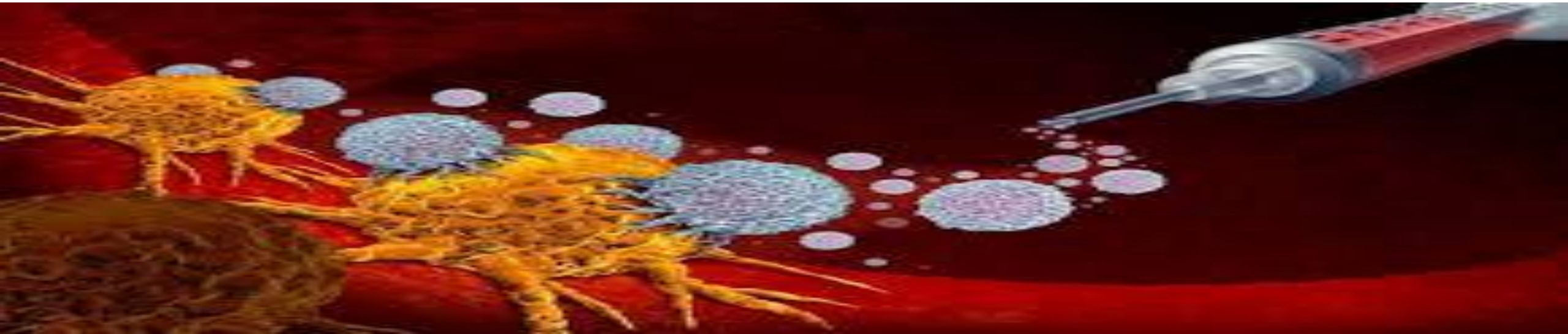
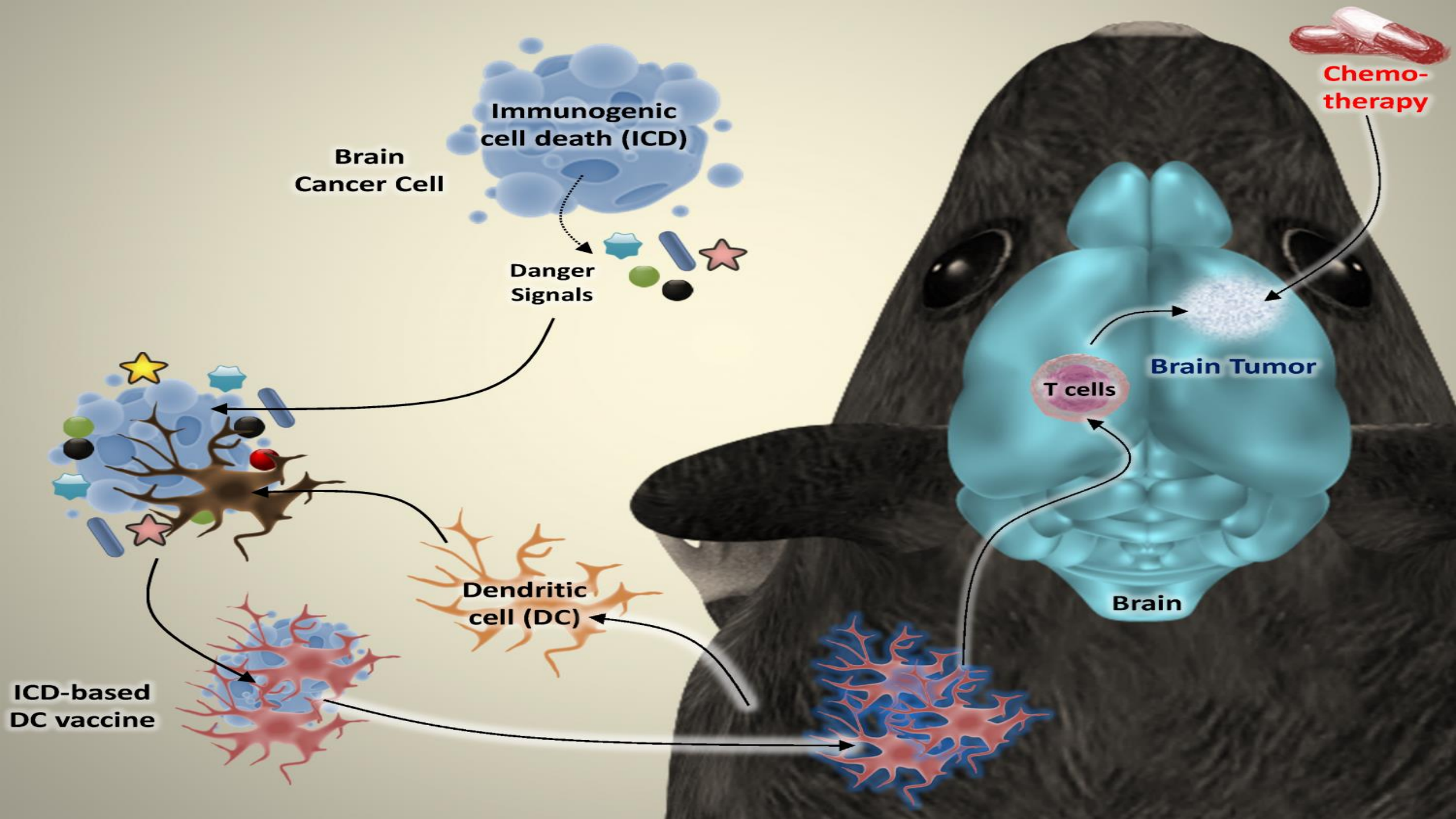
Immunotherapy for Brain Cancer

