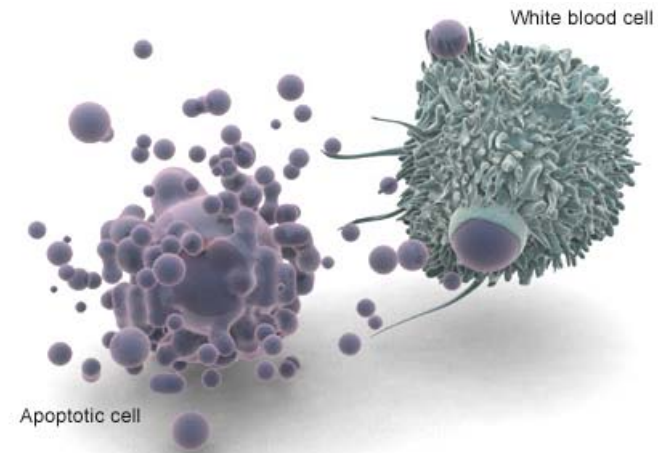


TLR-mediated Signal and Lymphopenia in Infection

Yu Zhang

Peking University Health Science Center



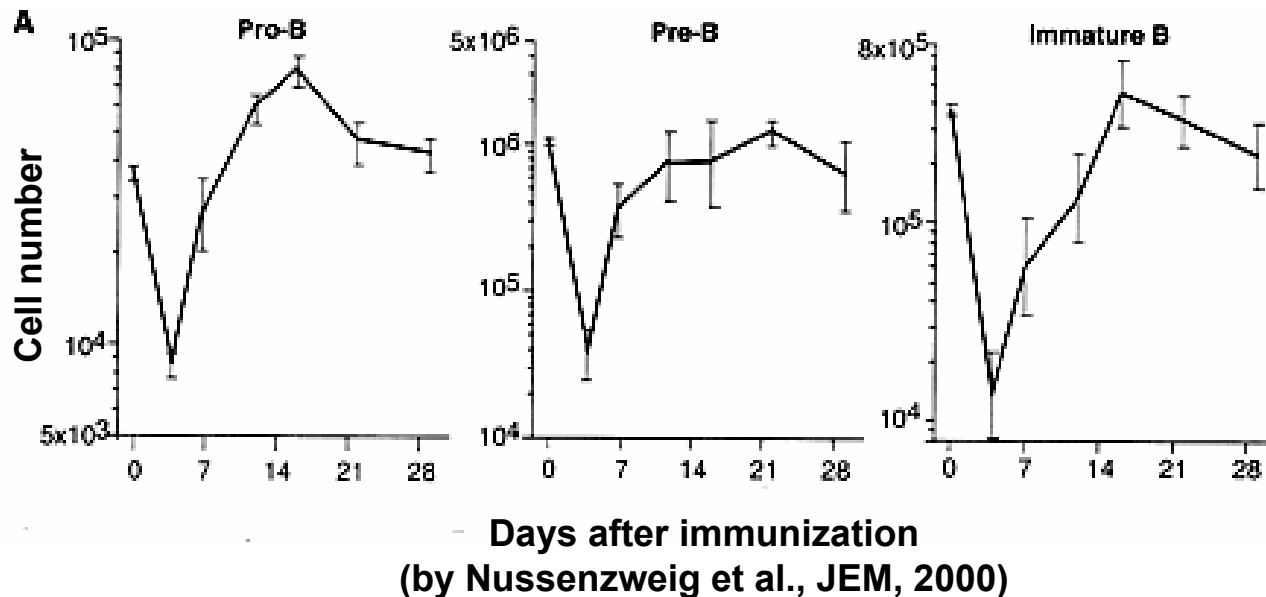
Lymphopenia in Infection

Reduced lymphocyte count in periphery
bacteraemia

severe viral infections

administration of adjuvant

Suppressed B lymphopoiesis in bone marrow



Mediators of Infection-induced Lymphopenia

Involvement of proinflammatory cytokines

$TNF\alpha \rightarrow CXCL12$ and $SCF \downarrow$

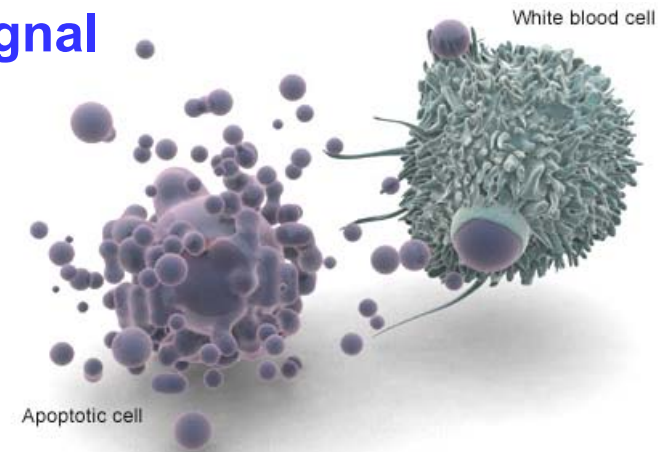
$IL-6 \rightarrow$ lymphoid vs. myeloid commitment

$IFN\alpha/\beta \rightarrow$ depletion of hematopoietic progenitors

What initiates the cascade?

