**The Amyloid Hypothesis as a “Six-Shooter”**

I frequently use the following analogy to help patients and families better understand the current state of our knowledge regarding the Amyloid Hypothesis of Alzheimer’s disease. It was formulated just over 25 years ago. The originators, Dennis Selkoe of the Brigham and Women’s Hospital in Boston and John Hardy of the University College of London, wrote a scholarly article about it in 2016. For those who wish and dare to delve further, link to:

<https://www.ncbi.nlm.nih.gov/pmcarticles/PMC4888851/>

What follows here is obviously somewhat oversimplified but gets at the essential points. Approaches to modify the presumed toxic effects of beta-amyloid are the focus for most current Alzheimer’s research clinical trials. These are referred to as Disease Modification Trials. Realistically, it is hoped they will slow down the progression of Alzheimer’s. To halt progression entirely or reverse deficits are probably not realistic goals just yet.

*Many researchers in this field, myself included, remain unconvinced anti-amyloid strategies will* work. Here is a summary of why we are still trying them, along with relevant concerns and criticisms. I recommend you first watch the NIH video on this website regarding “What is Alzheimer’s”. It provides a nice visual context for understanding what follows below.

**Beta-amyloid Protein is the Trigger:**

We have gained much knowledge from looking at information from many amyloid PET scans and spinal fluid levels of beta-amyloid protein. It is now clear a deposition of abnormal forms (Aβ42) of beta-amyloid protein (“triggers”, if you will) into the brain easily begins 10-15 years *before* onset of any symptoms for many if not most individuals who develop clinical symptoms of Alzheimer’s disease. These clinical symptoms can either be MCI (mild cognitive impairment – typically pure mild memory problems) or dementia (more functionally significant memory or other cognitive disorder).

This basic knowledge about beta-amyloid derives from a large study on aging adults, called the ADNI (Alzheimer’s Disease Neuroimaging Initiative) Study. This is a remarkable private-public partnership, with work beginning in 2004, in which a variety of tests are performed over many years on older individuals (volunteers) across the USA, attempting to better understand the natural history of Alzheimer’s disease. The ADNI website is at:

<http://www.adni-info.org/Home.html>

We further know there is a very *poor correlation between active cognitive symptoms (memory loss, poor judgement, language difficulties, etc.) and beta-amyloid deposition. Surprisingly, this abnormal deposition of beta-amyloid in the brain tissue appears to be an excellent biological marker (“biomarker”) for the presence of the disease, not its severity*. To perform serial amyloid PET scans will likely show us whether or not specific therapies “remove the triggers”, but if the triggers have been pulled, the bullets are already on the way.

The various strategies (prevent formation of beta-amyloid, get rid of it if already there, block its effects) are different ways to prevent this “trigger” from being effective. From clinical trials (using anti-amyloid vaccines) already performed for patients with mild-moderate dementia, it is pretty clear getting rid of the beta-amyloid (“triggers”) may be too late to alter Alzheimer’s progression. “The triggers were already fired and all 6 bullets were on the way”. *Could still be the right drug used at the wrong time, which is very much why anti-amyloid strategies are not “discarded”.*

At a more detailed level, these “triggers” are probably clumps (oligomers) of ~2-20 of these beta-amyloid proteins, containing extra amounts of Aβ42, as the actual culprits. Normally we make 2 forms of amyloid beta, Aβ42 and Aβ40. The number refers to how many amino acids compose them. The Aβ42 is the “bad kind”; it is “stickier”. Some of the anti-amyloid vaccines are better than others at blocking the effects of these oligomers, or help prevent oligomers from forming. Whether these differences in the drug actions of the various anti-amyloid vaccines are important or not are being investigated.

Increasingly, more recent clinical trials are focusing on “blocking the triggers before they have been pulled 6 times”. The same drug classes that failed further on in the disease, might work earlier on (e.g. MCI or even pre-clinical – before any symptoms in high risk people). That is, “let’s try to block the six-shooter trigger when it’s only been fired once, twice, or not yet at all,” so the bullets are not yet on the way.

