Harnessing the Immune System to Treat Cancers and Neurodegenerative Diseases

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ABSTRACT

This article is a brief primer on the immunotherapy of cancers utilizing antigen inhibitors (such as anti-Programmed death [PD]-1 and chimeric antigen receptor T-cell) and brain cancers (glioblastomas, whether primary, secondary, or recurring). A case is also made for the existence of a brain immune system, which allows a discussion of neurodegenerative disorders for which immunotherapy is (or could be) applied, including epilepsy, Parkinson's disease [PD], Alzheimer's disease, and other brain diseases. I also investigate the root cause of all neurodegenerative diseases and posit that it is the brain's autoimmune system that had run amok in its unsuccessful attempts to maintain "brain homeostasis." I also offer various approaches for taming (or regulating) the brain autoimmune system. Finally, I consider the risks, the benefits, and the future of immunotherapy, particularly brain immunotherapy.

Key words: Alzheimer's disease, antigen inhibitors, autoimmune diseases, brain immune system, brain protective barriers, cancer, chimeric antigen receptor T-therapy, epilepsy, glioblastomas, immunotherapy, neurodegenerative diseases, Parkinson's disease, systemic immune system

INTRODUCTION TO THE IMMUNE SYSTEM

The two component subsystems
The immune system consists of two component subsystems:
- The "innate" subsystem, which is, figuratively, a generalized attack against an invading enemy, is composed of highly specialized systemic cells and processes to eliminate or prevent pathogen growth
- The "acquired" or "adaptive" subsystem, which is, also figuratively, a follow-up-targeted attack against an isolated enemy, is highly specific to given pathogens and destroys invading pathogens and any toxic molecules they produce.

The immune system offers three benefits:
- It creates an immunological "memory" after the initial response to specific pathogens
- It leads to an enhanced response to subsequent encounters with those pathogens (this is also the very basis of vaccination)
- It provides long-lasting protection (also a basis of vaccination).

How does the immune system mount an immune response?
This is illustrated in a case of cancer.[1-3] Here,
- The body faces two major challenges: (1) It has difficulty distinguishing between normal and cancerous cells as the latter have sprung from the former, and (2) many cancer cells have developed various mechanisms to thwart the immune cells such as hiding from or/and even interfering with them.
- As part of the innate mechanism of protecting healthy tissue, T-cells (our defenders) inspect cancer cells for the presence

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on their surface of two requisite molecules before they attack them: (1) MHC molecules (these are large protein complexes) that cradle protein fragments or antigens, which are the targets presented to the T-cells by the D-(dendritic) cells; and (2) a co-stimulatory ligand that triggers the signal for the T-cells to attack. In the absence of either (1) or (2), or both, the T-cells simply move on. Thus, cancer cells can fool T-cells in two ways corresponding, respectively, to (1) and (2) above, namely, stop producing MHC molecules on their surfaces or display a form of co-stimulatory ligands that act as off-switches.

- The chimeric antigen receptor (CAR) technology (more about it later) has made it possible to genetically modify the T-cells in either of two ways to overcome the above two eventualities: (a) bypassing the D-(dendritic) cells, the T-cells could home-in directly on antigens that may be abundant on cancer cells without necessarily being presented by the MHC molecules or (b) obviating altogether the need for the two-step process described earlier for attacking the cancer cells.

Why does the immune system turn rogue?

The same immune system that is supposed to protect us under normal conditions becomes overwhelmed by excessive pathological insults and turns against us by causing autoimmune diseases (a "run-away" effect).

COMMON AUTOIMMUNE DISEASES

There are more than 80 autoimmune diseases [Table 1]. Let me cite a few without getting into much detail concerning any one of them. I mention in passing in which one of them has immunotherapy been applied:

In Table 1, three approaches to immunotherapy have surfaced: (1) Activating the immune system or (2) suppressing it or else (3) modulating it (taming it, slowing it down, calming it, and regulating it). More will be said later regarding these various approaches.

CANCER IMMUNOTHERAPY IN GENERAL

Immunotherapy essentially evolved from cancer treatment. It might be useful to (a) clarify why has not cancer been cured; (b) define cancer immunotherapy, in general; (c) summarize the recent history of cancer immunotherapy; (d) discuss its most important and recent evolution using antigen receptors (PD-1 and CAR T-cells); and (e) review its application to brain cancers (or glioblastomas [GBs]) as a prelude to applications in neurodegenerative disorders (NDDs).

Why hasn't cancer been cured?

Indeed, why hasn't cancer been cured despite a four-decade "war" against the disease and the expenditure of hundreds of billions

of dollars? essentially, because of our lack of understanding of the basic underlying molecular mechanisms. However, as cell biology and genetics became understood at a deeper level, newer targeted therapies have been designed. It now appears that cancer is less an organ disease and more a disease of molecular mechanisms caused by the mutation of specific genes.

What is cancer immunotherapy?

Cancer immunotherapy, a newly "emerging" concept in cancer therapy,[4,5] is the harnessing of the immune system to battle tumors. It represents an important paradigm shift in cancer treatment in that it targets the immune system, but not the tumor itself. It has been successful in inducing long-term remissions of hard-to-treat cancers in about one-third of patients. However, it does not help everyone (e.g., for patients with metastatic cancer, the odds remain long) and it has helped only a tiny fraction of cancer patients. Examples include a woman with a grapefruit-sized tumor in her lung from melanoma, who is alive and healthy 13 years later; a 6-year-old near-death from leukemia, now in the third grade, who is in remission; and a man with metastatic kidney cancer whose disease continued fading away even after treatment was stopped. However, despite these successes, we still need to identify other biomarkers that might offer answers and experiment with ways to make therapies more potent.

