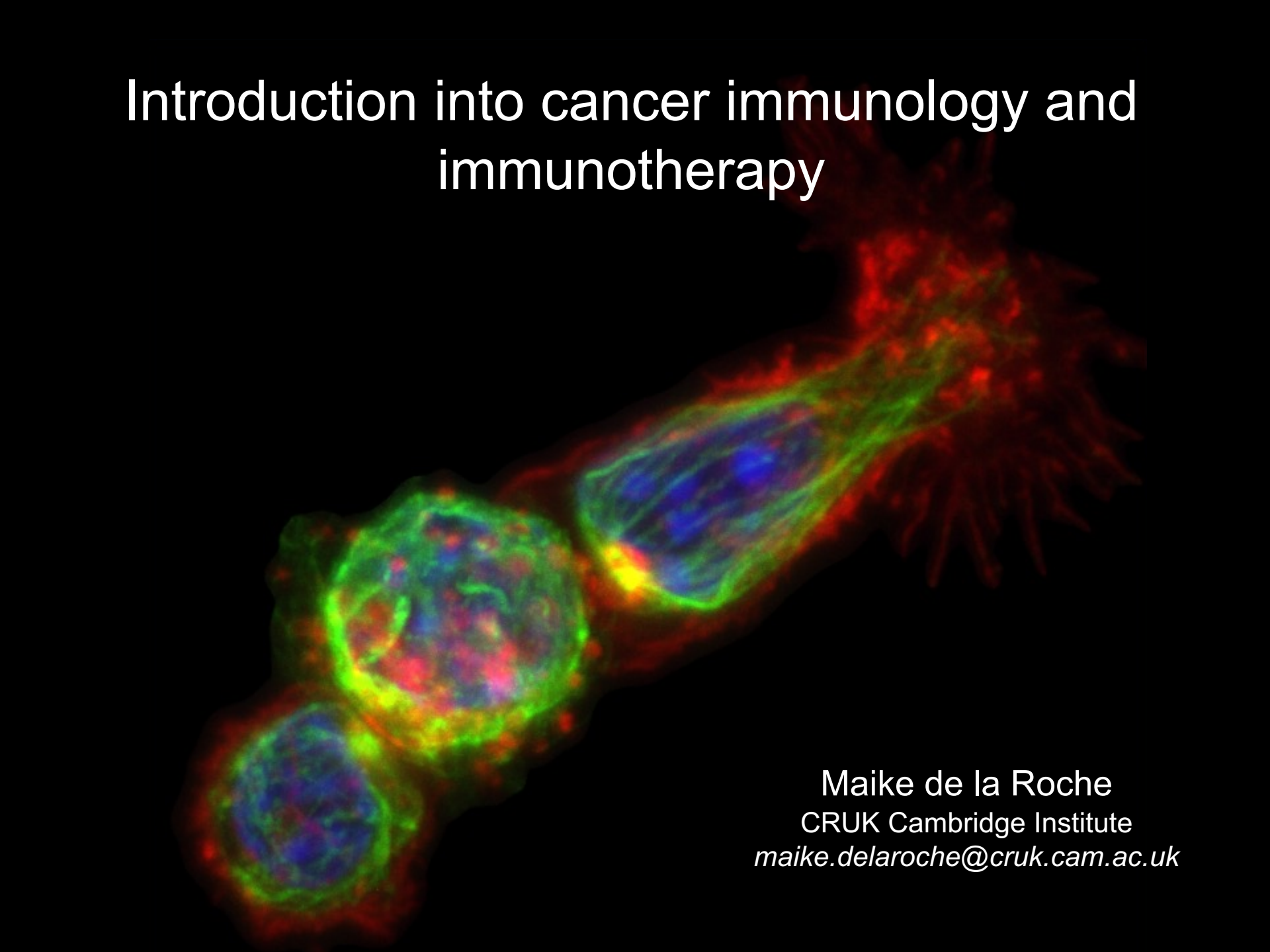
Introduction into cancer immunology and immunotherapy



Maike de la Roche
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Outline:

I) Introduction

II) Cancer immunology

a) Innate and adaptive immune cell subsets
b) Functions of (some) immune cells in the TME
c) Immune evasion by cancer

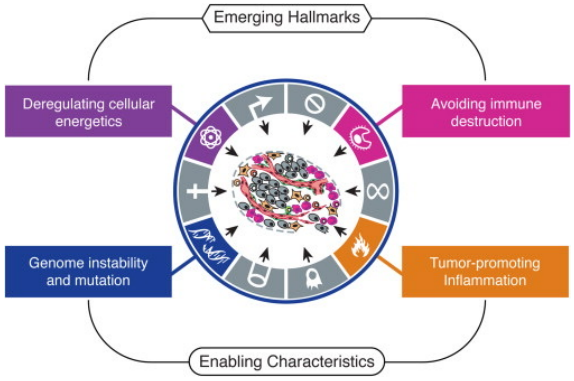
III) Immunotherapy

a) Overview
b) Strategies

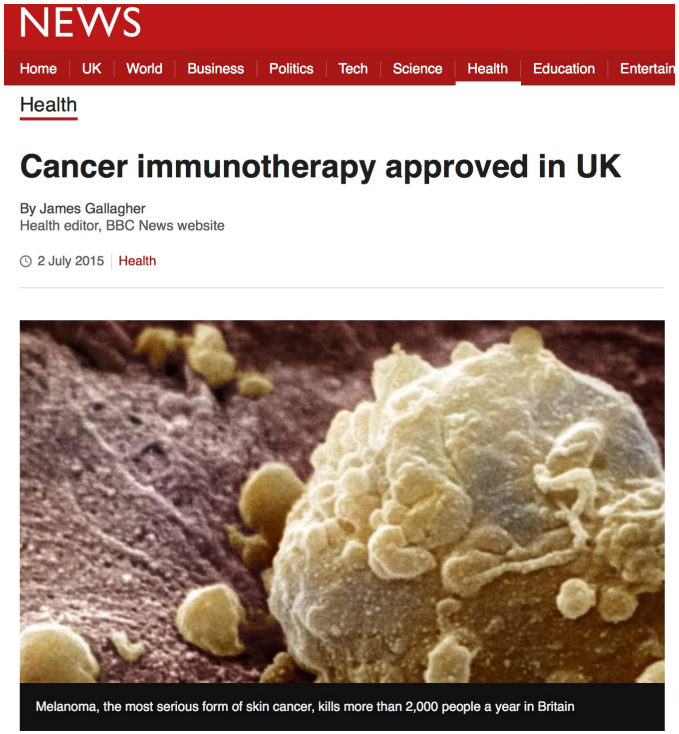
Immunotherapy makes the news

Cancer Immunotherapy:
Breakthrough of the year 2013

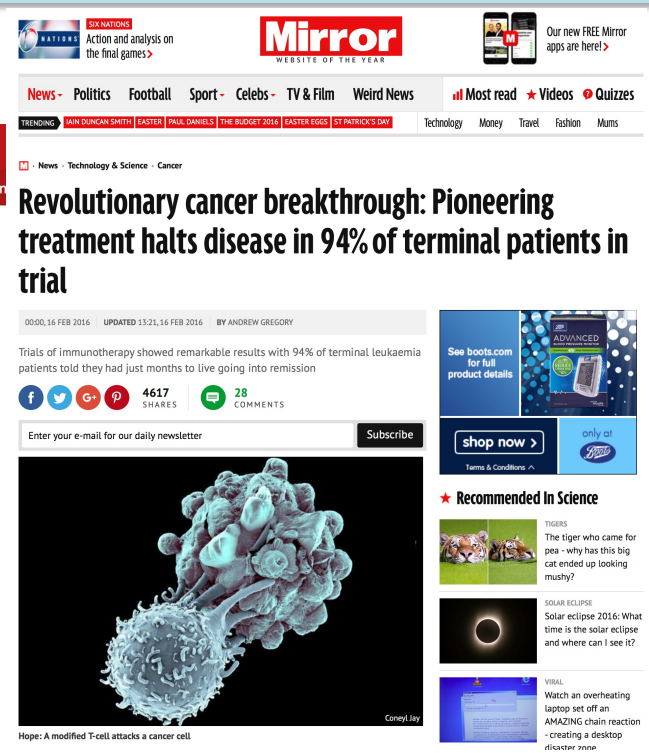
Science 2013



Hanahan and Weinberg, *Cell*, 2011



June 2014: Ipilimumab (anti-CTLA4)
July 2015: Nivolumab (anti-PD1)



Feb 2016: CAR T cell therapy in advanced leukemia

Dec 2015:
Adoptive CAR
(Chimeric Antigen
Receptor)
T cell therapy

Tumour immunology: an historic perspective

Paul Ehrlich (1909): Immune system continuously suppressed nascent transformed cells in our bodies. (Nobel prize, 1908).

Burnet and Thomas (1957): Tumour-associated antigens and the *cancer immunosurveillance hypothesis* – the immune system seeks out and destroys cancer cells.

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Strutman, Rygaard & Povlsen: Challenged cancer immunosurveillance hypothesis - athymic nude mice (T cells) are no more susceptible to tumorigenesis than wild-type mice.
> cancer immunosurveillance concept considered dead by 1978

Problems with these studies:
nude mice have αβT cells, NK cells, γδ T cells and observation period too short (3-7months)

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Renaissance 1990s:
Use of inbred strains (no allograft rejection) with compromised immune cell function (IFNg-/-, perforin-/-, Rag2-/-…), specific loss of immune cell subsets

>>> enhanced tumour susceptibility

Immunotherapy - using the immune system to combat cancer

William Coley

1890s: first cancer vaccine

1978: Discovery tumor specific antibodies

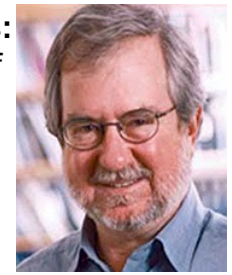
1988: 1st study with adoptive TIL transfer

Steve Rosenberg

1989: 1st functional CAR T cell

Zelig Eshar

Early 1990s: Discovery of checkpoint inhibitor anti-CTLA4



James Allison

Tasuku Hondo

Early 1990s: Discovery of checkpoint PD-1

Renaissance

1986: IFNα approved for cancer

1997: 1st antibody approved for cancer

1998: IL-2 approved for cancer

2010: 1st cellular immunotherapy approved for cancer

2010: 1st therapeutic vaccine approved for cancer

2011: 1st checkpoint inhibitor approved for cancer

2011: First effective CAR T reported. Paved the way for FDA approval

2018: Nobel prize- Allison and Hondo

Immune checkpoint pathways

The Nobel Prize in Physiology or Medicine 2018 was awarded

jointly to **James P. Allison** and **Tasuku Honjo**

“For their discovery of cancer therapy by inhibition of negative immune regulation."

II) Cancer immunology

Our Immune system:
a powerful and numerous work force

peripheral blood:

1ml

4.500.000 - 10.000.000

immune cells !!!!!!

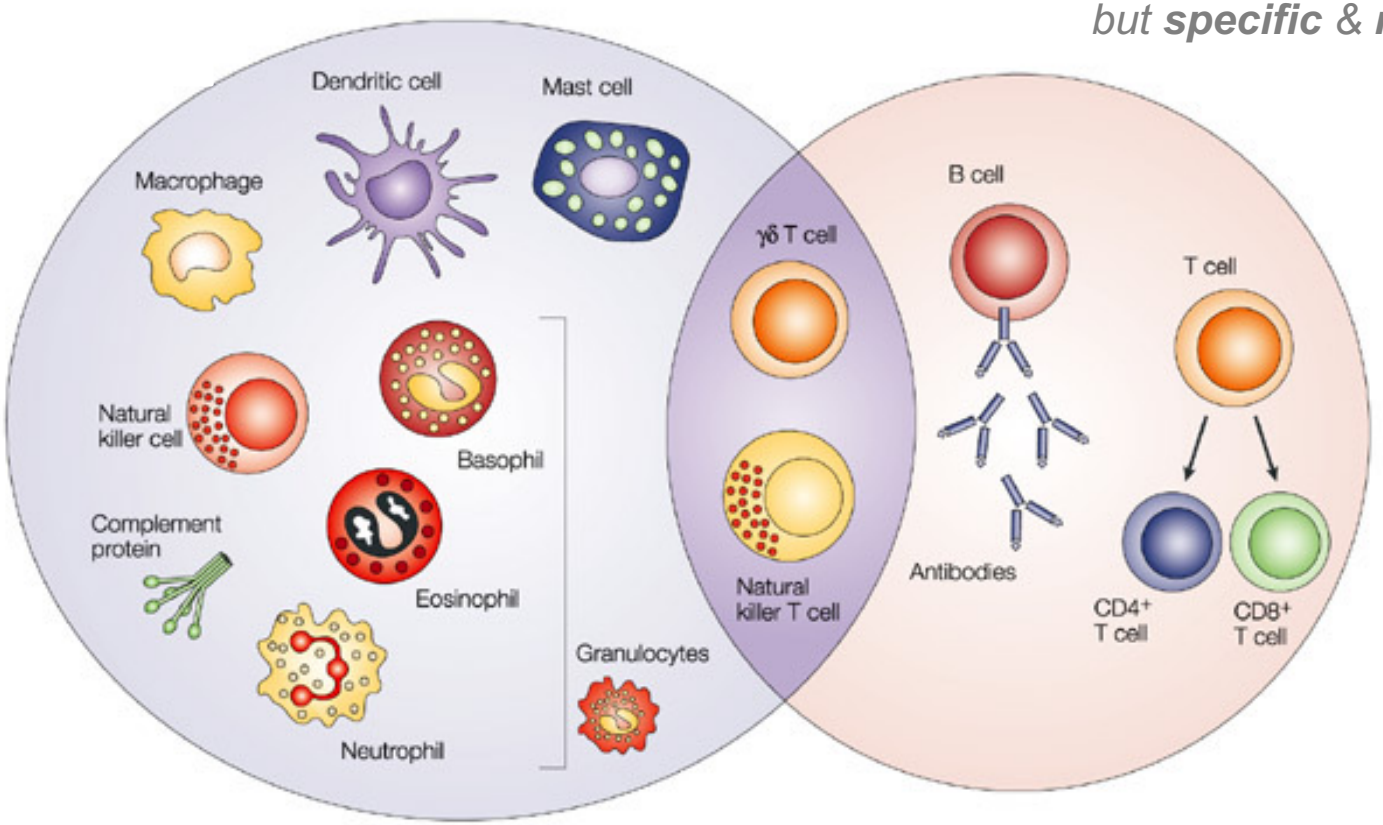
Our Immune system: the players

1st line of defense

(fast)

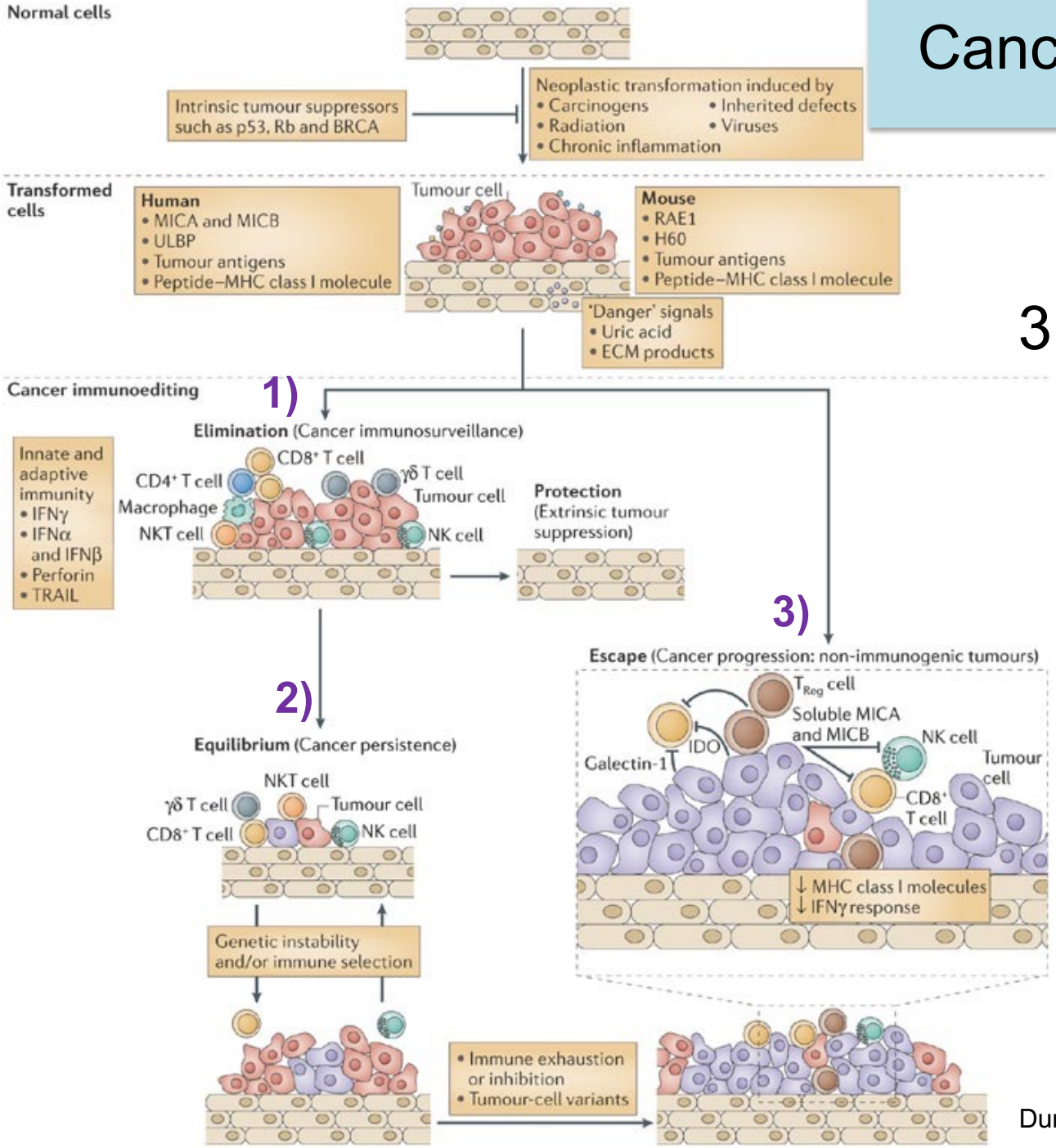
2nd line of defense

*(adaptive: slow but **specific** & **memory**)*



Glenn Dranoff, Nat Rev. Cancer (2004)

Cancer immunoediting



3 phases:

1) **Elimination** (Immune surveillance)

