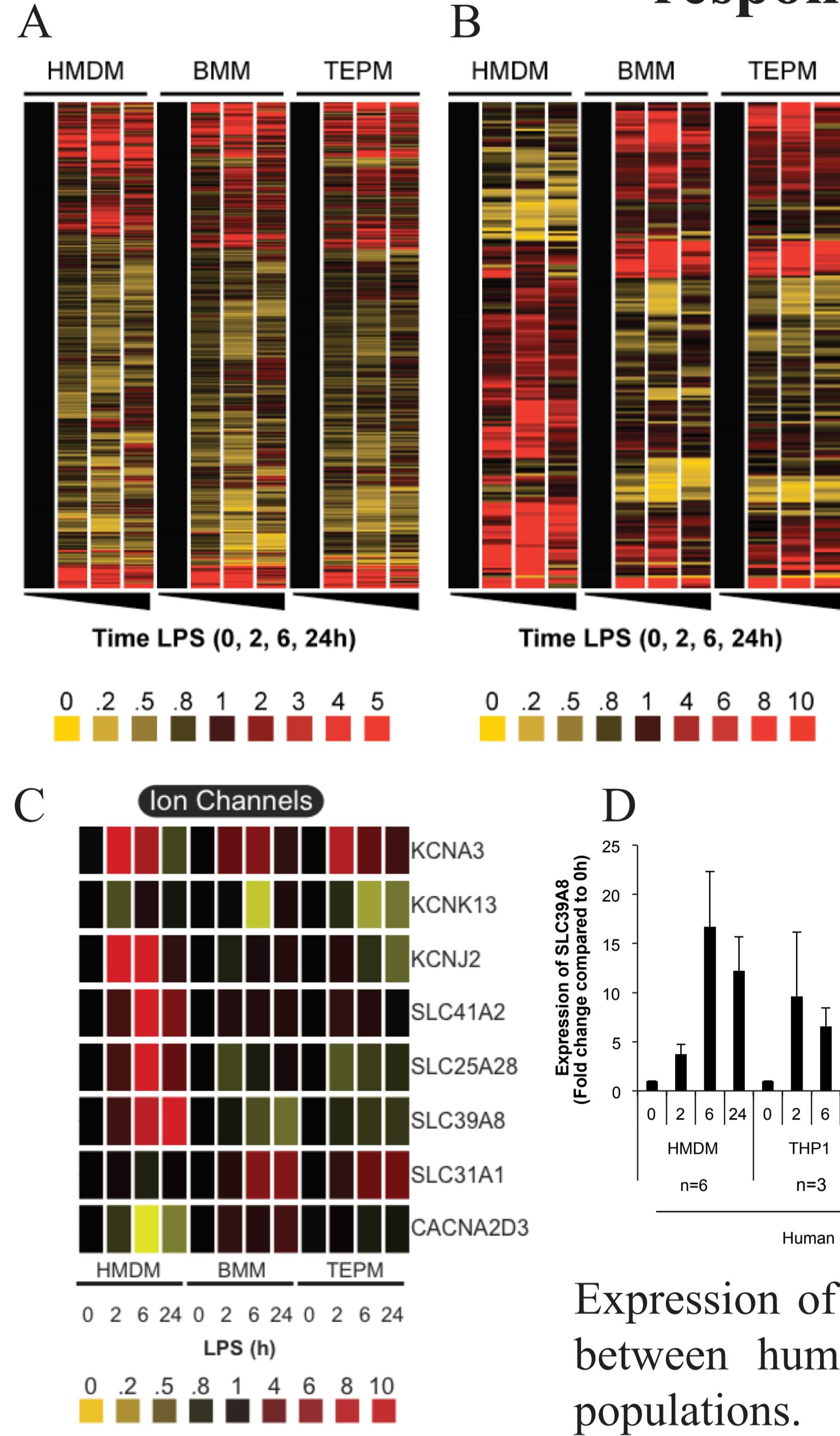


## I Introduction

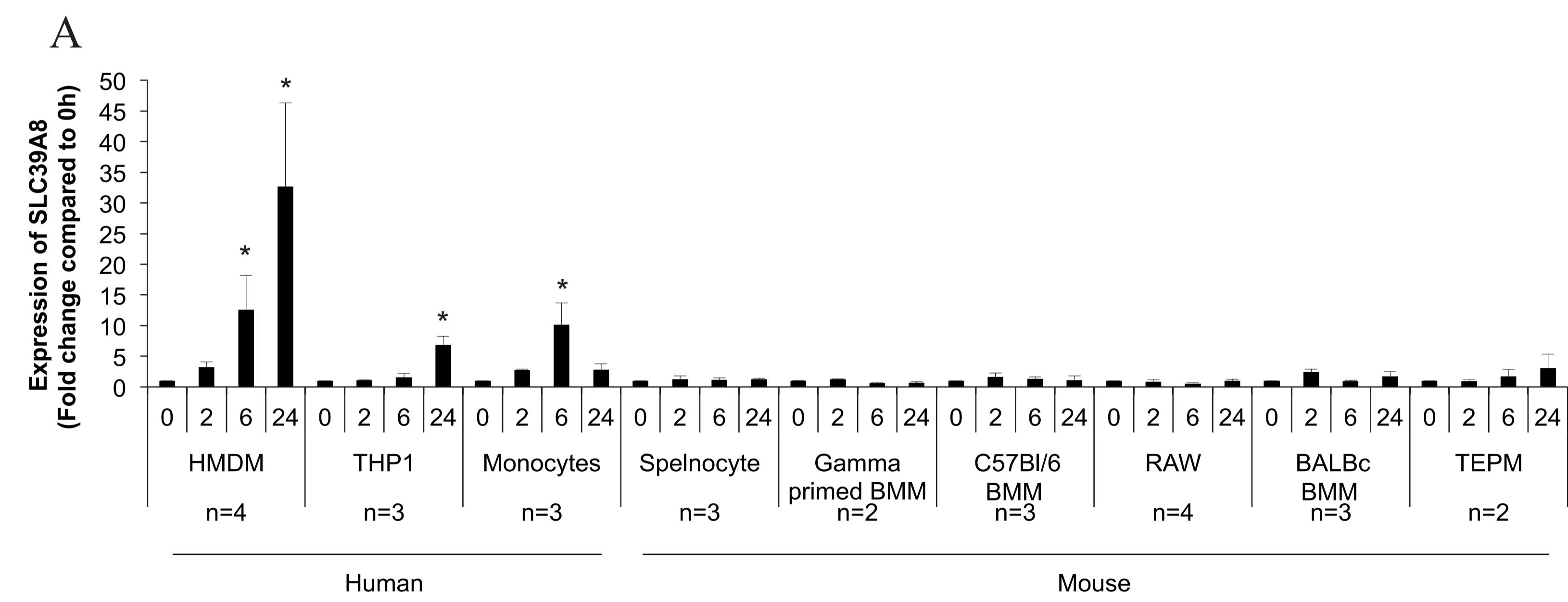
- Mice are widely used as models to study infection and immunity, but there are many differences in the immune responses of mice and humans [1,2].
- These differences can partly be attributed to the coevolution of the host immune system as a response to rapidly evolving pathogens.
- The innate immune system recognizes invading microbes through pattern recognition receptors such as Toll-like Receptors (TLRs) [3].
- This study used cross-species expression profiling to identify co-regulation and divergence in LPS (TLR4) responses between primary human and mouse macrophages, and investigated the functions of “human-specific” pathways in the anti-microbial response to *Salmonella enterica* serovar Typhimurium (SL1344).

## II Expression profiling of human and mouse macrophage responses to LPS



Expression of SLC41A2 mRNA is differentially regulated between human and mouse monocyte/macrophage cell populations.