Recent history of cancer immunotherapy

The following paragraphs retrace, perhaps comprehensively, and since its beginnings, the history of cancer immunotherapy:

- 1980s: Initial immunotherapeutic approach consisted of three steps: (1) drawing T-cells from the patient; (2) multiplying them in the laboratory; and (3) infusing the expanded number of cells into the body. It helped some patients, but it did not work for long as the cells tended to exhaust themselves and shut down soon after delivery.
- 1987: French researchers identified a new protein receptor on the surface of T-cells: Cytotoxic T-lymphocyte antigen 4 (CTLA-4), which puts the brakes on T-cells, preventing them from launching all-out immune attacks.
- 1998: James Allison suggested "blocking the blocker" (CTLA-4 molecule) to set the immune system free to destroy cancer, turning from immunosuppression as the focal point to immunosuppression manipulation as the target. He showed that antibodies against CTLA-4 erased tumors in mice.
- Mid-1990s: A Japanese biologist discovered a molecule expressed in dying T-cells, ("programmed death 1 [PD-1]"), another brake on T-cells.
- Mid-1990s–early 2000s: Development of cell turbocharging approaches in which the drawn T-cells are turbocharged before infusion into the body. Turbocharging means making the cells more abundant, more powerful, and longer-acting than previously. To become activated, T-cells must receive signals from a different group of immune system players, the D-(dendritic) cells that are also isolated from each patient. They then release certain

Table 1: Common autoimmune diseases, their action process, symptoms, and treatments

Autoimmune disease	Action process	Symptoms	Treatment (s)	Notes
Type 1 diabetes (aka juvenile diabetes)	Immune system antibodies attack and destroy insulin-producing cells in the pancreas		Insulin injections	A lifetime disease
Multiple sclerosis	Immune system attacks nerve cells Inflammation damages the central nervous system (CNS)	Pain Movement, balance, and coordination problems Weakness Blindness	Medicines for: Symptoms Slow down the illness Suppress the immune system	Scar builds up along the network that carries nerve signals from the brain to the rest of the body
Inflammatory bowel disease: Crohn's disease Ulcerative colitis	Immune system attacks intestines	Inflammation Abdominal pain Urgent bowel movements Diarrhea Rectal bleeding Fever Weight loss	Anti-inflammatory drugs Antibiotics Oral/injectable Suppress or slow down the immune system Surgery	CD attacks last part of intestines and colon UC attacks lining of the colon
Rheumatoid arthritis	Immune system produces antibodies that attach to joints' lining	Inflammation Swelling Pain Over time, damage to cartilage and bones Problems with heart and lungs	Oral/injectable palliative medications Medications to slow down the disease by •Reduce immune system's overactivity	If untreated, gradually permanent damage
Ankylosing spondylitis	Arthritis that affects Spine Chest Neck Hips Knees Organs	Pain and stiffness	Physical therapy Palliative medicines DMARDs Steroid shots Surgery	Bones may eventually join together and cause difficulty to move
Systemic lupus erythematosus	Autoimmune antibodies that can attach to tissues throughout the body: Joints Lungs Blood cells Nerves Kidneys	Joints pain Sensitivity to light Kidney problems Tiredness Rash over cheeks and nose	Non-steroidal anti-inflammatory drugs Slow down the immune system with prednisone (oral) steroid DMARDs Chemotherapy	Affects several body parts at the same time

(Contd...)

Table 1: (Continued)

Autoimmune disease	Action process	Symptoms	Treatment (s)	Notes
Addison's disease	Immune system attacks and damages adrenal glands Body cannot make enough of certain hormones	Trouble changing food into fuel Trouble keeping blood pressure stable Fatigue Darker skin patches	Medicines to replace missing/ insufficient hormones	
Graves' disease	Autoimmune system produces antibodies that stimulate the thyroid to make excess thyroid hormone ≥ hyperthyroidism	Shaking Weight loss Anxiety Slightly bulging eyes Nervousness Irritability Rapid heart rate Weakness Brittle hair	Drugs to slow down hormone production Surgical removal of part or all of thyroid	
Hashimoto's disease or chronic lymphocytic thyroiditis	Antibodies attack the thyroid gland slowly destroying cells that produce thyroid hormone ≥ hypothyroidism	Constipation Weight gain Tiredness Sensitivity to cold Hair loss Swollen front of throat Puffy face Depression	Medication to replace/ supplement missing hormones Oral synthetic thyroid hormone pill	Converse of Graves' disease (insufficient hormone production)
Alopecia areata	Antibodies attack hair follicles	Bare patches Total hair loss	Calm the immune system with medicine and help hair grow back	
Myasthenia gravis	Antibodies bind to nerves and cause signaling problems between nerves and muscles	Weakness Difficulty to control certain movements Eye problem affecting facial expression, speech, swallowing, chewing	Drugs Mestinon (pyridostigmine) Surgical removal of the thymus gland	
Guillain–Barre Syndrome	Immune system attacks nerves controlling muscles in the legs, arms, upper body	Weakness of arms and legs No feeling of heat or pain	Plasma exchange Plasmapheresis (blood filtering)	
Chronic inflammatory demyelinating polyneuropathy			Plasma exchange Plasmapheresis (blood filtering)	Similar to Guillain–Barre but symptoms last much longer. Same treatment

(Contd...)

Table 1: (Continued)

Autoimmune disease	Action process	Symptoms	Treatment (s)	Notes
Psoriasis	Body defenses trigger inflammation and makes skin cells grow too fast		Creams UV light Calms the immune system with medicines	
Vasculitis	Immune system attacks and damages blood vessels	Can affect any organ. Symptoms vary widely and can occur anywhere in the body	Reduces the immune system activity with prednisone Another corticosteroid	

DMARDs: Disease-modifying anti-rheumatic drugs

chemicals (cytokines) that boost the immune system even further. After a few days, the T-cells quiet down, allowing the body and the immune system to return to normal. Various turbocharging schemes were devised. Synthetic (not naturally occurring) D-cells can also be used; they are mimicked by magnetic beads coated with two proteins that can improve the D-cells' stimulatory behavior. The result of turbocharging is to provide ~100:1 more cells.