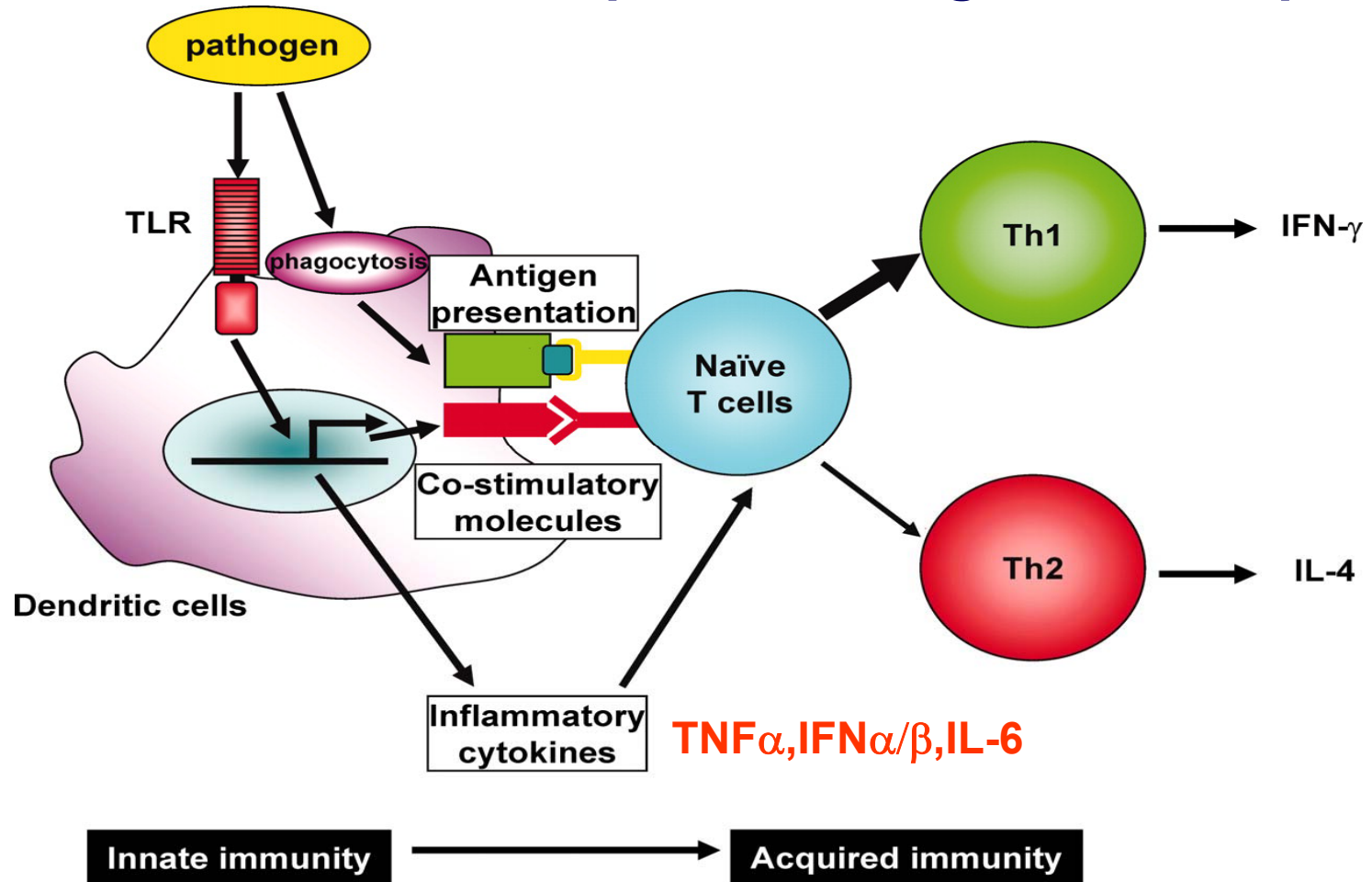
Independent of adaptive immunity

innate immunity — contribution