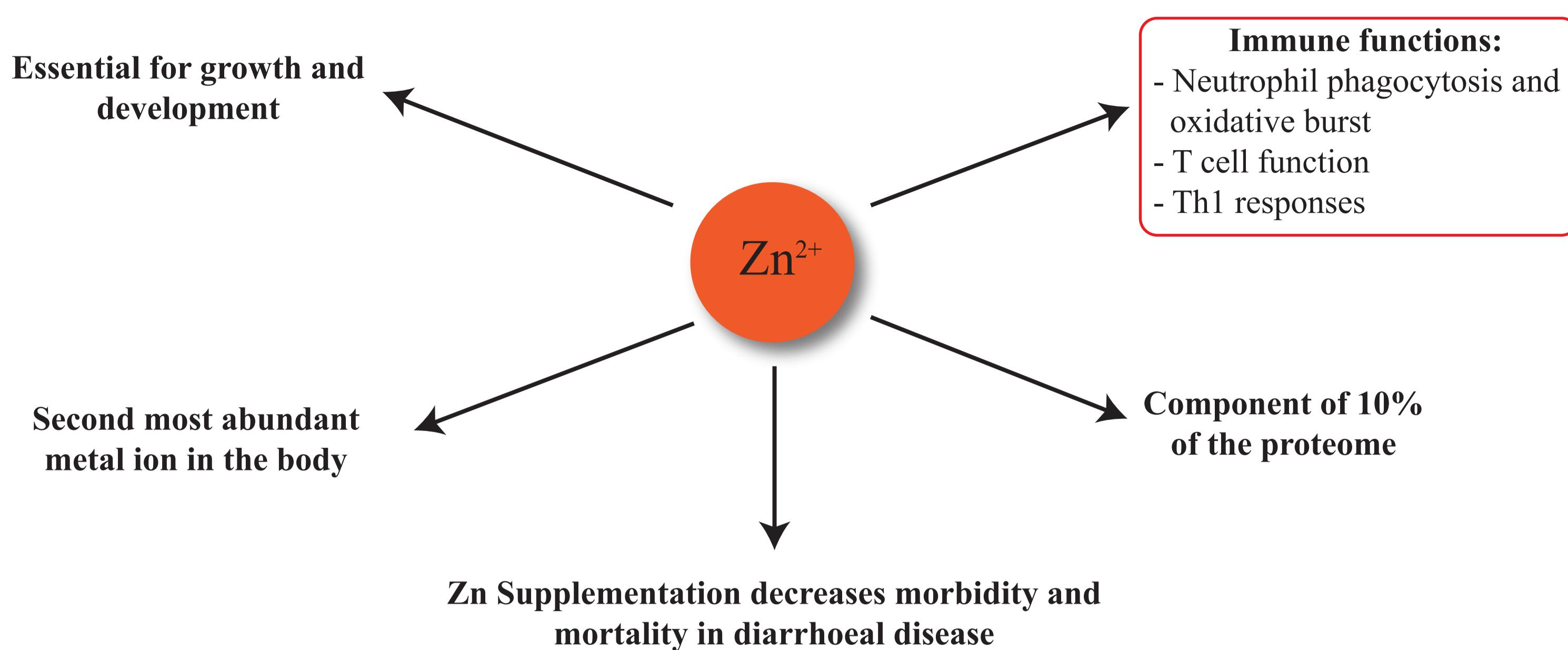
## III Expression of SLC39A8 mRNA was upregulated in human but not mouse macrophages by LPS or infection with *Salmonella*



(A) Expression of SLC39A8 was upregulated by LPS in all human monocyte / macrophage cell populations but not in mouse macrophages.

