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Emerging Analytical Strategies for the Rapid Detection of Biomarkers in Alzheimer's disease: Bridging Nanotechnology with Clinical Diagnostics: Review

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Abstract

Alzheimer disease (AD) has been the most common cause of dementia and a rising international health burden due to progressive neurodegeneration commonly many decades prior to clinical manifestations. Timely diagnosing and prompt intervention of AD is thus critical in ensuring that the outcomes of the patient are improved. The traditional methods of diagnosis like neuroimaging, cerebral fluid tests, and cognitive testing have played a significant role in the characterization of the disease but are constrained by their high cost, invasiveness, excessive time of processing and their lack of sensitivity at the preclinical stage. These shortcomings have prompted intense studies to come up with faster, sensitive, and minimally invasive biomarker detection systems.

Nanotechnology has become one of the game changers in the field of diagnostics in the recent past. Nanomaterials are gold nanoparticles, graphene-based structures, carbon nanotubes, metalorganic frameworks, and quantum dots, which have distinguished physicochemical properties that significantly improve the performance of the analysis. These nanostructures have the ability to be incorporated into electrochemical, optical, microfluidic, and lab-on-a-chip technologies to achieve ultra-sensitive detection of essential AD biomarkers like amyloid- 2 (A -2), tau, phosphorylated tau (p-tau), and neurofilament light chain. Their high level of surface reactivity, signal amplification and ability to work with small sample volumes is in favour of the creation of portable and point-of-care diagnostic systems.

Although these developments have taken place, there are various constraints to effective clinical translation, such as reproducibility, large scale nanomaterial fabrication, regulatory clearance, and its incorporation into clinical workflows. However, with continued interdisciplinary studies, these gaps continue to be filled, which brings nanotechnology-based biosensors a step closer to actual use.

Altogether, convergence of nanotechnology and sophisticated analytical strategies may provide a bright way of achieving fast, easy-access, and clinically relevant AD diagnostics, which may allow earlier diseases diagnosis and better disease control.

Keywords: Analytical Strategies, Alzheimer's disease, Nanotechnology, Clinical Diagnostics.

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Introduction

Alzheimer disease (AD) is a progressive neurodegenerative condition and an ultimate cause of dementia in the world and is one of the most significant global health issues with far reaching societal and economic consequences. Even after decades of research, the AD is challenging to diagnose in the initial stages of its development, and therapeutic interventions have the greatest probability of delaying the onset of the disease. Most of the present clinical evaluation methods are based on cognitive, neuroimaging, and cerebral spinal fluid (CSF) analyses, which despite being informative have a number of weaknesses such as invasiveness, high cost, lack of accessibility, and low sensitivity in the preclinical phase. Such diagnostic ability gaps in early diagnosis have enhanced the scientific interest to identify and detect effective biomarkers of the pathology of the AD in a fast and precise manner (1,2).

Recently, the biomarkers of amyloid-2 (A2), tau proteins, phosphorylated tau (p-tau), neurofilament light chain (NfL), and new aggregations of inflammatory and metabolic biomarkers have demonstrated potential in early and differentiated diagnosis. Nevertheless, to transform these biomarkers into clinical practice, there is a need to achieve analytical approaches that are sensitive, fast detection, and with the ability to be compatible with least invasive forms of samples like blood, saliva, and urine. Classical biochemical testing methods, such as ELISA and mass spectrometry testing, have proven to be highly diagnostic but are commonly time consuming, technically challenging and inapplicable to point -of-care (POC) testing or mass-population screening (3).

Nanotechnology has come along as a solution of these problems as it provides distinct physicochemical characteristics, i.e., increase in surface area, enhanced conductivity, and optical behavior-tuning possibilities which can greatly improve biosensing functions. Nanomaterials such as gold nanoparticles, carbon-based nanostructures, metal–organic frameworks, and quantum dots have been incorporated in new designs of biosensors, which are capable of detecting biomarkers with high sensitivity, label-free, and at a very fast rate. Nanotechnology and related high-end analytical instruments, including electrochemical sensors, optical biosensors, microfluidic, and lab-on-a-chip, are also changing the game in AD diagnostics (4).

This review points to the emerging strategies of analysis which use nanotechnology to attain quick, precise, and clinically significant detection of the biomarkers of Alzheimer disease. This paper will close the gap between the newly developed nanoscale technologies of sensing and their applications in the real-world clinical diagnostics by synthesizing the latest developments and assessing their translational potential (5).