- 1999: Engineered T-cells are still experimental antibodies that are slowly going mainstream. Five major drug companies (and a small biotechnology company, Medarex) are developing antibodies such as anti-PD-1.
- 2006–2008: First clinical trial using anti-PD-1 (39 patients; 5 different cancers): the tumors shrank and survival in a few patients stretched beyond what was imagined possible.
- Early 2010s: An enhanced cell turbocharging approach was developed where cells are genetically altered, so they can home in and attack certain kinds of cancer that originate in various types of white blood cells (particularly, leukemia and lymphoma).
- 2010: Bristol-Myers Squibb (which acquired Medarex) reported that patients with metastatic melanoma lived an average of 10 months on the anti-PD-1, compared with 6 months without it. It was the first time any treatment had extended life in advanced melanoma in a randomized trial. Nearly a quarter of the participants survived at least 2 years.
- 2010: With the combination (anti-CTLA-4 + anti-PD-1), some tumors grow before vanishing months later. Some patients kept responding even after the antibody had been discontinued, suggesting that their immune system had been fundamentally changed. However, some developed unnerving side effects, including inflammation either of the colon or of the pituitary gland.
- 2010: For years, Steven Rosenberg at the National Cancer Institute had harvested T-cells that had migrated into tumors, expanded them in the laboratory, and re-infused them into patients. He later developed the CAR therapy – a personalized treatment that involves genetically modifying a patient's T-cells to make them target tumor cells. In step (2) of the technique, several custom-built viruses could be theoretically employed for multiplying the T-cells (e.g., HIV).
- 2011: FDA approves Bristol-Myers Squibb's Ipilimumab (an anti-CTLA-4=CTL-4 inhibitor treatment) for metastatic melanoma. However, the course of the therapy involves a high cost (~$120,000).
- 2012–2015: Suzanne Topalian of Johns Hopkins University and Mario Sznol of Yale University reported on anti-PD-1 therapy in nearly 300 people: Tumors shrunk by about half or more in 31% of those with melanoma, 29% with kidney cancer, and 17% with lung cancer.

- 2013: Science selected cancer immunotherapy as the breakthrough of the year.
- 2014: The Food and Drug Administration (FDA) approves Pembrolizumab (Keytruda) for late-stage melanoma. This drug is one of a number of closely related therapies dubbed "immune checkpoint blockade." It belongs to the class of drugs called PD-1 inhibitors in that it inhibits the immune response against cancer cells. Normally, this effect is necessary to avoid an inappropriate over-reaction, such as an auto-immune disease. However, in cancer patients, it reinvigorates the immune system, allowing it to target and destroy cancer cells, but one must guard against a run-away of this effect. By blocking the PD-1 protein, the therapy allows the body to make T-cells that can chase after cancer. The combination (radiation + chemotherapy + Keytruda) has been applied to melanoma cancer. However, again, the treatment is expensive (~$150,000/year).
- August 2015: This was the famed case of former President Jimmy Carter (August 2015): Surgery removed a "small mass" from his liver, followed by focused radiation therapy to ablate four small melanoma lesions that had metastasized to his brain and further followed by a 12-week course of chemotherapy with Pembrolizumab (Keytruda).
- 2015: June of Memorial Sloan–Kettering reported that T-cell therapy put 45 of 75 adults and children with leukemia into complete remission, although some later relapsed.[5]
- Fall of 2015: Bristol-Myers Squibb reported that of 1800 melanoma patients treated with Ipilimumab (sold as Yerzov), 22% were alive 3 years later. The combination (Ipilimumab + anti-PD-1) led to "deep and rapid tumor regression" in almost one-third of melanoma patients.
- 2017 (August 30): FDA approves CAR T-cell therapy for the treatment of certain pediatric and young adult patients (up to 25 years of age) with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) who do not respond to treatment or had relapsed two or more times. This historic action made the first gene therapy available in the U.S.[6-10]

IMMUNOTHERAPY USING ANTIGEN INHIBITORS

There are two approaches using, respectively, PD-1 and CAR-T cells.

PD-1 inhibitors
- For whom does it work?
  - Less than half the patients
  - Best on tumors with "mismatched repair mutations"
  - Patients with few mutations must receive radiation or chemotherapy, which can create new tumors.

- How do the drugs work? Tumor cells can hide from T-cells by activating the PD-1 receptor. However, when this immune "checkpoint" is blocked by a PD-1 inhibitor, the T-cells see the tumor cells and can attack them. Drugs work best when the tumors have many mutations. Some of these mutations may alter genes so that they code for small stretches of abnormal proteins that the immune system sees as foreign proteins or antigens. The more mutations, the more of these "neoantigens" that can trigger an attack from T-cells that have been unleashed by a PD-1 inhibitor. PD-1 inhibitor has synergy with radiation.
- What is the treatment for certain individual cancers?
  - In advanced or unresectable melanoma: Pembrolizumab (Keytruda) is followed by Ipilimumab in patients with the V600 BRAF mutation. The effect lasts ~ 1.4–8.5 months and beyond in most patients. Side effects include fatigue, cough, nausea, pruritus, rash, anorexia, constipation, arthralgia, and diarrhea. Severe immune-mediated adverse effects involving the lungs, colon, liver, and endocrine glands are less frequent. The "triple attack" (surgery + focused radiation therapy [to ablate melanoma lesions that have metastasized to the brain] + chemotherapy with pembrolizumab [Keytruda]) may also be used.
  - In advanced lung cancer: Immunotherapy works because lung cancer has many mutations ~1000 more than usual (~10–100).
  - In colon, prostate, uterus, pancreas cancer: Immunotherapy is useless unless tumors have mismatched repair genes (case of 3–4% of cancer patients).
  - In liver cancer: The triple attack treatment (chemotherapy + thermal or ultrasound ablation + hyperthermia) using Bexarotene (re-purposed and repackaged into a sensitive prodrug nanobubble form) is inserted directly into the tumor, and ultrasound ablated to pop the bubbles to release the agent.

CAR-T cells inhibitors
- The technology merges gene therapy, synthetic biology, and cell biology in the laboratory. It involves four steps: (1) a batch of certain T-cells known to respond best to a given disease are extracted from the blood; (2) a custom-built virus is used to implant them with new genes; (3) cells are created that target a molecule (CD19) that is found on the surfaces of some cancers; and (4) the modified cells are then returned to the body, where their new DNA gives them a fresh set of targets to attack. It has been tested in dozens of studies (~1000 patients) in certain types of cancers (leukemia and lymphoma). Half or more of these patients are now living longer than expected and hundreds appear to be cancer-free.
- In the case of ALL: There was complete remission in 93% of the cases!

Refinements of the technology

A major refinement of the technology is overcoming the toxic effects that the treatments can trigger. As the number of T-cells doubles, roughly every 12 h, a runaway immune reaction called a cytokine storm is triggered, which can be fatal to certain patients. The biggest cytokine storms seem to come from the patients with the most advanced cancers. The solution is to give the sickest patients the lowest dose so that the T-cells multiply more slowly, reducing the chances of an immune-system overreaction.