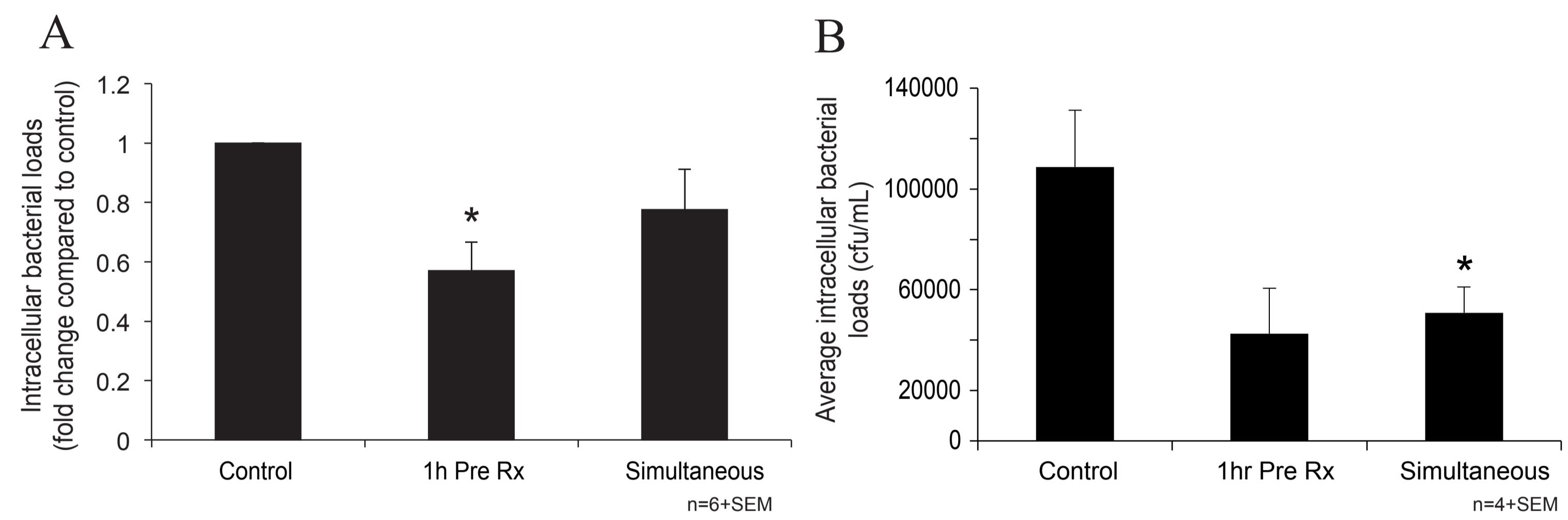
(B) Infection with *S. typhimurium* induced SLC39A8 mRNA expression in human (PMA differentiated THP-1 cells and monocyte derived macrophages) but not in C57Bl/6 mouse bone marrow-derived macrophages.

## IV Physiological roles of zinc



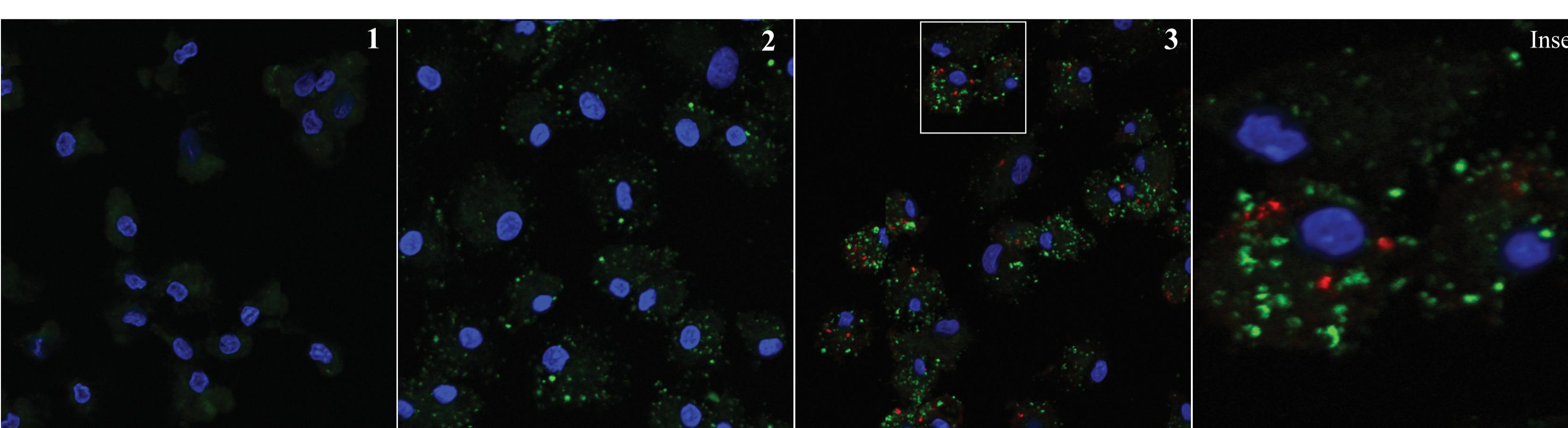
- The role of zinc as an essential micronutrient involved in maintaining a healthy immune response has been well documented [5,6].
- Clinical trials have shown that Zn supplementation decreases morbidity from gastrointestinal tract infections in children and infants [7].