Mohammad Faranoush

Professor of Pediatric Hematology Oncology

Iran University of Medical Sciences




Immunogenic
cell death (ICD)
Brain
Cancer Cell
Danger
Signals
Chemo-
therapy
Brain Tumor
T cells
Brain
Dendritic
cell (DC)
ICD-based
DC vaccine

Introduction

- Immunotherapy for cancer continues to gain both momentum and legitimacy as a rational mode of therapy and a vital treatment component in the emerging era of personalized medicine.
- Gliomas, and their most malignant form, glioblastoma, remain as a particularly devastating solid tumor whose standard treatment options proffer only modest efficacy and target specificity.
- Immunotherapy would seem a well-suited choice to address such deficiencies given both the modest inherent immunogenicity of gliomas and the strong desire for treatment specificity within the confines of the toxicity-averse normal brain.

Immunologic Barriers

- CNS studies highlighted vague nascent antigen presentation, low HLA-expression, blood-brain barrier (BBB)-imposed restrictions for immune access, and absent lymphatic participation, all conjuring the singular perception of the brain as an immunologic void.

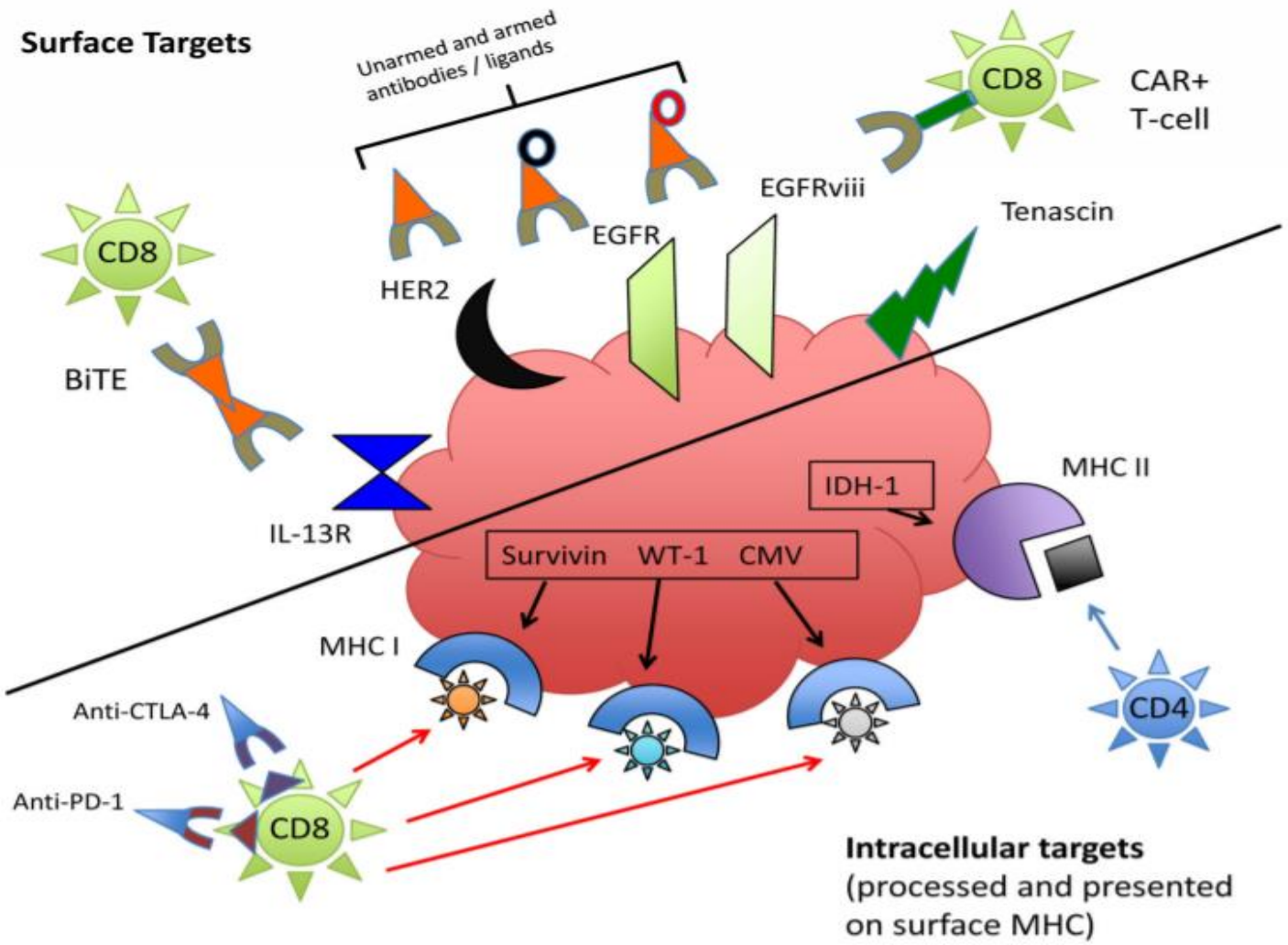
New Studies

- It is now accepted that intracerebral antigens move through CSF in the subarachnoid space, along the olfactory nerve, and across the cribiform plate to the nasal mucosa, where they subsequently drain into cervical lymph nodes (CLN)
- The CLN may be a requisite initiator to adaptive CNS immune responses, possessing unclear interplay with several brain-resident glial cells that have the capacity to mediate their own mode of HLA-restricted antigen presentation .

Blood Brain Barrier

- T-cells (and other immune effectors) must be granted access to the CNS in order to mediate these primed responses.
- Restrictions for such access are imposed by the blood-brain barrier (BBB), which is designed to restrict the promiscuous transport of proteins and other molecules from the circulation to the parenchyma, and which also limits immune cell transit.
- The BBB likely does not represent the unpassable seal to immune cell trafficking initially purported, however
- This is particularly true in instances of its disruption, often the case in the setting of GBM
- Even when it remains undamaged, circulating immune cells are capable of penetrating an intact BBB to perform routine immune surveillance functions

Targeting typical GBM antigens



Immunotherapy

- Immunotherapy is class of treatments that take advantage of a person’s own immune system to help kill cancer cells.
- There are currently three FDA-approved immunotherapy options for brain and nervous system cancers.

Targeted antibodies

- Targeted antibodies are proteins produced by the immune system that can be customized to target specific markers on cancer cells in order to disrupt cancerous activity, especially unrestrained growth.
- Antibody-drug conjugates (ADCs) are equipped with anti-cancer drugs that they can deliver to tumors.
- Bi-specific T cell-engaging antibodies (BiTEs) bind both cancer cells and T cells in order to help the immune system respond more quickly and effectively.

