Journal club

Fate Mapping Reveals Origins and Dynamics of Monocytes and Tissue Macrophages under Homeostasis

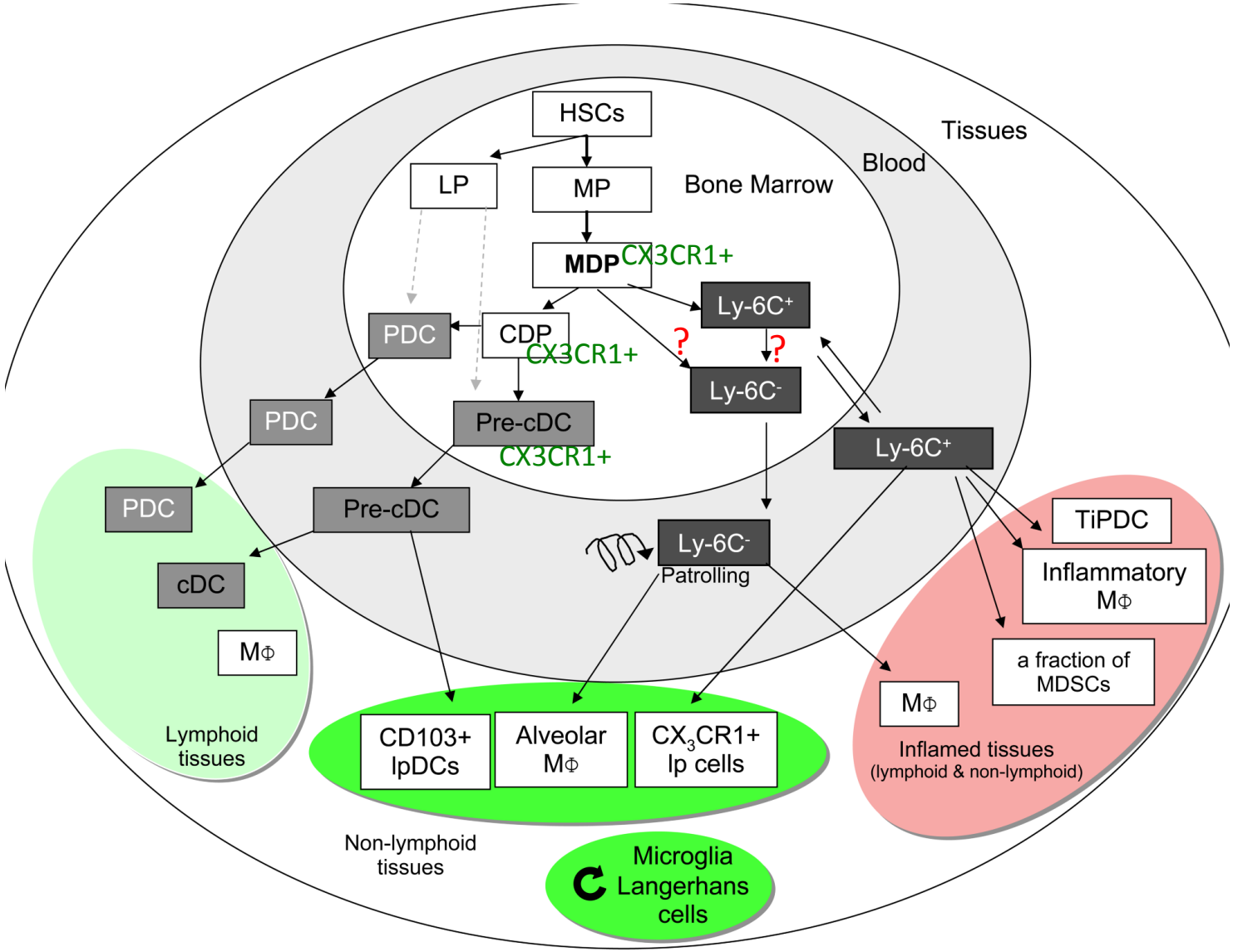
Simon Yona,[1,6,7] Ki-Wook Kim,[1,6,8] Yochai Wolf,[1,6] Alexander Mildner,[1] Diana Varol,[1] Michal Breker,[1] Dalit Strauss-Ayali,[1] Sergey Viukov,[2] Martin Guilliams,[3,9] Alexander Misharin,[4] David A. Hume,[5] Harris Perlman,[4] Bernard Malissen,[3] Elazar Zelzer,[2] and Steffen Jung[1,*]

Immunity *38*, 79–91, January 24, 2013

Francesca Ronchi

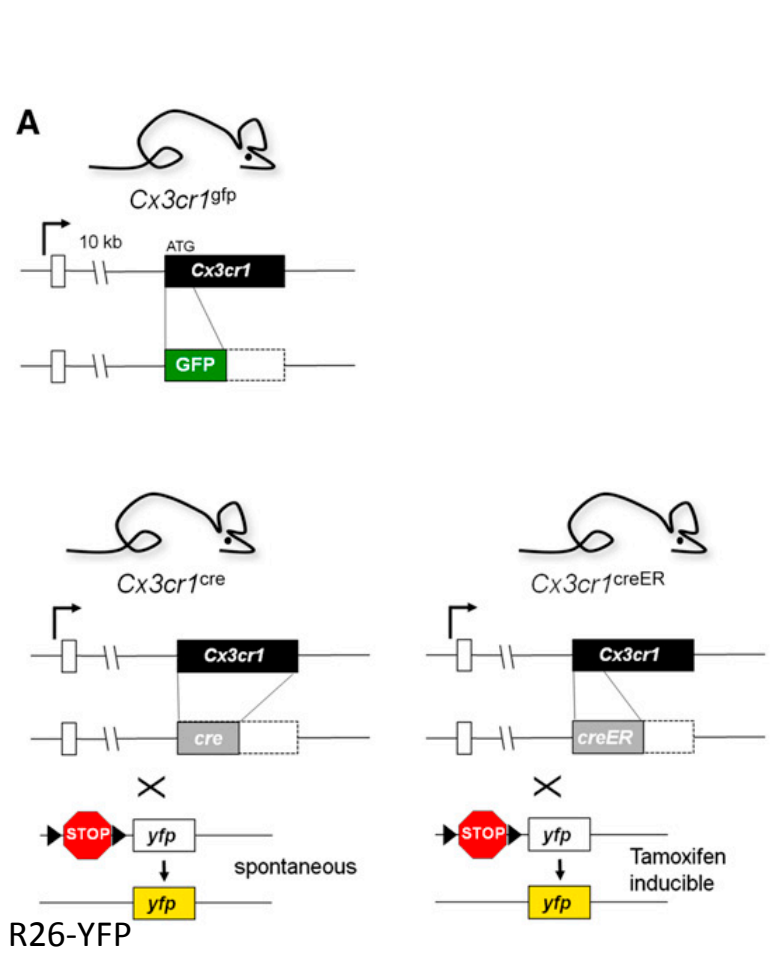
June, 21st 2013

Background



Modified from *Geissmann, F., Science 2010*

Resident macrophages have a dual origin



Tamoxifen: 1 month continuosly

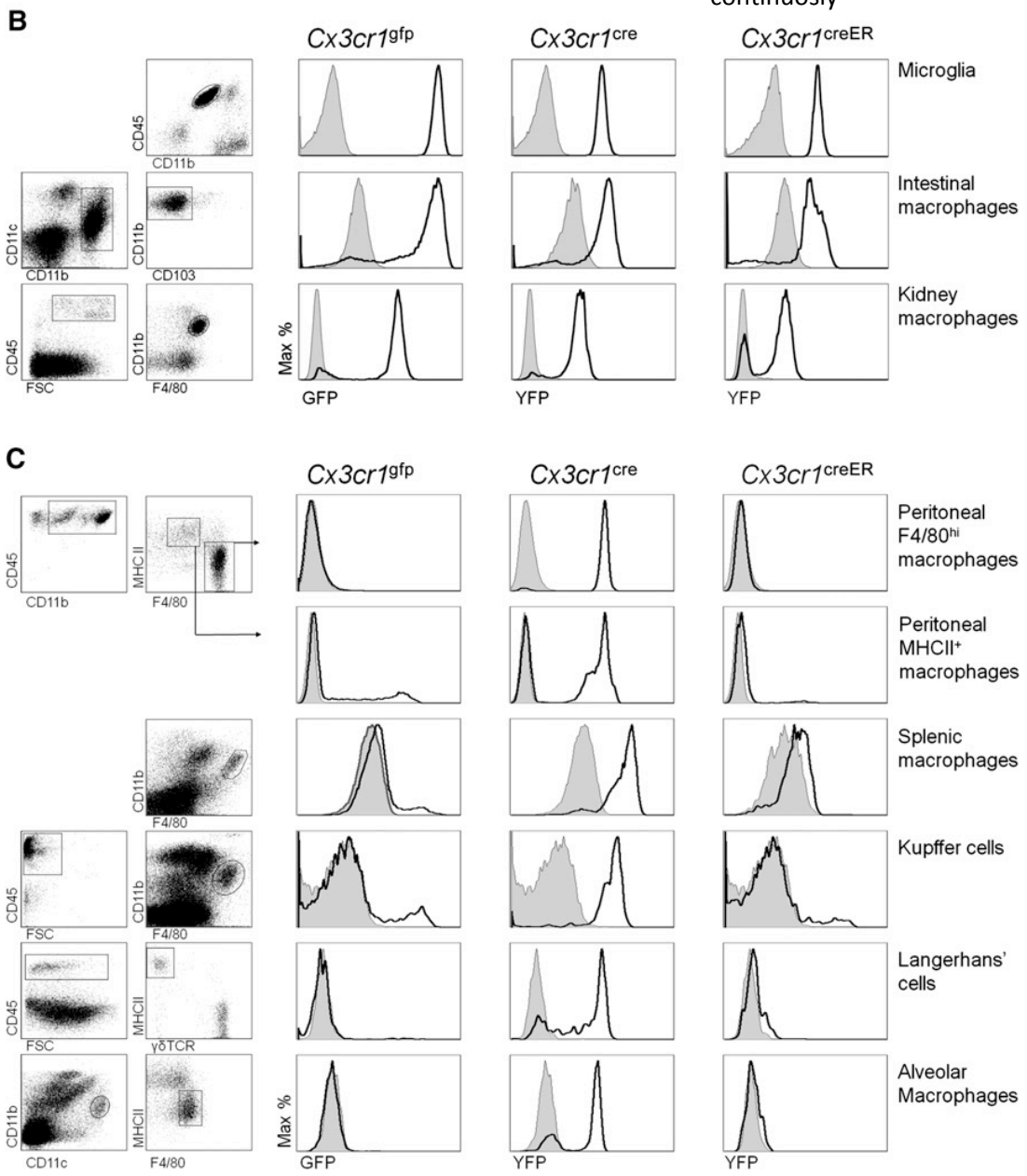
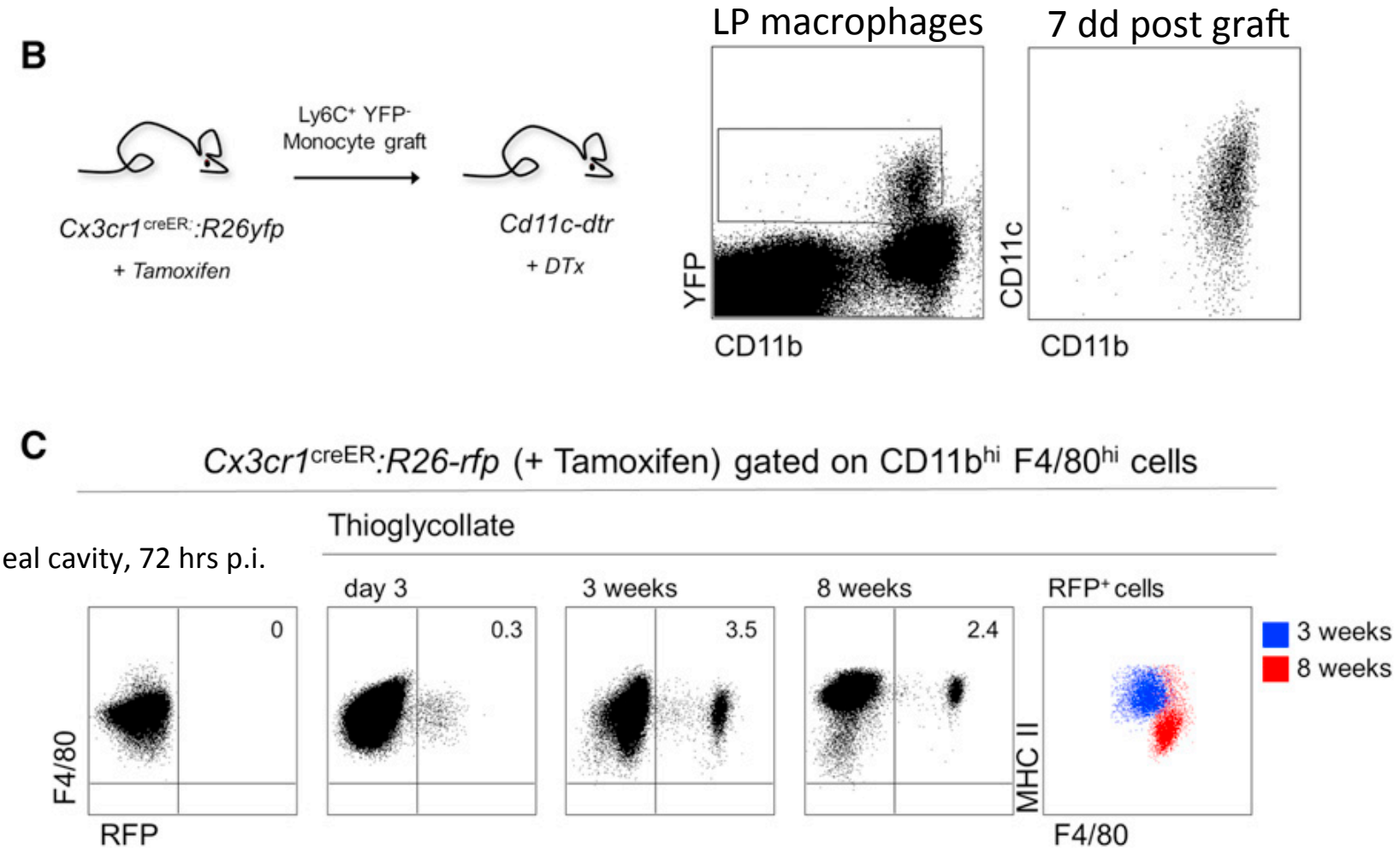


