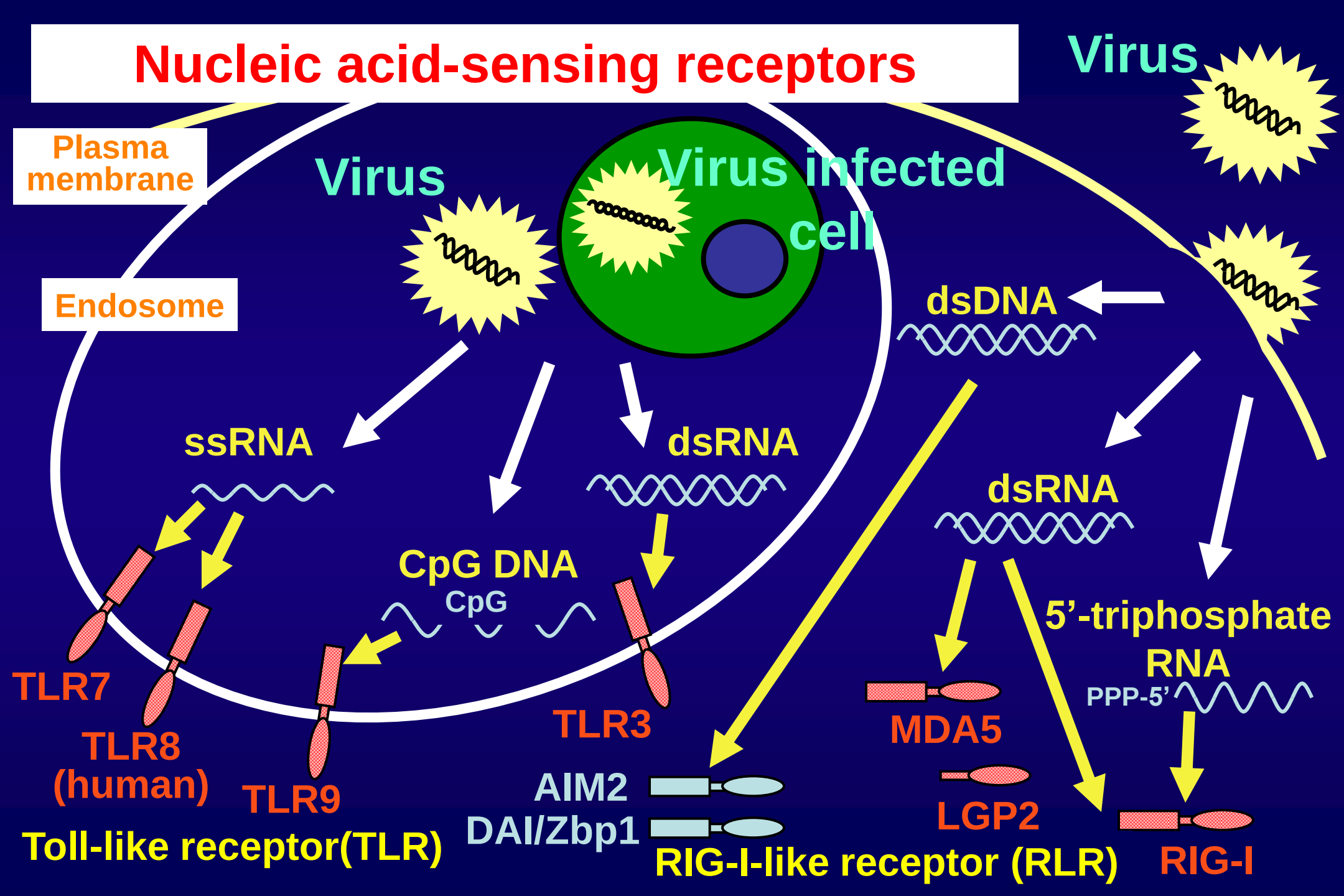
ワクチンフォーラム2010
September 14, 2010

核酸アジュバントによる樹状細胞活性化の分子メカニズム

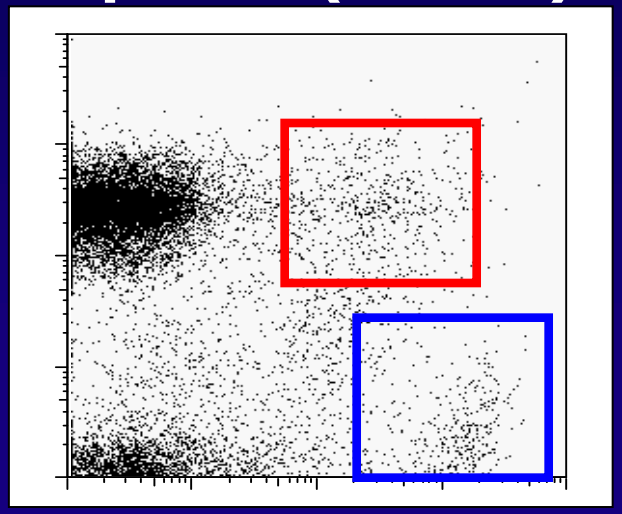
理研　免疫・アレルギー科学総合研究センター
生体防御研究チーム
改正　恒康

Homepage:http://www.riken.jp/hosdef/index.html

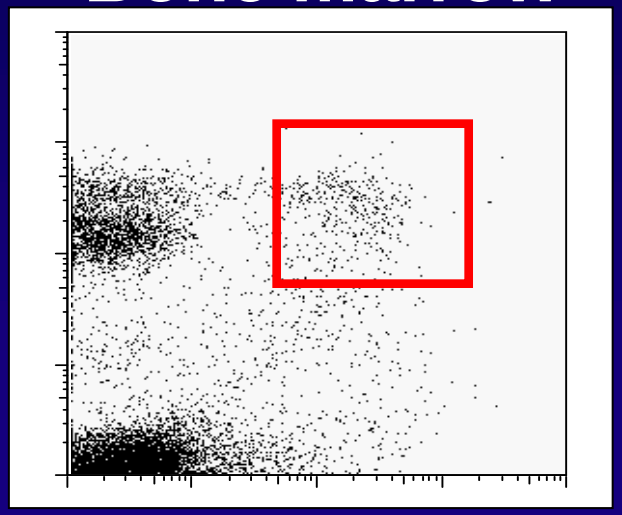

Nucleic acid-sensing receptors
Virus
Plasma membrane
Virus
Virus infected cell
Endosome
dsDNA
ssRNA
dsRNA
dsRNA
CpG DNA
CpG
5’-triphosphate RNA
PPP-5’
TLR7
TLR8 (human)
TLR9
TLR3
MDA5
AIM2
DAI/Zbp1
LGP2
Toll-like receptor(TLR)
RIG-I-like receptor (RLR)
RIG-I

Conventional and plasmacytoid DC

Spleen (whole)

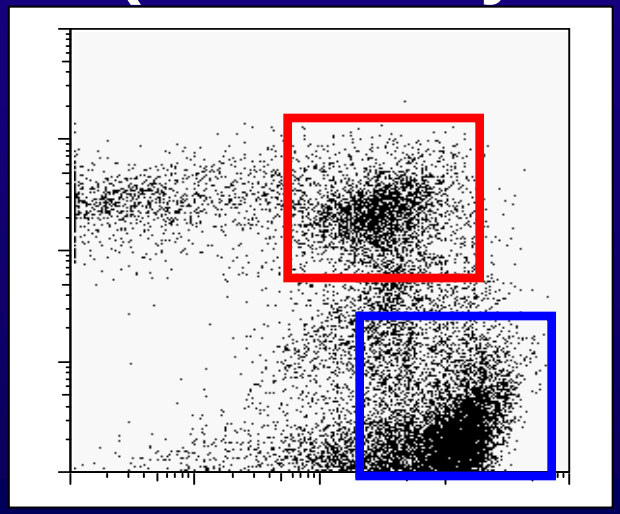


Bone marrow



B220

Spleen (CD11c+ by MACS)