2) **Equilibrium**

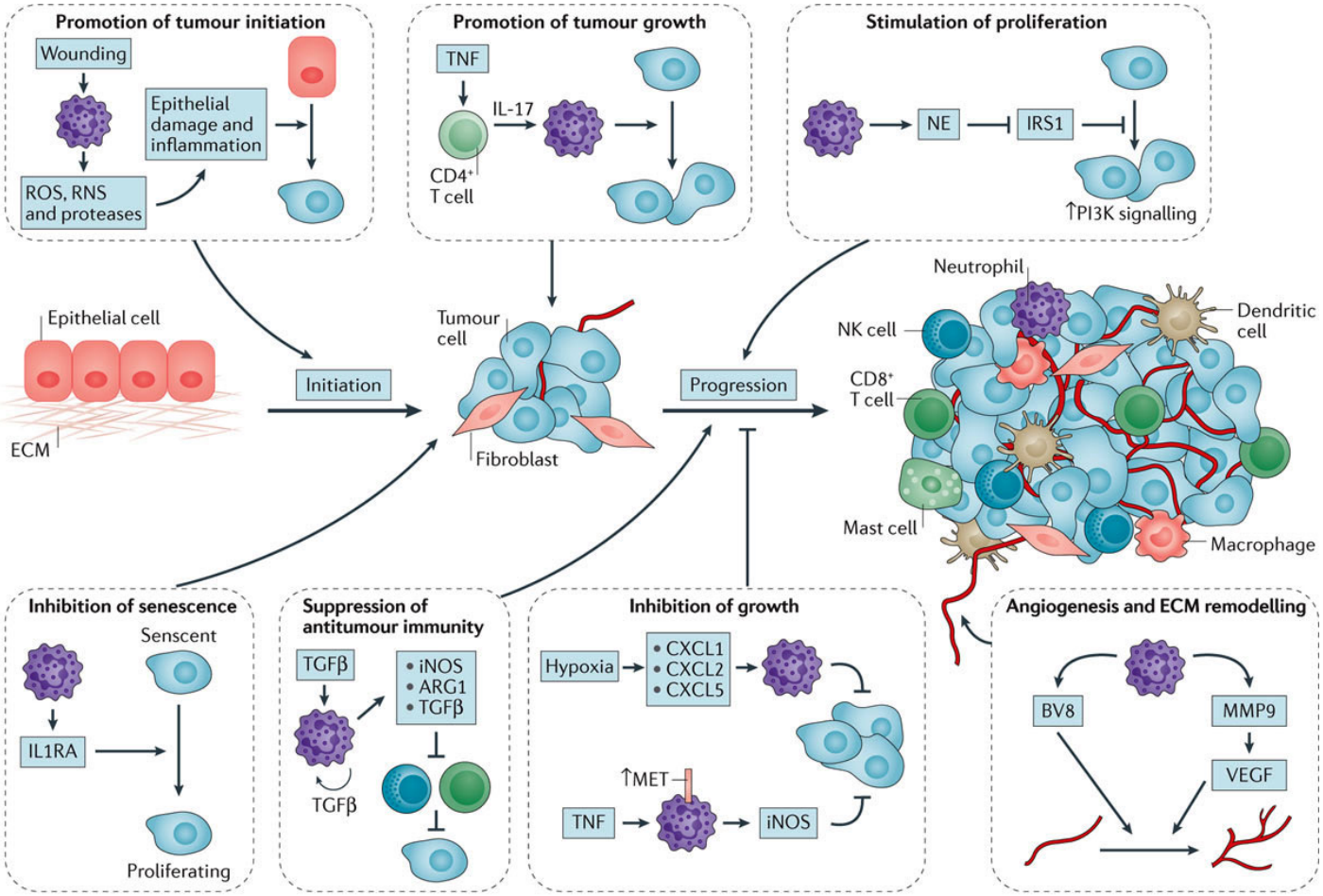
3) **Escape**

Dunn, Koebel, Schreiber, *Nat Rev Imm*, 2006

Neutrophils

Most abundant immune population in humans (50-70% of all leukocytes) & tumours can increase numbers further

Can oppose or potentiate cancer progression depending on signals received from cancer and stromal cells in the tumour microenvironment



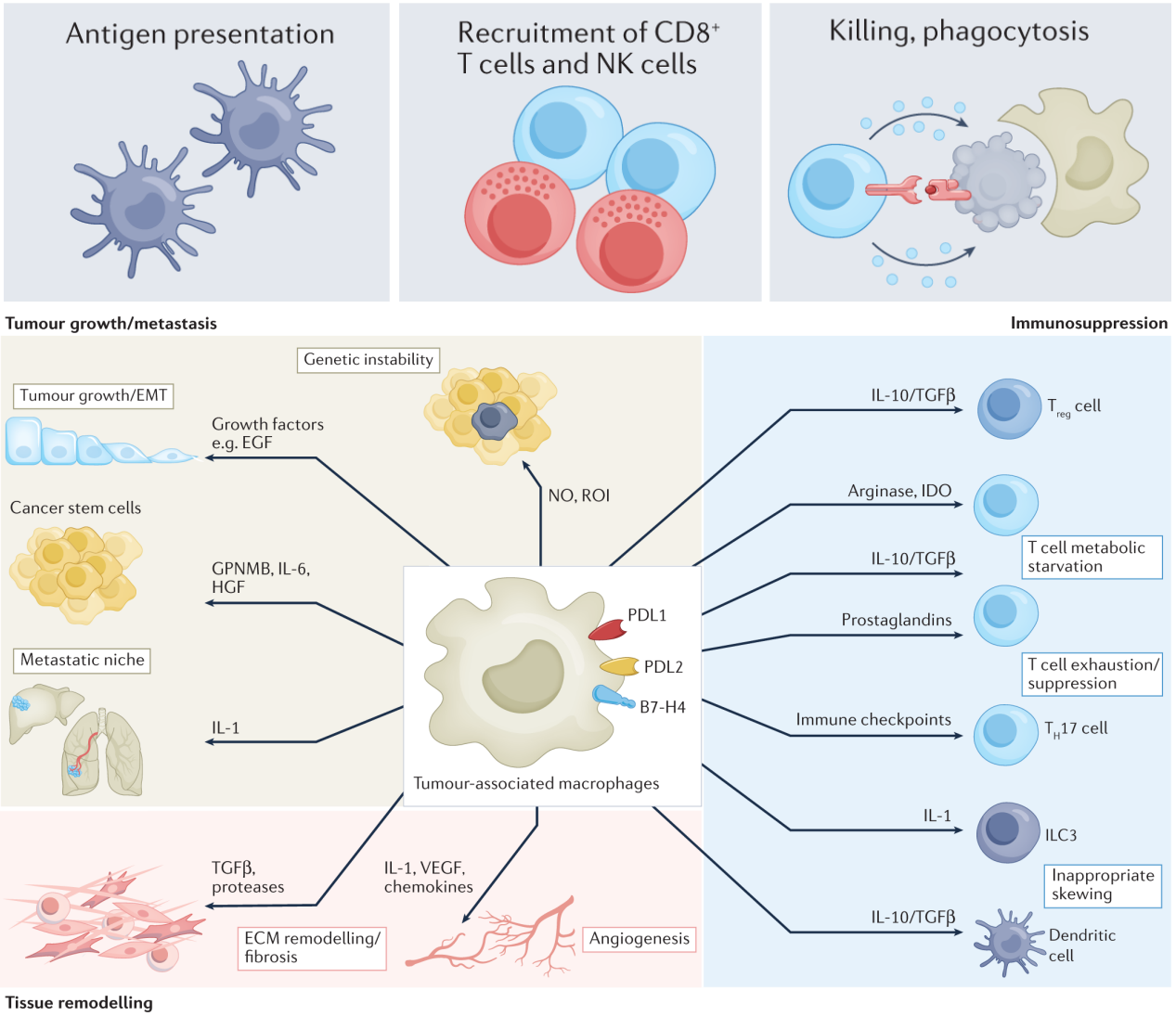
Coffelt et al, Nature Rev Cancer, 2016

Macrophages

M1 versus M2

anti-tumour

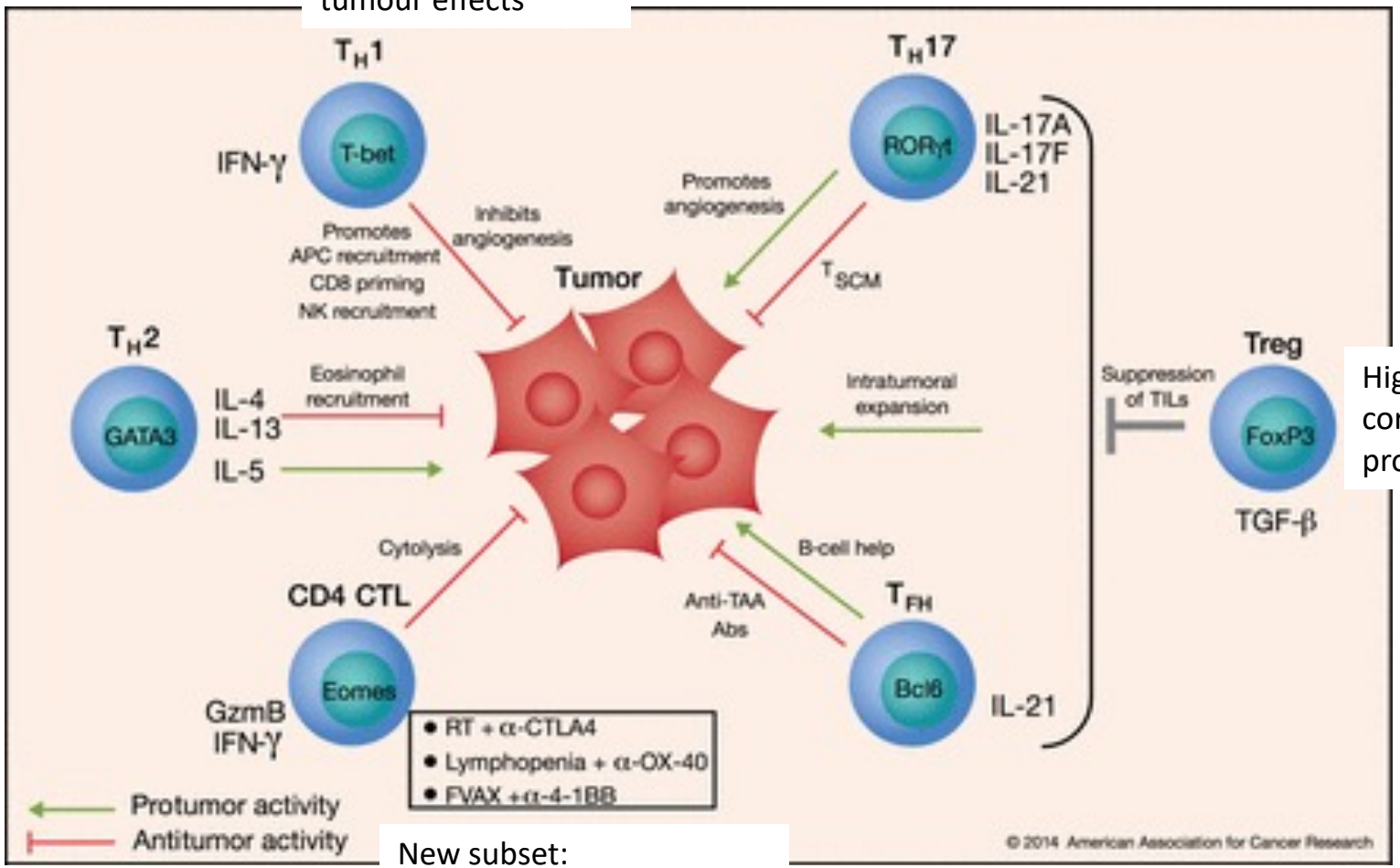
pro-tumour



Mantovani et al, Nature Rev Drug Discovery, 2022

CD4+ T cell subsets
(The Helpful and the Not-so-Helpful)

T_H1 polarized CD4 have many anti-tumour effects



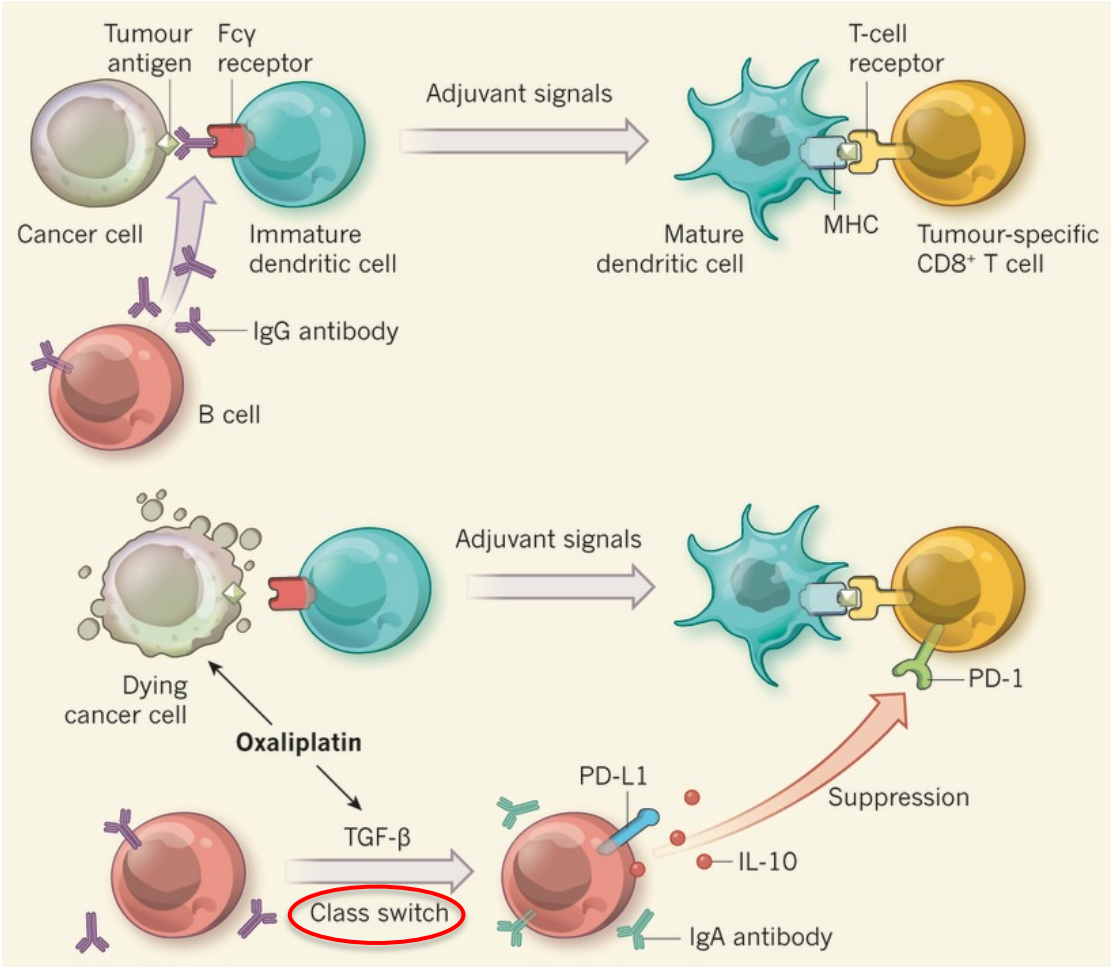
High levels of Tregs correlate with poor prognosis

New subset:
Cytotoxic CD4 T cells can kill tumour cells in an MHCII mediated fashion

Kim et al, Cancer Imm Research, 2014

B cells

anti-tumour antibodies described for long time, but anti-tumour effect of antibody-producing B cells are rare



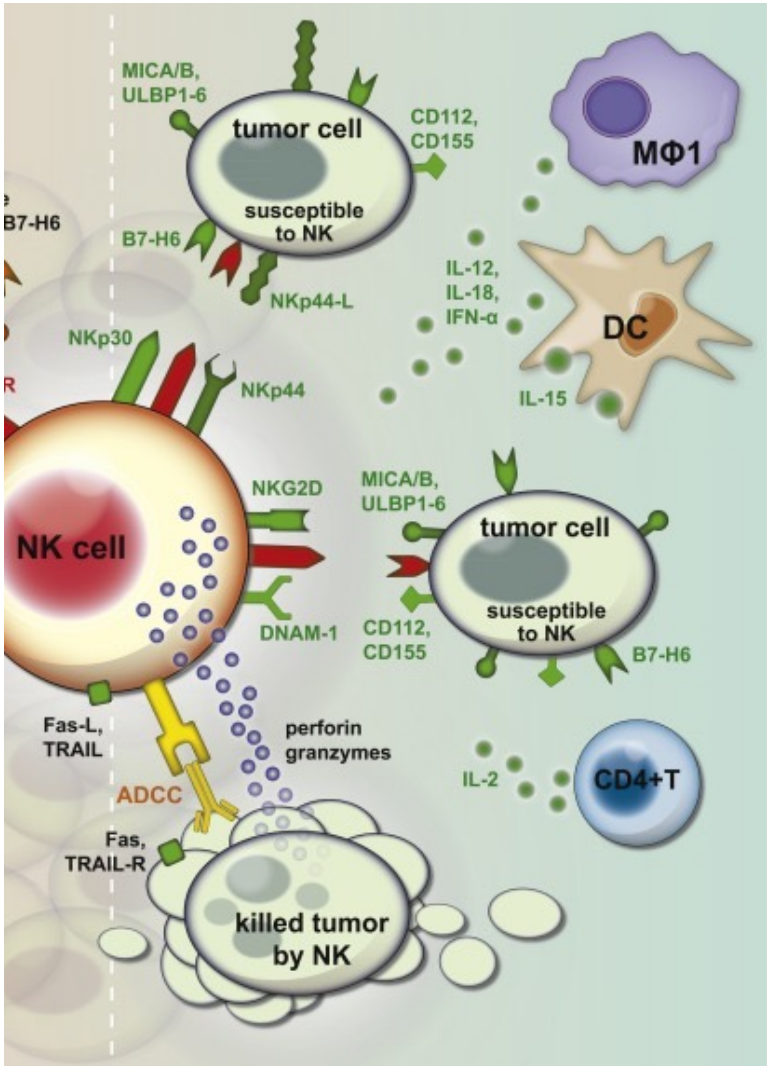
\+

therapeutic IgG
+adjuvant

\-

Zitvogel and Kroemer, Nature 2015

Natural Killer cells



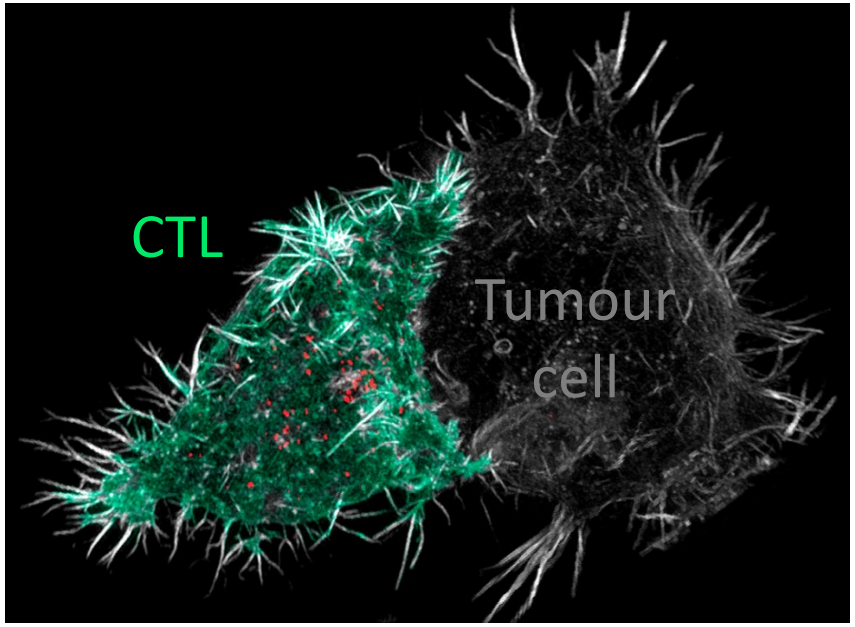
+/- interactions with tumour cells are mediated via activating (green) and inhibitory (red) receptors

>surplus activating signals lead to perforin and granzyme release and tumour cell killing

Tumour cell apoptosis also achieved through FasL, TRAIL, ADCC (antibody-dependent cellular cytotoxicity, FcγRIIIa/CD16)

Pahl and Cerwenka, Immunobiology 2016

$CD8^+$ T cells are <u>crucial</u> for the immune mediated control of cancer



Block malignant tumour progression

DuPage *et al*, *Nature* (2012)
Matsushita *et al*, *Nature* (2012)

Associated with good prognosis in many human cancers

Galon *et al*, *Science* (2006)
Fridman *et al*, *Nat. Rev. Cancer* (2012)

Checkpoint blockade (α-CTLA4,α-PD1)

