November 15, 2017

Dear Regina,

Welcome to BioMarketing Insight's monthly newsletter.

We have a new look to our newsletter. Love to receive your feedback.

Last month I covered "How to Use Social Media Successfully." If you missed last month's article, click here to read it. . This month we'll cover " New Information to Unlocking the Pathology of Alzheimer's Disease."

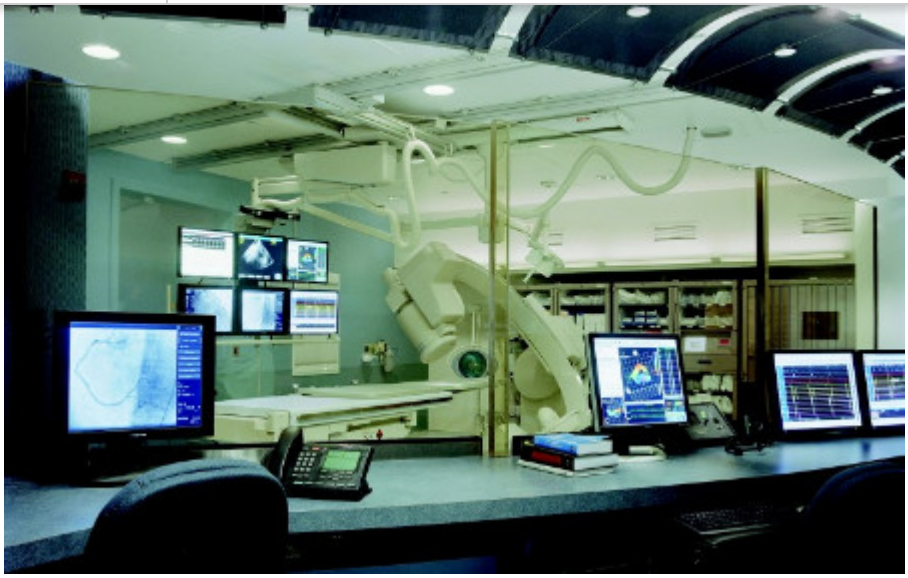
Read on to learn more about this topic and other current news. The next newsletter will be published on December 15th, 2017.

We encourage you to share this newsletter with your colleagues by using the social media icons below, or by simply forwarding this newsletter or use the link below.

Please email me, Regina Au, if you have any questions, comments, or suggestions.

Sincerely,
Regina Au
Principal, New Product Planning/
Strategic Commercial Consultant
BioMarketing Insight

Table of Contents



Developing a Product? Commercializing a Product?

If you are developing a product and have not conducted the business due diligence to determine commercial viability or success, contact me for an appointment. For successful commercial adoption of your product or looking to grow your business, contact me for an appointment.

For more information on our services, click on the links below:

Product Development
Market Development
Marketing Strategies

Top

CABA 美中生物医药协会
Chinese-American BioMedical Association

Save the Date: December 9, 2017 - CABA Medical Device and Diagnostics Innovation Symposium (MDDI)

The theme of this year's symposium is "Innovation, Commercialization and Collaboration." I am pleased to announce that I will be speaking on 3D Printing; How This Disruptive Technology Helped the Life Science and Healthcare Industry to Innovate. For more

This symposium provides a great opportunity to network with hundreds of professionals including scientists, entrepreneurs, investors and other industry professional to foster investments, partnership & collaboration for the United States and China.

Top

Save the Date: February 13 - 14, 2018 - Healthcare Internet of Things

The healthcare industry is at the advent of a digital evolution, spurred by a growing community of web-enabled products and services including the Cloud, smart and connected devices, and a more health-conscious and tech-savvy population. According to Frost & Sullivan, the internet of medical things is expected to grow at CAGR of 26.2% to reach $72 billion by 2021.

I am pleased to announce that I will be moderating a panel discussion on "Medical Devices and Wearables – Product Adoption (Compliance) and Market Access" at the Healthcare IoT Conference in San Francisco, CA. For more information, click here. But stay tuned for more details to come.

