# Chemotherapy…what's not to like?

Chemotherapeutics kill rapidly dividing/growing cells by damaging DNA and blocking DNA replication. The first purposeful chemotherapies were used to treat childhood leukemias in the 1950/60s

<u>Rapidy growing cells are:</u>

**1. Cancer cells**

2. Hair follicles

3. Cells lining the intestines/colon

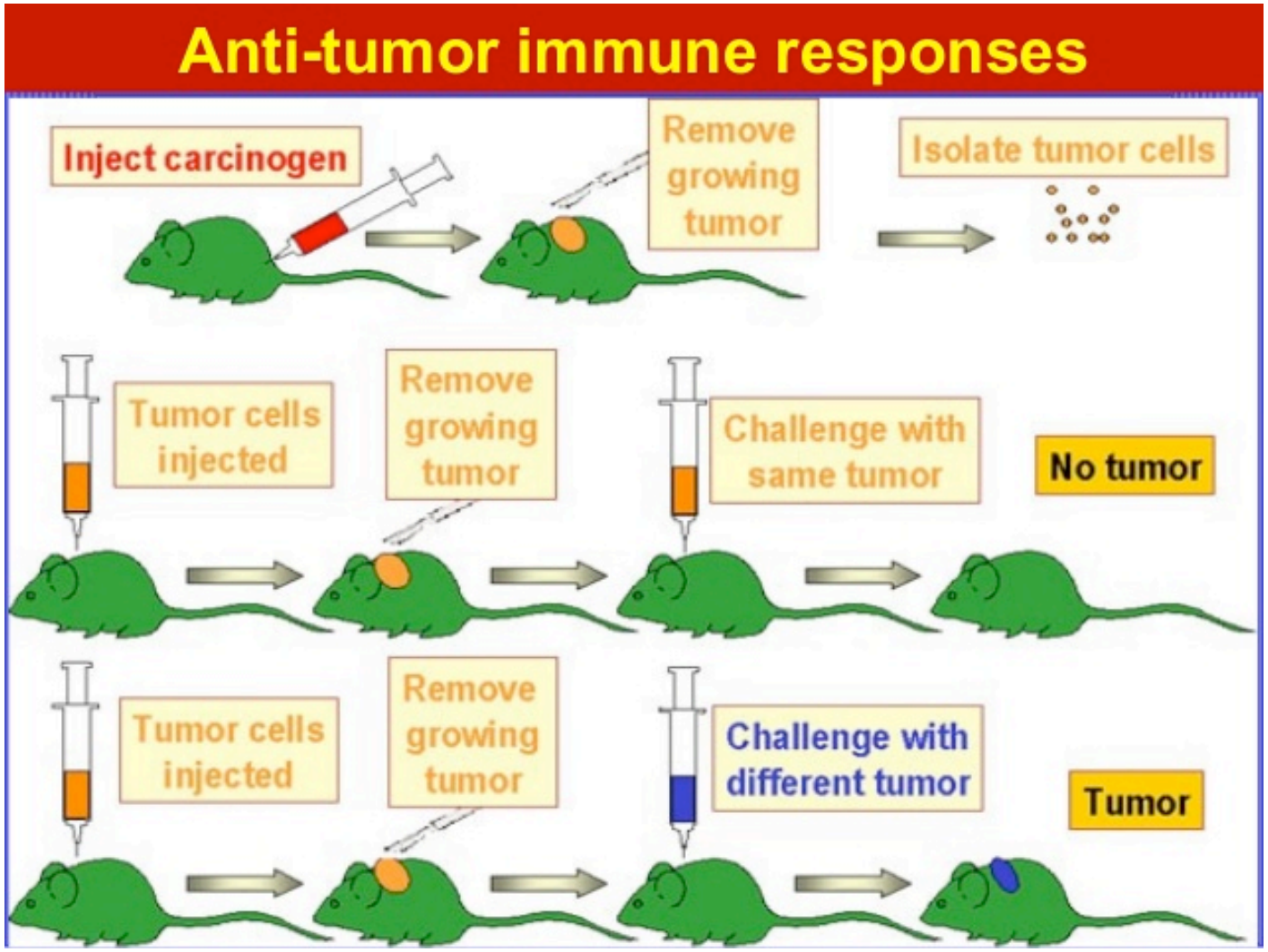
4. Cells of the immune response, i.e. T cells…ooops.
   You need these cells to fight the cancer!

# FROM CANCER IMMUNOSURVEILLANCE TO IMMUNOEDITING: TIMELINE

- In 1909, ***Paul Ehrlich*** predicted that the immune system repressed the growth of carcinomas that he envisaged would otherwise occur with great frequency.
- Fifty years later as immunologists gained an enhanced understanding of transplantation and tumor immunobiology and immunogenetics, ***F. Macfarlane Burnet and Lewis Thomas*** revisited the topic of natural immune protection against cancer .
- Burnet believed that tumor cell-specific neo-antigens could provoke an effective immunologic reaction that would eliminate developing cancers (***Burnet,1957,1964,1971***).

**He was correct, but didn't know what he and the immune response to cancer were up against! Cancers can acquire many means to escape the immune response.**

Burnet's experiment showed that the (mouse's) immune system could respond to cancer cells and protect from a later challenge by the same cancer but not a different cancer.



# THE JOB OF THE IMMUNE SYSTEM IS TO RECOGNIZE "FOREIGN" CELLS AND ELIMINATE THEM.

1. Antigen presenting cells – Macrophages and Dendritic Cells recognize foreign cells, eat them up, chew them up and "present" their antigens to T lymphocytes (T cells).
   N B: They must NOT eat "self" cells or deadly autoimmune responses can occur.

