

Rocka Agata, Psiuk Dominika, Piędel Faustyna, Żak Klaudia, Brzezińska Agnieszka. Nanotechnology in Amyloid Lateral Sclerosis (ALS) - review. *Journal of Education, Health and Sport*. 2020;10(7):197-203. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2020.10.07.021>  
<https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2020.10.07.021>  
<https://zenodo.org/record/3957538>

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

© The Authors 2020;

This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland  
Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike. (<http://creativecommons.org/licenses/by-nc-sa/4.0/>) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.  
The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 25.06.2020. Revised: 05.07.2020. Accepted: 23.07.2020.

## Nanotechnology in Amyloid Lateral Sclerosis (ALS) - review

Agata Rocka<sup>1</sup>, Dominika Psiuk<sup>1</sup>, Faustyna Piędel<sup>1</sup>, Klaudia Żak<sup>1</sup>,  
Agnieszka Brzezińska<sup>1</sup>

<sup>1</sup>Faculty of Medicine, Medical University of Lublin, Chodźki Street 19, 20-093 Lublin, Poland

Agata Rocka; agatarocka2@gmail.com; ORCID:0000-0003-4738-3160

Dominika Psiuk; dominika.psiuk@gmail.com; ORCID: 0000-0003-3319-3489

Faustyna Piędel; faustyna.piedel@gmail.com; ORCID:0000-0002-8280-498X

Klaudia Żak; zakklaudia3@gmail.com; ORCID:0000-0003-2421-2553

Agnieszka Brzezińska; brzezinska2agnieszka@gmail.com; ORCID: 0000-0001-5730-8813

### SUMMARY

**Introduction and purpose:** Amyloid Lateral Sclerosis (ALS) is progressive, cachectic neurodegenerative disease. The lack of effective therapy, which could prevent disease progression and minimize degeneration of motor neurons, contributes to unceasing exploration for novel therapeutic methods. Nanotechnology remains one of the most promising areas among novel agents in neurodegenerative diseases treatment. Recent studies have shown that application of nanoparticles for drug delivery might develop greater effects in ALS treatment. The aim of the study is to analyze literature (database PubMed) for potential nanotechnology usage in ALS therapy.

**A brief description of the state of knowledge:** Nanotechnology is one of the most promising agent in many aspects of medicine, for example drug delivery, cancer therapy and wound healing. There are different kinds of nanoparticles for example gold, silver, metal-oxide, silica, lipid-based. There was one randomized clinical trial that used nanoparticles to improve bioavailability of turmeric, potential anti-inflammatory agent, in patients with ALS. This study showed that using nanoparticles is safe. Most of the recent analysis were carried out using animal models. Promising results were demonstrated in many studies.

**Conclusions:** The available research confirms the usefulness of nanotechnology in increasing the effectiveness of ALS treatment. Animal studies have produced surprising results. Nanoparticles can improve the absorption of drugs and bioavailability, affecting the clinical improvement of patients, which gives new possibilities and therapeutic perspectives for patients with ALS. Personalized therapy based on using molecules and profound control of such therapy can greatly improve the effectiveness of treating people with ALS.

**Key words:** nanotechnology, nanoparticles, neurology, ALS

### **Introduction and purpose:**

Amyloid Lateral Sclerosis (ALS), also known as Motor Neurone Disease (MND), is progressive, cachectic neurodegenerative disease, invading both upper and lower motor neurons and leading to loss of ability to control muscles and thereafter to paralysis. The disease is lethal and death is the consequence of respiratory failure, which is caused by respiratory muscles inefficiency [1,2]. The etiology of disease remains unknown, pathogenesis unclear. In Poland nearly 3 thousand patients happen to suffer from ALS [3]. In Europe annual morbidity rate is 2,16, while in the world it is about 1,9 per 100 000 people [4,5]. It is forecasted that in 2040 number of ALS cases would increase to 376 674 [6]. Nowadays there is no efficient therapy in order to treat ALS. The most recent FDA-approved medicines are riluzol and edaravone, yet few therapeutic options force to search for novel agents in ALS treatment. Exploring new therapeutic areas will hopefully contribute to improve patients life quality and extend their lifetime [7, 8, 9]. One of the most promising domain is nanotechnology, as nanoparticles are widely known for enabling drug delivery although the blood-brain barrier (BBB), as BBB is one of the main limitation in central nervous system diseases treatment. Nanoparticles not only provide better therapeutic effects, but also are believed to demonstrate neuroprotective and neuroactive activities [10].

