

# Long-term innate immune memory via effects on bone marrow progenitors

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Fondation Mérieux  
*Off-Target Effects of Vaccination*  
June 2015

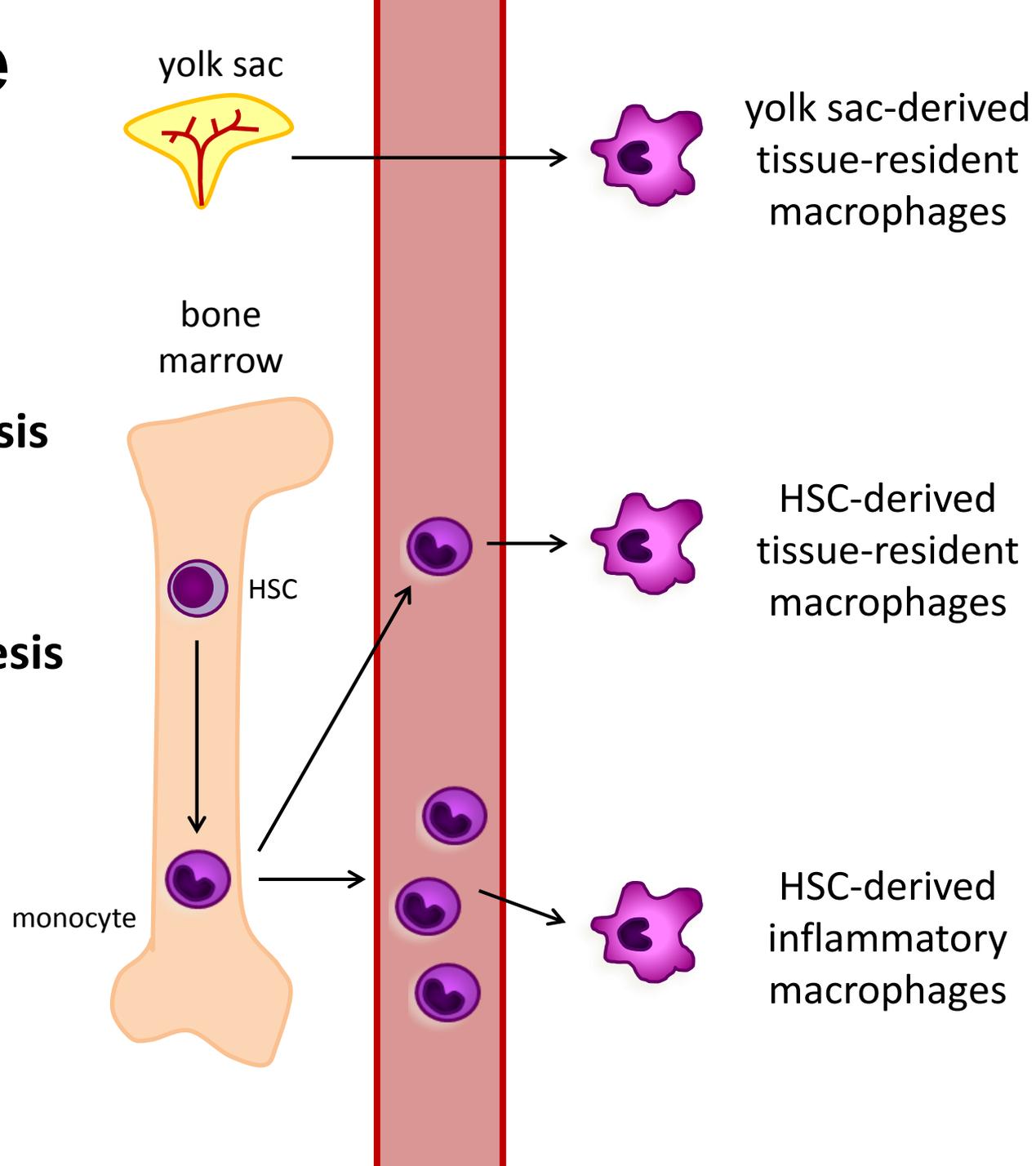
# Macrophage Origins

## Primitive Hematopoiesis

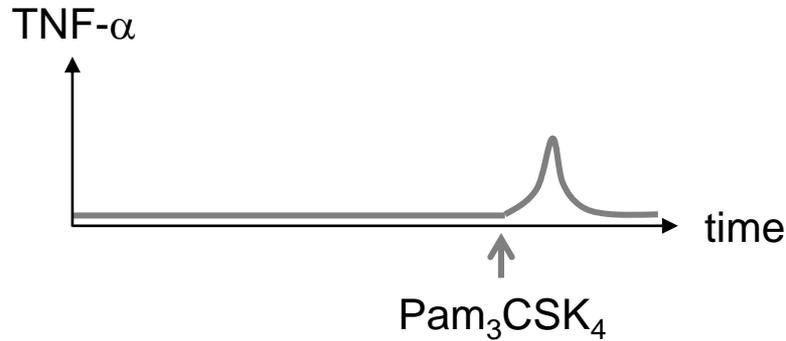
- yolk sac

## Definitive Hematopoiesis

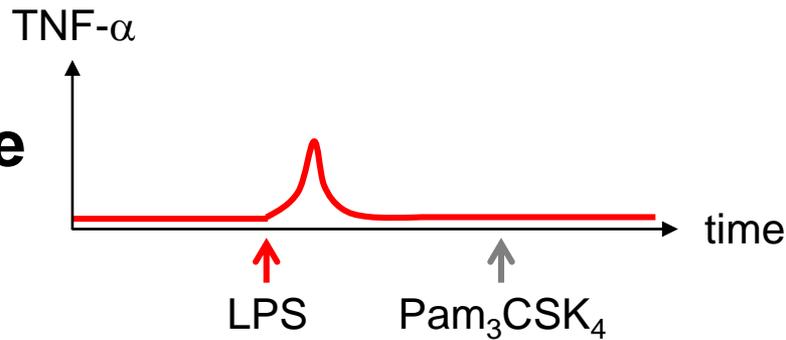
- fetal liver
- bone marrow



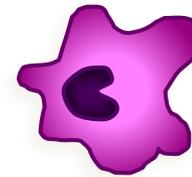
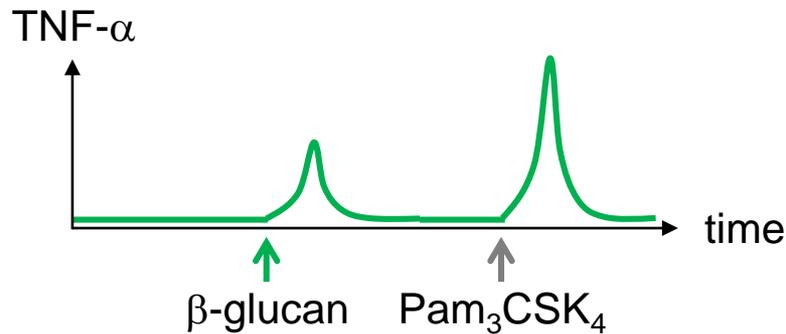
# Inflammatory gene regulation