Other approaches work on blocking the cleavage enzymes that cause the beta-amyloid protein to form in the first place (see the NIH video on this site). Think of the cleavage enzymes as two required scissors to cut a longer string to size, one different scissor for each end. Of these two cleavage enzymes, blocking one of them (gamma-secretase) is probably too dangerous as it is a necessary component for other vital cellular processes. The other cleavage enzyme (beta-secretase) looks more promising. The original proof of possibility for this comes from an observation of people from Iceland (socialized medicine permits very complete DNA databases!).

It turns out folks older than 85 in Iceland, who seemed “protected” from developing Alzheimer’s, have a natural genetic variation causing their beta-secretase cleavage enzyme from full functioning… leading to a lower amount of beta-amyloid being formed throughout their lives. These observations are a naturally-occurring rationale for trying drugs to partially block beta-secretase activity. That is “decrease the number of triggers”. Again this strategy may fail if the “triggers have already been pulled”. Also, there may be a difference between decreasing trigger production later in life (once symptoms have begun) as opposed to a lifetime of, genetically, having made and been exposed to fewer triggers.

Other medications attempt to “jam the firing pin”, so that even if a trigger is pulled, the bullet doesn’t fire. These drugs work by blocking beta-amyloid from binding to brain cells. That binding triggers a cascade of events leading to the death of brain cells to which the beta-amyloid attaches.

**Tau Protein as the Bullets:**

If beta amyloid protein is the trigger, what are the bullets? This is a very complicated question, with many possible answers. We understand many details of what brain cells look like as they die and what pathways get activated in those dying cells. It still remains unclear how the ”bullets” begin those processes of brain cell death. Tau protein is a major candidate.

Again referring to the NIH video, tau proteins maintain the integrity of the microtubules. Think of the microtubules like the vehicle tubes in “The Jetson’s” and tau protein as the struts and girders holding them up and together. These microtubules are critical to allow for proper processing of the energy, waste and information functions of brain cells. It appears these tau proteins gain an “arm” (hyperphosporylation), causing them to pull away from the microtubules and aggregate. As the brain cell then dies, it releases clumps (oligomers) of hyperphophorylated tau that might “infect” another brain cell to which it is attached. Remember each brain cell is part of a network or networks with other brain cells. These clumps of abnormal tau seem to elicit a similar pattern of cell death by “hijacking” the next cell’s normal functions, acting as an ”information virus (akin to a computer virus, not a living thing)” and so on to the next cell in the network. Sort of “ricocheting bullets”, to carry our six-shooter analogy forward.

Some recent disease modification drugs are being used to try to block these tau oligomers from “spreading” their ill-effects to other cells in the network. Again, as with beta-amyloid we need to be mindful of using the right drug at the right point in the disease.

We are now just about 15-20 years into actual human clinical research for Alzheimer’s disease modification. We have learned a great deal about what does not work with hints of what might. We are now at the second level of trials, having learned from the first round. Perhaps these newer will work, perhaps not. We will never know unless they are explored.

Some thoughts about participating in Alzheimer’s Clinical Trials, based on years of experience.

* You are volunteering … all on our research team appreciate and respect this.
* Of course we hope each person is on an active, safe drug that will benefit them.
	+ However, you may be on placebo for a time
	+ The drug could ultimately be proven useless, harmful or both
	+ You must have some sense of a greater good (your descendants, friends who have the disease) as a motivation, beyond yourself.
* Be fully informed when you sign an Informed Consent to perform in a clinical trial
* Remember all Clinical Trials run until “last in, last out”. For example, if it is a 3 year trial but takes 3 years to fully recruit, it will be 6 years before all results are in … be patient.
* You often will never know whether you were or were not on “active” drug
* As an investigator, your doctor truly does not know if any given investigational drug will work or not, which one is “better”… if we knew would not need to run the trials
* You are pioneers… enjoy the role and privilege!