

A POSSIBLE DIAGNOSIS FOR ALZHEIMER'S
USING NANOTECHNOLOGY

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ABSTRACT

Worldwide, it is estimated that there are 18 million sufferers of Alzheimer's disease. Because of the aging population, it is thought that this figure could almost double to 34 million by 2025.¹ This shows the growing problem of the disease. The people thought to be suffering from Alzheimer's face a big problem in the diagnosis of their disease but could bio-barcode assay be the great medical breakthrough that we have been searching for? Could new developments in nanopores help us to understand more about the disease and provide a new diagnosis technique?

INTRODUCTION

Alzheimer's disease is a brain disease that destroys thinking and memory skills that eventually leaves you unable to complete simple tasks². Alzheimer's disease (AD) is named after the gentleman who discovered the disease in 1906, Dr Alois Alzheimer. He was a German Neurologist who identified 'an unusual disease of the cerebral cortex' which had affected a 55 year old woman. The woman had experienced memory loss, disorientation, hallucinations and the disease eventually proved to be fatal. When a post-mortem of Dr Alois Alzheimer's patient was done, it was found that there were abnormalities in her brain; the cerebral cortex was thinner and senile plaques were also found which seemed out of the ordinary in a woman of only 55. Alzheimer also discovered neurofibrillary tangles in her brain³ (Fig. 1). All of these irregularities were signs of what we now call Alzheimer's disease.

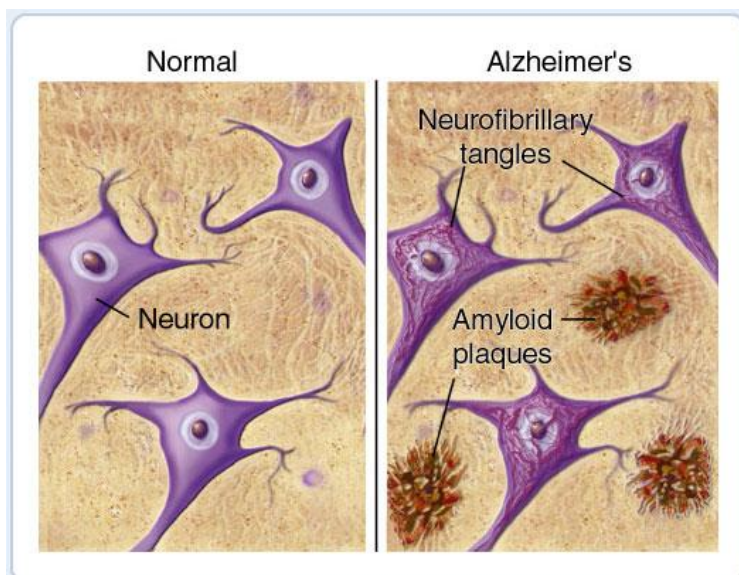


Figure 1 – Shows the neurofibrillary tangles (www.ahaf.org)

It was only on post-mortem that it was found that the woman had this disease. While she was alive, apart from her strange behaviour, there were no signs that the woman had what we know now as Alzheimer's disease. There is still the growing problem of how Alzheimer's is diagnosed. Many patients are just diagnosed through the process of exclusion.

Some believe that nanotechnology could offer a solution. A basic definition of nanotechnology "is the engineering of functional systems at the molecular scale." Nanotechnology is about changing living systems on a molecular level. Molecular machines can be created on such a small scale. The theoretical capabilities of nanotechnology were envisioned by physicist Richard Feynman who said:

"I want to build a billion tiny factories, models of each other, which are manufacturing simultaneously. . . The principles of physics, as far as I can see, do not speak against the possibility of manoeuvring things atom by atom. It is not an attempt to violate any laws; it is something, in principle, that can be done; but in practice, it has not been done because we are too big."

These capabilities were envisioned by Feynman in 1959 but no advance was really made until the 1980's⁴. At the moment, we are in the height of scientific advance and there are many possibilities for nanotechnology in the future including developments in medicine. This paper will specifically focus on how nanotechnology could be used in the diagnosis of Alzheimer's disease.

DISCUSSION

Thus far, there are no specific tests for Alzheimer's disease pre-mortem and doctors simply have to diagnose patients through the method of exclusion (ruling out any other possible diseases that could be causing the symptoms)⁵. Although this method works to a degree, it would be more efficient and reliable for doctors to have a fully conclusive test.