Overview of Alzheimer's disease and Current Biomarker Landscape

The complex sequence of cellular and molecular events, which eventually results in the dysfunction of the synapses, the loss of neurons and the development of a progressive cognitive impairment is the characteristic feature of AD (6). The pathology of AD focuses on the abnormality of the amyloid precursor protein (APP) which is a transmembrane glycoprotein that is highly expressed in neurons. In physiological conditions, APP is regulated mainly by the non-amyloidogenic pathway via 8 -secretase, producing soluble APP-a fragments, which do not develop toxic aggregates. In AD, however, there is a switch to the amyloidogenic pathway in which amyloid-2 (A2) peptides, and, more specifically, amyloid-24 (A24) and amyloid-25 (A25) are produced by sequential cleavage with 2 -secretase (BACE1) and 7 -secretase. These biochemical pathways are shown in Figure 1 that underscores the structure of APP, cleavage sites, and that certain mutations like A673V can change A 0 production, resistance to

degradation, propensity to fibrillize, and A 040/A 042 ratios. All these modifications contribute to augmented ABB load and augmented plaque development (7).

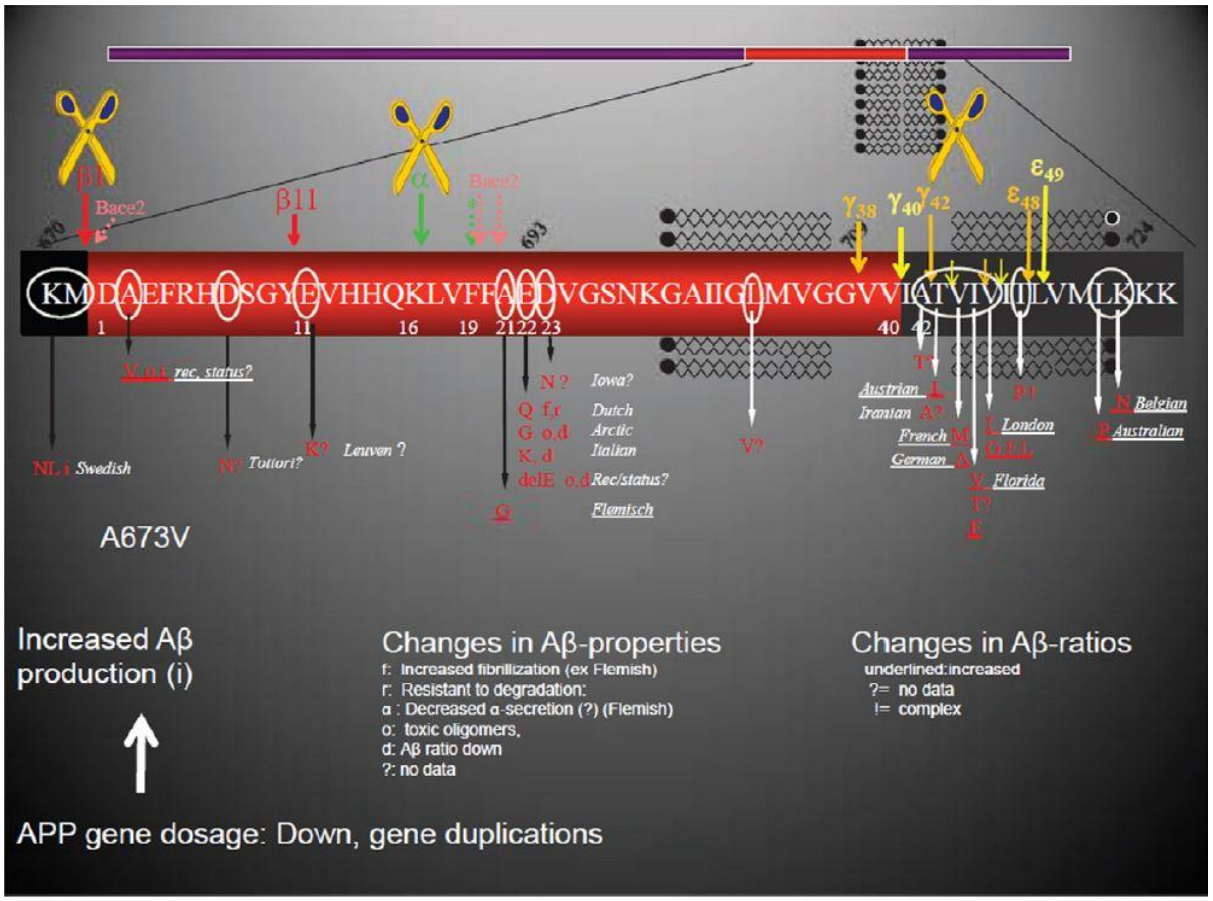


Fig 1: Overview of dominantly inherited mutations were grouped around the sites of the amyloid beta (A) protein sequence of 2 -secretase, 2 -secretase and2 -secretase. The mutation seen (white circle) and the amino acid replacement (red font) (Bateman et al., 2011). To interpret the reference to color in this figure legend, the reader is referred to the version on the web.