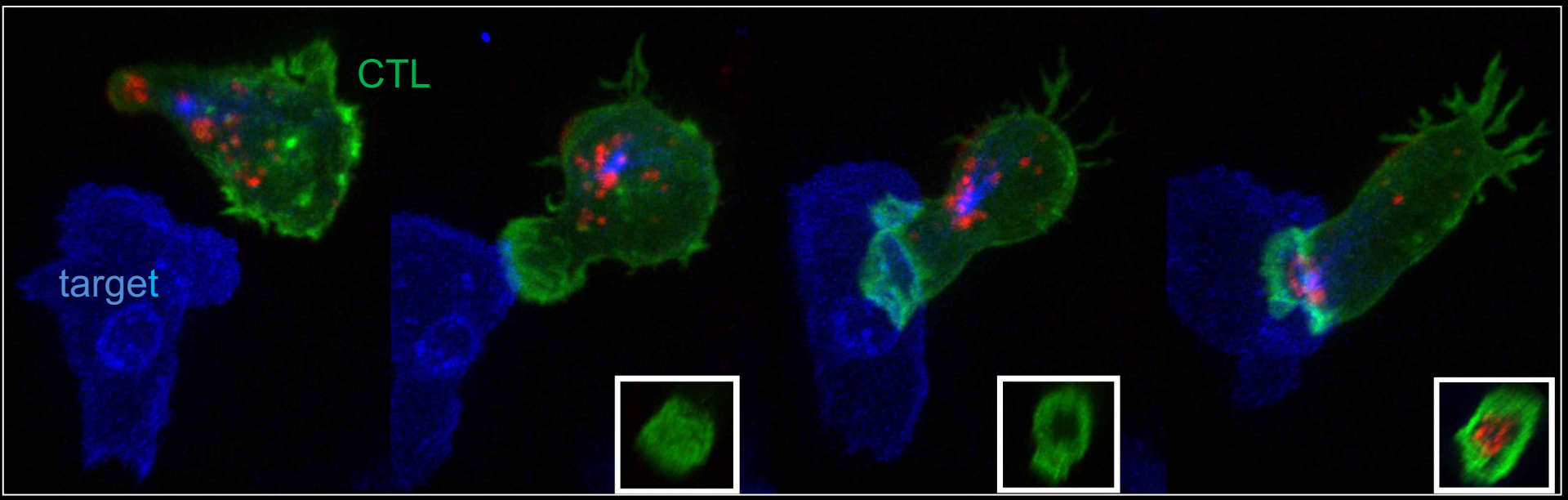
Hodi *et al*, *NEJM* (2010)
Wolchok *et al*, *NEJM* (2013)
Turmeh *et al*, *Nature* (2014)

Adoptive T cell therapy

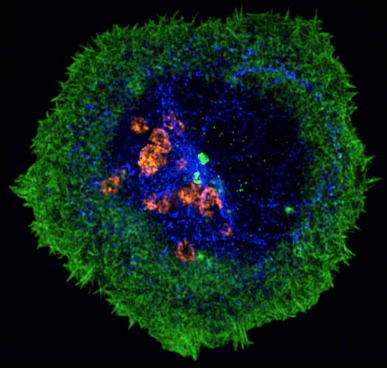
Hinrichs and Rosenberg, *Imm. Rev.* (2013)

The mechanism of CTL Killing

actin
centrosome
lytic granules

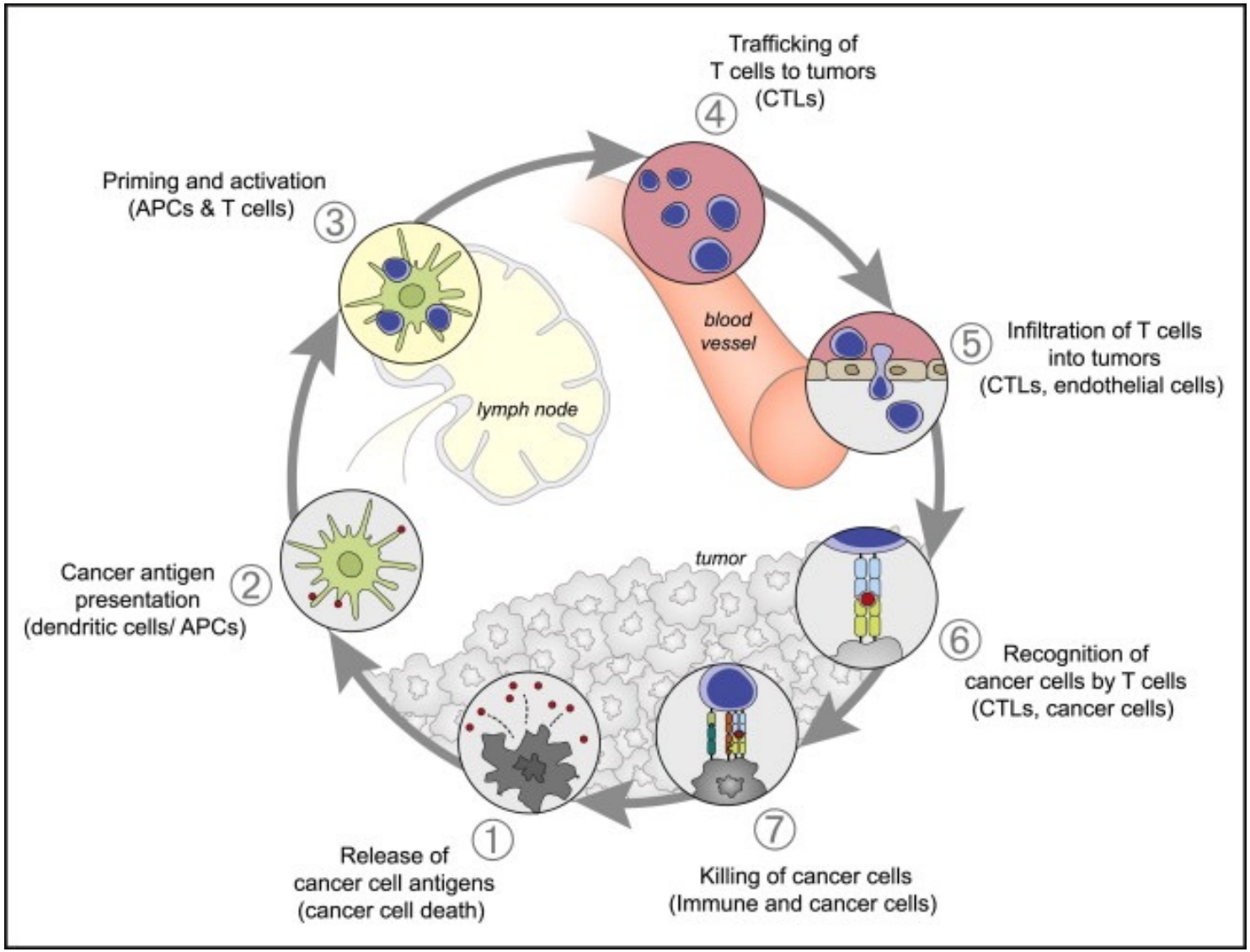


reorganisation of the actin and microtuble cytoskeleton enables CTL killing



Griffiths lab

The Cancer-Immunity Cycle

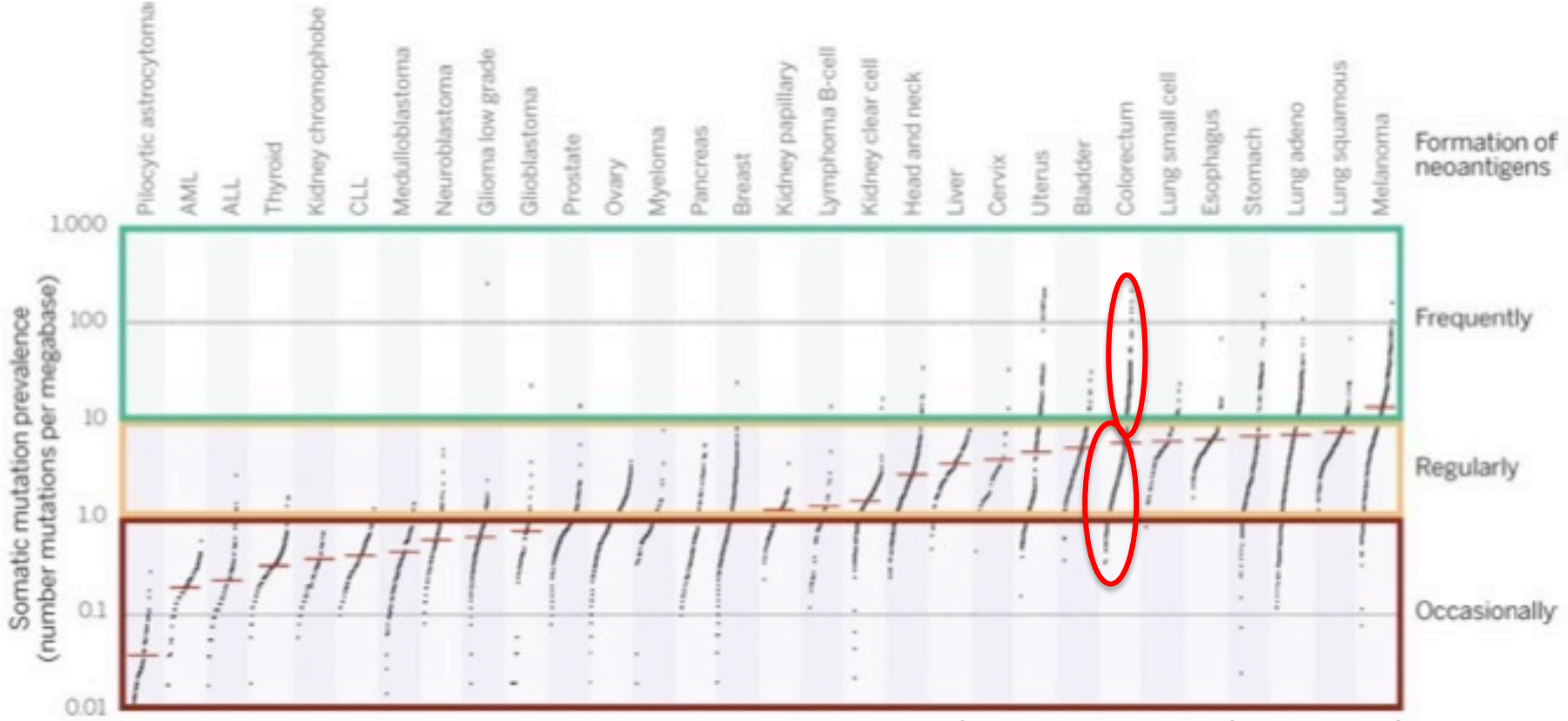


Chen and Mellman, *Immunity* 2013

What do T cells “see”?

I) Tumour associated antigens (TAAs): overexpressed, lineage-specific antigens

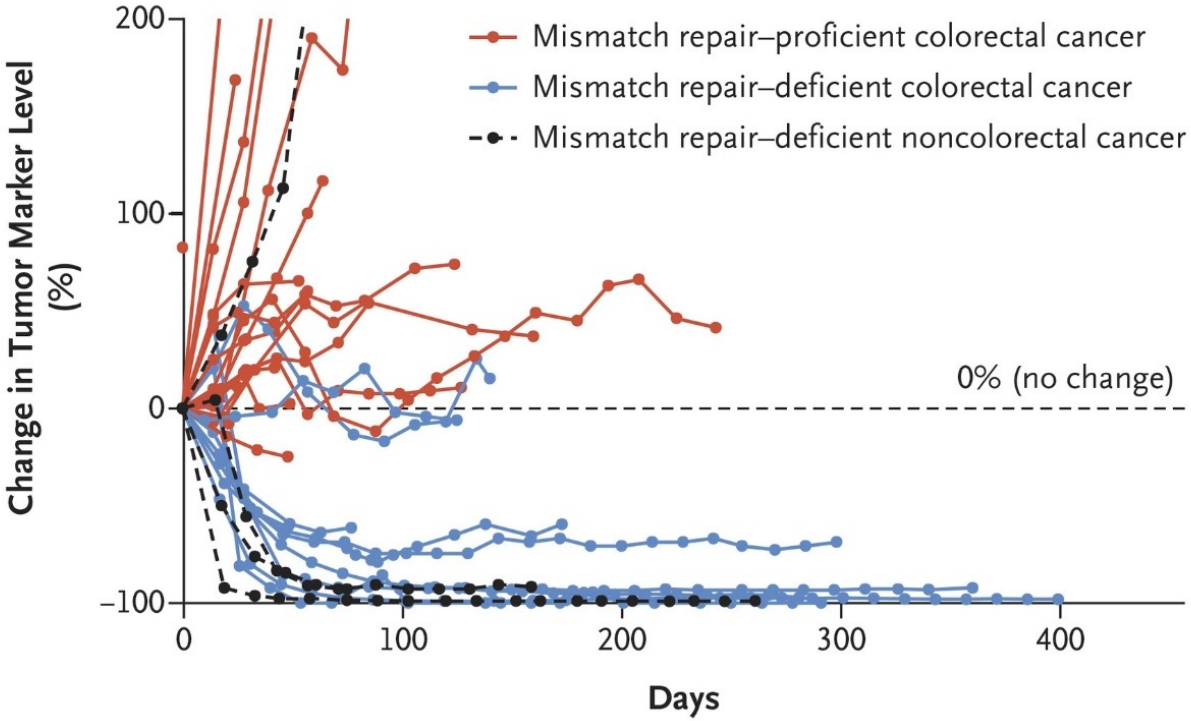
II) Tumour specific antigens (TSAs): Neoantigens, mutations in the tumour genome lead to expression of mutant proteins

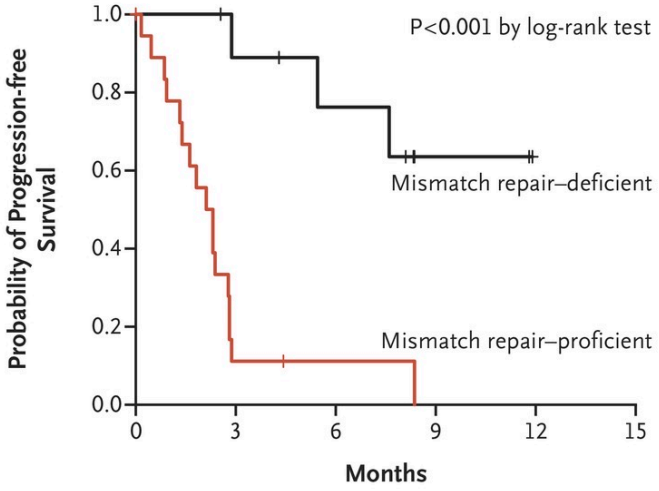


Schumacher and Schreiber, Science, 2015

T cells vs neoantigen repertoire

Pembrolizumab (anti-PD1) therapy

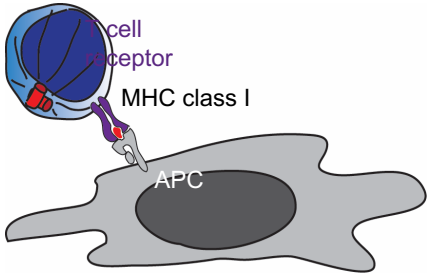


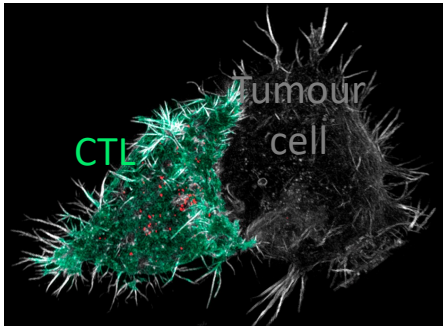


Dung et al. *N Engl J Med,* 2015

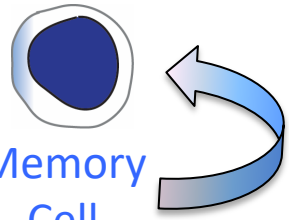
Advantages of anti-cancer CD8$^+$ T cell responses

specific

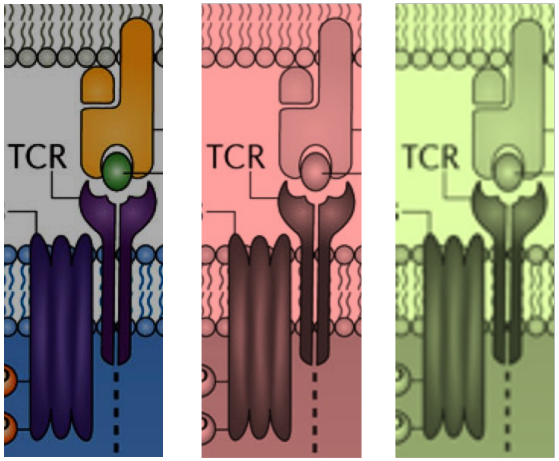




durable

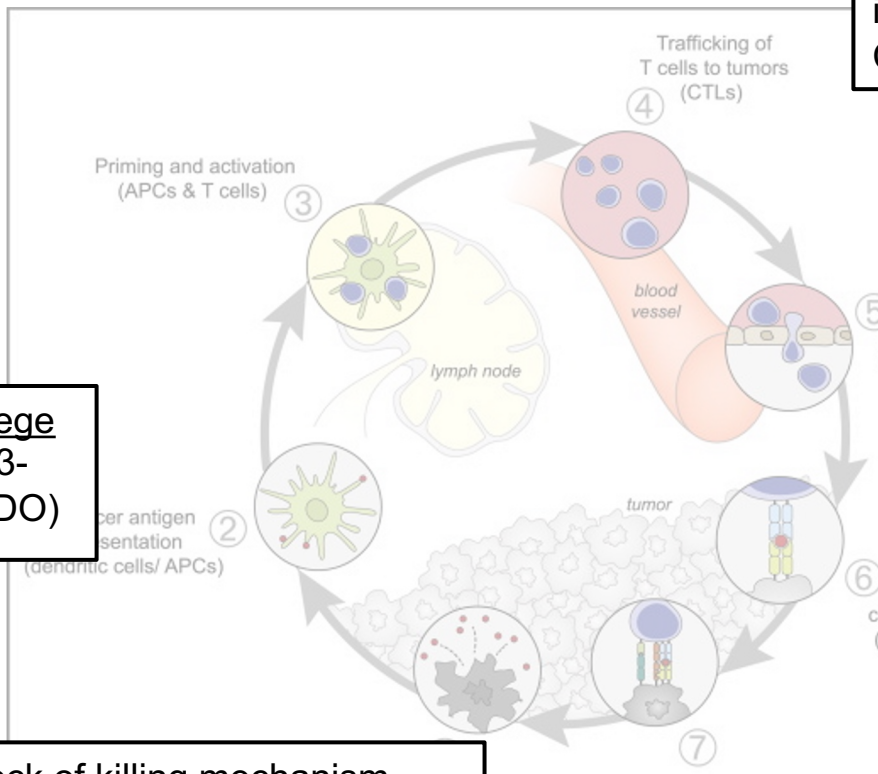


adaptable/evolving



Immune evasion mechanisms

Immune evasion mechanisms of the CD8 T cell response



T cell exclusion
inhibition of extravasation
CTL trapped in stroma

TCR/CD28 signalling
- PD-L1/L2 (tumour) - PD1(T cell): SHP-1,-2 recruitment

Immune privilege
- Indolamine 2,3-dioxygenase (IDO)

Antigen presenting machinery
downregulation/loss of MHCI
Shedding of NKG2D ligands (e.g. MICA/B)

Block of killing mechanism
- PI9/SPI-6 inhibit GzmB protease -
- Decreased CD95/FAS expression and function
- Decoy receptors (CD95L)