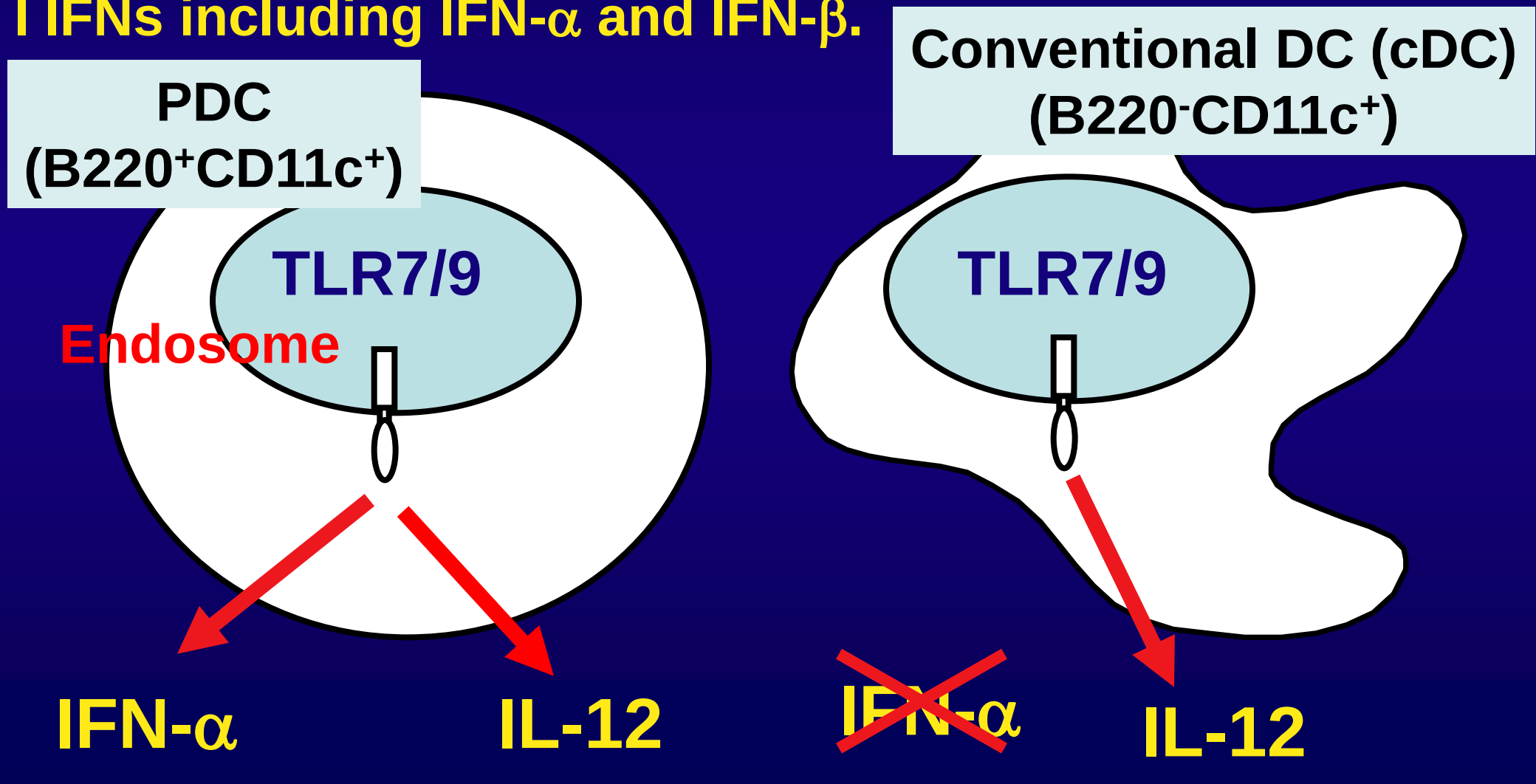
CD11c

Plasmacytoid DC

Conventional DC

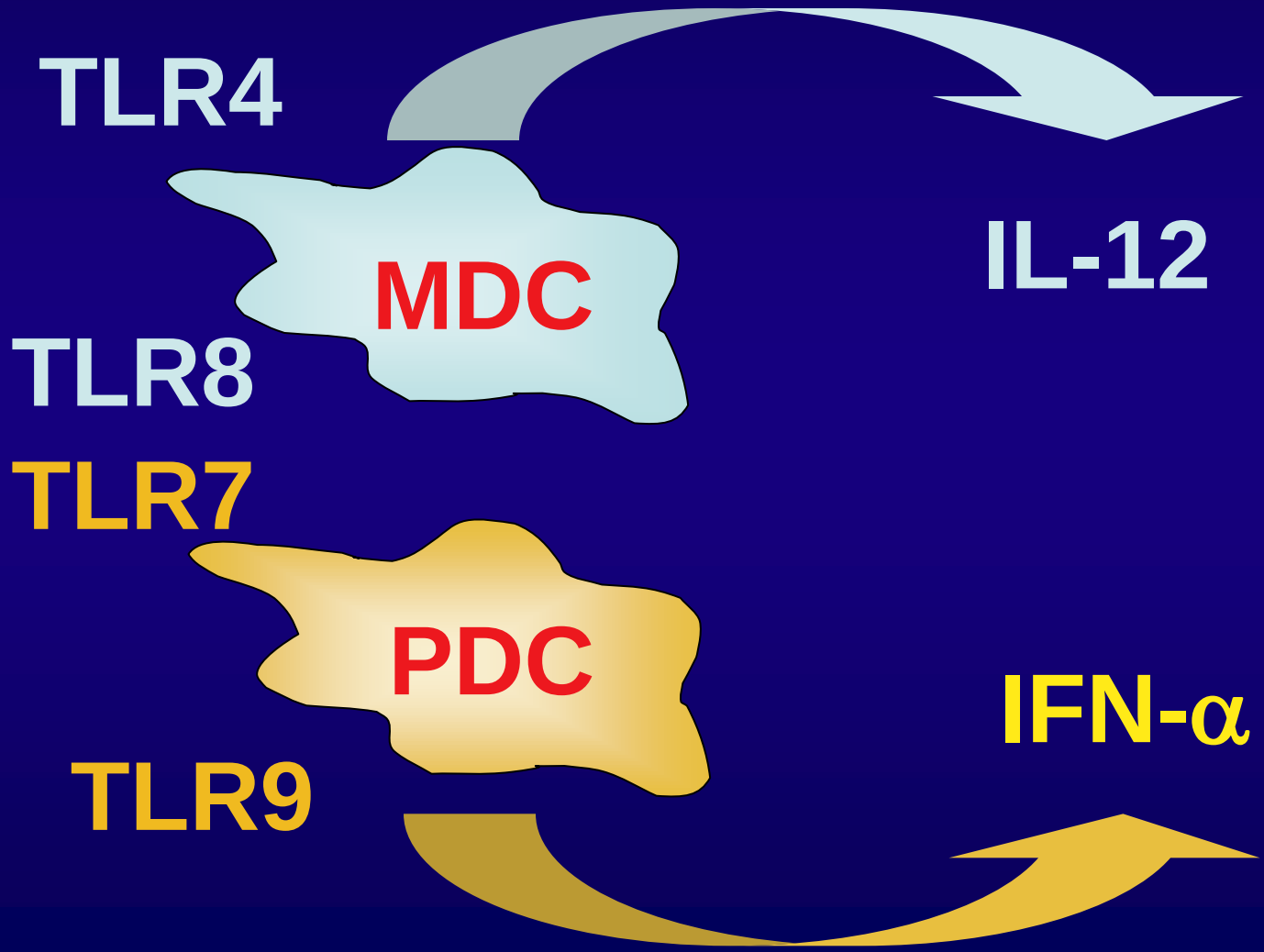
Plasmacytoid DC

PDC expresses nucleic acid sensing TLRs, TLR7 and TLR9 exclusively among pathogen sensors. In response to TLR7/9 stimuli, pDC can produce vast amounts of type I IFNs including IFN-α and IFN-β.

