Why (How to) Harness the Immune System to Treat Pediatric Cancer?

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Modalities of Cancer Therapy

- Chemotherapy
- Radiation
- Surgery
- Targeted Therapy
- Immunotherapy

Immunotherapy – a definition

- "cancer immunotherapy attempts to AMPLIFY or REPROGRAM the inherent capacity of immune cells to eliminate tumor cells"
- Goals:
  - Specific
  - Persistence (if possible)
  - Potent

Ceppi et al. (2017) Eur J Pediatrics

Quick Review of Normal Immune Response

- The immune system has cytotoxic mechanisms, capable of killing any kind of altered cell
- Main Players for today's discussion – B Lymphocytes and T Lymphocytes
- B Lymphocytes: Production of antibodies that bind to an antigen on the cell surface
- T Lymphocytes: Production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, & cytokines in response to an antigen (foreign) – releases toxins

Simple…

- Surveillance:
  - T cells continuously scan for abnormal cells using the T cell receptor (TCR)
  - Scans cell surface peptides (proteins) – like a bar code
  - If the scan is normal the T cell moves on
  - If the scan is abnormal and identified as altered or foreign the T cell is activated and secretes cytokines and factors
- Mutated Proteins
  - Cell proteins can mutate (and do mutate) and this changes the peptide expression on the cell surface (neoanitgens)
  - The T cells SHOULD be able to recognize this as altered or foreign
  - The more mutations the greater number of altered and expressed peptides (neoantigens) on the cell surface – makes it easier for the TCR to identify a “bad” cell

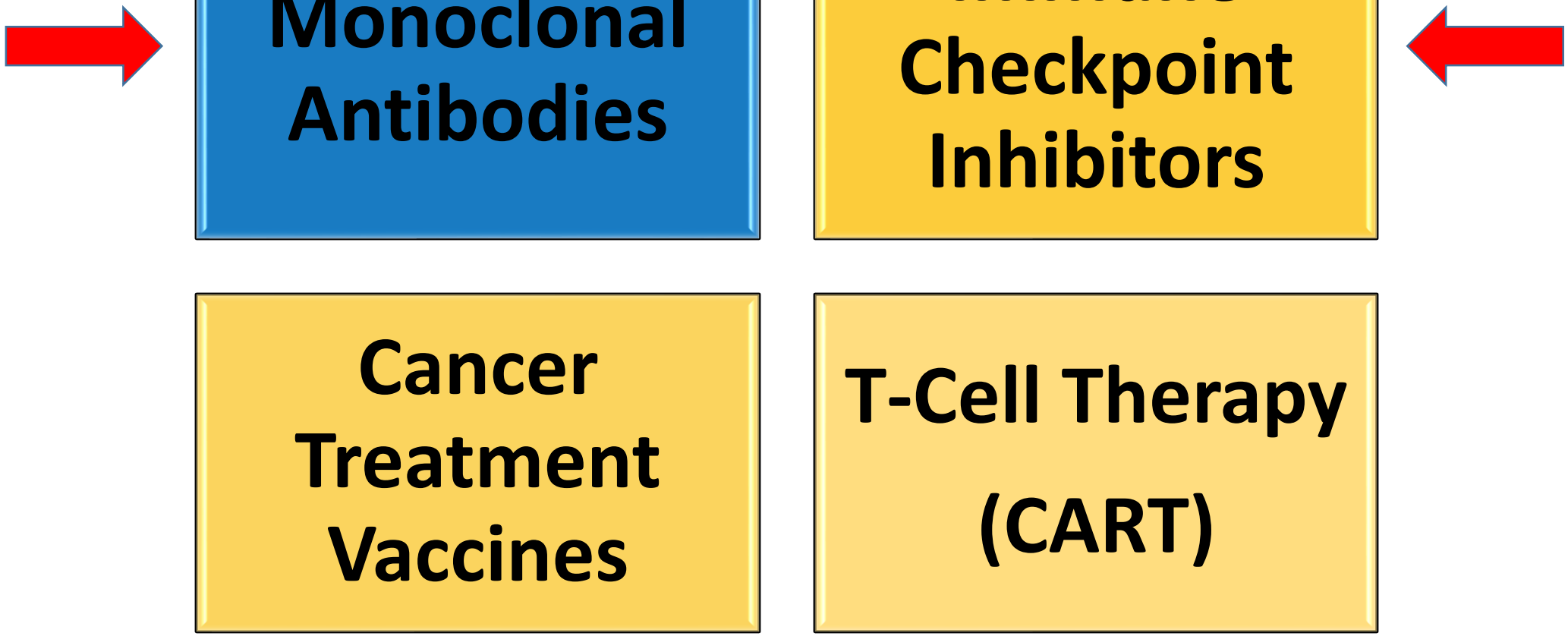
The problem…..