of TLR signal

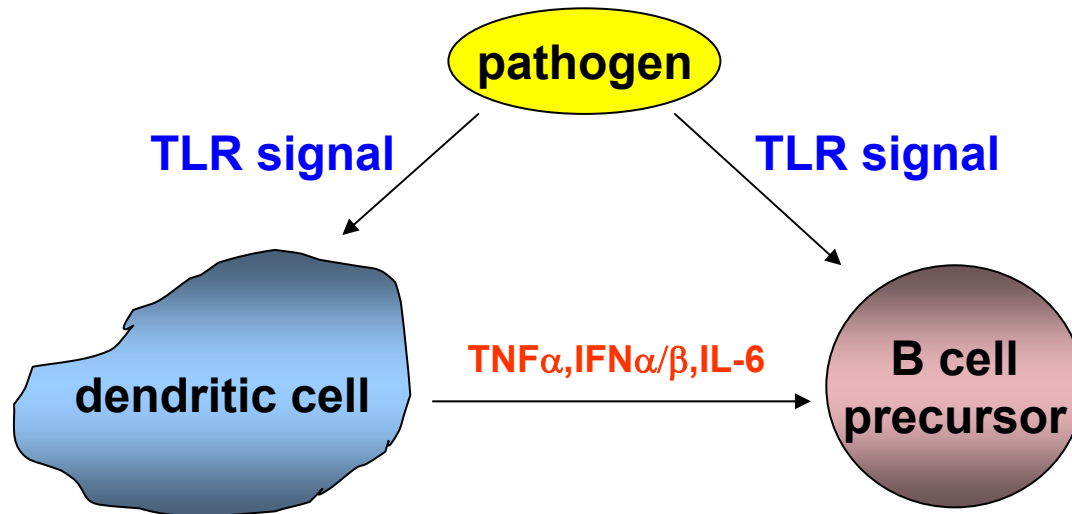


Toll-like Receptor (TLR) in Host Defense