The formation of extracellular A2 peptides is followed by the subsequent behavior of the latter in the neural environment becoming a decisive factor in the disease development. Soluble A B monomers are capable of forming oligomers, which are the most neurotoxic components because they are able to disrupt synaptic signaling. With time, these oligomers then develop to be insoluble plaques of amyloid (8). In Figure 2, the neuron-astrocytes-microglia-vessels interaction is dynamic and contributes to the regulation of ABB transport, clearance, and deposition. Apolipoprotein E (ApoE), primarily produced by the astrocytes, is largely involved in A 8 aggregation propensity and A 2 trafficking, and various ApoE isoforms affect clearance ability. Microglial cells are trying to ingest A 2 but can become dysfunctional or inflammatory as the disease spreads. Also, A1 interacts with surfaces of receptors LRP1, LDLR and HSPG on neural and vascular surfaces influencing its absorption and clearance into the blood (9).

All these processes compose the basic pathological markers of AD; extracellular amyloid-2 plaques and intracellular neurofibrillary tangles made up of hyperphosphorylated tau protein. This has led to the emergence of a number of biomarker categories that are clinically relevant. These are the ratios of A2 and A40 in CSF and plasma, total tau (t-tau), phosphorylated tau (e.g., p-tau181, p-tau217), neurofilament light chain (NfL) and neuroinflammation and synaptic dysfunction. The knowledge of the relationship between these biomarkers with the underlying mechanisms as illustrated in Figures 1 and 2 gives the basis of developing fast and sensitive tools of analysis that can ultimately diagnose AD before the neurons have irrevocably damaged (10).

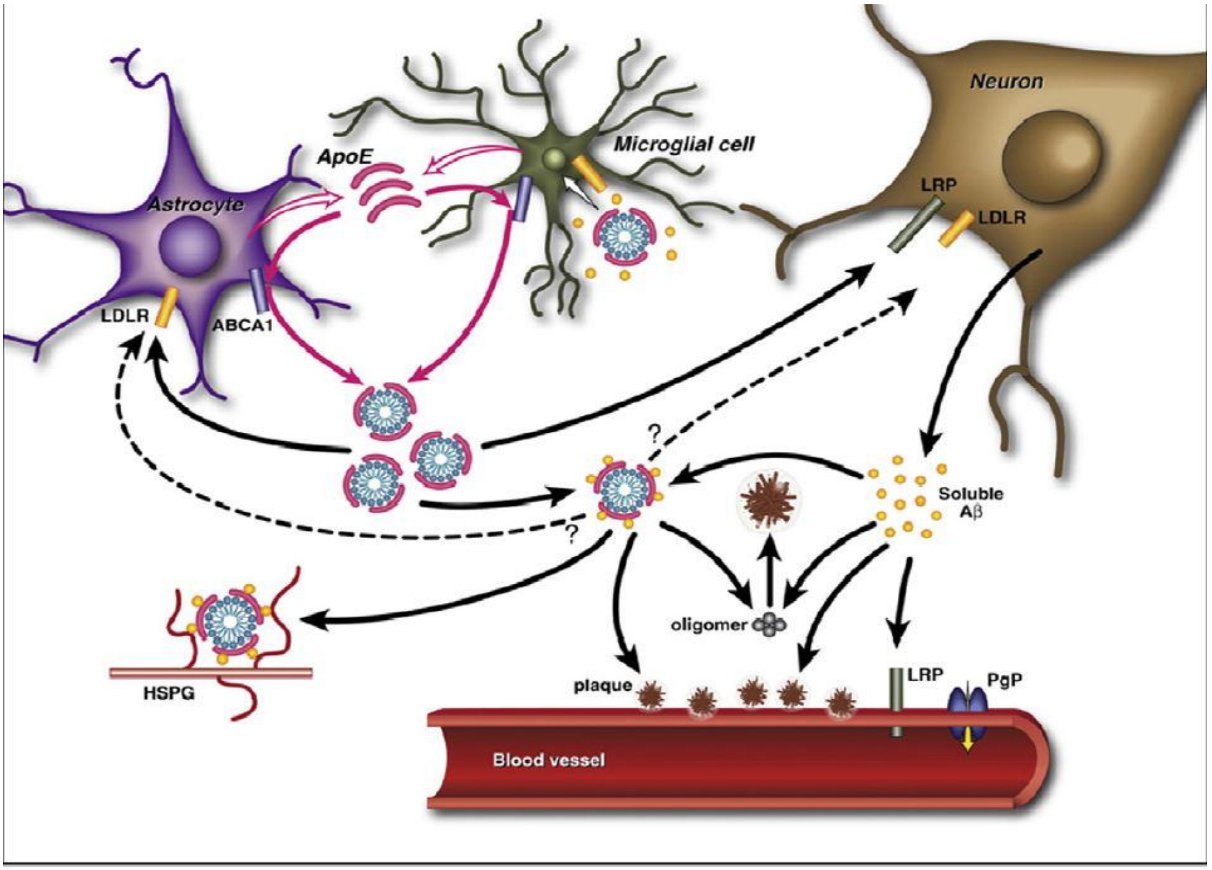


Fig. 2. Role ofApoE on Aβ peptide metabolism and deposition (Kim et al., 2009).