This review analysed the available studies using the "PubMed" database, and the search criteria used the search term "nanotechnology amyotrophic lateral sclerosis". The work focuses on available and conducted trials. The aim of the work is to assess the use of nanotechnology in the treatment of ALS.

## **Description of the state of knowledge:**

### **Nanotechnology in neurology science:**

Nanotechnology is novel research area, which refers to structures, devices, systems and functions at atomic and molecular scale. Nowadays, it's one of the most promising agent in many aspects of medicine, for example drug delivery, cancer therapy and wound healing. Currently clinical approved nanotechnology products are simply constructed and do not comprise drug components, however the real phenomenon is behind the binding nanoparticles with medicines and bioactive molecules, on which aspects latest studies focus [11,12,13].

There was a few studies based on applications of carbon nanotubes (CNTs) both *in vitro* and *in vivo*. *In vitro* studies showed that CNT application can influence neuronal differentiation, neural stimulation and neural interface. Specific levels of nanotubes mediate neuronal growth and differentiation, by causing neural cells to manifest a stronger reaction on cellular adherence and migration and protein expression. Longer and more branching of neurons were also distinguished when using CNTs. Studies shown, that combining nanotubes with growth substrates is even more beneficial and can be used for imitating nerve construction aiming to nerve regeneration. Moreover, CNTs was observed to regulate human neural stem cells (hNSCs) by conducting its differentiation, excitation and maturation. Studies suggest, that usage of CNTs could be mighty beneficial in various neurological diseases treatment, such as tumors, neurodegenerative diseases and stroke [14]. Nanodiamonds (NDs) for example were responsible for upregulation of anti-apoptotic factor STAT3 and stimulation of brain-derived neurotrophic factor (BDNF), which regulates neuronal growth. NDs also demonstrated ability to alter the uptake and storage of neurotransmitters such as GABA and glutamate, which are crucial in neurodegenerative disorders pathology. Those findings not only revealed neuroprotective aspects of nanoparticles, but also implied possibility to exploit nanotechnology for bioimaging, thus earlier disease detection and proper intervention [15].

### **Types of nanoparticles used in ALS**

Among all nanoparticles which are used in ALS, we can enumerate such ones as gold, silver, metal-oxide, silica, lipid-based nanoparticles [16]. Here, we describe some of those, which have the biggest potential in neurodegenerative diseases.

The first group - metal nanoparticles include gold, silver and metal-oxide nanoparticles, among which gold nanoparticles are the best documented. All of them readily cross blood-brain barrier (BBB), have good optical properties, can reduce oxidative stress. They are also characterized by cytotoxicity, difficulty to target and lack of degradation. Gold nanoparticles (AuNPs) are known due to optical properties of gold core and a surface plasmon resonance (SPR), which allow nanoparticles absorb light [17,18]. It can be utilized in imaging through X-rays or micro-CT scanning [18,19]. Silver nanoparticles (AgNPs) can be injected intraperitoneally and then they can reach the hippocampus fast [20]. In addition, silver has antibacterial characteristics, which cause anti-inflammatory effect and reduce reactive oxygen species (ROS). However, AgNPs are toxic for neurons and can accumulate in central nervous system (CNS) [21,22,23]. Metal-oxide nanoparticles such as iron oxide (Fe<sub>3</sub>O<sub>4</sub>), cerium oxide (CeO) and zinc oxide (ZnO) are mainly used to reduce oxidative stress

in the brain, their properties are used in magnetic resonance imaging (MRI) [24]. Cerium and zinc oxide can reduce nitrosative stress, common in neurodegenerative diseases [25].

In the second group quantum dots (QDs) are qualified. They have long photostability, good optical properties, they are biocompatible. The other difference is a way of administration - QDs can be aerosolized and they reach the brain rapidly, which, in consequence, can induce pro-inflammatory response of microglia. The other disadvantage of this nanoparticle is their small size which limits drug delivery [26,27,28].