Top

Why Our Microbiome is Important to Our Physiology and Diseases

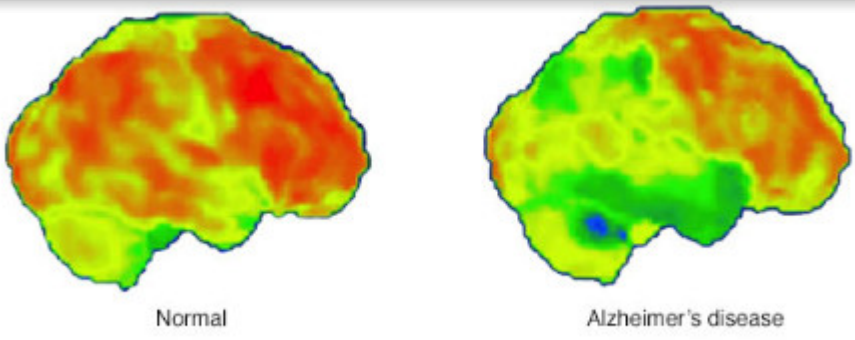
Physiology and Diseases" was published in the International Journal of Clinical Pharmacology & Pharmacotherapy. This article reviews the results of the Human Microbiome Project and the factors that affect our microbiome in relation to our healthy state and dysbiosis or disease state. To read the article, click here.

Top

Immunooncology: Can the Right Chimeric Antigen Receptors T-Cell Design Be Made to Cure All Types of Cancers and Will It Be Covered?

I am pleased to announce that my article on "Immunooncology: Can the Right Chimeric Antigen Receptors T-Cell (CAR-T) Design Be Made to Cure All Types of Cancers and Will It Be Covered?" has been published in Journal of Pharmaceutics. This article reviews the mechanism, design and administration of CAR-T cells, and whether payers will pay for this new technology. To read the article, click here.

Top



New Information to Unlocking the Pathology of Alzheimer's Disease

Definition of terms:

In a healthy brain, there are nerve cells or neurons (triangle figures) and synapses (the branches or legs coming out of the nerve cells) as depicted in Image 1. In AD, there are fewer nerve cells and synapses. Plaques are abnormal clusters of beta amyloid protein fragments that build up between nerve cells depicted as orange balls in Image 1. Dead and dying nerve cells (triangle figures) contain tangles, which are made up of twisted strands of a protein called tau.

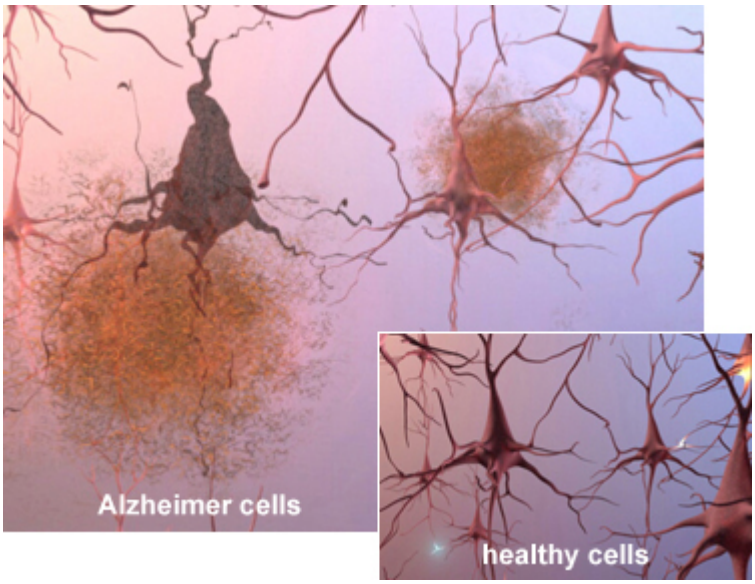


Image 1: Inside the brain; plagues are the orange cluster ball of beta amyloid protein near the nerve cell and the tangles are inside the dead or black nerve cells near the plague clusters. Source: © 2017 Alzheimer's Association. All rights reserved. Illustration by Stacy Jannis.

Beta Amyloid is derived from a larger protein found in the fatty membrane surrounding nerve cells and are chemically "sticky" and can gradually builds up to form plague. See

Tau proteins - function to stabilize microtubules and provide flexibility. These proteins are abundant in nerve cells. Microtubules are known to support neuronal architecture similar to railroad tracks, organelle transport, and it is believed that microtubules may act as 'information carriers' in the neuron.