Furthermore

3. Limitations of Conventional Diagnostic Methods

Although there have been enormous progressions in the pathology of the Alzheimer disease (AD), the diagnostic tools that are currently in clinical application still have considerable limitations that inhibit their ability to detect the disease in its early stages and their application widely. Other traditional methods are neuropsychological testing, structural and functional neuroimaging (MRI, CT and PET), and biochemical tests done on samples of cerebrospinal fluid (CSF). Although these ways have had their role to play in the characterization of AD, they lack efficacy in the form of quick, minimally invasive, and cost effective screening solutions that are applicable in large populations (11).

Neuroimaging techniques such as amyloid-PET and tau-PET have high diagnostic specificity but have constraints whereby they are expensive to operate, they need specific imaging equipment and they have radiotracers. Likewise, A2 assays in CSF of A 2, A 0 and total tau and phosphorylated tau are considered to be some of the most dependable diagnostic methods, which, however, include lumbar puncture as an invasive intervention, which many patients prefer to avoid. Moreover, mass spectrometry and ELISA-based systems though accurate demand well-equipped labs, qualified human resources, and long processing times and thus are not suitable in point of care (POC) settings (12).

Considering these shortcomings, the conventional procedures usually do not detect AD at its preclinical or prodromal stages, when therapeutic interventions can be most effective. There has consequently been an escalating urgency to identify the need to develop fast, scalable and sensitive technologies to measure biomarkers. This diagnostic capability gap has led to the emergence of new nanotechnology-based analytical approaches that will soon turn the process of AD biomarker detection into a more user-friendly and accessible one (13).

Table 1. Key Limitations of Conventional AD Diagnostic Methods

Diagnostic Method	Limitations	Clinical Impact
Neuroimaging (PET, MRI)	High cost, limited availability, radiotracer exposure	Restricts use to specialized centers; not suitable for early mass screening
CSF Biomarker Assays	Invasive lumbar puncture, patient discomfort	Lower patient compliance, limits routine testing
ELISA & Mass Spectrometry	Long processing time, need for skilled personnel, expensive equipment	Not feasible for point-of-care or rapid diagnosis
Cognitive Testing	Low sensitivity in early stages, confounded by education/language factors	Often detects AD only after significant neuronal damage

Advances in Nanotechnology for Biomarker Detection

The novelty of nanotechnology has quickly become a revolution in the detection of biomarkers of Alzheimer disease (AD) because nanomaterials have unique physicochemical properties. With their great surface-to-volume ratio, controllable optical and electrical, and excellent bioconjugation capacity, these materials have never been seen before in terms of sensitivity and specificity in a biosensing platform. Consequently, nanotechnology detection plans are increasingly being viewed alongside the traditional diagnostic assays as potentially useful alternatives due to rapid analysis and reduced sample volumes as well as the ability to work with minimally invasive biofluids including blood, saliva, and urine (14).

Due to the superior conductivity and plasmonic characteristics, gold nanoparticles (AuNPs) have been extensively used as electrochemical and colorimetric biosensors. They are optimally suited to determine weak signals of low concentration of AD biomarkers including A2B, tau, and phosphorylated tau species (15). Moreover, carbon-based nanomaterials such as graphene, graphene oxide (GO), and carbon nanotubes (CNTs) have shown superior performance in electron transfer and high ability to load biomolecules and thus, they can detect pathogenic peptides and proteins in an ultra-sensitive manner. These nanostructures improve the biosensor sensitivity and decrease background noise which leads to higher reliability of analysis (16).

The other two technologies of emerging AD diagnostics are quantum dots (QDs) and metal-organic frameworks (MOFs). Quantum dots are capable of providing bright, stable fluorescence that can be used to image and optically detect biomarker-probe interactions, and MOFs can be customized to provide porosity and surface chemistry that can be used to selectively trap and preconcentrate biomarkers. These nanomaterials have been integrated into microfluidics and lab-on-a-chip systems, which have now driven development to high-speed and miniaturized platforms that can take point-of-care (POC)-level tests (17).

