Toll R-9 Signaling Mediates the Anti-Inflammatory Effect of Probiotics in Experimental Colitis

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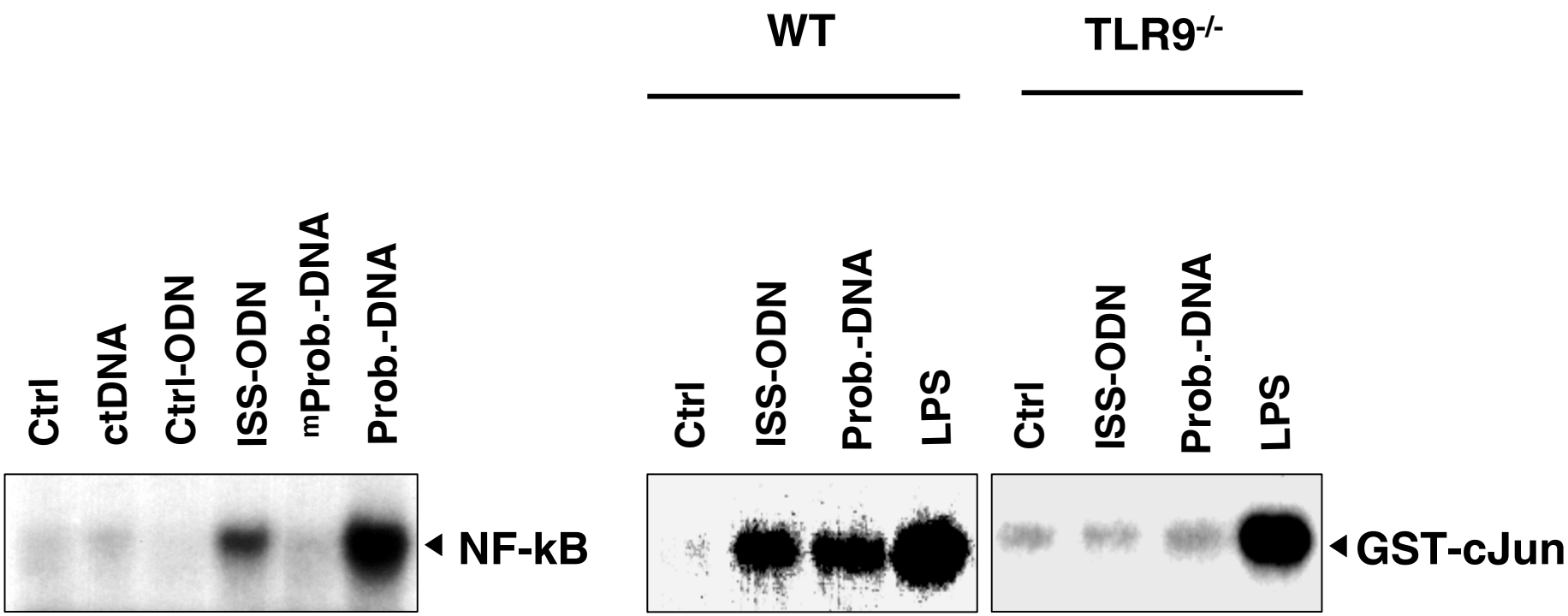
BACKGROUND

- Live probiotics attenuate experimental colitis and are effective in IBD

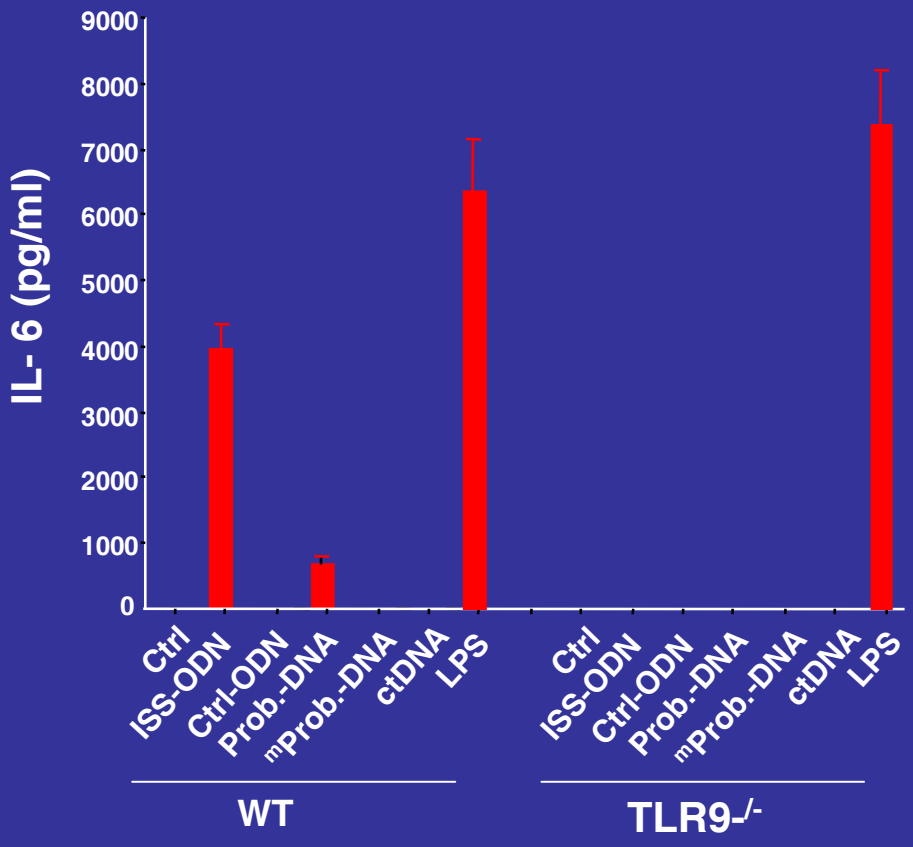
- Immunostimulatory DNA sequences containing the CpG motif, common in certain bacterial genomes, ameliorate experimental colitis