Immunesuppressive cells
Tregs, MDSCs, M2 macrophages

III) Immunotherapy

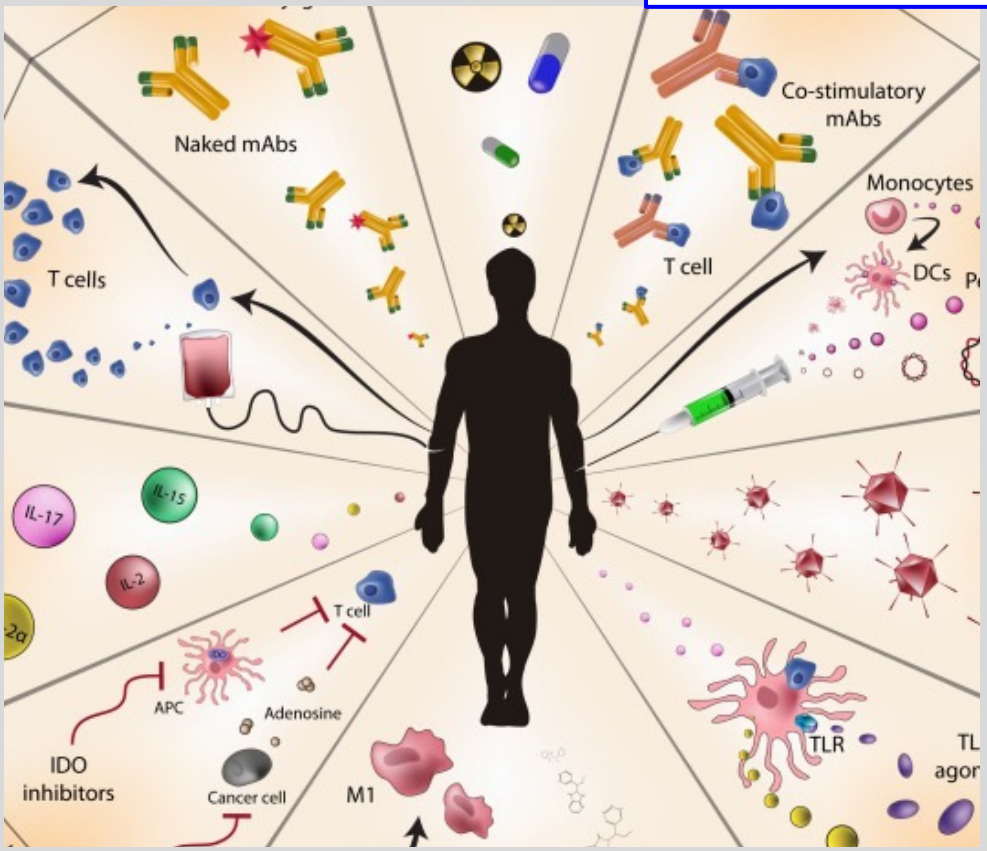
Many immunotherapeutic approaches

Bispecific Engagers

Antibody Drug conjugates

Immunomodulatory antibodies:
I) Checkpoint blockers
II) Costimulatory antibodies

Adoptive T cell therapy



Cytokines

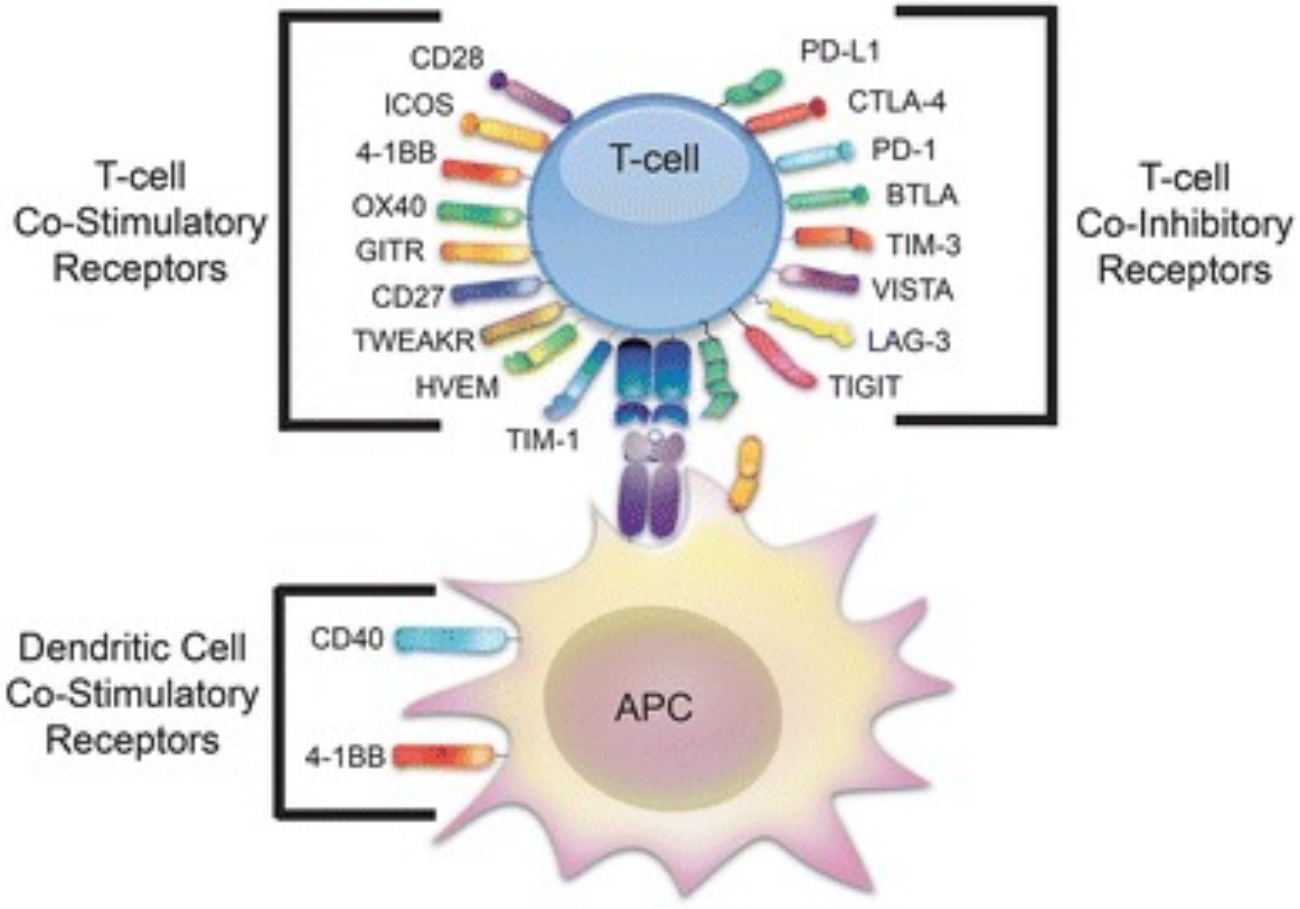
Cancer vaccines

Oncolytic viruses

Immune checkpoint pathways

Normally maintain self-tolerance and limit collateral tissue damage during anti-microbial immune response

Co-opted by cancer to evade immune destruction



Ai and Curran, *Cancer Immunol. Immunother.* 2015

Immune checkpoint pathways

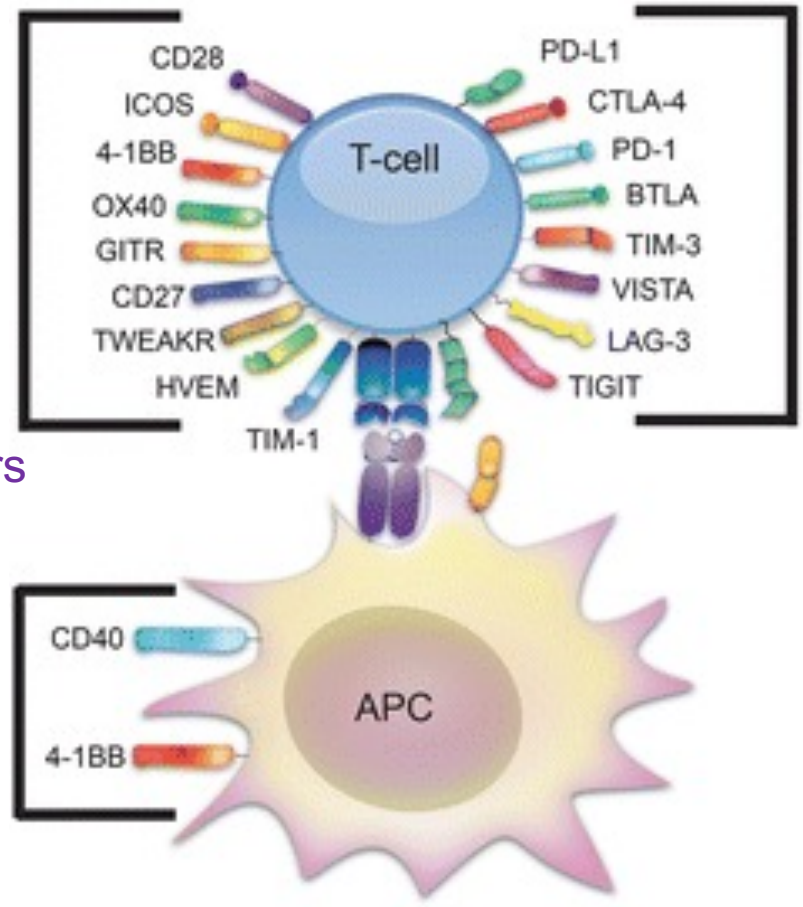
Required to maintain self-tolerance and limit collateral tissue damage during anti-microbial immune response

Co-opted by cancer to evade immune destruction

2 therapeutic approaches:

(1)

Engaging Costimulatory receptors



(2)

Blocking immune checkpoints

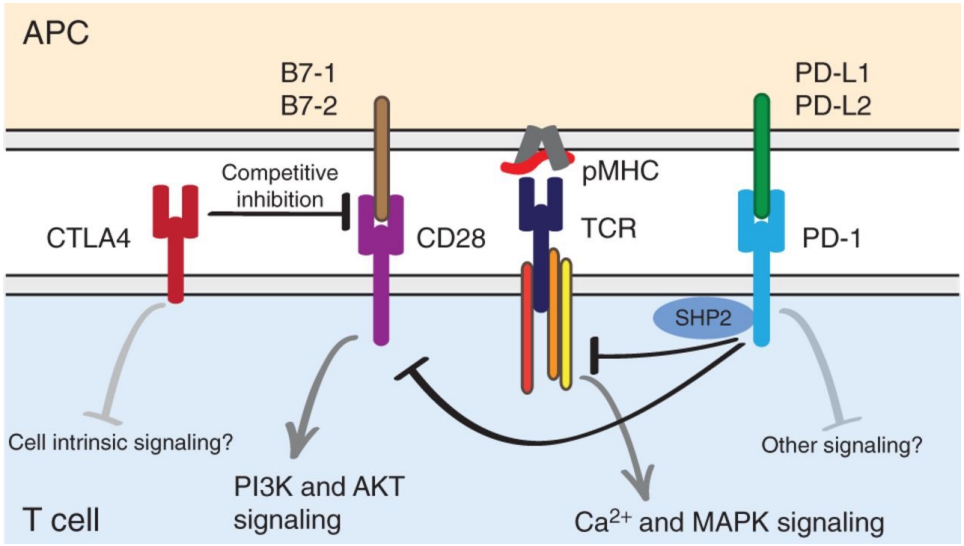
e.g. blocking anti-CTLA-4, anti-PD-1, anti-PD-L1 can mediate durable cancer regressions by

"unleashing the brakes"

Ai and Curran, *Cancer Immunol. Immunother.* 2015

Immune checkpoint blockade: Mechanisms of action?!?

How and where?



<u>Block of inhibition of immune activation and effector differentiation:</u>
anti-PD1 – alleviate TCR signaling inhibition
CD28 activation - co-stimulation
anti-CTLA4 – alleviate TCR signaling inhibition

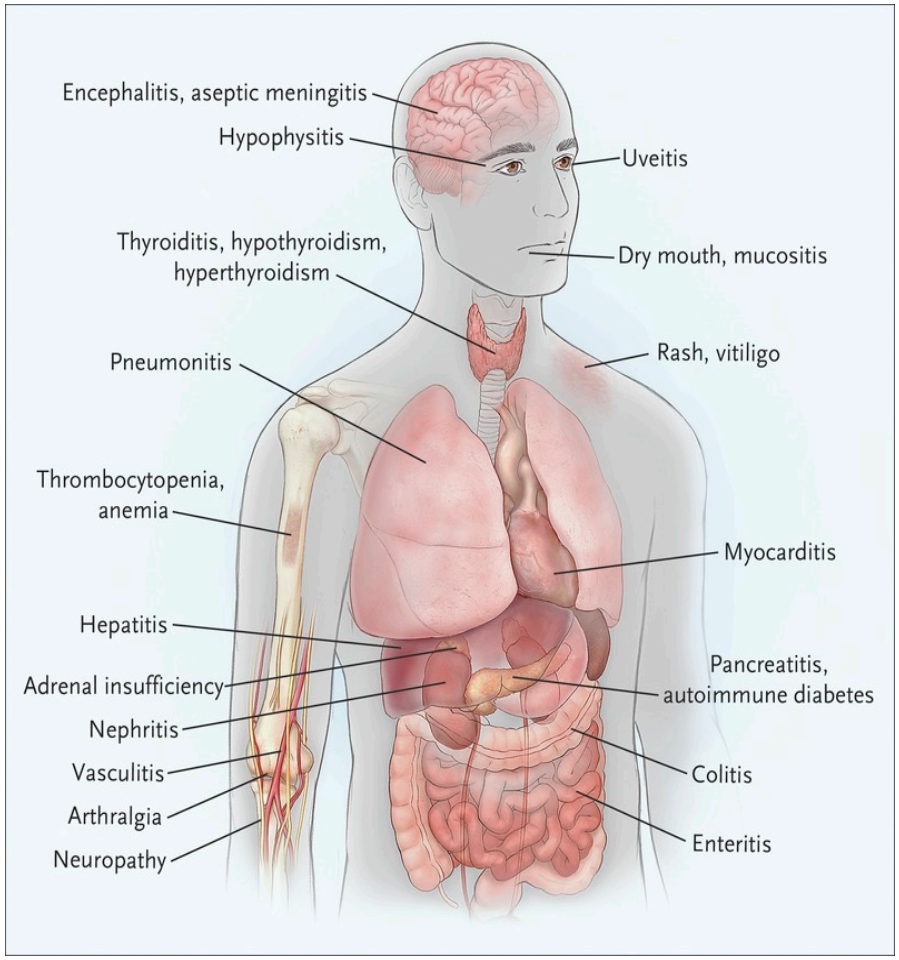
<u>Depletion of Tregs from TME:</u>
FcγR-dependent uptake by tumour infiltrating macrophages (CTLA-4)

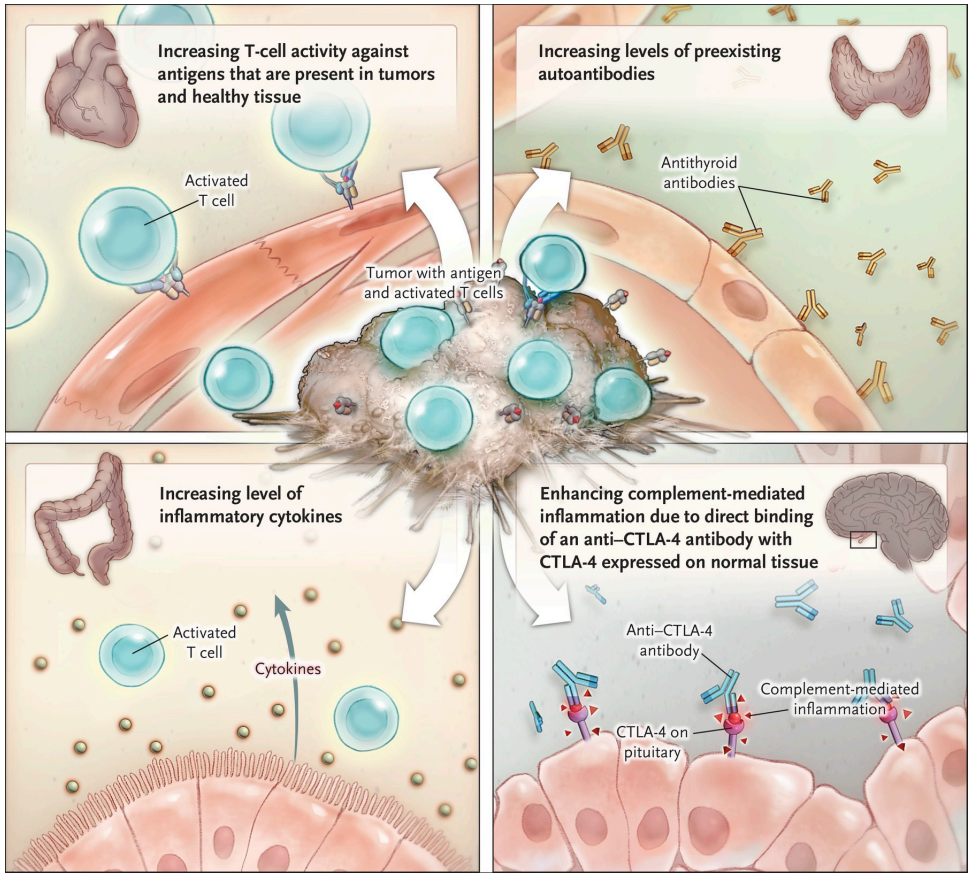
<u>Increase in metabolic fitness of effector cells:</u>
c-MYC, PI3K/AKT/mTOR

<u>Resistance:</u>
Innate (tumour cell intrinsic): JAK1/2 mutations, loss of b2M
Adaptive: IFNγ-driven PD-L1 upregulation in tumour or leukocytes

Adverse immune-related effects of checkpoint blockade & possible mechanisms

autoimmune manifestations





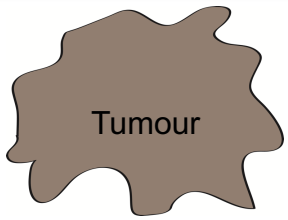
Postow et *al*, *NEJM*, 2018

> Some Immune-Related Adverse Events can correlate with improved survival (e.g. rash & vitiligo in melanoma patients) *Freeman-Keller et al, Clinical Cancer Research, 2015*

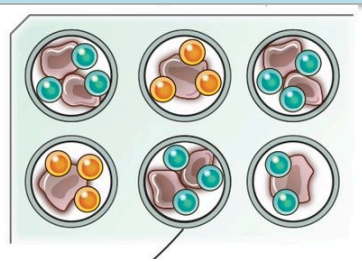
> management: systemic steroids (immune suppression may compromise the anti-tumour response)

Adoptive T cell therapy

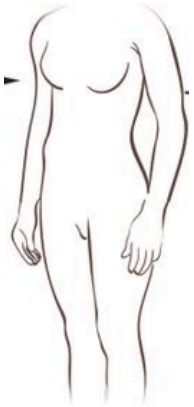
1)



TILs



Expansion
&
quality control



Adapted from Rosenberg and Restifo *Science* 2015

Adoptive T cell therapy

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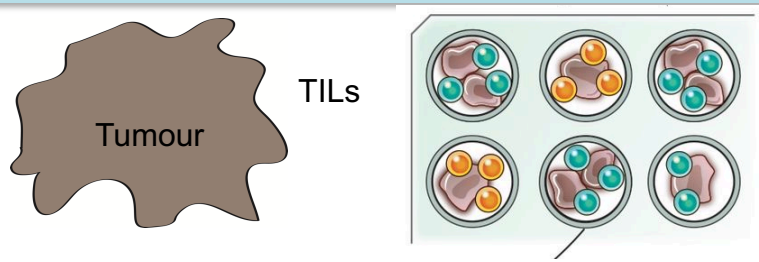

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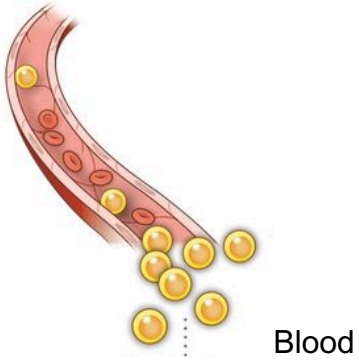
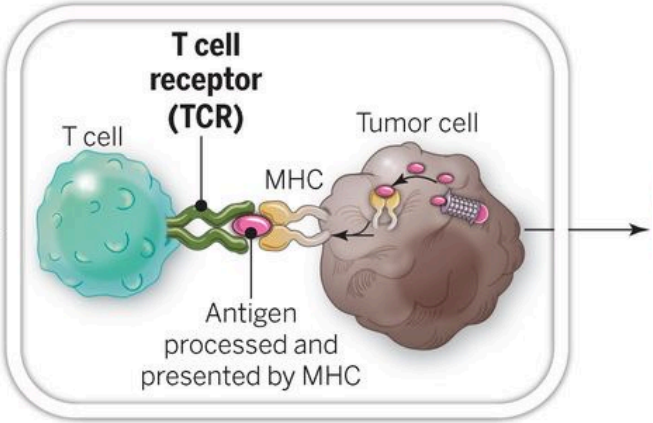
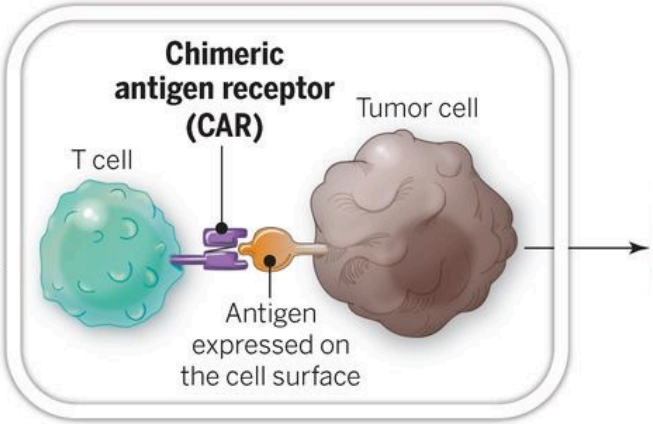
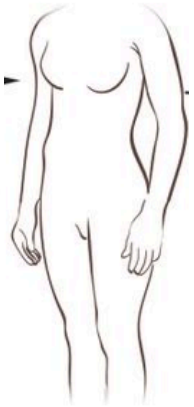




