IMMUNOTHERAPY FOR CANCER – A NEW HORIZON

Ekaterini Boleti MD, PhD, FRCP
Consultant in Medical Oncology
Royal Free London NHS Foundation Trust

ASCO Names Advance of the Year: Cancer Immunotherapy

“No recent cancer advance has been more transformative than immunotherapy. These new therapies are not only transforming patient lives, they are also opening intriguing avenues for further research”

ASCO President Julie M. Vose

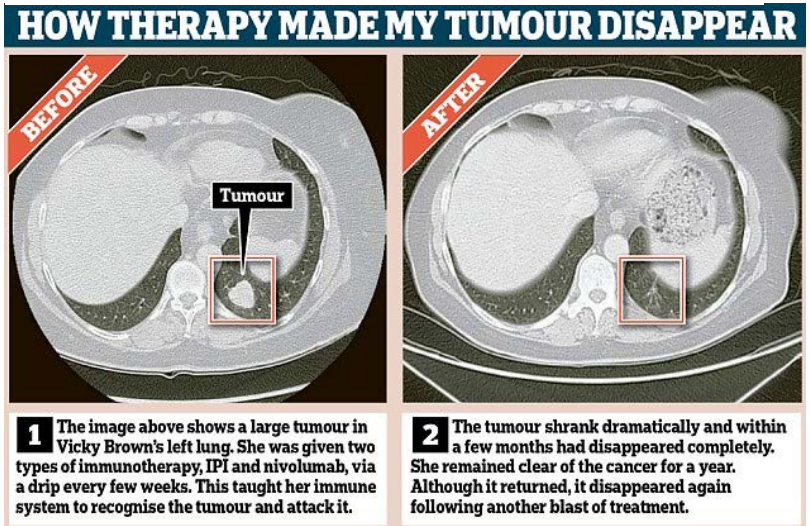
BBC

Have we cured cancer?

THE Sun

We had fatal cancer ‘cured’ by new vaccine therapy

Daily Mail



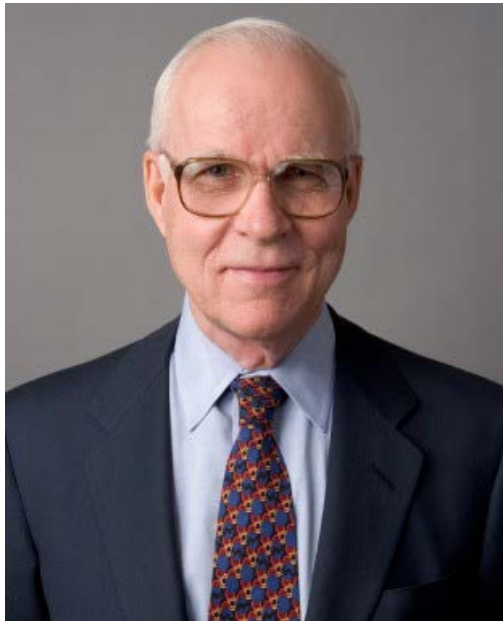
The story of Cancer Immunotherapy
Is it really new?

William B. Coley
The Father of Cancer Immunotherapy

Worked on the potential of cancer immunotherapy in relation to bacterial infections

Lloyd J. Old
Tumour Immunology

Introduction of BCG in cancer immunotherapy
Explored links of MHC & leukaemia
Discovered TNF
Discovered with other two research groups, p53,
Identified tumour immunogenicity of heat shock proteins
Identified the link between EBV & nasopharyngeal carcinoma



What has changed?

- Advances in our understanding of the fundamental principles of tumour immunology
  - Ability to successfully translate them into clinical practice
- New technology tools and advances in genetic engineering facilitate our understanding of the principles of tumour immunotherapy and support further development of new generation therapies
- Facilitate the exploration of potential biomarkers of response to treatment
- Fast track FDA & EMA approval of drugs and a plethora of clinical trials provide the opportunity for testing and confirming outcomes

So far…

- Fast-track approvals

- **Melanoma**
  - Ipilimumab
  - Pembrolizumab,
- **Non-small cell lung cancer (SCC & non-SCC)**
  - Nivolumab
- **Prostate cancer**
  - Sipuleucel-T
- **Acute Lymphocytic Leukaemia**
  - Blinatumomab

HOW DID IT ALL START?