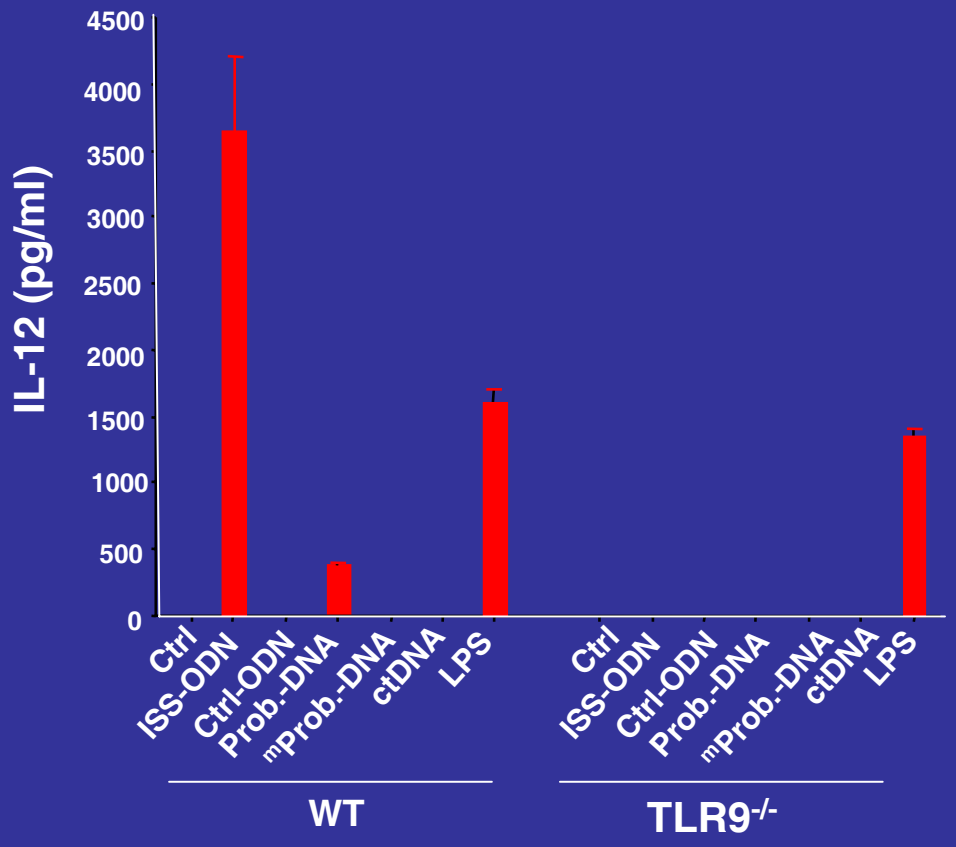
Is the beneficial effect of probiotics due to the immunostimulatory properties of their DNA???

Immunostimulatory Profile of Probiotic DNA (I)