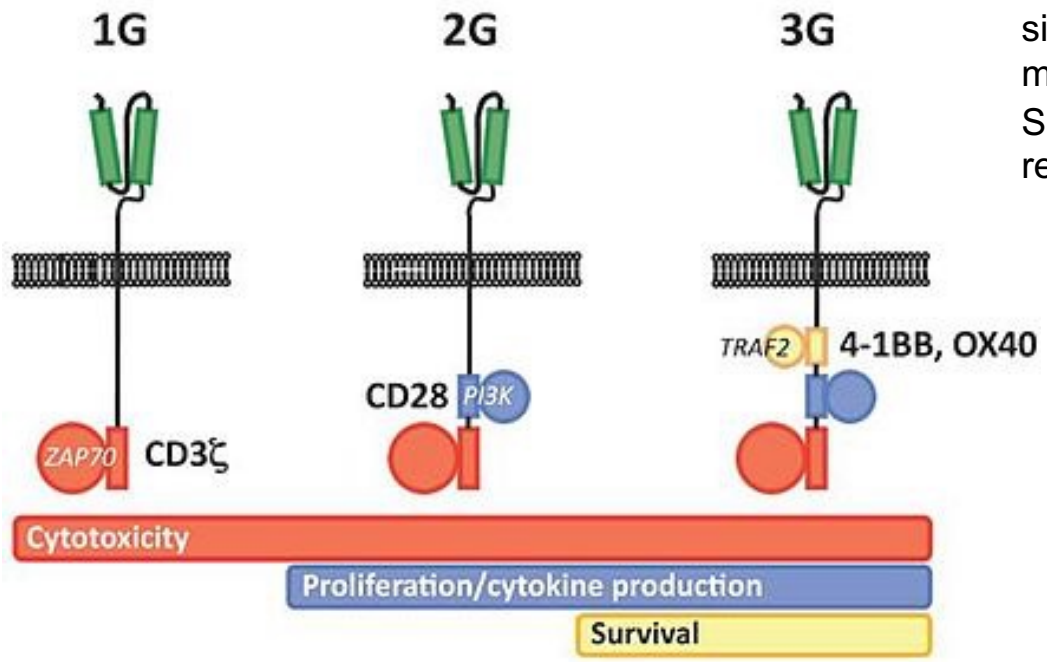


Expansion & quality control



Adapted from Rosenberg and Restifo Science 2015

CAR-T cell (Chimeric Antigen Receptor T cell) design



Casucci et al, Journal of Cancer 2011

Ectodomain (recognition)

Signal peptide (ER)>Glycosylation + PM

Antigen recognition region (e.g. single chain variable fragments from monoclonal antibodies)

Spacer (flexile to facilitate antigen recognition)

Transmembrane domain

Endodomain (function)

Here evolution of design to make CARs more effective

Yescarta (CD19, Novartis) approved for B-ALL & DLBCL, 2017 (US), 2018 (EU)
Kymriah (CD19, Gilead) approved for DLBCL, 2017 (US), 2018 (EU)
Tecartus (CD19, Gilead) approved for ALL, Mantle Cell Lymphoma, 2020 (US), 2020 (EU)
Breyanzi (CD19, Juno Therapeutics) approved for DLBCL, 2021 (US), 2022 (EU)
Abcema (BCMA, Bristol Myers Squibb) approved for Multiple Myeloma, 2021 (US), 2021 (EU)
Abcema (BCMA, Johnson and Johnson) approved for Multiple Myeloma, 2022 (US), 2022 (EU)

Adverse immune related effects of CAR-T therapy

July 2016: Juno Therapeutics halted a trial after 3 young leukemia patients died of cerebral edema (chemotherapy drug fludarabine), overall 5 out of 68 patients died during study

Cytokine release syndrome (CRS, "Cytokine Storm")

- fever, nausea, extreme fatigue, difficulty breathing, low blood pressure, organ swelling
- Exacerbated in patients with high tumour load
- IL-6, TNF-α, IFN-γ release following immune cell activation (often accompanied by macrophage activation syndrome and tumour lysis syndrome)

>>> reduced number of infused CAR T–cells, anti-IL-6 antibody, steroids

On-target, off tumour toxicities

CD19 targeted CAR T-cells deplete B cells

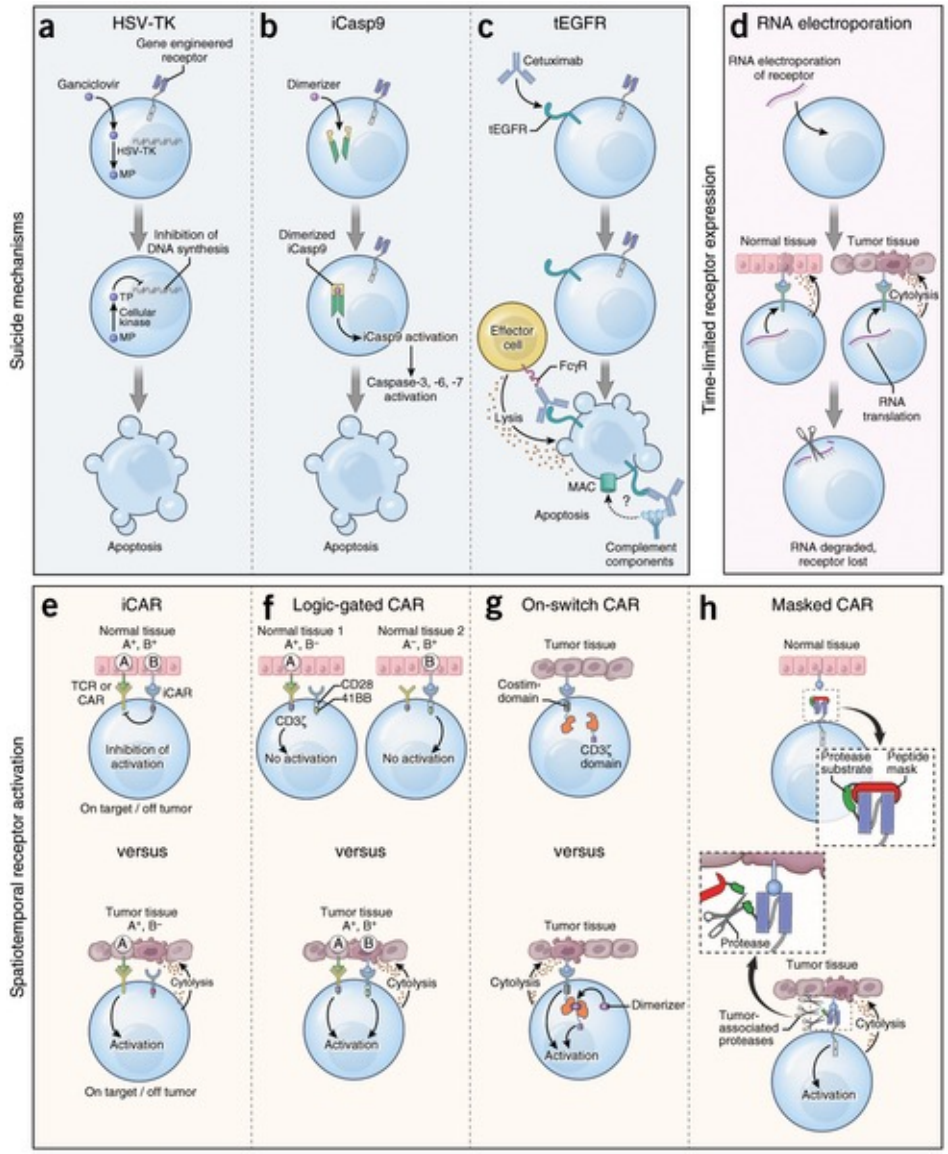
>>> infusions of gamma globulin

Carbonic Anhydrase IX-targeted CAR T-cells for renal cancer target normal bile duct epithelial cells, HER2-targeted CAR T-cells for CRC lead to pulmonary infiltration.

Off-target toxicities

CAR T-cells targeting healthy cells (e.g. Titan, a protein in heart muscle)

Towards safety and tissue selectivity of gene-engineered T cells



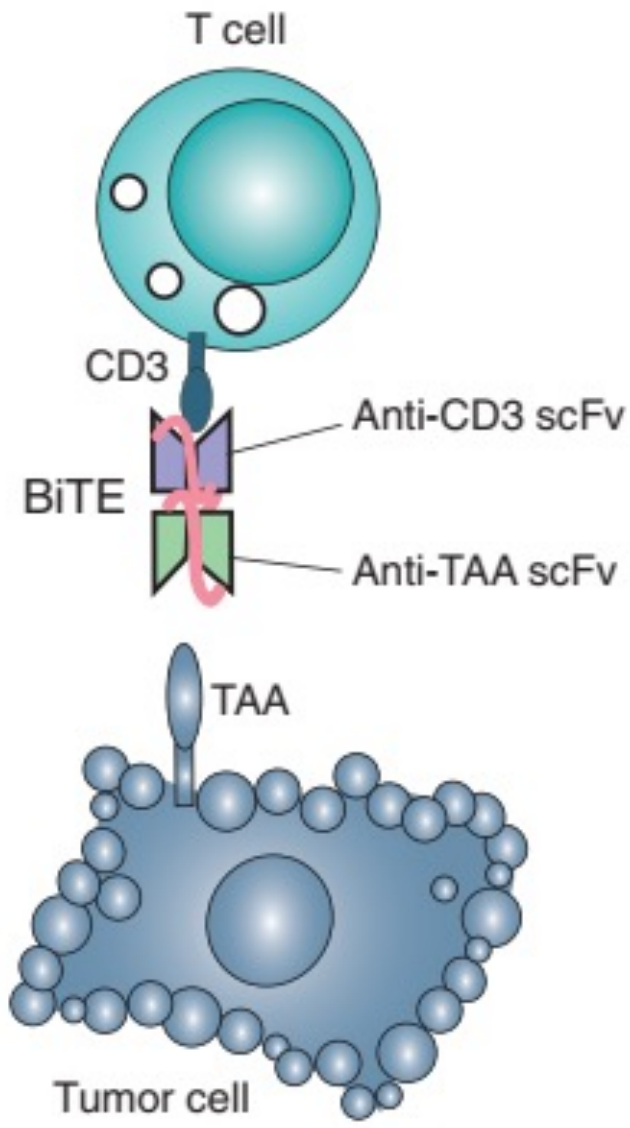
I) Suicide genes

II) Spatial-temporal control of receptor expression

III) Conditional receptor expression

Klebanoff et al, Nature Medicine 2016

Bispecific T cell engagers - BiTEs



Recruits endogenous CD4 and CD8 T cells to TAA expressing tumour cells

No need to deplete endogenous T cells during treatment

Not a durable response

Blinatumomab approved for B-ALL, 2017

Slanley et al, Cancer Discovery 2018

Bispecific T cell engagers - BiTEs

Table 1. Comparison of CAR T cells and BiTEs

	CAR T cell	BiTE
Structure	A synthetic gene construct encoding an scFv against tumor antigen linked to activation and costimulatory motifs.	A recombinant protein composed of two linked scFvs; one binds to CD3 on T cells and the other to target a tumor antigen on tumor cells.
Effector cell types	Engineered $CD8^+$ and $CD4^+$ T cells (5). Less-differentiated subsets displaying better antitumor activity *in vivo* (T_{SCM} and T_{CM}; ref. 10).	Endogenous $CD8^+$ and $CD4^+$ T cells (13). Antigen-experienced T_{EM} but not T_N effective (14).
Immune synapse	Atypical (15).	Typical (17–19).
Serial killing	Yes (16).	Yes (22).
Killing mechanisms	Perforin and granzyme B (16), Fas/Fas-L, or TNF/TNF-R.	Perforin and granzyme B (17).
Trafficking	Active. Trafficking of CAR T cells involves comprehensive interactions between various molecules and cell–cell interactions (57).	Passive. Biodistribution depends on factors related to rates of diffusion through vascular endothelium, fluid flow rates, and interaction with target.
Toxicity	CRS, neurotoxicity, B-cell aplasia (31, 49).	CRS, neurotoxicity, B-cell aplasia (62, 64).
Clinical applications	Pretreatment lymphodepleting regime using cyclophosphamide and fludarabine. Premedicate with acetaminophen and an H1-antihistamine. One infusion.	No lymphodepletion regime required. Premedicate with dexamethasone. Repeat administration necessary, including continuous i.v. infusion regimens.
FDA approval	Yescarta was approved to treat adult patients with relapsed/refractory large B-cell lymphoma in 2017. Kymriah was approved to treat patients up to 25 years of age with refractory/relapsed B-ALL in 2017.	Blinatumomab was approved to treat relapsed/refractory B-ALL in 2014 and 2017.
Other characteristics	Individually produced for each patient.	"Off the shelf" reagents.

Slanley et al, Cancer Discovery 2018

Obstacles to overcome

side effects/ safety

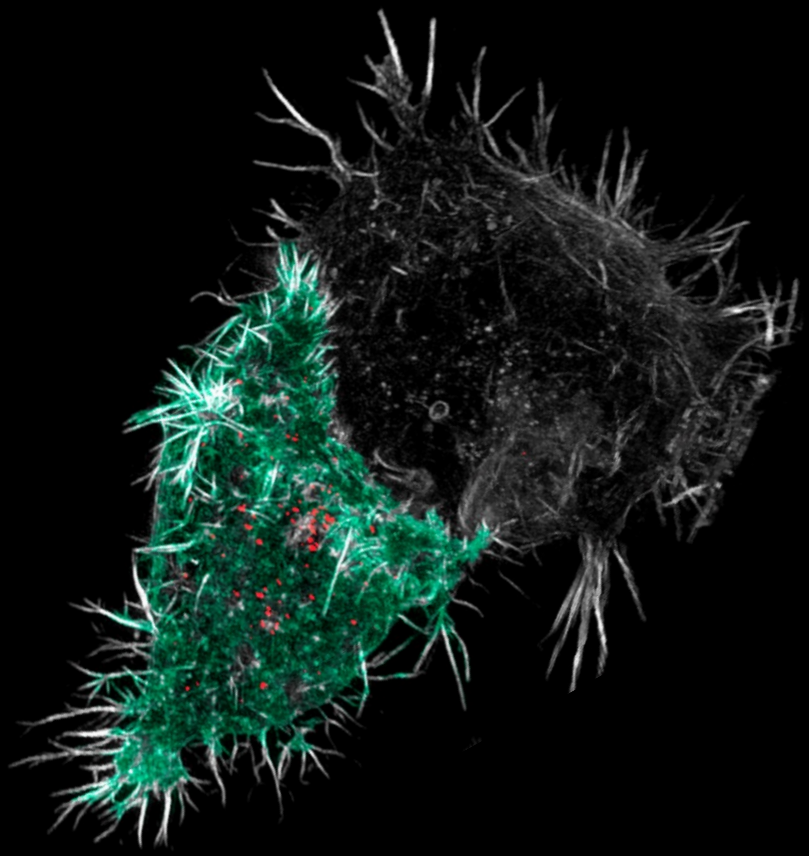
response rates

combinations ?

lack of suitable targets

performance of cells

Take home messages:

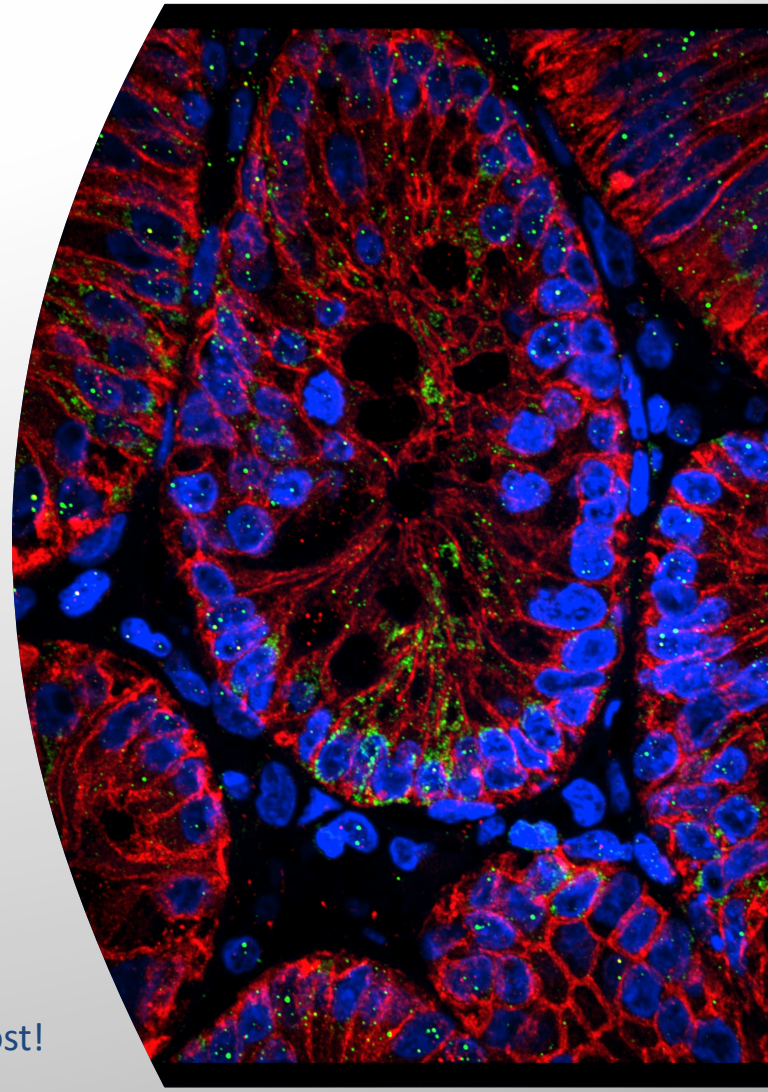


The tumour microenvironment is composed by many different immune and non-immune cell subsets.

Immunotherapy holds great promises!

In order to achieve most effective immunotherapy we must understand more about the complex networks and functional mechanism active in the tumour microenvironment (> combinational therapies).

Novel immunotherapeutics against LGR5+ cancers



Maike & Marc de la Roche
CRUK Cambridge Institute

in part unpublished – please do not post!