The next group - lipid nanoparticles include liposomes, micelles, exosomes. Liposomes, made of lipid bilayers, are one of the most popular nano carriers, because they can carry both hydrophilic and lipophilic compounds [29]. One of the studies developed liposomes which could enhance delivery of siRNA or plasmid DNA to the cells of the brain, thanks to which treatment with stem cell was more effective [30]. Liposomes can be used in Alzheimer's Disease, because they reduced apoptosis, cleared  $\beta$ -amyloid plaques in neurons and induced neurogenesis [28]. Micelles are lipid monolayers, much smaller than liposomes, so that micelles easily pass the BBB [31]. Exosomes can contain any cellular molecule for example proteins, lipids, DNA, RNA and siRNA. Like others lipid nanoparticles, they cross the BBB easily. In addition, they can be naturally observed in cerebrospinal fluid (CSF) [32].

#### **Available trials in the literature:**

There is one double-blind, randomized trial, which enhance the safety and efficacy of nanocurcumin as an anti-inflammatory and antioxidant in adults with amyotrophic lateral sclerosis (ALS). To take advantage of the absorption of curcumin, gelatin nanoparticles (nanomicelles) SinaCurcumin were used. Fifty four patients with ALS were randomly assigned into two groups - one control group receiving placebo and other receiving nanocurcumin and riluzole, the novel drug approved for ALS therapy. The study showed that using nanocurcumin is safe and demonstrated longer survival probability when compared with placebo [33].

The study conducted by Marcuzzo S. et al. confirmed the effectiveness of using gold nanoparticles (NPs) as a carrier for the FM19G11 factor (hypoxia-inducible factor modulator). The authors of the study emphasized that FM19G11 is very likely to be able to activate the PI3K / AKT and UCP2 signal transduction pathway, which by inducing SOX2, OCT4, TERT and miR-19a genes affects epSPC (ependymal stem progenitor cells) cells in the spinal cord by inducing their proliferation and self-renewal. The effect on the proliferation of epSPC cells may be a potential pathway in counteracting neurodegeneration. Researchers confirmed that administration of FM19G11 with NP is more effective than administration of FM19G11 alone. NP probably contribute to the penetration of a more concentrated dose of the drug into the cell, but the study did not show a direct effect of NP on epSPC proliferation [34].

Other study exploring nanotechnology in ALS pathogenesis and treatment shows the potential use of combining cerium with nanoparticles (CeNPs). Cerium exhibits antioxidant properties, whereas the role of oxidative stress in the pathomechanism of ALS is strongly emphasized. Nanoparticles would promote cerium penetration into the central nervous system and they also show a relatively long duration and activity in brain tissue. An *in vitro* model and mice as experimental animals were used for this study. In the *in vitro* model, CeNPs

demonstrated the ability to resist various forms of oxidative stress in brain tissue, and showed a significant extension of cell viability, with the neuroprotective effect being revealed at much higher doses. This refers to the length and quality of mice lives - in the CeNPs group the rate of decline in the number of mice was lower and animals from this group were less likely to fall over [35].

The Nabi B et al study presents promising results of using nanoparticles and riluzole in order to improve the penetration across the blood-brain barrier. *In vivo* study used rats as experimental animals. Rats were randomized into four groups, in which the first groups received RIZ and the others received RIZ, RIZ CSNPs and RIZ-Tf CSNP respectively. In the groups treated with RIZ CSNP and RIZ-Tf CSNP, a significant reduction in oxidative stress was noted. The results of the pharmacokinetic study showed that CSNP RIZ-Tf nanoparticles were significantly better delivered to the brain via the intranasal route compared to the RIZ solution. This suggests a promising therapeutic approach to administering riluzole to patients with ALS [36].

### **Conclusions**

Available studies confirm the usefulness of nanotechnology in increasing the effectiveness of ALS treatment. So far, animal studies have produced promising results. Nanoparticles can improve drug bioavailability and thus improve clinical outcomes, which gives new opportunities in treating ALS patients. Those findings also implied possibility to exploit nanotechnology for bioimaging and afterwards earlier disease detection and proper intervention.