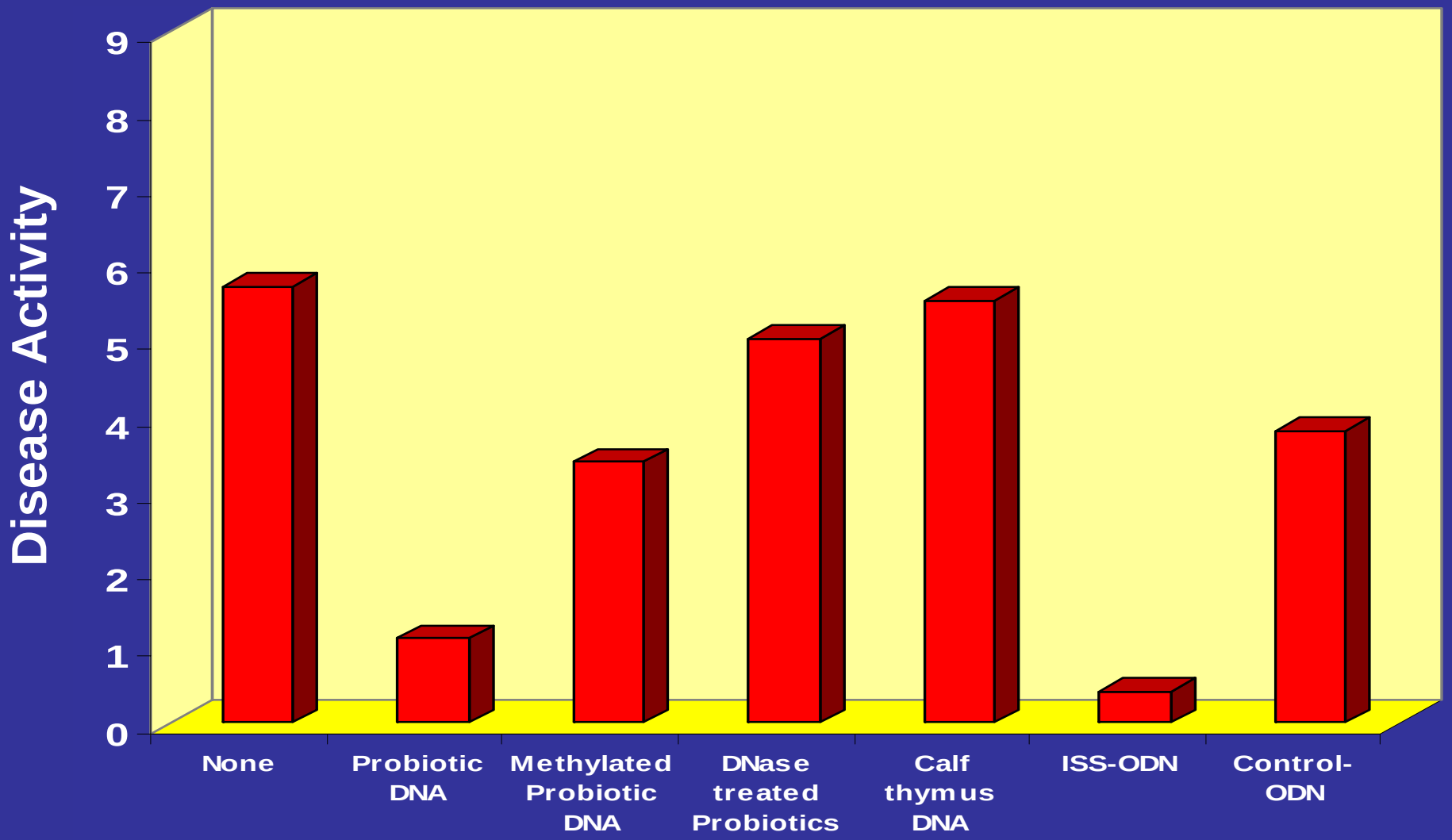


Immunostimulatory Profile of Probiotic DNA (II)