Targeted Antibodies

- Antibody targets under evaluation in brain cancer clinical trials include:
  - **EGFR: (Epidermal Growth Factor Receptor)**
    - A pathway that controls cell growth and is often mutated in cancer
  - **GD2: (Disialoganglioside Ag)**
    - A pathway that controls cell growth, adhesion, and migration, and is often abnormally overexpressed in cancer cells
  - **HER2:(Human Epidermal Growth Factor Receptor 2)**
    - A pathway that controls cell growth and is commonly overexpressed in cancer and associated with metastasis
  - **VEGF/VEGF-R: (Vascular Endothelial Growth Factor/Receptor)**
    - A pathway that can promote blood vessel formation in tumors

Targeted Antibodies

- **Bevacizumab (Avastin®):**
    - A monoclonal antibody that targets the VEGF/VEGFR pathway and inhibits tumor blood vessel growth; approved for advanced glioblastoma
- **Dinutuximab (Unituxin®):**
    - A monoclonal antibody that targets the GD2 pathway; approved for first-line treatment of high-risk pediatric neuroblastoma
- **Naxitamab-gqgk (Danyelza®):**
    - A monoclonal antibody that targets the GD2 pathway; approved in combination with GM-CSF for a subset of patients with advanced neuroblastoma

Immune Checkpoint Blockade

- The physiologic provisions for routine immunologic shutdown are termed “immune checkpoints” and are furnished by molecules on activated T-cells, signaling via which precipitates inactivation (cytotoxic T-lymphocyte-associated protein 4,CTLA-4) or even apoptosis (Programmed cell death protein 1,PD-1).
- Conversely, blockade or antagonism of these same molecules and their intracellular signaling pathways can potentiate T-cell responses, and even render them insensitive to tumor-mediated inhibition

CTLA-4 Blockade

- CTLA-4 blockade increases the availability of CD28 co-stimulation, thereby amplifying/ perpetuating T-cell activation and either directly or indirectly inhibiting Treg activity, as Tregs similarly express CTLA-4 at high levels
- Resultant T-cell activation is global and antigen non-specific, creating a response that is potent, but not inherently “directed.”
- Promising phase III results led to FDA approval of anti-CTLA-4 (ipilimumab, Bristol Myers Squibb) for patients with metastatic melanoma in 2010
- Although preclinical studies have proven extremely promising , multi-center clinical trials in GBM are only now being initiated (NCT02017717).
- Clinical experience with CNS disease to date has been solely in patients harboring small intracranial melanoma metastases , experience which proved safe, yielding no instances of CNS autoimmunity.

Programmed Death-1 (PD-1)

- Programmed death-1 (PD-1, CD279) is a member of the CD28 family expressed on activated T cells, B cells, dendritic cells, and macrophages
- PD-1 engages two ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC), both members of the B7 family.
- PD-L1 is expressed on a variety of immune and non-hematopoietic cells, while PD-L2 is restricted to myeloid cells.
- The PD-1 pathway functions to down-modulate inflammatory responses under physiological conditions and may be exploited by cancers en route to immunologic escape.
- PD-1 is also highly expressed on Tregs, and signaling enhances their suppressive function upon ligand engagement.
- The molecule is detected on a large proportion of TILs,and PD-1 ligands (especially PD-L1) are up-regulated on the surface of numerous tumor types, including GBM , a phenomenon linked to inferior clinical outcomes in a variety of cancers .

Cancer vaccines

- Cancer vaccines are designed to elicit an immune response against tumor-specific or tumor-associated antigens, encouraging the immune system to attack cancer cells bearing these antigens.
- Cancer vaccines can be made from a variety of components, including cells, proteins, DNA, viruses, bacteria, and small molecules.

Cancer vaccine

- Cancer vaccine targets under evaluation in brain cancer clinical trials include:
    - **MUC1:**
        - A sugar-coated protein that is commonly overexpressed in cancer
    - **Personalized neoantigens:**
        - These abnormal proteins arise from mutations and are expressed exclusively by tumor cells
    - **Tumor-associated antigens:**
        - Proteins often expressed at abnormally high levels on tumor cells and can be used to target them; also found on normal cells at lower levels

Adoptive cell therapy

- Adoptive cell therapy takes a patient’s own immune cells, expands or otherwise modifies them, and then reintroduces them to the patient, where they can seek out and eliminate cancer cells.
- In CAR T cell therapy, T cells are modified and equipped with chimeric antigen receptors (CARs) that enable superior anti-cancer activity.
- Natural killer cells (NKs) and tumor infiltrating lymphocytes (TILs) can also be enhanced and reinfused in patients.