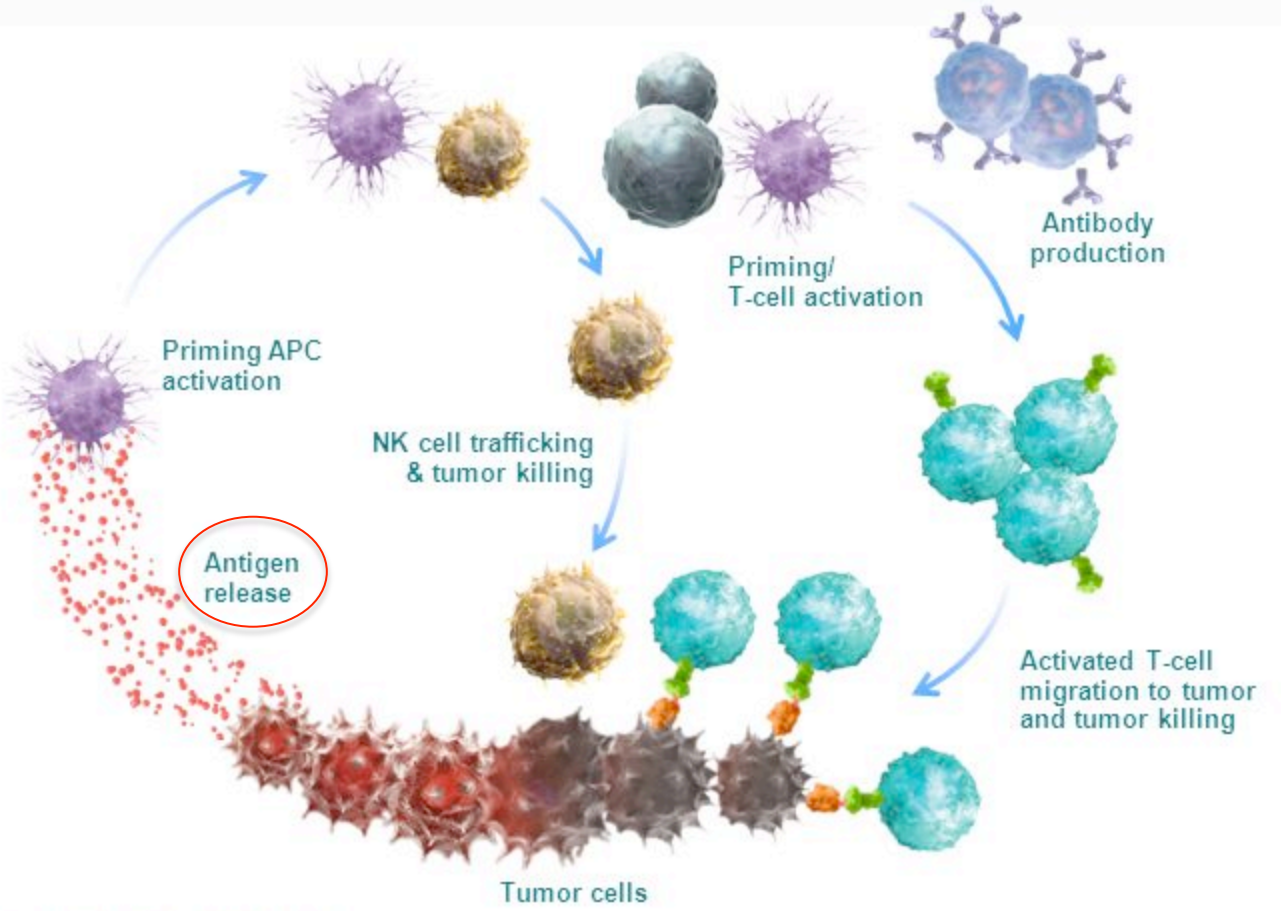
2. There are several types of "self" tags called "don't eat me" signals that prevent cells of self being eaten up. Cancers have co-opted one of these, CD47 to cloak themselves in "selfness" and avoid immune surveillance by APCs

3. There are billions of T cells circulating in the body each with a different receptor to recognize antigens (pieces of foreign cells/proteins) presented to them. When the piece of antigen recognizes the receptor on a T cell, that T cell rapidly divides resulting in a large number of identical T cells that match the antigen.

4. The activated T cells can either stimulate B cells to make antibodies vs the antigen OR…T cells can develop into cytotoxic T cells that can attack and kill the foreign cell that contains the original foreign antigenic protein. The more mutated and different from self cells the cancer is, the more likely the immune system can attack it.

5. EVERY STEP is a balance of **positive vs negative** signals to <u>control the response</u>!

# Immune Surveillance: Identification and Elimination of Cancer Cells by the Immune System[1-5]




APC, antigen-presenting cell; NK, natural killer.


1. Abbas AK et al. *Cellular and Molecular Immunology*. 7th ed. Philadelphia, PA: Elsevier Saunders;2012.
2. Mellman I et al. *Nature*. 2011;480:480-489.
3. Boudreau JE et al. *Mol Ther*. 2011;19(5):841-853.
4. Janeway CA Jr et al. *Immunobiology: The Immune System in Health and Disease*. 5th ed. New York, NY: Garland Science; 2001.
5. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264.