## V Zinc decreased intracellular survival of *Salmonella* in HMDMs and PMA differentiated THP-1s



HMDMs (A) and PMA differentiated THP-1 cells (B) were treated with 200µM or 300µM zinc respectively. Cells were treated either 1h prior to infection or simultaneously with infection. Decreased intra-macrophage *Salmonella* survival was observed at 24h post infection in zinc treated cells as compared to controls.

## VI LPS and *Salmonella* trigger zinc redistribution within human macrophages

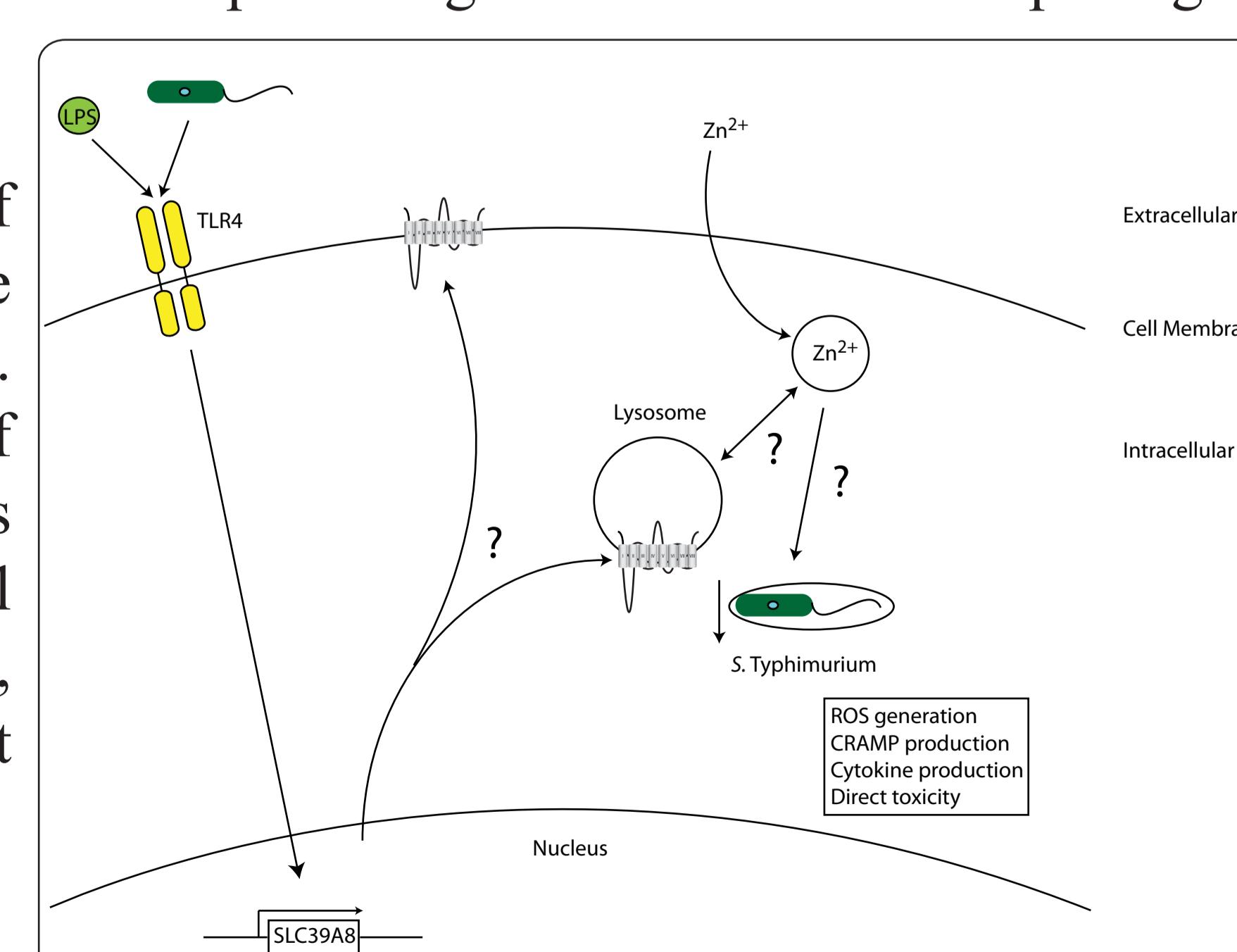


- HMDMs were either left untreated (1), stimulated with LPS (2) or infected with *Salmonella* (3) for 24h and then treated with FluoZin-3 AM. Zn was localized within discrete punctate vesicles as a response to LPS or *Salmonella*. No colocalization of *Salmonella* (red) and zinc (green) was seen (inset).
- This suggests that zinc could have an indirect effect on limiting intracellular *Salmonella* survival.

## VII Conclusion

SLC39A8 was induced in human, but not mouse macrophages in response to pathogen challenge, and may play a role in antimicrobial responses against the intracellular pathogen *S. typhimurium*.

We hypothesise that the stimulation of TLRs by *S. typhimurium* results in the upregulation of expression of SLC39A8. This regulates intracellular localization of zinc into specific compartments, which is utilised by the cell in antimicrobial responses such as the production of ROS, CRAMP, cytokines and/or in direct antimicrobial toxicity.