Together, together with developments of nanotechnology, the diagnostic landscape is being re-defined to allow detection of the AD biomarkers at an earlier stage, which in most cases occurs before clinical symptoms. Not only do these innovations enhance the performance of the analytical functions, but also help in the creation of small-sized, inexpensive, and easy-to-use diagnostic instruments that are likely to be used in mass screening and timely medical treatment (18,19,20).

5. Emerging Analytical Platforms Integrating Nanomaterials

Nanotechnology combined with the analytical platforms has resulted in the invention of very sensitive, fast and small systems used to detect the biomarkers of Alzheimer's disease (AD). These new platforms make use of the special characteristics of nanomaterials to improve signal transduction, molecular recognition and real time detection- functions that traditional diagnostic instruments frequently fail to achieve. Consequently, the inclusion of nanomaterials into systems is emerging as a viable option in point-of-care (POC) testing and at the screening of the illness at an early stage (20,21,22).

One of the most widely investigated platforms is the electrochemical biosensors. The inclusion of

nanomaterials, e.g. gold nanoparticles, carbon nanotubes and graphene derivatives enable such sensors to have very low limits of detection of A-beta peptides, tau, p-tau isoforms and other proteins related to AD. They are especially attractive in the context of clinical setting where speed and accessibility are the key attributes of a product (23,24,25).

Optical sensing platforms, such as surface-enhanced Raman spectroscopy (SERS) and fluorescence-based sensors, and plasmonic biosensors, also have shown tremendous potential. Nanostructures, including quantum dots, plasmonic nanorods and metal-organic frameworks, are able to improve optical reactions and enable selective detection of biomarkers-probe interactions on a high sensitivity level. These technologies have benefits of multiplexing whereby many biomarkers can be detected at the same time and this is very important in enhancing diagnostic accuracy (26,27,28).

The other significant development is the microfluidic and lab-on-a-chip systems. This can be achieved by incorporating nanomaterial-based sensing units into microchannels that enable fast processing of small samples in microchannels and automated biomarker capture. They can separate, react, and detect in one chip, which will greatly save time in analyzing and minimise dependency on operators. These systems, together with either smartphone-based readouts or even portable detectors, have great prospects of being used in decentralized and home-based monitoring (29,30,31).

Collectively, these platforms are transforming the future of AD diagnostics because they are accelerating, increasing the sensitivity, and making biomarker detection clinically more accessible (32,33,34).

Table 2. Examples of Nanomaterial-Integrated Analytical Platforms for AD Biomarker Detection

Platform Type	Integrated Nanomaterials	Biomarkers Targeted	Key Advantages
Electrochemical Sensors	AuNPs, CNTs, Graphene	Aβ42, Aβ40, Tau, p-Tau	High sensitivity, low cost, rapid response
Optical Sensors	Quantum Dots, Plasmonic Nanorods, MOFs	Aβ peptides, Tau isoforms	Strong optical signals, multiplexing capability
SERS-based Platforms	Metallic Nanostructures (Ag, Au)	Aβ oligomers, Tau	Ultra-sensitive detection, label-free measurement
Microfluidic Devices	Nanocomposites, Magnetic Nanoparticles	Multiple AD biomarkers	Low sample volume, automation, POC feasibility
Lab-on-Chip Systems	Graphene-based films, AuNP-modified electrodes	Aβ, Tau, Inflammatory markers	Fast processing, compact design, portable readout

Clinical Applications and Translation Challenges

Even though nanotechnology-based platforms of analysis have demonstrated significant potential in the laboratory, there are a number of issues with translating these advancements into clinical practice. Clinical utility of any diagnostic tool is not only based on its performance in terms of analysis but also on other factors like reproducibility, scalability, regulatory approval and compatibility with the real-world clinical environment. In the case of Alzheimer disease (AD), where there is a need to detect the condition at an early stage and precisely, the bench-bedside path will have to traverse technical and logistical obstacles. (35,36,37).

Clinical validity and reproducibility in various patient groups is one of the key issues. Biosensors based on nanomaterials often display a high level of sensitivity in regulated laboratory environments, but they can be prone to changes in sample composition, biomarker levels and non-specific substances that are often present in biological fluids. This inconsistency brings up the issue of assay stability and reliability in use in a standard clinical setting (38,39).

The other impediment is a concern relating to standardization and mass production of nanomaterials. The

accurate manipulation of the nanoparticle size, morphology, and surface chemistry is a key to the stability of biosensors functionality. Nonetheless, the process of increasing production keeping the uniformity is complicated and expensive. FDA and EMA also have stringent characterization of nanomaterials including evaluation of possible toxicity and long-term biocompatibility to be used in clinics (40,41).

To implement these technologies in clinical practice, it is necessary to resolve operational and infrastructure-related limitations. The introduction of nanotechnology-based diagnostic platforms might require the use of new equipment, training of healthcare staff, or changes to the laboratory procedures. These options may be counterintuitive in resource constrained settings as the diagnostic potential of the technologies is high (42,43).