Bio-barcode Assay

The discovery of Amyloid beta-Derived Diffusible Ligands (ADDLs) in 1996 provided scientists with more knowledge about how Alzheimer's was caused and took hold. The term 'amyloid' means a fibular plaque therefore the term ADDL was derived to have 3 major differences to amyloid. They are:

- ADDLs have a peptide chain of 1-42 whereas amyloid has a shorter chain of just 1-40.
- Amyloid is insoluble whereas ADDLs are soluble.
- The ADDLs are ligands so therefore bind to a specific set of postsynaptic proteins.

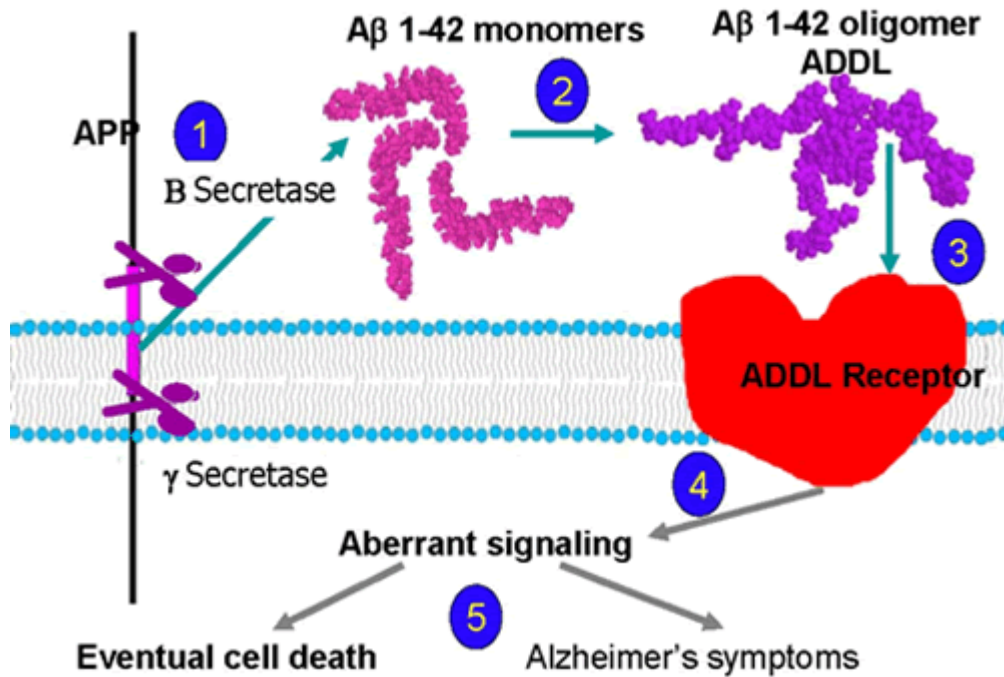


Figure 2 - (www.acumenpharm.com) - Shows the normal process versus what happens if a patient has AD

The diagram (Fig. 2) shows the normal process of APP, producing the amyloid beta peptide chain. This chain is usually 40 amino acid long, however, some of the amino acid chains are 42 amino acids long. This causes a significant change in the performance of the peptide chains. Most of the time, the 42 chain is cleared before it can do any harm. When it does not clear, it can cause Alzheimer's disease. The problems begin when at stage 3, the oligomer ADDL binds to the receptor and initiates aberrant signalling. ADDLs are considered to be the neurotoxins of Alzheimer's disease. After this had occurred, the patient has an average of 10 years left to live⁶. Without a diagnosis, this can be stressful for the patient. Could we speed up this diagnosis process?

Scientists are always looking for new ways in which to detect markers for Alzheimer's disease but so far have been unsuccessful. There is one method in which one measures the tau protein concentration in the cerebrospinal fluid or plasma but this seems to have a significant overlap in those that suffer from Alzheimer's disease and those who are healthy. Therefore, this method has been discarded due to its inconclusive results⁷.

After the discovery of ADDLs, a new method was developed which targeted the pathogenic markers such as the ADDLs. The ADDLs are found in the cerebrospinal fluid. However, this method was soon discarded as during the early stages of Alzheimer's disease, the concentration of ADDLs were so low, that it could not be detected.

In 2005, a study was conducted at Northwestern University. The study went more in depth into the technique of measuring the concentration of ADDLs in the cerebrospinal fluid. They discovered a major breakthrough in the diagnosis of Alzheimer's disease.

This ground-breaking new method is called ultrasensitive nanoparticle-based bio-barcode assay. At the University, a study took place in which 30 subjects were taken. 15 of them had been diagnosed with the disease through post-mortem; they were deceased. The other 15 were living and did not have AD. The extraordinary sensitivity of the bio-barcode assay allowed the researchers to determine the concentration of ADDLs in the deceased subjects (those with dementia) were consistently higher than the levels in those who were not suffering from Alzheimer's disease⁸.