Improvements on the technology

Besides the elegance of the idea of boosting the body's own defenses, the technology offers another big advantage over traditional chemotherapy: Once they have done their job, the engineered T-cells stick around in the body, offering protection against re-infection or recurrence of a cancer possibly for a decade or more. Further, CAR-T could be combined with other therapies to perhaps provide durable cures for certain types of blood cancer and, hopefully also, other kinds of tumors while also better controlling deleterious side effects some of which could be fatal.

Expansion to other cancers

Expanding the ALL results to other cancers is difficult, because to prime a T-cell to attack, it needs to be given precise coordinates. Otherwise, it may lock onto and destroy something else in the body. Unfortunately, besides CD19, which is found in only a few cancers, we currently know of no other chemical target that is specific to cancer alone. The solution, then, would be to tweak cells to attack when sensing two different target chemicals instead of one. In isolation, neither target may be unique to cancer cells, but the combination might be.

Other applications of engineered T-cells

Such expansions would address a wide range of diseases (HIV, immune deficiencies, autoimmune disorders, cancers that affect B-cells, etc.). As also mentioned earlier, the technology offers another big advantage over traditional drugs: Once they have done their job, the engineered T-cells stick around in the body, offering protection against re-infection or the recurrence of a cancer possibly for a decade or more.

Toxicities

Because of the attending toxic effects, the Association of Community Cancer Centers and its Institute of Clinical Immuno-Oncology want to ensure that: (a) non-oncologist physicians are made aware of immune-related toxicities (e.g., pneumonitis, colitis) from the new agents; (b) do not confuse them with chemotherapy or infection; (c) save time and the risk of prescribing the wrong treatment; and (d) educate cancer patients by providing them information about their immunotherapies.

CASE OF GLIOBLASTOMA

The case of GBs is a particularly vexing one. I highlight below the present situation.

Therapies

Several therapies are available for treating GBs. Unfortunately, chemotherapy has little durable benefit with tumors recurring within several months. Other therapies include surgery, conformal radiotherapy, boron neutron therapy, intensity-modulated proton beam therapy, antiangiogenic therapy, alternating electric field therapy, and immunotherapy.[11-13]

Frequency and treatment

GB is the second most common form of cancer after meningioma, representing 15% of brain tumors. It is more common in males than females. The survival rate is ~1 year, and only 5% of the people affected survive for 5 years. The standard treatment consists of (1) surgery (maximal resection) followed by (2) radiochemotherapy together with concomitant chemotherapy (temozolomide) and (3) adjuvant treatment.

Prognosis

Patients with the methylated MGMT promoter gene (O6-alkylguanine DNA alkyltransferase) (MGMT is a "SUICIDE" DNA repair enzyme) experience best results. However, there are no cures at present.

Risk factors

We recognize the following risk factors:
- Genetic:
    - Genetic disorders such as neurofibromatosis (uncommon)
    - Certain genetic disorders that are associated with an increased incidence of gliomas
- Neurofibromatosis (types 1 and 2)
- Tuberous sclerosis
- von Hippel–Lindau syndrome
- Li-Fraumeni syndrome
- Turcot syndrome
    - Age: Over 50 years, most commonly around 64 years of age
    - Sex: Male (for unknown reasons, GB is slightly more common in men than women)
    - Ethnicity: Caucasians, Hispanics, and Asians are more at risk
- Existing conditions:
    - Previous treatment with radiation therapy (there is a small link with ionizing radiation)
    - Having a low-grade astrocytoma, which, given enough time, often develops into a higher-grade tumor
- Environmental conditions:
    - Toxicities: Lead exposure in the workplace.

Treatment difficulties

The following difficulties are experienced during treatment:

- Tumor cells are very resistant to conventional therapies
- The brain is susceptible to damage due to conventional therapy
- The brain has a very limited capacity to repair itself
- Many drugs cannot cross the blood–brain barrier (BBB) to act on the tumor.

Treatment

Disease-modifying treatment is immunotherapy, as discussed above for cancers, in general. Otherwise, treatment remains symptomatic with the use of the following drugs: Anticonvulsant corticosteroids; phenytoin (concurrent with radiation); corticosteroids (dexamethasone); and surgery. Other treatment modalities are conformal radiotherapy; boron neutron capture therapy; intensity-modulated proton beam therapy; chemotherapy; antiangiogenic therapy; alternating intermediate frequency electric field therapy; the Optune tumor treating fields (electrical device that appeared to boost 5-year survival rate from 5% to 13%); vaccines (a vaccine against cytomegalovirus has shown benefit for glioma patients in an early trial); and palliative therapy and lifestyle changes.

IMMUNOTHERAPY OF NEURODEGENERATIVE DISEASES

As the application of immunotherapy to Neurodegenerative diseases (NDD) is rather new, it will be helpful (a) to explain what is the brain immune system, including the role of the brain-protective barriers (BPBs) (among which the Blood Brain Barrier (BBB)); (b) how is immunotherapy treatment applied to NDDs; and (c) the attendant risks and benefits. I also put forward a bold proposal whereby all NDDs are, in fact, brain autoimmune diseases that have run amok, which could be cured by modulating the brain immune system and suggest some novel approaches.

Is there a brain immune system?

Owing to the presence of the BPBs at the interface between the central nervous system (CNS) and the periphery and their muted response to neuroinflammation, it has been widely assumed heretofore that the brain (and, more generally, the CNS) is immune privileged. In other words, the brain's vaguely understood component of the immune system, as distinct from the rest of the body's immune system, is generally able to handle, treat, and overcome any adverse pathologies developing therein. However, in contrast to this earlier dogma, it is now evident that the CNS does contain immune capabilities and that neuroinflammation is likely to play an important role in most, if not all, NDDs. In addition, the BPBs contribute to the development of inflammation through either normal immune signaling or disruption of the basic physiological barrier mechanisms. However, it is difficult to distinguish between normal and disrupted barrier function because of the physiological changes that take place as part of normal development from childhood to aging and senescence. This is less difficult in a number of NDDs that have been clearly associated with the barriers' disruptions (opening, modification, distortion, etc.). In parallel with immunotherapy as an emergent therapy for cancer, I advance the opinion that brain immunotherapy should also become a similar therapy for brain cancers (GBs) and NDDs. If proven, this approach would represent a paradigm shift in our therapeutic approach to brain cancer and NDDs.[14-19]

I am therefore affirming that the brain has its own specially tailored immune system, separate from the rest of the body. Further, mobilizing cells from the systemic immune system does not always cause harm to the brain but, when well controlled, may in fact even help in coping with various brain pathologies. Further, the peripheral immune response contributes to neuroinflammatory conditions – this is well-established in multiple sclerosis (MS) and amyotrophic lateral sclerosis (Lou Gehrig's), stroke, and epilepsy among other disorders. The BPBs play an important role in maintaining the homeostatic environment of the brain and the CNS, and damage to their various structural or/and functional components may contribute significantly to disease etiology or progression.