Fig.1

Ly6C^{-} YFP^{+} monocytes give rise to macrophages in peripheral tissues



Absence of YFP labelling in resident CX3CR1^{-} macrophages means that there is no ongoing steady state contribution of monocytes to peripheral macrophages. These cells are prenatally originated and then maintained themselves.

Fig.2

YFP+Ly6C+ and Ly6C- monocytes are sequencially generated

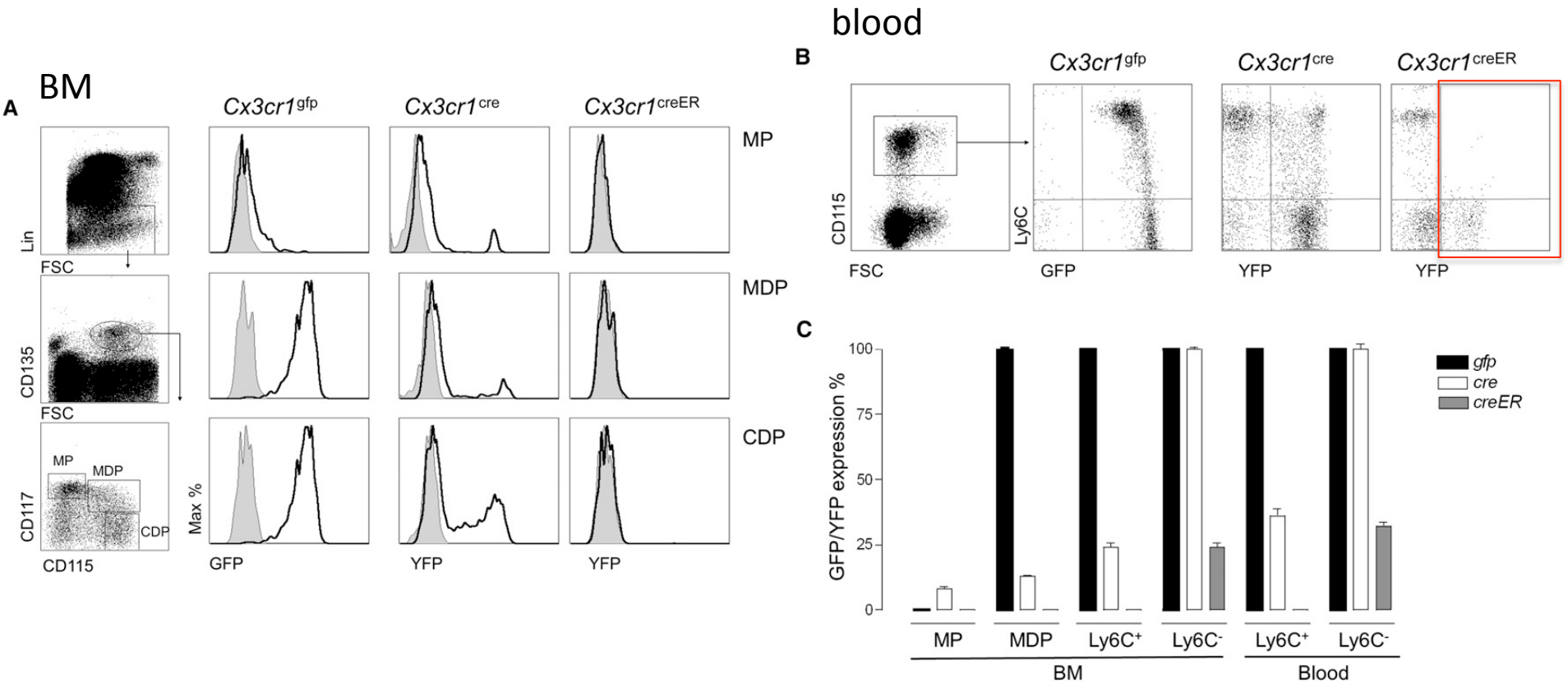
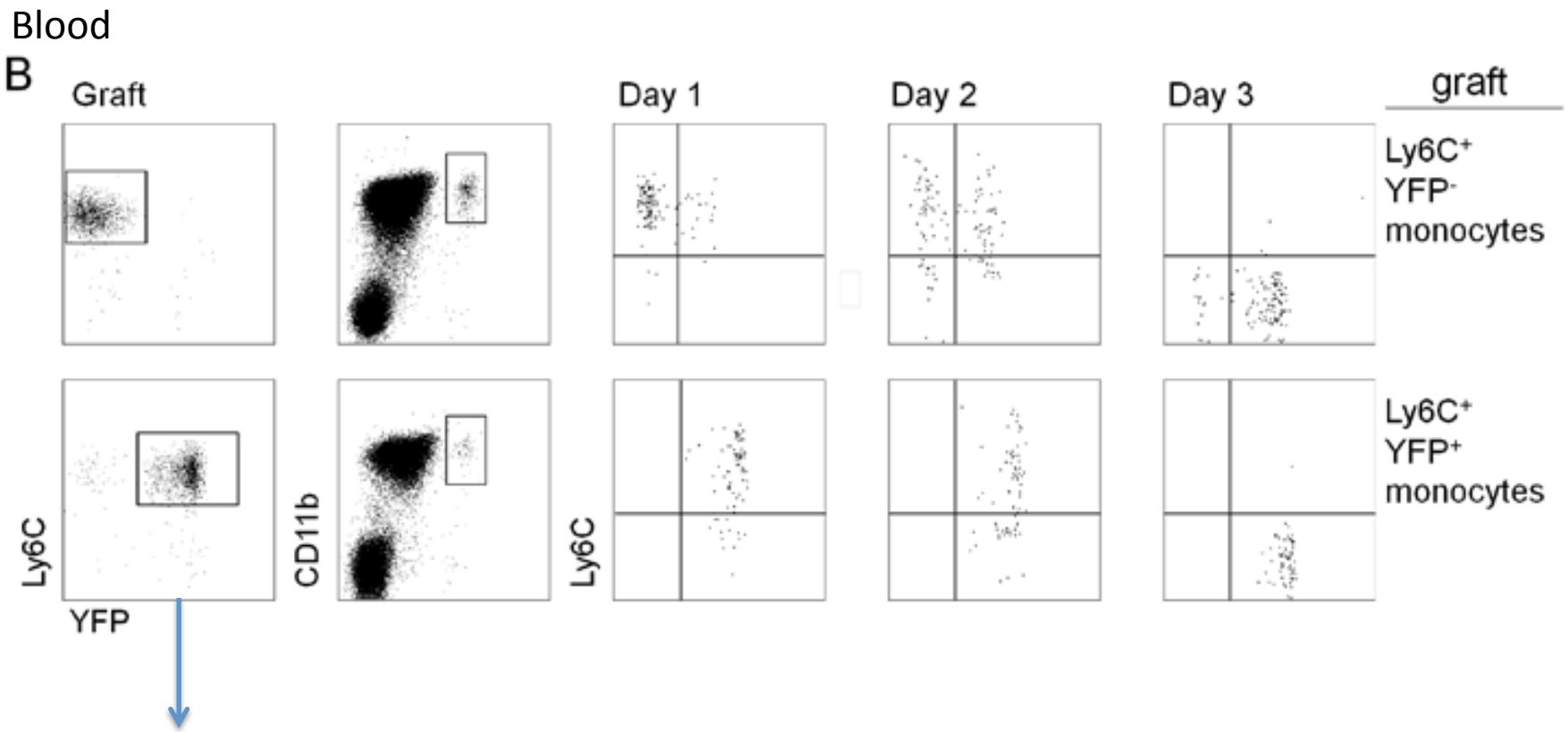


Fig.3

Adoptively transferred Ly6C^{+} (BM and) spleen monocytes differentiate into Ly6C^{-} monocytes