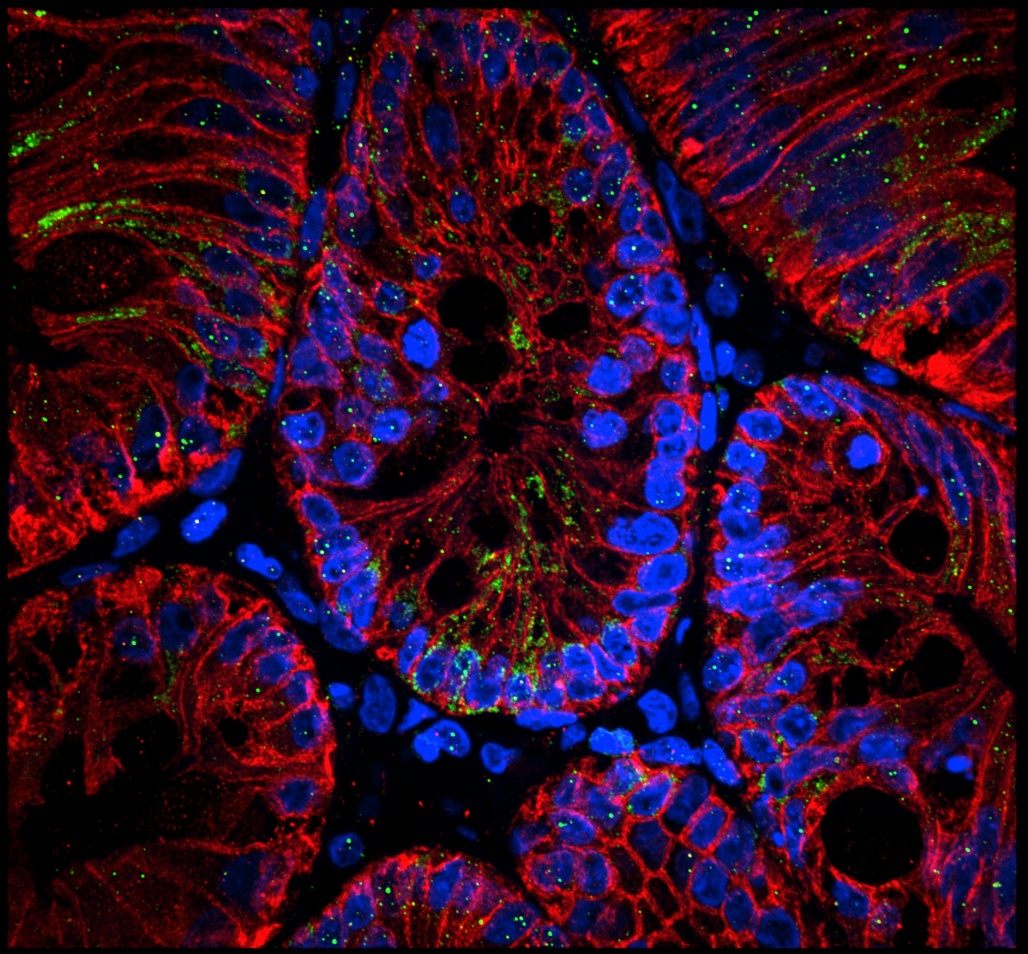
CANCER RESEARCH UK | CAMBRIDGE INSTITUTE

Together we will beat cancer

Immunotherapies based on a novel antibody to LGR5

Nico Mueller

Chrysa Kapeni

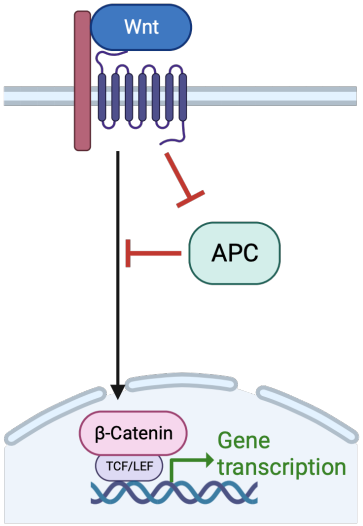


PCT/GB2023/050512

LGR5 expression in colorectal cancer

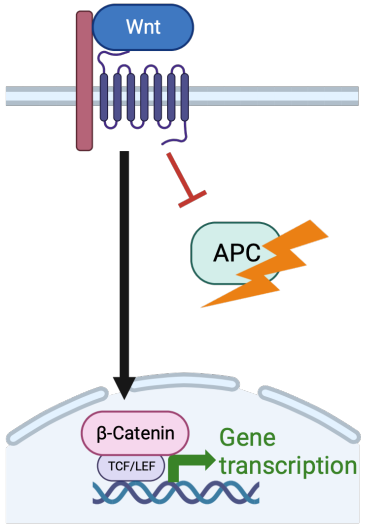
Regulation of the Wnt pathway in healthy cells and cancer

Stem cell homeostasis & tissue development



Gut intestinal epithelia, liver, pancreas, mammary gland, hair follicles, etc…

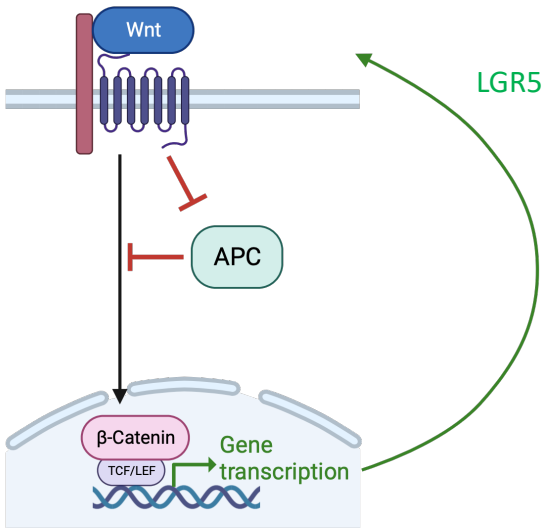
Cancer cells



Colon cancer, gastric cancer, pancreatic cancer, liver cancer, breast cancer, skin cancer etc…

Leucine rich repeat containing G protein-coupled receptor 5 (LGR5) is a Wnt pathway target gene overexpressed in cancers

Stem cell homeostasis & tissue development



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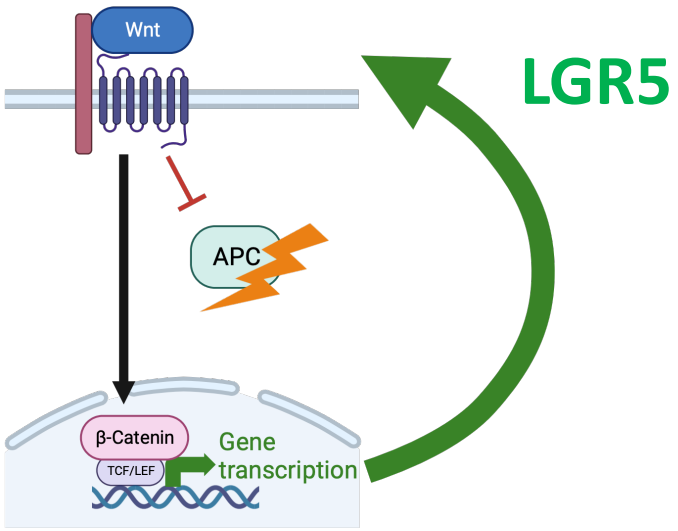
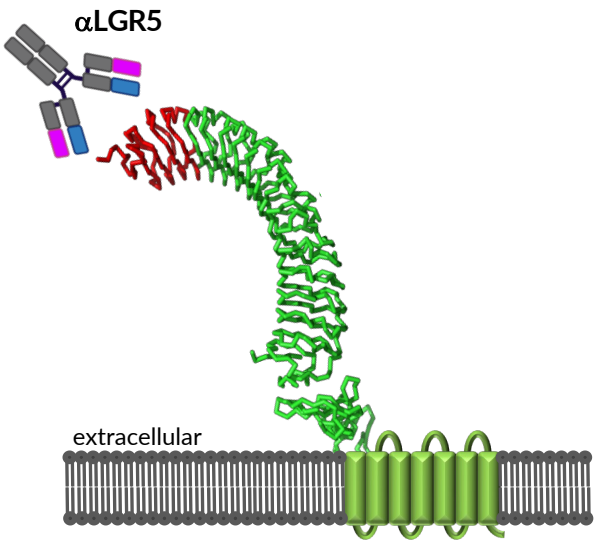
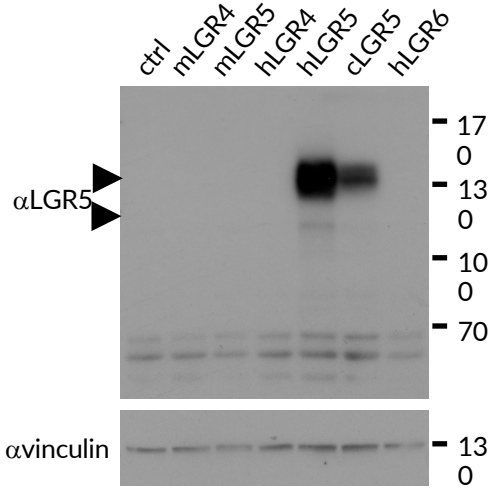


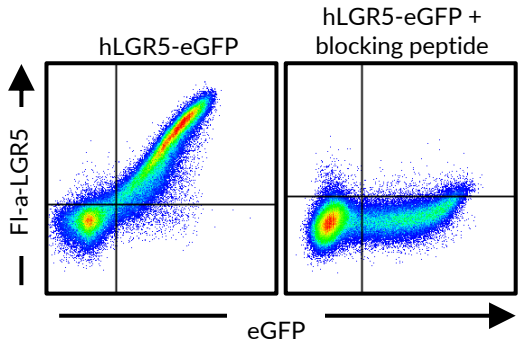
Colon cancer, gastric cancer, pancreatic cancer, liver cancer, breast cancer, skin cancer etc…

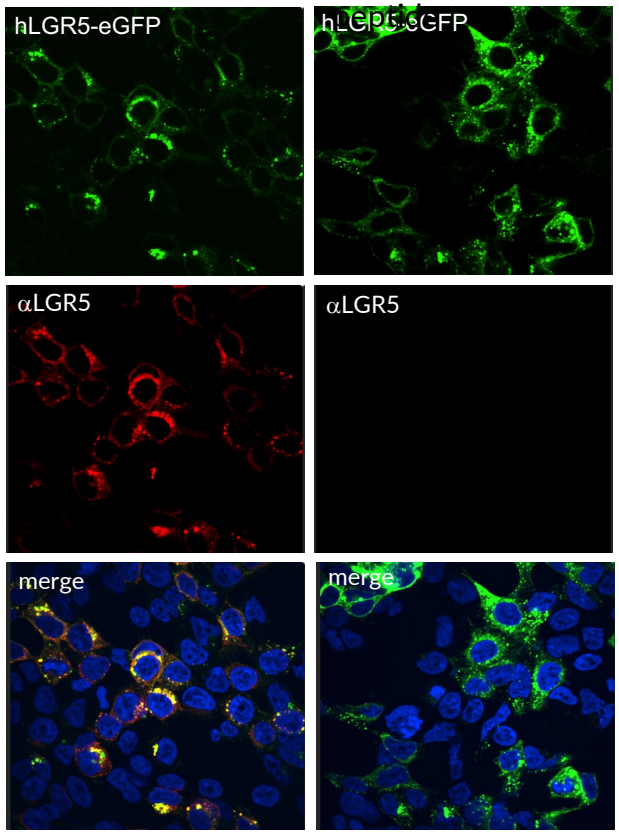
The novel α-LGR5 is an effective and specific antibody



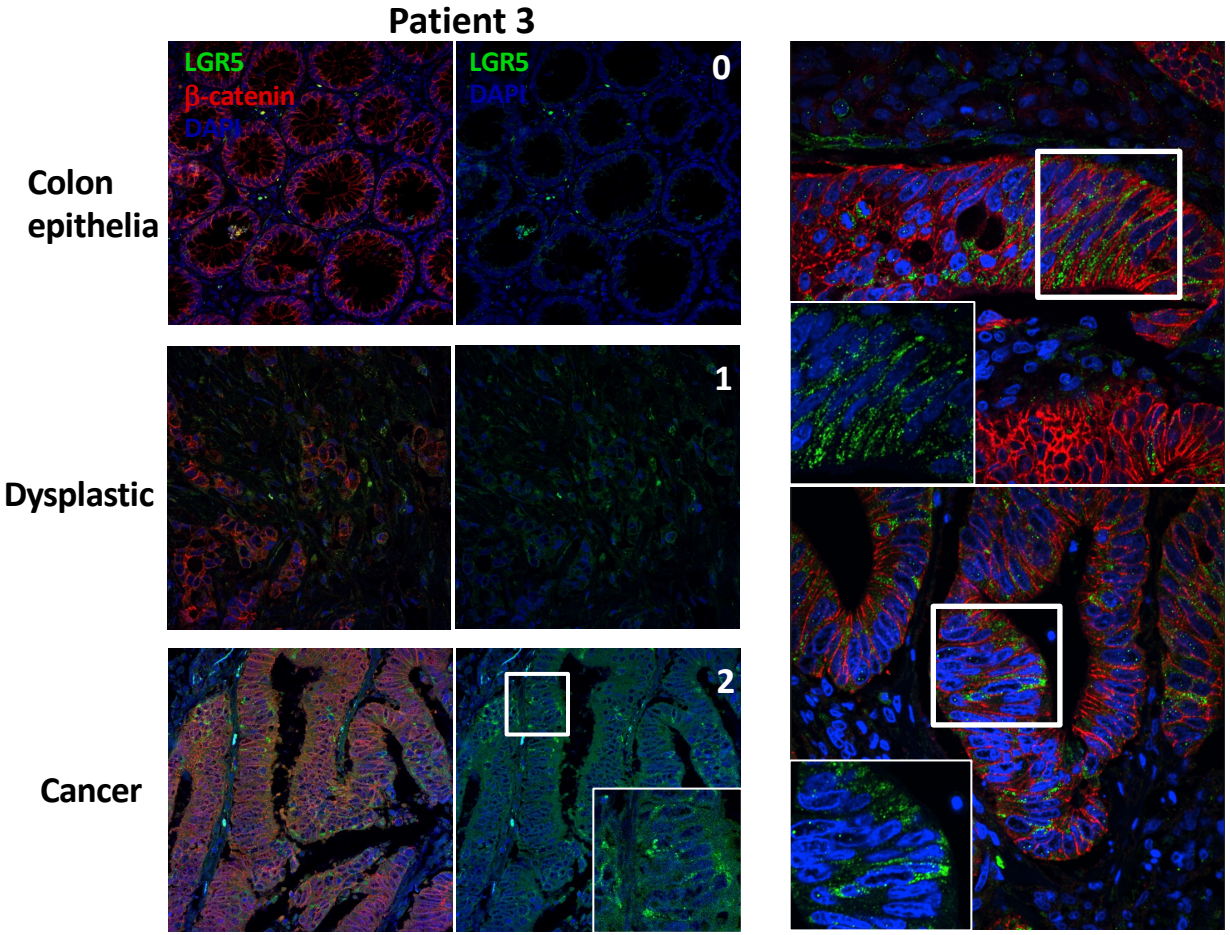
developed and validated by:
de la Roche labs (Cambridge) in cooperation with Mikkel-Ole & Karsten Skjoedt (Copenhagen)







LGR5 protein levels in colorectal cancer detected by α-LGR5



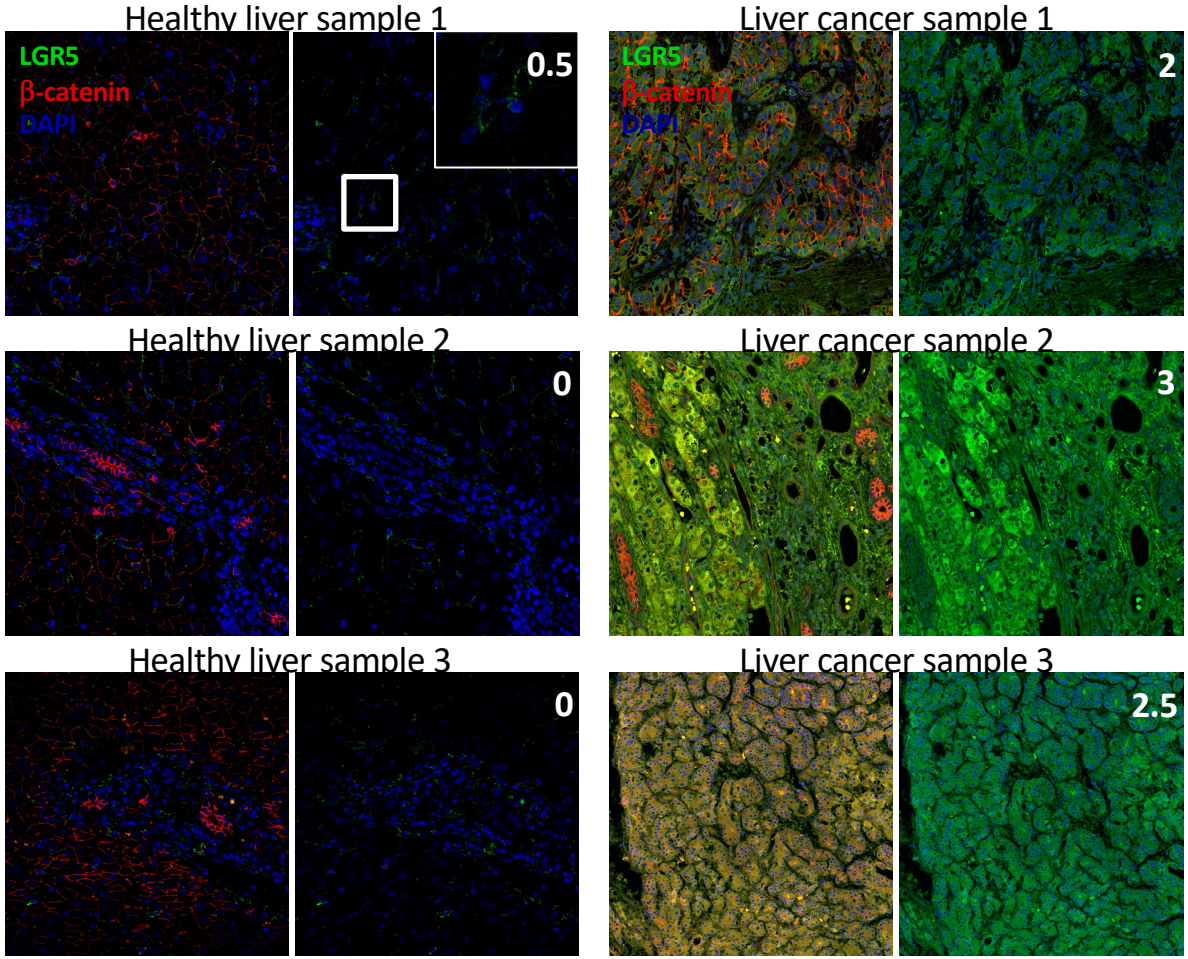
Colorectal cancer

UK ~40,000 patients diagnosed per annum

Incidence rate: 82 males & 54 females /100,000 patients

5-year survival of ~13%

LGR5 protein levels are elevated in hepatocellular carcinoma



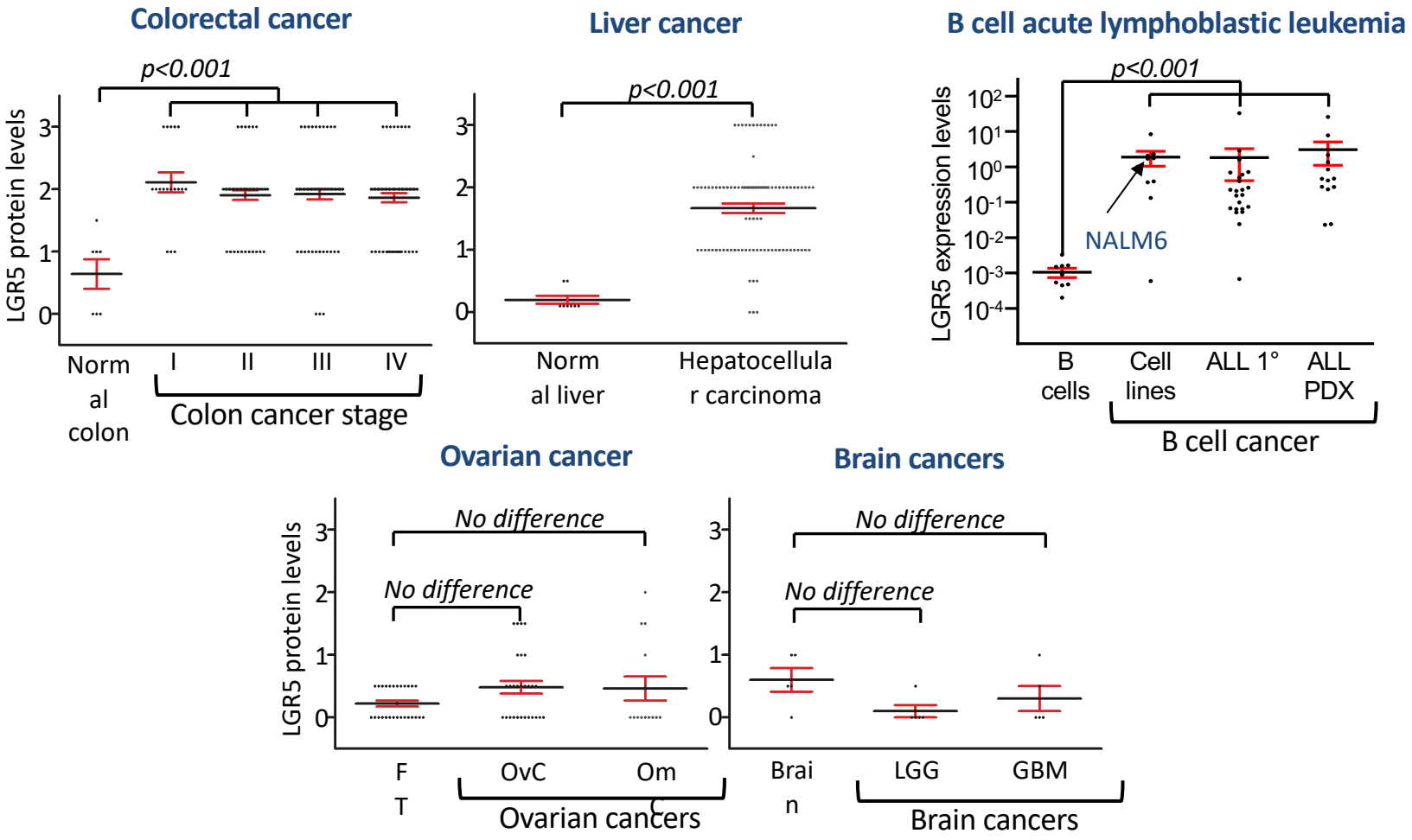
Liver cancer

UK ~ 6,000 new cases every year

Incidence rate: 14 males and 6 females / 100,000 patients

5-year survival ~34%

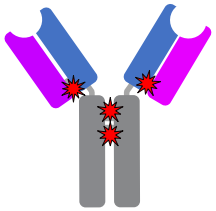
Census of LGR5 protein expression in cancers



