The greatest challenge to finding new treatments to AD is:

1. Funding from all agencies that normally fund AD research is at a historic low. This along with the traditional bias inherent in our peer review system holds back any hope for developing effective drugs to treat AD. The NIA, which is the primary government agency that funds AD research, is doing the best they can with a system that still carries significant bias towards funding research groups that hold strong lobbying power within the scientific community. Unfortunately, our scientific peer review system continues to be too easily influenced by entrenched scientific review committees, and the NIH staff is left powerless to correct damaging political decisions. The scientists who serve on these committees are too fearful to speak out against established investigators in the field in fear of retribution against their own research programs.

As too often seen in Washington DC, the people in power are more concerned with keeping power (and the funding that goes with it) for themselves and their friends, than doing their job which is to serve the best interests of the patients and their families. The Alzheimer's Association lost money in the financial collapse of 2007-08, lessening their ability to fund research, and they have many of the same inherent problems discussed above in our peer review system. The pharmaceutical companies are losing billions of dollars every year to patent expiration causing them to gut their research and development efforts. The drug pipelines are becoming drier each day with diminishing input from a weakened R&D effort.

2. We have undergone a significant paradigm shift in our approach to creating new therapeutics. Frustration from legislators that the system wasn't producing drugs fast enough forced a change in the way we perform science. Rather than taking the traditional approach of building from the ground up with knowledge based science (e.g. basic science research) we have decided to take the "shot in the dark" approach with little if any scientific backing or forethought. Current research funding is disproportionately appropriated towards "translational" proposals with the hope (and a prayer) that a new miracle drug will be found, lacking well tested and knowledge based scientific ideas. I suspect one of the reasons for this shift in the scientific method is the increasing tendency towards "instant gratification" that all of us have become accustomed to in our lives. This may explain the frustration with the "old" way of doing science, but doesn't necessarily mean it will work for producing new drug treatments.

3. I don't know about other fields, but in the AD field there continues to be a disproportionate amount of money spent on ideas that have been tested for decades that have yet to show any success. This may be explained by the fact the scientists perpetuating these ideas are still in power and don't want to give up their jobs (or power) yet, even at the expense of families living with AD. They may feel very strongly about their long held beliefs, but this doesn't justify excessive domination of research dollars.

4. One potential solution is to fund more basic science research. We don't have to completely abandon the high risk "shot in the dark" strategy, but simply appropriate more funding to basic science initiatives rather than putting all our eggs in the "translational" basket.

Another solution is to fund <u>truly</u> novel ideas and spend less money on ideas (amyloid based) that haven't worked for decades. Simply changing (not eliminating amyloid based research) the proportion of funding amongst various research ideas would be helpful.

These strategies, however, are long sighted and politically unpopular. Many people have become addicted to or expect "instant gratification" (e.g. bench to bedside in less than 4 years) and institutions (and scientists) with power do not want to lose their grip on the power (and money) they hold. This is where true leaders capable of acting selflessly are needed to change the way the system works. My willingness to speak out and express the opinions of many scientists in the field may lead to the demise of my career in this field, but I can't go along with the charade any longer.