Normal immune mechanisms in the CNS are often thought to be different from those of the periphery. For instance, the immune response in the brain can be substantial (e.g., in response to meningitis) but, by contrast, a loss of immunity is also reported (e.g., cerebral infections). It is the muted inflammatory response in the brain following an injury that was the original rationale behind the concept of the CNS being an immune-privileged site.

What is currently unclear is: (a) How the BPBs themselves contribute to inflammatory signaling in neurological disease? (b) Which specific barrier mechanisms are altered in response to inflammation? and (c) the fundamental question remains as to whether the BBB is a component of the etiology of the diseases or a consequence of it?

Pathogens in the brains of patients with NDDs

Bacteria, viruses, fungi, and other microbes are part of a growing list of pathogens found in the brain [Table 2]. Microbes in the brain may indicate meningitis or encephalitis, two diseases that are active infections with inflammation. For diseases such as Alzheimer's disease (AD) and other NDDs that were not thought to be infectious, finding pathogens in the brain is both surprising and concerning.

Permeability of the Blood Brain Barrier (BBB)

The BPBs are actually five protective barriers that hinder the delivery of therapeutic drugs to the brain. They describe the

Table 2: Various pathogens in the brain		
Pathogen	**Origin/cause**	**Effects**
Porphyromonas gingivalis (P. gingivalis) bacterium(*)	Mouth	Some of the proteins made by this microbe have been found in brains
Fusobacterium nucleatum bacterium	Mouth	
Prevotella intermedia bacterium	Mouth	
Herpes simplex virus		Lives for years in nerve cells that supply the face and lips. Can migrate back up the same nerve and into the brain producing mild inflammatory response
Syphilis	*Treponema pallidum* (a spirochete type of bacterium)	Can live in the body for decades, eventually infecting the brain and causing dementia
Lyme disease	*Borrelia burgdorferi* carried by the deer tick *Ixodes*	
Ehrlichia		Infects white blood cells
Babesia (relative of the malaria parasite)		Infects red blood cells
Bartonella		Infects blood vessels
AD	Many different organisms. Further, by sterile inflammation not from invading pathogens	Also harbor fungi

Source: Fymat[20]

five main interfaces between the CNS and the periphery. These are (1) the BBB that extends down the spinal cord; (2) the brain–cerebrospinal fluid (CSF) B barrier; (3) the brain inner (iCSF) barrier; (4) the brain outer (oCSF) barrier; and (5) the brain–retinal barrier. All interfaces are physical and metabolic barriers that serve to regulate and protect the microenvironment of the brain. Barriers are composed of a monolayer of brain capillary endothelial cells forming tight junctions.

The BBB limits access to the brain to small nonpolar molecules by passive diffusion or catalyzed transport of large and/or polar molecules. It hinders the delivery of most pharmaceuticals (diagnostic, therapeutic agents) to the brain.[20]

The organisms listed in Table 2, and others, get into the brain because of the BBB's permeability.

Other avenues for reaching directly the brain are intranasal and intrasinus access, the gut (through the vagus nerve that connects it to the brain), and even through the eyes.

NDD

There are approximately 400 known NDDs (some of which classified as mental disorders). A number of them are due to a disruption or failure of the BBB [Table 3].

Now, I briefly review some pertinent aspects of three of the basic NDDs, namely, epilepsy, PD, and AD.

Epilepsy

Many promising antiepileptic dugs are excluded from the brain by the BBB. They are thus clinically unusable in spite of their significant potency and selectivity. Multiple drug resistance is only one of the aspects in BBB research that may impact how we define, prevent, and treat seizure disorders. Seizures in a number of disorders (GLUT1 deficiency; acquired deficiencies resulting from brain tumors, head trauma, systemic and immune triggers) result from a leaky BBB and neuroinflammation.[21,22]

Gene therapy is being studied in some types of epilepsy. However, medications that alter the immune function, such as intravenous (IV) immunoglobulins, are currently poorly supported by evidence.

Parkinson's Disease (PD)

Dopamine does not cross the BBB. Its precursor, levodopa, can pass through the BBB to the brain where it is readily converted to dopamine. It temporarily diminishes the motor symptoms of PD. Unfortunately, only 5–10% of the drug crosses the barrier with much of the remainder being metabolized to dopamine elsewhere in the body, where it causes a variety of side effects.

Three assumptions underlie the immunotherapeutic strategy for PD therapy: (1) alpha-synuclein is accessible in the

Table 3: Some brain diseases and their corresponding effects on the BBB			
Disease	**BBB factor**	**Disease**	**BBB factor**
Alzheimer	Disruption/breakdown	Multiple sclerosis (immune system deficiency)	Breakdown
Brain abscess	Unknown mechanism	Neuromyelitis optica (Devic's disease)	Breakdown
Cerebral edema	Opening (due to hypoxia)	Prion and prion-like diseases (Parkinson, Alzheimer)	Unknown penetration mechanism
De vivo	Unknown mechanism	Progressive multifocal leukoencephalopathy	Disruption
Epilepsy	Disruption/failure	Rabies	Increased permeability
HIV encephalitis (latent HIV crosses the BBB)	Damage (inflammatory)	Systemic inflammation (sterile, infectious)	Disruption
Meningitis	Disruption	Trypanosomiasis (sleep thickness)	Disruption

Source: Fymat[20]. BBB: Blood–brain barrier

extracellular space (trans-synaptic spreading); (2) antibodies against alpha-synuclein reach the brain in sufficient quantity; and (3) they trap alpha-synuclein aggregates when these are released ("spread") into the extracellular synaptic space.[23-25]

There are several limitations of active and passive immunotherapy. Importantly, the low amount of antibodies passing the BBB may be overcome in two separate ways: (1) coupling antibodies to the peptide penetration; (2) modulating the aggregation of alpha-synuclein (i.e., blocking or reducing the aggregation of its monomers to oligomers or later on to fibrils).