Development of α-LGR5 into three therapeutic modalities

Antibody-drug conjugate

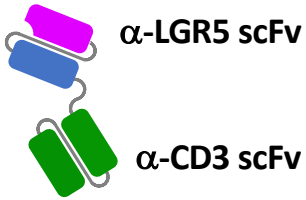
(ADC)



♦ Sulfatase-cleavable arylsulfate linker [1]

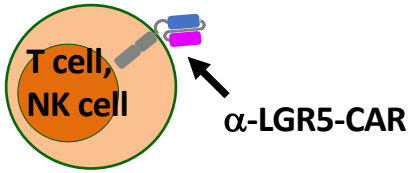
✸ Monomethyl Auristatin (MMAE)

Bispecific T cell engager



Chimeric antigen receptor

(CAR)



[1] Walsh et al. 2020 Chemical Science
(Prof. David Spring, Dept of Chemistry, University of Cambridge)

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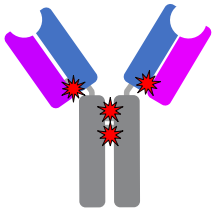

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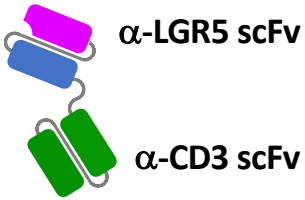

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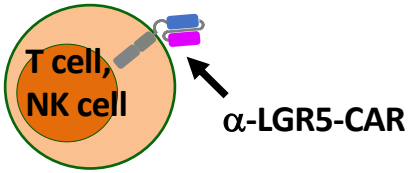

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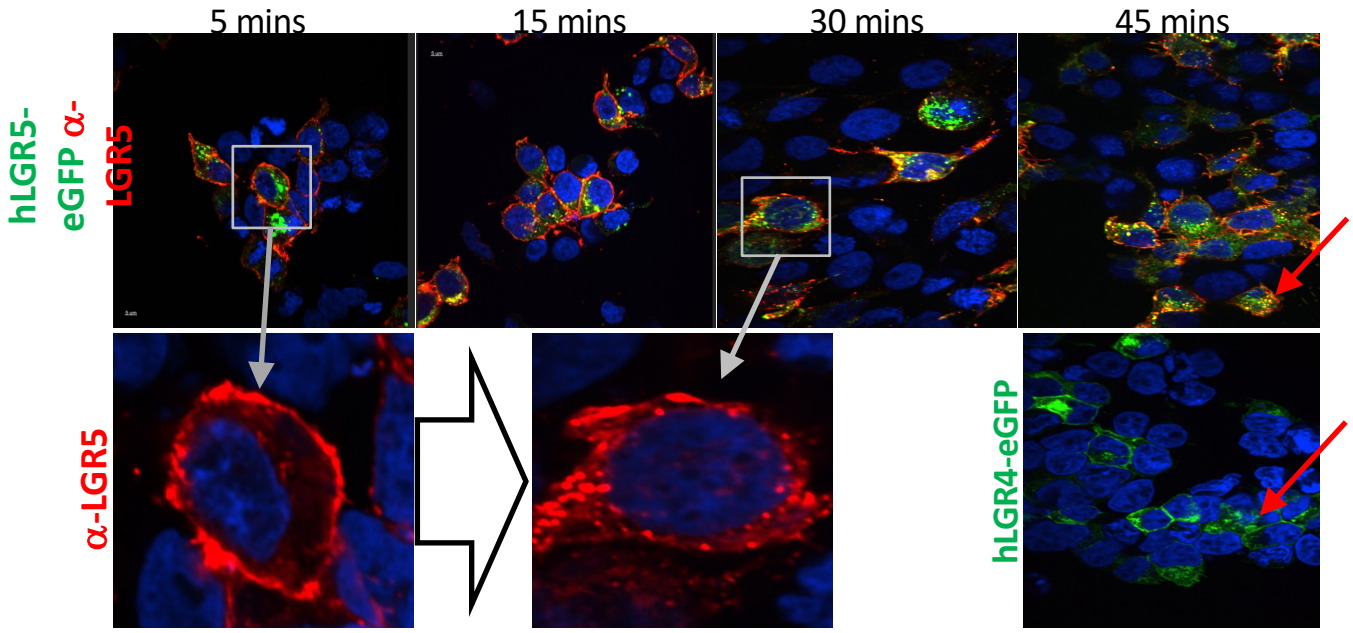
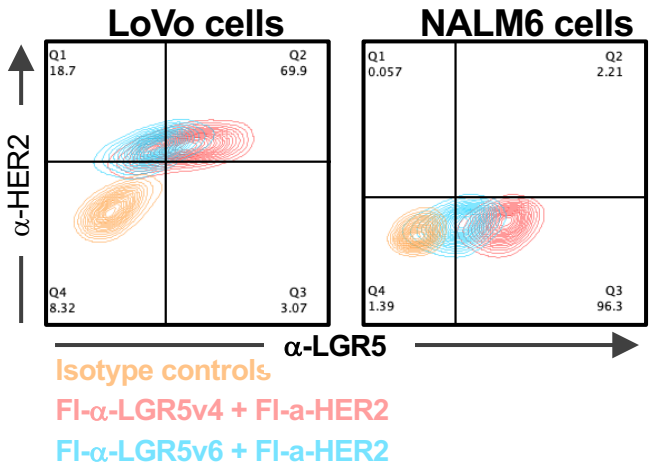
Fluorescent α-LGR5 is rapidly and specifically internalized



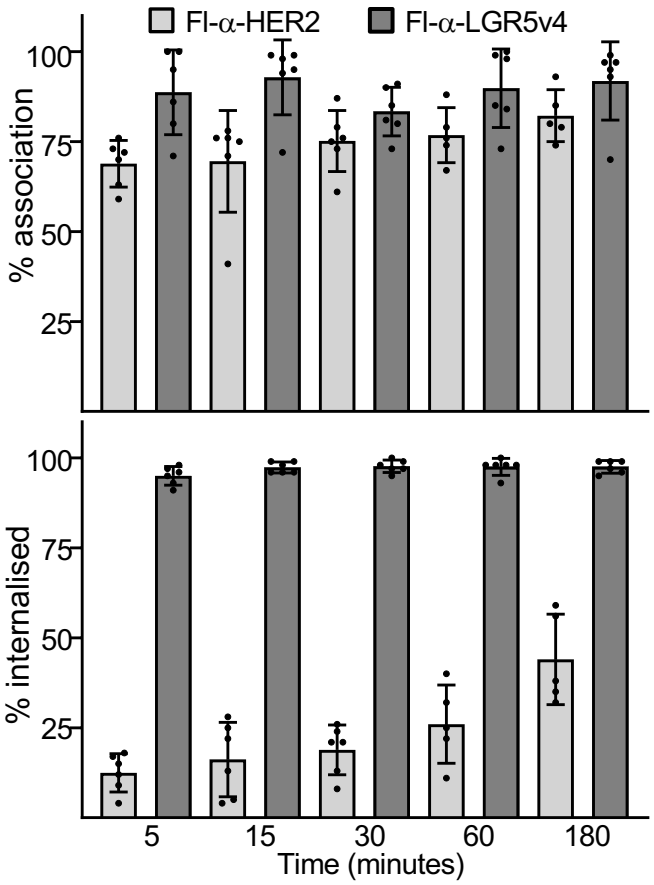
Rapid internalization of α-LGR5 specific to LGR5 overexpressing cells

No internalization of α-LGR5 in LGR4 overexpressing cells

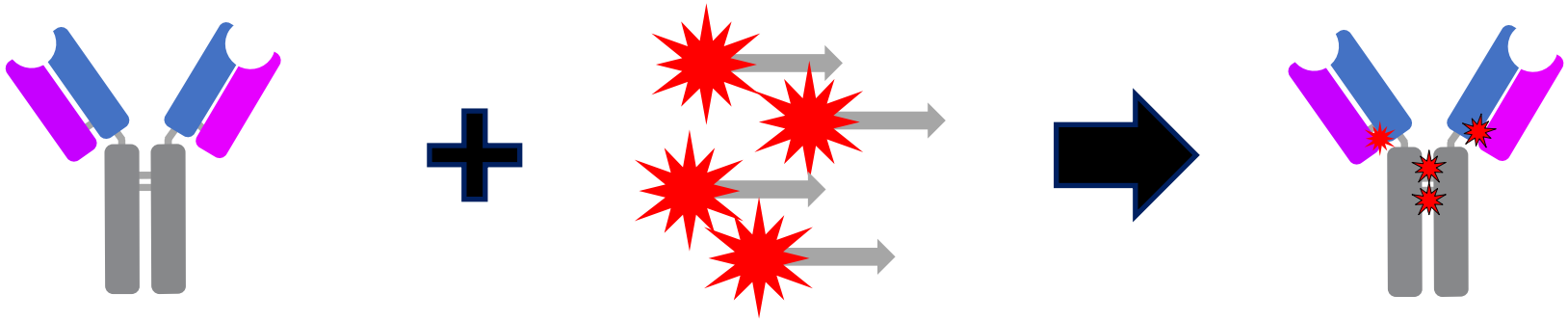
α-LGR5 internalization by CRC cells is much more rapid than α-HER2



LoVo cells:



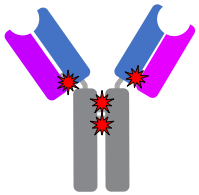
Precise ultra stable α-LGR5-ADC combines two novel technologies



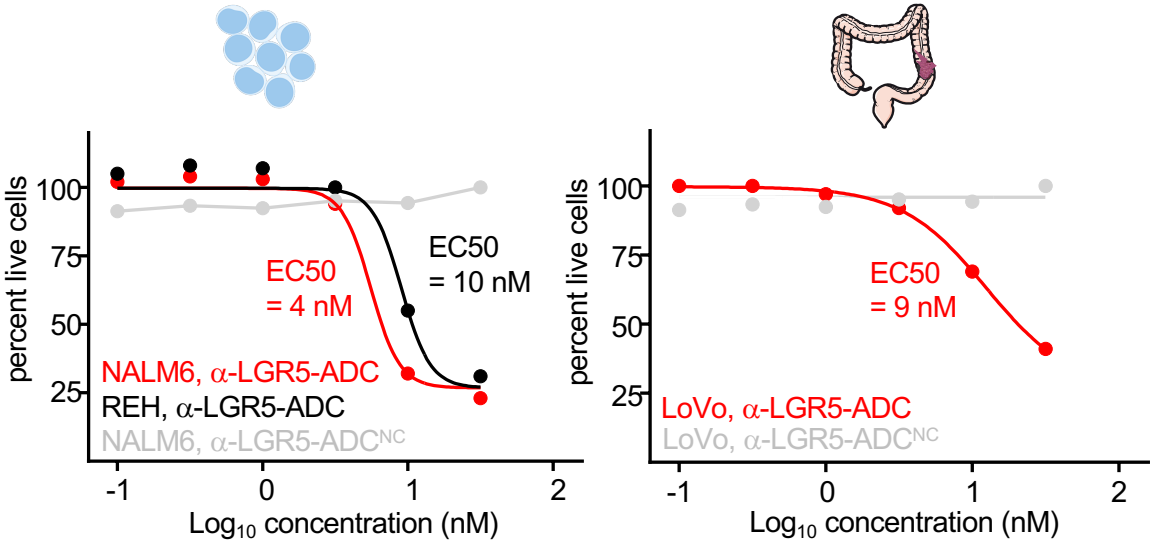
Technology 1:
WO2023/166318
Highly-specific antibody recognizing LGR5-expressing cancer cells

Technology 2:
WO2020/025108
State-of-the-art payload linking technology

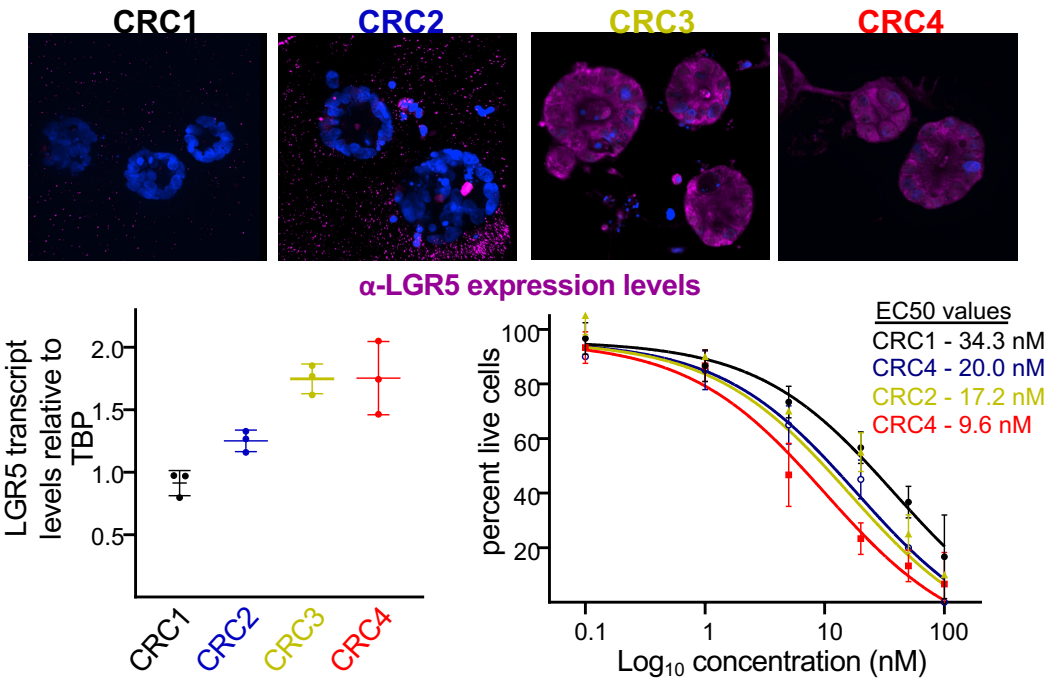
Precision ultra stable α-LGR5-ADC



α-LGR5-ADC is specific and effective at targeting LGR5+ cell lines

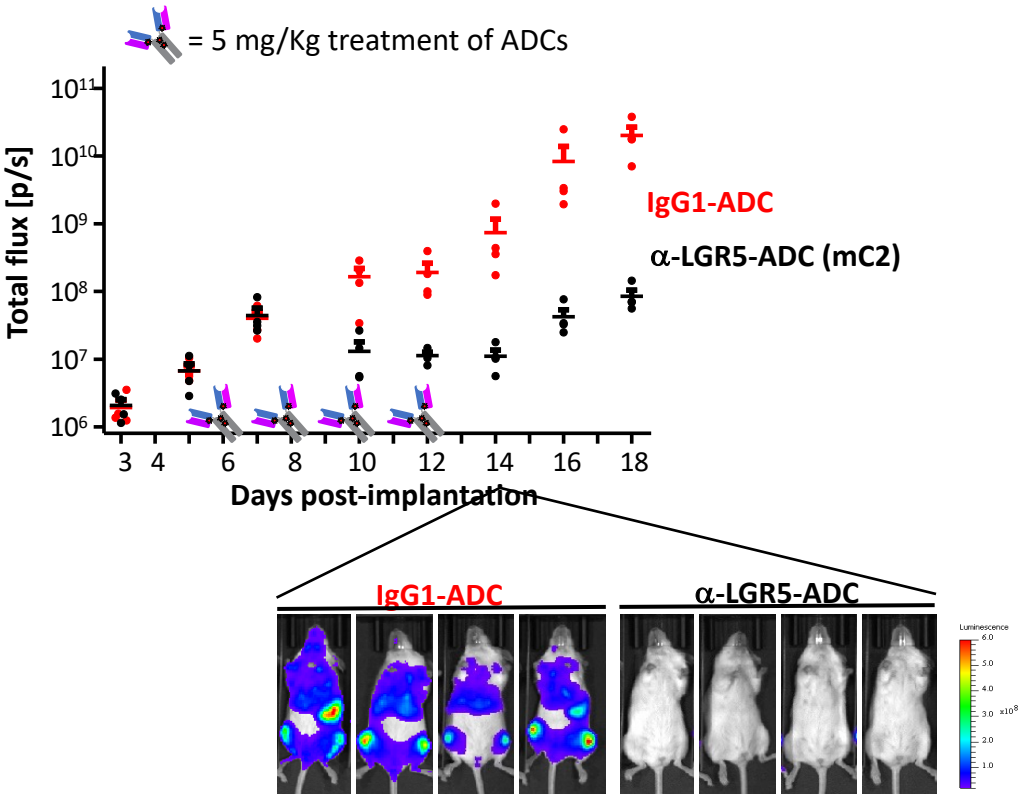


Higher LGR5 levels in PDO models display greater sensitivity to α-LGR5-ADC treatment



In vivo targeting of NALM6 tumours with α-LGR5-ADC

IVIS dynamic monitoring of NALM6 tumours



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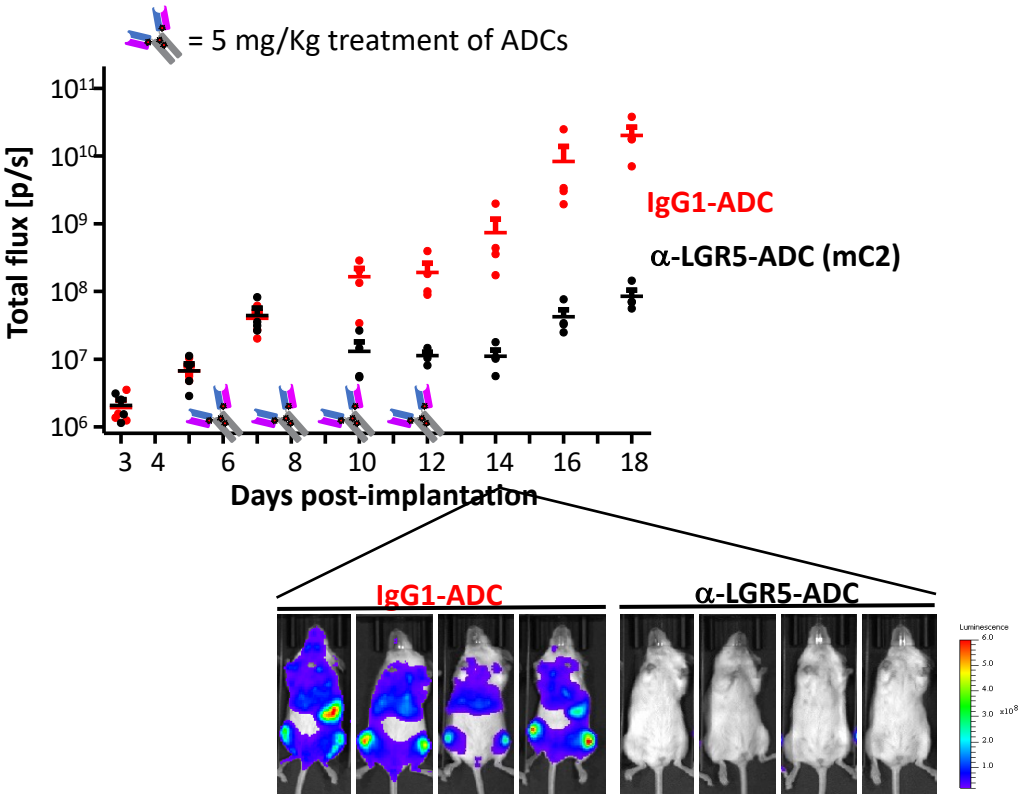
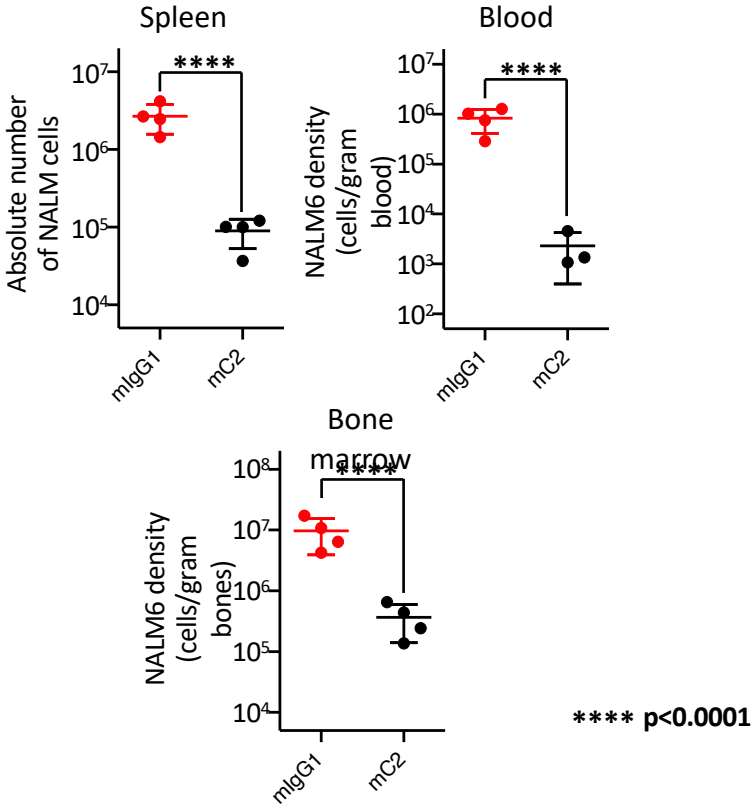