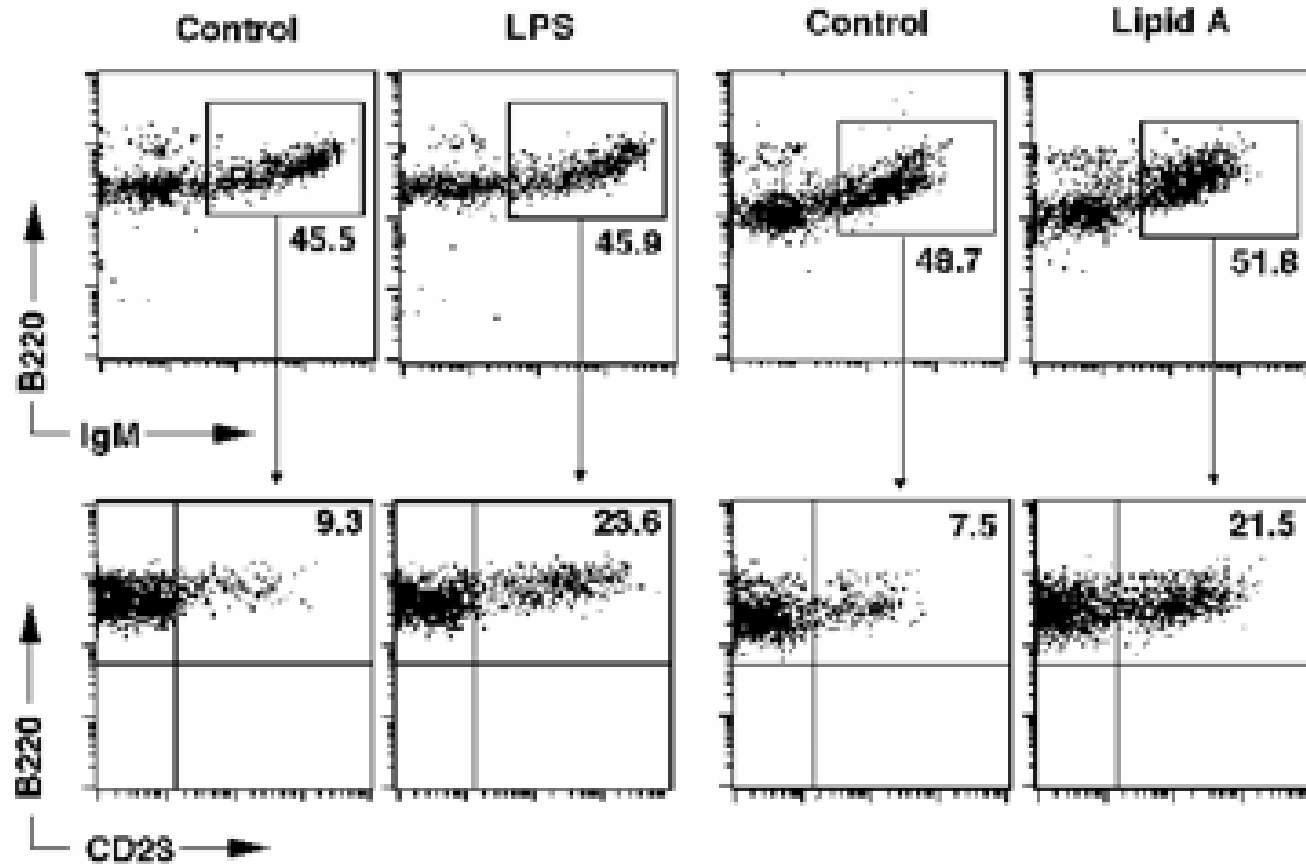
TLR — best characterized pattern recognition receptors