- Cancer cells have found a way to be “invisible” to the immune system through their evolution (and surface expression)

The solution…..

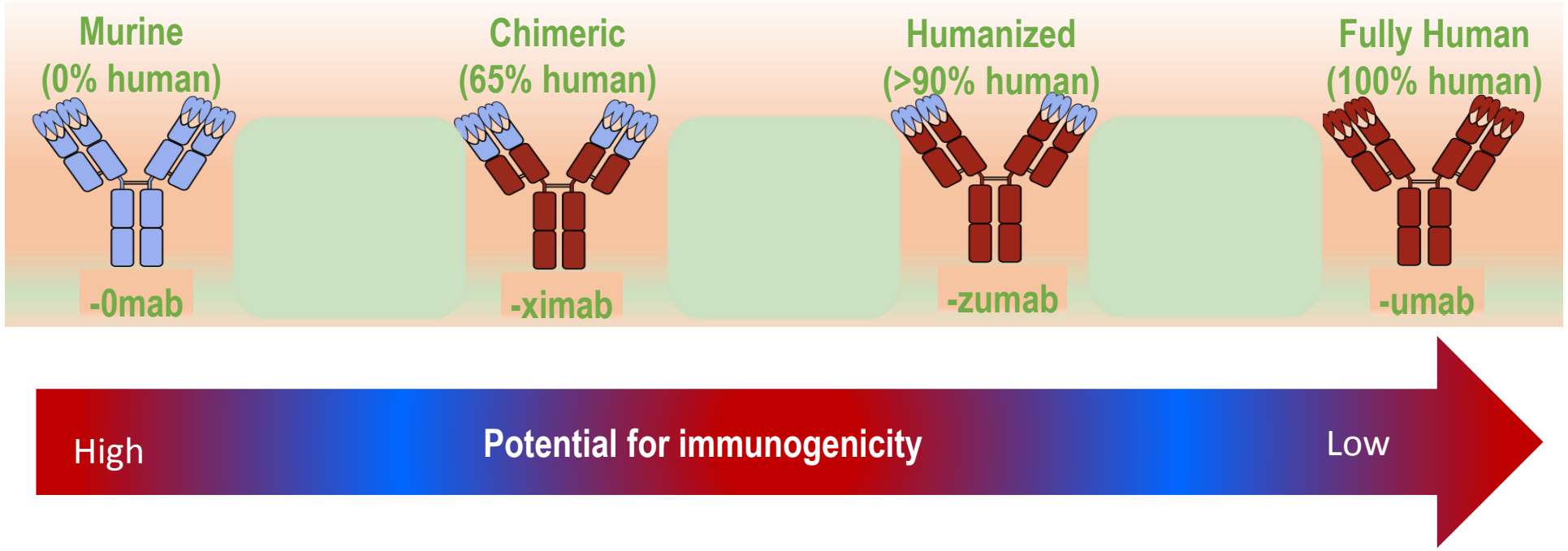
- New Immunotherapies allow the host immune system to regain its ability to execute its inherent cytotoxic capacity on tumor cells
- This can be done by:
  1. Identifying TARGETS on the cell surface and make it possible to HIT the tumor cells with tailored antibodies
  2. Administer targeted therapies that “release the brakes” and make the tumor cell visible to immune cells

Types of Immunotherapy



Monoclonal Antibodies

- Synthetic biologics that bind to any antigen on the tumor cell surface:
  1. Facilitate antibody-dependent cellular cytotoxicity by the host's immune system or via complement-mediated killing
  2. Serve as a vector for a toxic to be endocytosed
  3. Block tumor cells signaling pathways (ex. checkpoint inhibitors – coming up)