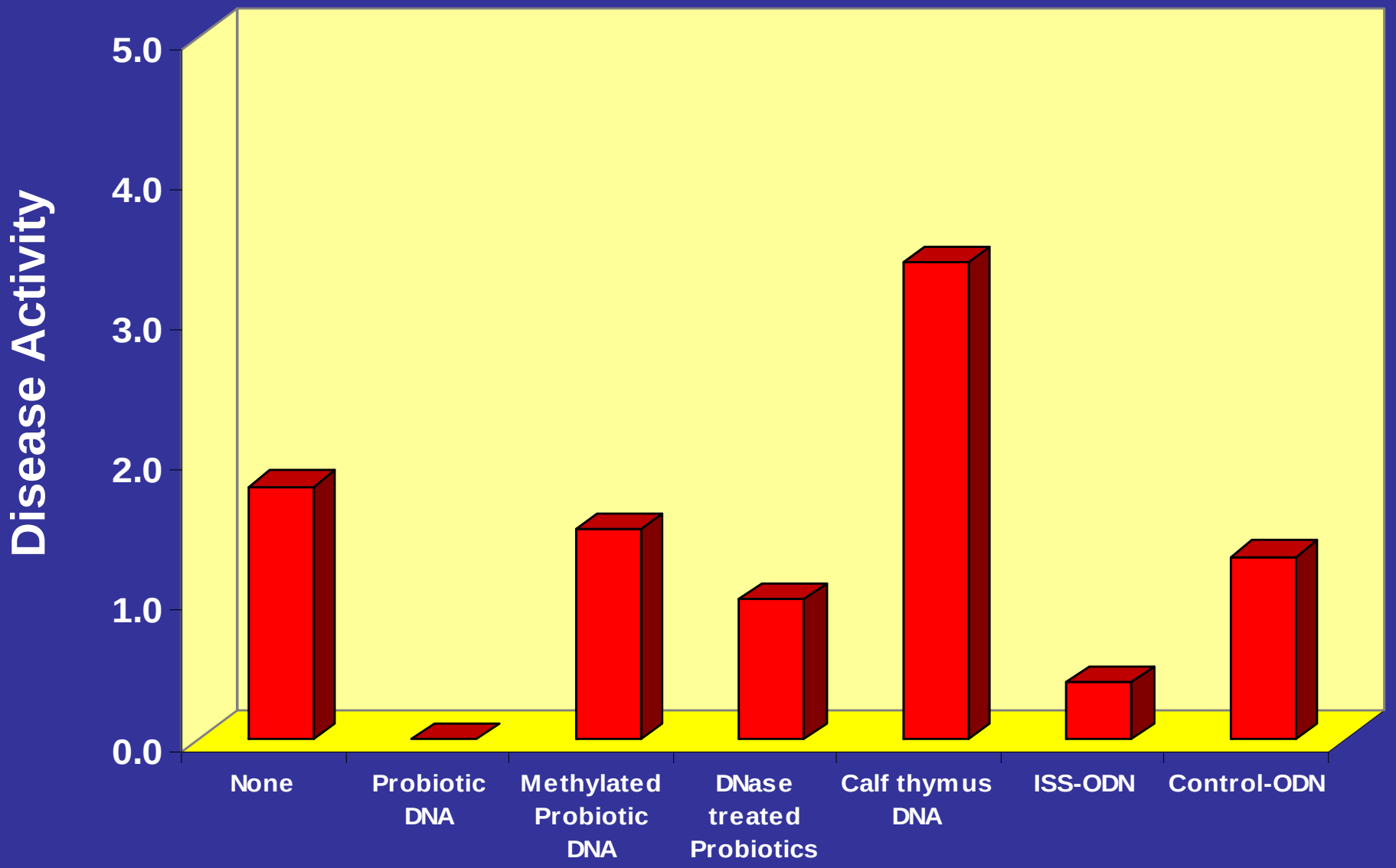




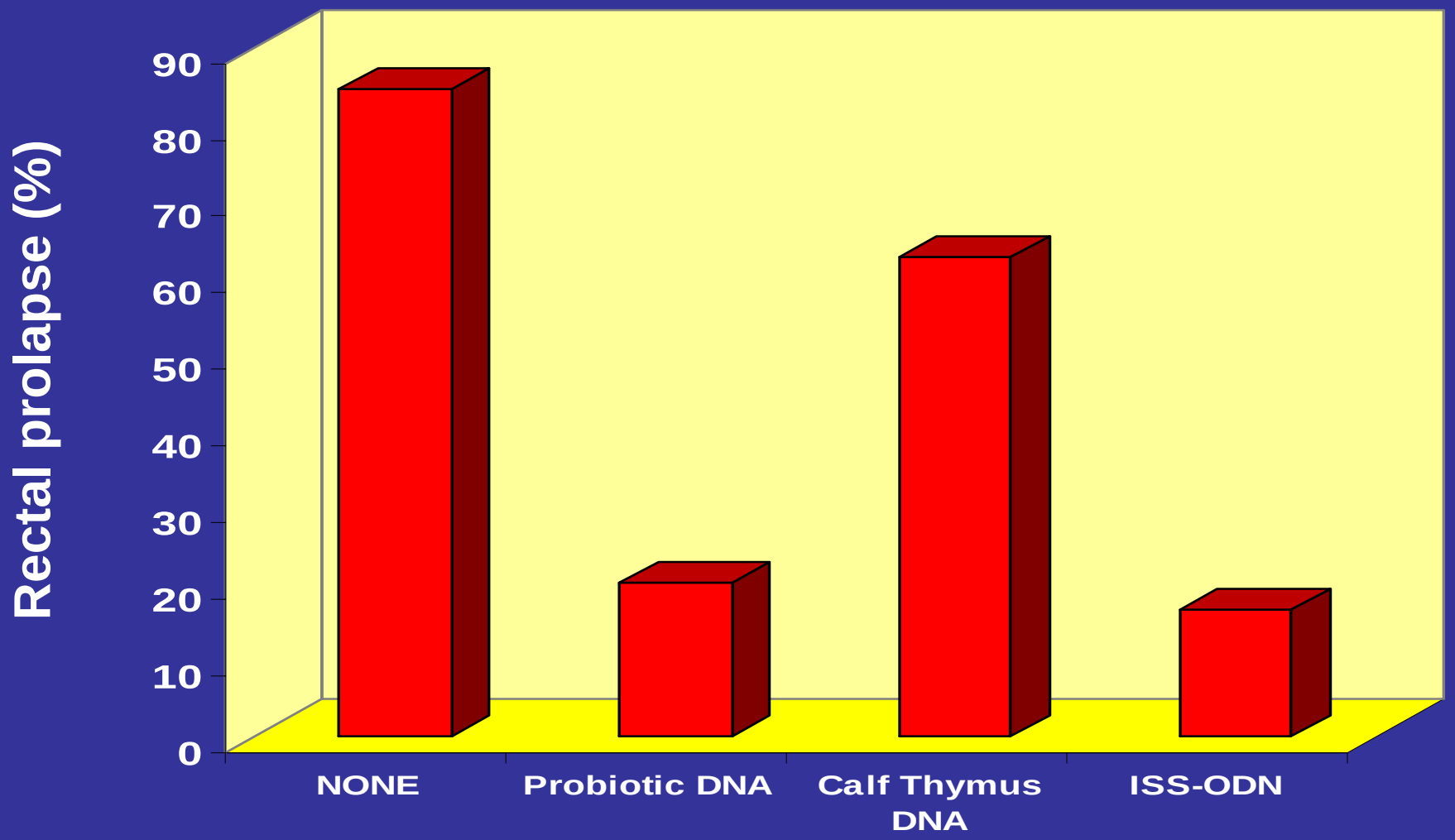
Effect of DNA