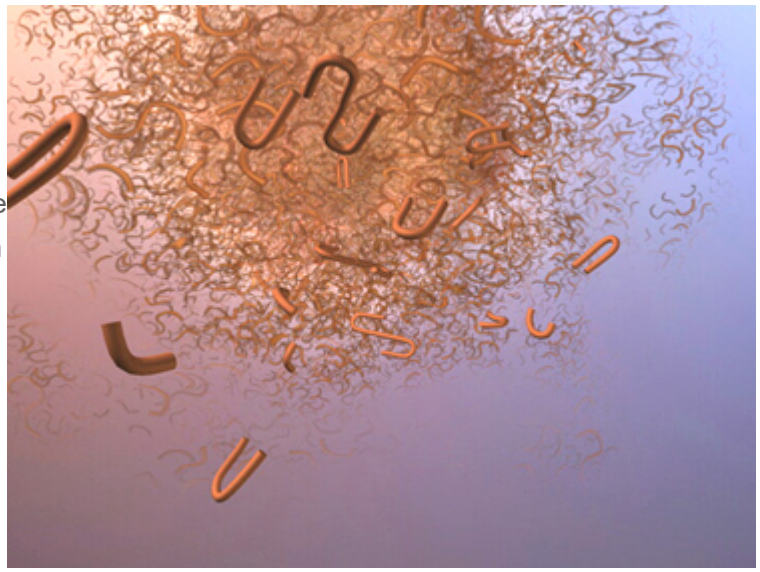


Image 2: Beta amyloid plaque.
Source: © 2017 Alzheimer's Association. All rights reserved. Illustration by Stacy Jannis.

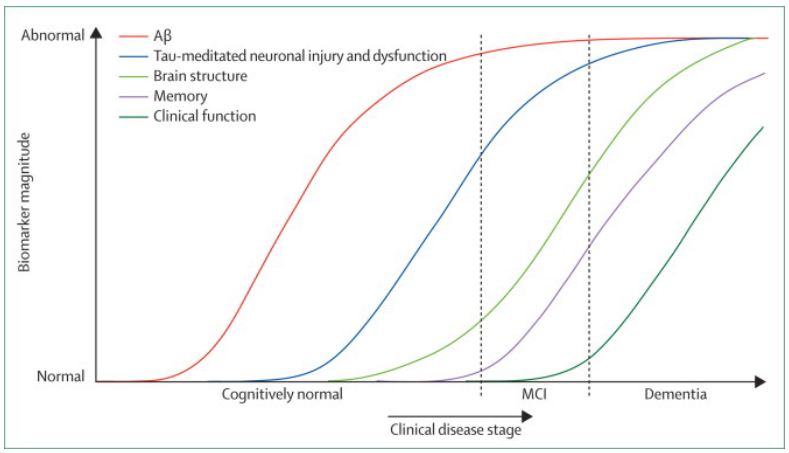
Introduction:
For years, investigators have believed that the pathology of Alzheimer's disease (AD) was driven by the production and deposition of the β-amyloid peptide (Aβ). But investigators have not been able to prove or at least there is a weak to nonexistent correlation between the amount of neuritic plaque pathology in the human brain and the degree of clinical dementia.

Today, researcher have found substantial evidence to indicate that the solubility of Aβ, and the quantity of Aβ in different pools, may be more closely related to disease state. New imaging technologies such as positron emission tomography (PET) scan, including new amyloid imaging agents or radioactive drugs (tracers) that studies the metabolic activity or body function have made it possible to track amyloid pathology along with disease progression in living patients.

It is now believed that the two hallmark pathologies required for a diagnosis of Alzheimer's disease (AD) are the extracellular plaque deposits of the β-amyloid peptide (Aβ) and the flame-shaped neurofibrillary tangles (NFTs) of the microtubule binding protein tau. Early onset forms of AD are associated with genetic markers or mutations in either the precursor protein for Aβ (the β-amyloid precursor protein, APP) or in presenilin-1 (PS1) or presenilin-2 (PS2). Despite this genetic evidence and the involvement of Aβ in inducing synaptic dysfunction, disrupting neural connectivity, the amounts and distribution of Aβ deposition have only shown to be weakly correlated with the clinical expression of

It has been generally accepted that there are a number of precursors or measurable biomarkers need to occur before the brain develops AD. The hypothetical timeline of biomarker events that occur are depicted in Figure 1. Each stage will be discussed in more detail regarding the pathological evidence to this hypothesis and additional information required to further the science in discovering the pathology behind AD.