# WHAT IS CANCER IMMUNOTHERAPY?
# … a way to make cancer cells visible to the immune system

**NOT JUST ONE WAY/THING…ONE SIZE DOES NOT FIT ALL...**
**WHICH APPROACH FITS WHICH CANCER? WHICH PATIENTS?**

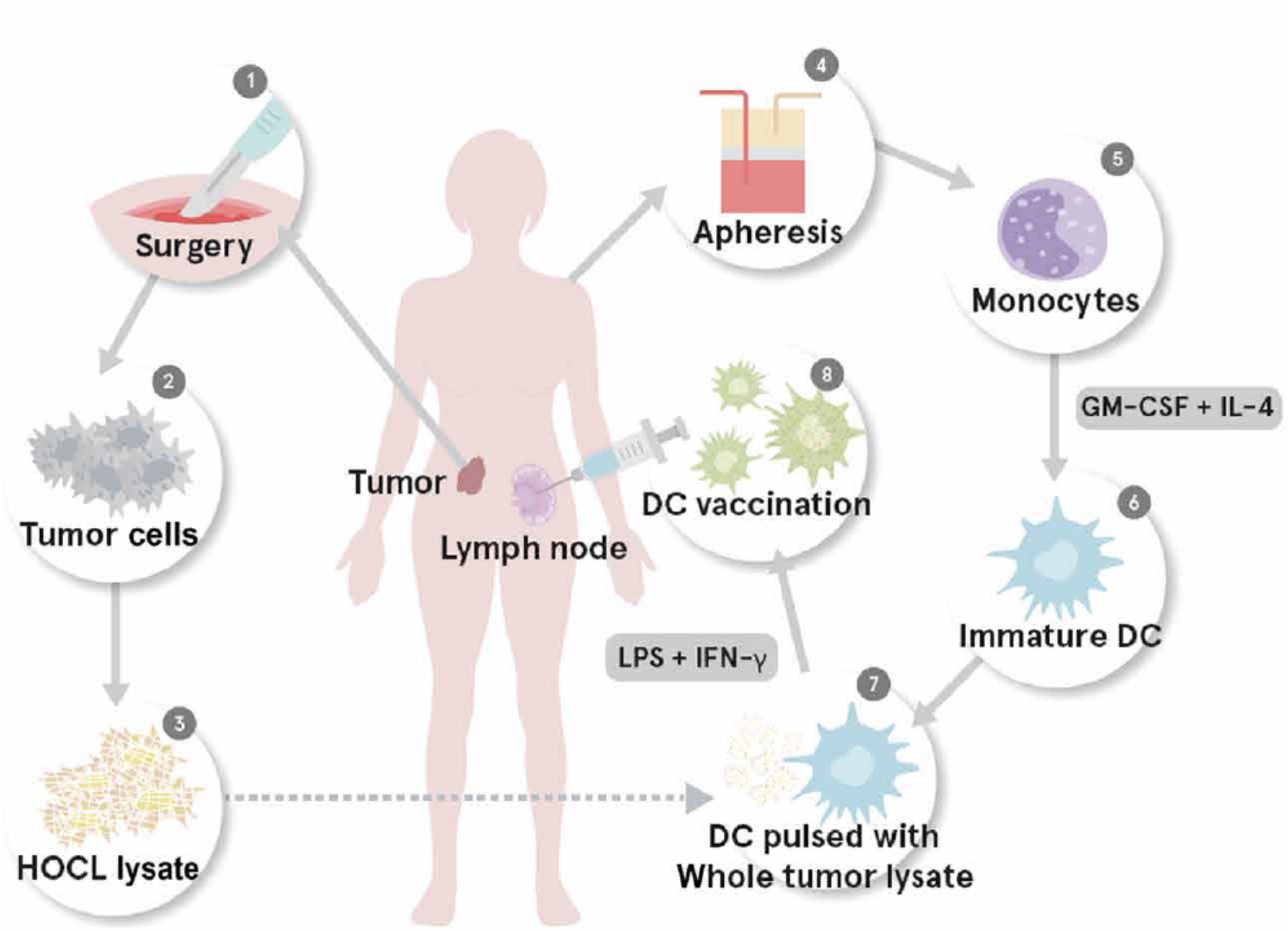
1. **Cancer vaccines**
   A. At first were just killed cancer cells of the same type as the patient's cancer but derived from cultured cancer cells from other patients' tumors.

   B. Then the patient's own cancer cells or cell/protein extracts used to innoculate the patient along with adjuvants to stimulate the immune system.

   C. Sequencing of the patients cancer cell transcriptome(s) provides a list of "neo-antigens", i.e. proteins that are different from those of the patient's normal cells, which are then chemically synthesized, combined with antigen presenting cells (DCs) and injected w adjuvants.

   D. Not surpisingly, the cancers that are best controlled by any immunotherapy are cancers that are the most highly mutated..i.e. Different from self cells.

# How to make a personalized cancer vaccine

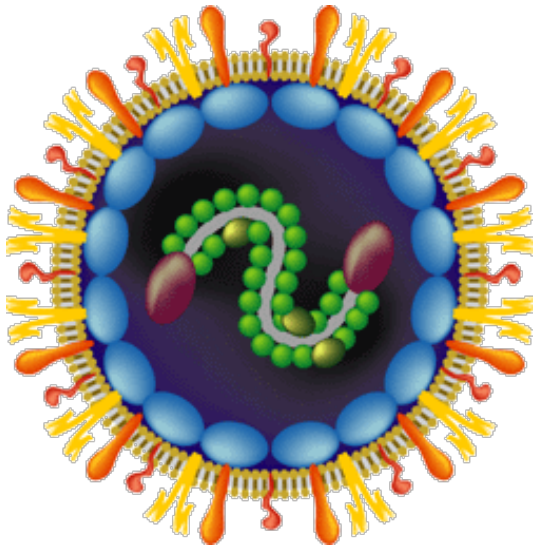


# WHAT IS CANCER IMMUNOTHERAPY?

NOT JUST ONE THING…ONE SIZE DOES NOT FIT ALL...WHICH TYPE FITS WHICH CANCER?

