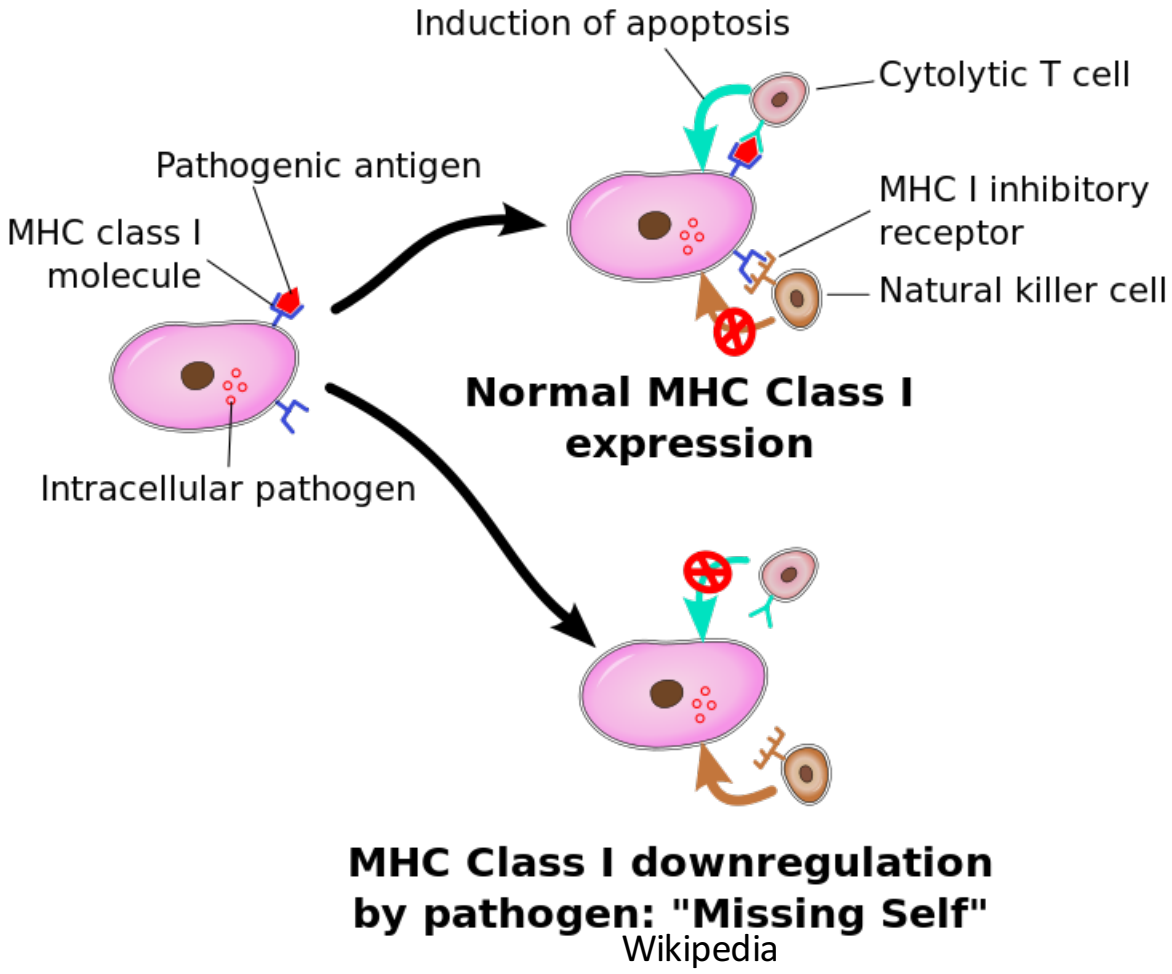
hausted T-cells. TIM-3 blunts T-cel responses and induces apoptosis (suicide)
or activity. Blockade of TIM-3 is effective against mouse models of melanoma

ciated with exhausted T-cells. Blocking TIGIT and PD-L1 and TIM-3 increases

T-cells and enhance their activity. Members of the TNFR (tumor necrosis

d on the surface of T-cells, natural killer cells & monocytes. 4-1BB binds to
ncreased expression of proteins that protect T-cells from apoptosis.
king CTLA-4, activating CD40, use of cellular vaccines, or with radiation
ver damage. Combination of these mAbs with mAbs targeting tumor cells

Natural killer cells are cells of the innate immune system which kill foreign cells and cancer cells specific antigens, but kill cells that don't express the 'self' antigen MHC I and are therefore not response or tolerance (dampening of the adaptive immune response).



Wikipedia

Glucocorticoid-induced TNFR-related protein (GITR) (aka superfamily member 18) is expressed cell proliferation, cytokine production and resistance to suppression. User of anti-GITR agonist melanoma, fibrosarcoma, etc. Early clinical studies are in progress.