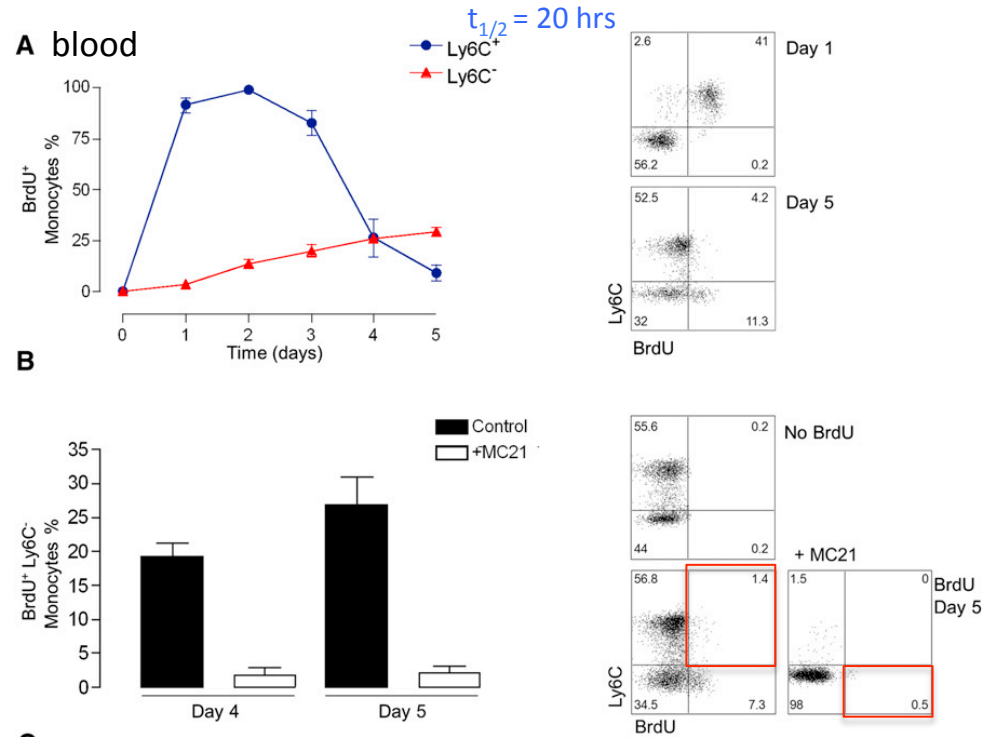


From Cx3cr1^{cre}:R26-YFP mice
Txp in WT congenic mice

Fig.S4

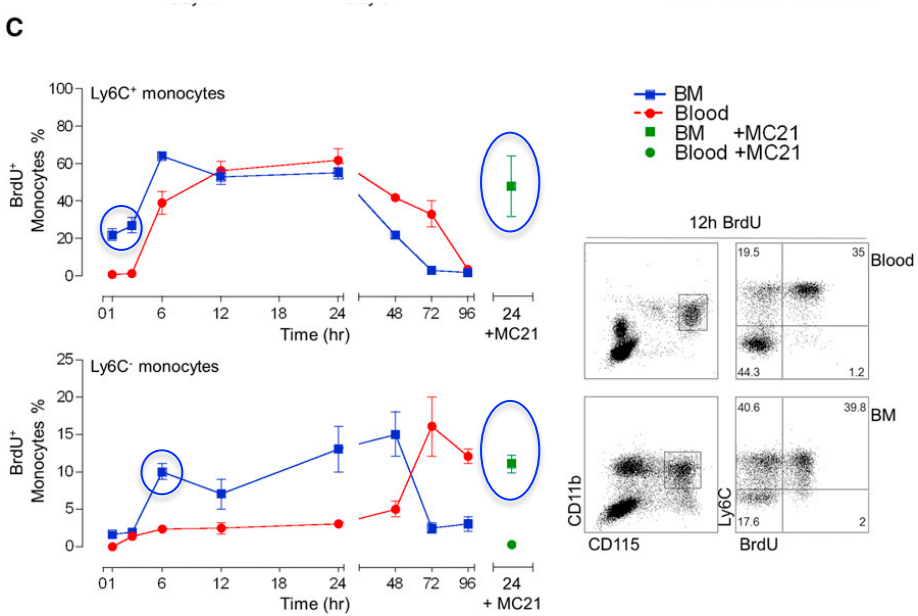
Monocyte subset dynamics: Ly6C$^+$ monos are precursors of Ly6C$^-$ monos

i.p. 2 mg BrdU



(MC21: i.p. every 48 hrs, 44 ng/mouse/time)

1X i.p. 2 mg BrdU



Ly6C$^-$ BM monos are generated in the BM and Ly6C$^-$ blood monos are generated in the blood

Fig.4

Impaired BM exit of Ly6C^{+} blood monocyte affects the Ly6C^{-} cell compartment

Mixed BM chimera: CCR2$^{+/+}$ CX3CR1$^{GFP/+}$ CD45.1^{+} : CCR2$^{-/-}$ CX3CR1$^{GFP/+}$ CD45.2^{+}

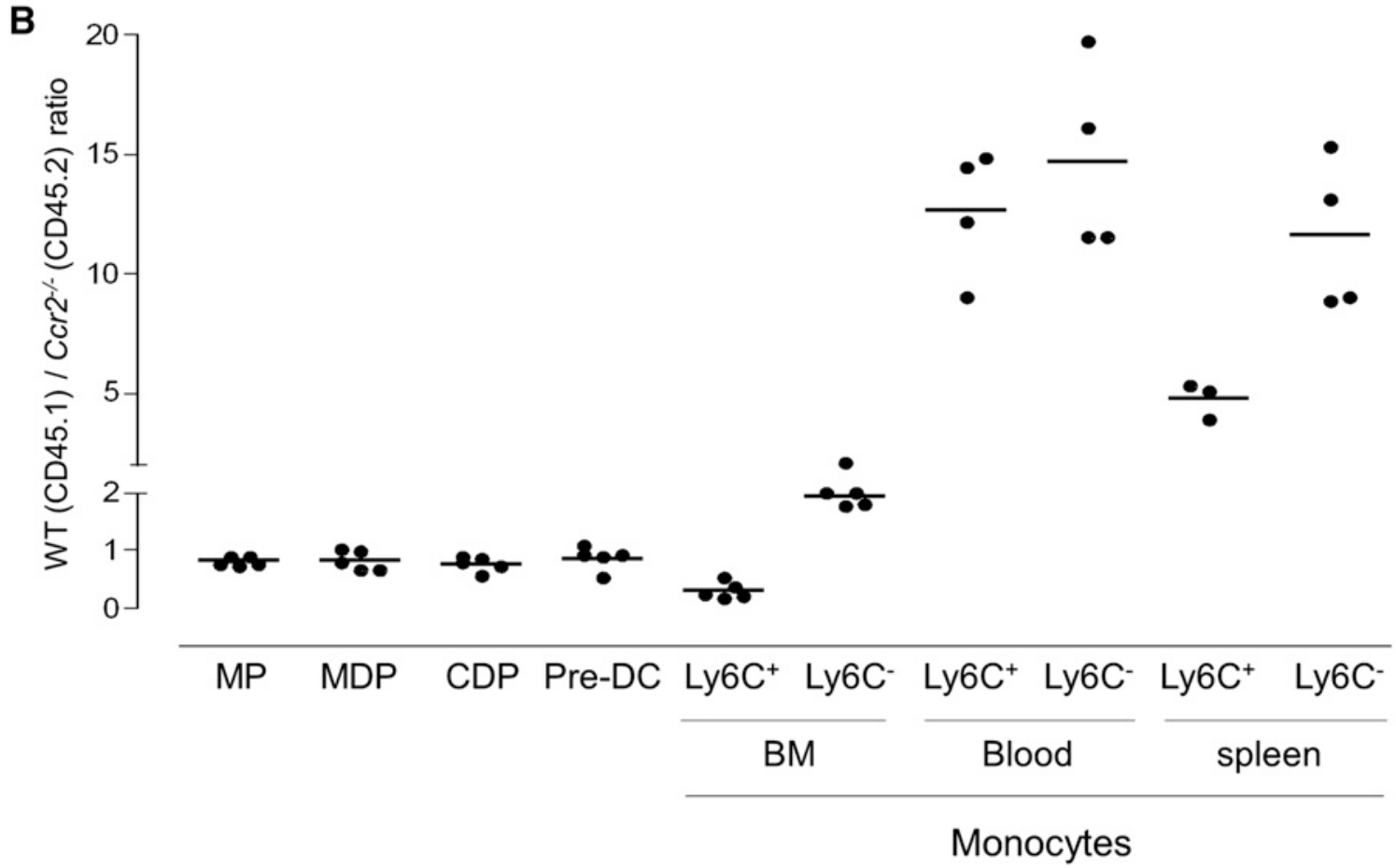
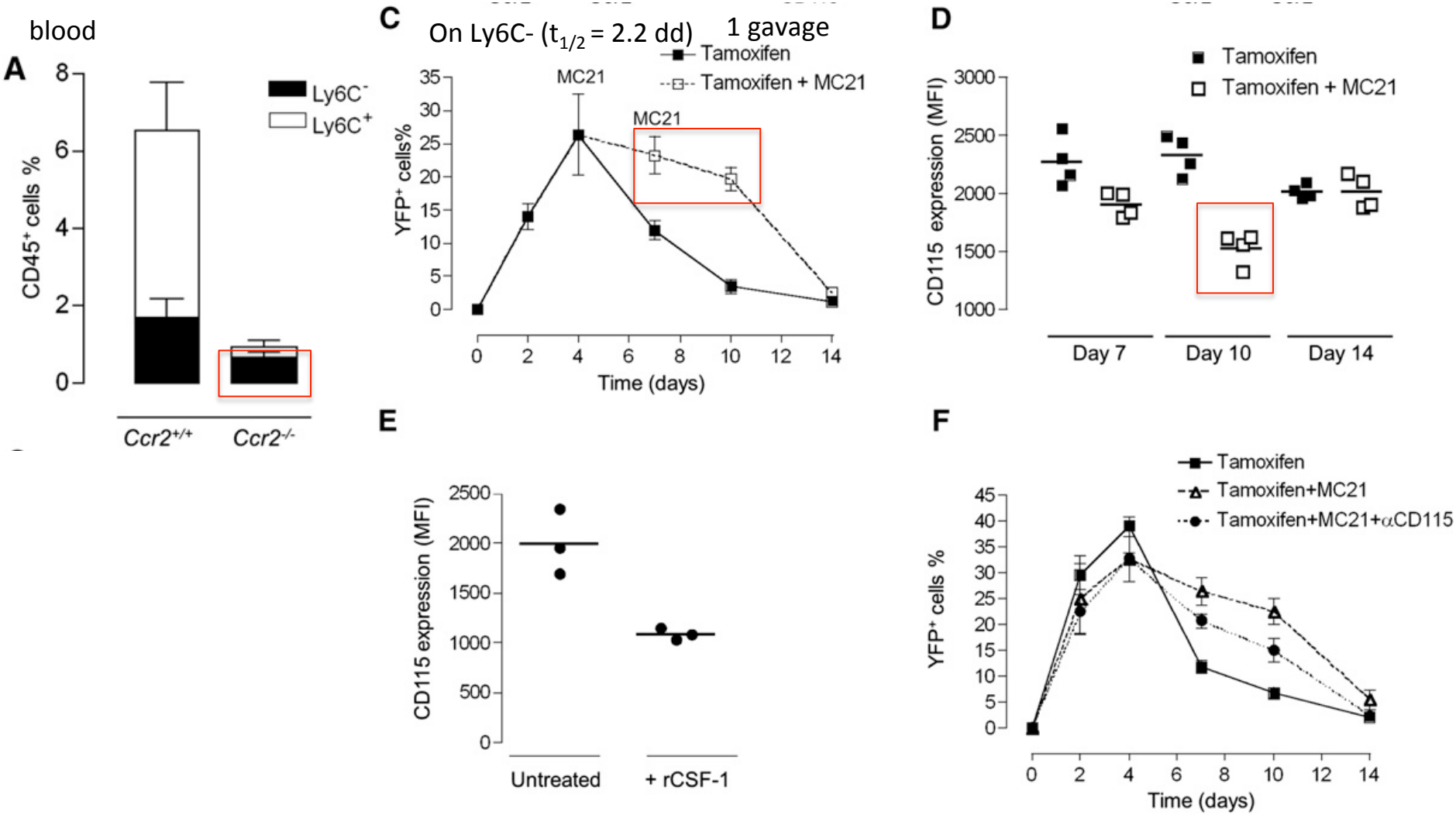


Fig.5

Prevalence of Ly6C$^+$ blood monocytes determines the circulation half-life of Ly6C$^-$ blood cells