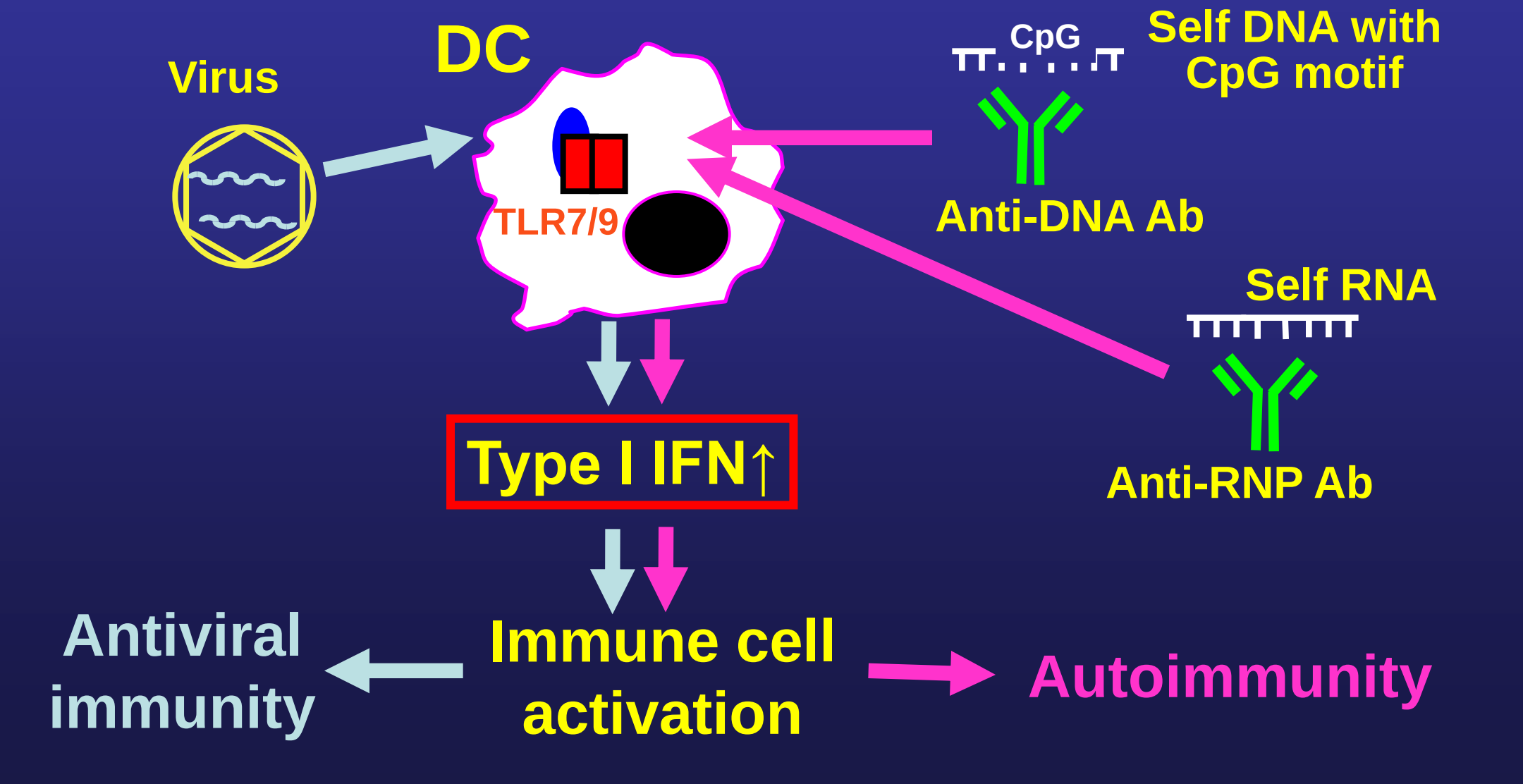


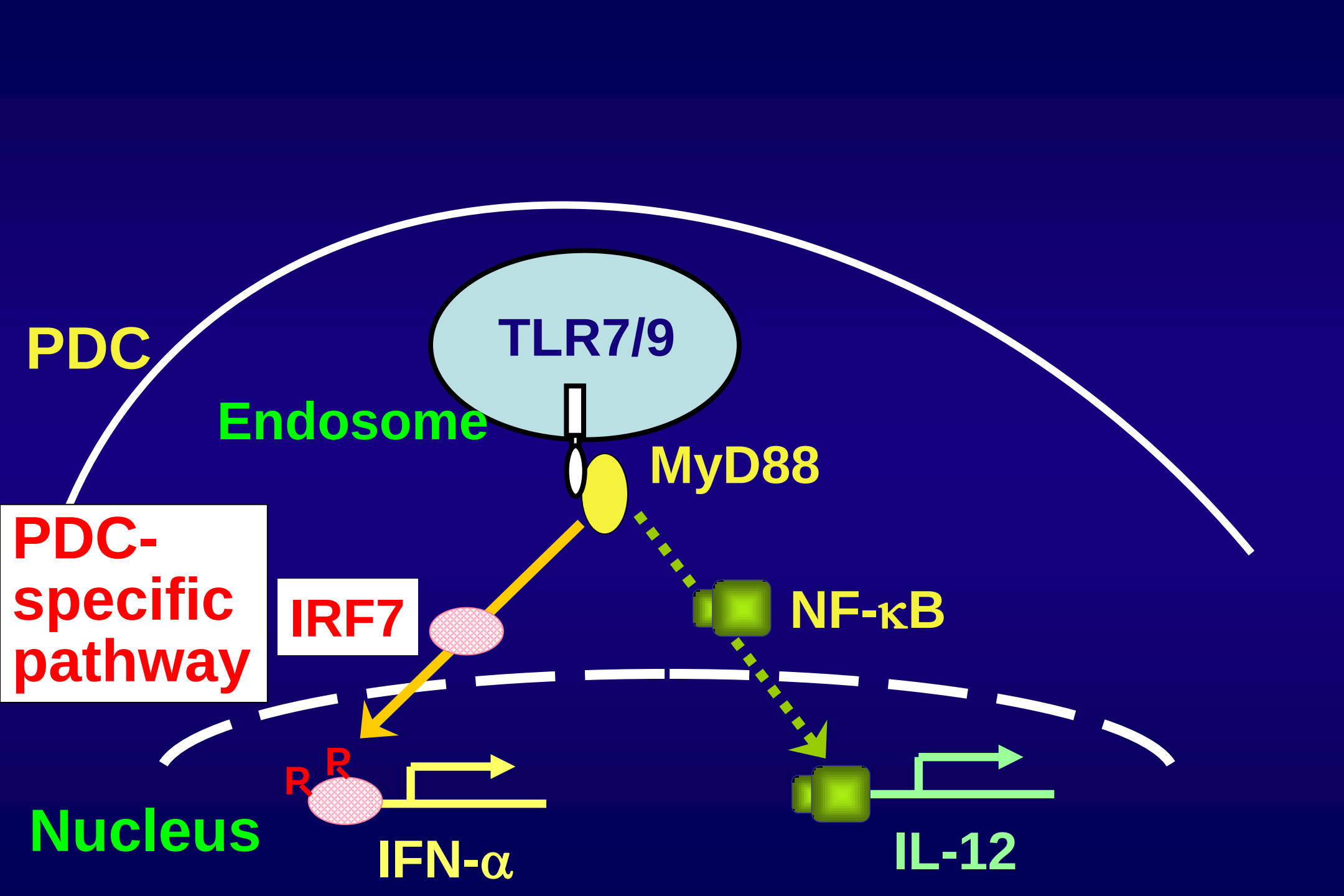
In human

Human DC subsets

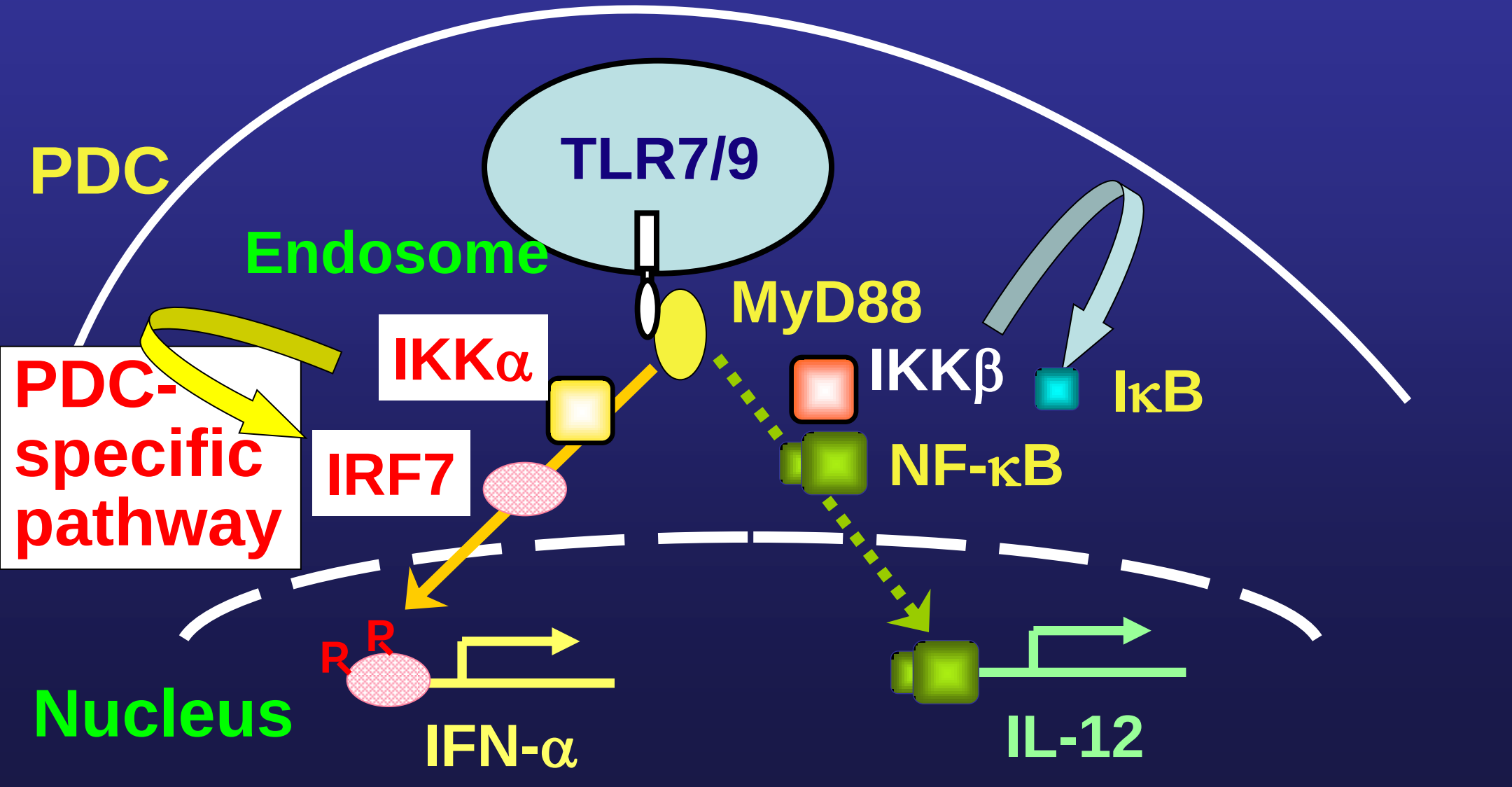


Type I IFN induction through TLR7/9 signaling is critical not only for antiviral immunity but also for pathogenesis of autoimmune diseases.



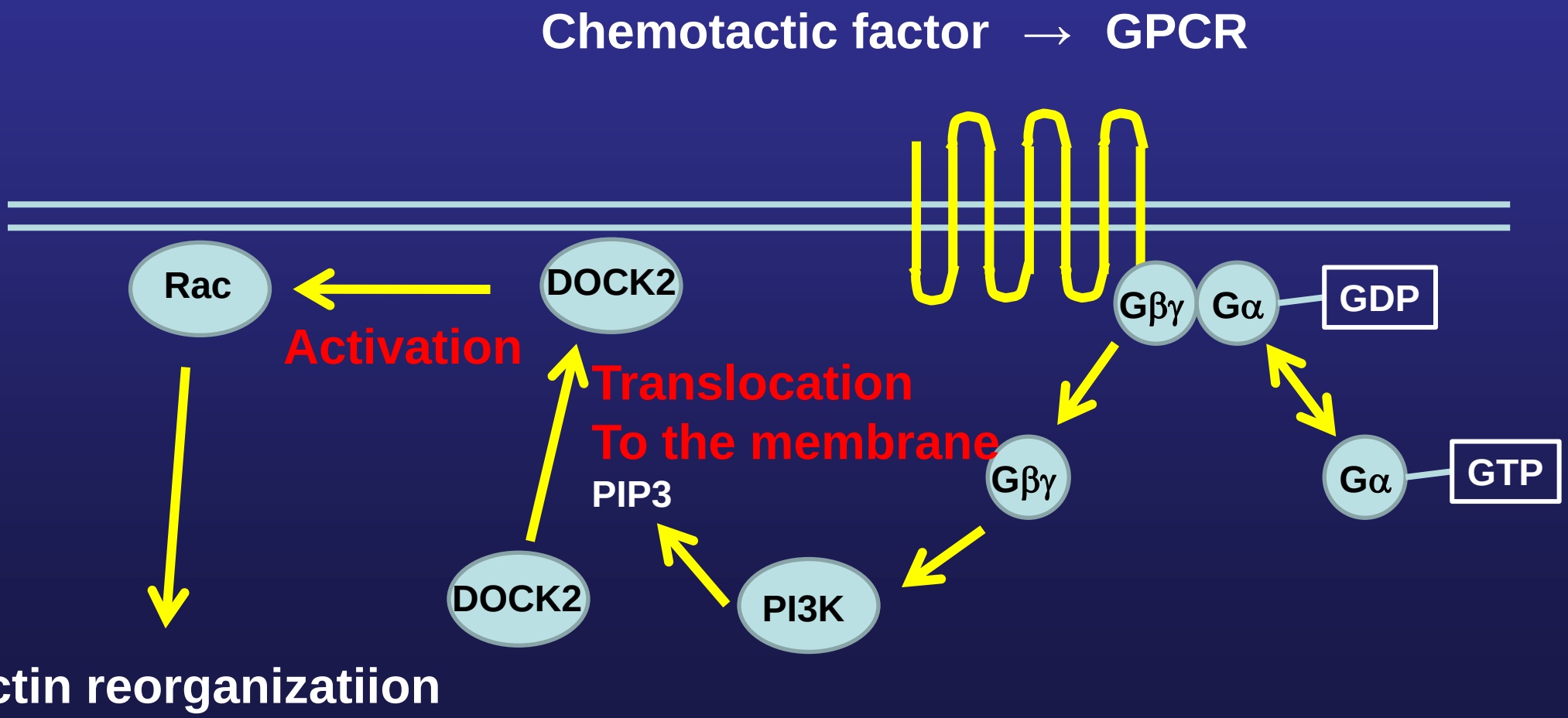

PDC
TLR7/9
Endosome
MyD88
PDC-specific pathway
IRF7
NF-κB
R
R
Nucleus
IFN-α
IL-12

IKKα is critical for TLR7/9-induced type I IFN production through the association with and activation of IRF-7 in pDC. (Hoshino et al. nature 2006.)



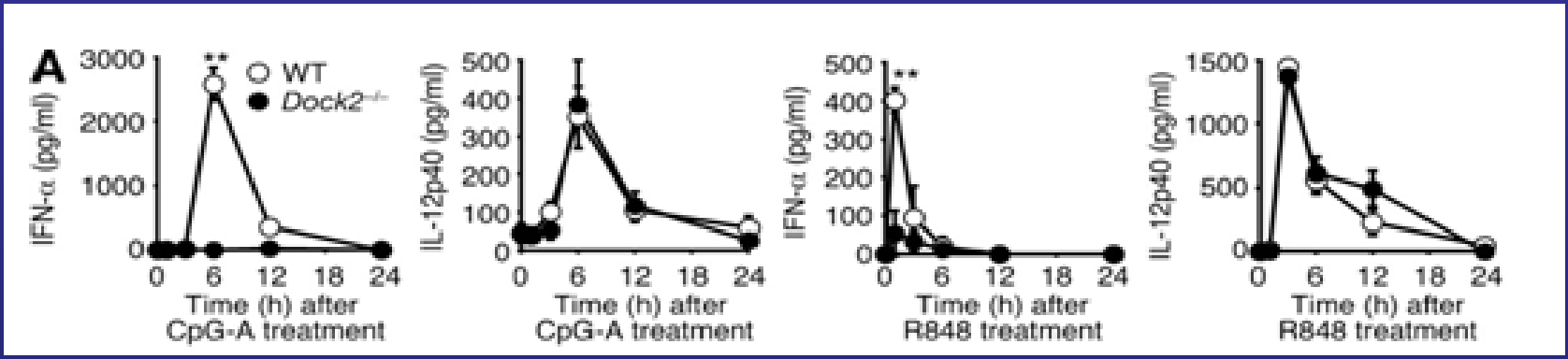
DOCK2

The Rac activating molecule at the downstream of neutrophil GPCR

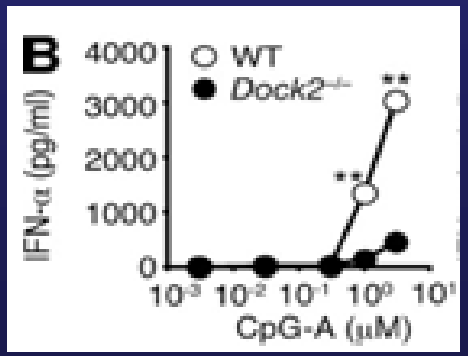


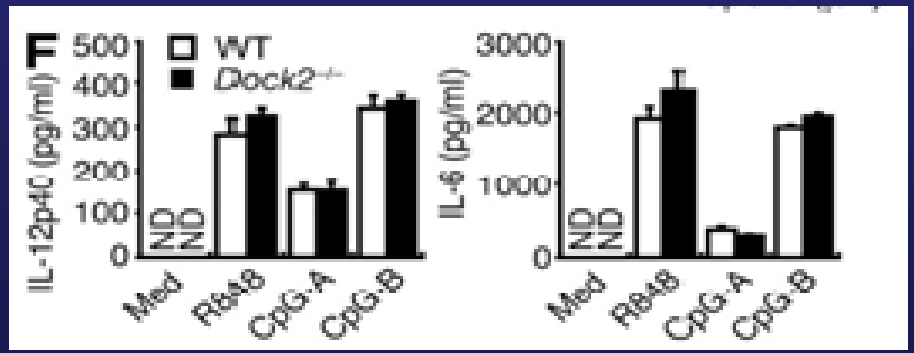
DOCK2 is required for TLR7/9-mediated type I IFN induction in pDC