Innate Immunity

- **Evolutionary conserved across vertebrates & non-vertebrates**
- **Quick but non-specific immune responses to pathogens**
  - **Epithelial barriers**
  - **Effector cells**
    - Monocytes
    - Macrophages
    - Natural killer cells
    - Dendritc cells
    - Neutrophils
    - Eosinophils
  - **Humoral components**
    - Complement proteins
    - Collectins

Adaptive Immunity

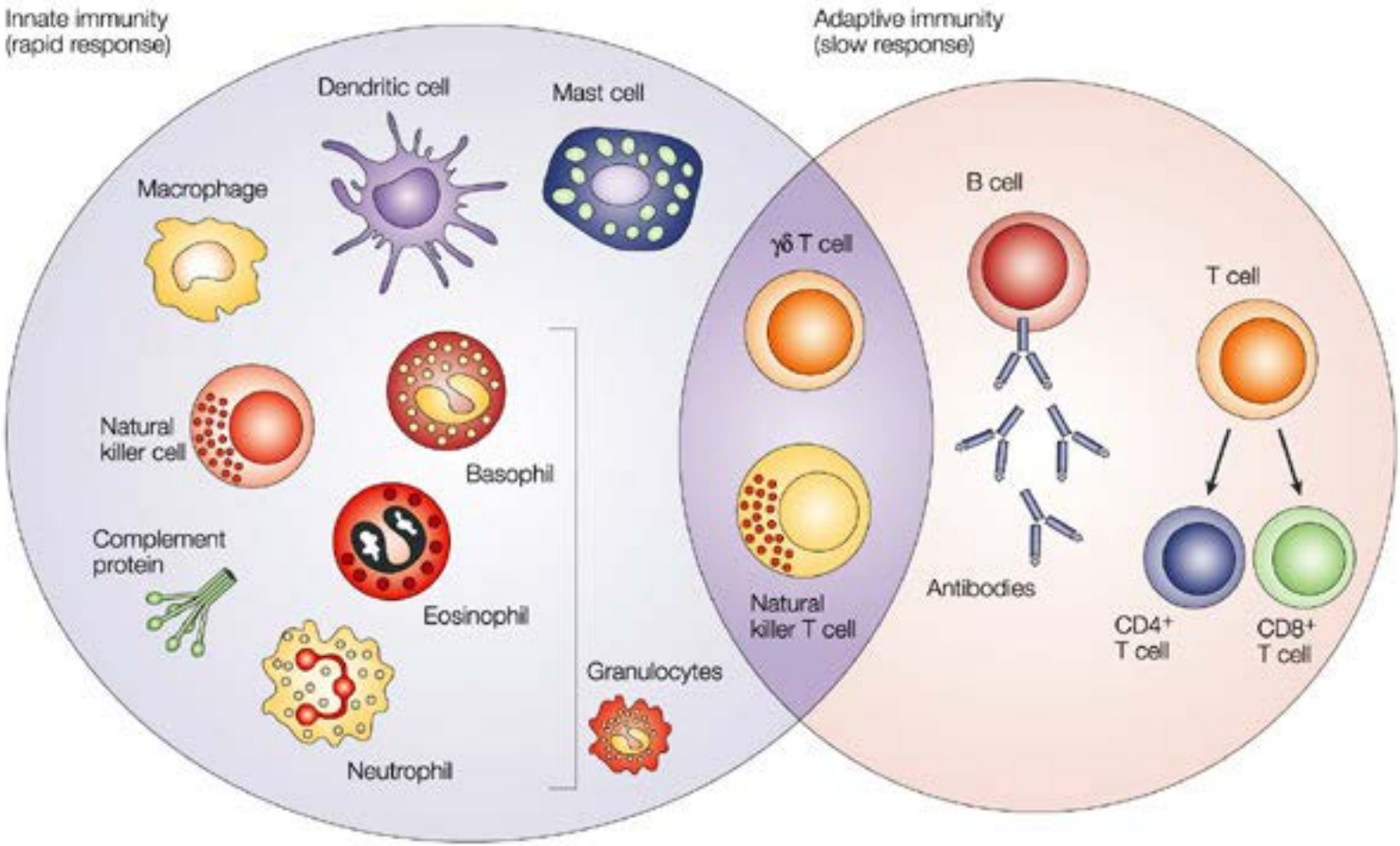
Three features

- **Diversity**
- **Specificity**
- **Memory**

- **T cells**
  - Using T cell receptors recognise epitopes presented on the surface of cells by MHCI/II surface receptors
- **B cells** recognise antigens (Ag) via
  - B cell receptors (BCR)
  - Soluble BCR component - Antibodies (Ab) - by direct binding to Ag in serum