Moreover, despite the efforts of point-of-care (POC) devices to make the process of biomarkers detection easier, it is important to guarantee the accuracy of the data, ease of use, and connectivity. Devices that are aimed at the home-based or decentralized testing should be capable of giving reliable results without any technical knowledge. Their meshing with digital health services, electronic medical records and telemedicine systems can positively affect the monitoring but also causes some concerns associated with data security and privacy (44).

In spite of such difficulties, the clinical potential of AD diagnostics based on nanotechnology takes a considerable scale. Further improvements in nanofabrication, microfluidics and biosensor engineering coupled with stringent clinical testing are likely to bridge the experimental innovation and clinical practice divide. These technologies promise to bring about earlier diagnosis, personal monitoring, and clinical management that is more effective in the treatment of Alzheimer disease as they become more mature (45).

Conclusion and Future Perspectives

Early and quick identification of the biomarkers of the Alzheimer disease is a pressing issue to enhance the diagnosis of patients and their treatment. Although traditional diagnostic procedures have been useful they have been hampered with limitations that necessitate the requirement of more accessible, sensitive and minimally invasive solutions. Leveraging nanotechnology has provided fresh horizons in the development of highly sensitive analysis platforms that can be used to detect low-abundance biomarkers more quickly and accurately.

These technologies are still yet to be fully integrated into the clinical practice although this work is very promising, several challenges have to be overcome first such as standardization, mass production, regulatory approval and real world validation. On-going interdisciplinary partnerships among clinicians, engineers and materials scientists will be important in order to develop and pin-point these platforms and make them clinically prepared.

Finally, biosensing approaches based on nanotechnology have enormous potential to revolutionize the AD diagnostics and earlier diagnosing, personalized monitoring, and more effective therapeutic interventions will be offered in the future.

References

1. Abramowski, D., Wiederhold, K.H., Furrer, U., Jaton, A.L., Neuenschwander, A., Runser, M.J., Danner, S., Reichwald, J., Ammaturo, D., Staab, D., Stoeckli, M., Rueeger, H., Neumann, U., Staufenbiel, M., 2008. Dynamics of Abeta turnover and deposition in different beta-amyloid precursor protein transgenic mouse models following gamma- secretase inhibition. J. Pharmacol. Exp. Ther. 327, 411–424.
2. Ahmed, M., Davis, J., Aucoin, D., Sato, T., Ahuja, S., Aimoto, S., Elliott, J.I., Van Nostrand, W.E., Smith, S.O., 2010. Structural conversion ofneurotoxic amyloid-β1-42 oligomers to fibrils. Nat. Struct. Mol. Biol. 17, 561–567.

3. Aisen, P.S., Gauthier, S., Ferris, S.H., Saumier, D., Haine, D., Garceau, D., Duong, A., Suhy, J., Oh, J., Lau, W.C., Sampalis, J., 2011. Tramiprosate in mild-to-moderate Alzheimer's disease—a randomized, double-blind, placebo-controlled, multi-centre study (the Alphase study). Arch. Med. Sci. 7, 102–111.

4. Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., Cole, G.M., Cooper, N.R., Eikelenboom, P., Emmerling, M., Fiebich, B.L., Finch, C.E., Frautschy, S., Griffin, W.S., Hampel, H., Hull, M., et al., 2000. Inflammation and Alzheimer's disease. Neurobiol. Aging 21, 383–421.

5. Allsop, D., Howlett, D., Christie, G., Karran, E., 1998. Fibrillogenesis of beta-amyloid. Biochem. Soc. Trans. 26, 459–463

6. Alzheimer's & Related Disorders Society of India, 2010. In: Shaji, K.S., Jotheeswaran, A.T., Girish, N., Bharath, Srikala, Dias, Amit, Pattabiraman, Meera, Varghese, Mathew (Eds.), The dementia India report: prevalence, impact, costs and services for dementia. ARDSI, New Delhi. ISBN: 978-81-920341-0-2.

7. Alzheimer's Association, 2012. Alzheimer's disease facts and figures. Alzheimers Dement. 8, 131–168.

8. Andreadis, A., Brown, W.M., Kosik, K.S., 1992. Structure and novel exons ofthe human tau gene. Biochemistry 31, 10626–10633.

9. Auld, D.S., Kar, S., Quirion, R., 1998. β-Amyloid peptides as direct cholinergic neuromodulators: a missing link? Trends Neurosci. 21, 43–49.

10. Backstrom, J.R., Lim, G.P., Cullen, M.J., Tokes, Z.A., 1996. Matrix metalloproteinase-9 (MMP-9) is synthesized in neurons of the human hippocampus and is capable of degrading the amyloid-beta peptide (1–40). J. Neurosci. 16, 7910–7919.

