

# Commentary: different immunological mechanisms govern protection from experimenta...

[Health & Medicine](#)



**ASSIGN  
BUSTER**

A commentary on

[Different immunological mechanisms govern protection from experimental stroke in young and older mice with recombinant TCR ligand therapy](#)

by Dotson, A. L., Zhu, W., Libal, N., Alkayed, N. J., and Offner, H. (2014).

*Front. Cell. Neurosci.* 8: 284. doi: 10.3389/fncel.2014.00284

Translational research to discover therapeutic targets for stroke has not fared well in developing new treatments for patients. The three most pressing issues are the choice of therapeutic target, animal model, and timepoint of administration of treatment. This manuscript “ Different immunological mechanisms govern protection from experimental stroke in young and older mice with recombinant TCR ligand therapy” provides a fresh approach toward developing stroke treatments ( [Offner et al., 2014](#) ). This study examines treating with recombinant TCR ligand (RTL) in both young and older mice 4 hours after MCAO. RTL consist of the specific domains of MHC II molecule and inhibits activation of T cells toward inflammation. The novelties of this study are several fold including: (1) inhibition of a specific immunoinflammatory pathway to avoid total immunosuppression, (2) use of elderly mice to mimic the population of human patients and (3) administration at a clinically relevant timepoint.

For a number of years, researchers have reported the entry of immune cells into the area of the infarct, which leads to further neurodegeneration.

However, targeting this immune response as a treatment for stroke remains elusive ( [Iadecola and Anrather, 2011](#) ). In the past several years, the spleen

has been reported to be a focal point for the immune system to mount an

<https://assignbuster.com/commentary-different-immunological-mechanisms-govern-protection-from-experimental-stroke-in-young-and-older-mice-with-recombinant-tcr-ligand-therapy/>

inflammatory response that exacerbates stroke-induced neurodegeneration ( [Offner et al., 2006](#) ; [Vendrame et al., 2006](#) ). In fact, ablation of the spleen reduces inflammation and neural cell death in the rodent brain after experimental stroke ( [Ajmo et al., 2008](#) ; [Ostrowski et al., 2012](#) ; [Jin et al., 2013](#) ). Blockade of interferon gamma signaling has been reported to be neuroprotective in experimental stroke ( [Liesz et al., 2009, 2011](#) ; [Seifert et al., 2014](#) ) although other groups have reported alternative results in their model systems ( [Chu et al., 2000](#) ; [Lambertsen et al., 2004](#) ). T cells are the main effector cell of this neurodegenerative response and responsible for the release of the proinflammatory interferon gamma, which is a potent activator of microglia becoming neurotoxic ( [Boehm et al., 1997](#) ; [Mebius and Kraal, 2005](#) ). Moreover, addition of interferon gamma reverses the neuroprotection provided by splenectomy, demonstrating that this cytokine plays a major role in the spleen eliciting response resulting in further neural death after stroke ( [Seifert et al., 2012](#) ). As shown in this study, administration of RTL directly inhibits the T cell response to stroke, which concomitantly deactivates the splenic response as well in both young and old mice.

This treatment reduced infarct volumes in both age groups by altering the immune response to this neurological insult. Most interestingly, the recombinant TCR ligand differentially affected components of the immune response in the elderly and young mice but still resulted in a blunted immune response reducing neurodegeneration. This study illuminated differences in the immune cell composition and inflammatory expression between these two age groups in response to stroke. This is one of the few

studies that enlists elderly animals which begins to provide insight into the differences in the physiological responses to stroke between young and the aged animals. Such differences in young and elderly could be responsible for the failure to translate findings at the bench to those in the clinic since the vast majority of studies use greatly cheaper young ones. More studies using elderly rodents will further supply additional insight in translating stroke treatment from the preclinical research to the clinical setting. This study sets the basis for future ones to develop new therapeutic approaches for a treatment for stroke.

## **Conflict of Interest Statement**

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## **References**

Ajmo, C. T. Jr., Vernon, D. O., Collier, L., Hall, A. A., Garbuzova-Davis, S., Willing, A., et al. (2008). The spleen contributes to stroke-induced neurodegeneration. *J. Neurosci. Res.* 86, 2227–2234. doi: 10.1002/jnr.21661

[PubMed Abstract](#) | [PubMed Full Text](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Boehm, U., Klamp, T., Groot, M., and Howard, J. C. (1997). Cellular responses to interferon-gamma. *Annu. Rev. Immunol.* 15, 749–795. doi: 10.1146/annurev.immunol.15.1.749

<https://assignbuster.com/commentary-different-immunological-mechanisms-govern-protection-from-experimental-stroke-in-young-and-older-mice-with-recombinant-tcr-ligand-therapy/>

[Pubmed Abstract](#) | [Pubmed Full Text](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Chu, C. Q., Wittmer, S., and Dalton, D. K. (2000). Failure to suppress the expansion of the activated CD4 T cell population in interferon gamma-deficient mice leads to exacerbation of experimental autoimmune encephalomyelitis. *J. Exp. Med.* 192, 123-128. doi: 10. 1084/jem. 192. 1. 123