## References

- Mestas J, Hughes CC. Of mice and not men: differences between mouse and human immunology. *J Immunol* 2004;172:2731-8.
- Haley PJ. Species differences in the structure and function of the immune system. *Toxicology* 2003;188:49-71.
- Takeda K, Akira S. TLR signaling pathways. *Semin Immunol* 2004;16:3-9.
- Schroder K, Irvine K and Taylor M et al. Conservation and Divergence in Toll-like Receptor 4-regulated gene expression in primary human versus mouse macrophages. *PNAS* (revision submitted Feb 2011).
- Haase H, Rink L. The immune system and the impact of zinc during aging. *Immun Ageing* 2009;6:9.
- Prasad AS, Beck FW, Endre L, Handschuh W, Kukuruga M, Kumar G. Zinc deficiency affects cell cycle and deoxythymidine kinase gene expression in HUT-78 cells. *J Lab Clin Med* 1996;128:51-60.
- Bhandari N, Mazumder S, Taneja S, et al. Effectiveness of zinc supplementation plus oral rehydration salts compared with oral rehydration salts alone as a treatment for acute diarrhea in a primary care setting: a cluster randomized trial. *Pediatrics* 2008;121:e1279-85.

Acknowledgements - Cancer Council Australia for laser scanning microscopes  
- Endeavour IPRS and UQRS for scholarship funding