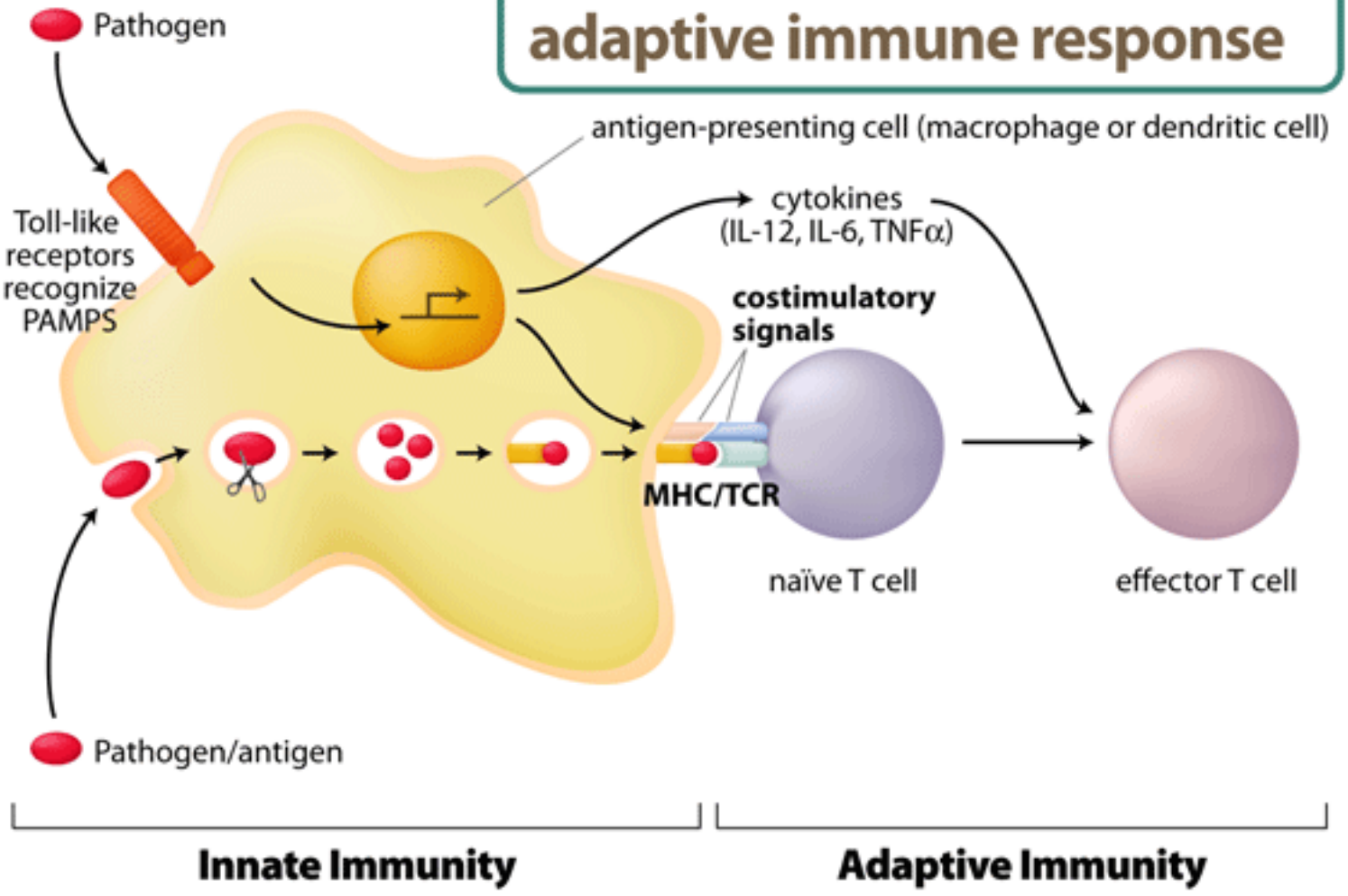
  - Diversity & specificity of TCR & BCR receptors are generated by a somatic recombination process