on DSS Induced Colitis



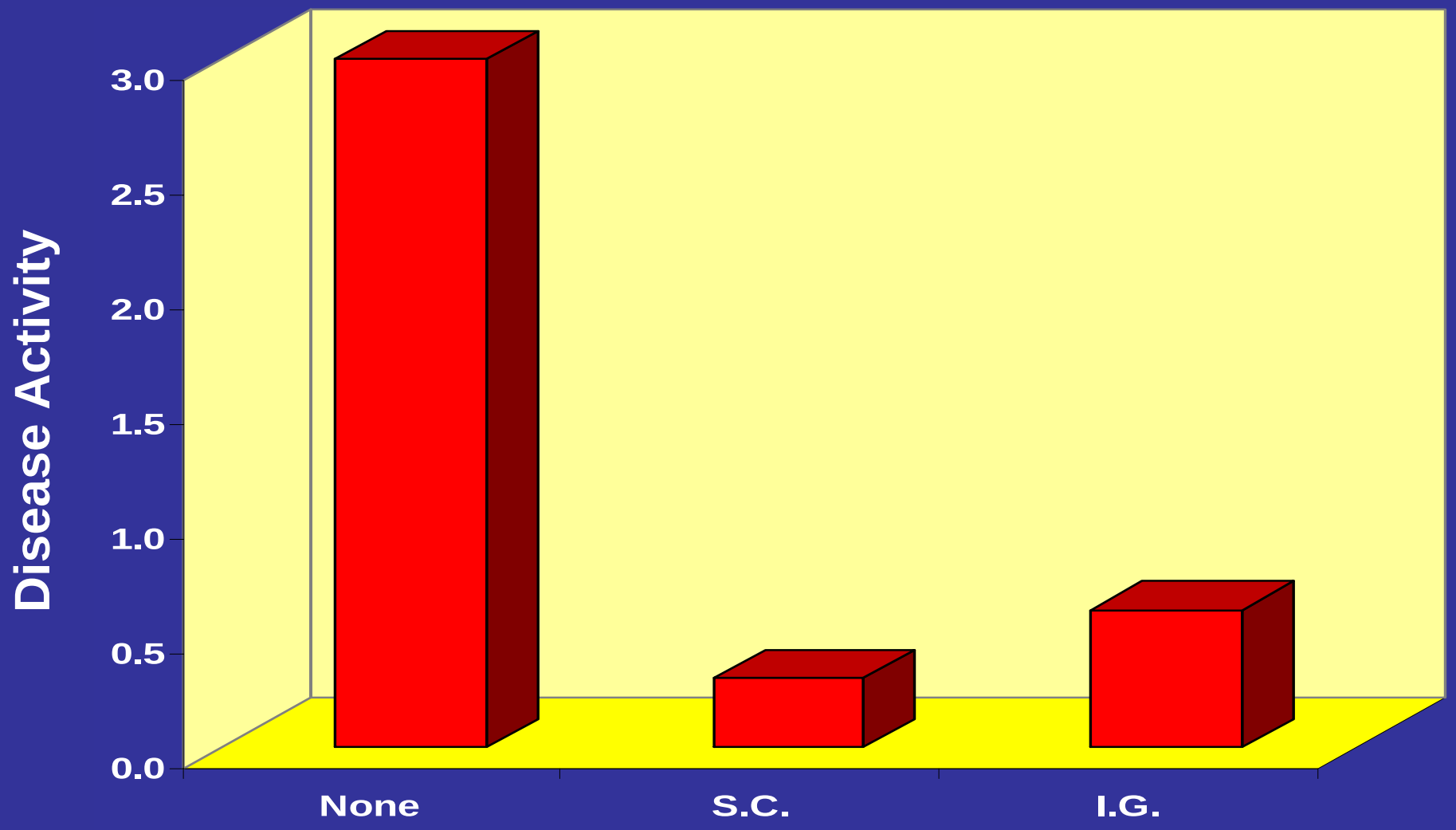
Effect of DNA on TNBS Induced Colitis