Serum cytokine level after injection of TLR7/9 agonists



Cytokine production from TLR7/9-stimulated pDC

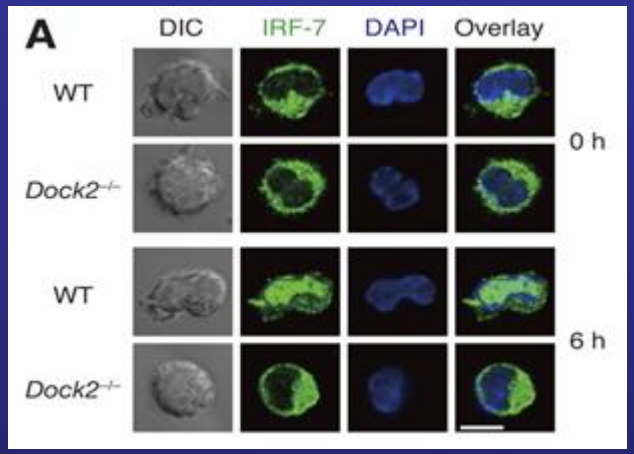


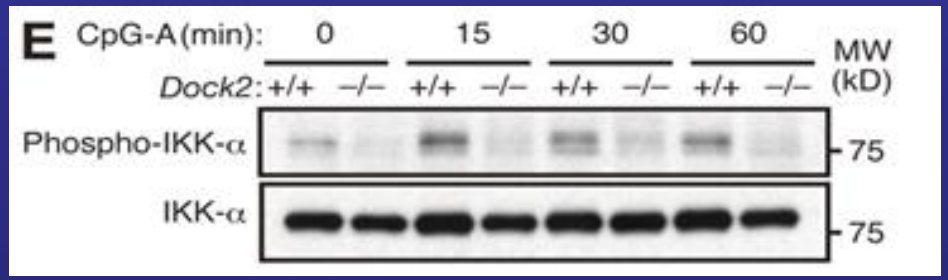


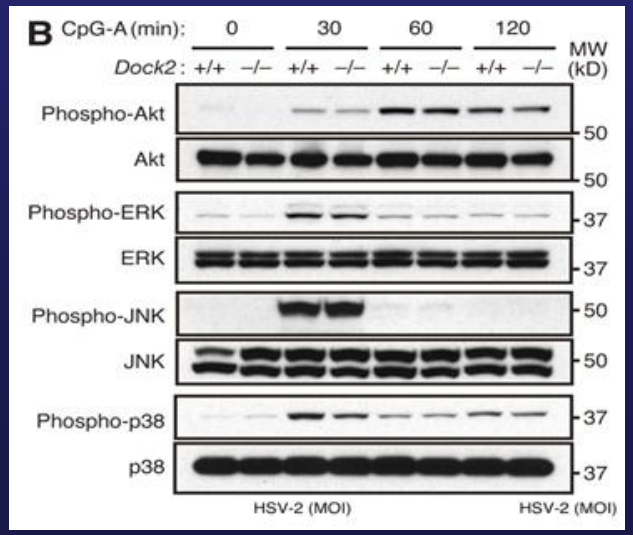
Gotoh K et al. J Exp Med 2010,207:721-730.

DOCK2-mediated Rac activation is critical for IKKα activation in pDCs.

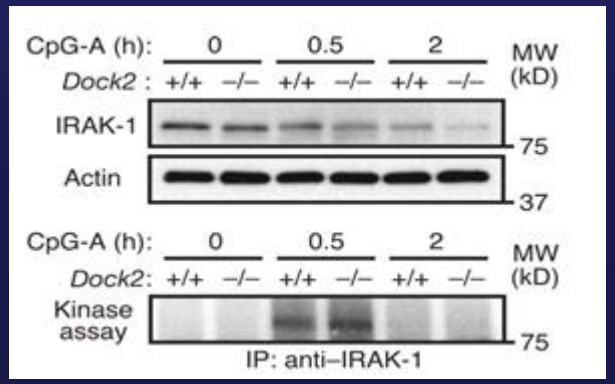
Impairment of IRF-7 nuclear translocation and IKKα phosphorylation induced by TLR9 stimuli





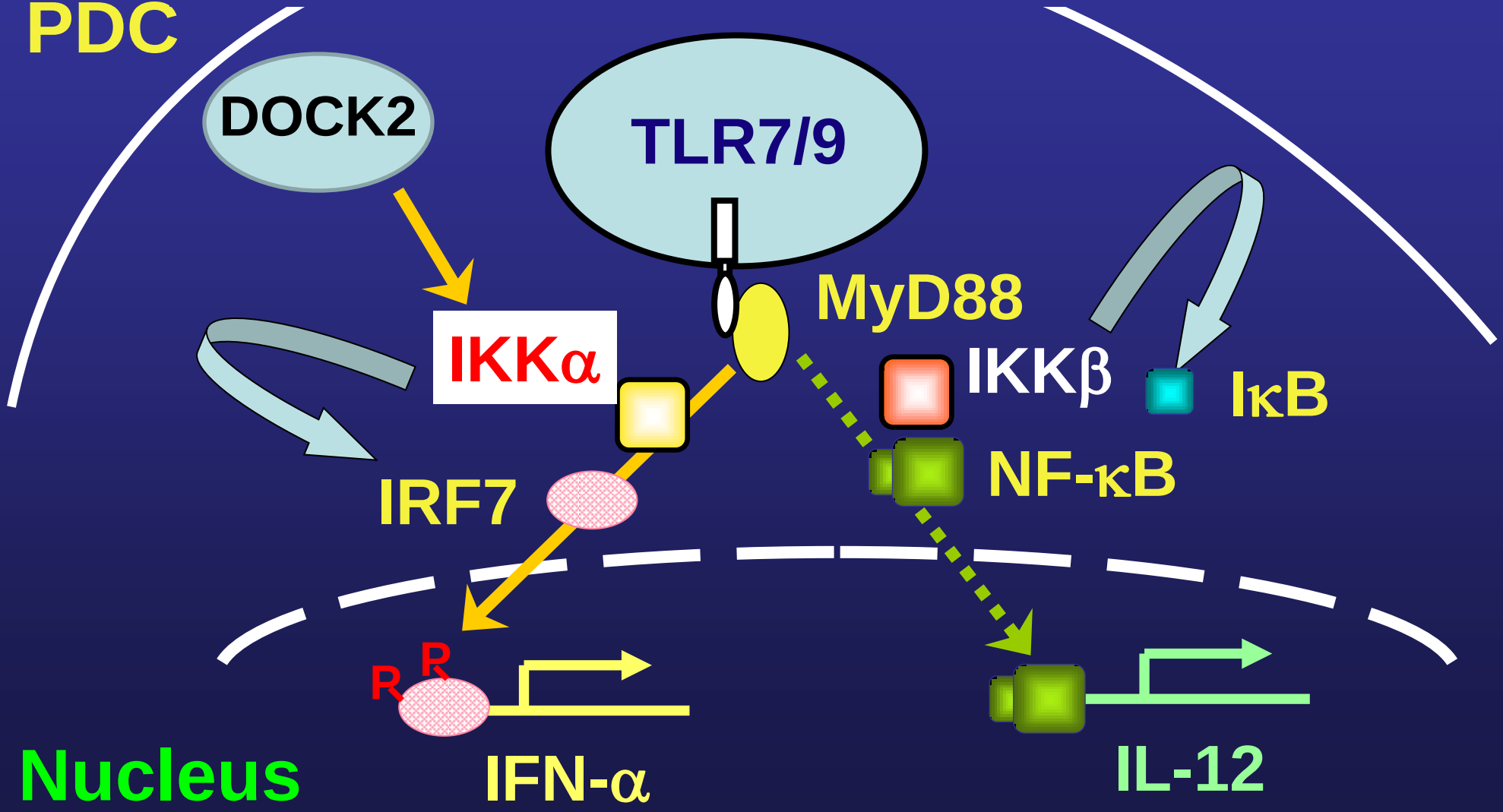


Akt, ERK, JNK, p38, and IRAK-1 activation is intact.



Gotoh K et al. JEM 2010,207:721-730.