Figure 1: Scientist now believe that the first Stage is Cerebral Spinal Fluid and Interstitial Fluid Clearance rather than Aβ in red. Source: From Jack et al. Lancet Neurol 2010



Stages of Alzheimers

Stage 1: Cerebral Spinal Fluid (CSF) and Interstitial Fluid (ISF) Clearance

a) β-amyloid Clearance

It was theorized that the pathology of Alzheimer's disease (AD) was driven by the over production and deposition of the β-amyloid peptide. AD classified as dementia can be divided into two groups: 1) early-onset AD (EOAD) and 2) sporadic or late-onset AD (LOAD). EOAD affects a minority of AD patients, whereas LOAD afflicts over 95% of patients with AD. Both EOAD and LOAD are characterized by excessive accumulation of toxic forms of amyloid-β (Aβ), which has been hypothesized to result from an imbalance between its production and clearance. Today, it is believed that the deposit of Aβ protein is due to the malfunction in the clearance of Aβ protein rather than the over production that leads to accumulation of Aβ protein. Emerging evidence also suggests that Aβ clearance is impaired in both early-onset and late-onset forms of AD as Aβ proteins can be detected and measured in the CSF and ISF.

Soluble Aβ can be removed from the brain by various clearance systems, including enzymatic degradation and cellular uptake, transport across the blood–brain barrier (BBB) and blood–cerebrospinal fluid barrier (BCSFB), interstitial fluid (ISF) bulk flow, and cerebrospinal fluid (CSF) absorption into the circulatory and lymphatic systems.

Mouse studies conducted in the early 2000s, demonstrated that the majority (75%) of extracellular Aβ (eAβ) is cleared by the BBB, with only a minority (10%) being cleared by ISF bulk flow. However, recent imaging studies suggested that ISF bulk flow—facilitated

The presence of neuritic plaques that are composed for the most part of highly insoluble Aβ in the brain parenchyma is required for a diagnosis of AD. Deposits of tau protein are also present, although they are also found in a number of less common neurodegenerative diseases, notably in the absence of neuritic plaques.

b) Tau Clearance

Tau is an intracellular neuronal protein that stabilizes axons and microtubules. Intracellular tau (i-tau) can undergo two transformations that are relevant to its clearance: modification and release. Tau modification is regulated by phosphorylation. In AD, i-tau is hyperphosphorylated, which induces the formation of insoluble Neurofibrillary Tangles (NFTs) that cannot readily be cleared, and can also be neurotoxic. Neuronal activation, neuronal death and increased i-tau concentration or aggregation triggers the release of i-tau into the extracellular space, leading to elevated CSF tau levels.

The clearance of Tau from the brain is not well understood but it appears to be less complex than beta amyloid since there seems to be no evidence that it is cleared by the BBB, except after brain injury, when BBB permeability is temporarily increased. Tau is hypothesized to be cleared from the brain primarily by degradation, ISF bulk flow, and CSF absorption clearance.

Studies at Children's Hospital in Boston have recently discovered that there are two types of Tau proteins, soluable tau (good tau) and insoluable tau (possibly hyperphosphoylated tau). The significant of both has not been determined yet but one can guess that the soluable tau gets cleared and the insoluable tau induces the formation of insoluable NFTs which in turn lead to the death of nerve cells. More information will be discuss in Stage 3: Tau-mediated neuronal injury and dysfunction.

The pathological accumulation of Aβ and tau proteins in the brain can be inferred by analyzing their levels in the CSF. Specifically, Aβ accumulation into extracellular plaques is marked by decreased CSF levels of Aβ1–42, and tau accumulation into NFTs is marked by increased CSF levels of total tau and hyperphosphorylated tau. In addition, PET can be used to assess Aβ brain accumulation directly, and PET for tau is currently under investigation.

Stage 2: Beta-Amyloid Plaque

Scientists know that the accumulation of Aβ plague is toxic and the most logical course of action is to eliminate or decrease the amount of plaque to prevent AD. However, numerous pharmaceutical companies have conducted clinical trials to demonstrate this, but it has not resulted in the prevention or decrease the progression of AD. Why some

forms plaques.

