

The Immunosuppressed Traveller

l.g.visser@lumc.nl



37-yo physical therapist

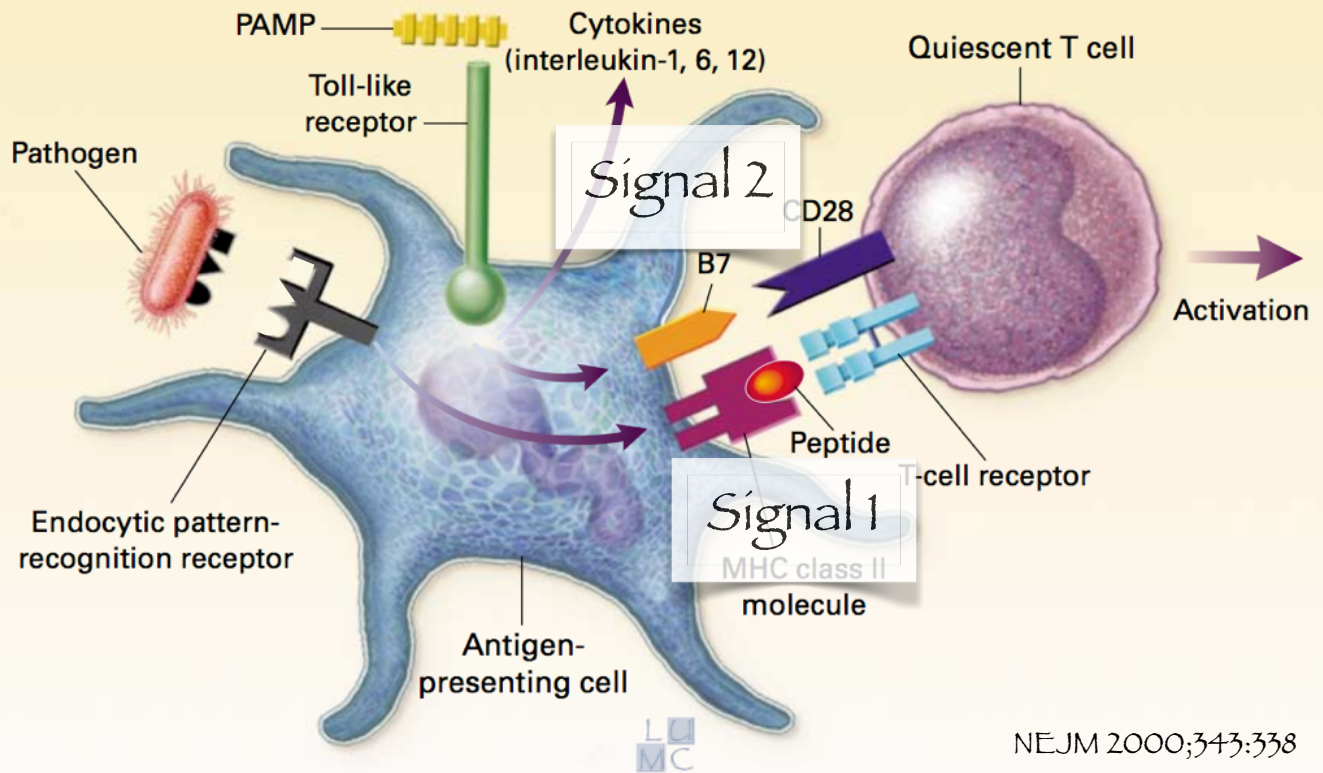
2000 Kidney transplantation