### **Bibliography:**

- 1.Orsini M, Oliveira AB, Nascimento OJ, Reis CH, Leite MA, de Souza JA, Pupe C, de Souza OG, Bastos VH, de Freitas MR, Teixeira S, Bruno C, Davidovich E, Smidt B. Amyotrophic Lateral Sclerosis: New Perspectives and Update. *Neurol Int.* 2015 Sep 24;7(2):5885.
- 2.Oskarsson B, Gendron TF, Staff NP. Amyotrophic Lateral Sclerosis: An Update for 2018. *Mayo Clin Proc.* 2018;93(11):1617-1628.
- 3.Kubiszewska J, Kwieciński H. Stwardnienie boczne zanikowe. *Postępy Nauk Med* 2010; 6: 440–448.
- 4.Logroscino G, Traynor BJ, Hardiman O, Chiò A, Mitchell D, Swingler RJ, Millul A, Benn E, Beghi E; EURALS. Incidence of amyotrophic lateral sclerosis in Europe. *J Neurol Neurosurg Psychiatry.* 2010 Apr;81(4):385-90.
- 5.Chiò A. et al. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. *Neuroepidemiology* 41, 118–130 (2013).
- 6.Arthur KC, Calvo A, Price TR, Geiger JT, Chiò A, Traynor BJ. Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. *Nat Commun.* 2016 Aug 11;7:12408. doi: 10.1038/ncomms12408. PMID: 27510634; PMCID: PMC4987527.
- 7.Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. *N Engl J Med.* 1994;330(9):585-591.
- 8.Orrell R.W. Motor neuron disease: Systematic reviews of treatment for ALS and SMA. *Br. Med. Bull.* 2009;93:145–159.

9. Bhandari R, Kuhad A, Kuhad A. Edaravone: a new hope for deadly amyotrophic lateral sclerosis. *Drugs Today (Barc)*. 2018;54(6):349-360.
10. Mazibuko Z, Choonara YE, Kumar P, et al. A review of the potential role of nano-enabled drug delivery technologies in amyotrophic lateral sclerosis: lessons learned from other neurodegenerative disorders. *J Pharm Sci*. 2015;104(4):1213-1229.
11. Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. *ACS Nano*. 2009;3(1):16-20.
12. Bayda S, Adeel M, Tuccinardi T, Cordani M, Rizzolio F. The History of Nanoscience and Nanotechnology: From Chemical-Physical Applications to Nanomedicine. *Molecules*. 2019;25(1):112. Published 2019 Dec 27.
13. Saeedi M, Eslamifar M, Khezri K, Dizaj SM. Applications of nanotechnology in drug delivery to the central nervous system. *Biomed Pharmacother*. 2019;111:666-675.
14. Xiang C, Zhang Y, Guo W, Liang XJ. Biomimetic carbon nanotubes for neurological disease therapeutics as inherent medication. *Acta Pharm Sin B*. 2020;10(2):239-248.
15. Saraf J, Kalia K, Bhattacharya P, Tekade RK. Growing synergy of nanodiamonds in neurodegenerative interventions. *Drug Discov Today*. 2019;24(2):584-594. doi:10.1016/j.drudis.2018.10.012
16. Vissers C, Ming GL, Song H. Nanoparticle technology and stem cell therapy team up against neurodegenerative disorders. *Adv Drug Deliv Rev*. 2019 Aug;148:239-251.
17. Male D, Gromnicova R, McQuaid C. Gold Nanoparticles for Imaging and Drug Transport to the CNS. *Int Rev Neurobiol*. 2016;130:155-198.
18. Swierczewska M, Lee S, Chen X. The design and application of fluorophore-gold nanoparticle activatable probes. *Phys Chem Chem Phys*. 2011;13(21):9929-9941.
19. Curry T, Kopelman R, Shilo M, Popovtzer R. Multifunctional theranostic gold nanoparticles for targeted CT imaging and photothermal therapy. *Contrast Media Mol Imaging*. 2014;9(1):53-61.
20. Alev G, Daza J, Herrera AS, et al. Nanoparticles as Alternative Strategies for Drug Delivery to the Alzheimer Brain: Electron Microscopy Ultrastructural Analysis. *CNS Neurol Disord Drug Targets*. 2015;14(9):1235-1242.
21. Gonzalez-Carter DA, Leo BF, Ruenraroengsak P, et al. Silver nanoparticles reduce brain inflammation and related neurotoxicity through induction of H<sub>2</sub>S-synthesizing enzymes. *Sci Rep*. 2017;7:42871. Published 2017 Mar 2.
22. Tang J, Xiong L, Wang S, et al. Distribution, translocation and accumulation of silver nanoparticles in rats. *J Nanosci Nanotechnol*. 2009;9(8):4924-4932.
23. J. Skalska, L. Struzynska. Toxic effects of silver nanoparticles in mammals—does a risk. *Folia Neuropathol* 2015; 53 (4): 281-300.
24. Sintov AC, Velasco-Aguirre C, Gallardo-Toledo E, Araya E, Kogan MJ. Metal Nanoparticles as Targeted Carriers Circumventing the Blood-Brain Barrier. *Int Rev Neurobiol*. 2016;130:199-227.
25. Dowding JM, Song W, Bossy K, et al. Cerium oxide nanoparticles protect against A $\beta$ -induced mitochondrial fragmentation and neuronal cell death. *Cell Death Differ*. 2014;21(10):1622-1632.
26. Hopkins LE, Patchin ES, Chiu PL, Brandenberger C, Smiley-Jewell S, Pinkerton KE. Nose-to-brain transport of aerosolised quantum dots following acute exposure.