DOCK2 regulates TLR7/9-induced IRF-7 activation through IKKα

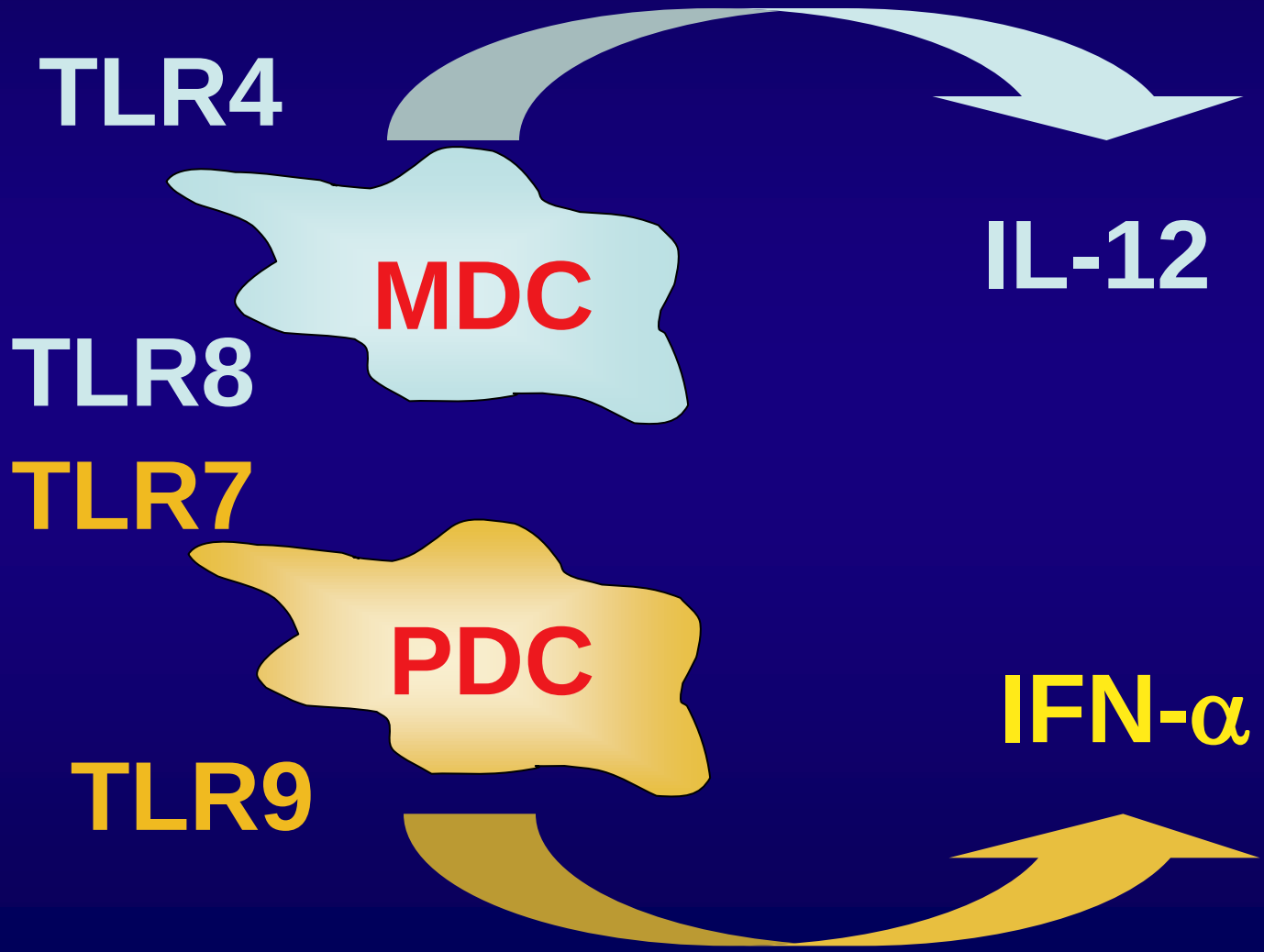


Effects of IKK inhibitor on human pDC

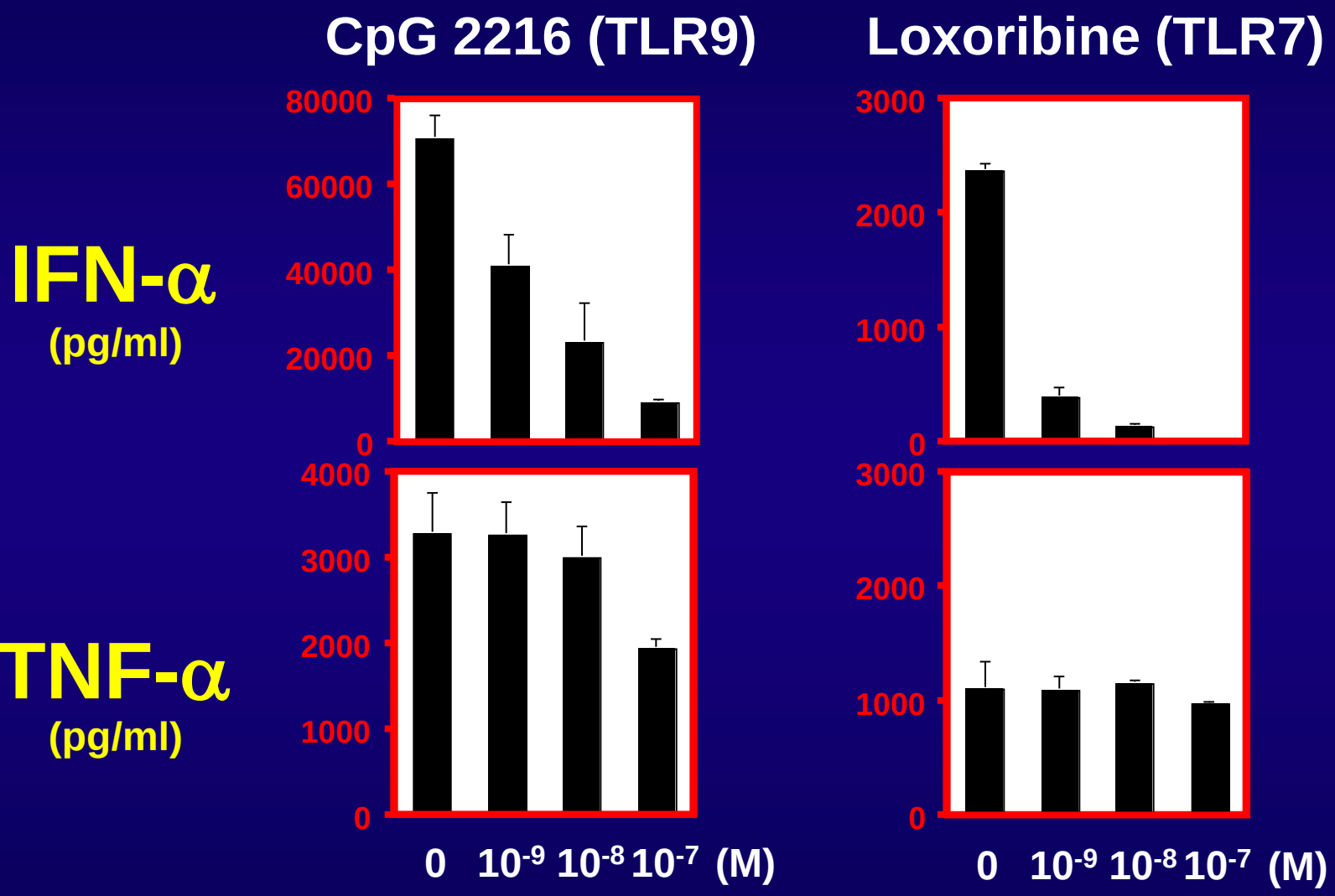
関西医科大学
尼川龍一先生、伊藤量基先生との共同研究
R. Miyamoto, et al.
Arthritis Research Therap, in press.

In human

Human DC subsets

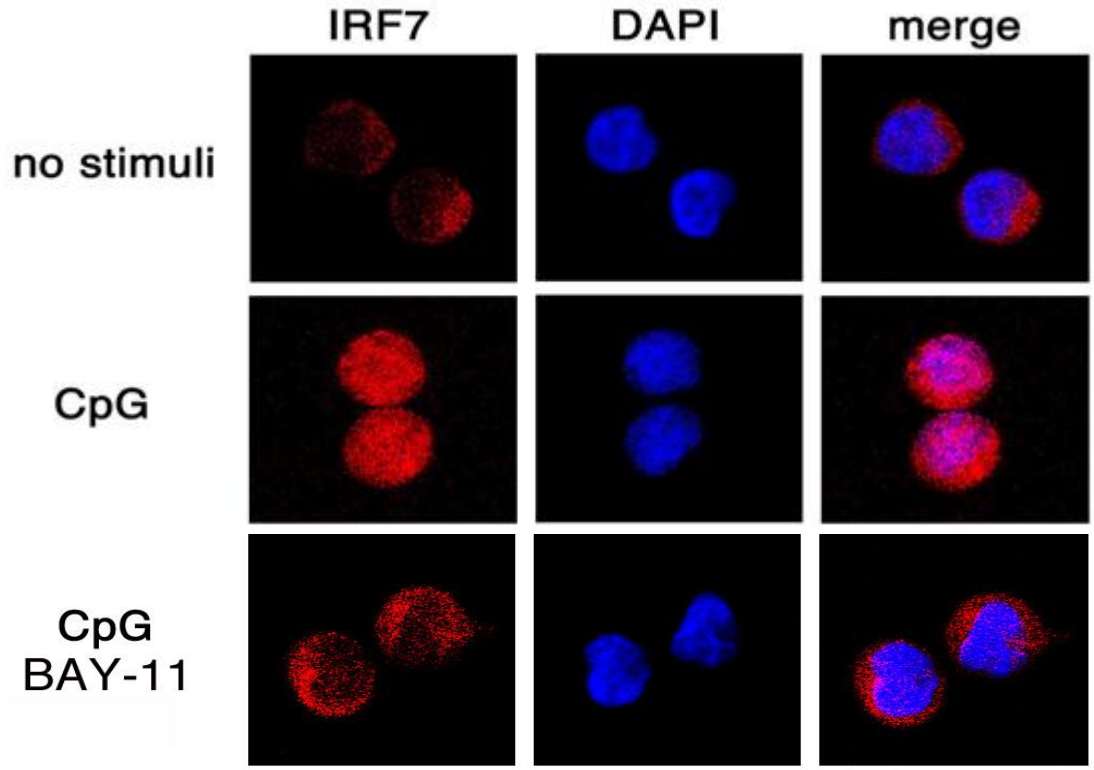


IKK阻害剤(BAY-11)は TLR7/9刺激によるpDCからのI型IFN産生誘導を阻害する



Cf. IC_{50} (for IκBα phosphorylation)=10μM

BAY-11/スタチンはpDCのIRF7の核内移行を阻害する

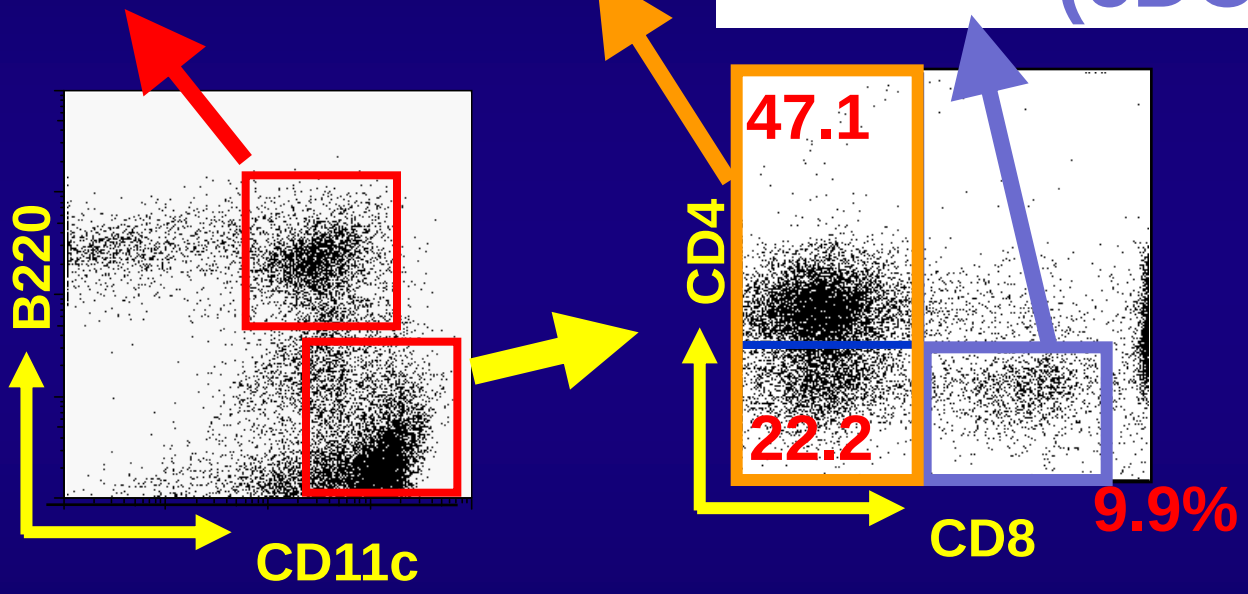


樹状細胞サブセットとその特性

Plasmacytoid DC
(pDC)

CD8$^-$CD4$^+$ cDC
CD8$^-$CD4$^-$ cDC

CD8$^+$ conventional DC
(cDC)