prednisolone, 5 mg, od
mofetil mycophenolate, 500 mg, bid

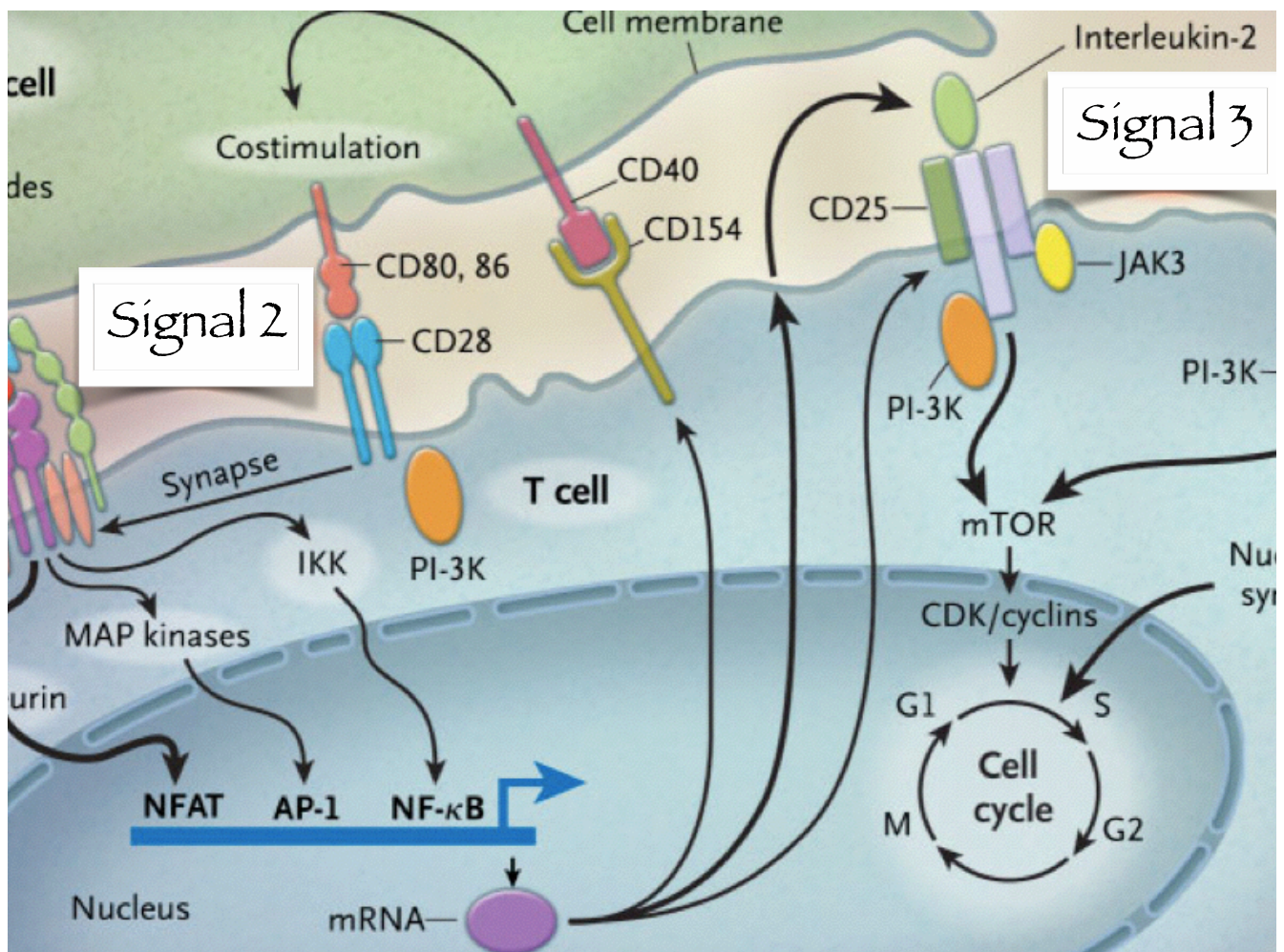
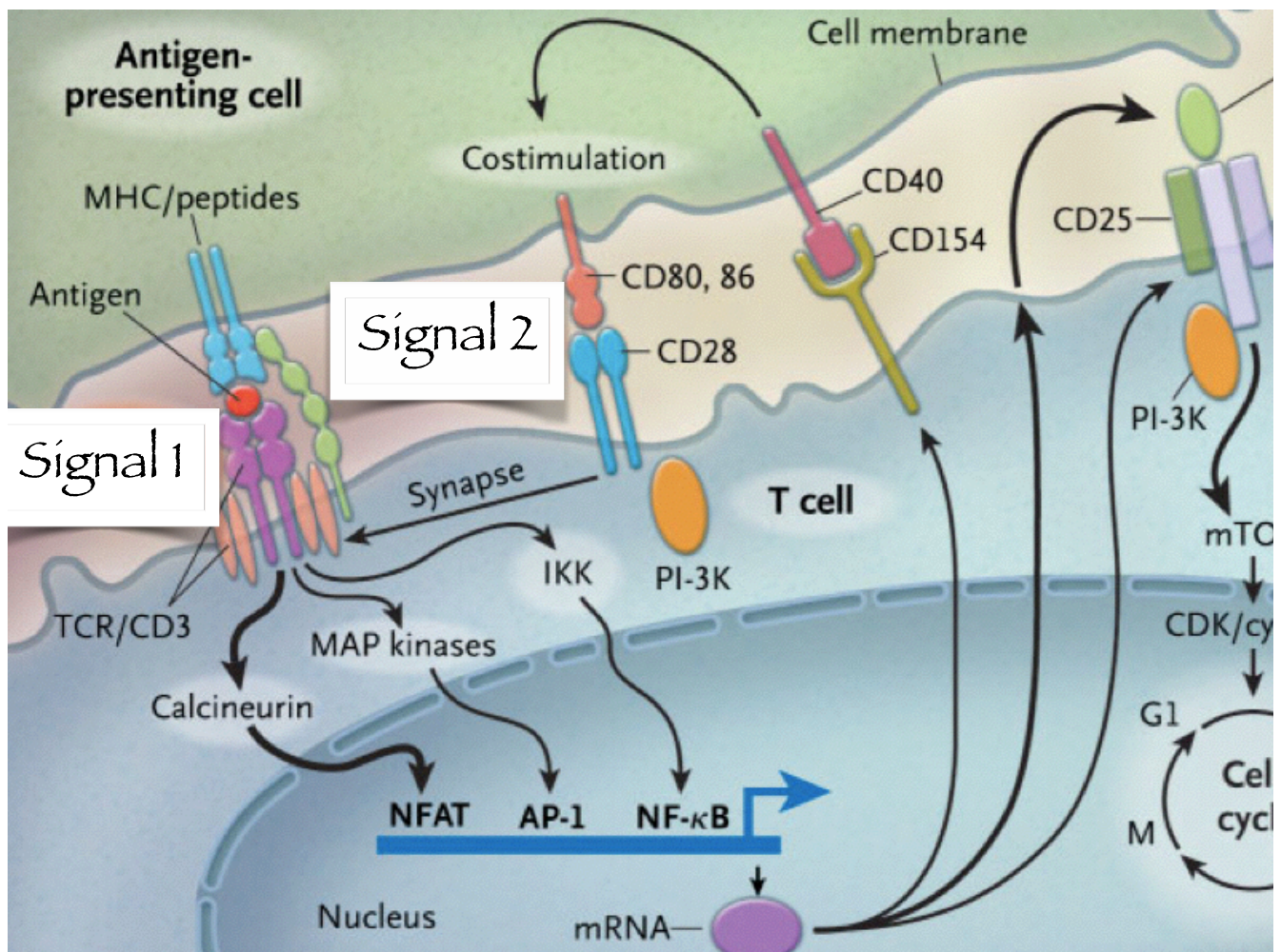
India, 12W