2. **Oncolytic viruses** – display selectivity for infecting cancer vs normal cells.

Several viruses have been shown to have efficacy vs tumors in mice and other animals and a few have had success in human trials with a very good safety profile.



**Many viruses have been studied as potential anti-cancer agents**

1912- Tumor regression in cancer patients following rabies vaccination

| | |
|---|---|
| • Vaccinia virus | solid tumors, HCC |
| • Influenza virus | EAC, human cancers |
| • Measles virus | glioma, ovarian cancer, myeloma, solid tumors |
| • Parvovirus | glioma |
| • Mumps virus | various cancers (Japan) |
| • Herpes simplex virus | solid tumors |
| • Newcastle disease virus | solid and hematologic tumors |

1965 – MD Anderson initiates virotherapy of cancer program.

## Oncolytic Newcastle Disease Virus for cancer therapy: old challenges and new directions

*Future Microbiol*. 2012 March ; 7(3): 347–367

**Dmitriy Zamarin**[1,*] and **Peter Palese**[2]

Summary of clinical trials with NDV-based cellular vaccines and oncolysates

| Vaccine preparation | Type of cancer | Type of study and patient number (n) | Clinical outcome | Ref. |
|---|---|---|---|---|
| NDV 73T oncolysate | Stage II and III melanoma | Phase II, n=83, historical controls | Improved OS* | [129–131,134,142,148] |
| NDV Italien oncolysate | Stage III melanoma | Phase II, n=24, historical controls | No benefit | [149] |
| NDV 73T oncolysate | Advanced renal cell carcinoma | Phase II, n=208, historical controls | Improved PFS* | [137] |
| NDV Ulster Whole-cell | Colorectal cancer with liver metastases | Phase III, n=51 Phase II, n=23 | Improved PFS, improved OS for colon cancer subgroup | [133,135,147] |
| NDV Ulster Whole-cell | Resectable colorectal cancer | Phase II, n=57, historical controls | Improved OS | [139] |
| NDV La Sota Whole-cell | Resectable colorectal cancer | Phase III, n=567 | Improved OS | [144] |
| NDV Ulster Whole-cell | Metastatic renal cell carcinoma | Phase II, n=40, historical controls | Improved OS | [138] |
| NDV Ulster Whole-cell | Advanced ovarian cancer | Phase II, n=82, historical controls | Improved PFS | [156] |
| NDV Ulster Whole-cell | Glioblastoma | Phase II, n=23, concurrent controls | Improved PFS and OS | [146] |
| NDV Ulster Whole-cell | Advanced head and neck | Phase II, n=18, historical controls | Improved OS | [157] |
| NDV Ulster Whole-cell | Stage III melanoma | Phase II/III, n=29 | No benefit | [145] |

* OS: overall survival,

* PFS: progression-free survival

# WHAT IS CANCER IMMUNOTHERAPY?

NOT JUST ONE THING…ONE SIZE DOES NOT FIT ALL...WHICH TYPE FITS WHICH CANCER?

**3. Chimeric antigen receptor T cells**

FIRST need to identfy a protein/antigen on the surface of the cancer cell that is ideally NOT found on normal cells.

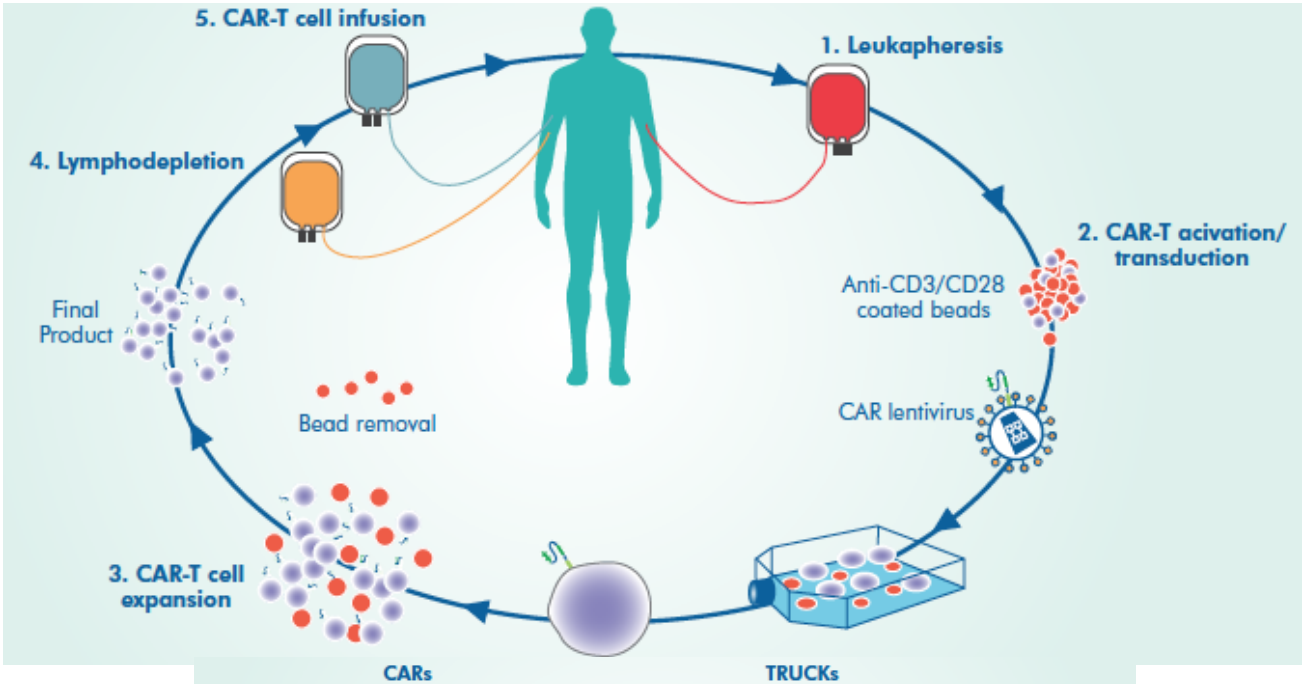
THEN, develop a monoclonal antibody specific for that antigen.