**tolerance**

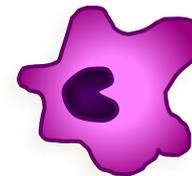


**training**



epigenetic  
modifications

metabolic  
changes

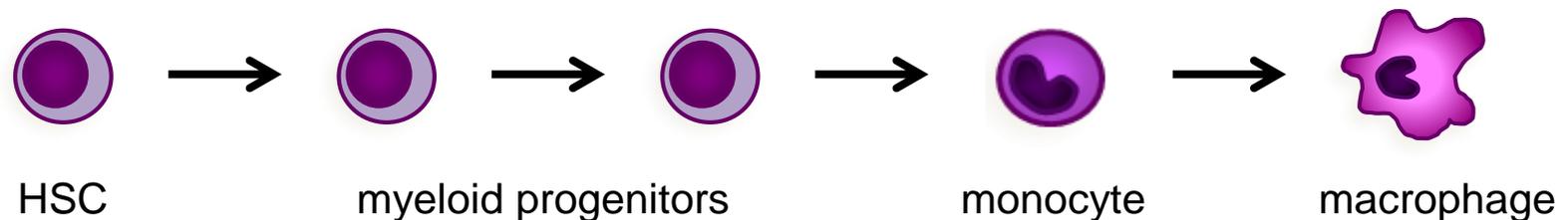


# Macrophage Memory?

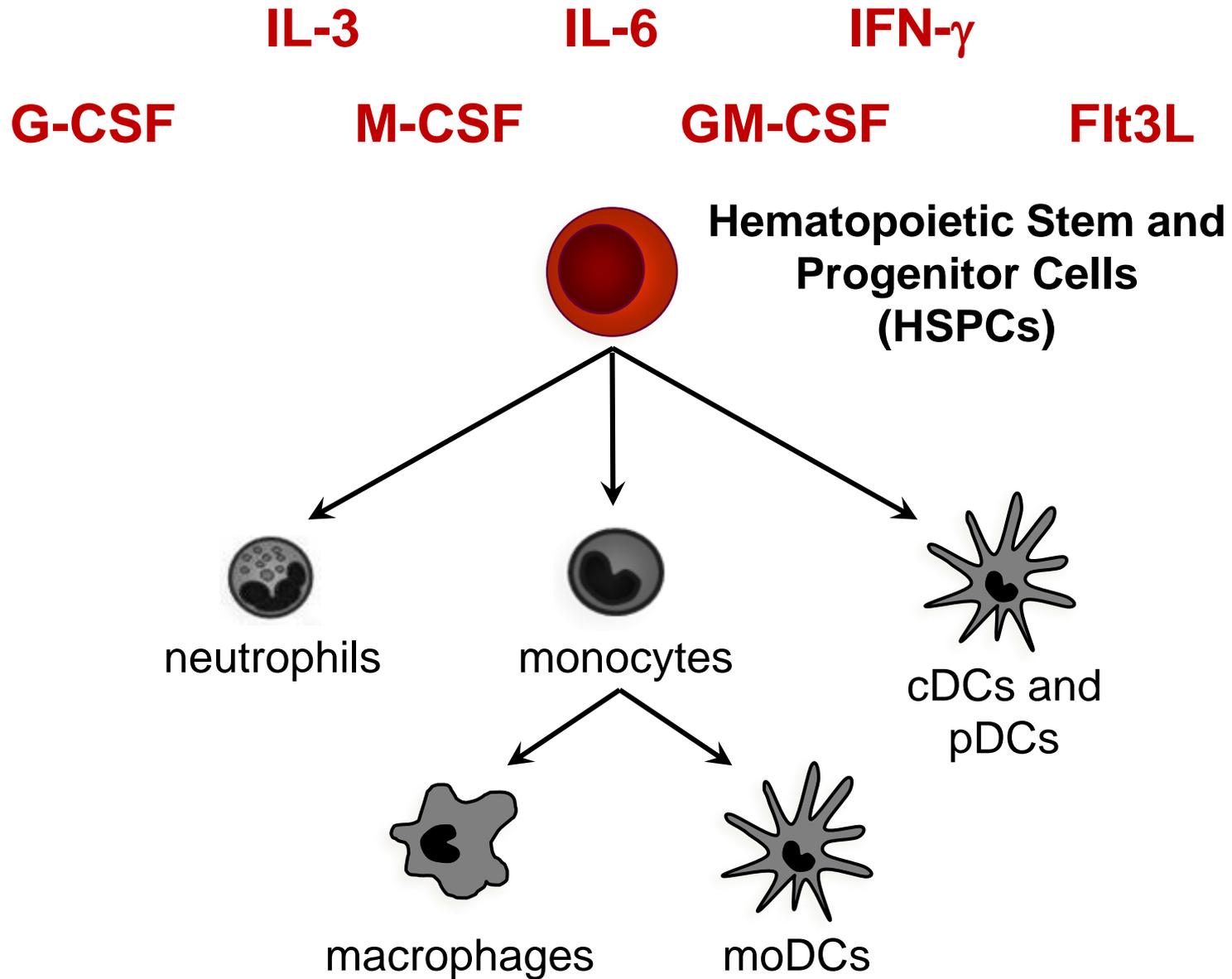
Epigenetic and metabolic changes could underlie trained immunity in long-lived macrophages

But what about short-lived macrophages?

Could changes in macrophage function be maintained via programming of their precursors i.e. hematopoietic stem cells and progenitors?



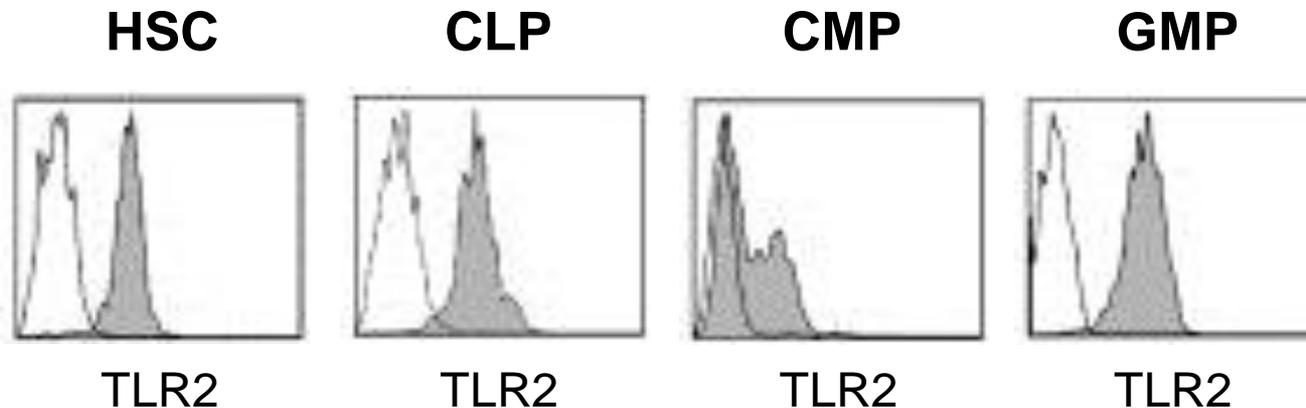
# microbial components



# Microbial Detection by HSPCs

- HSPCs express pattern recognition receptors, including Toll-like receptors (TLRs)

e.g.



Nagai et al. (2006) *Immunity* 24:801-12

- TLR stimulation can drive or promote production of neutrophils, macrophages, DCs, NK cells *in vitro* and *in vivo* in the steady-state and under emergency conditions

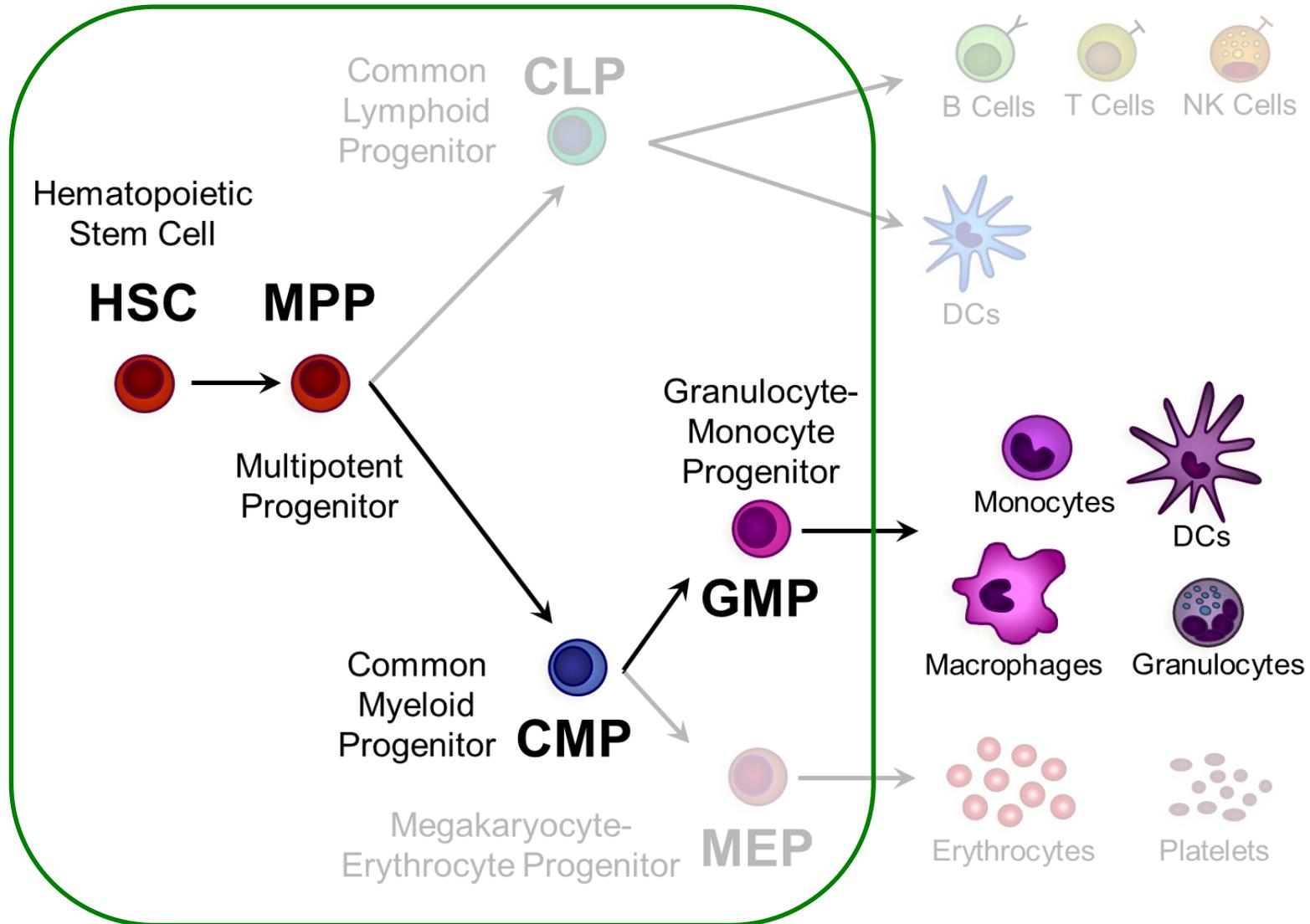
Does exposure of HSPCs to TLR agonists  
alter the function of the  
macrophages they produce?