Cell-based immunotherapy

- Cell-based immunotherapy targets under evaluation in brain cancer clinical trials include:
  - ***GD2:***
    - A pathway that controls cell growth, adhesion, and migration, and is often abnormally overexpressed in cancer cells
  - ***HER2:***
    - A pathway that controls cell growth and is commonly overexpressed in cancer and associated with metastasis
  - ***Tumor-associated antigens:***
    - Proteins expressed at abnormally high levels on tumor cells that can be used to target them; also found on normal cells at lower levels

Immunomodulators

- Immunomodulators manipulate the “brakes” and “gas pedals” of the immune system.
- Checkpoint inhibitors target molecules on immune cells to unleash new or enhance existing immune responses against cancer.
- Cytokines regulate immune cell maturation, growth, and responsiveness.
- Adjuvants can stimulate pathways to provide longer protection or produce more antibodies.

Immunomodulators

- Immunomodulator targets under evaluation in brain cancer clinical trials include:
  - **CSF1/CSF1R:**
    - Blocking this pathway can help reprogram cancer-supporting macrophages
  - **CTLA-4:**
    - Blocking this pathway can help promote expansion and diversification of cancer-fighting T cells
  - **IDO:**
    - Blocking this enzyme's activity can help prevent cancer-fighting T cells from being suppressed
  - **PD-1/PD-L1:**
    - Blocking this pathway can help prevent cancer-fighting T cells from becoming "exhausted," and can restore the activity of already-exhausted T cells

Immunomodulators

- Granulocyte-macrophage colony-stimulating factor (GM-CSF):
    - An immunodulatory cytokine; approved in combination with naxitamab-gqgk for a subset of patients with advanced neuroblastoma
- Pembrolizumab (Keytruda®):
    - A checkpoint inhibitor that targets the PD-1/PD-L1 pathway; approved for subsets of patients with advanced brain or nervous system cancers that have high microsatellite instability (MSI-H) or high tumor mutational burden (TMB-H)

Oncolytic virus

- Oncolytic virus therapy uses viruses that are often, but not always, modified in order to infect tumor cells and cause them to self-destruct.
- This can attract the attention of immune cells to eliminate the main tumor and potentially other tumors throughout the body.

Oncolytic Virus

- **Adenovirus:**
  - A family of common viruses that can cause a wide range of typically mild effects including sore throat, fatigue, and cold-like symptoms
- **Herpes simplex virus:**
  - A virus that can cause the formation of sores on the mouth and genitals
- **Measles:**
  - A highly contagious virus that infects the respiratory tract and can cause measles
- **Vaccinia virus:**
  - A virus that belongs to the poxvirus family and can cause smallpox in humans

Challenges:

- Designing, Effecting, and Monitoring Our Success
- We must acknowledge, understand, and counter the limitations imposed by relying on often impaired host cellular immunity to mediate our therapies in an immunologically “distinct” compartment.

Future Directions

- Immunotherapy is now poised to be a more ubiquitous component to the ever-emerging collage that will be personalized medicine.
- The immunophenotypes and efficacy of various immune-based therapies amidst the tumor classes remains almost entirely uncharacterized, however.
- Such characterization will be an important step to developing personalized treatment combinations predicated on pathological diagnosis and the genomic technologies

Summary

- Progress towards brain cancers by using immunotherapy is slowly moving forward.
- The general focus now is directed towards specific methods.
- These specific humoral methods include using monoclonal antibodies and scFV (single chain)fragmented antibodies.
- Specific cellular approaches include using TILs/CTLs, alloreactive CTL stimulated by MLRs(mixed lymphocyte reaction), all appear to have generated some clinical success.
- Active immunization with autologous DCs that have been loaded with tumor-antigens also appear to generate long-term survivors.
- Glioma cells seem to possess numerous tumor-associated antigens.
- Identification of other strategies that can be combined with immunotherapy approaches will certainly improve our success against these lethal brain cancers.


THANK YOU