Nomenclature

- Starts with prefix given by the manufacturer and always ends in MAB
- 1st subsystem: What the drug targets & possible side effects
  - t or tu = tumor
- 2nd subsystem: How the drug was engineered
  - e = hamster
  - i = primate
  - **o = mouse**
  - **xi – chimeric**
  - **zu = humanized**
  - **u = fully human**

Examples

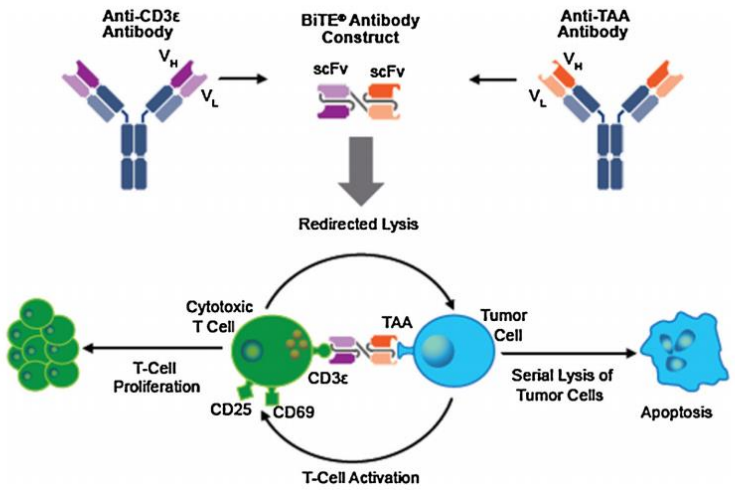
- Inotuzumab
  - tu – targets the tumor directly
  - zu – humanized
- Blinatumomab
  - tu – targets the tumor directly
  - mo- Murine
- Rituximab
  - tu - targets the tumor directly
  - Xi – chimeric

Monoclonal Antibodies

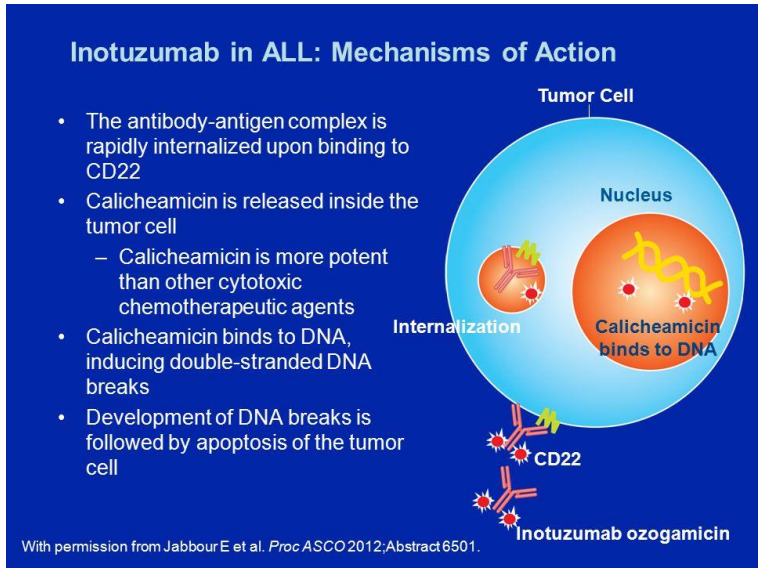
Cancer Type	Target	MAB	Success
Neuroblastoma	GD2	Dinutuximab	Yu et al. (2010) NEJM Anti-GD2 chimeric antibody in conjunction with cytokines improved survival in patients with High Risk Neuroblastoma
Malignant B Cell Lymphoma	CD20	Rituximab	Minard-Colin et al. (2016) J Clin Oncology Chimeric antibody in combination with chemotherapy increased both EFS and OS in pediatric patients with High Risk B Lymphoma
PTLD (Post Transplant Lymphoproliferative Disease)	CD20	Rituximab	Gross et al. (2012) COG Report Chimeric antibody in combination with chemotherapy to successfully treat PTLD following both solid organ and bone marrow transplant
Hodgkin Lymphoma (conjugate)	CD30	Brentuximab	Fabbri et al. (2017) Antibody drug conjugate delivering toxin improves survival in relapsed HL