Innate & Adaptive Immunity



Nature Reviews | Cancer

Innate immunity is critical to adaptive immune response

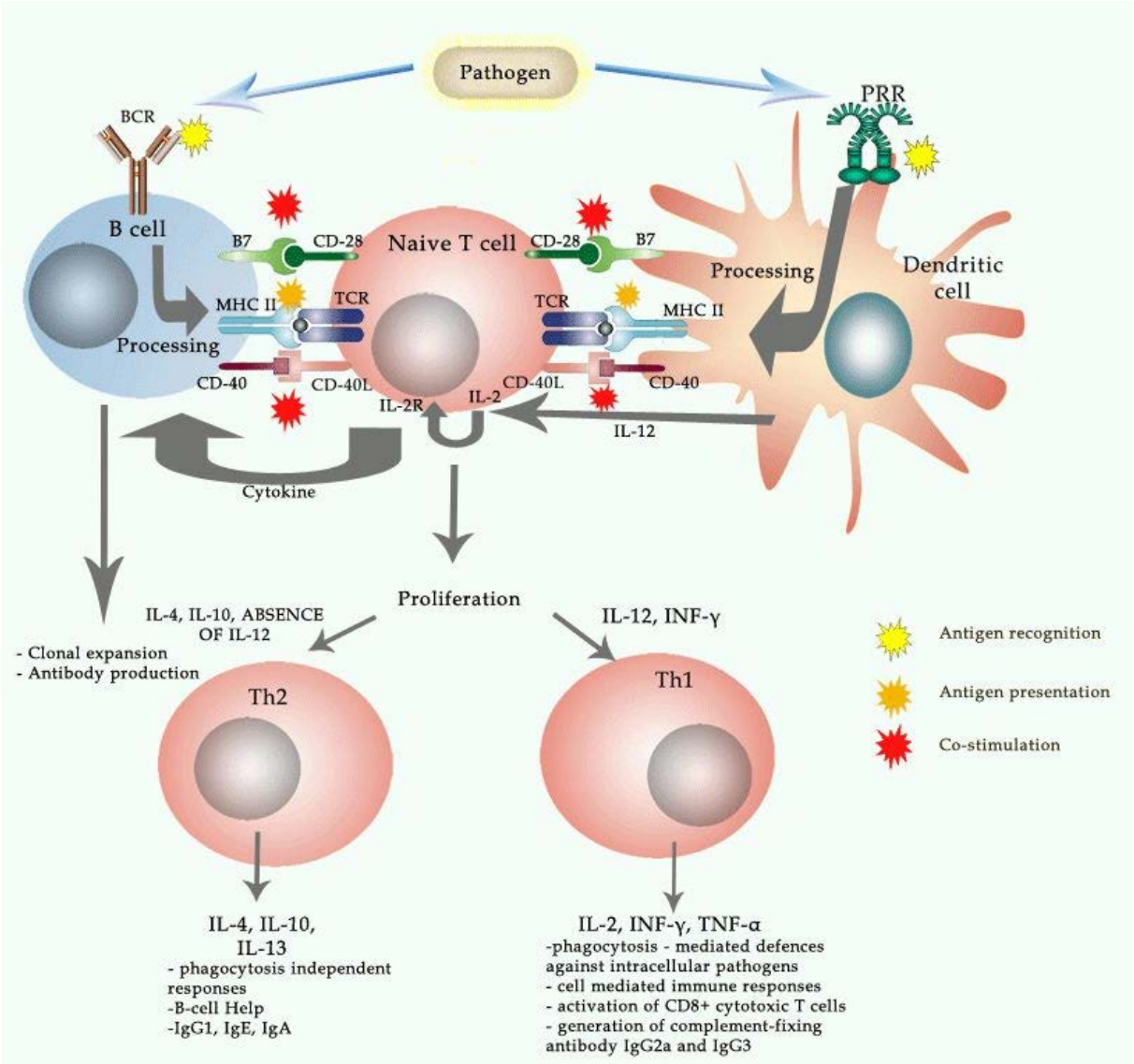


T cells & Cancer

- **Cytotoxic T cells express CD8**
  - Upon activation can directly kill cancer cells
  - Activation requires two signals
    - Recognition of Ag via TCR & MHCI molecules
    - Co-inhibitory (CTLA-4) & co-stimulatory (CD28) molecules bind to ligand on target cancer cells
    - Promote 'tolerogenic' state or cytotoxic effect