Hypothesis: TLR Signaling Leads to Lymphopenia in Infection

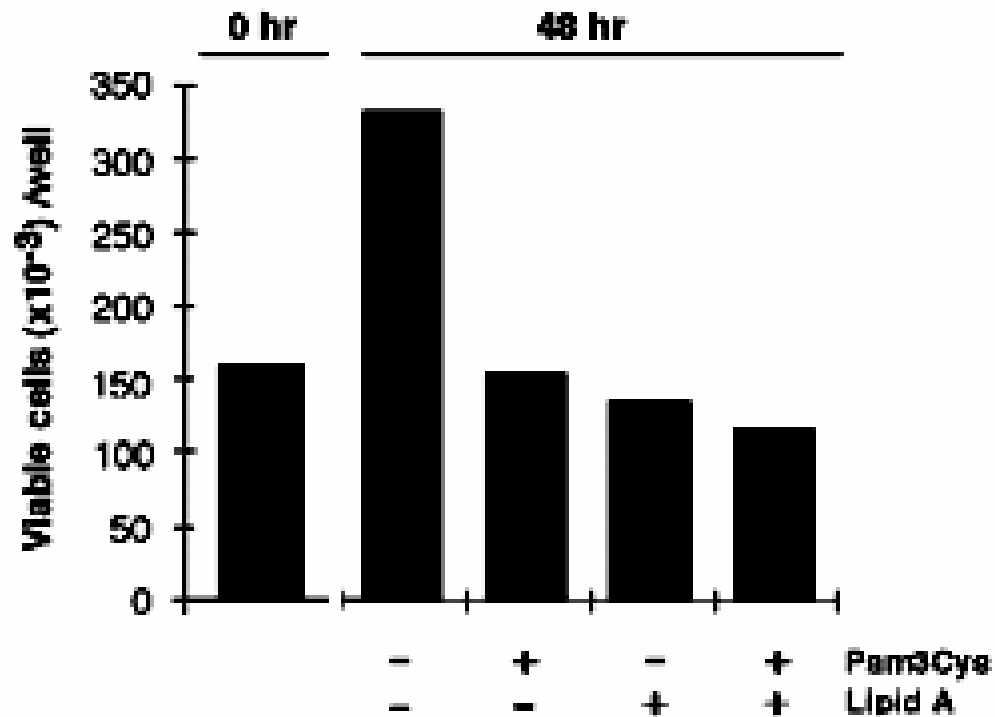


Direct Effect of TLR-mediated Signal on B Cell Development



by Nobrega et al., JI, 2005

Direct Effect of TLR-mediated Signal on B Cell Development



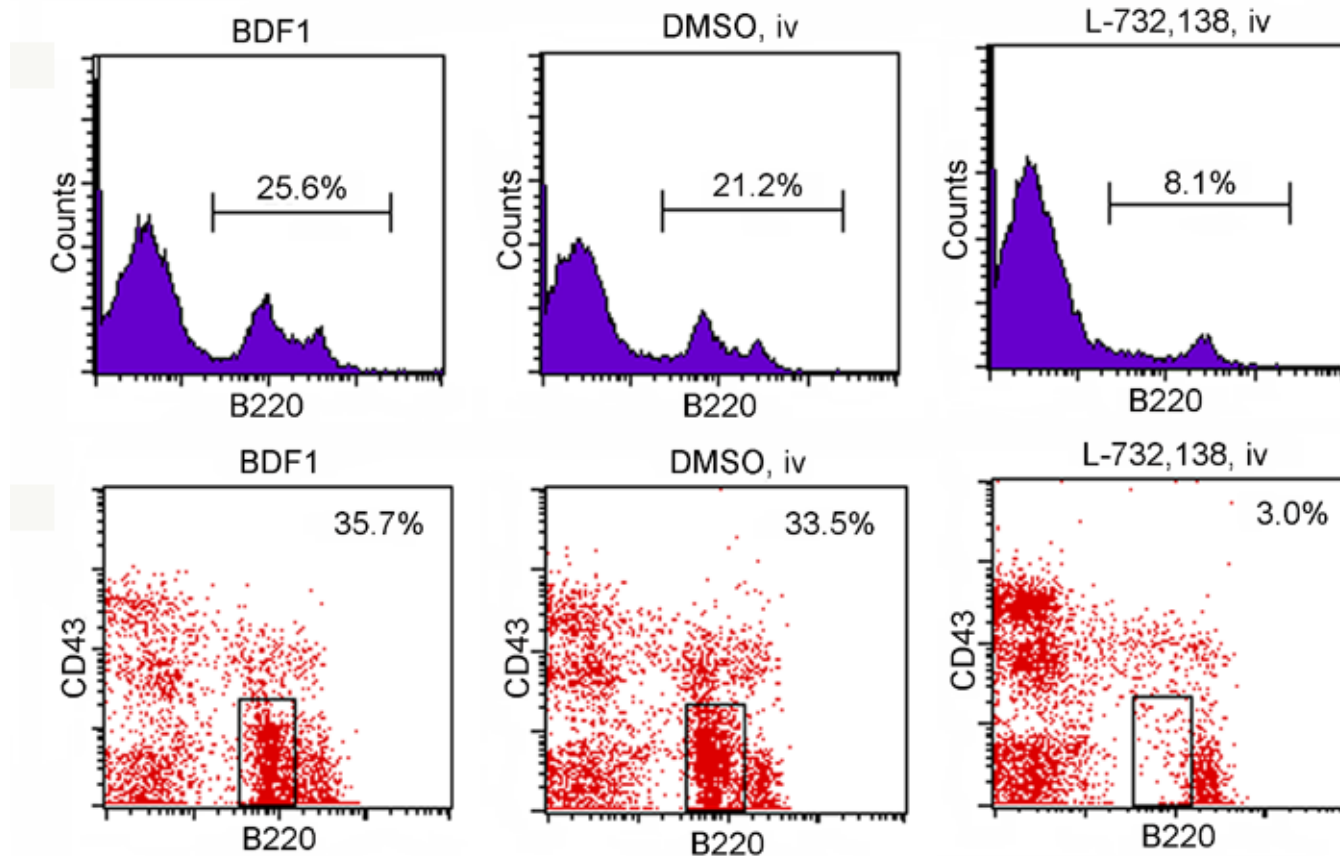