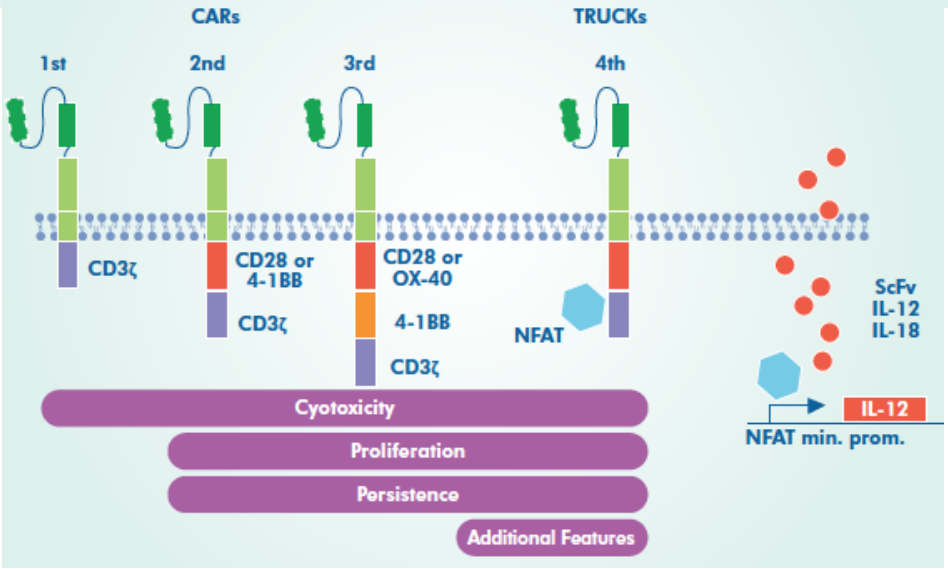
THEN, graft the extracellular “recognition domain” of the antibody onto the intracellular modules that activate T cells when the antigen binds to the external domain thus creating the CAR, or Chimeric Antigen Receptor.

THEN harvest the patients own T cells, transfect them in culture with the DNA construct encoding the new CAR, express the construct in vitro, test for functionality the give the modified T cells expressing the new CAR back to the patient...

THEN....

# CAR T cell Immunotherapy steps



# WHAT IS CANCER IMMUNOTHERAPY?

NOT JUST ONE THING…ONE SIZE DOES NOT FIT ALL...WHICH TYPE FITS WHICH CANCER?

**4. "Checkpoint" inhibitors – Abs that block the tumor's inhibition of immune system**

It has taken 50 years to understand the normal self-regulation of the immune response and 20 years to figure out how cancers have taken advantage of these mechanisms to evade the immne system.

When the immune system gears up to fight off an infectious pathogen or attack a foreign cell somewhere in the body, e.g. a transplanted organ or a cancer cell with mutations that mark it as "foreign", as the immune response ramps up it also begins to produce feed-back inhibitors of that response to avoid a dangerous "over reaction".

Cancers have co-opted these natural inhibitors of several steps in the immune response to protect themselves from immune attack.

These inhibitors are called "**check points**" in the immune response and the antibodies that block them are referred to as "**check point inhibitors**".