CD40 is a member of the TNFR family expressed on APCs: dendritic cells, macrophages, monocy express the ligand CD40L. When T-cell CD40L binds to CD40 on APCs, the APC increases expres maturation. mAbs can either target CD40 on tumor cells or on immune cells; the latter is proba anti-CD40 agonist mAbs has ben very effective. [Khalil et al., 2016]

OX40 (TNFR superfamily 4) is expressed on T-cells, NK cells and neutrophils (another innate im proliferation, survival and secretion of cytokines that stimulate helper T cells and blunts activity

s or cells infected with viruses. NK cells act quickly and are not specific for
of the body. NK cells also have roles in shaping the adaptive immune

d on activated T-cells but all regulatory T-cells. Activation of GITR increases T-
mAbs causes tumor rejection & immune memory in mouse models of

ytes, B cells and on cancer cells: melanoma, lymphoma, leukemia. T-cells
sion of MHC II and pro-inflammatory cytokines. B- cell CD40 stimulates
ably more significant. For pancreatic cancer the combination of chemo and

mune cell). OX40L is expressed on APCs. Binding of T-cell OX40 causes
y of regulatory T-cells and increases their death. Preclinical binding of OX40

causes antitumor responses by killer and helper T-cells and immunological memory. Phase I clin

Combining checkpoint blockade & co-stimulation
So, taking off the brake and stomping on the accelerator: co-stimulatory agonist mAbs with blo
cancer??). [Khalil et al., 2016]

CAR-T-cell therapy (chimeric antigen receptor) uses ex-vivo (in lab out of body) manipulation o

- Expansion of tumor-infiltrating lymphocytes;
- Gene transfer of synthetic sTCR or chimeric antigen receptor (CAR) into T-cells.

CAR uses a single-chain variable fragment (receptor crafted from an antibody gene and the tran
domain) that sees peptides that don't need to be bound to MHC (aka HLA). This simplifies T-cel
activated and co-stimulated (without APCs??). The next generation of CARs will include more c

Armored CAR T-cells add a second trans gene that gives protection from cell death or increases
CD40L. [Khalil et al., 2016]

CD19-targeted CAR-T-cells are used for B cell lymphomas since CD19 is expressed on B cells bu
chemo to knock down regulatory T-cells prior to the immunotherapy. Some ex-vivo techniques
persistence of the CAR-T-cells is critical and is higher in pediatric patients. Chemotherapeutic c
better than others. CART therapy may make allogenic stem cell transplantation unnecessary. B
large number of other targets for blood cancers in addition to - or instead of - CD19.

CART side-effects include: cytokine-release syndrome; macrophage activation syndrome; neur
be predicated by serum levels of C-reactive protein. [Khalil et al., 2016]

CART for solid tumors is in exploratory stages. Challenges include: immunosuppressive tumor
cells. [Are parts of the ASPS fusion protein unique?] Clincals: mesotheldioma; ovarian; CNS, etc
See Jackson, H. J., Rafiq, S. & Brentjens, R. J. Driving CAR T cells forward. Nat. Rev. Clin. Oncol. 1

Escape from CART can occur by tumor antigen shift, loss of CAR T-cells, loss of CAR T-cell functi
Find a way to get CAR T-cells into the tumor site. Add immunomodulatory therapy to be sure C

Three examples of armored CAR T-cells

- Add second trans gene: chimera of PD-1 extracellular domain with CD28 intracellular sign
  melanoma.
- Trans genes for continual expression of co-stimulatory molecules on CAR T-cells: CD40L,
- Trans genes for secreted IL-2, IL-15, or IL-12. CAR T-cells used as micro-delivery system fo
  inhibition.

nical trial in melanoma is promising. [Khalil et al., 2016]

ockade of PD-1 or PD-L1 is seen as promising and in trials (vs. advanced

of T-cells by several means:

nsmembrane, signaling domain of the T-cell receptor and a co-stimulatory
ll activation: when the transgenic T-cells see antigen they are primed,
ostimulatory domains to provide greater activation. [Khalil et al., 2016]

s ability to kill or changes the tumor microenvironment: IL-12, 4-1BBL or

ut not other immune cells. Clinical success has been seen and seems to require
s appear to exhaust T-cells prior to treatment with them. Survival or
onditioning prior to CAR-T seems critical and some agents and regimens are
Better for B-ALL than CLL. [Khalil et al., 2016] Researchers are looking at a

ological toxicity. These issues are treated with antibodies or steroids and can

microenvironment; heterogeneity of antigens; collateral damage to normal
.
10.1038/nrclinonc.2016.36 (2016).

ion. So? Target multiple tumor antigens. Use 'conditioning chemotherapy.
AR T-cells can be functional, or use armored CART.

naling domain. Better persistence and clearance in syngenic mouse

4-1BBL. The latter allows trans-co-stimulation of neighboring T-cells.
or non-toxic local levels of cytokines. Enhances persistence and resistance to

Does ASPS have a high TIL burden?

References:

Khalil, D., Smith, E.L., Brentjens, R.J., Wolchok, J.D. (2016) The future of cancer treatment: imm
Critical Oncology, 13.5 (May): 273-

unomodulation, CARs and combination immunotherapy, Nature Reviews