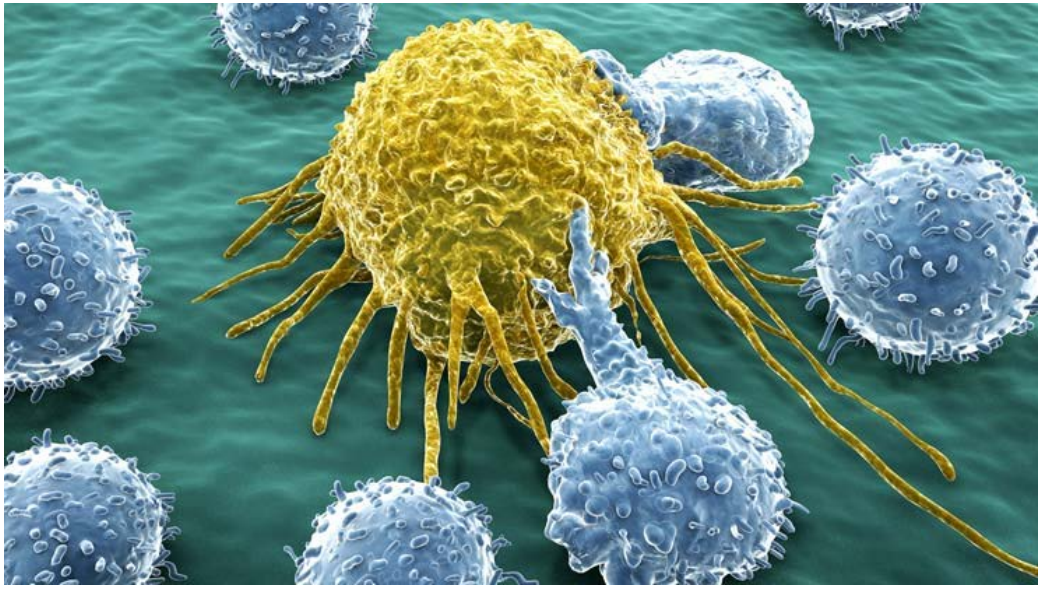
- **Helper T cells express CD4**
  - Facilitate immune responses involving cytotoxic T cells, B cells & the innate immune system
  - Upon stimulation with Ag in the context of MHCII molecules, naïve CD4+ T cells differentiate into
    - **T_H1** (secrete IFN and promote anti-viral and anti-tumour responses)
    - **T_H2** (secrete IL-4 & IL-13, amy reduce tumour immune responses
    - **T_H17**
    - **T_{reg}** (promote tumour escape mechanisms & reduce immune responses)

Innate Immunity may Trigger Adaptive Immune Responses via Antigen Processing & Presentation by Macrophages & Dendritic Cells



Aims of Cancer Immunotherapy

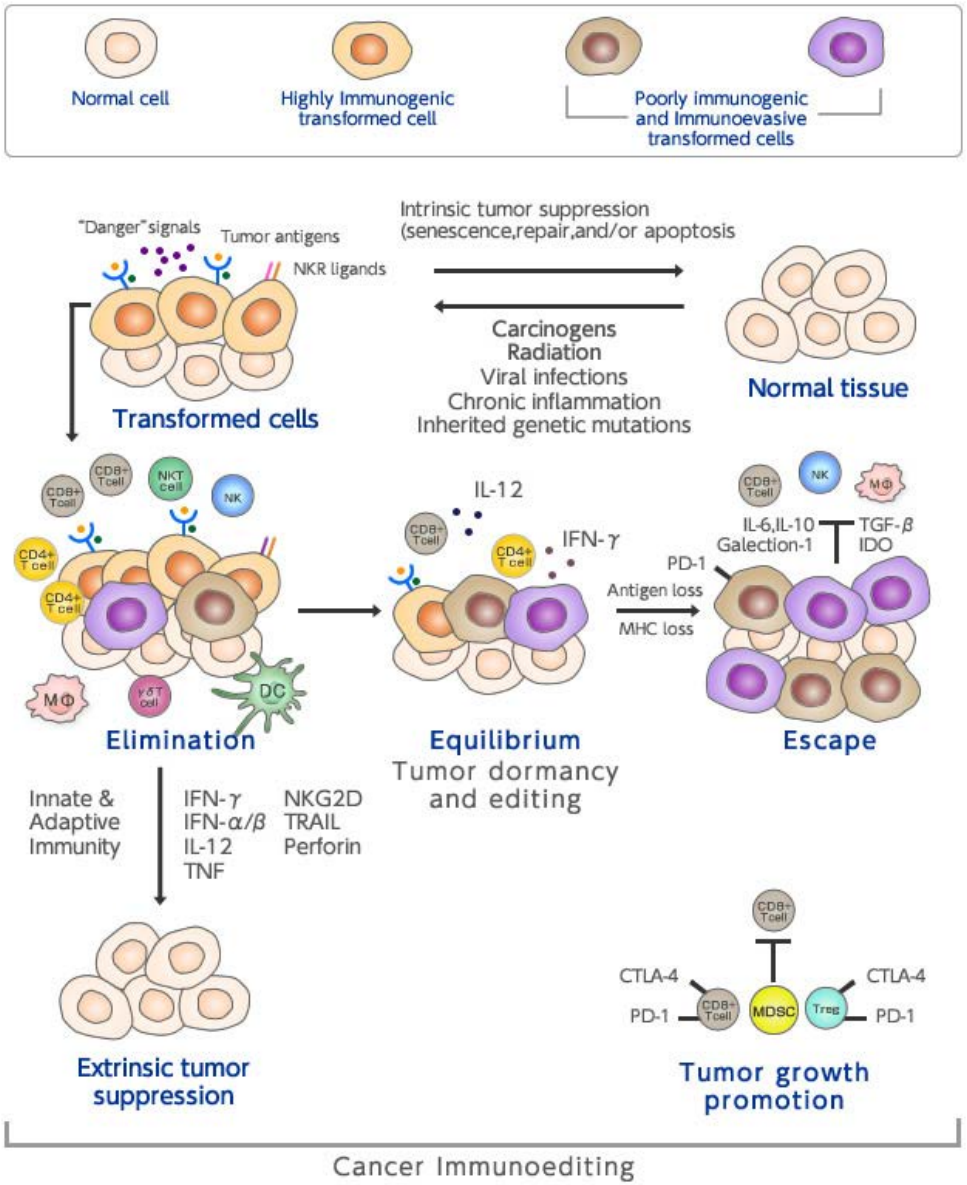
- Block immunosuppressive mechanisms
- Increase the function of endogenous anti-tumour T cells to develop clinically effective immune responses
- Identify biomarkers to
  - understand potential mechanisms of action
  - define parameters associated with clinical responses and toxicities