Here are a few hypothesis regarding this matter:

1) While the minimum or maximum amount of Aβ deposition could contribute to the onset of the disease it's probably that it is highly individualized similar to personalized medicine. It has been theorized that Aβ exerts its major effects early by triggering a cascade of events that, once begun, proceed independently of Aβ being removed. It is unclear to the exact mechanism of this theory except to surmise that the continued accumulation of misfolded hyperphosphorylated tau, leads to further neuron loss.

2) Another possible explanation is that specific form or forms of Aβ are responsible for the massive neuronal death that accompanies this disease.

Stage 3: Tau-mediated neuronal injury and dysfunction

Tau proteins control the microtubule stability through isoforms and phosphorylation. Hyperphosphorylation of tau proteins (possibly insoluable tau) can cause the helical and straight filaments to twist or tangle (NFTs). These tangles contribute to the pathology of Alzheimer's disease.

Tangles form inside dying cells. Tangles are twisted fibers of a protein called tau. In healthy areas, tau regulated the microtubules that help keep the transport system in tack like a railroad track. But in areas where tangles are forming, the twisted strands of tau (hyperphosphorylated) essentially destroys the transport system so that nutrients and other essential supplies can no longer move through the cells, which eventually die.

Though most people develop some plaques and tangles as they age, those with Alzheimer's tend to have an abundant amount of them. The plaques and tangles tend to form in a predictable pattern, beginning in areas important in learning and memory and then spreading to other regions.

When a brain affected by Alzheimer's disease is examined, all six isoforms of tau are often found hyperphosphorylated in paired helical filaments. Deposits of abnormal aggregates enriched with tau isoforms have also been reported in some other neurodegenerative diseases.

Stage 4: Brain Structure, Memory, Clinical Function

The pathology as to the events that need to occur in order for these three stages to progress, is unclear and more basic research needs to be done, but there are a number of hypothesis:

1. Neuroinflammation - where pieces of Aβ protein activate the immune system that promotes inflammation and possible destroys brain cells through the innate immune system.
2. Neuroinflammation that does not reproduce the classic characteristics of inflammation in the periphery, but may induce neurodegenerative events; including plaque formation, dystrophic neurite growth, and excessive tau phosphorylation.

2) That specific form or forms of Aβ are responsible for the massive neuronal death that accompanies the disease. There are currently no imaging or scientific tools available to confirm this theory in distinguishing the difference between what maybe disease-related Aβ from less relevant forms thus, weakening the correlation with clinical stages.

3) Recent findings show that glucose may play a factor in AD. A recent study conducted by the National Institute on Aging (NIA), part of the National Institutes of Health, demonstrated that abnormalities in glycolysis or the breakdown of glucose in the brain, is connected to the severity of Alzheimer's Pathology. Reduction in brain glycolysis produces higher levels of brain glucose which correlated to more severe plaques and tangles found in the brains of people with AD. Severer reduction in brain glycolysis were also related to the expression of symptoms of AD, such as problems with memory.

Top

Closing Thoughts

The pathology of the brain is so complex, that it is only until now after decades of research and the invention of specialized imaging equipment and various other scientific tools have researchers begun to unravel the mystery of the brain. The one thing researchers have agreed upon is that in order to prevent or slow the progression of the disease, one needs

It is a consensus that both beta amyloid and tau proteins play an important part of the pathology, but the debate remains on whether we need to reduce the aggregation of both or is it even feasible to reduce both in order to halt the progression of AD. Scientist know that soluable Aβ and tau is cleared from the brain, and that insoluble Aβ leads to plaque and hyperphosphorylated tau or possibly insoluable tau induces the formation of tangles.

We know the disease is not a linear progression and that there may be a host of other factors such as impaired glycolysis, specific forms of disease related Aβ, and neuroinflammation that is non-characteristic of inflammation in the periphery can perhaps one or all are involved in this cascade of events. Like personalized medicine, depending on what form of beta amyloid and tau is accumulated, individual thresholds to beta amyloid and tau to trigger this cascade, glycolysis abnormalities, genetic biomarkers, co-morbidities and the list goes on even pathology that scientists may not have discovered yet, could all influence in varying degrees whether one would develop AD. Solving this puzzle is very similar to solving a Rubix Cube for the first time.

Which theory is correct and which is incorrect? Only time will tell.

Top

Should you have any questions or need of assistance with your business due diligence, determining your product's value proposition and economic value of your product, feel free to contact me at 781-935-1462 or regina@biomarketinginsight.com.