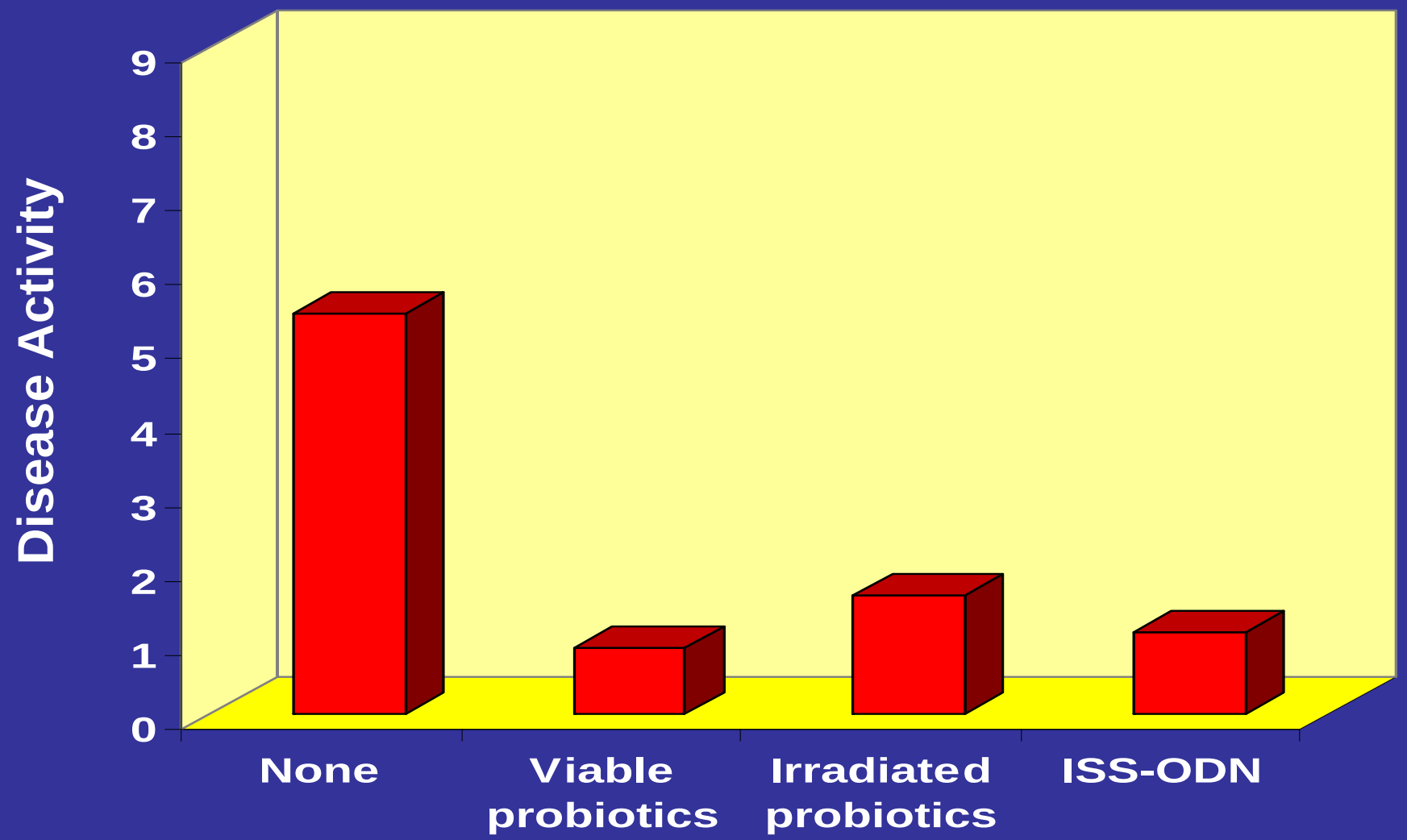
Effect of DNA on Spontaneous Colitis in IL-10 KO Mice