In opposition to antibodies, small molecules may readily pass the BBB to deliver therapeutic compounds. Three such drugs are close to or under very early development (ANLE138b, NPT200-11, and NPT100-18a). Unfortunately, the results from such drugs cannot yet been reported.

AD

Five reasons underlie the current dreadful situation:
1. There is no drug that would prevent the disease from developing from earlier conditions – subjective cognitive impairment and mild cognitive impairment – to full-blown AD. As of this writing (May 2018), there are no drugs that reliably prevent or slow the progression of AD. Drug targets are now focusing on brain inflammation (to be distinguished from infection), cholesterol buildup, and tau protein accumulation in patients' brains, which correlate with (but not necessarily cause) cognitive decline (Note: Because diabetes increases the risk for AD, some have equated AD with "brain diabetes" and proposed using insulin nasal sprays as a potential treatment)
2. The idea of identifying the cause of the amyloid-beta (Aβ) production, removing it, and then removing the Aβ, has not yet been tested

3. While in transgenic mice, AD is caused by the accumulation in the brain of synapse-destroying plaques of a protein called Aβ by a series of demonstrated steps; this is not the case for humans. Either intervening in, or interfering with, those steps or eliminating the Aβ plaques could, theoretically, arrest AD. Unfortunately, in humans, this did not prove to be the case. While the compounds tested performed as intended, the end result was not as expected. Thus, when antibodies that bind to the amyloid to remove it were tested, the amyloid was removed but the patients got neither better nor worse. If the compound was designed to block the enzyme needed to produce the amyloid, again it performed well but the disease still remained or worsened. These results invalidate the amyloid hypothesis, all the theories based thereon, and all the associated mouse laboratory tests
4. The other abnormality, i.e., the neurofibrillary tangles inside the neurons themselves (these are long stringy tangles of a protein called tau), has long been overshadowed by the focus on the amyloid plaques; and
5. AD may not be, as generally assumed, a single disease treatable with a single (or a combination of a few) drug(s).

Many hypotheses (theories) have been advanced for explaining AD. These are all based on risk factors. In 2017, Bredesen[26] posited that all previous hypotheses (except the genetic hypothesis; ApoE genes) had failed because premised on the wrong assumptions that AD is a single disease caused by the accumulation of Aβ plaques. This "inter-synaptic amyloid cascade" hypothesis is still generally regarded (perhaps erroneously) as one (if not the) cause of AD, the other being the "intra-neurons tau accumulation" hypothesis for the neurofibrillary tangles. The issue is whether Aβ is the cause of the disease, or merely an element of it, or even the normal immune response of the brain to neuroinsults?

Bredesen further claimed that AD is the natural immune (protective) response of the brain to a variety of long-standing insults (or risk factors), approximately 36–40, perhaps a little bit more.[27] In addition to genetics, the threats have been categorized under three metabolic and toxic categories (inflammation/infection; neurotrophy; toxic exposures), the INT hypothesis.[27,28] While it is a crisper exposition of the disease, the INT hypothesis is subsumed in the published literature, except perhaps and importantly for the neurotropic aspect. Corresponding biochemical markers are listed in Table 4.

According to the INT hypothesis, there are three main subtypes of AD, each driven by different chemical processes, each requiring different treatment, and AD may exist in either one or a partial combination of these subtypes.[27]

Under such an assault, often lasting for decades, the immune response has run amok. An otherwise normal, healthy, protective brain "housekeeping" process has gone haywire. The defense mechanism includes producing the Alzheimer's associated amyloid. Being overactive in general, the chemically active immune system sometimes attacks the body's own tissues (an autoimmune reaction). In sum, the physiological system is not functioning as intended.[27,28]

Currently approved drugs, such as donepezil (aricept) and memantine (namenda), and other approved drugs namanzaric

Table 4: Biochemical markers of the three subtypes of Alzheimer's disease		
Subtype #	**Biochemical markers**	**Notes**
1. Inflammatory 2XApoE4 (quickest response to treatment)	1. Increased C-reactive protein 2. Decreased albumin: Globulin ratio 3. Increased interleukin-6 (IL-6) 4. Increased tumor necrosis factor (TNF) 5. Abnormal metabolism and hormones 6. Increased homocysteine	1. A measure of inflammation caused by infectious agents (bacteria, viruses, fungi), radicals, AGE products, trauma, damaged proteins, damaged lipids (ox-LDL), etc. 2. Albumin is a key blood protein; globulin is a catchall name for~60 blood proteins 3. IL-6 rises with inflammation 4. TNF (another protein) rises with inflammation 5. Insulin resistance 6. Like in subtype # 2
2. Neurotrophic 1 or 2XApoE4 (slower response to treatment)	1. Suboptimal hormones levels 2. Reduced vitamin D 3. Insulin resistance 4. Increased homocysteine	
3. Toxic 1XApoE3	1. Atrophied brain regions 2. Neuroinflammation and vascular leak 3. Zinc: Copper ratio much higher than 1 4. Frontotemporal depression or abnormal AD 5. Hormonal abnormalities 6. Heavy metal (copper, mercury) and biotoxin (e.g.,, molds) levels	1. Evidenced by MRI 2. Evidenced by MRI 4. Abnormal PET 5. A dysfunctional hypothalamus+pituitary gland+adrenal gland axis shows in blood tests as low cortisol, high reverse T3 (thyroid test), low free T3, low pregnenolone, low estradiol, low testosterone, other hormonal abnormalities
Glycotoxic	1. High glucose 2. High insulin	1. Causes glycation and inflammation 2. Results in insulin resistance