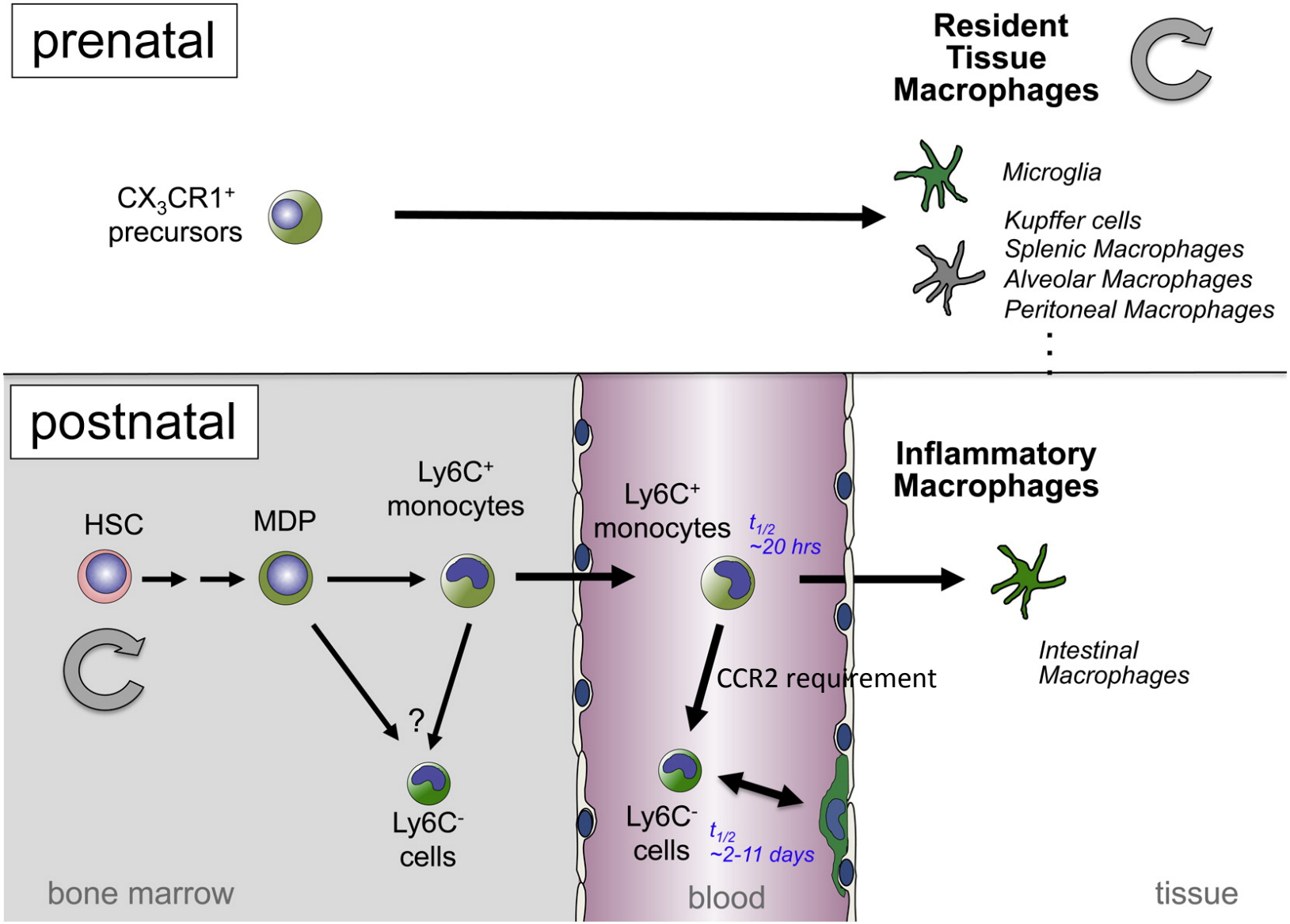


	Ly6C$^-$ monocyte half-life (days)	R^2
Tamoxifen	2.35	0.95
Tamoxifen + MC21	11.1	0.99
Tamoxifen + MC21 + αCD115	5.33	0.93

(αCD115: i.p. every 72 hrs, 200 μg/mouse/time)

Fig.6

Conclusion



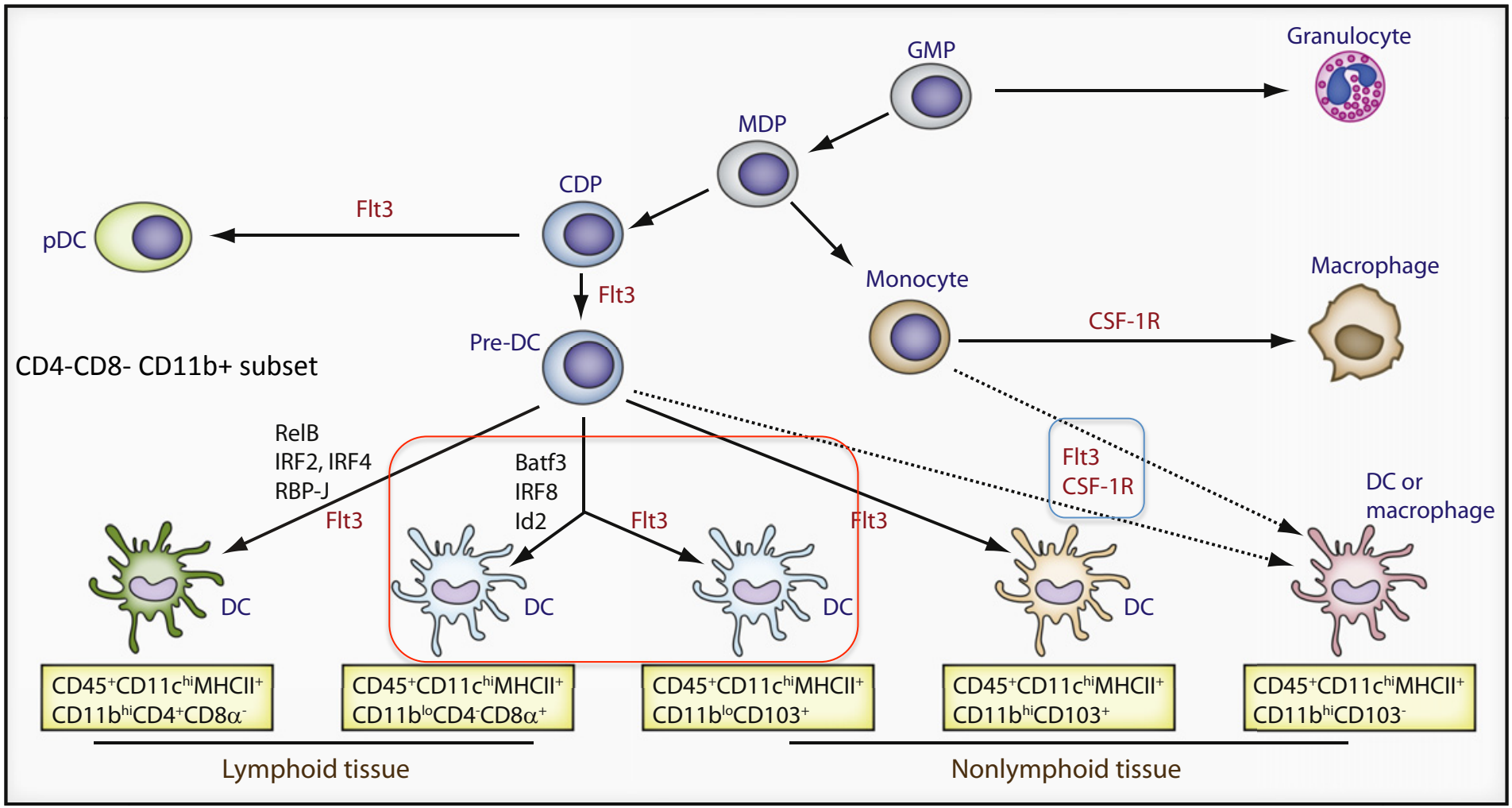
Immunity *38*, 79–91, January 24, 2013

IRF4 Transcription Factor-Dependent CD11b^{+} Dendritic Cells in Human and Mouse Control Mucosal IL-17 Cytokine Responses

Andreas Schlitzer,[1,9] Naomi McGovern,[2,9] Pearline Teo,[1] Teresa Zelante,[1] Koji Atarashi,[3] Donovan Low,[1] Adrian W.S. Ho,[1] Peter See,[1] Amanda Shin,[1] Pavandip Singh Wasan,[1] Guillaume Hoeffel,[1] Benoit Malleret,[1] Alexander Heiseke,[4] Samantha Chew,[1] Laura Jardine,[2] Harriet A. Purvis,[2] Catharien M.U. Hilkens,[2] John Tam,[5,6] Michael Poidinger,[1] E. Richard Stanley,[7] Anne B. Krug,[4] Laurent Renia,[1] Baalasubramanian Sivasankar,[8] Lai Guan Ng,[1] Matthew Collin,[2] Paola Ricciardi-Castagnoli,[1] Kenya Honda,[3] Muzlifah Haniffa,[2] and Florent Ginhoux[1,*]