Cancer Immunoediting *(Schreiber et al., Science, 2011)*

- Positive & negative actions of the immune system that define responses on developing tumours
- Continuous process
- Three phases
  - Elimination
  - Equilibrium
  - Escape
- Can result in
  - Complete elimination of tumours
  - Acquisition of tumour immune resistance and survival in a steady state
  - Non-recognition by immune mechanisms and tumour growth

Cancer Immunoediting



Mechanisms of tumour escape

- **Tumour-intrinsic**
  - Anergy
  - Exhaustion of activated T cells with endogenous immune checkpoint molecules
    - Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)
    - Programmed cell death 1 (PD-1)
    - T cell immunoglobulin 3 (Tim-3)
    - Lymphocyte activation gene 3 (LAG-3)

- **Tumour extrinsic**
  - TGF-β, IL-10
  - Direct impact on the tumour micro-environment & the recruitment of anti-inflammatory cells
  - Use of tolerogenic antigen presenting cells (APCs) & regulatory T cells ($T_{reg)}$
  - Inhibition of cytotoxic T lymphocytes

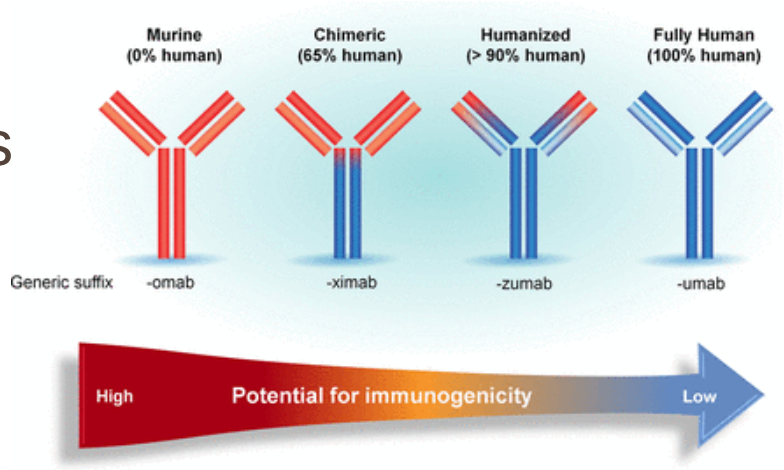
RECENT ADVANCES

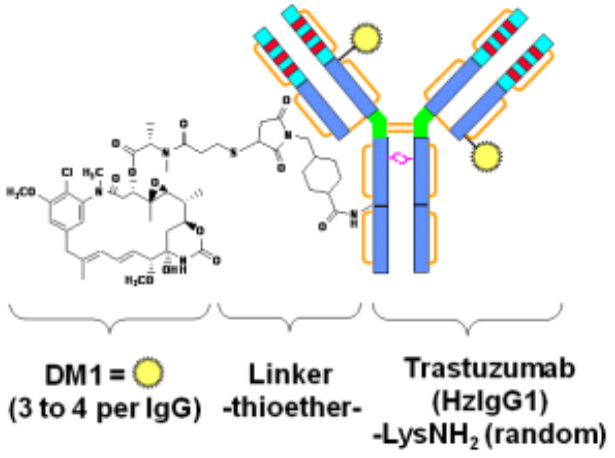
Types of therapies

- Improved versions of old classics
- Advances in Cancer Vaccine Therapy
- Adoptive Therapy
- Immune checkpoint Inhibition

Monoclonal Antibodies (Mabs)

- The ‘magic bullet’ concept
- From murine to fully human Mabs
- Action in a Fc-dependent way
  - ADCC
  - ADCP
  - CDC
- Action in a Fc-independent way
  - Direct apoptosis
  - Agonistic/antagonistic interactions
- Ab-drug congugates (ADC)
  - Improved efficacy
  - Trastuzumab etmansine (T-DM1)