Monoclonal Antibodies - Cont'd

Cancer Type	Target	MAB	Success
B Cell ALL (peptide bridge)	CD19(CD3)	Blinatumomab Bispecific antibody	von Stackelberg et al. (2016) JCO AALL1331 – results pending
B Cell ALL (conjugate)	CD22	Inotuzumab	Kantarjian, H. et al. (2016) NEJM (Adult) INNOVATE Bhojwani et al. (2017) JCO (Pediatric Retrospective Data) AALL1621 – Results pending



G. Zugmaier et al. / Molecular Immunology 67 (2015) 58–66



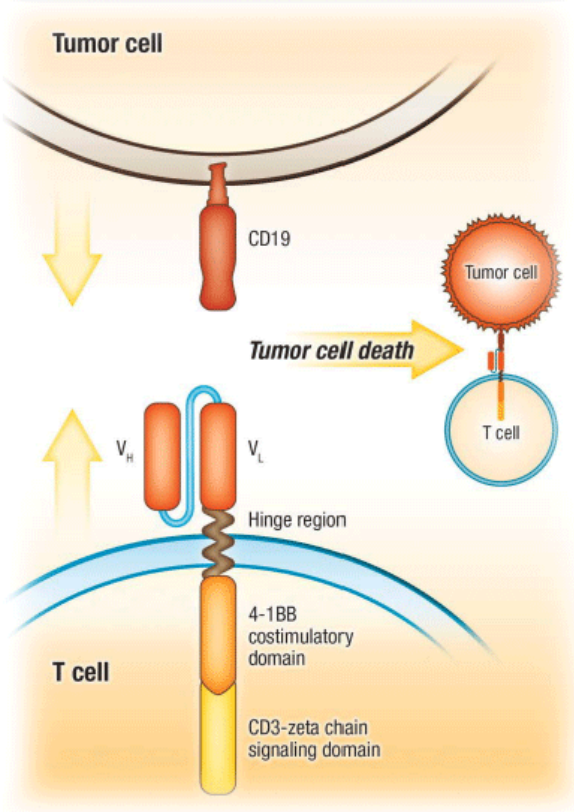
New Toxicities!

Adverse Events	Antibody Examples
Severe Neuropathy	Brentuximab, anti-GD2 MAB Dinutuximab
Infusion Reactions	Rituximab
Cytokine Release Syndrome	Blinatumomab
Infectious Complications	Rituximab
Sinusodal Obstructive Syndrome (SOS)/VOD	Inotuzumab

- New mechanisms of action mean new toxicity profiles
- Must consider what cells share TARGETS and will also be affected
- Must consider what response will be altered or enhanced for cell death – ex. T Cell Activation – release of cytokines!
- Consider in the context of combination therapy

CART cells…..

- Modified T cells designed to recognize a specific antigen on the tumor cell surface



A new problem emerges….cancer cells are smart

- Focusing on CD19 directed therapy (Blina and CART) for B ALL

- New patterns of relapse!?!
  1. Extramedullary Sites (CD19+)
  2. CD19 - Relapse (antigen loss)

- Cancer cells continue to evolve with the goal of SURVIVING…
  - Do they find a protective environment to live and thrive?
  - Can they mutate to change surface expression to evade the tailored therapy?
    - Antigen loss!