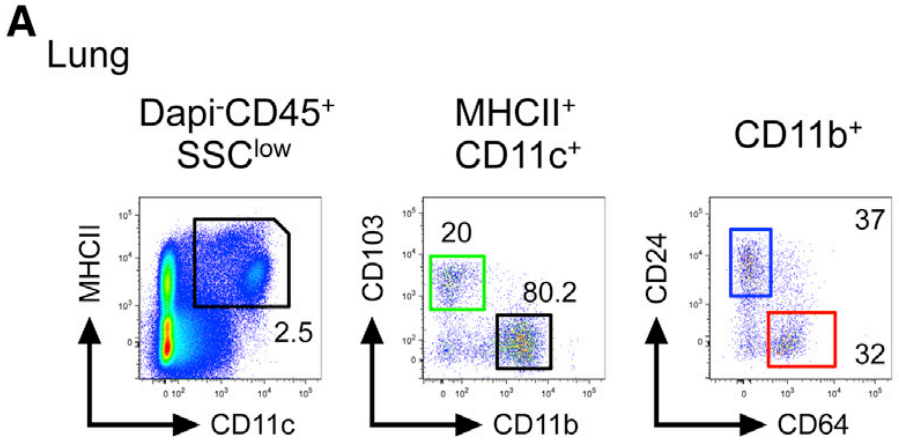
Immunity *38*, 970–983, May 23, 2013

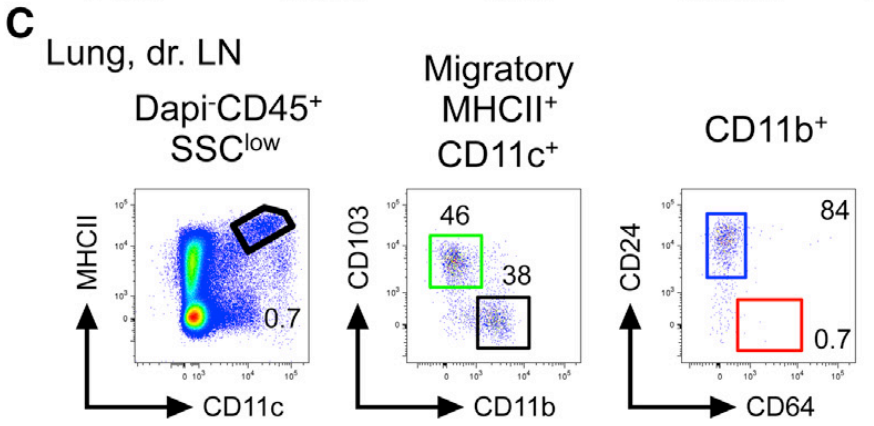
Background

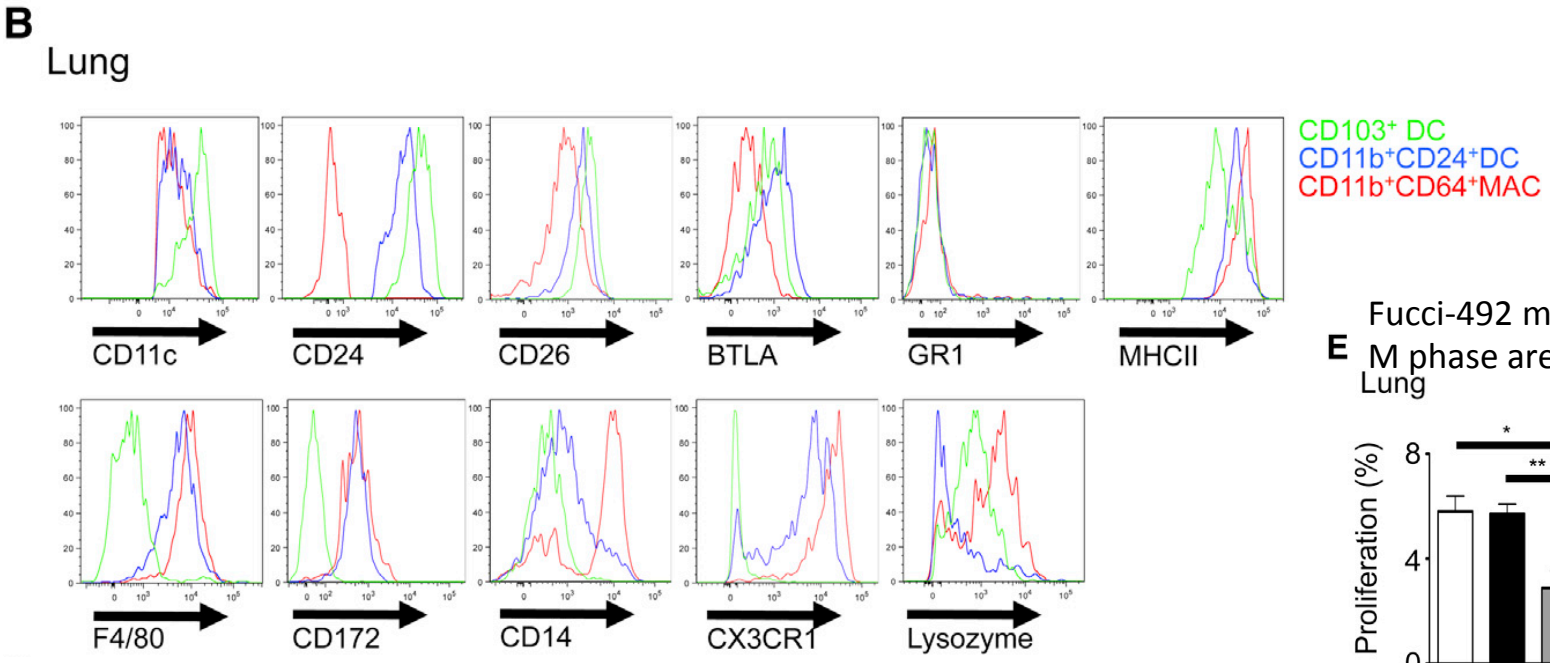


Modified from *Hashimoto D. et al, Immunity 2011*

Heterogenicity in lung CD11b⁺ DC population.







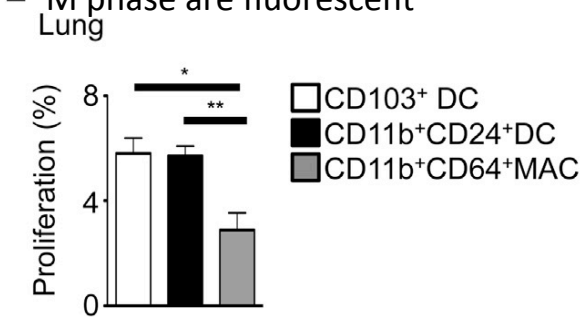


Fig.1

Lung CD11b⁺CD24⁺CD64⁻ Cells Are Bona Fide Flt3-dependent DCs, whereas CD11b⁺CD24⁻CD64⁺ Cells Are Csf-1r-dependent Macrophages

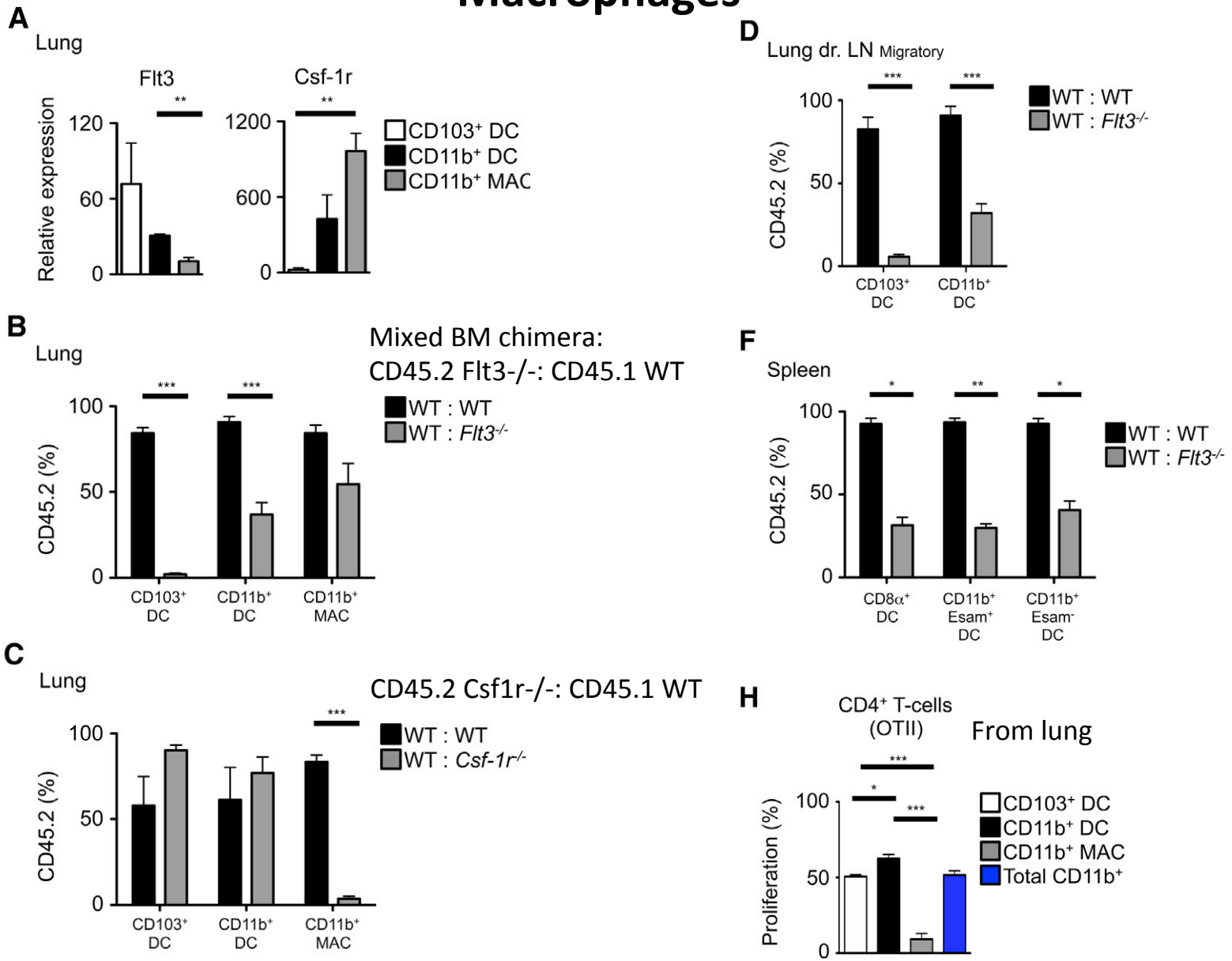


Fig.2

Lung CD11b$^+$ DCs are IRF4-dependent

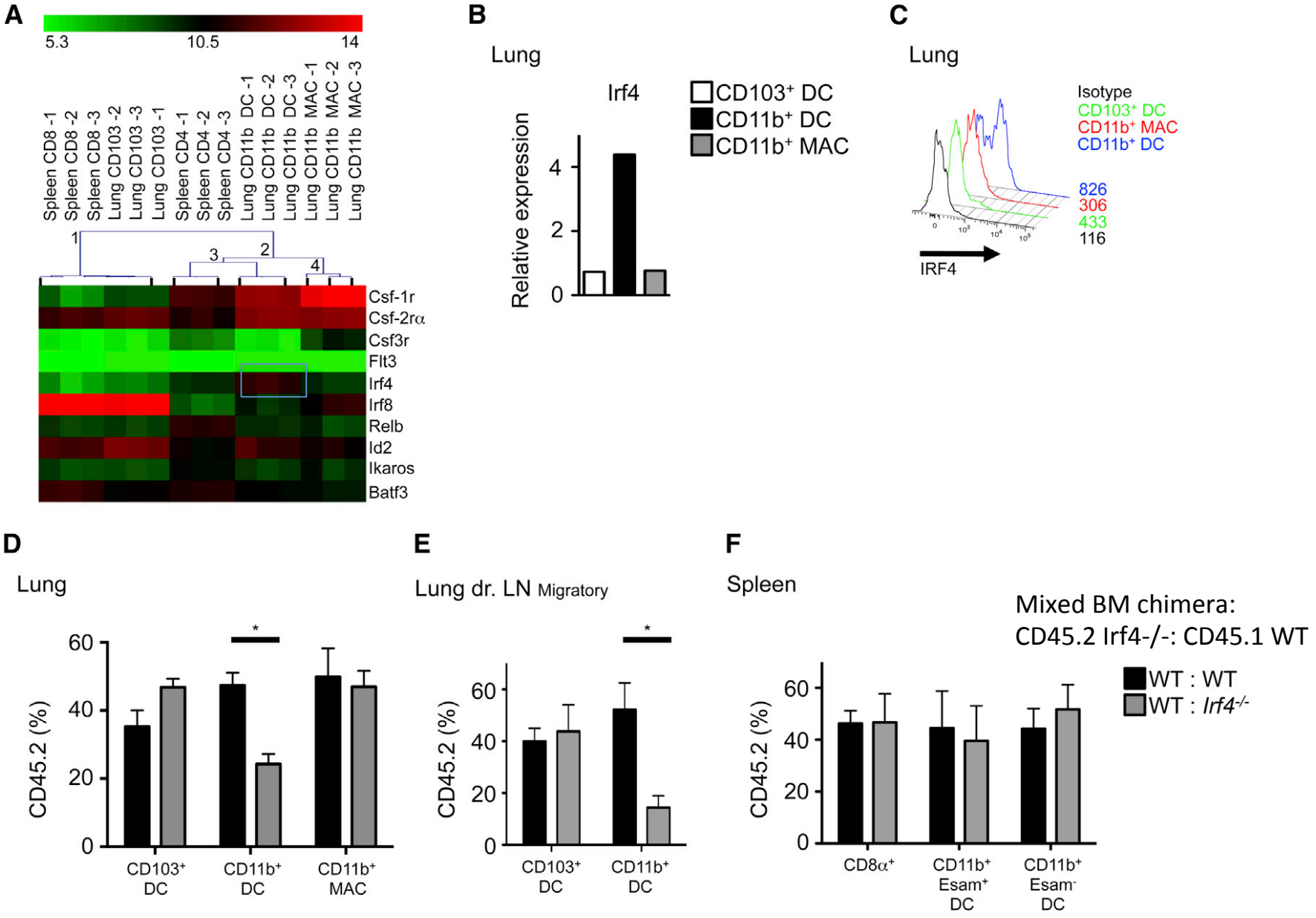


Fig.3

Like in the lung, gut CD11b⁺CD24⁺CD64⁻ cells are bona fide DCs, whereas CD11b⁺CD24⁻CD64⁺ cells are macrophages