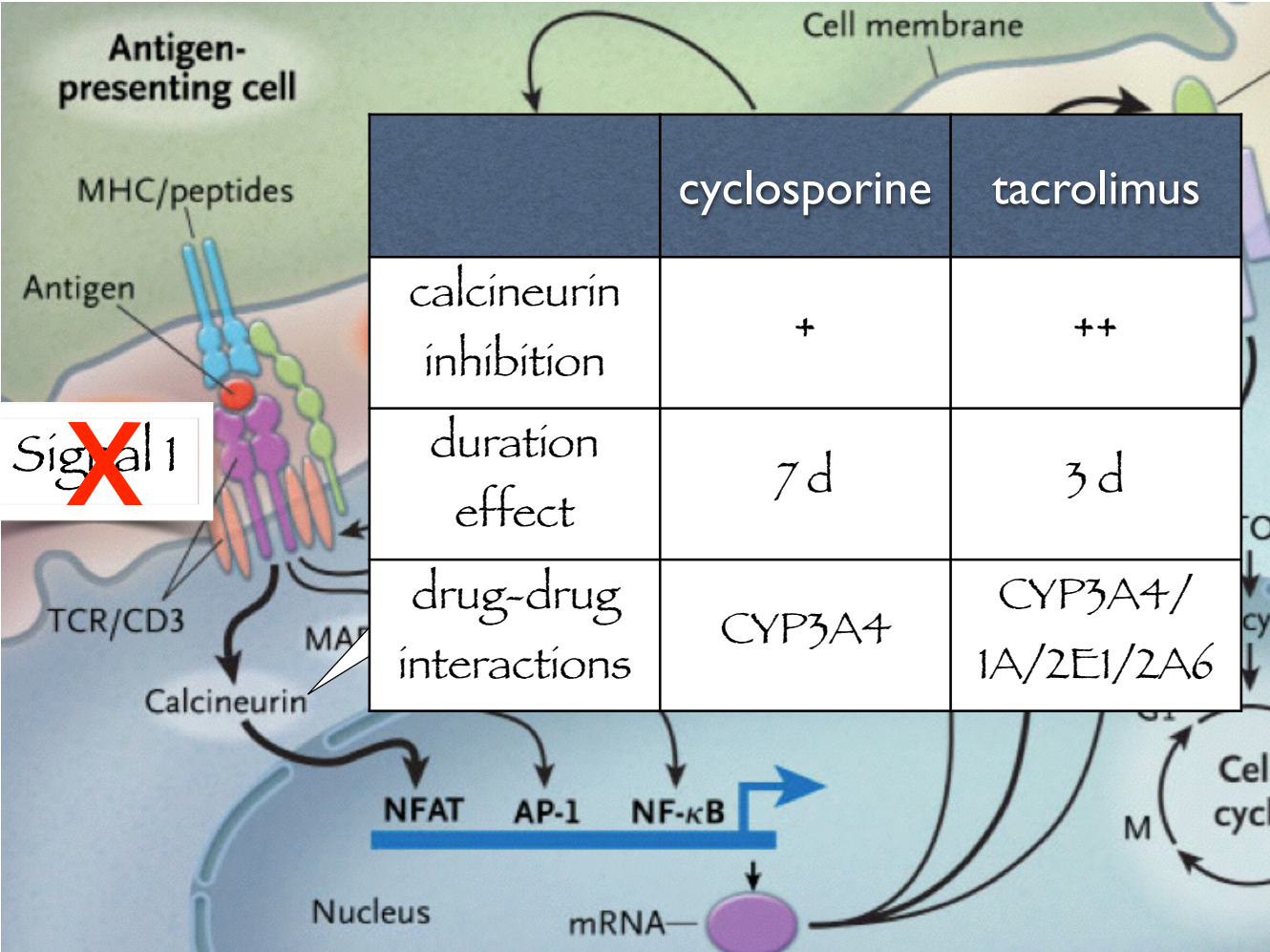
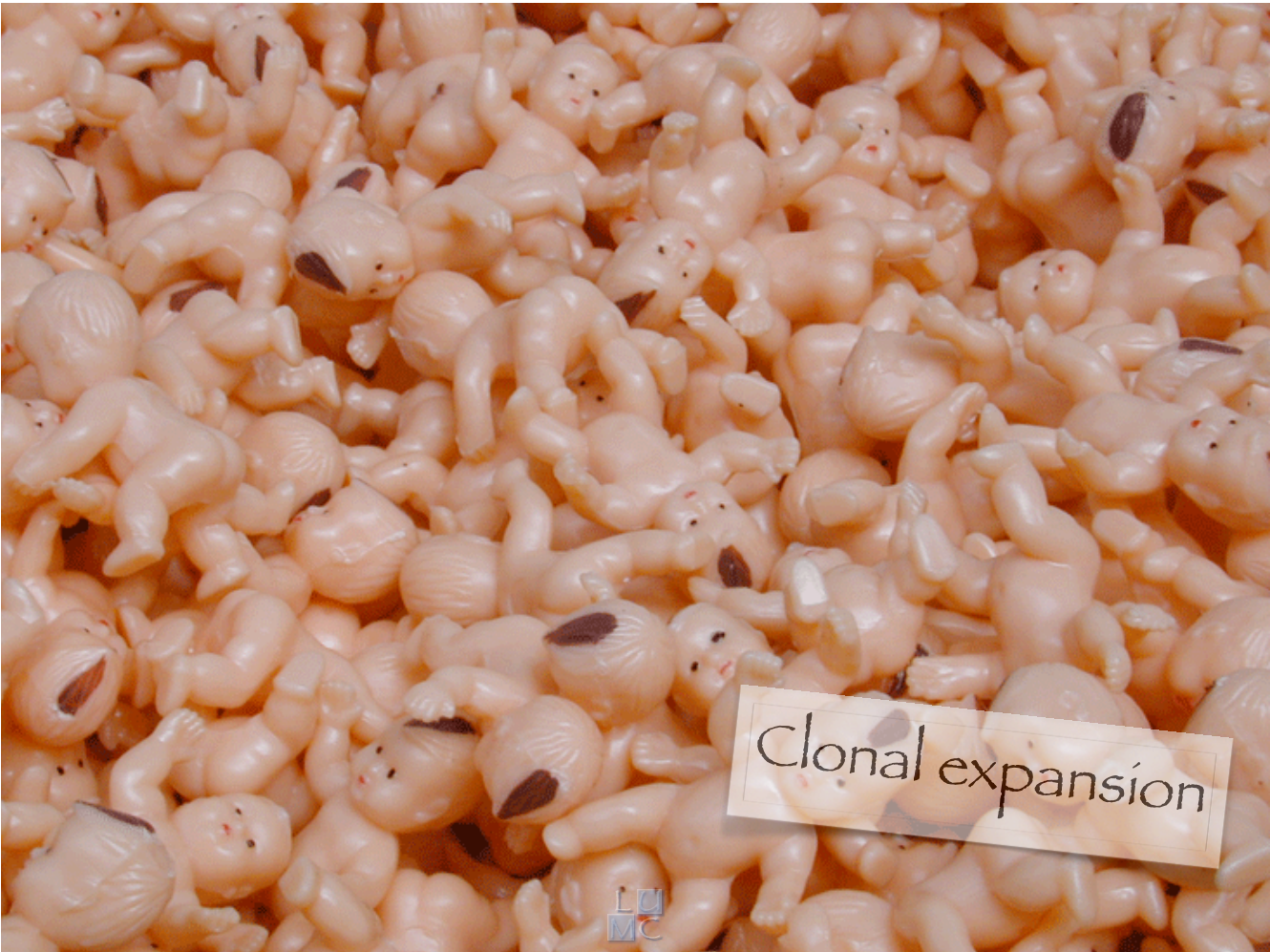