**Detection of a TLR2 agonist by hematopoietic stem and progenitor cells  
impacts the function of the macrophages they produce**

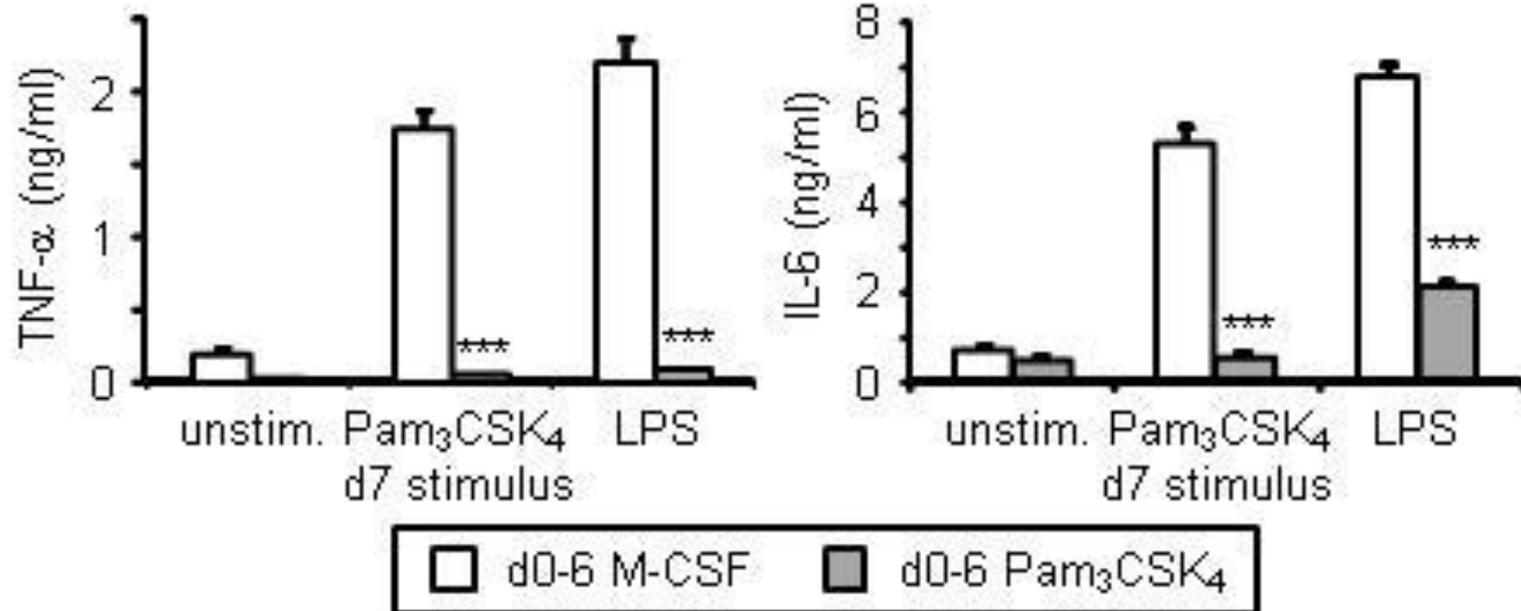
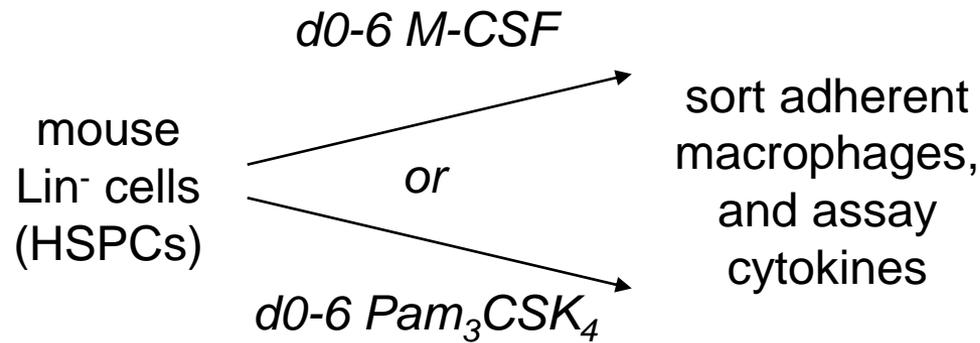
Yanez et al. (2013) *European Journal of Immunology* 43:2114-2125

# Myelopoiesis

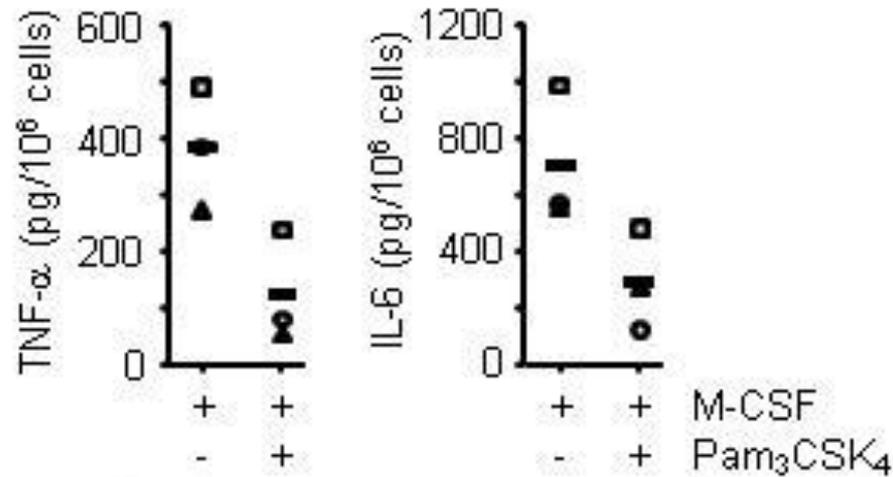
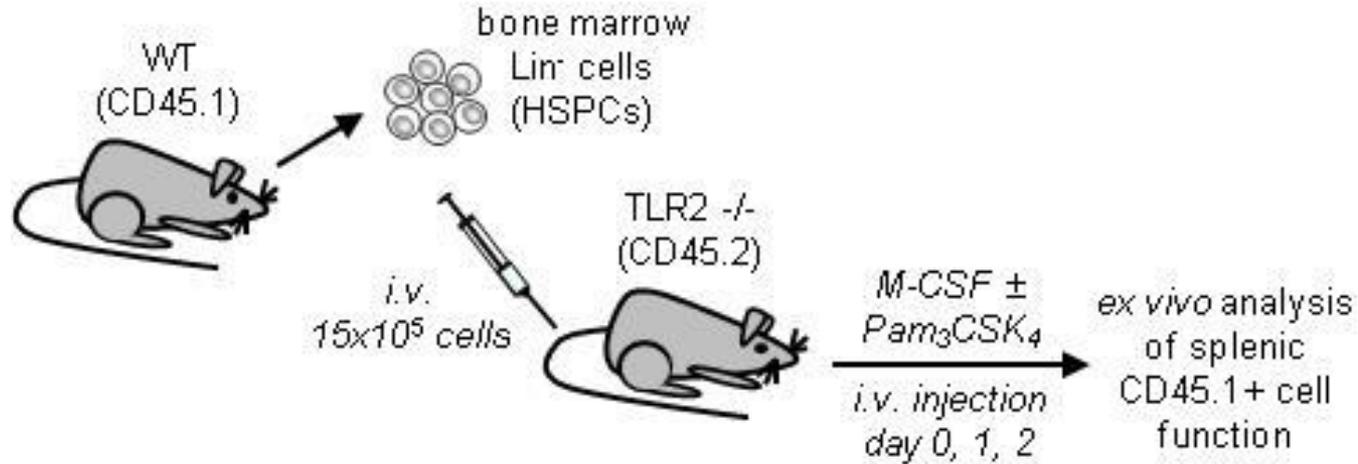
mouse HSPCs = Lin- cells