11. Bahr, B.A., Bendiske, J., 2002. The neuropathogenic contributions of lysosomal dysfunc- tion. J. Neurochem. 83, 481–489.

12. Bali, J., Halima, S.B., Felmy, B., Goodger, Z., Zurbriggen, S., Rajendran, L., 2010. Cellular basis of Alzheimer's disease. Ann. Indian Acad. Neurol. 13, S89–S93.

13. Ballatore, C., Lee, V.M., Trojanowski, J.Q., 2007. Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. Nat. Rev. Neurosci. 8, 663–672.

14. Barage, S.H., Sonawane, K.D., 2014. Exploring mode of phosphoramidon and Aβ peptide binding to hECE-1 by molecular dynamics and docking studies. Protein Pept. Lett. 21, 140–152.

15. Barage, S.H., Jalkute, C.B., Dhanavade, M.J., Sonawane, K.D., 2014. Simulated interactions between endothelin converting enzyme and Aβ peptide: insights into subsite recog- nition and cleavage mechanism. Int. J. Pept. Res. Ther. http://dx.doi.org/10.1007/ s10989-014-9403-2.

16. Barnes, K., Walkden, B.J., Wilkinson, T.C., Turner, A.J., 1997. Expression of endothelin- converting enzyme in both neuroblastoma and glial cell lines and its localization in rat hippocampus. J. Neurochem. 68, 570–577.

17. Bartus, R.T., Dean 3rd, R.L., Beer, B., Lippa, A.S., 1982. The cholinergic hypothesis ofgeriatric memory dysfunction. Science 217, 408–414.

18. Bateman, R.J., Aisen, P.S., De Strooper, B., Fox, N.C., Lemere, C.A., Ringman, J.M., Salloway, S., Sperling, R.A., Windisch, M., Xiong, C., 2011. Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. Alzheimers Res. Ther. 3, 1–13.

19. Bates, K.A., Verdile, G., Li, Q.X., Ames, D., Hudson, P., Masters, C.L., Martins, R.N., 2009. Clearance mechanisms of Alzheimer's amyloid-beta peptide: implications for thera- peutic design and diagnostic tests. Mol. Psychiatry 14, 469–486.

20. Behan, D.P., Khongsaly, O., Owens, M.J., Chung, H.D., Nemeroff, C.B., De Souza, E.B., 1997. Corticotropin-releasing factor (CRF), CRF-binding protein (CRF-BP), and CRF/CRF-BP complex in Alzheimer's disease and control postmortem human brain. J. Neurochem. 68, 2053–2060.

21. Bentahir, M., Nyabi, O., Verhamme, J., Tolia, A., Horre, K., Wiltfang, J., Esselmann, H., De Strooper, B., 2006. Presenilin clinical mutations can affect gamma-secretase activity by different mechanisms. J. Neurochem. 96, 732–742.

22. Benzinc, William c., Mufson, Elliott j., 1995. Apolipoprotein E immunoreactivity within neurofibrillaty tangles: relationship to tau and PHF in Alzheimer's disease. Exp. Neurol. 132, 162–171.

23. Bertram, L., Tanzi, R.E., 2008. Thirty years ofAlzheimer's disease genetics: the implications of systematic meta-analyses. Nat. Rev. Neurosci. 9, 768–778.

24. Bertram, L., Lill, C.M., Tanzi, R.E., 2010. The genetics of Alzheimer disease: back to the future. Neuron 68, 270–281.

25. Black, R.A., Rauch, C.T., Kozlosky, C.J., Peschon, J.J., Slack, J.L., Wolfson, M.F., Castner, B.J., Stocking, K.L., Reddy, P., Srinivasan, S., et al., 1997. A metalloproteinase disintegrin that releases tumour-necrosis factor-alpha from cells. Nature 385, 729–733.

26. Black, R.S., Sperling, R.A., Safirstein, B., Motter, R.N., Pallay, A., Nichols, A., Grundman, M., 2010. A single ascending dose study of bapineuzumab in patients with Alzheimer disease. Alzheimer Dis. Assoc. Disord. 24, 198–203.

27. Blennow, K., de Leon, M.J., Zetterberg, H., 2006. Alzheimer's disease. Lancet 368, 387–403.

28. Borgegard, T., Gustavsson, S., Nilsson, C., Parpal,S., Klintenberg, R.,Berg, A.L., Rosqvist, S., Serneels, L., Svensson, S., Olsson, F., et al., 2012. Alzheimer's disease: presenilin 2-sparing gamma-secretase inhibition is a tolerable Abeta peptide- lowering strategy. J. Neurosci. 32, 17297–17305.