*How does this affect response to
vaccination?*

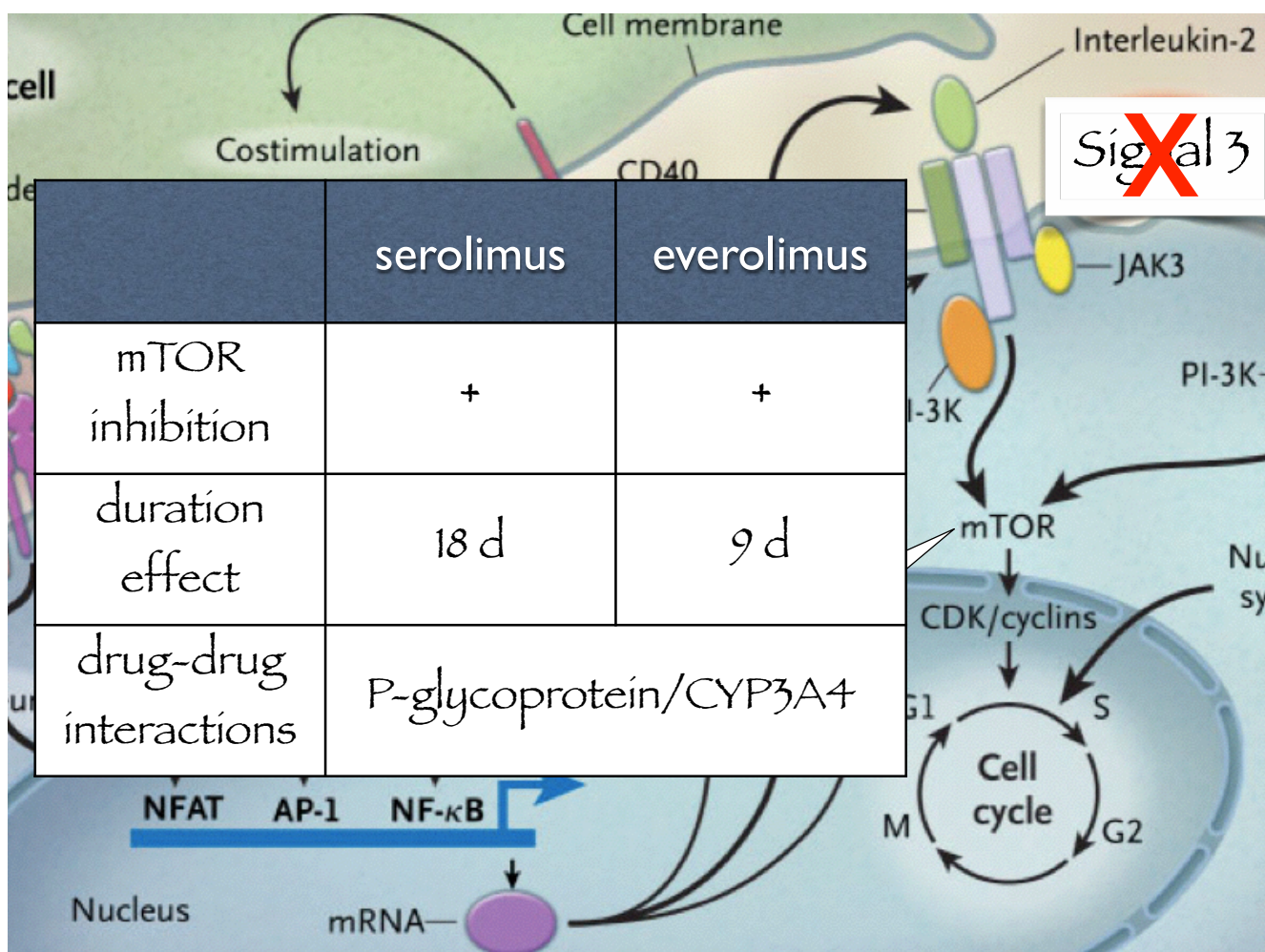