by Nobrega et al., JI, 2005

Sequence Alignment of HK-1 and Known Tachykinins

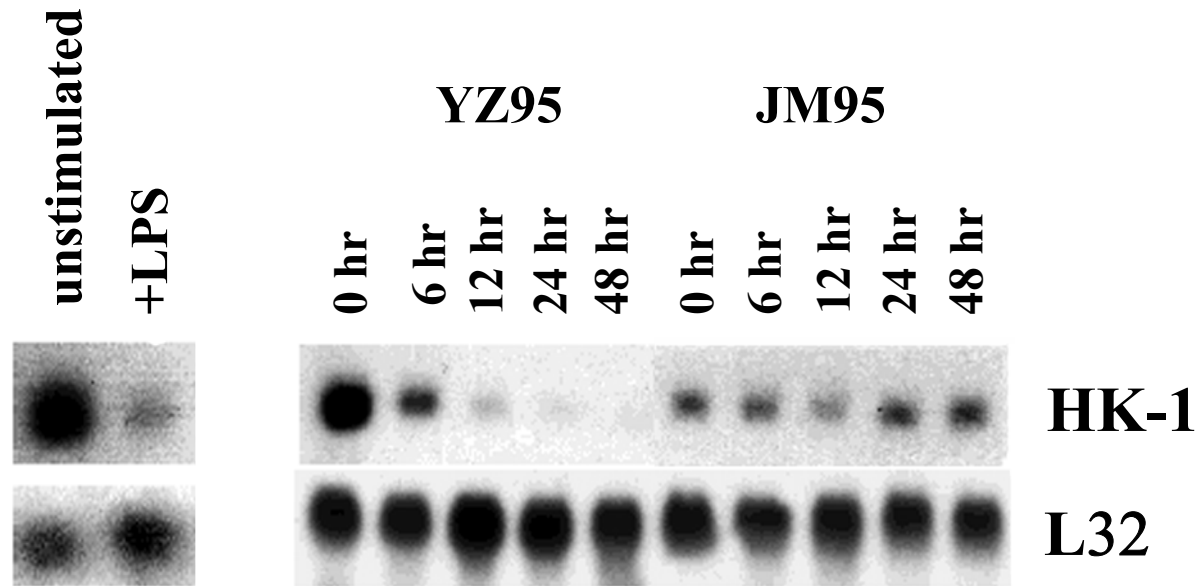
HK-1	R	S	R	T	R	Q	F	Y	G	L	M-NH2
Substance P	R	P	K	P	Q	Q	F	F	G	L	M-NH2
Neurokinin A	H	K	T	D	S	S	F	V	G	L	M-NH2
Neurokinin B	D	M	H	D	F	F	F	Y	G	L	M-NH2