Residual NALM6 cells



**** p<0.0001

Development of α-LGR5 into three therapeutic modalities

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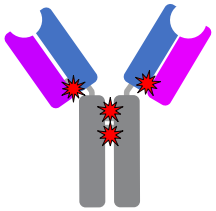
(ADC)



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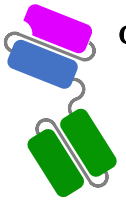

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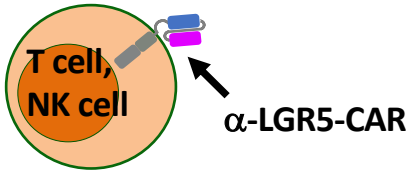

[1] Walsh et al. 2020 Chemical Science
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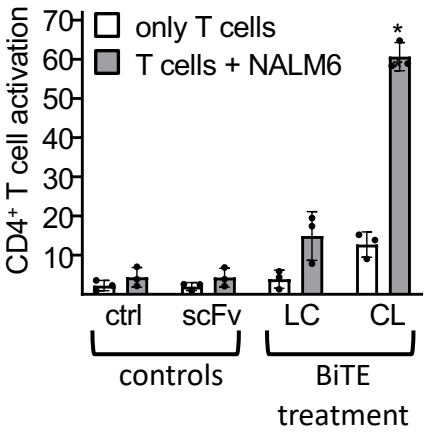
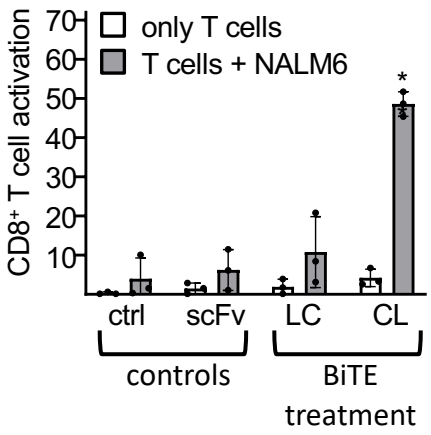
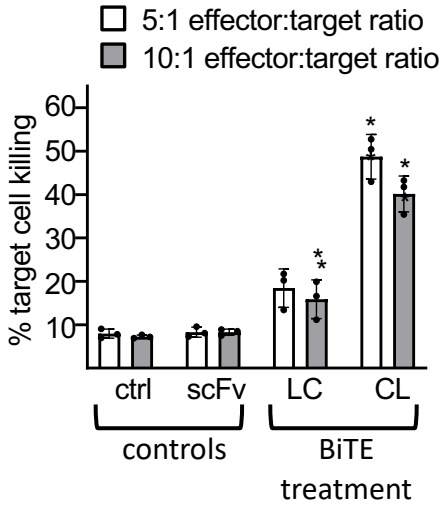
Efficient targeting of cancer cells with α-LGR5-BiTE

T cell activation

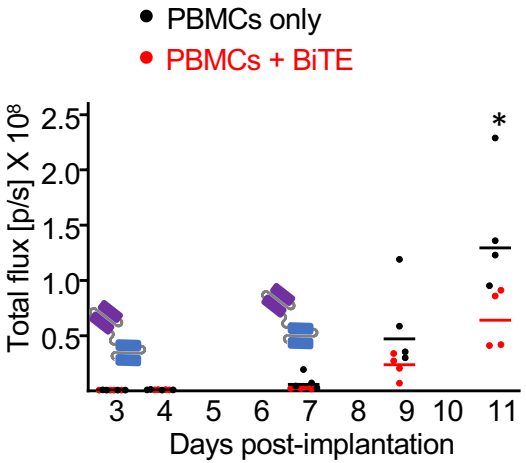


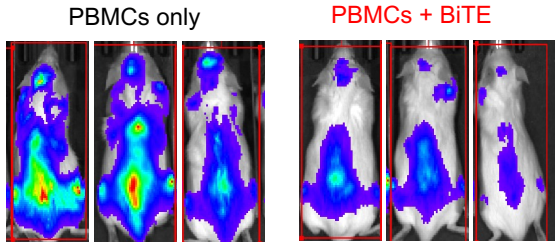


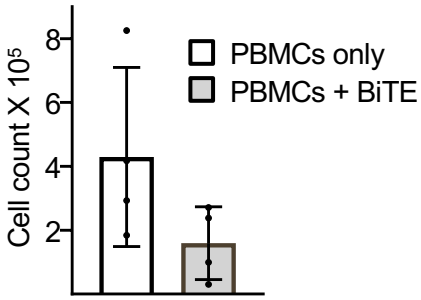
Tumour killing



The α-LGR5-BiTE shows pre-clinical efficacy







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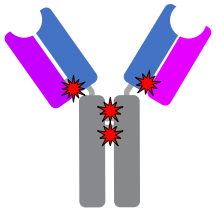

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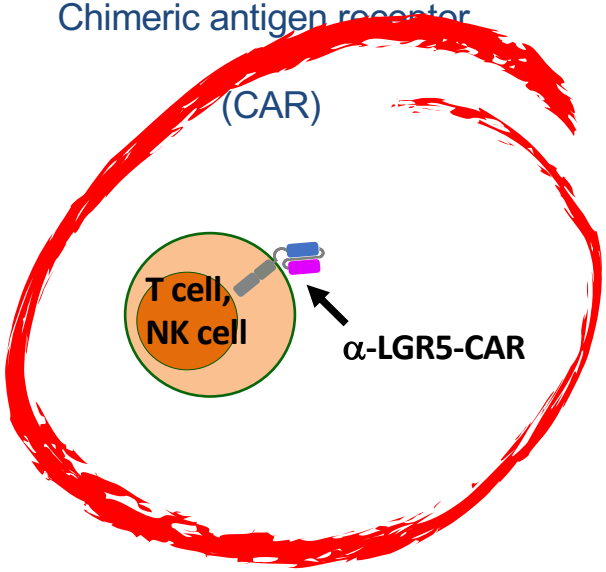

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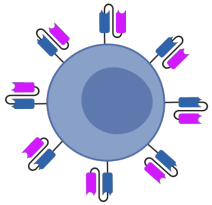
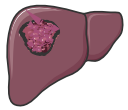
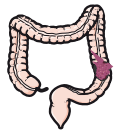
α-LGR5 CAR T cells have efficacy *in vitro* & *in vivo*



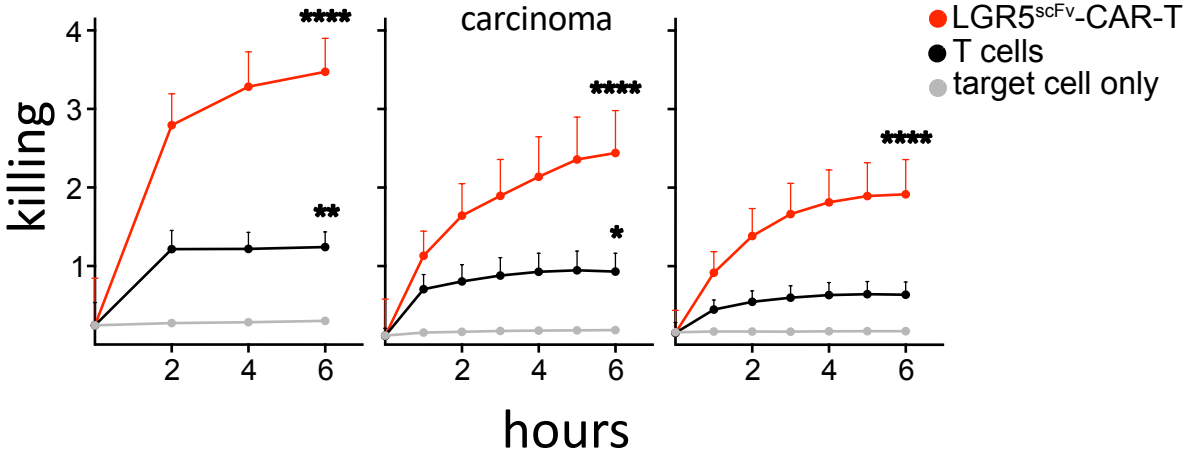
preB-ALL

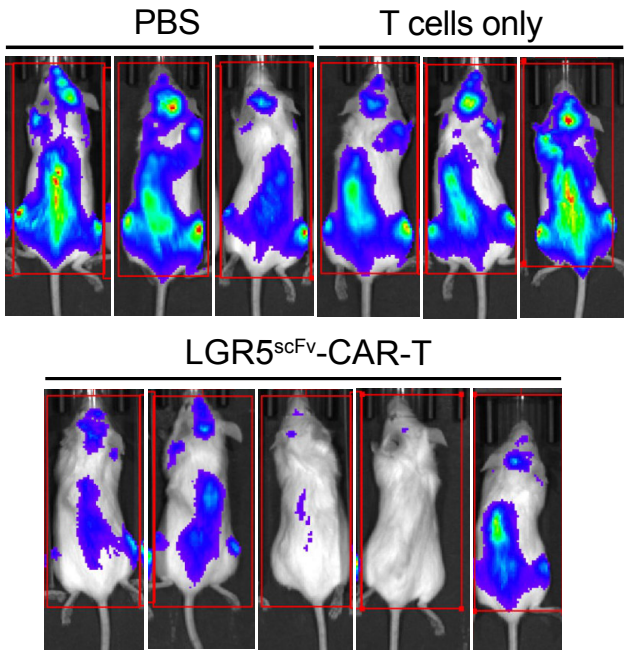


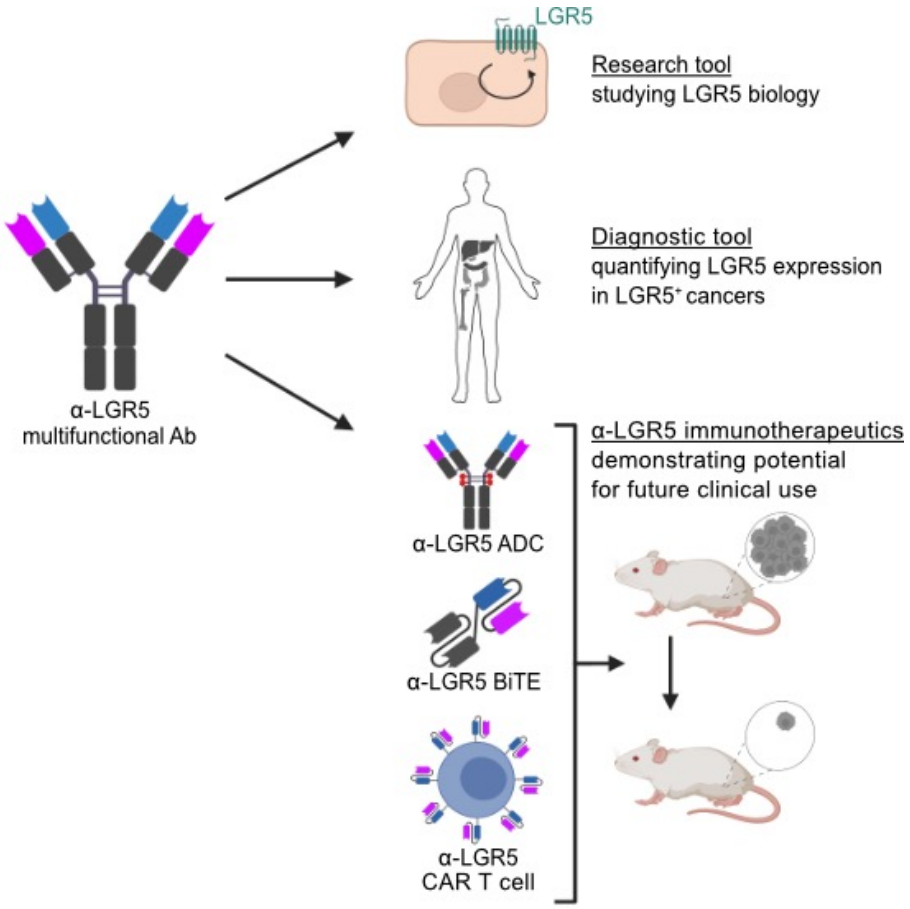
Hepatocellular carcinoma



Colorectal cancer







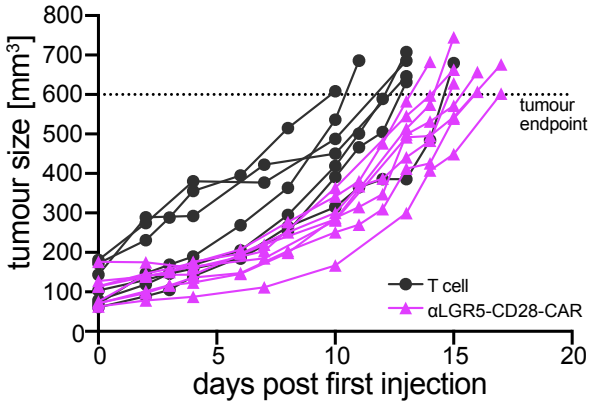
Chen & Mueller et al, *EMBO Mol Med 2024*

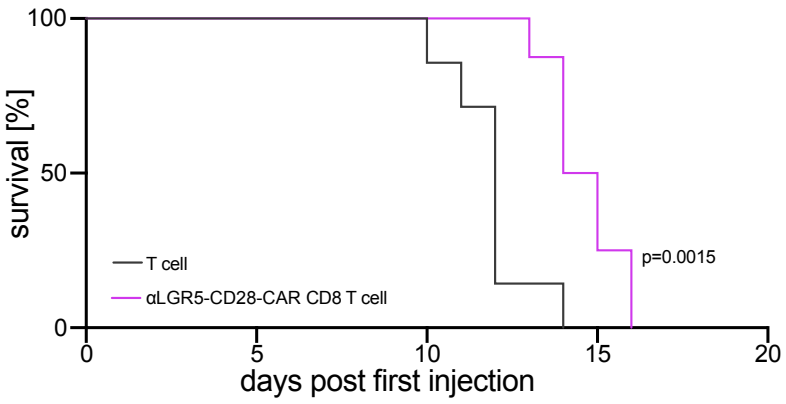
Summary:
Immunotherapeutics based on our versatile mAb against LGR5

Unique opportunity to match disease characteristics with suitable therapeutic modalities

PCT/GB2023/050512
patent filed (int. phase)

In vivo α-LGR5-CAR-T cell targeting of solid HCC tumours



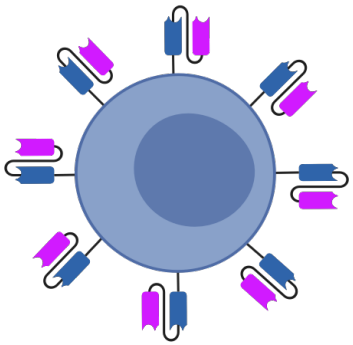


***Problems* of CAR T cell therapies against *solid* cancers:**

(1) Lack of good targets

(2) suppression of effector function in the TME

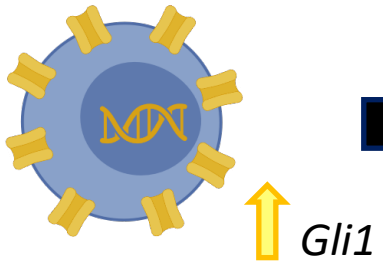
Solution:



Technology 1:

PCT/GB2023/050512

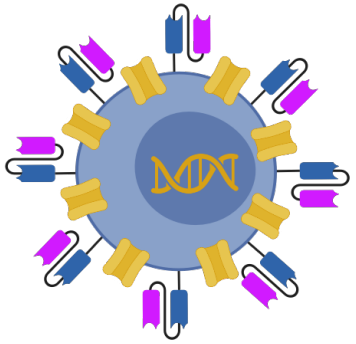
Novel CAR directing T cells to LGR5+ cancer cells



Technology 2:

PCT/EP2023/058052

Supercharging killing via L-type Ca^{2+} channels



Superkiller α-LGR5 CAR T cells

CATAPULT Cell and Gene Therapy

UNIVERSITY OF CAMBRIDGE enterprise

CANCER RESEARCH HORIZONS

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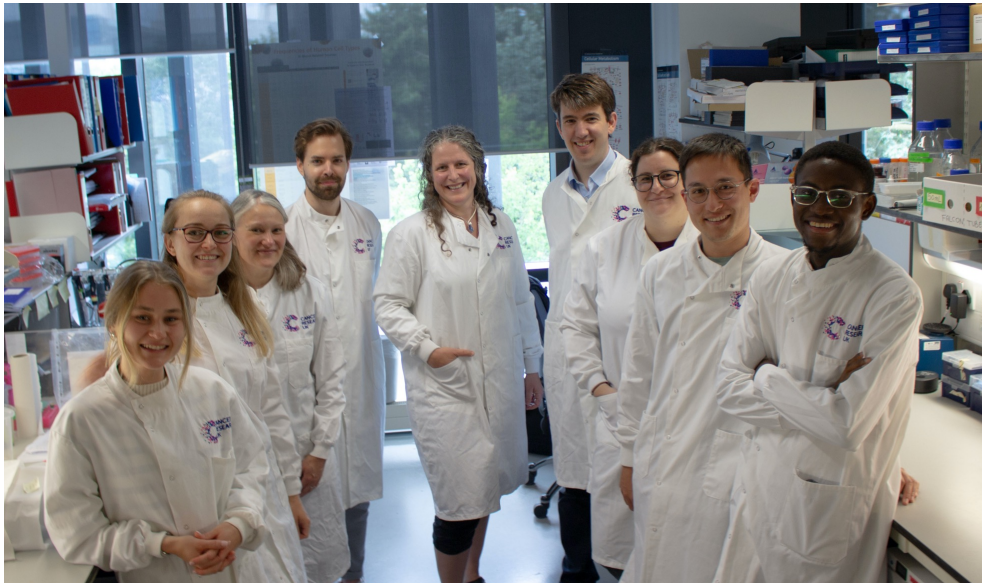

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Kate Fife, Lynn Cream & our patients

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BRU, Microscopy, Flow cytometry, Histology, Bioinformatics, PKB, Genomics, RICS, Proteomics

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