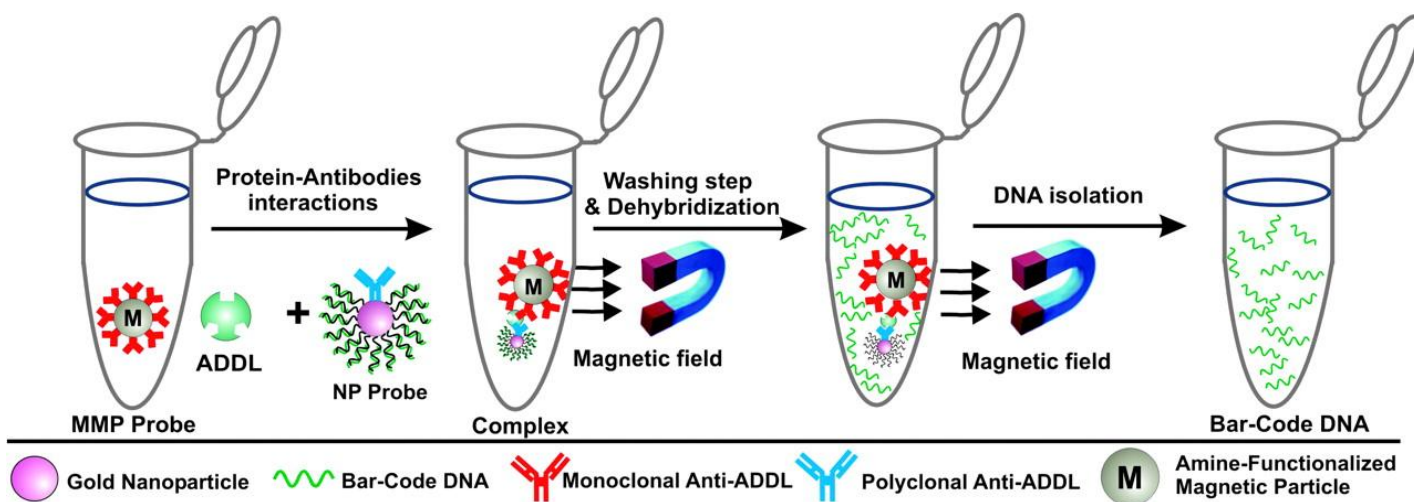


Figure 3 - (www.ncbi.nlm.nih.gov) The process of bio-barcode assay

Bio-barcode assay is used for the detection of proteins and nucleic acid. In the diagram (Fig. 3) you can see that the assay uses MMP probes (magnetic microparticles) which bind to the ADDL which are then sandwiched which an NP probe (oligonucleotide-modified gold nanoparticles). This sandwiched structure of MMP probe, ADDL and NP probe is then modified with double stranded DNA and an

anti-ADDL. After this, the solution is washed and then using a magnet, the MMPs are immobilised. This therefore gives hundreds of barcode DNA strands⁹.

This method was used on the 30 subjects. The results of this bio-barcode assay are as follows:

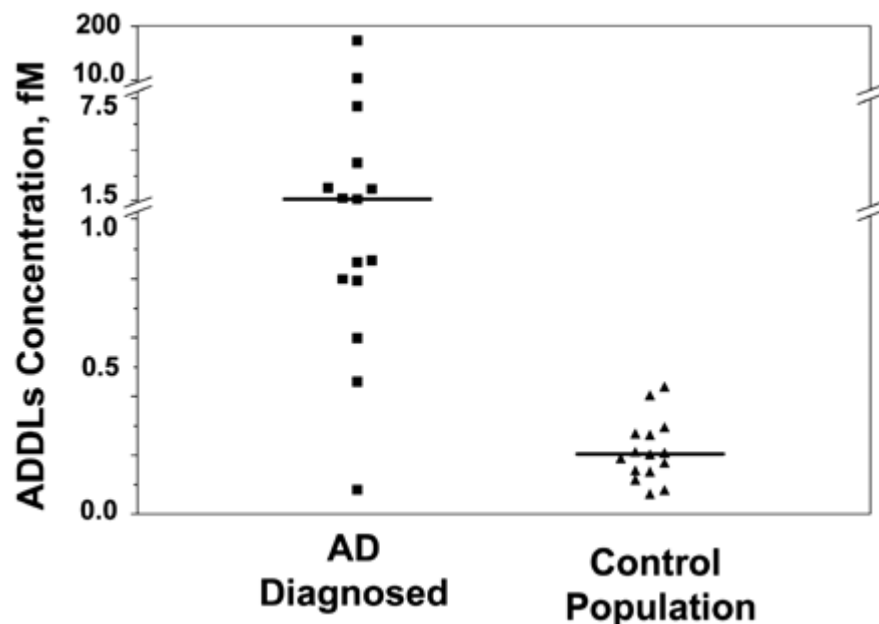


Figure 4 - (www.pnas.org) The results from the study carried out at Northwestern University

We can conclude that the study is very significant in our understanding of bio-barcode assay. The study shows us that we can use this technique to measure the concentration of the pathogenic ADDL. However, the sample size of just 30 subjects is very small therefore, before the technique can be used clinically, further validating tests need to be done on a larger sample size to prove that the results are reliable¹⁰.