- Nanotoxicology. 2014 Dec;8(8):885-93. doi: 10.3109/17435390.2013.842267. PMID: 24040866; PMCID: PMC3992067.
27. Dubertret B, Skourides P, Norris DJ, Noireaux V, Brivanlou AH, Libchaber A. In vivo imaging of quantum dots encapsulated in phospholipid micelles. *Science*. 2002;298(5599):1759-1762.
28. Guo JW, Guan PP, Ding WY, et al. Erythrocyte membrane-encapsulated celecoxib improves the cognitive decline of Alzheimer's disease by concurrently inducing neurogenesis and reducing apoptosis in APP/PS1 transgenic mice. *Biomaterials*. 2017;145:106-127.
29. Zhang B, Yan W, Zhu Y, et al. Nanomaterials in Neural-Stem-Cell-Mediated Regenerative Medicine: Imaging and Treatment of Neurological Diseases. *Adv Mater*. 2018;30(17):e1705694.
30. Tamaru M, Akita H, Nakatani T, et al. Application of apolipoprotein E-modified liposomal nanoparticles as a carrier for delivering DNA and nucleic acid in the brain. *Int J Nanomedicine*. 2014;9:4267-4276.
31. Cunha S, Amaral MH, Lobo JM, Silva AC. Therapeutic Strategies for Alzheimer's and Parkinson's Diseases by Means of Drug Delivery Systems. *Curr Med Chem*. 2016;23(31):3618-3631.
32. Zhang ZG, Chopp M. Exosomes in stroke pathogenesis and therapy. *J Clin Invest*. 2016 Apr 1;126(4):1190-7.
33. Ahmadi M, Agah E, Nafissi S, et al. Safety and Efficacy of Nanocurcumin as Add-On Therapy to Riluzole in Patients With Amyotrophic Lateral Sclerosis: A Pilot Randomized Clinical Trial. *Neurotherapeutics*. 2018;15(2):430-438.
34. Marcuzzo S, Isaia D, Bonanno S, et al. FM19G11-Loaded Gold Nanoparticles Enhance the Proliferation and Self-Renewal of Ependymal Stem Progenitor Cells Derived from ALS Mice. *Cells*. 2019;8(3):279.
35. DeCoteau W, Heckman KL, Estevez AY, et al. Cerium oxide nanoparticles with antioxidant properties ameliorate strength and prolong life in mouse model of amyotrophic lateral sclerosis. *Nanomedicine*. 2016;12(8):2311-2320.
36. Bushra Nabi, Saleha Rehman, Mohammad Fazil, Saba Khan, Sanjula Baboota & Javed Ali (2020) Riluzole-loaded nanoparticles to alleviate the symptoms of neurological disorders by attenuating oxidative stress, *Drug Development and Industrial Pharmacy*, 46:3, 471-483.