



## Cover Story

## Towards a preventive treatment of Alzheimer's disease with multi-functional liposomes



In the United States alone, more than 5 million people are estimated to have Alzheimer's disease (AD). The decades of the search for a cure for AD have not been fruitful, mainly due to the lack of understanding of the disease. Current treatment of AD is based on several drugs that alleviate some symptoms but do not affect the progression of the disease [1]. The amyloidogenic amyloid- $\beta$  ( $A\beta$ ) peptide, released from the physiological protein amyloid-precursor protein (APP), has remained the primary target for a therapeutic intervention in AD for years.  $A\beta$  has been believed to play a pivotal role in the etiology of AD based on many epidemiological, genetic, biological and biochemical studies: very high levels of  $A\beta$  accumulate in the brains of AD patients; hyperphosphorylation of Tau (another hallmark of the disease) is considered a result of exposure of neurons to  $A\beta$ ; individuals with genetic mutations, leading to brain  $A\beta$  accumulation, develop AD; and patients with Down syndrome accumulating  $A\beta$  develop signs of AD with plaques with neurodegeneration. Clinical trials based on reducing  $A\beta$  levels, however, have been disappointing. It is possible that the amyloid hypothesis may not be valid, but at the same time, it is also possible that the clinical trial design has not been optimal [2].

It is nowadays recognized that brain  $A\beta$  pathophysiological alterations preceding AD are taking place decades before the appearance of the first signs of dementia. Thus, disrupting the production of  $A\beta$ , or removing the already accumulated brain amyloid after AD is diagnosed, may not be the right approach. Such an approach can hardly rescue the existing substantial synaptic and neuron loss, failing to exert a clinical benefit. This is an extremely significant point, because it suggests that the right approach in dealing with AD may be to initiate the treatments on very early stages of AD, or in general, as soon as possible. There are currently almost 40  $A\beta$ -related trials based on higher dosing of drugs and focusing on milder AD patients. The work by Professor Massimo Masserini of the University Milano-Bicocca and his colleagues at the Mario Negri Institute in this issue [3] has tested the efficacy of a multifunctional liposome formulation on a pre-symptomatic mouse model of the disease.

The Masserini team performed a long term treatment with liposomes (composed of sphingomyelin and cholesterol (1:1 molar ratio) with phosphatidic acid for  $A\beta$  binding and a modified apolipoprotein E-derived peptide) on transgenic mice, starting before they display the symptoms of the disease (such as memory impairment evaluated by the novel object recognition test), for 7 months to reach an age of 12 months, at which untreated animals show frank memory impairment and brain  $A\beta$  accumulation and plaque deposition. A significant outcome of this investigation is that an early treatment with liposomes prevents memory impairment, otherwise occurring in untreated mice. In fact, the cognitive performance in terms of memory evaluation of

treated transgenic animals remained comparable to that of healthy ones for the entire duration of the treatment. Another relevant result of this study is that brain  $A\beta$  accumulation was delayed by 30% in treated AD mice. Moreover, a magnetic resonance imaging analysis showed that the ventricle volume of treated transgenic mice was 22% smaller, while entorhinal cortex thickness was 10% higher than untreated AD mice and were comparable to healthy animals. In addition, the present study showed that a few months after discontinuation of the treatment, mice still displayed brain  $A\beta$  burden lower than untreated animals, suggesting that the treatment is effective also for a certain period after its discontinuation. Animals treated with liposomes at all doses did not show signs of central or systemic toxicity.

The study by the Masserini group suggests that a very early treatment with multi-functional liposomes is able to delay or prevent relevant features of AD, and thus, it can be a useful disease-modifying therapy. Accumulation and deposition of brain  $A\beta$  is believed to begin even 10-20 years prior to the onset of clinically detectable symptoms, providing a wide pre-symptomatic time window for intervention with preventive therapies [4]. This implies that future therapies need to rely on better and very early diagnostics, which are not yet available. Identification of potential AD patients can be followed by preventive treatment. An important point here is that the scientists have identified the right question, i.e., whether AD can be prevented, instead of how to cure the disease. The advances in new drug development and new drug delivery systems begin with asking the right questions. The study by the Masserini group has shown the right path toward finding clinically useful formulations for preventing AD.

## References

- [1] A. Kumar, A. Singh, E. Ekavali, A review on Alzheimer's disease pathophysiology and its management: an update, *Pharmacol. Rep.* 67 (2) (2015) 195–203.
- [2] S.O. Bachurin, E.V. Bovina, A.A. Ustyugov, Drugs in clinical trials for Alzheimer's Disease: The major trends, *Med. Res. Rev.* (2017), <http://dx.doi.org/10.1002/med.21434>.
- [3] S. Mancini, C. Balducci, E. Micotti, E. Tolomeo, G. Forloni, M. Masserini, F. Re, Multifunctional liposomes delay phenotype progression and prevent memory impairment in a presymptomatic stage mouse model of Alzheimer disease, *J. Control. Release* 258 (2017) 121–129.
- [4] R.A. Sperling, J. Karlawish, K.A. Johnson, Preclinical Alzheimer disease: the challenges ahead, *Nat. Rev. Neurol.* 9 (1) (2013) 54–58.

Kinam Park  
Purdue University  
Departments of Biomedical Engineering and Pharmaceutics  
West Lafayette, IN 47907, USA  
E-mail address: [kpark@purdue.edu](mailto:kpark@purdue.edu)