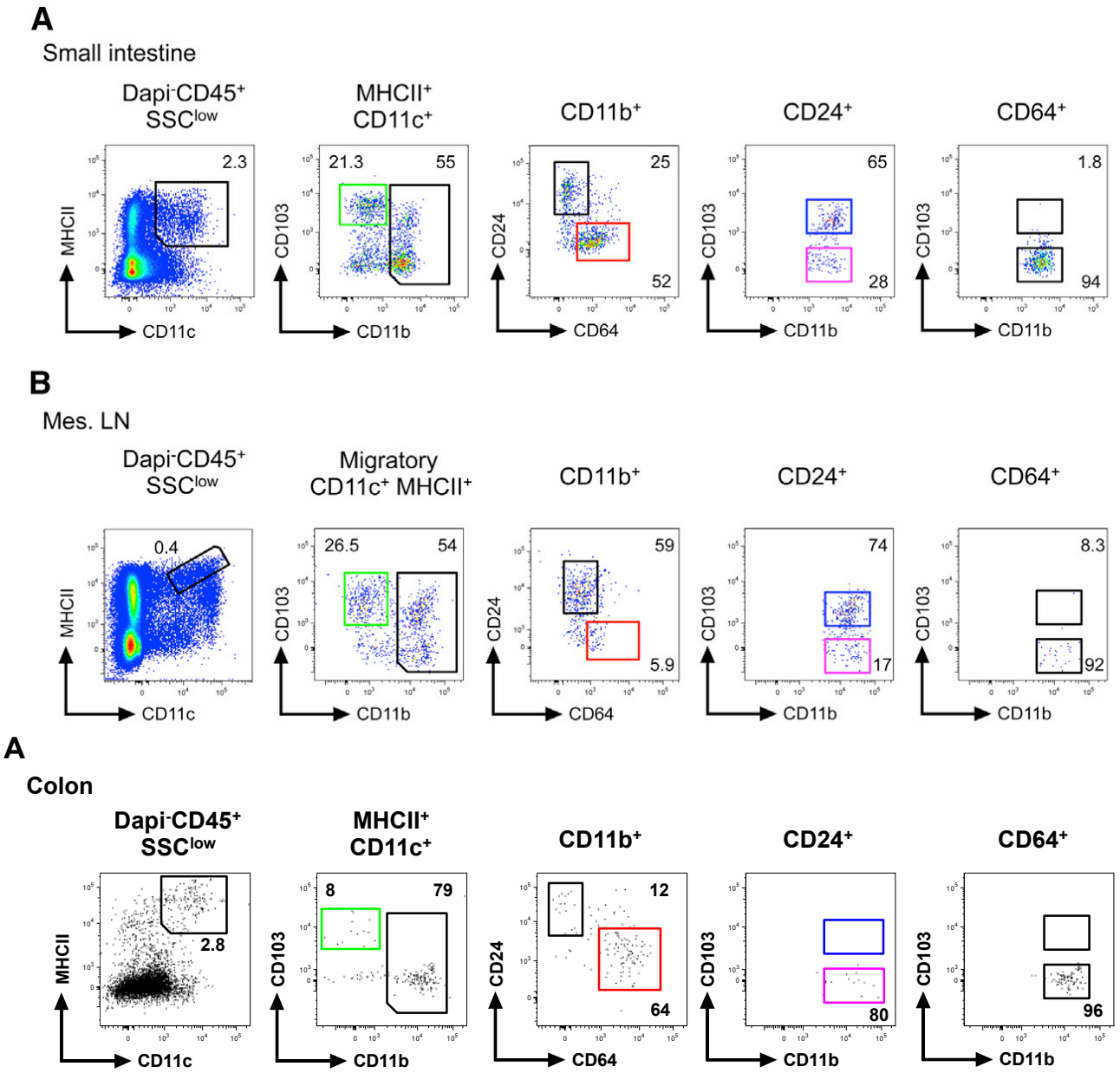


Fig.4 + Fig.S3

Gut lamina propria CD24^{+}CD103^{+}CD11b^{+} DCs are dependent on IRF4

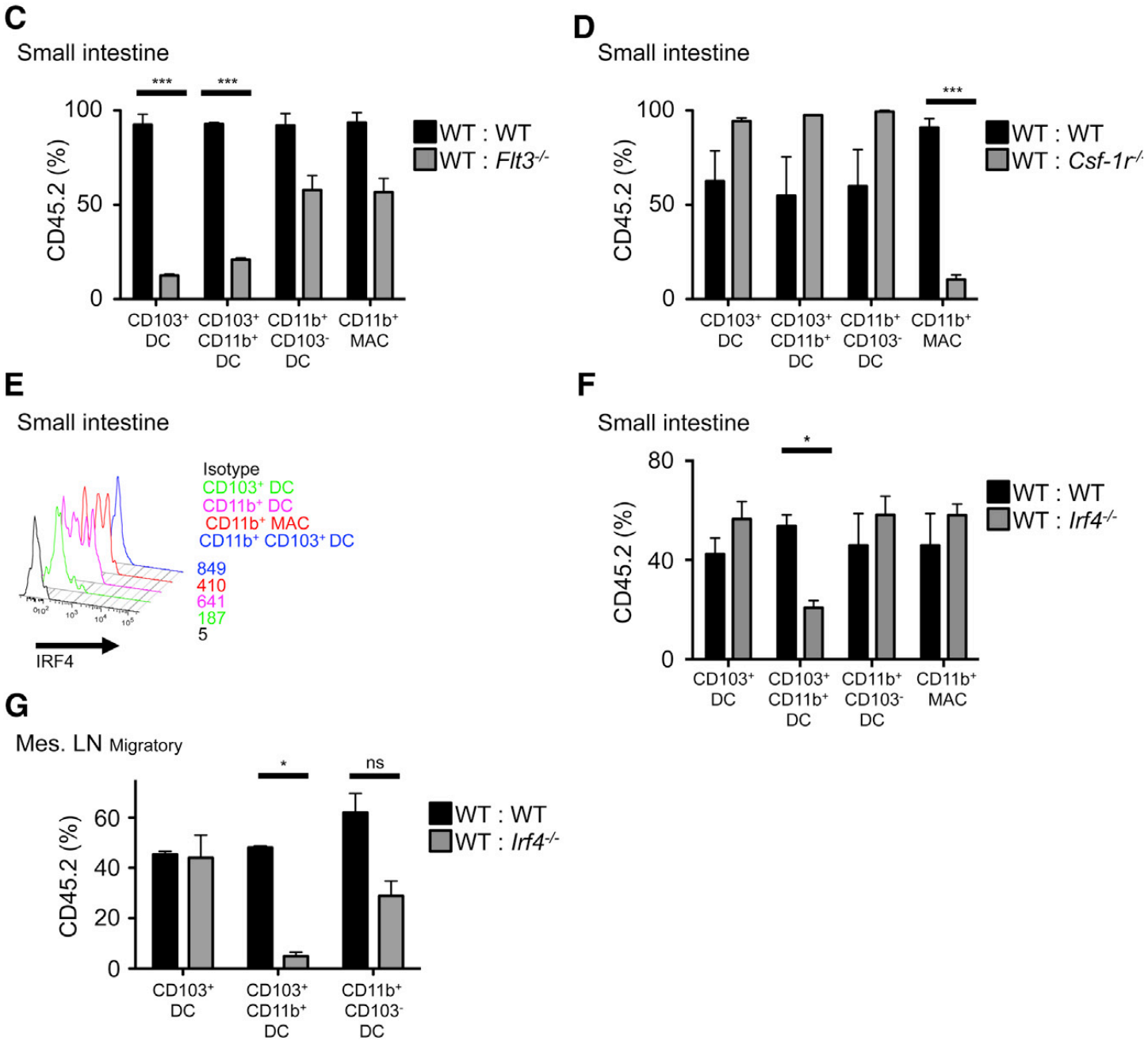
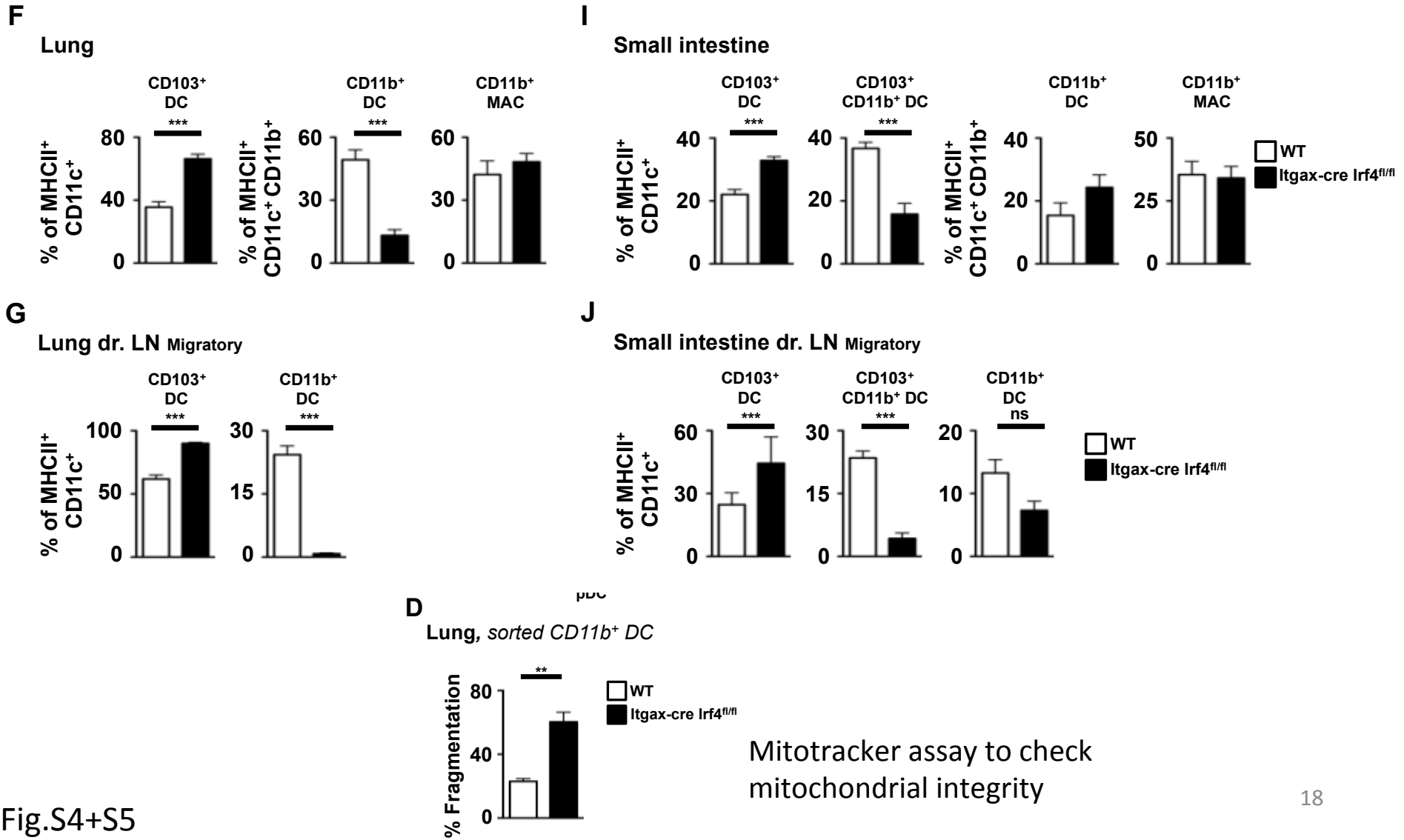