29. Bowen, D.M., Smith, C.B., White, P., Davison, A.N., 1976. Neurotransmitter-related enzymes and indices of hypoxia in senile dementia and other abiotrophies. Brain 99, 459–496.

30. Braak, H., Braak, E., 1994. Morphological criteria for the recognition of Alzheimer's disease and the distribution pattern of cortical changes related to this disorder. Neurobiol. Aging 15, 355–356 (discussion 379–380).

31. Brandt, R., Leger, J., Lee, G., 1995. Interaction of tau with the neural plasma membrane mediated by tau's amino-terminal projection domain. J. Cell Biol. 131, 1327–1340.

32. Brooks, W.S., Kwok, J.B., Kril, J.J., Broe, G.A., Blumbergs, P.C., Tannenberg, A.E., Lamont, P.J.,Hedges, P.,Schofield, P.R., 2003. Alzheimer's disease with spastic paraparesis and ‘cotton wool’ plaques: two pedigrees with PS-1 exon 9 deletions. Brain 126, 783–791.

33. Bruins, M.E., Janssen, A.E., Boom, R.M., 2001. Thermozymes and their applications: a review of recent literature and patents. Appl. Microbiol. Biotechnol. 90, 155–186.

34. Burgos-Ramos, E., Hervas-Aguilar, A., Aguado-Llera, D., Puebla-Jimenez, L., Hernandez- Pinto, A.M., Barrios, V., Arilla-Ferreiro, E., 2008. Somatostatin and Alzheimer's disease. Mol. Cell. Endocrinol. 286, 104–111.

35. Burns, A., lliffe, S., 2009. Alzheimer's disease. BMJ 338, b158. Burns, A., Jacoby, R., Levy, R., 1990. Psychiatric phenomena in Alzheimer's disease. I: disorders of thought content. Br. J. Psychiatry J. Ment. Sci. 157, 72–76 (92-74).

36. Butler, M., Shelanski, M.L., 1986. Microheterogeneity of microtubule-associated tau proteins is due to differences in phosphorylation. J. Neurochem. 47, 1517–1522.

37. Caccamo, A., Oddo, S., Billings, L.M., Green, K.N., Martinez-Coria, H., Fisher, A., LaFerla, F.M., 2006. M1 receptors play a central role inmodulating AD-like pathology in transgenic mice. Neuron 49, 671–682.

38. Caldwell, C.C., Yao, J., Brinton, R.D., 2014. Targeting the prodromal stage of Alzheimer's disease: bioenergetic and mitochondrial opportunities. Neurotherapeutics. http:// dx.doi.org/10.1007/s13311-014-0324-8.

39. Campion, D., Flaman, J.M., Brice, A., Hannequin, D., Dubois, B., Martin, C., Moreau, V., Charbonnier, F., Didierjean, O., Tardieu, S., et al., 1995. Mutations of the presenilin I gene in families with early-onset Alzheimer's disease. Hum. Mol. Genet. 4, 2373–2377.

40. Carson, J.A., Turner, A.J., 2002. Beta-amyloid catabolism: roles for neprilysin (NEP) and other metallopeptidases? J. Neurochem. 81, 1–8.

41. Carty, N.C., Nash, K., Lee, D., Mercer, M., Gottschall, P.E., Meyers, C., Muzyczka, N., Gordon, M.N., Morgan, D., 2008. Adeno-associated viral (AAV) serotype 5 vector mediated gene delivery of endothelin-converting enzyme reduces Abeta deposits in APP + PS1 transgenic mice. Mol. Ther. 16, 1580–1586.

42. Castano, E.M., Prelli, F., Wisniewski, T., Golabek, A., Kumar, R.A., Soto, C., Frangione, B., 1995. Fibrillogenesis inAlzheimer's disease ofamyloid beta peptides and apolipoprotein E. Biochem. J. 306 (Pt 2), 599–604.

43. Cataldo, A.M., Hamilton, D.J., Nixon, R.A., 1994. Lysosomal abnormalities in degenerating neurons link neuronal compromise to senile plaque development in Alzheimer disease. Brain Res. 640, 68–80.

44. Chen, G., Chen, K.S., Knox, J., Inglis, J., Bernard, A., Martin, S.J., Justice, A., McConlogue, L., Games, D., Freedman, S.B., et al., 2000. A learning deficit related to age and beta- amyloid plaques in a mouse model of Alzheimer's disease. Nature 408, 975–979.

45. Choi, D.S., Wang, D., Yu, G.Q., Zhu, G., Kharazia, V.N., Paredes, J.P., Chang, W.S., Deitchman, J.K., Mucke, L., Messing, R.O., 2006. PKCepsilon increases endothelin converting enzyme activity and reduces amyloid plaque pathology in transgenic mice. Proc. Natl. Acad. Sci. U. S. A. 103, 8215–8220.