[Pubmed Abstract](#) | [Pubmed Full Text](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Iadecola, C., and Anrather, J. (2011). The immunology of stroke: from mechanisms to translation. *Nat. Med.* 17, 796-808. doi: 10. 1038/nm. 2399

[Pubmed Abstract](#) | [Pubmed Full Text](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Jin, R., Zhu, X., Liu, L., Nanda, A., Granger, D. N., and Li, G. (2013). Simvastatin attenuates stroke-induced splenic atrophy and lung susceptibility to spontaneous bacterial infection in mice. *Stroke* 44, 1135-1143. doi: 10. 1161/STROKEAHA. 111. 000633

[Pubmed Abstract](#) | [Pubmed Full Text](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Lambertsen, K. L., Gregersen, R., Meldgaard, M., Clausen, B. H., Heibol, E. K., Ladeby, R., et al. (2004). A role for interferon-gamma in focal cerebral ischemia in mice. *J. Neuropathol. Exp. Neurol.* 63, 942-955.

[Pubmed Abstract](#) | [Pubmed Full Text](#) | [Google Scholar](#)

Liesz, A., Suri-Payer, E., Veltkamp, C., Doerr, H., Sommer, C., Rivest, S., et al. (2009). Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke. *Nat. Med.* 15, 192–199. doi: 10. 1038/nm. 1927

[Pubmed Abstract](#) | [Pubmed Full Text](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Liesz, A., Zhou, W., Mracsko, E., Karcher, S., Bauer, H., Schwarting, S., et al. (2011). Inhibition of lymphocyte trafficking shields the brain against deleterious neuroinflammation after stroke. *Brain* 134(Pt 3), 704–720. doi: 10. 1093/brain/awr008

[Pubmed Abstract](#) | [Pubmed Full Text](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Mebius, R. E., and Kraal, G. (2005). Structure and function of the spleen. *Nat. Rev. Immunol.* 5, 606–616. doi: 10. 1038/nri1669

[Pubmed Abstract](#) | [Pubmed Full Text](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Offner, H., Dotson, A. L., Zhu, W., Libal, N., and Alkayed, N. J. (2014). Different immunological mechanisms govern protection from experimental stroke in young and older mice with recombinant TCR ligand therapy. *Front. Cell. Neurosci.* 8: 284. doi: 10. 3389/fncel. 2014. 00284

[CrossRef Full Text](#) | [Google Scholar](#)

Offner, H., Subramanian, S., Parker, S. M., Wang, C., Afentoulis, M. E., Lewis, A., et al. (2006). Splenic atrophy in experimental stroke is accompanied by increased regulatory T cells and circulating macrophages. *J. Immunol.* 176, 6523–65231. doi: 10. 4049/jimmunol. 176. 11. 6523

<https://assignbuster.com/commentary-different-immunological-mechanisms-govern-protection-from-experimental-stroke-in-young-and-older-mice-with-recombinant-tcr-ligand-therapy/>

[Pubmed Abstract](#) | [Pubmed Full Text](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Ostrowski, R., Schulte, R., Nie, Y., Ling, T., Lee, T., Manaenko, A., et al. (2012). Acute splenic irradiation reduces brain injury in the rat focal ischemic stroke model. *Transl. Stroke Res* . 3, 473–481. doi: 10. 1007/s12975-012-0206-5

[Pubmed Abstract](#) | [Pubmed Full Text](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Seifert, H. A., Collier, L. A., Chapman, C. B., Benkovic, S. A., Willing, A. E., and Pennypacker, K. R. (2014). Pro-inflammatory interferon gamma signaling is directly associated with stroke induced neurodegeneration. *J. Neuroimmune Pharmacol* . doi: 10. 1007/s11481-014-9560-2. [Epub ahead of print].

[Pubmed Abstract](#) | [Pubmed Full Text](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Seifert, H. A., Leonardo, C. C., Hall, A. A., Rowe, D. D., Collier, L. A., Benkovic, S. A., et al. (2012). The spleen contributes to stroke induced neurodegeneration through interferon gamma signaling. *Metab. Brain Dis* . 27, 131–141. doi: 10. 1007/s11011-012-9283-0

[Pubmed Abstract](#) | [Pubmed Full Text](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Vendrame, M., Gemma, C., Pennypacker, K. R., Bickford, P. C., Davis Sanberg, C., Sanberg, P. R., et al. (2006). Cord blood rescues stroke-induced changes in splenocyte phenotype and function. *Exp. Neurol* . 199, 191–200. doi: 10. 1016/j. expneurol. 2006. 03. 017

[Pubmed Abstract](#) | [Pubmed Full Text](#) | [CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/commentary-different-immunological-mechanisms-govern-protection-from-experimental-stroke-in-young-and-older-mice-with-recombinant-tcr-ligand-therapy/>