# Cytokine production by TLR2-derived and M-CSF-derived macrophages

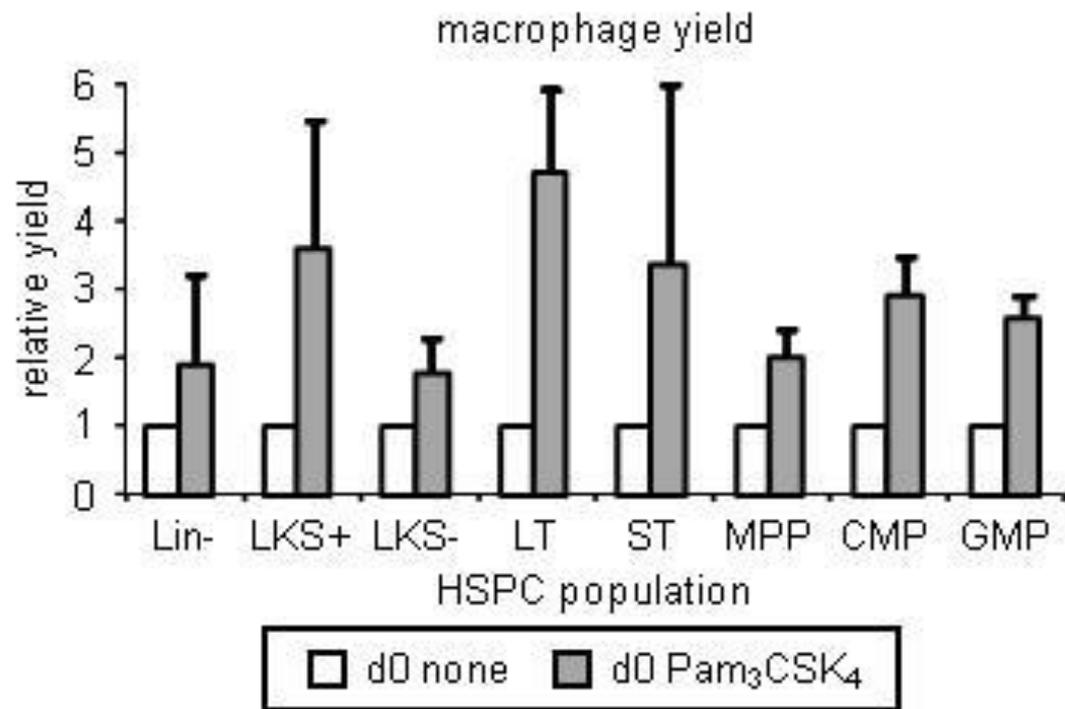
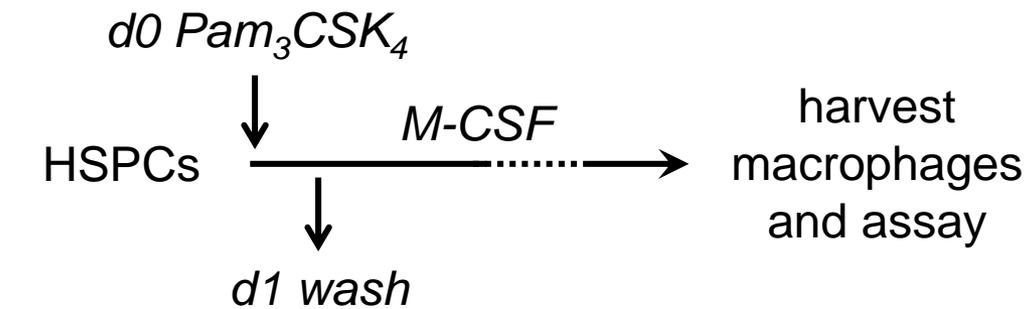
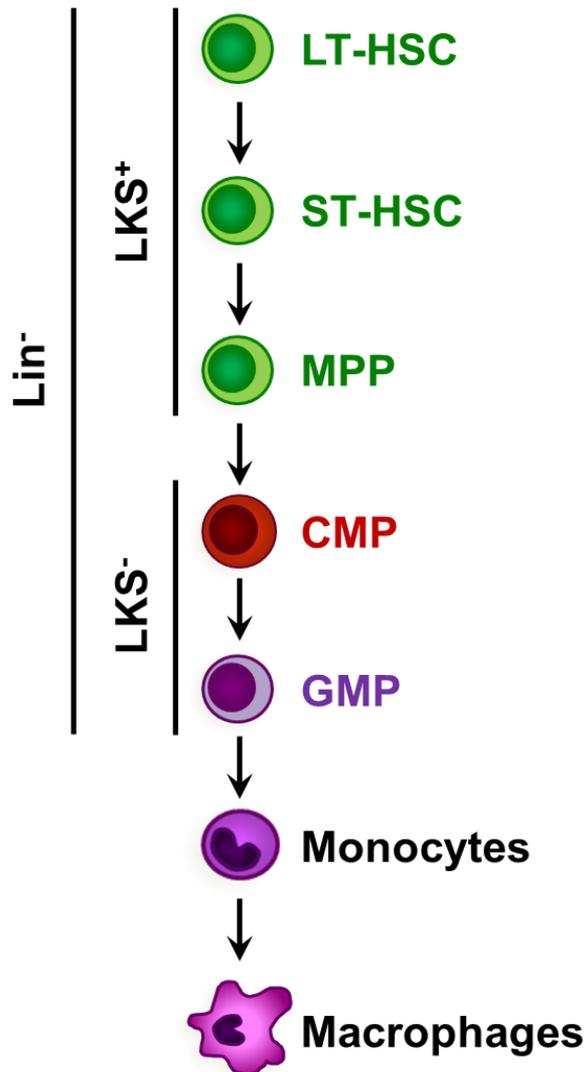