Prototype molecule: Substance P
Pain transmission and inflammation
Neuronal origin

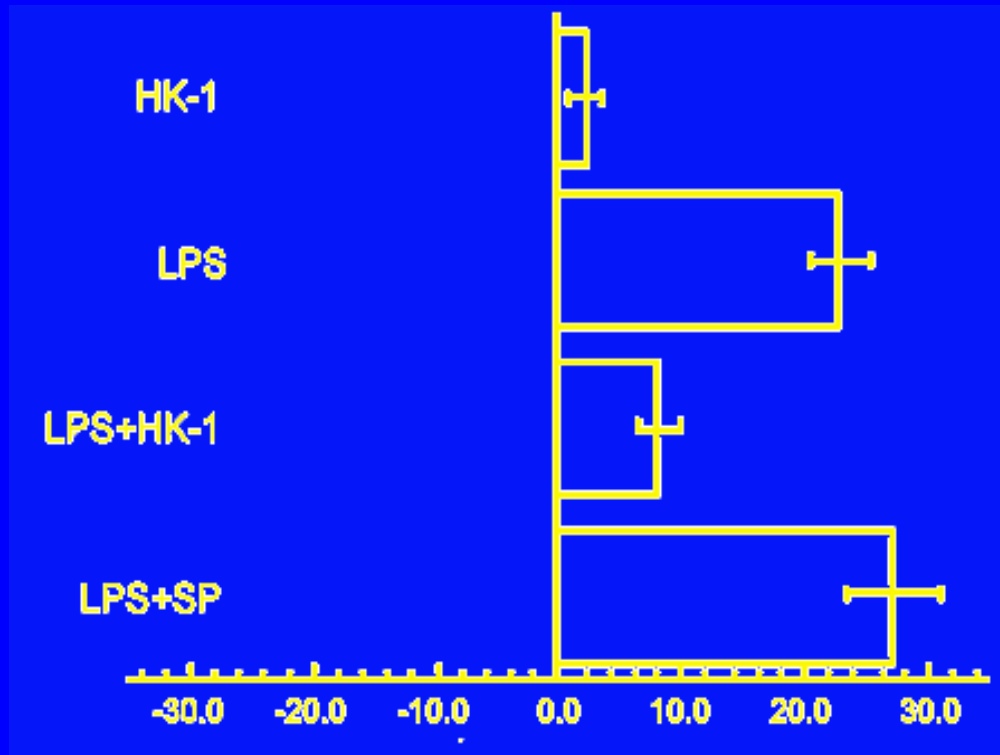
B Lineage Developmental Defects in Tachykinin Antagonist-treated Mice