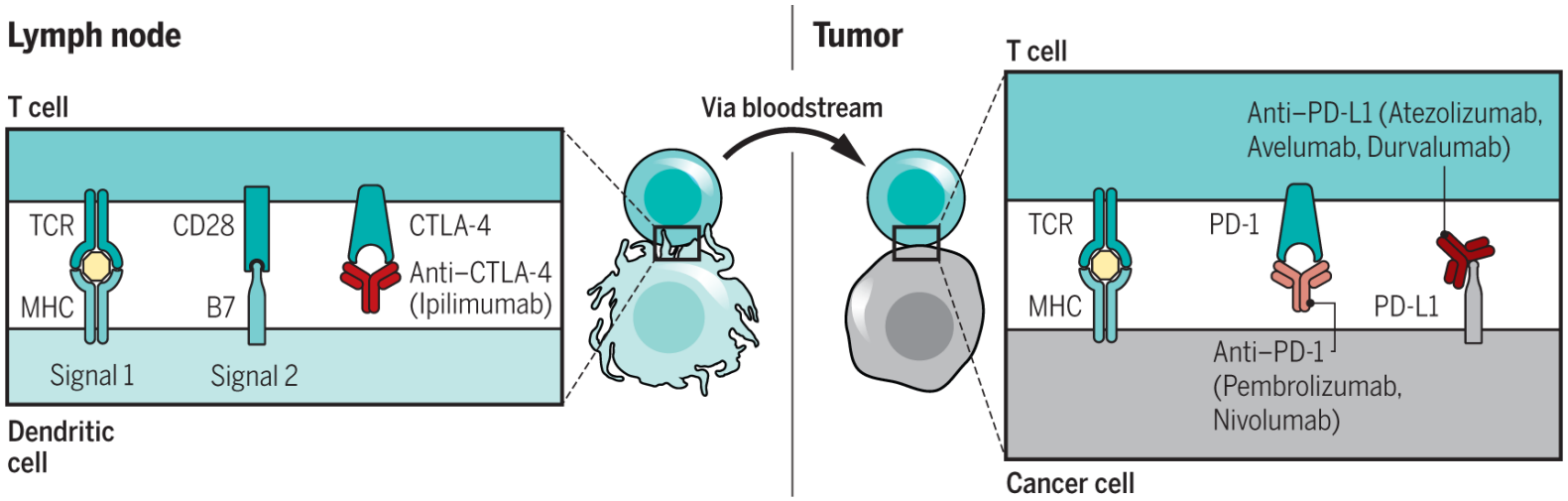



**Fig. 1. Blockade of CTLA-4 and of PD-1 and PD-L1 to induce antitumor responses.** (**Left**) CTLA-4 is a negative regulator of costimulation that is required for initial activation of an antitumor T cell in a lymph node upon recognition of its specific tumor antigen, which is presented by an antigen-presenting cell. The activation of CTLA-4 can be blocked with anti–CTLA-4 antibodies. (**Right**) Once the T cells are activated, they circulate throughout the body to find their cognate antigen presented by cancer cells. Upon recognition, the triggering of the TCR leads to the expression of the negative regulatory receptor PD-1, and the production of IFN-γ results in the reactive expression of PD-L1, turning off the antitumor T cell responses. This negative interaction can be blocked by anti–PD-1 or anti–PD-L1 antibodies.

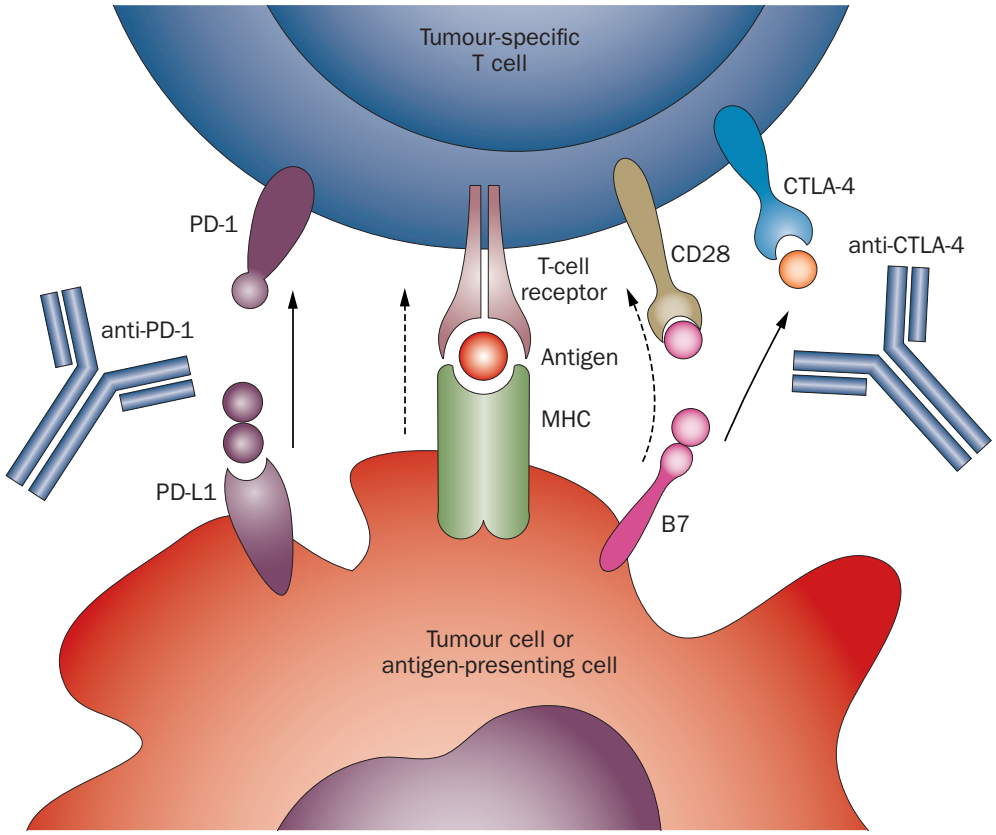
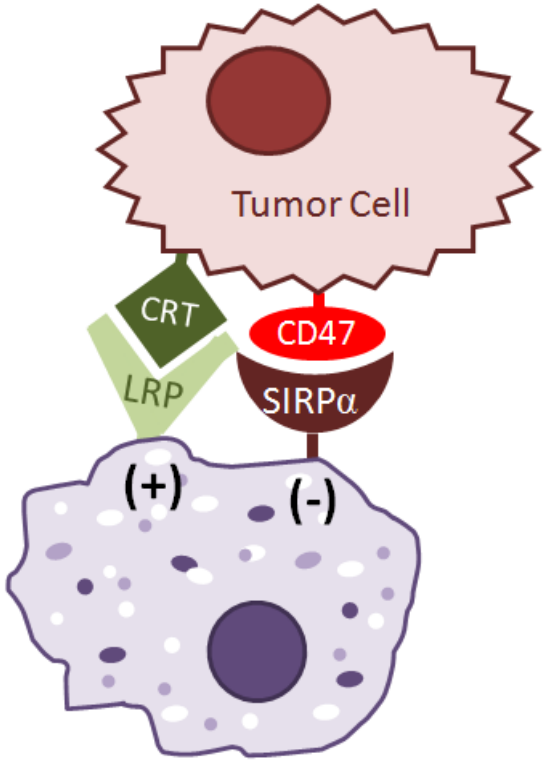
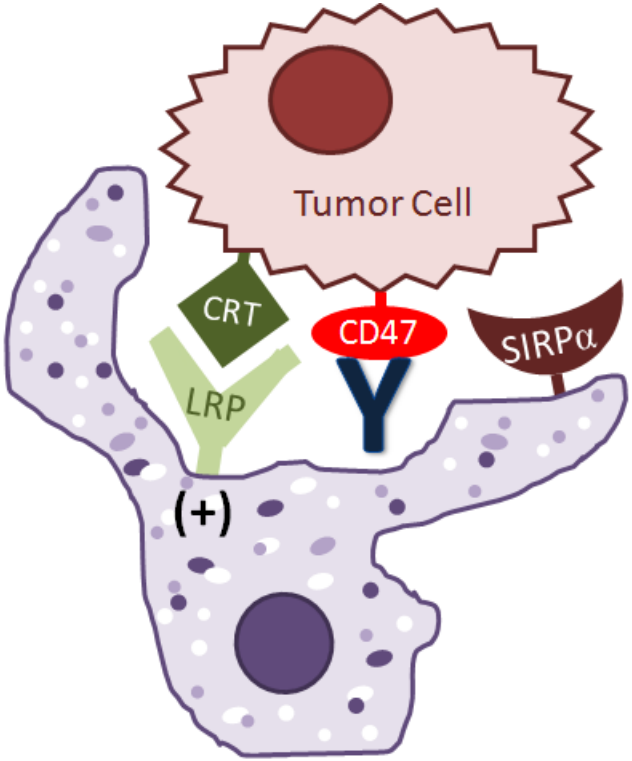