Types of Immunotherapy

Monoclonal Antibodies

Immune Checkpoint Inhibitors

Cancer Treatment Vaccines

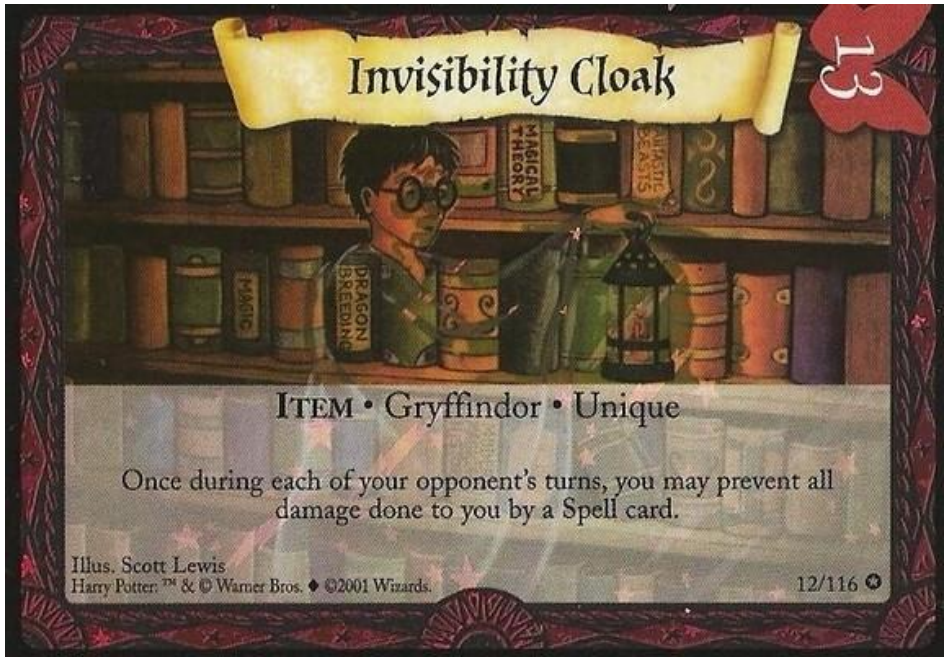
T-Cell Therapy (CART)

Check Points are Normal!

- Checkpoints, or “applying the brakes” occurs in normal cells
- Surface expression of checkpoint molecules limits the T cell response to self antigens and prevents autoimmunity
- Tumor cells through evolution have “learned” to express checkpoint molecules in order to evade the normal immune response
  - The TCR does not recognize them as altered and does not induce response

Immunomodulatory Agents

- Checkpoint inhibitors are targeted agents that block the specific mechanisms (checkpoints) underlying the tumors ability to evade the immune system
- Removes the Invisibility Cloak!