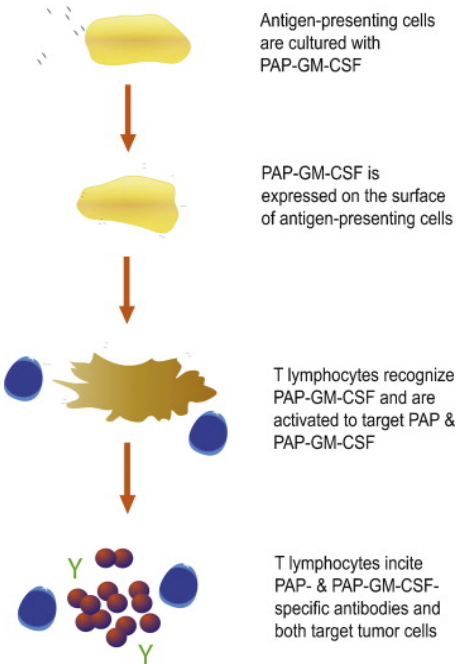




Cancer Vaccines

- Aim to induce an adaptive immune response to a cancer Ag
- Therapeutic rather than prophylactic
- Tumour Associated Ag vs Tumour Specific Ag
- Challenging to generate a specific effective immune response
  - Achieve limited number of developed Ag-specific T cells
  - Suboptimal target Ag selection
  - Strong immunosuppressive signals limit T cell activity
  - Vaccine-induced T cells with limited anti-tumour activity

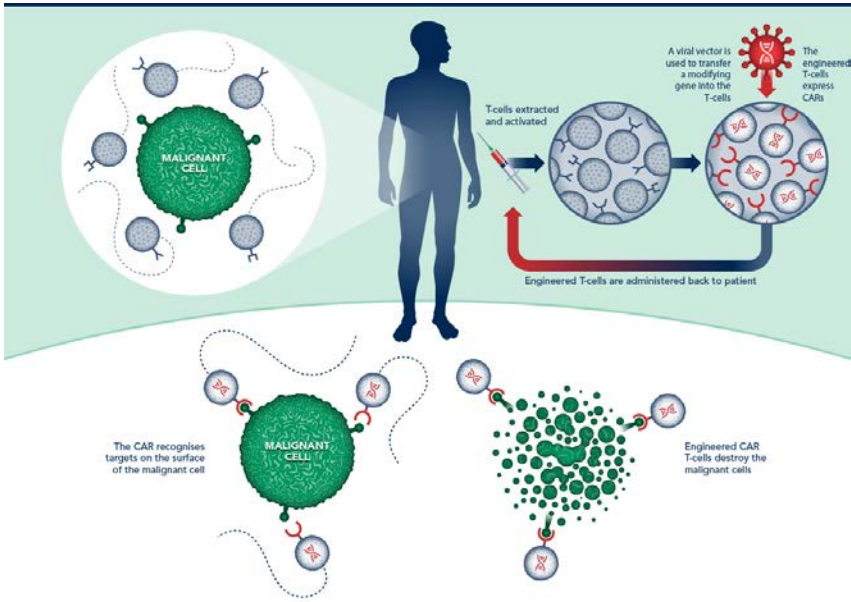
- **Sipuleucel-T**
- FDA-approved, 2010
- Autologous APC vaccine
  - Harvest pt's Ag presenting cells
  - Expose to tumour Ag ex vivo
  - Return to patient
- OS prolonged by 4.1 mo
- 3yr survival improvement 31.7% vs 23.0%



Adoptive therapy

- *Ex vivo* manipulation of autologous T cells
  - Gene insertion of a chimeric Ag receptor (CAR)
  - Engineered TCR
  - Expansion of endogenous tumour infiltrating lymphocytes (TIL)
- Re-infusion to generate effective immune responses
- Ability to tumour binding & direct activation without Ag binding via a TCR/MHC complex