Source: References[27,28]. There are three types of ApoE: ApoE2, 3, and 4, each with 1 or 2 variants (alleles). Most people carry two alleles of ApoE3 (one from the father, one from the mother) leading to an AD risk of~9%. Those who carry a single copy of ApoE4 have an AD risk of~30%, and those who carry two copies of ApoE4 have a risk well above 50%, that is, will develop AD (but not always) through the inflammatory subtype. The ApoE effects are (a) to increase the risk of AD because it reduces the clearance of the Aβ peptides; (b) it enters the nucleus and binds very efficiently to DNA, thus reprogramming cells; (c) it is involved in 17,000 genes out of a total of 20,000 genes in the entire human genome, thus also playing a role in cardiovascular disease, inflammation, and more. The ages of onset of AD are typically: For ApoE4 (2 alleles): 40s–50s; for ApoE4 (1 allele): Late 50s–60s; and for no copies of ApoE4: 60s–70s. People who have high cholesterol or heart disease are more sensitive to the gene's negative cognitive effects. (2) Other genes: PS1, 2 also increase the risk of AD. They account for <5% of cases. (3) A team of Australian and Japanese scientists announced a novel blood test to detect Aβ buildup in the brain. Measurements of the protein and its precursors in blood can predict Aβ deposition, paving the way for an efficient screening tool for AD, the team reported. Aβ: Amyloid-beta, PS1, 2: Presenilin-1, 2, AD: Alzheimer's disease, MRI: Magnetic resonance imaging, PET: Positron emission tomography

(=donepezil+memantine), rivastigmine (exelon), and galantamine (razadyne), alleviate symptoms in a limited way. All these drugs treat only the symptoms while the disease progresses.

In the hope to prevent, delay, minimize, or reverse AD, Bredesen[27] has proposed a four-step approach: (1) identify and address which of the many potential contributors to the three AD subtypes a patient's brain responds to defensively. This can be accomplished according to well-established tests; (2) minimize or better remove as many of these contributors as possible; (3) remove the amyloid itself; and (4) follow the diet, exercise, stress, sleep (DESS) principle where the diet is a modified ketonic (so-called Ketoflex 3/12). (Note: Other variants of the classic ketonic diet are medium chain triglycerides, modified Atkins diet, and low glycemic index treatment). Still other diets include dietary approaches to stop hypertension (DASH), caloric restriction, and Mediterranean-DASH Intervention for Neurodegenerative Delay. The aims are to (1) prevent and reduce inflammation; (2) optimize neurotropic factors, including hormones; and (3) eliminate toxins (particularly toxic metals: Copper, mercury), including glycotoxins and biotoxins. Unfortunately, while helpful, this program addresses the risks *not* the cause of AD. Again, this approach will not offer a cure as RISK IS NOT CAUSATION!

ROOT CAUSE OF NEURODEGENERATIVE DISEASES (NDD)

The root cause of all NDDs is the brain's autoimmune system that had run amok in its unsuccessful attempts to maintain "brain homeostasis." In the case of AD, neurons sport receptors called amyloid precursor proteins (APPs). When APPs grab hold of netrin-1 (molecules floating by in the intercellular environment), they send signals (so-called "synaptoblastic signals") to the neurons to keep them healthy and functional. This is the "synapse-building phase." When this process fails, it defaults to opposite signals (so-called "synaptoclastic signals") instructing the neurons to commit suicide and to APPs to produce more Aβ, thereby outnumbering netrin-1. This is the "synapse-dismantling phase." As a consequence, the APPs are less likely to grab netrin-1 and more likely to keep grabbing Aβ. Any effective treatment for AD might therefore be to include a method to rebalance the synapse building and dismantling phases. One such approach would be to identify all different contributors to APPs (or AD's risk factors) and to address all (or as many) of them.[27] Unfortunately, despite its logic, this is again addressing the risks not the root cause(s) of the disease.

The cure would be to temper (or tame) and regulate the brain autoimmune system to tolerate rather than fiercely combat the synaptoclastic signals such as by the use of regulatory CAR-T_{reg}-cells,[29] not with DESS (however, symptomatically helpful DESS might be). The above idea builds upon work done in diabetes type I, an incurable disease so far, in which the autoimmune system is taught to tolerate the insulin-producing cells of the pancreas so that it does not destroy the diabetic patient's ability to produce the glucose-regulating insulin. The similar idea should form the basis for treating other incurable diseases, especially NDDs. The overarching purpose is to tame down the hyperactive autoimmune system by employing molecules that can induce an immune response (antigens) or engineered immune cells that can train the autoimmune system to tolerate the process or tissue it is on track to damage. The above solution requires a deep understanding of the molecular basis of autoimmunity (brain autoimmunity, in particular) as well as advances in genetic engineering and cell-based therapy. (Caution must nonetheless be exercised as deploying the immune system to treat certain diseases can also trigger autoimmune diseases, e.g., in the case of cancer, it may trigger such autoimmune diseases as rheumatoid arthritis and colitis).

WAYS TO TEMPER A ROGUE AUTOIMMUNE SYSTEM

Two approaches are suggested below to temper a rogue autoimmune system.[29]

- T_{reg}-cells: These cells are the main immune players. They act as the brakes of the immune system. Similarly to other T-cells, T_{reg}-cells rein in the immune cells that are doing damage. It has been suggested that the body can be made to produce the T_{reg}-cells required to dampen a certain autoimmune response by dosing people who are affected with the same antigen or antigens that the immune system wrongly interprets as a reason to attack. This was tested for MS, demonstrating less brain inflammation. This is similar to vaccination in which, if administered without the immune system stimulants called adjuvants that are usually included in vaccine formulations, antigens can induce a calming effect through T_{reg}-cells.
- CAR-T_{reg} cells: The patient's T_{reg}-cells can be removed from the body, engineered to respond to specific antigens that have been wrongly recognized by the immune system as being foreign, and then returned. This is the very principle of CAR T-cells (here %) that have been FDA approved and now applied to cancer treatment. They can be used to dampen harmful inflammation.[10,30]

IMMUNOTHERAPY RISKS, BENEFITS, AND FUTURE PROMISE

We have seen that:
a. For epilepsy: Gene therapy is being studied in some

types of epilepsy. Medications that alter the immune function, such as IV immunoglobulins, are currently poorly supported by evidence.

b. For Parkinson:

