



## Cover story

## Antibody transport within the brain



Antibodies have become among the most promising therapeutic classes for new drug development, with many approved products for autoimmune disorders and cancer. Six of the top ten blockbuster drugs are antibody-based molecules, each with over \$6 billion in annual sales as of 2012. Antibodies are highly specific to the target epitopes, and thus are expected to be highly potent. Unfortunately, however, not all monoclonal antibodies are shown to be effective in clinical trials. Antibodies have yet to be approved to treat neurological disorders, such as Alzheimer's disease or Parkinson's disease. There remain significant questions about the optimal routes of delivery for these proteins to achieve targeted pre-clinical and clinical endpoints [1]. Indeed, immunotherapy approaches in mouse models of Alzheimer's disease have resulted in different responses depending on whether antibodies were delivered centrally or systemically [2]. Better understanding is required on the fate of antibodies at key interfaces, such as the blood–brain barrier, blood–cerebrospinal fluid barriers, and the contact points between brain cells and the extracellular fluid within the brain parenchyma [1,3].

In this issue, Professor Robert Thorne and his colleagues at the University of Wisconsin–Madison describe new findings about the diffusion and central distribution of full-length antibodies within the living brain [4]. They used the method of integrative optical imaging to quantitatively measure the diffusion of fluorescently labeled immunoglobulin G (IgG) antibodies in both water (free diffusion) and within the extracellular spaces of the rat brain (effective diffusion). Their measurements provide the first quantitative data for antibody diffusion in the brain *in vivo* and show that IgG diffuses 10-fold faster in water than in the brain extracellular space. They suggest that IgG's reduced diffusion coefficient in the brain can be partially explained by previously described effects related to hydrodynamic size and hindered diffusion in the narrow brain extracellular space, as well as rapid reversible binding to fixed elements such as cell surface receptors. They also compared *in vivo* diffusion measurements from integrative optical imaging and *ex vivo* measurements of diffusion at the brain–cerebrospinal fluid boundary following a controlled intrathecal infusion of antibody. The two methods were found to agree reasonably well. The new measurements allow them to illustrate the whole brain distribution of antibodies that may result from central infusion in different species because diffusion profiles are expected to be similar regardless of differences in brain size.

With all the resources and funding being spent on developing new disease-modifying neurotherapeutics, we still do not understand the factors that govern their entry into and distribution within the central

nervous system. The lagging discovery and development of new neurotherapeutics compared with other drugs for non-neurological indications indicate that our current understanding is very limited [1,5]. Faster diffusion in water than in the brain extracellular space is intuitive, but the 10-fold difference has many implications. Diffusion distances from the systemic circulation into the brain across cerebral capillaries are likely too short (<20  $\mu\text{m}$ ) for this slower diffusion to make that much of a difference. Thus, the lack of antibody activities observed in many clinical trials must be dependent on additional factors, including the blood–brain barrier. If, however, antibodies are delivered by central delivery approaches (intraventricular, intrathecal, and intraparenchymal), transport over much longer distances (up to many centimeters) is required, and thus, slower diffusion could have undesirable consequences. This new work from the Thorne group should help in the effort to better understand antibody transport into and within the brain, moving us one step closer to using these biotherapeutics in the treatment of brain disorders.

## References

- [1] M. Hammarlund-Udenaes, E.C.M. de Lange, R.G. Thorne (Eds.), *Drug delivery to the Brain: physiological Concepts, Methodologies and Approaches*, Springer, New York, 2014, p. 731.
- [2] D.R. Thakker, M.R. Weatherspoon, J. Harrison, T.E. Keene, D.S. Lane, W.F. Kaemmerer, G.R. Stewart, L.L. Shafer, Intracerebroventricular amyloid-beta antibodies reduce cerebral amyloid angiopathy and associated micro-hemorrhages in aged Tg2576 mice, *Proc. Natl. Acad. Sci. U. S. A.* 106 (2009) 4501–4506.
- [3] D.J. Wolak, R.G. Thorne, Diffusion of macromolecules in the brain: implications for drug delivery, *Mol. Pharm.* 10 (2013) 1492–1504.
- [4] D.J. Wolak, M.E. Pizzo, R.G. Thorne, Probing the extracellular diffusion of antibodies in brain using *in vivo* integrative optical imaging and *ex vivo* fluorescence imaging, *J. Control. Release* 197 (2015) 78–86.
- [5] D.W. Choi, R. Armitage, L.S. Brady, T. Coetzee, W. Fisher, S. Hyman, A. Pande, S. Paul, W. Potter, B. Roin, T. Sherer, Medicines for the mind: policy-based “pull” incentives for creating breakthrough CNS drugs, *Neuron* 84 (2014) 554–563.

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