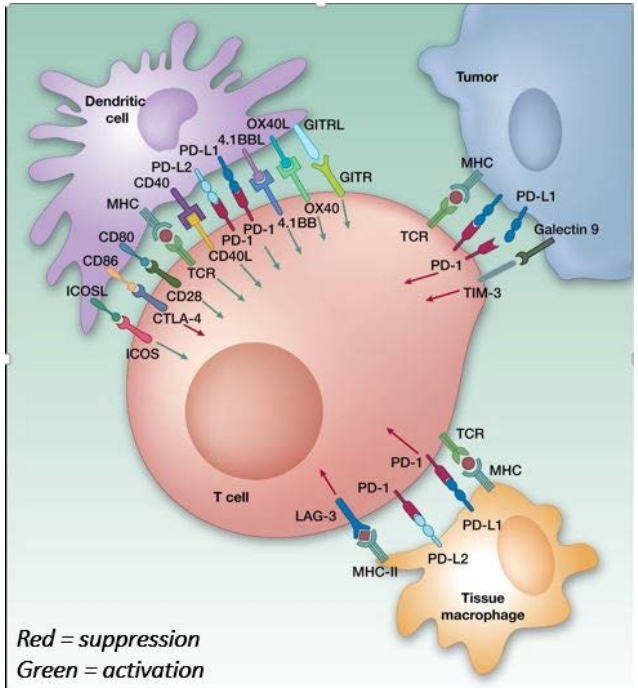
- CAR-T therapy
  - CLL & ALL using anti-CD19 CAR T cells
- Engineered TCR
  - toxic (trials in sarcoma & melanoma)
- TIL expansion & re-infusion
  - Trials in melanoma



Immune Checkpoint Inhibition

- T cells have ‘checkpoints’ ie PD-1 & CTLA-4

which protect against auto-immunity & excessive immune responses to an infection



- Tumours can also take advantage of such immune inhibitory mechanisms and escape immune elimination

- Unlike classic immunotherapy strategies which aim at stimulating T cell responses against TSAs the aim is to avoid turning off the immune system by checkpoint mechanisms

Checkpoint Inhibibitor Therapies

CTLA-4 blockade

- Co-inhibitory checkpoint receptor on the surface of T cells
- Reduces T cell responses by inducing downstream inhibitory signalling and competitively binding with the B7 ligand on the surface of APCs

- CTLA-4 blockade improves survival in studies of patients with melanoma

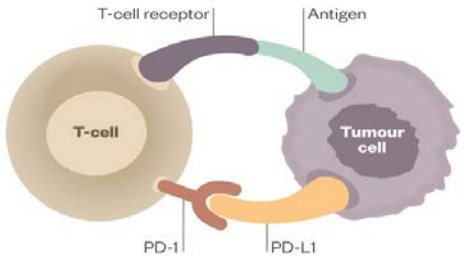
Ipilimumab +/- gp100 peptide vaccine vs gp100 alone

10.1/10.0 mo vs 6.4 mo (NEJM, 2010)

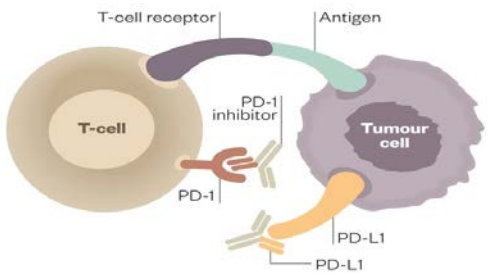
- Durable responses (21% 3-yr survival)
- Autoimmune side effects
- FDA, EMA & NICE approved

Checkpoint Inhibibitor Therapies
PD-1 blockade

- PD-1 is an immune inhibitory receptor on the surface of T cells which binds with PD-L1 on the surface of tumour cells



Deactivated T cell



Activated T cell

- **Nivolumab & Pembrolizumab** (anti PD-1 MAbs)

Both approved for the treatment of metastatic melanoma

Nivolumab licensed for the treatment of SCC and non-SCC NSCLC

Also currently being tested in renal cell cancer, bladder cancer and haematological malignancies

Checkpoint Inhibitor Therapies
Points of interest

- Checkpoint blockade therapies have revolutionised cancer immunotherapy and opened new avenues in the management of cancer patients
- Technological advances support the development of new agents and diagnostic tools
- New agents emerge and improved outcomes are expected
- Public awareness allows rapid completion of trials and expedited results promise faster drug approval and access by patients

Challenges

- Identify the right sequence for administering the new agents
- Establish if combination therapies (chemotx or more than one immunotherapy agents) can provide improved outcomes
- New toxicity profiles have emerged that require specialised & careful monitor
- Current methods for evaluation of response appear unable to capture the pattern of responses – new validated response criteria are required
- Need to identify biomarkers that will
  - facilitate patient selection deriving maximum benefit from treatment
  - Avoid/minimise toxicity
- Immunotherapy Clinical Trial Design

Cancer Immunotherapy
Summary

- Advances in our understanding of the functions of the immune system & emerging new technologies translate into clinical success stories
- Benefits are seen across more than one types of immunotherapy
- Optimal sequences of treatment and wider access are future challenges as well as the considerable cost of therapies
- Research-based clinical trials combining immunotherapy with other treatment modalities should be encouraged

Thank you