TLR7/9 expression
Type I IFN production

TLR3 expression
Crosspresentation

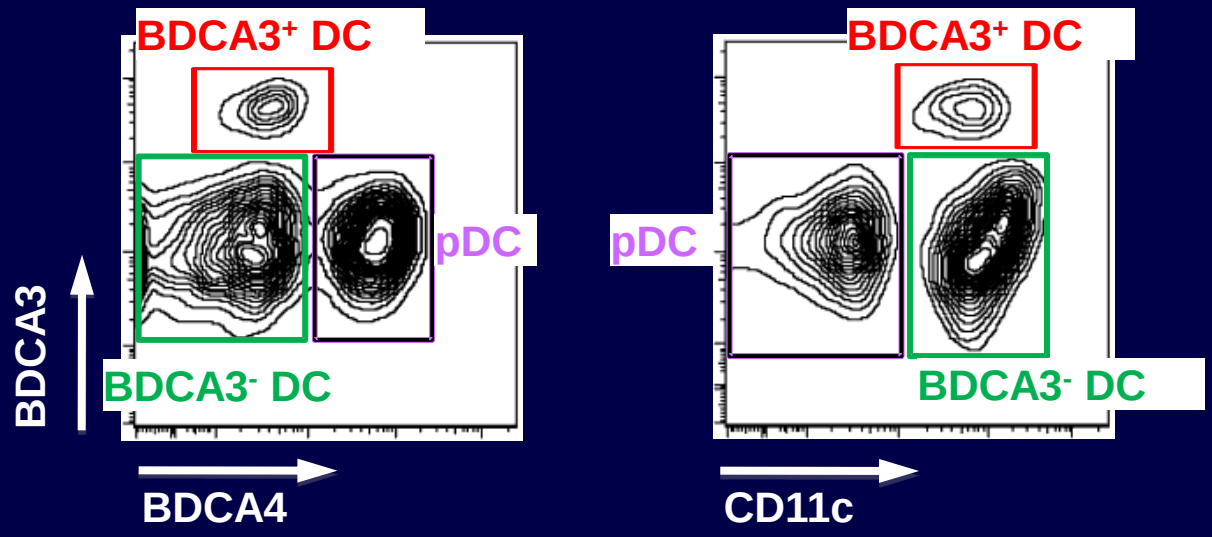
In vivo splenic DC

Xcr1 is selectively expressed in CD8α+ DCs

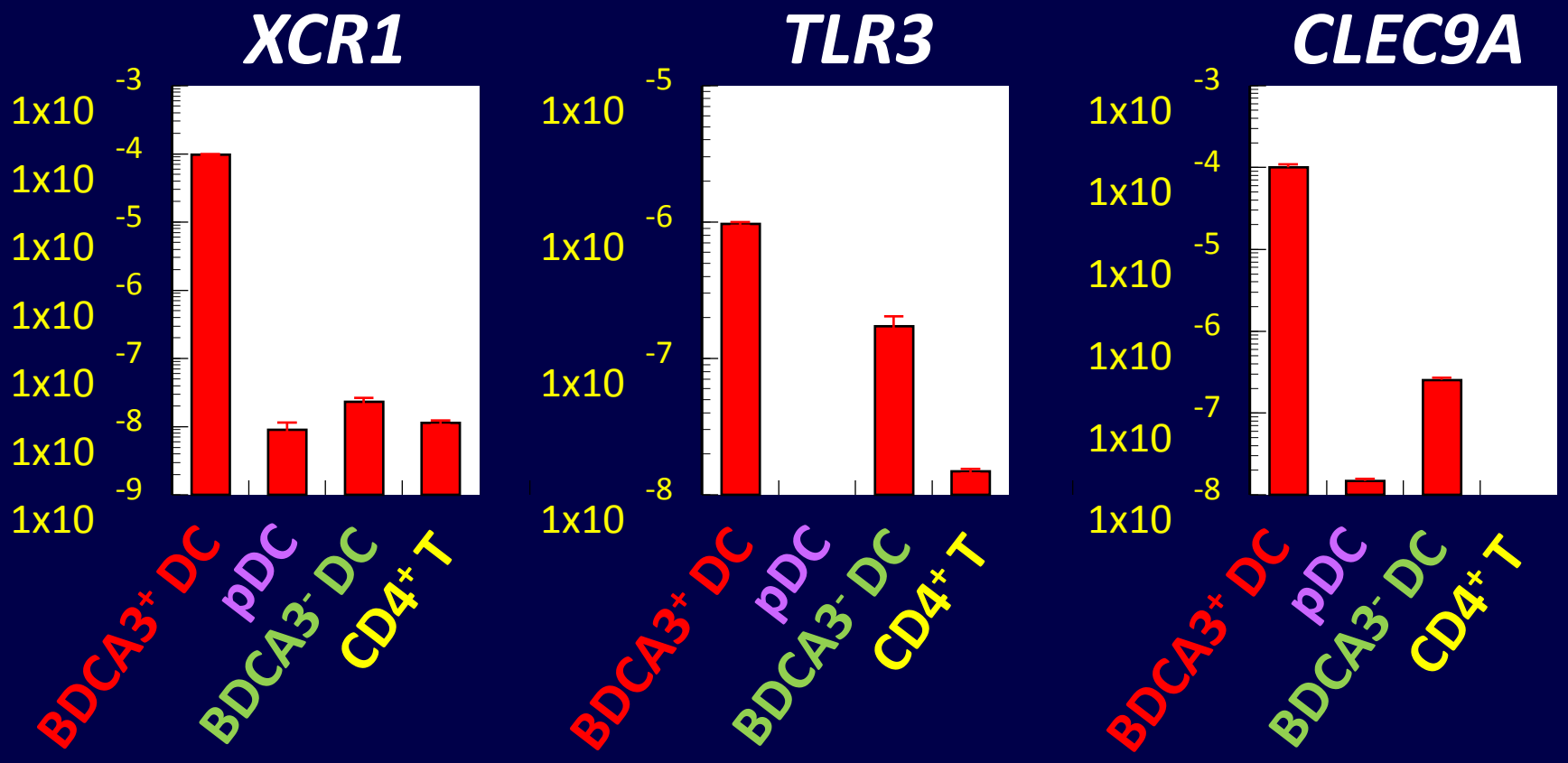
Common name	Probe ID	pDC	CD8α$^+$ DC	CD8α$^-$ DC
Ccr1	1419609_at	0.6	4.7	1.5
	1419610_at	0.2	1.5	0.3
Ccr2	1421187_at	40.6	27.7	27.4
	1421186_at	24.1	15.0	16.2
	1421188_at	18.9	11.9	8.4
	1460067_at	3.3	2.1	2.0
Ccr3	1422957_at	0.6	0.1	0.4
Ccr4	1421655_a_at	0.2	0.5	0.2
Ccr5	1424727_at	67.2	10.3	5.5
	1422259_a_at	31.5	4.6	1.6
	1422260_x_at	37.2	2.7	1.8
Ccr6	1450357_a_at	3.4	2.3	13.9
Ccr7	1423466_at	1.8	97.7	71.6
Ccr8	1422291_at	0.0	0.0	0.1
Ccr9	1421920_a_at	146.1	15.5	3.0
	1421919_a_at	143.5	14.4	2.4
	1427419_x_at	73.6	7.8	0.4
	1440432_at	2.1	1.5	1.3
	1442758_at	7.7	1.2	0.7
Cx3cr1	1450019_at	0.1	4.3	4.0
	1450020_at	0.0	3.9	6.6
Cxcr3	1449925_at	56.2	19.3	3.8
Cxcr4	1448710_at	88.0	96.5	96.5
Cxcr6	1425832_a_at	0.9	0.5	1.2
	1422812_at	0.5	0.4	0.6
Xcr1	1422294_at	0.4	57.7	2.6

Human peripheral blood DCs are divided into three subsets

Human DCs from peripheral blood
------Lineage (CD3, CD14, CD16, CD19, CD56) negative & HLA-DR positive

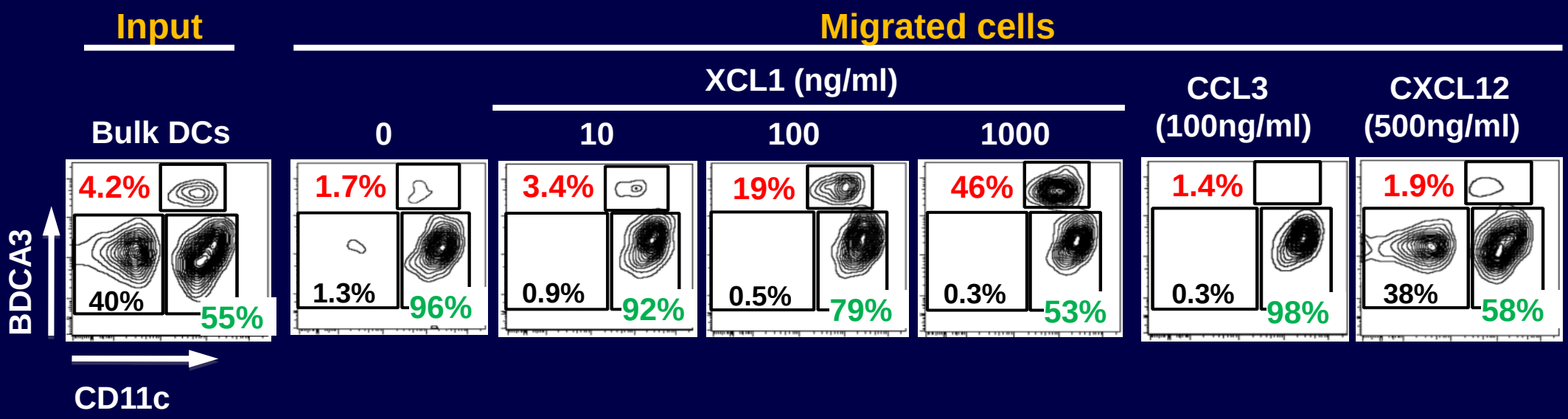


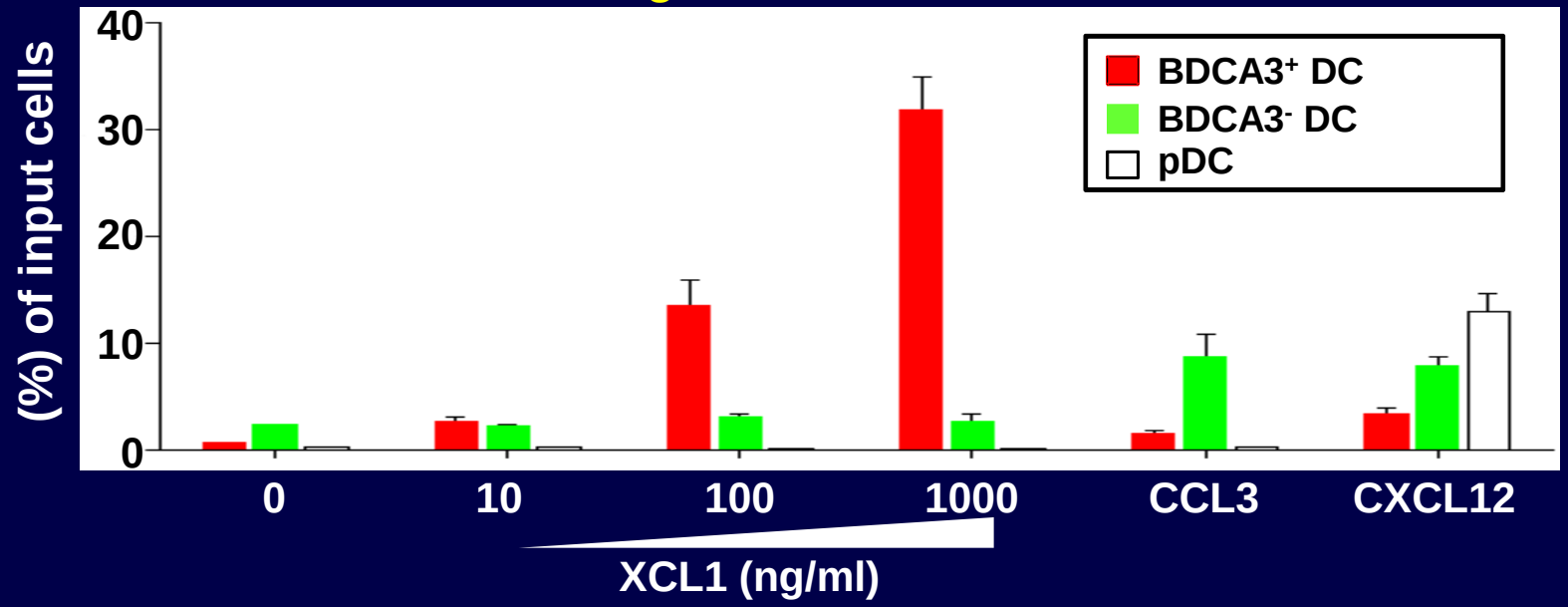
Human *XCR1* is selectively expressed in BDCA3$^+$ DC