# Cytokine production by macrophages derived from HSPCs exposed to a TLR2 agonist *in vivo*

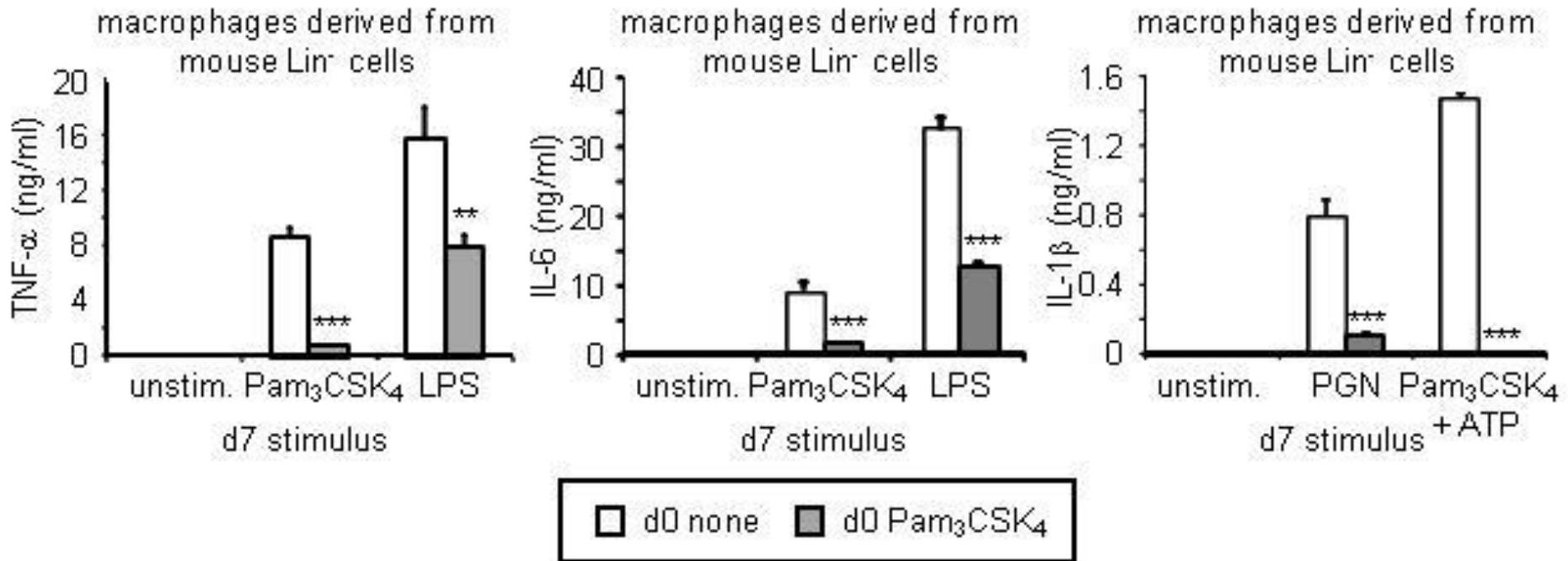


d4 ex vivo LPS stimulation

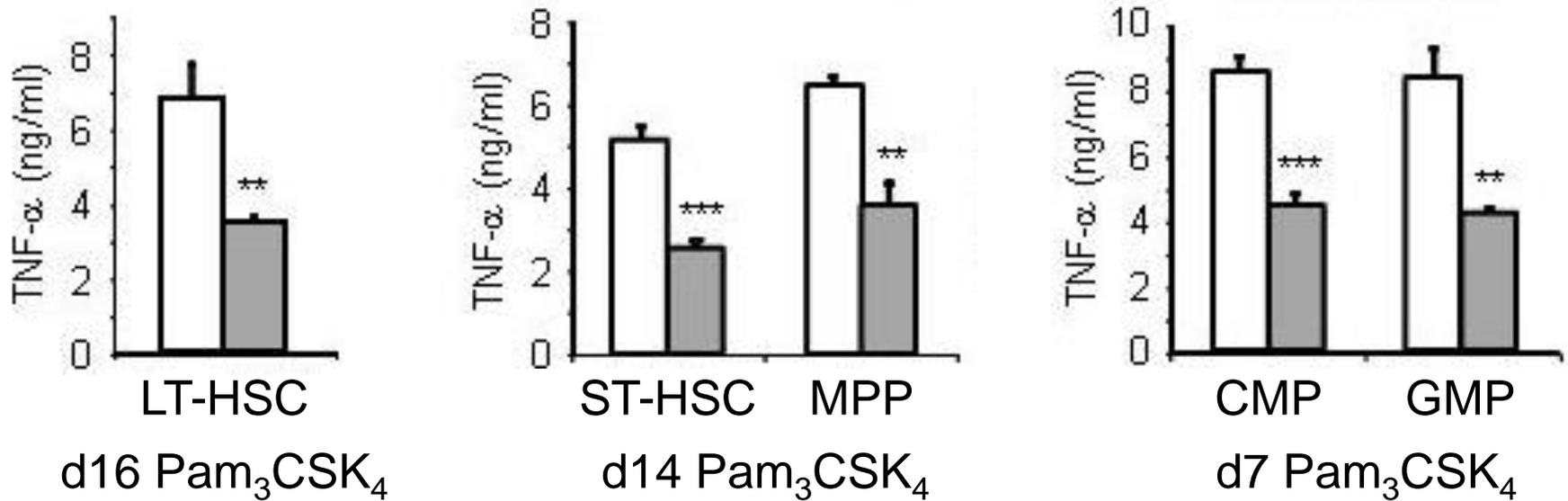
# Macrophage production by HSPCs exposed to a TLR2 agonist



# Cytokine production by macrophages derived from HSPCs exposed to a TLR2 agonist

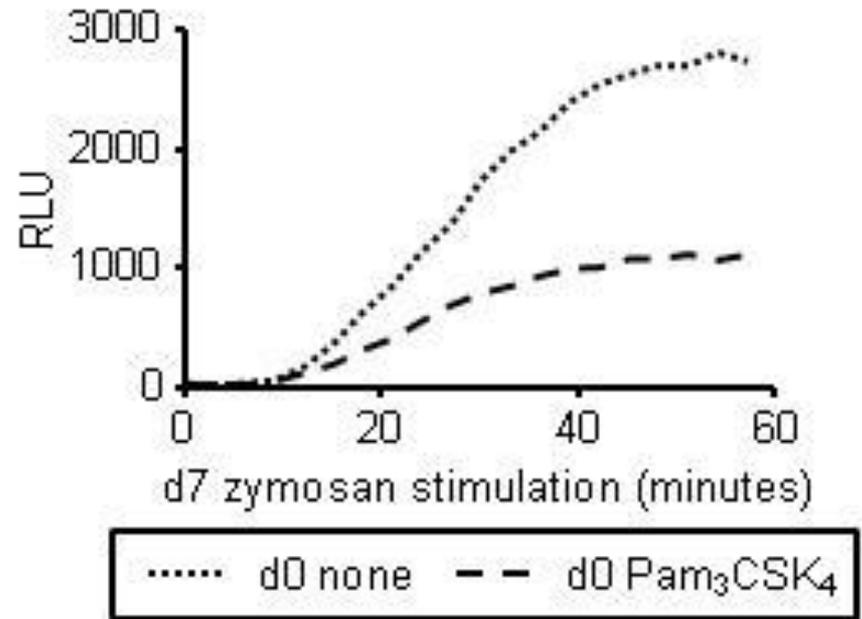
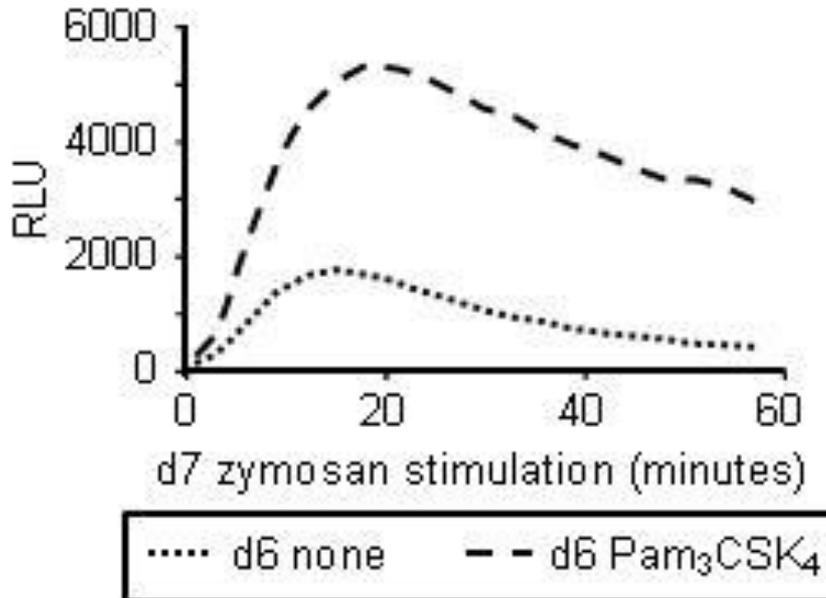
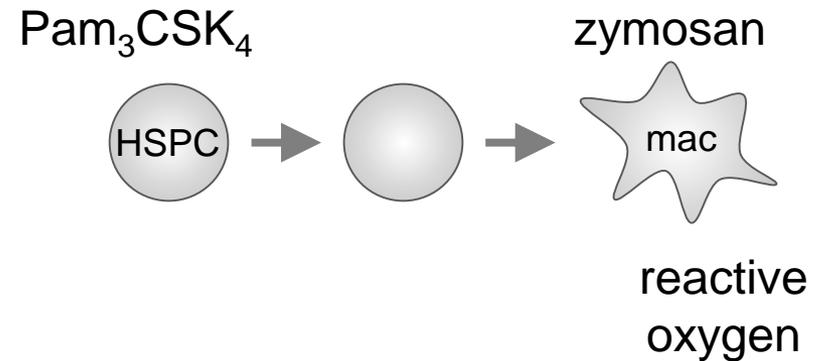
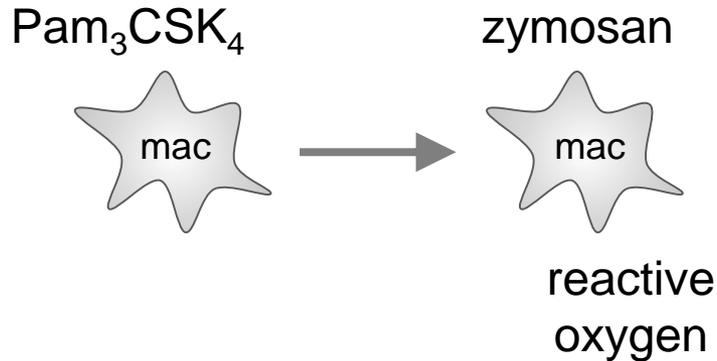