Nanopores

Another study at the University of Michigan has recently discovered a tiny tunnel-shaped tool called a nanopore that may help us to further understand Alzheimer's disease.

This study was conducted by Michael Mayer, an associate professor of Biomedical and Chemical Engineering. The concept of the study is a nanopore is drilled in a silicon chip. An oily coating is applied to the chip traps and transports a specific molecule or protein through the nanopore. This coating also allows you to adjust the size of the pore with precision. Michael Mayer said . "It allows us to gain understanding about their size, charge, shape, concentration and the speed at which they assemble." He also said that this new technology could help us diagnose and

understand what happens in a category of neurodegenerative disease such as Alzheimer's disease.

The coating resembles that of the coating on a male silk moth's antenna. One main research track in this study is the proteins called amyloid-beta peptides. As already mentioned, these are the proteins that are thought to damage the fibres and affect the brain in Alzheimer's disease. Therefore, by the use of this method, the ADDLs that cause Alzheimer's can be precisely located. By locating these proteins in the body we can conclude whether the patient has Alzheimer's or not.

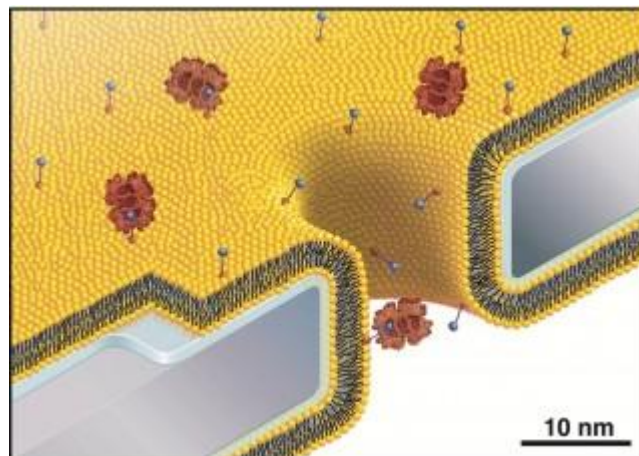


Figure 5 – (www.newswise.com) This is a nanopore. It is a measurement device that enables the study of one single molecule or protein. The ADDL proteins that cause Alzheimer's can be isolated and studied for use to be able to gain a greater understanding of the disease.

This technology is still in its infancy and even the most advanced nanopores can become clogged, therefore they are not used widely in the laboratory environment¹¹.

Nanotechnology is about changing living systems on a molecular level. This raises a few ethical issues as we are changing nature. As long as people are educated about new technologies and developments in nanotechnology, they will want the science to develop so will support the work of the scientists. Much of the research into nanotechnology is funded in a public way; therefore, the public deserve to know what research is being undertaken. If we can educate the wider population, we can create collective intelligence¹².

CONCLUSION

The potential for the use of nanotechnology to diagnose Alzheimer's disease seems promising. The bio-barcode assay technique has formulated a way in which ADDLs can be identified. The study which was undertaken supports the technique of measuring the concentration of ADDLs. It is important to note that the sample size was only 30 people and there were two overlaps between the Alzheimer's sufferers and the control group. If the bio-barcode assay technique was to be fully conclusive and to be implemented in a clinical environment, more extensive tests would have to be undertaken and the sample pool would have to be much larger to be of statistical significance. Theoretically, the technique would be a great new way to diagnose this fatal disease but there is not yet enough evidence for the technique to be implemented.

The nanopores have the possibility to provide us with a lot of information about the proteins that cause Alzheimer's disease. The small scale allows a single protein to be targeted. This could be very advantageous as it gives us the ability to isolate the protein that causes the disease allowing further analysis on the ADDLs to take place. On the other hand, this technique is still very new and underdeveloped, a major problem being the tubes becoming clogged. If this problem could be conquered, it could help us to understand a lot more about the disease and also to diagnose the disease.

In the future, the conclusion that can be drawn from this paper is that if further research was carried out into both of the methods, they have the potential to be very useful in the medical advances of the 21st Century.

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