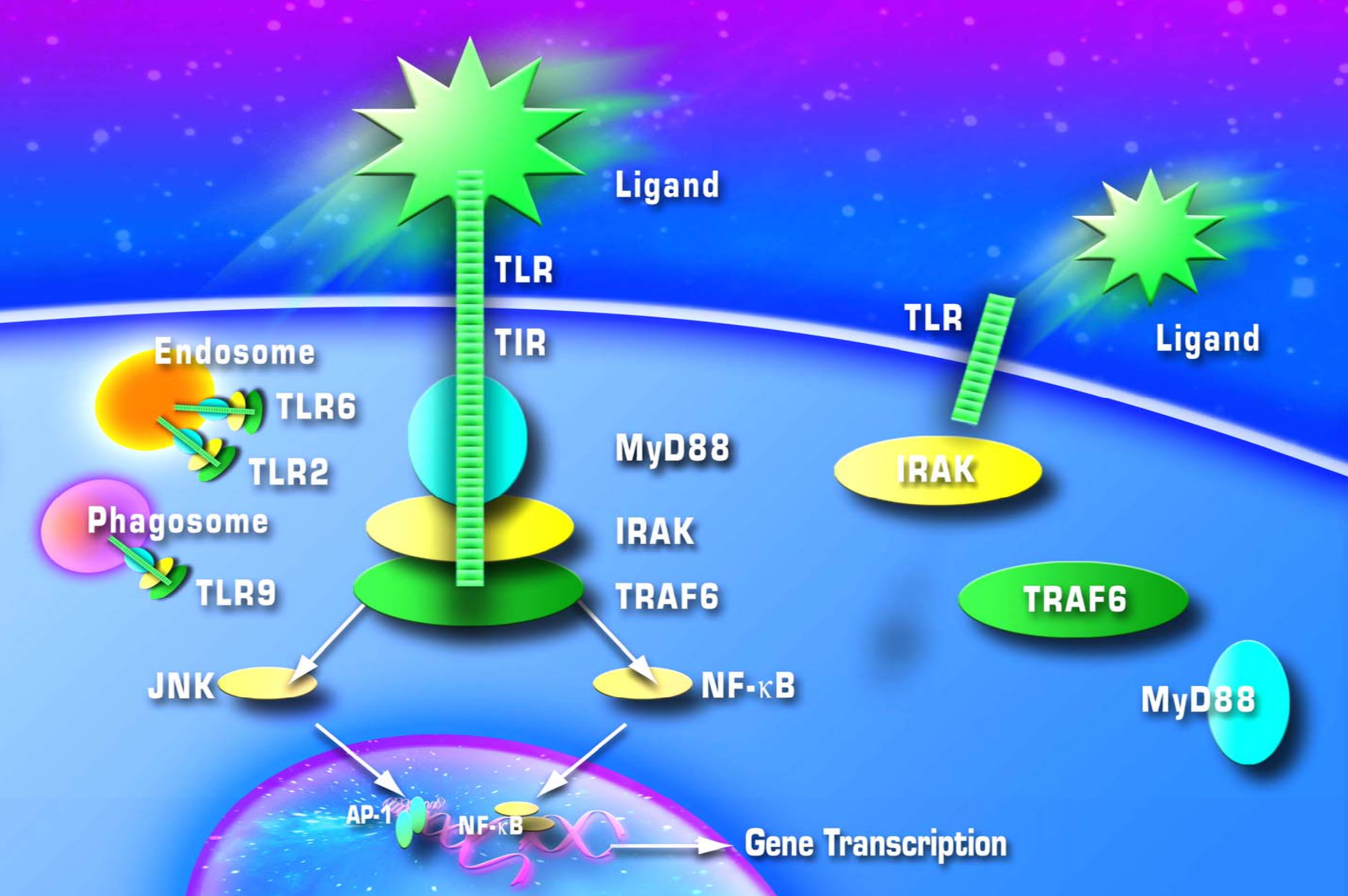


Effect of E.coli DNA on DSS Induced Colitis

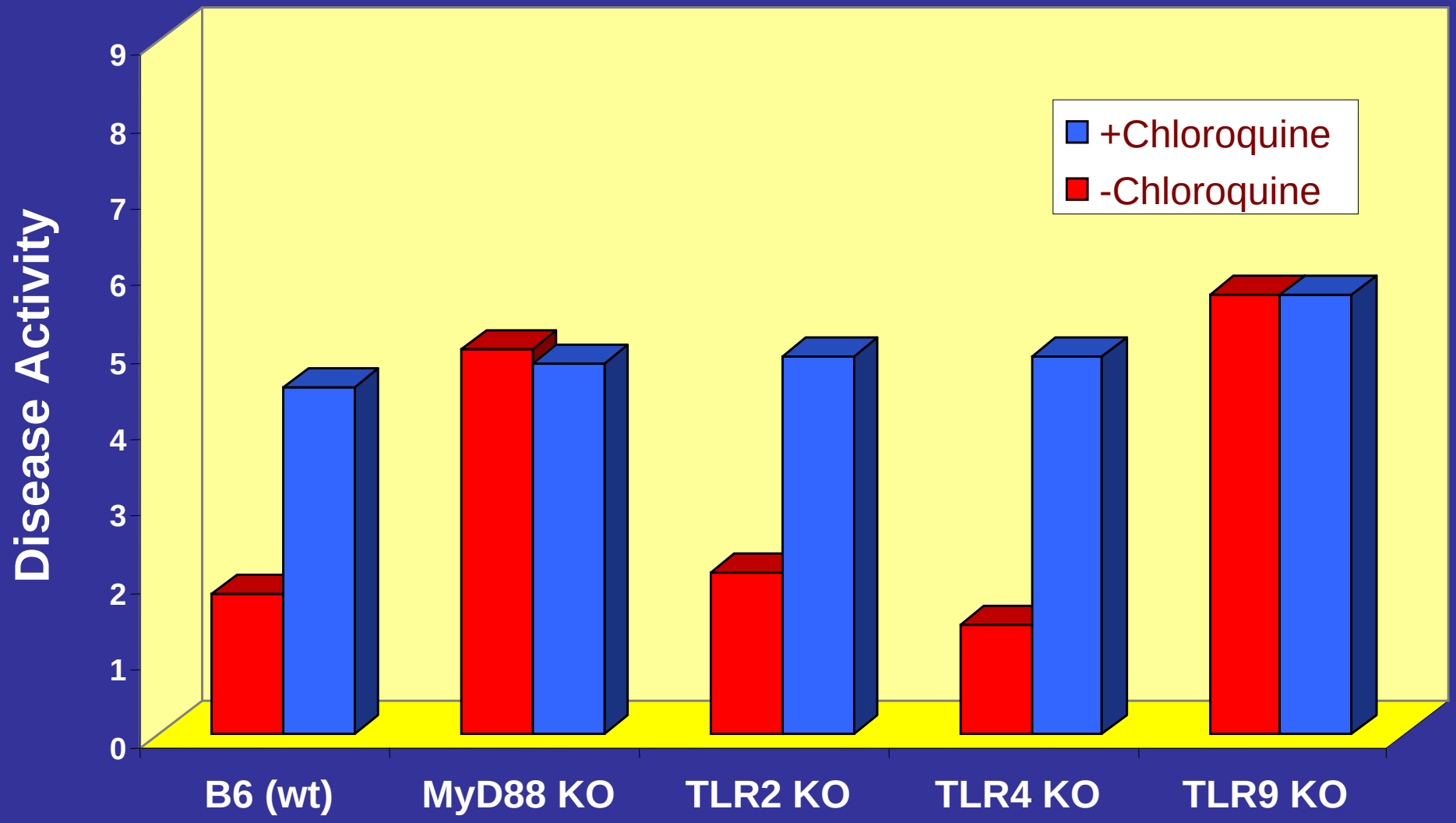


Effect of Probiotics on Chronic DSS Induced Colitis




Ligand
TLR
TIR
Endosome
TLR6
TLR2
Phagosome
TLR9
MyD88
IRAK
TRAF6
JNK
NF-κB
AP-1
NF-κB
Gene Transcription
TLR
Ligand
IRAK
TRAF6
MyD88