**Figure 2** | Immune checkpoint blockade. This approach to immunotherapy is exemplified by antibodies directed against CTLA-4 (ipilimumab, tremilimumab), which block the immunosupression mediated by the interaction between B7 family members (on antigen-presenting cells) and CTLA-4 (on $CD8^+$ and $CD4^+$ T cells). A second major checkpoint, mediated by the interaction between PD-1 on T cells and its ligand PD-L1 on either antigen-presenting cells or tumour cells, has been the subject of several recent clinical trials, and has shown evidence of efficacy in both non-small-cell lung cancer and renal cell carcinoma.

# Anti-CD47 Promotes Phagocytosis of Tumors

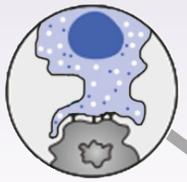
*mAb blocks the "don't eat me" signal sent by CD47*

| Steady State | Anti-CD47 mAb Therapy |
| --- | --- |
|  |  |
| Pro- & Anti-Phagocytic Signals<br>No Phagocytosis | Pro-Phagocytic Signal (sent by CRT)<br>**Phagocytosis** |

# *CD47 blockade promotes uptake of tumor cells by macrophages and dendritic cells which present antigens to stimulate an anti-tumor T cell response*

## Innate Immune System

Phagocytosis of Cancer Cells by Macrophages
- Blocking-only and dual-function anti-CD47