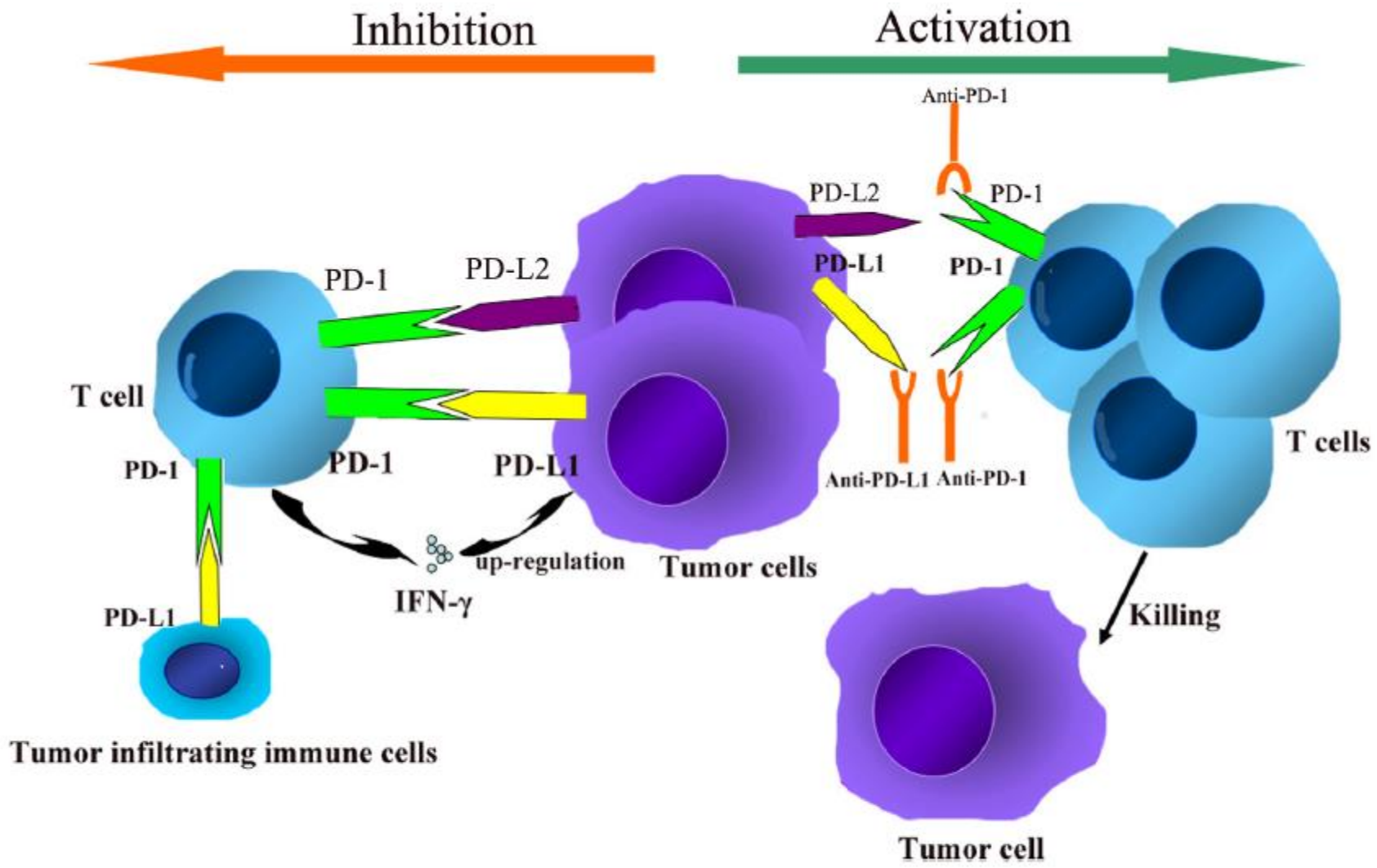


Fig. 1. The mechanism of anti-PD-1 and anti-PD-L1 checkpoint blockades. PD-1 is expressed by T cells. PD-L1 is expressed in tumor cells and tumor infiltrating immune cells. Combination of PD-1 and PD-L1/PD-L2 contribute to the suppression of T-cell function. Inhibiting the interaction of PD-1 and its ligands can significantly enhance T cell function, resulting in antitumor activity.

Meng et al. (2015) Cancer Treatment Reviews

Checkpoint Inhibitors

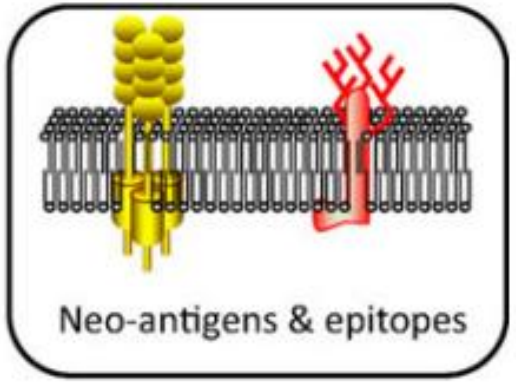
Cell Surface Receptor	Examples	
PD-1 (Programmed Cell Death Receptor)/PDL-1	• Nivolumab • Pembrolizumab	• Pruritis, rash, diarrhea • pneumonitis, vitiligo, colitis, hepatitis, thyroiditis
CTLA-4 (Cytotoxic T lymphocyte-associated protein 4)	• Ipilimumab	• Pancreatitis, pneumonitis, colitis, endocrinopathies, transaminitis

- Very promising trials in adult cancers, in Melanoma, Renal Cell Carcinoma and non-small cell Lung Cancer – FDA Approved!
- The same success has not been seen in first in pediatric trials – Why?

Mutational Load

- Adult cancers have high mutational load – many mutational changes leads to increased surface expression of neoantigens
- More neoantigens makes the tumor cell more visible to the TCR once the “brakes” have been removed with a checkpoint inhibitor
- Pediatric cancers have low mutational load! Less expression of neoanitgens
- A subgroup of pediatric patients with mismatch repair genes have high mutational load – and might benefit from checkpoint inhibitors
  - Open trial at SickKids within the NAIT program – Nivolumab

Can we overcome?



Mutational Load

- Induce mutational changes – with chemotherapy and radiation – to increase mutational changes and expression of surface neoantigens?
- This would increase the targets for the T cells once the “brake” is removed by the checkpoint inhibitor

Antigen Loss

- CAR T cells with multiple antigen targets (CD19 and 22)
- Similar for Blinatumomab – can we create a similar agent with multiple targets?

Questions? I'll try…..