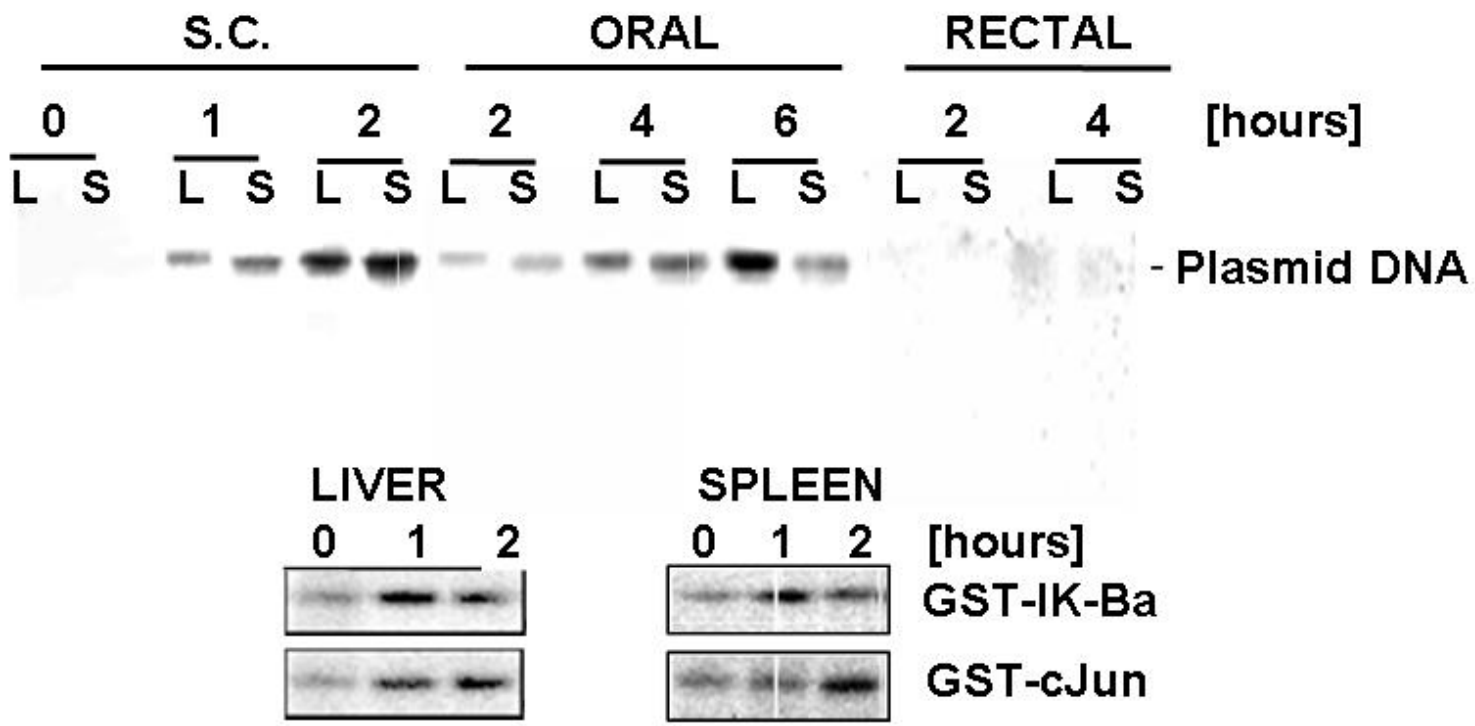
Effect of Irradiated Probiotics and Chloroquine on DSS Induced Colitis



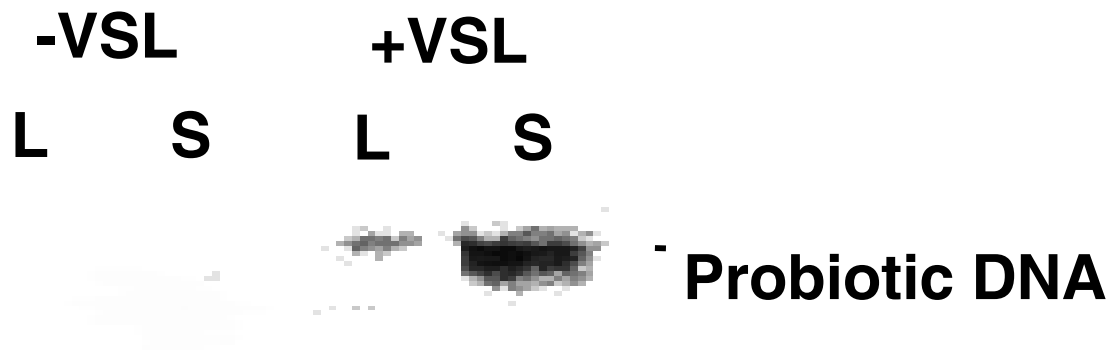
Probiotic DNA: Intragastric vs. Intrarectal Administration

Treatment	DAI	MPO	HS
None	7.3 ± 0.5	1.9 ±0.1	7.5 ± 0.9
Probio. DNA (i.g.)	3.2 ± 0.7	1.3 ± 0.1	3.0 ± 0.4
Probio. DNA (i.r.)	5.9 ± 1.2	1.9 ± 0.1	6.5 ± 1.1
ISS-ODN (i.g.)	3.6 ± 0.7	1.1 ± 0.1	2.8 ± 0.6
ISS-ODN (i.r.)	6.3 ± 0.7	1.9 ± 0.3	5.9 ± 0.7
CT DNA (i.g)	5.7 ± 1	2.0 ± 0.2	6.3 ± 1.4
Cont-ODN (i.g.)	6.7 ± 0.8	1.9 ± 0.2	5.7 ± 0.3

Detection of pDNA After Oral Administration At Systemic Sites



Detection of Probiotic DNA After Oral Administration at Systemic Sites



CONCLUSIONS

1. Probiotic DNA has immunostimulatory activity

2. The protective effect of probiotics is mediated by their own DNA and TLR-9 signaling is essential

3. Probiotic DNA is absorbed from the UGI tract

CONCLUSIONS CON'T

4. Live bacteria are not required to attenuate colitis since non-viable probiotics are equally effective

5. Probiotics may be of value in the treatment and maintenance of IBD in remission