# Cytokine production by macrophages derived from HSPCs exposed to a TLR2 agonist

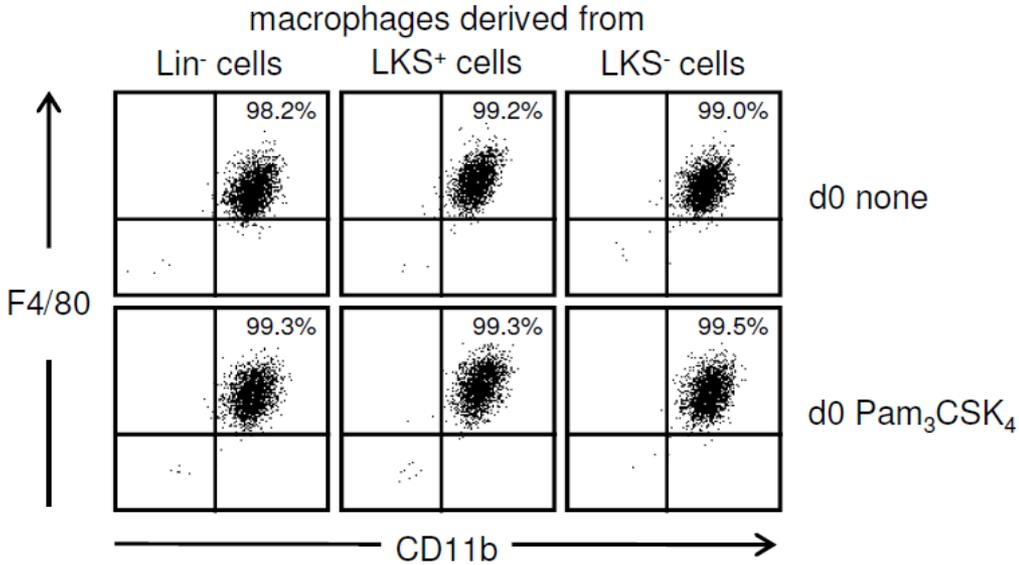
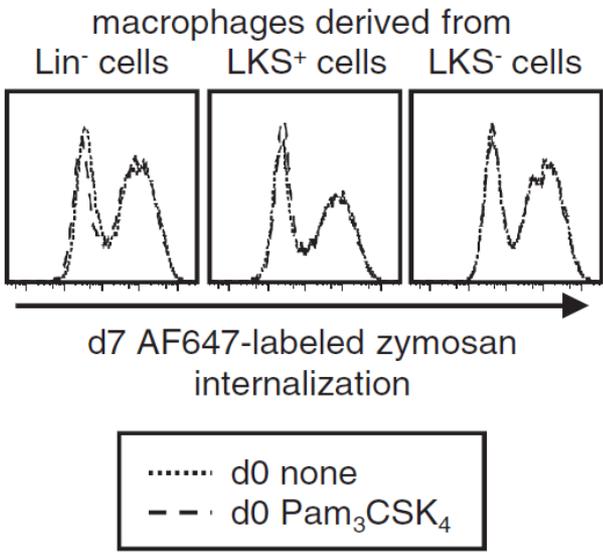


□ d0 none    ■ d0 Pam<sub>3</sub>CSK<sub>4</sub>

# Are macrophages derived from TLR2 agonist-exposed HSPCs “tolerized”?

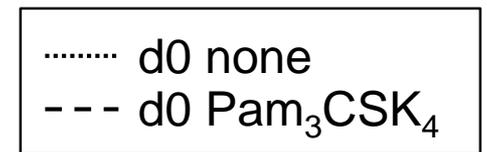
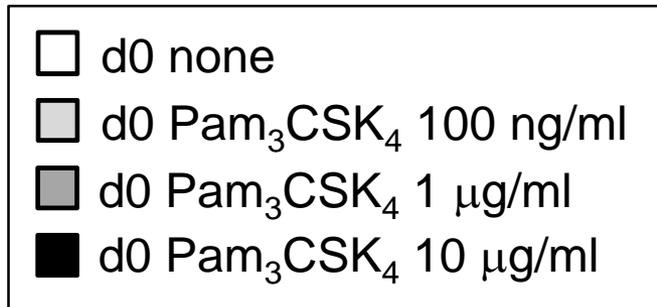
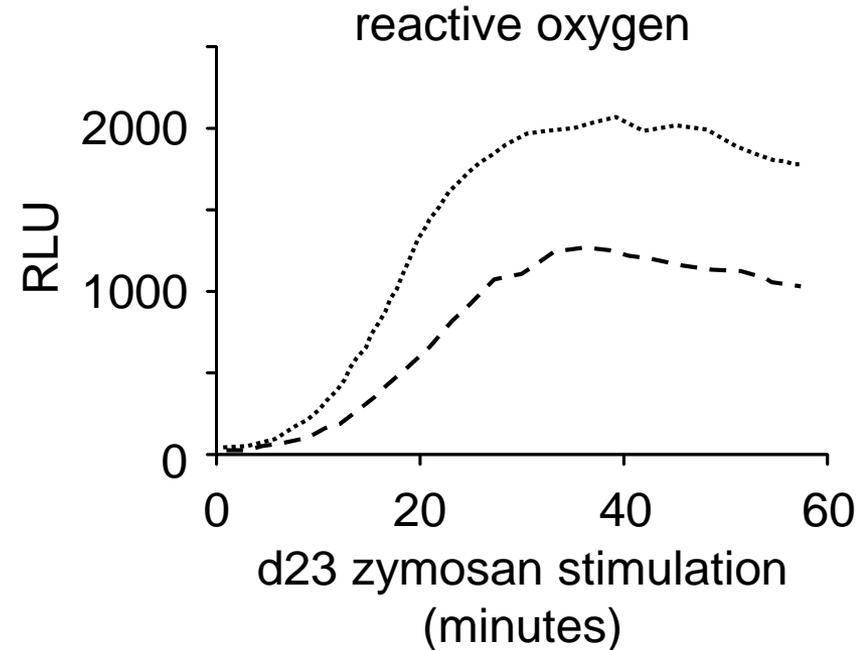
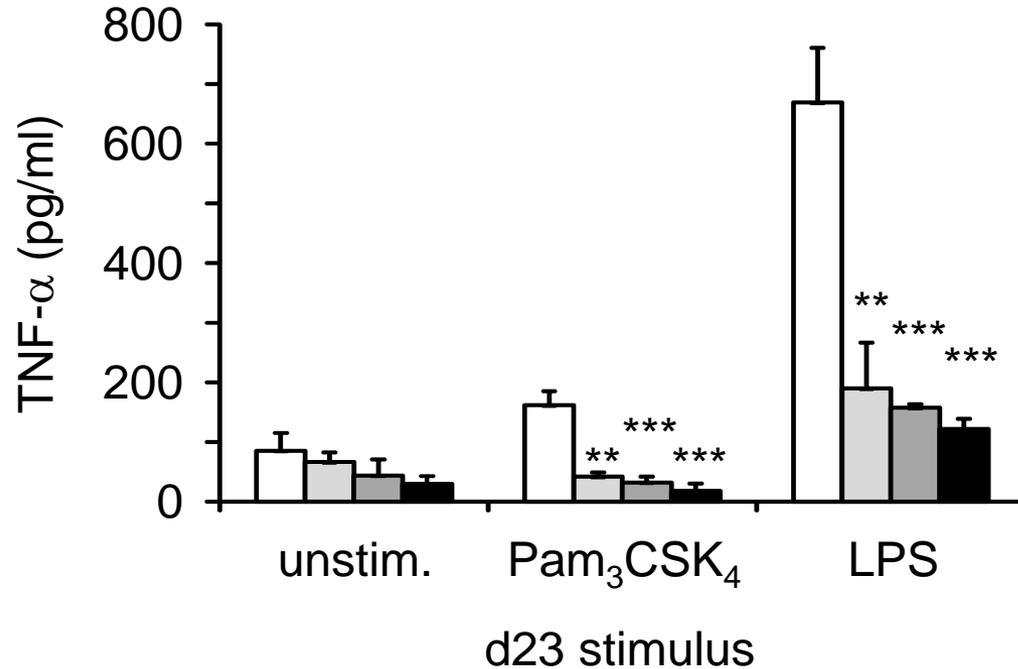


# Macrophages derived from TLR2 agonist-exposed HSPCs do not appear to be immature



# TLR2 stimulation of human HSPCs programs macrophage function

macrophages derived from human CD34<sup>+</sup> cells



**Progenitors**



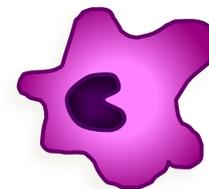
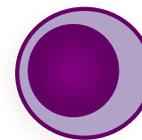
**Monocytes**