- Active or passive immunotherapy (as currently employed) has been of limited use because of the low amount of antibodies passing the BBB.
- Increasing the amount of antibodies passing through the BBB may be accomplished in two separate ways: (a) coupling antibodies to the peptide penetratin or/and (b) modulating the aggregation of alpha-synuclein (i.e., blocking or reducing the aggregation of its monomers to oligomers or later on to fibrils).
- Three drugs are close to or under very early development (ANLE138b, NPT200-11, and NPT100-18a): In opposition to antibodies, these small molecules readily pass the BBB and can deliver therapeutic compounds.

c. For Alzheimer:

- All the underlying theories are premised on addressing risk factors, not the cause(s), and are therefore invalid except in a palliative sense.
- There are no drugs that would prevent, reverse, or delay the disease.
- The DESS approach might be helpful in a palliative sense, but not curative.
- I submitted that AD (like other NDDs) is a hyperactive brain autoimmune disease that needs fundamentally to be regulated.

d. For all NDDs:

- The root cause is a hyperactive brain autoimmune system that has run amok (a system that has turned rogue and induced a runaway effect).
- The brain autoimmune system can be regulated using T_{reg}-cells or engineered CAR T_{reg}-cells (in analogy with cancer and type I diabetes).
- We need to understand even better the fundamental biological and molecular mechanisms of brain immunity and autoimmunity and mechanisms of resistance to immunology.
- We need to better master the confluence of gene therapy, synthetic biology, and cell biology.
- In the meantime, DESS can be symptomatically helpful.

CONCLUSIONS

While protective, the immune system can turn rogue and give rise to several autoimmune diseases. In the case of cancer, including brain cancers (GBs), immunotherapy is an emergent anti-cancer therapy. Beginning with the earlier discoveries of CTL-4 and PD-1, immunotherapy has rapidly evolved during the past decade. Using synthetic biology, we are able to overcome some natural limitations (e.g., overcoming the need for MHC molecules that cradle the target antigens presented by the D-cells to the T-cells and for co-stimulatory ligands that trigger the signal for the T-cells to attack). By genetically modifying the T-cells, we can direct the T-cells to home-in directly on antigens that may be abundant on cancer cells. The technology has, however, its limitations: No other molecule than CD19 is known that is a specific cancer target and there are toxic effects. However, the technology can be refined so as not to exclusively depend on the presence of CD19 and can be tailored to patients so as to avoid the deleterious effects of cytokine overproduction (or storms) that could be fatal for some. The technology can further be improved by combining it with other complementary therapeutic approaches in a multi-prong attack (surgery + radiation therapy + chemotherapy + thermal ablation). Its future is very promising, and we can foresee the CAR-T-cells approach being successfully tried in many forms of cancer.

The applications of immunotherapy to neurodegenerative diseases (epilepsy, PD, AD, etc.) are very recent. As it turns out, and contrary to earlier assumptions, the brain and the CNS are not immune privileged and possess their own immune system distinct from but interacting with the systemic system. What is currently unclear is whether the brain protective barriers contribute to inflammatory signaling in neurological disease and which specific barrier mechanisms are altered in response to inflammation. The fundamental question also remains as to whether the BBB is a component of the etiology of these diseases or a consequence of it. We have posited that these diseases are autoimmune diseases resulting from an overactive immune system that has run amok and have further suggested natural and synthetic approaches to modulate such behavior to prevent, modify, slow down, or even cure these diseases. Such suggestions have benefited from recent advances in, and confluence of, natural and synthetic biology, genetic engineering, and stem cell therapy.

ABBREVIATIONS USED

AA: Alopecia areata; AD: Addison's disease; AD: Alzheimer's disease; AED: Anti-epileptic drugs; ALL: Acute lymphoblastic leukemia; ALS: Amyotrophic lateral sclerosis; APP: Amyloid precursor proteins; AS: Ankylosing spondylitis; BBB: Blood–brain barrier; B(CSF)B: Brain–CSF barrier; B(iCSF)B: Brain–inner CSF barrier; B(oCSF)B: Brain–outer CSF barrier; BPB: Brain-protective barrier; BRB: Brain–retinal barrier; CAR: Chimeric antigen receptor; CD: Crohn's disease; CIDP: Chronic inflammatory demyelinating polyneuropathy; CLT: Chronic lymphocytic thyroiditis; CNS: Central nervous system; CTLA: Cytotoxic T-lymphocyte antigen; DASH: Dietary approaches to stop hypertension; DESS: Diet, exercise, stress, sleep; DMARD: Disease-modifying anti-rheumatic drugs; GB: Glioblastoma: GBS: Guillain–Barre syndrome; GD: Graves' disease; HD: Hashimoto's disease; IBD: Inflammatory bowel disease; LGIT: Low glycemic index treatment; MAD: Modified Atkins diet; MCI: Mild cognitive impairment; MCT:

Medium chain triglycerides; MDR: Multiple drug resistance; MG: Myasthenia gravis; MIND: Mediterranean-DASH intervention for neurodegenerative delay; MS: Multiple sclerosis; NCI: (U.S.) National Cancer Institute; NDD: Neuro-degenerative disorders; NSAID: Non-steroidal anti-inflammatory drugs; PD: Programmed death; PD: Parkinson's disease; RA: Rheumatoid arthritis; SCI: Subjective cognitive impairment; SLE: Systemic lupus erythematosus; T1D: Type 1 diabetes; TMZ: Temozolomide; UC: Ulcerative colitis.

DISEASES/DISORDERS CITED

Alzheimer's disease; Amyotrophic lateral sclerosis (Lou Gehrig's disease); Diabetes; Epilepsy; Li-Fraumeni syndrome; Mild cognitive impairment; Multiple sclerosis; Neurofibromatosis (types 1 and 2); Parkinson's disease; Psoriasis; Stroke; Subjective cognitive impairment; Tuberous sclerosis; Turcot syndrome; Vasculitis; von Hippel–Lindau syndrome.

DRUGS LISTED

Anticonvulsant corticosteroids; Bexarotene; Dexamethasone (a corticosteroid); Donepezil (Aricept); Galantamine (Razadyne); Ipilimumab (Yerzov); Levodopa; Memantine (Namenda); Mestinon (Pyridostigmine); Namanzaric (=Donepezil+Memantine); Pembrolizumab (Keytruda); Phenytoin; Rivastigmine (Exelon); Temozolomide.

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