Fig.4

IRF4 has a prosurvival role and its absence in mucosal tissue CD11b^{+} DCs leads to apoptosis

Itgax-Cre mice x IRF4$^{fl/fl}$ GFP = excision of IRF4 only on CD11c^{+} cells which became GFP^{+}



Mitotracker assay to check mitochondrial integrity

Fig.S4+S5

CD11b^{+}CD24^{+} DCs in SI (and lung) control Th17 responses

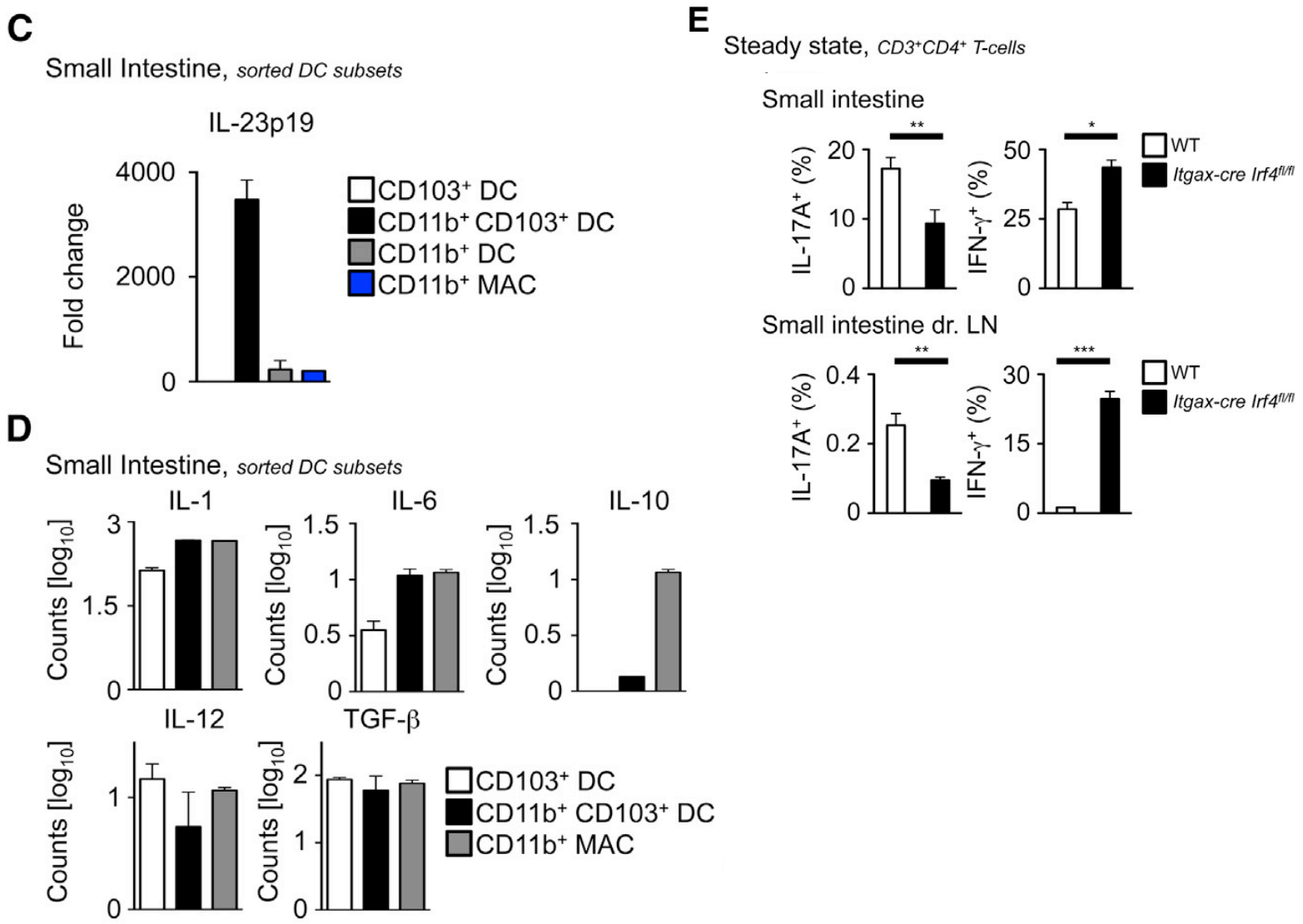


Fig.5

IRF4-dependent CD24^{+}CD11b^{+} lung DCs control Th17 cell responses

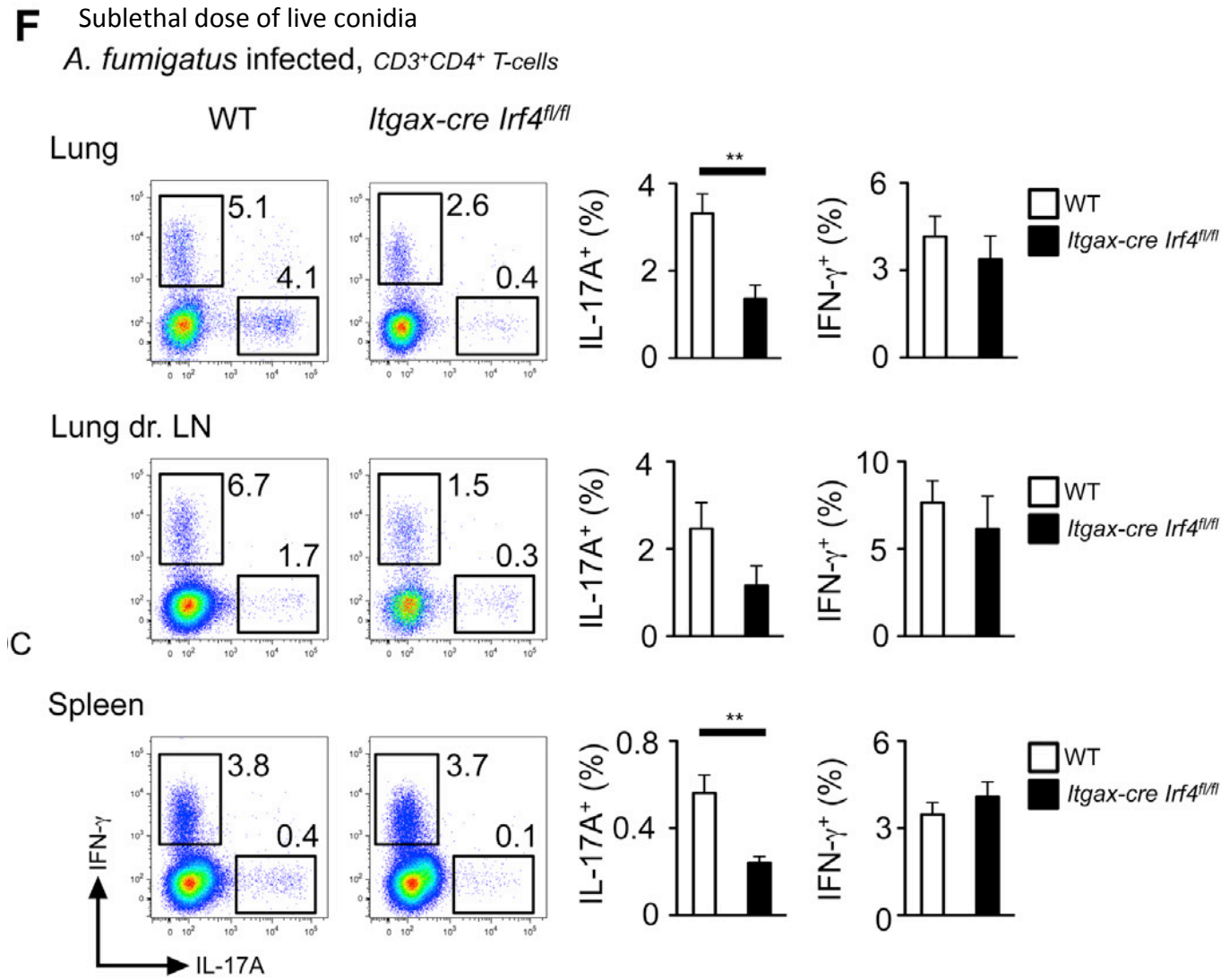


Fig.5

Homology between human CD1c$^+$ DCs and murine CD11b$^+$ DCs.