**Macrophages**



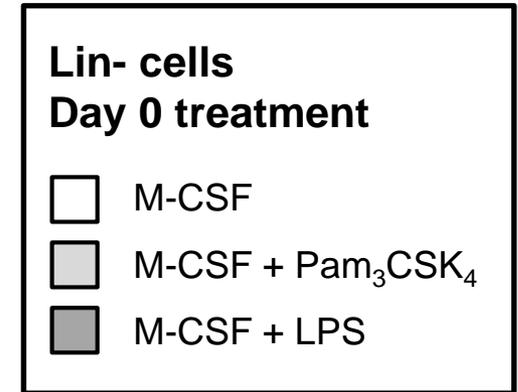
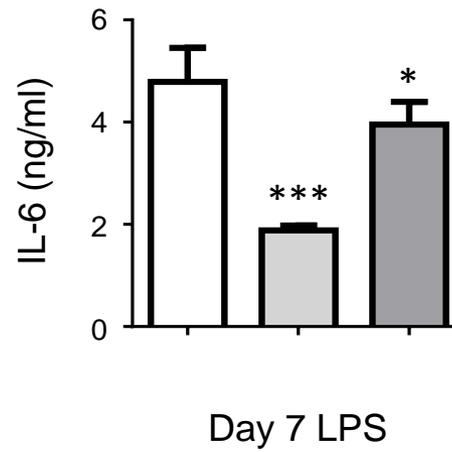
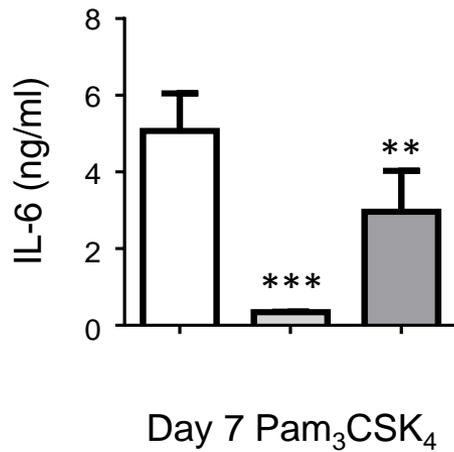
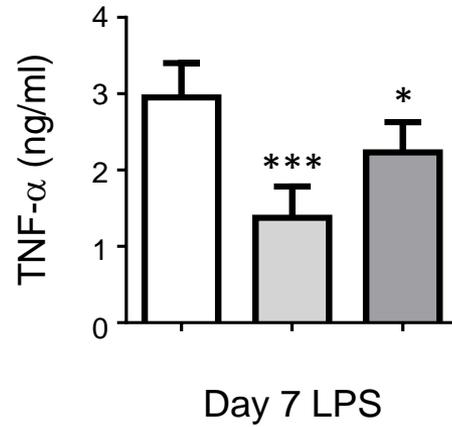
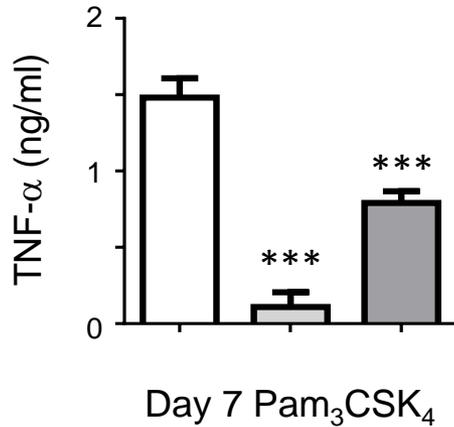
**TLR2  
agonist**



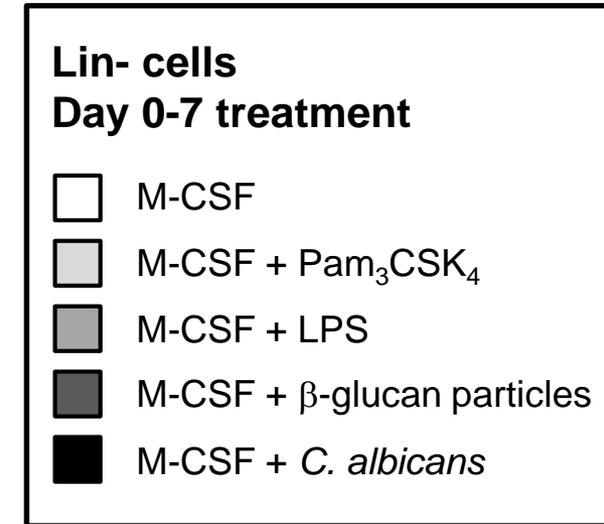
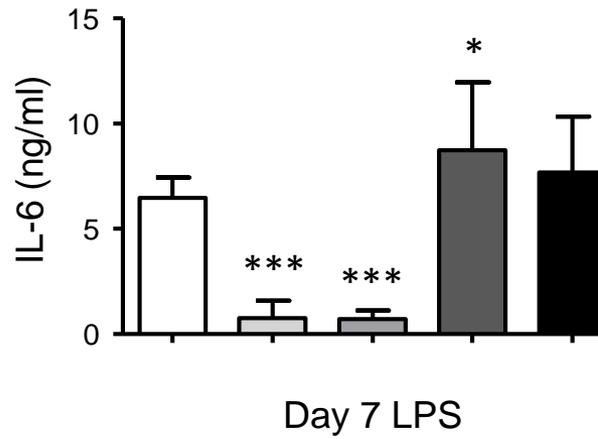
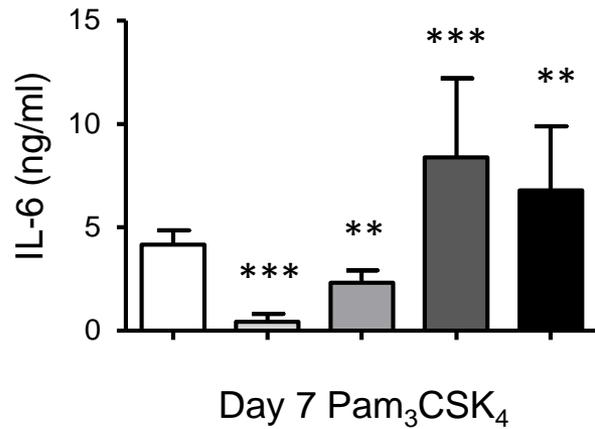
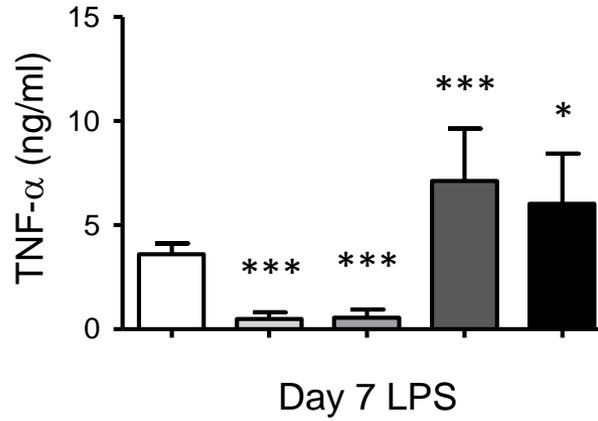
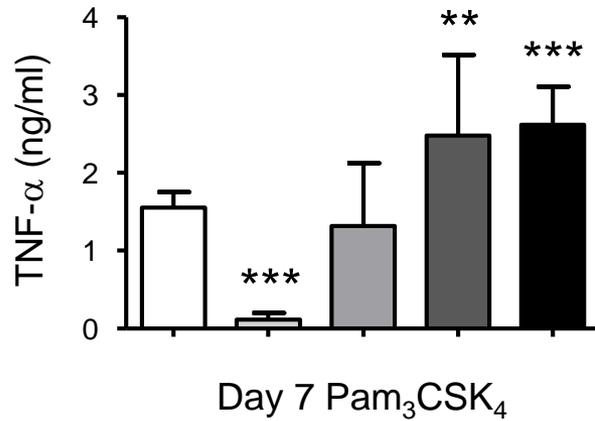
**increased macrophage yield**

**reduced cytokine and ROS  
production upon stimulation**

# Effects of other microbial components on programming of macrophage function



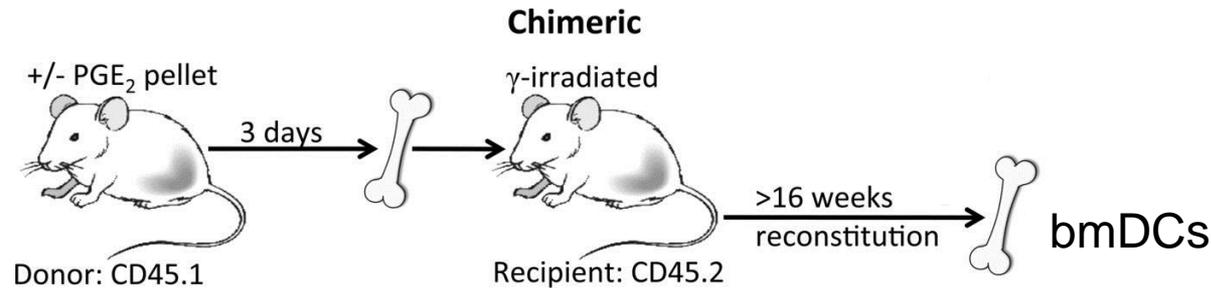
# Effects of other microbial components on programming of macrophage function