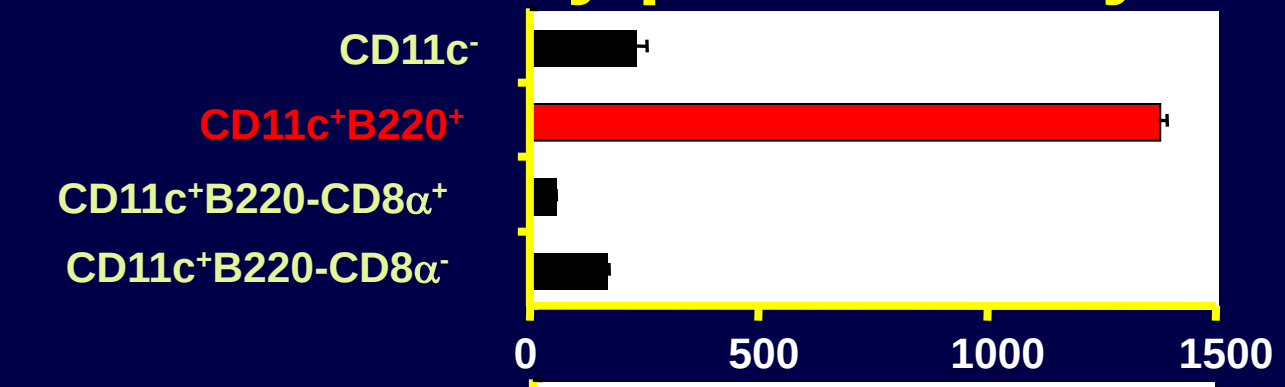
RT-PCR

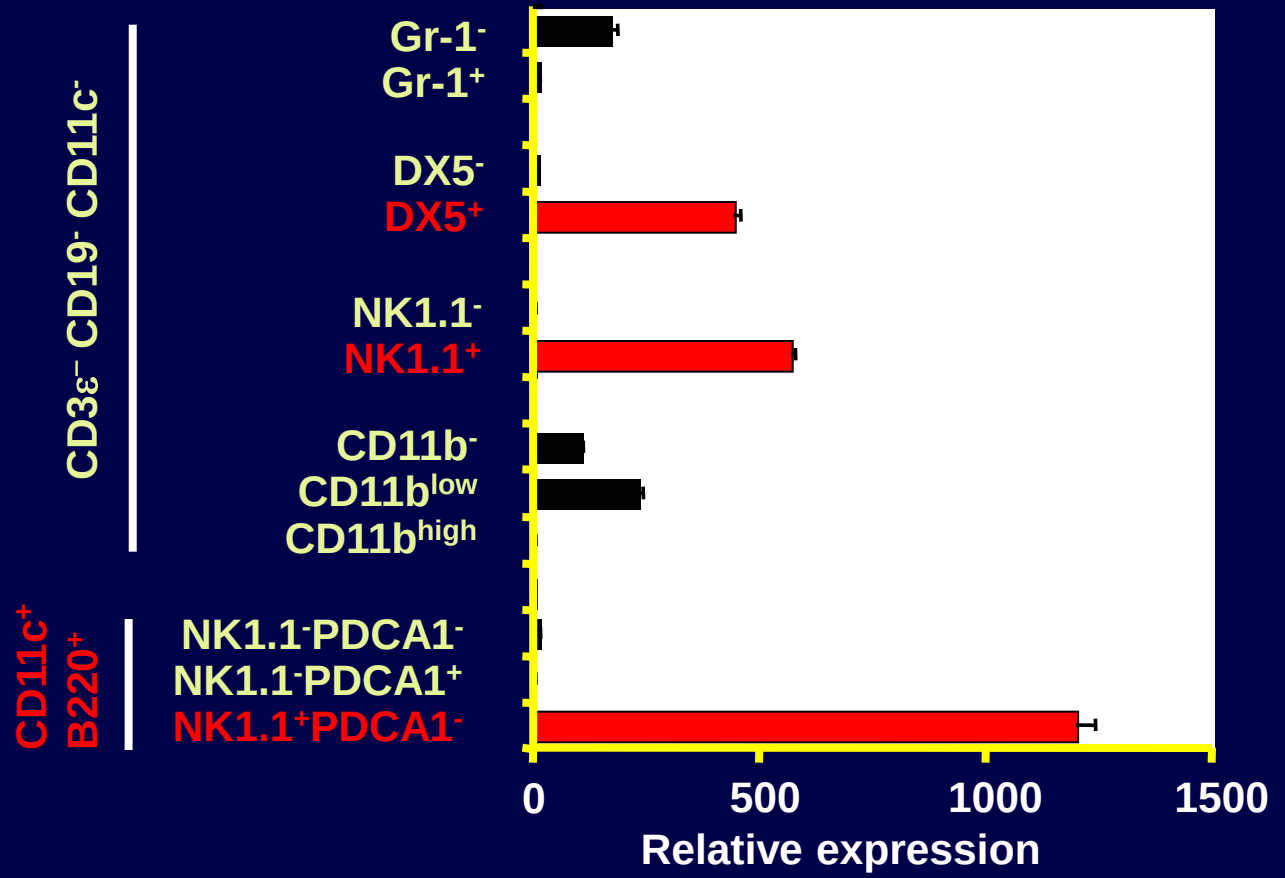
BDCA3^{+} DCs dominantly migrate to XCL1