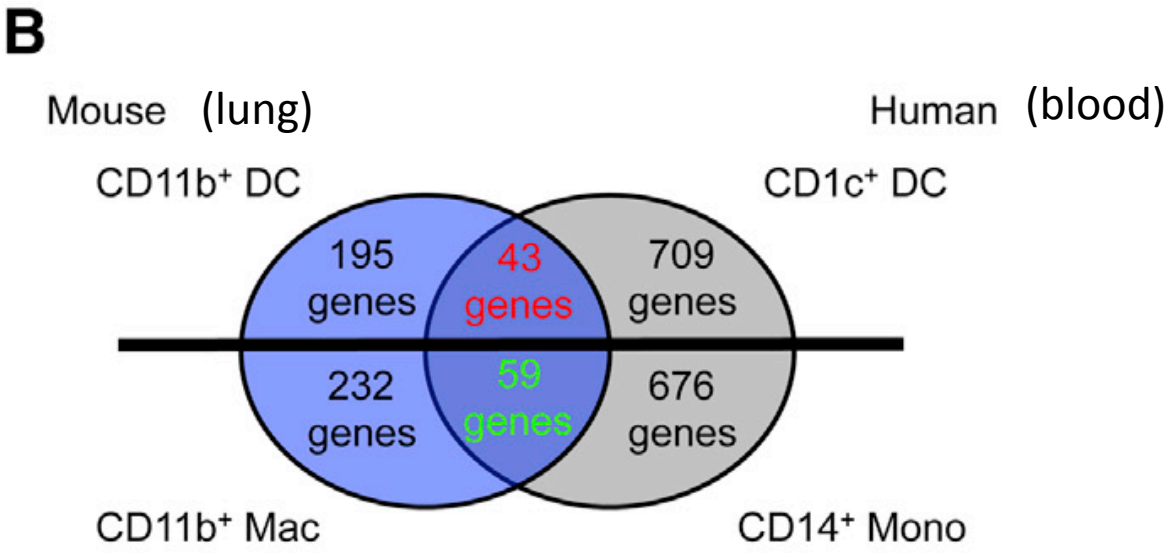


Fig.6

Human IRF4 expressing CD1c⁺ DCs induce IL-17 T helper response

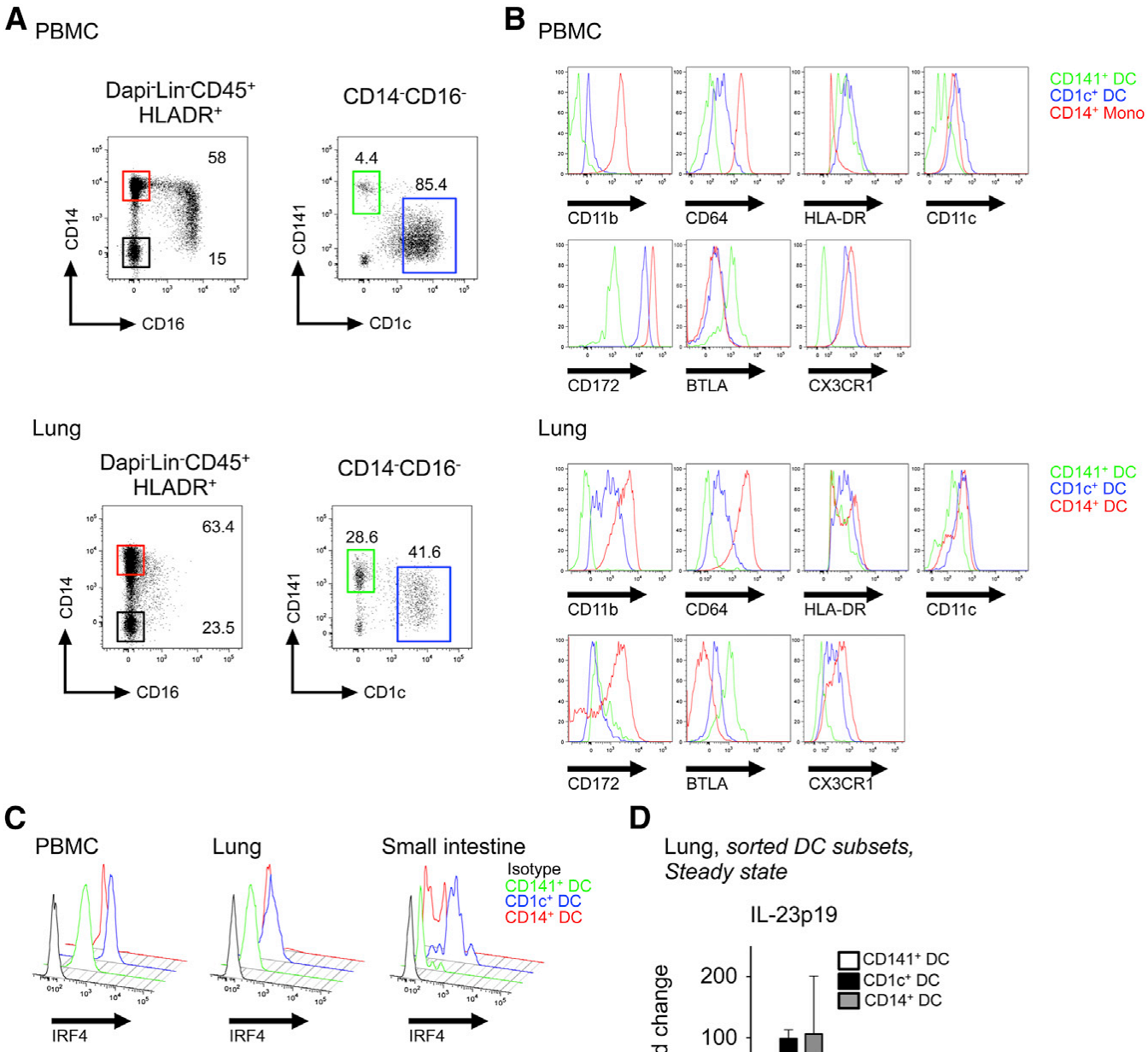


Fig.7

Human IRF4 expressing CD1c$^+$ DCs induce IL-17 T helper response

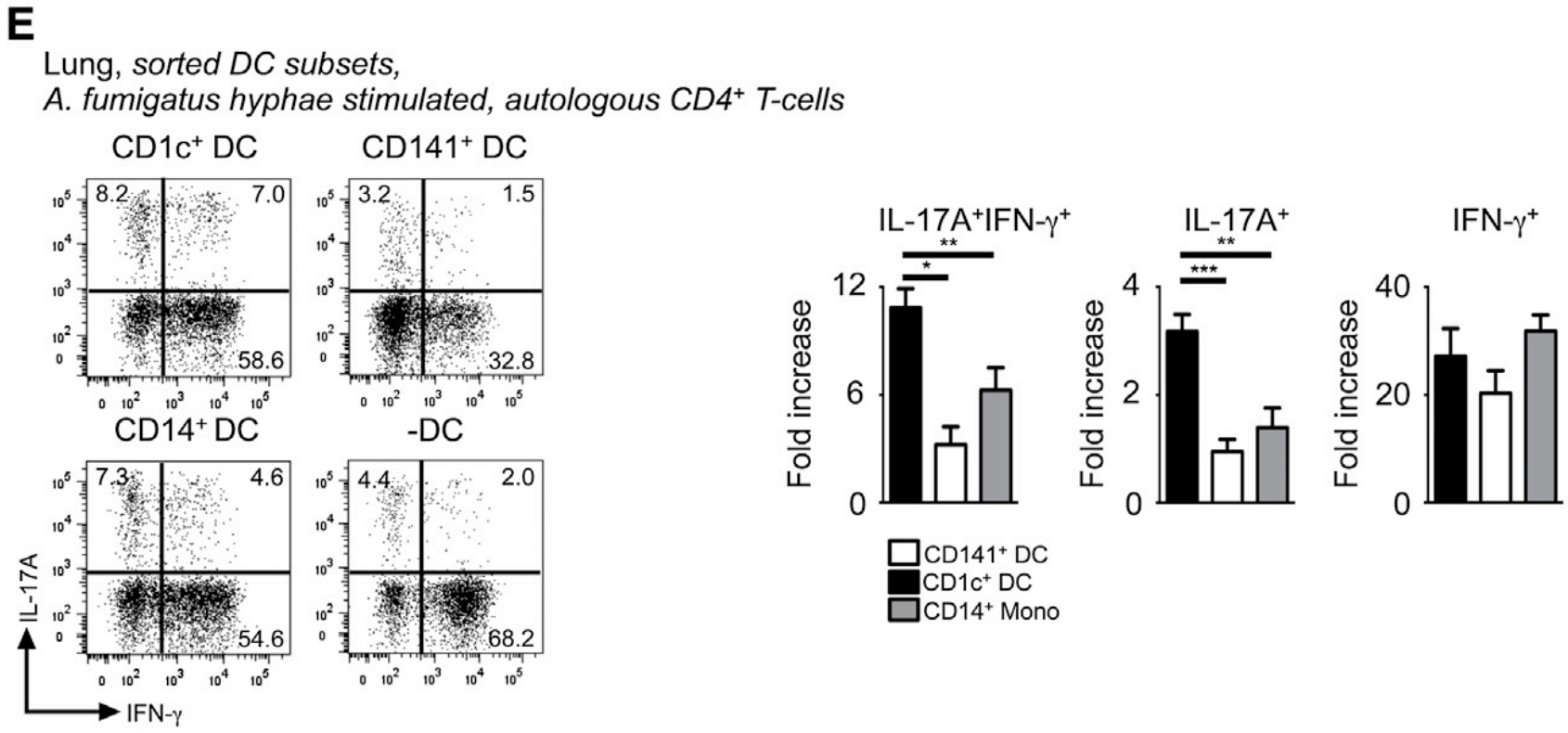


Fig.7

Conclusion

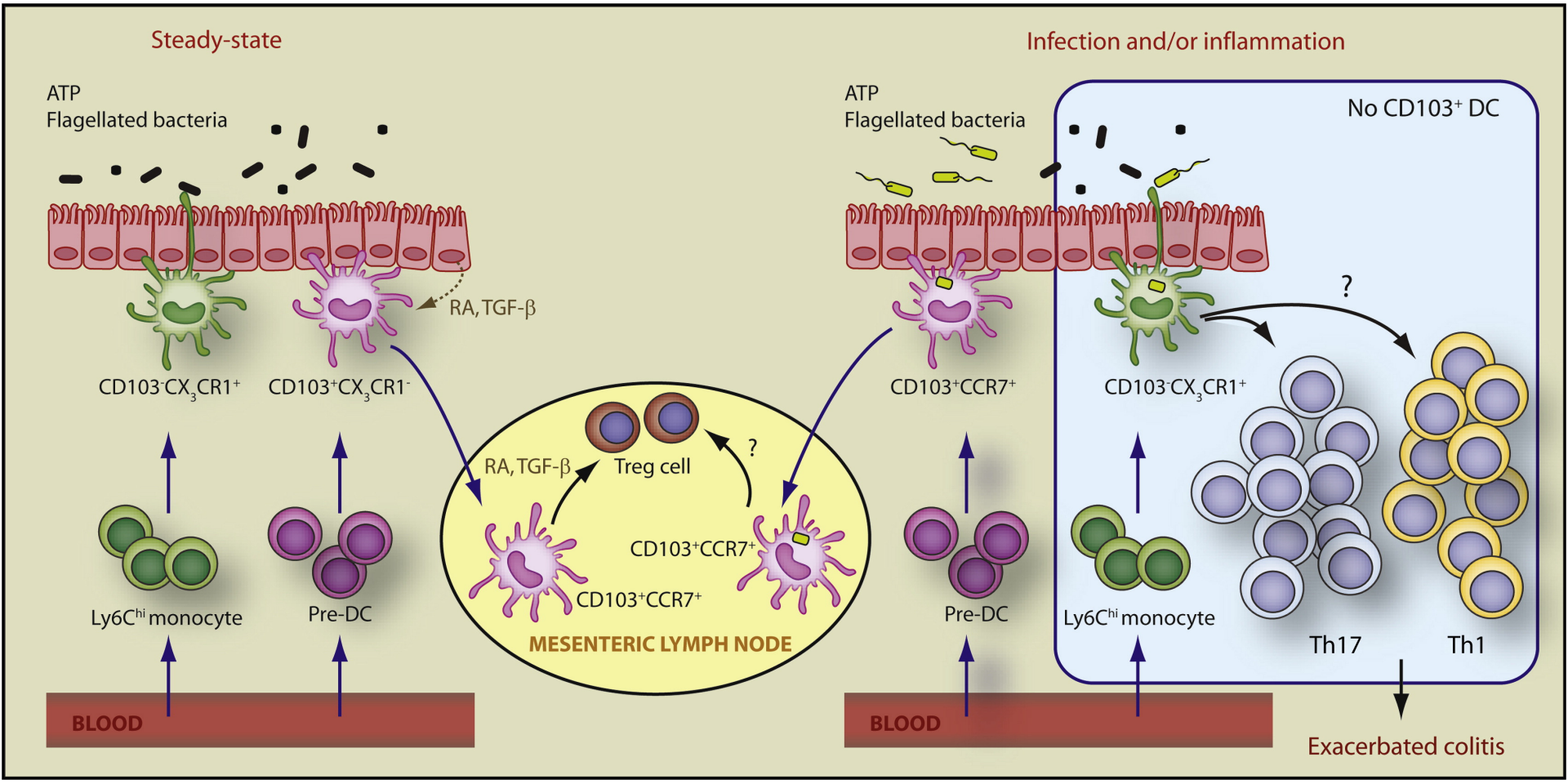
- Identification of FLT3-dependent $CD11b^{+}CD24^{+}CD64^{-}$ bona fide DCs and CSF-1R-dependent $CD11b^{+}CD24^{-}CD64^{+}$ MACs in steady state lung and SI: existence of a mucosal $CD11b^{+}$ DC lineage?

- DC specific IRF4 deficiency did not fully ablate lung or gut $CD24^{+}CD11b^{+}$ DCs, suggesting that IRF4 is not involved in their differentiation but rather in their survival or proliferation.

- IRF4 involvement is not at the DC progenitor level. IRF4 appears to have a prosurvival effect on NLT $CD11b^{+}$ DCs because the remaining lung $CD11b^{+}$ DCs lacking IRF4 exhibited enhanced mitochondrial fragmentation compared to WT cells.

- Characterization of human and murine $IRF4^{+}CD11b^{+}$ DCs found in mucosal tissues that control Th17 T cell differentiation through the secretion of IL-23 during steady state and inflammation. Human lung and blood $CD1c^{+}$ DCs pulsed with *A. fumigatus* hyphae were superior at inducing IL-17A production by autologous $CD4^{+}$ T cells.

Background



Rescigno M, Immunity 2009