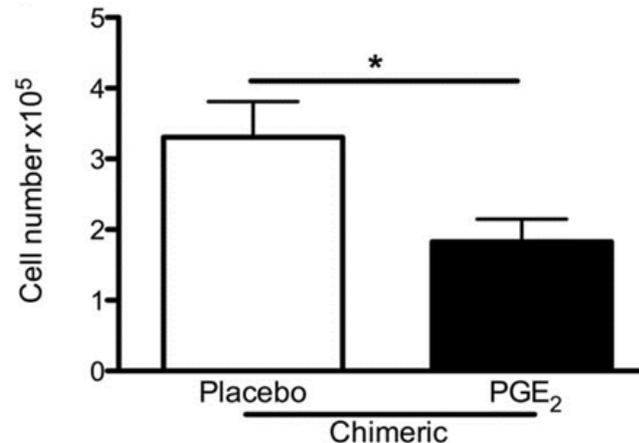
# Effects of UV and PGE2 on HSPCs

*Prue Hart, Telethon Kids Institute, Perth, Australia*

- UV exposure => immunosuppressive; inefficient T cell priming by DC cells; PGE2-mediated
- effect persists following bone marrow transplantation



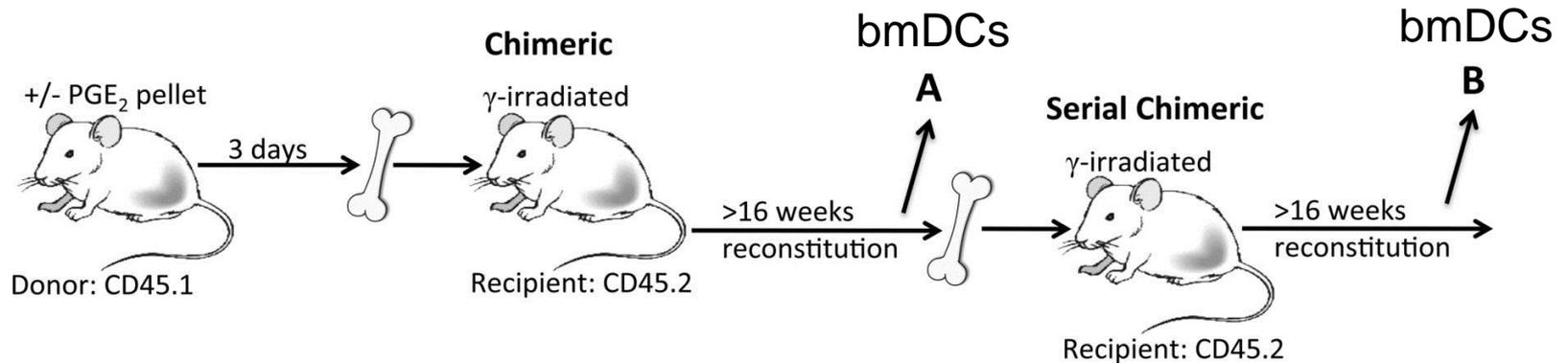
↓ migration of adoptively transferred bmDCs to draining lymph nodes  
=> inefficient T cell priming



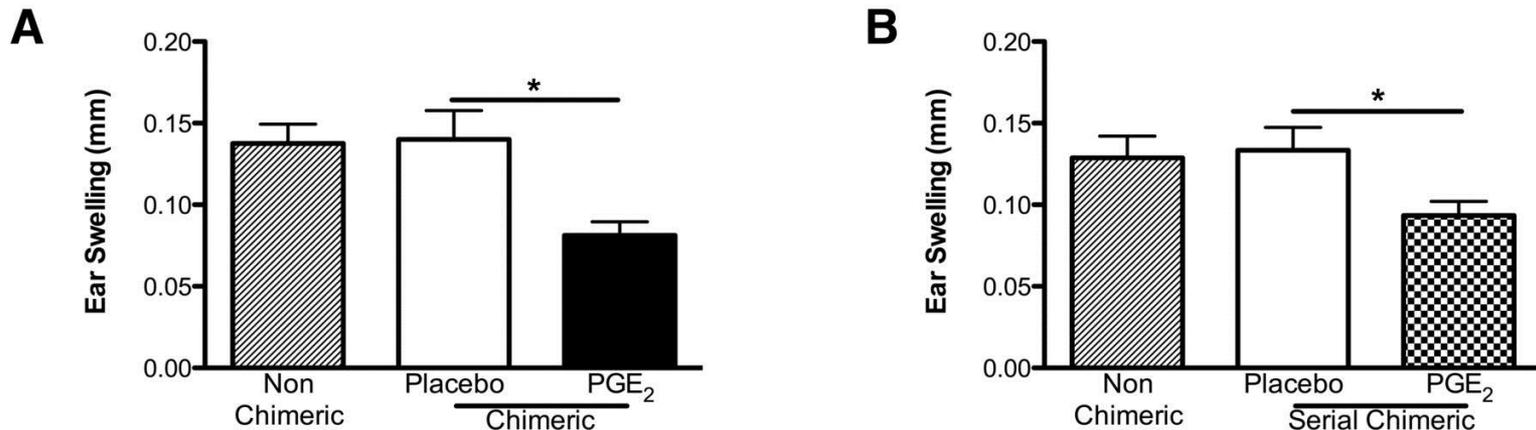
# Effects of UV and PGE2 on HSPCs

Prue Hart, Telethon Kids Institute, Perth, Australia

- UV/PGE2 effect persists upon serial bone marrow transplantation



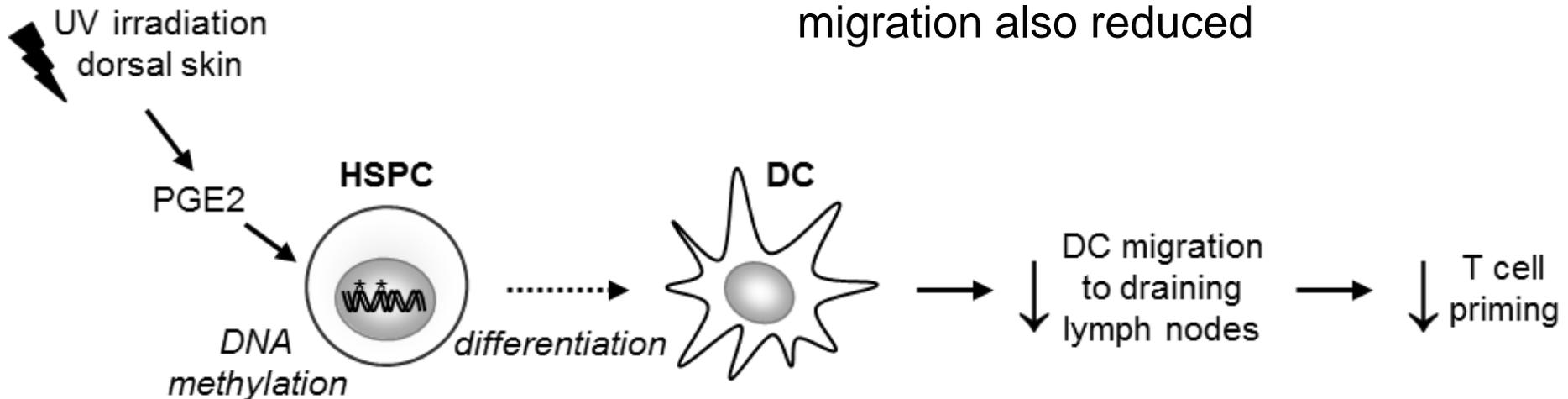
bmDCs => contact hypersensitivity assay



# Effects of UV and PGE2 on HSPCs - reduced myeloid cell migration

*Prue Hart, Telethon Kids Institute, Perth, Australia*

- macrophage and neutrophil migration also reduced



Ng et al. (2013) *Journal of Immunology* 190:5471-84

Scott et al. (2014) *Journal of Leukocyte Biology* 95:225-32

# Summary

- Hematopoietic stem and progenitor cells possess the machinery to detect and respond to cytokines, microbial products, damage etc.
- Endogenous factors and microbial products regulate innate immune cell differentiation in the steady-state and during emergency myelopoiesis
- Epigenetic modifications propagated through myelopoiesis have the potential to impact innate immune cell function for long periods

# Potential implications for non-specific effects of vaccination

- Mechanism to extend innate immune memory?
- Positive v. negative effects?
- Live v. inactivated vaccines – detected differently?
- Direct v. indirect detection by HSPCs?
- Programming of NK cells/other innate lymphoid cells?
- Early v. later life effects, immunosenescence?
- Role for microbiome?

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