## Tumor Cytotoxicity

Direct Killing of Cancer Cells
- Dual-Function Anti-CD47

## Adaptive Immune System

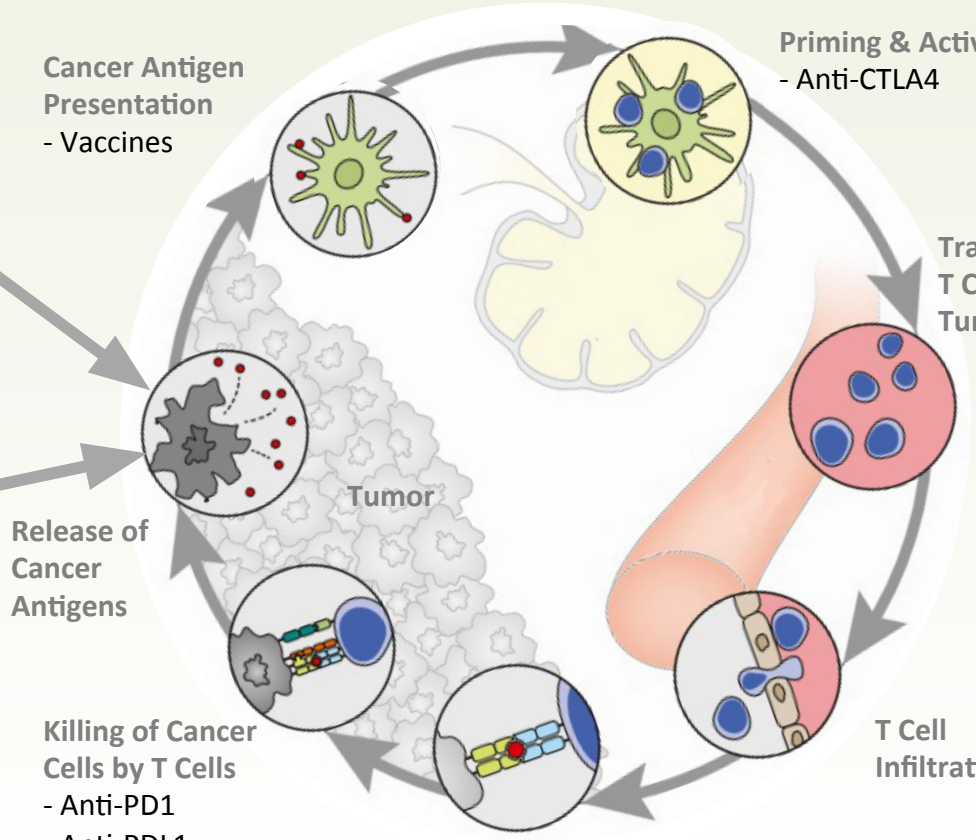





Figure adapted from Chen and Mellman 2013

## Many human tumors express high levels of CD47
## CD47-hi tumors are more deadly than CD47-low tumors

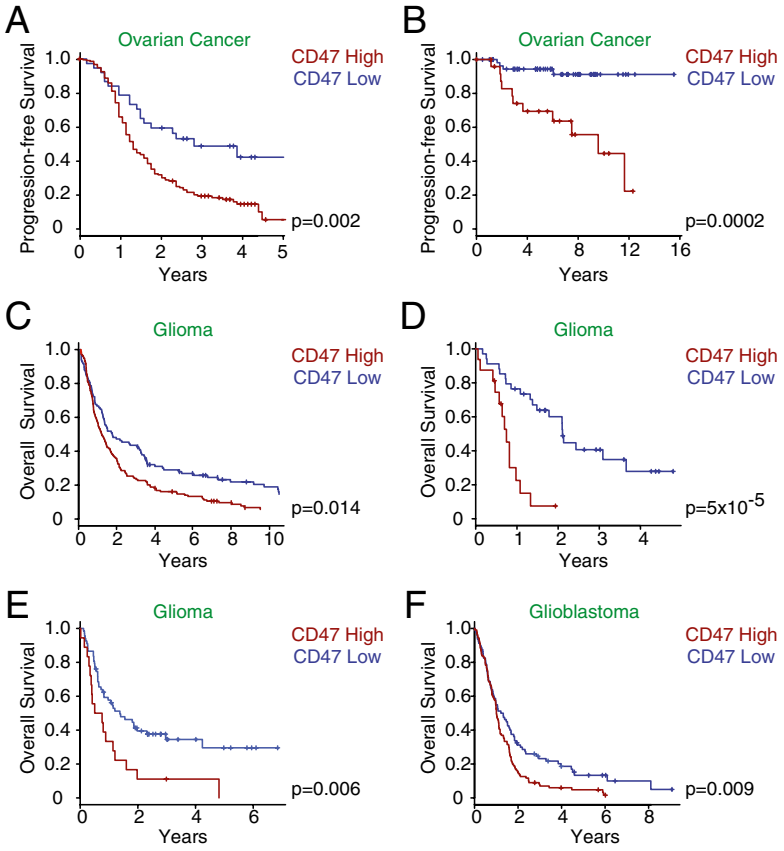
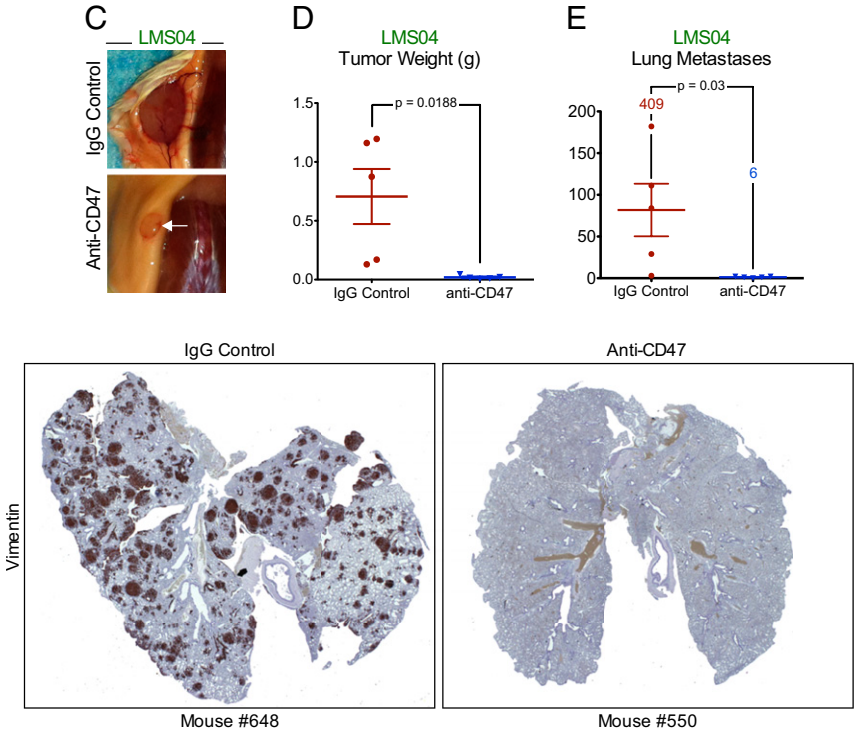



**Fig. 2.** CD47 mRNA expression levels may be a prognostic factor in solid tumors. Increased levels of CD47 mRNA expression were correlated with decreased probability of progression-free survival of ovarian cancer (*A* and *B*) and overall survival of glioma (*C–E*) and glioblastoma (*F*). See also Table S1.

Willingham et al. PNAS 2012

## Human Leiomyosarcomas express high levels of CD47 and growth of these tumors in mice is inhibited by humanized B6H12 (anti-human CD47 mAb)




Edris et al. PNAS 2012