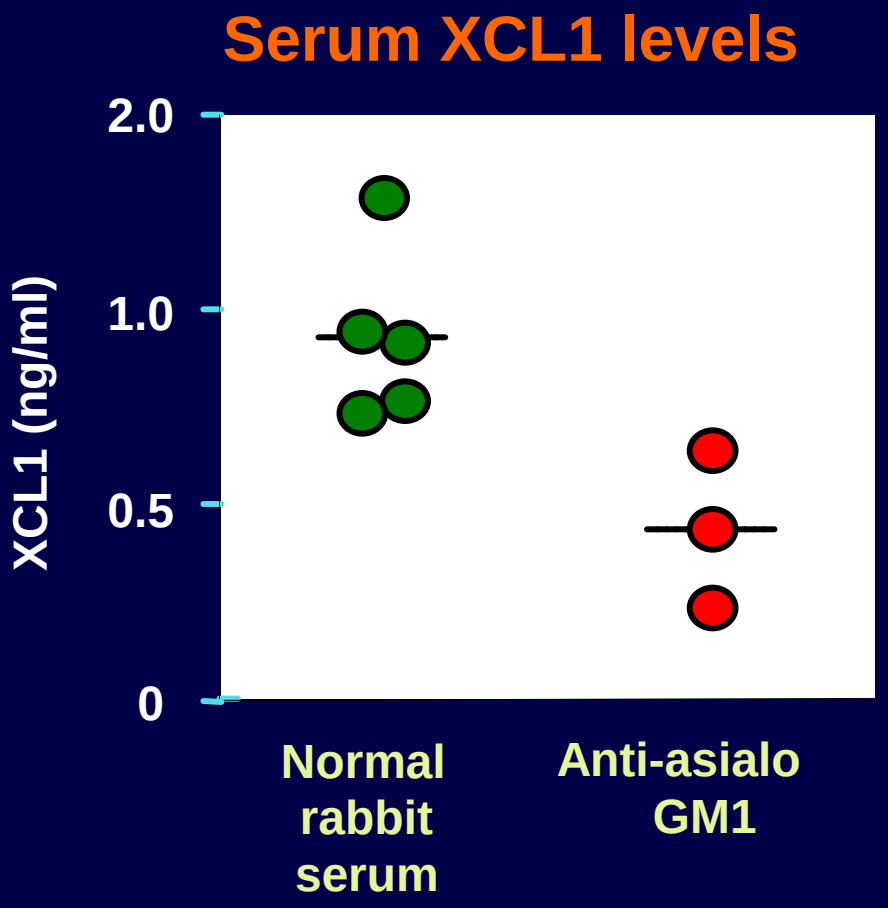


XCL1 is mainly produced by NK cell

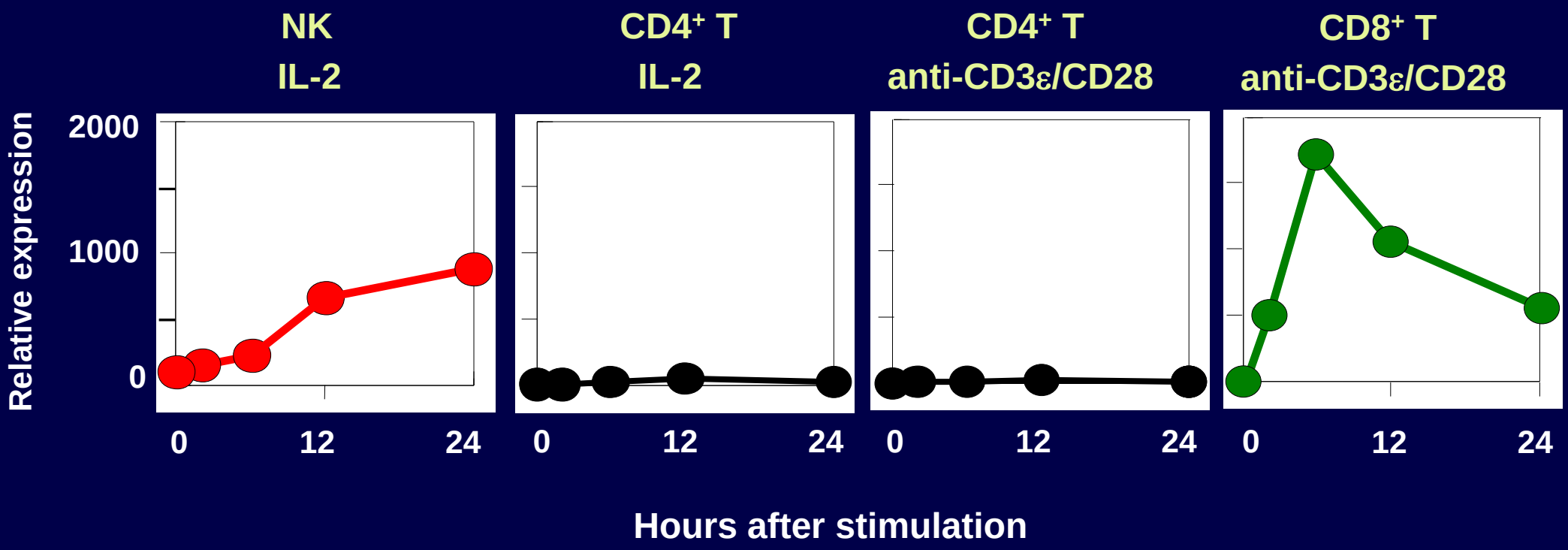




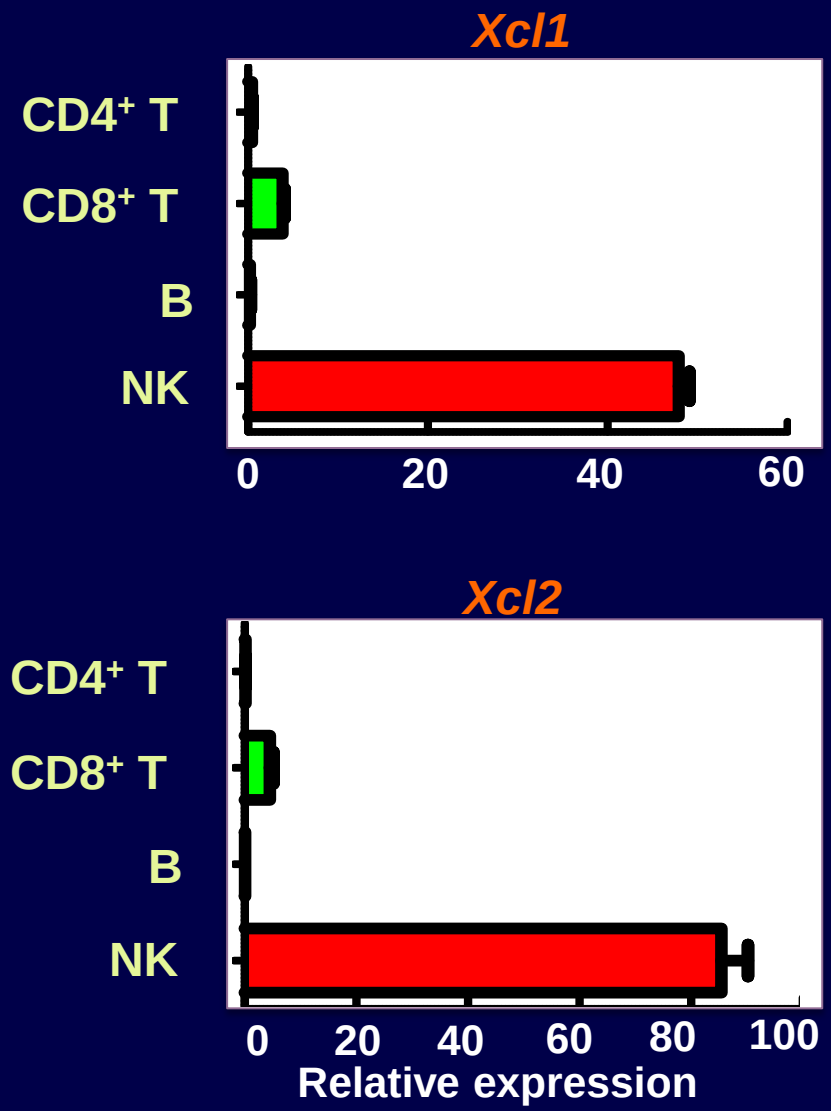
Serum XCL1 levels were decreased in NK cell depleted mice

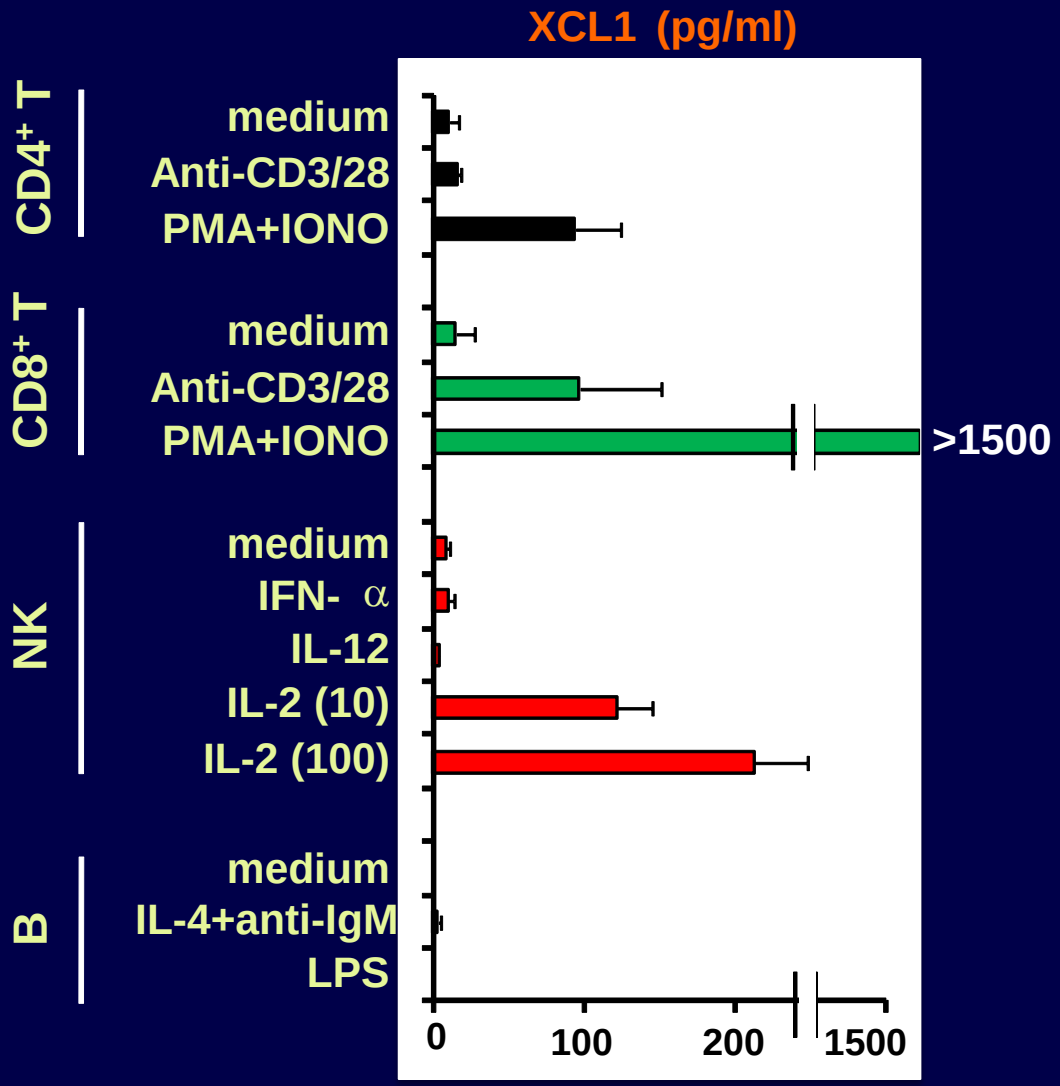


CD8$^+$, but not CD4$^+$, T cells increase *Xcl1* expression upon activation

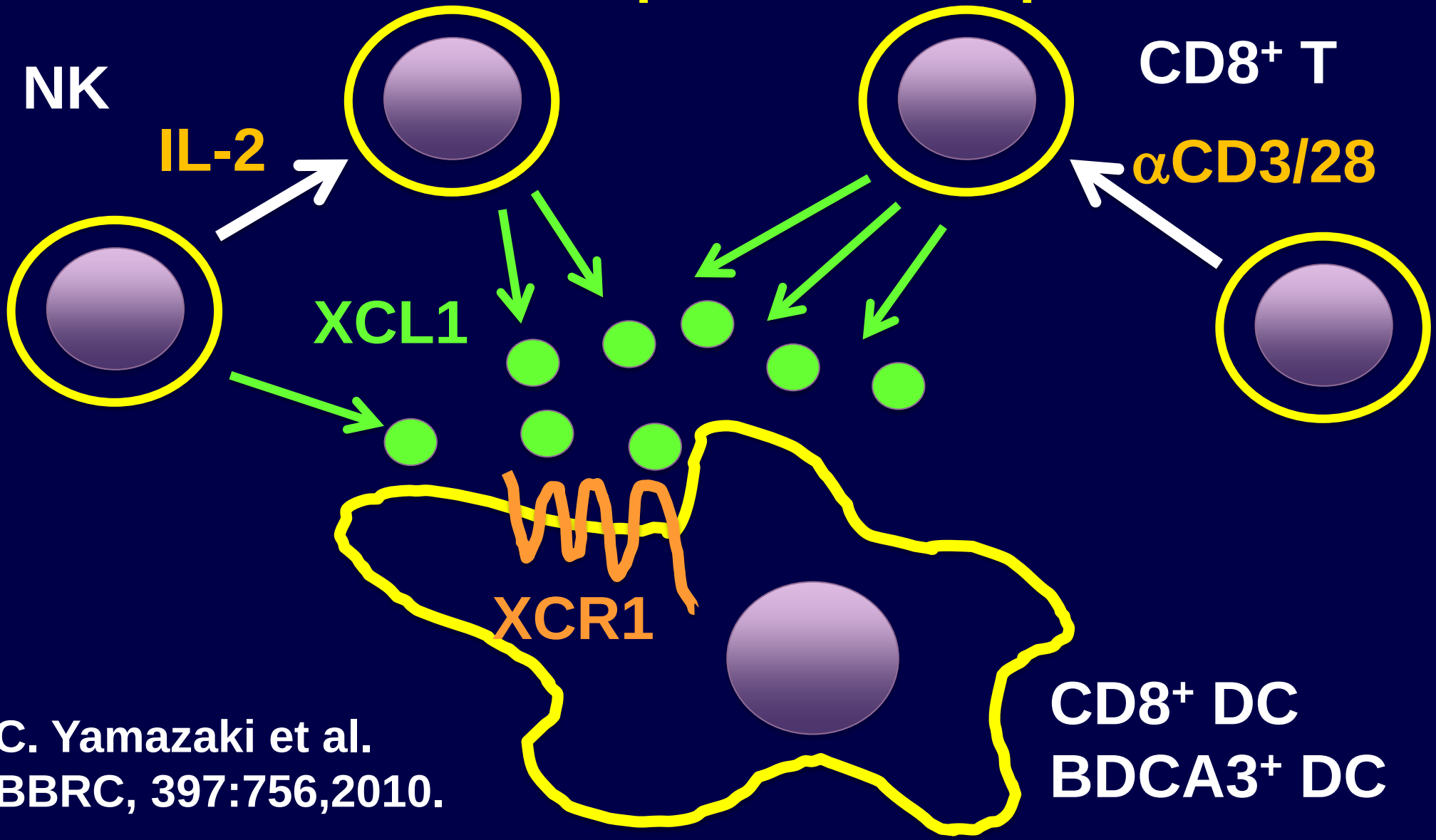


Human CD8+ T cell and NK cell also can express XCR1 ligands





XCL1/XCR1 in innate and adaptive CTL responses



C. Yamazaki et al.
BBRC, 397:756,2010.