Regulated HK-1 Expression in 70Z/3 Cells by LPS

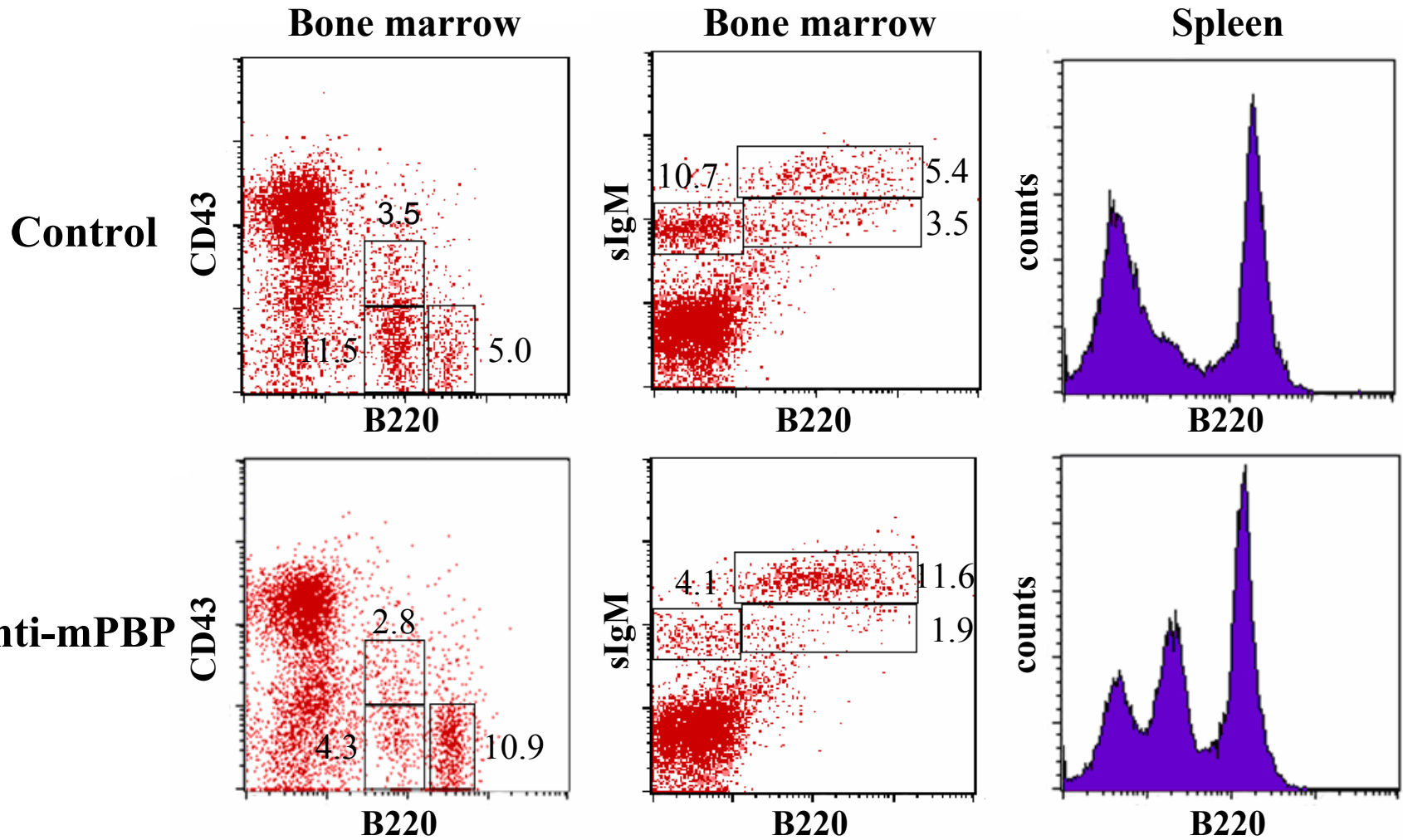


Rescue of LPS-induced apoptosis of 70Z/3 cells by HK-1



Changes in percentage of PI-stained 70Z/3 cells

Altered B Lymphopoiesis Following Treatment with Anti-CXCL7 Antibodies



Studies in Progress

1. TLR-mediated signals and infection-induced lymphopenia
2. Regulation of B lymphopoiesis by TLR signals in vitro
 - commitment
 - pro-B cell progression
 - transition from immature to mature B cells
3. Molecular mediators
 - HK-1
 - CXCL7