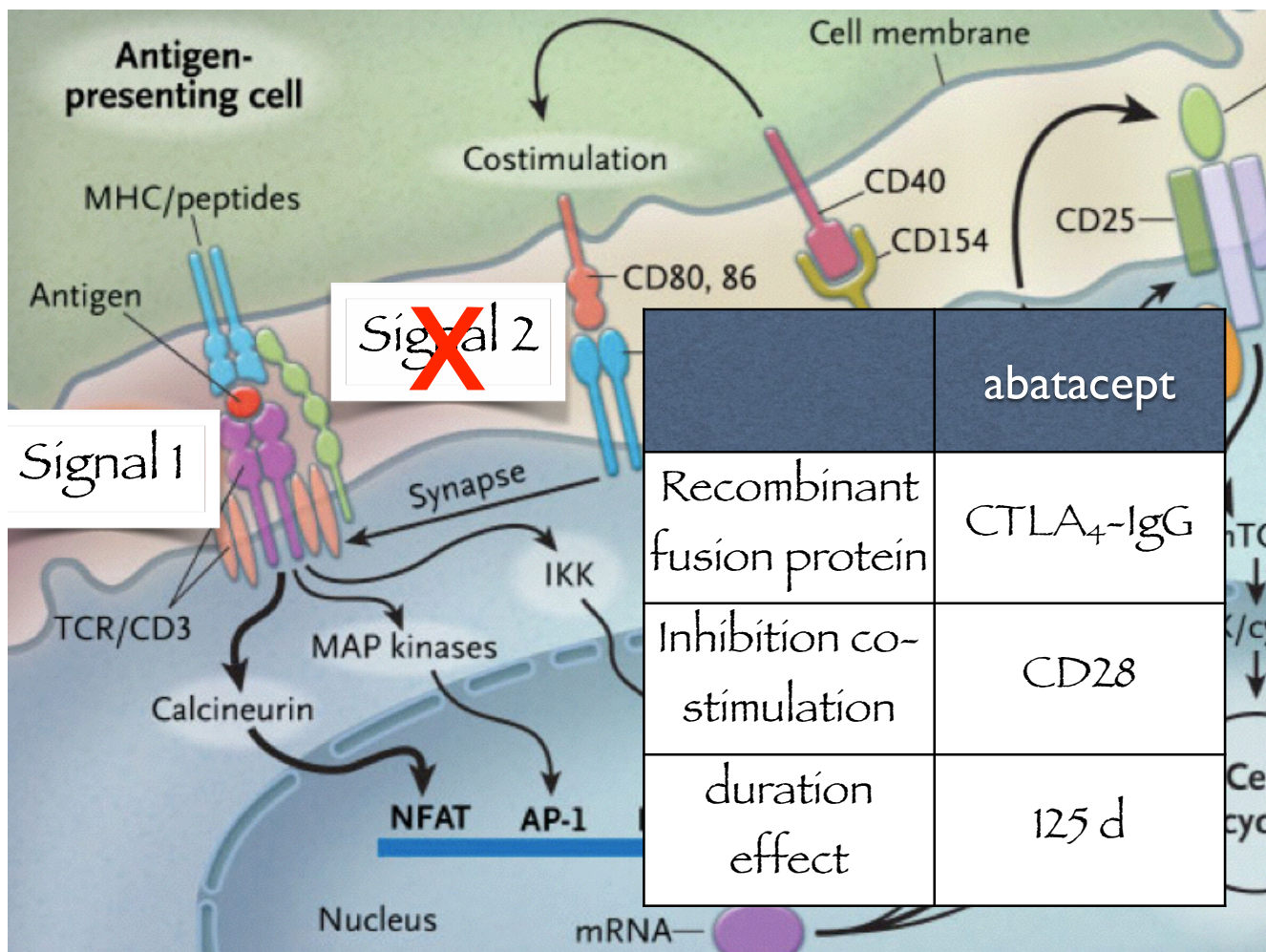


Vaccine adjuvant

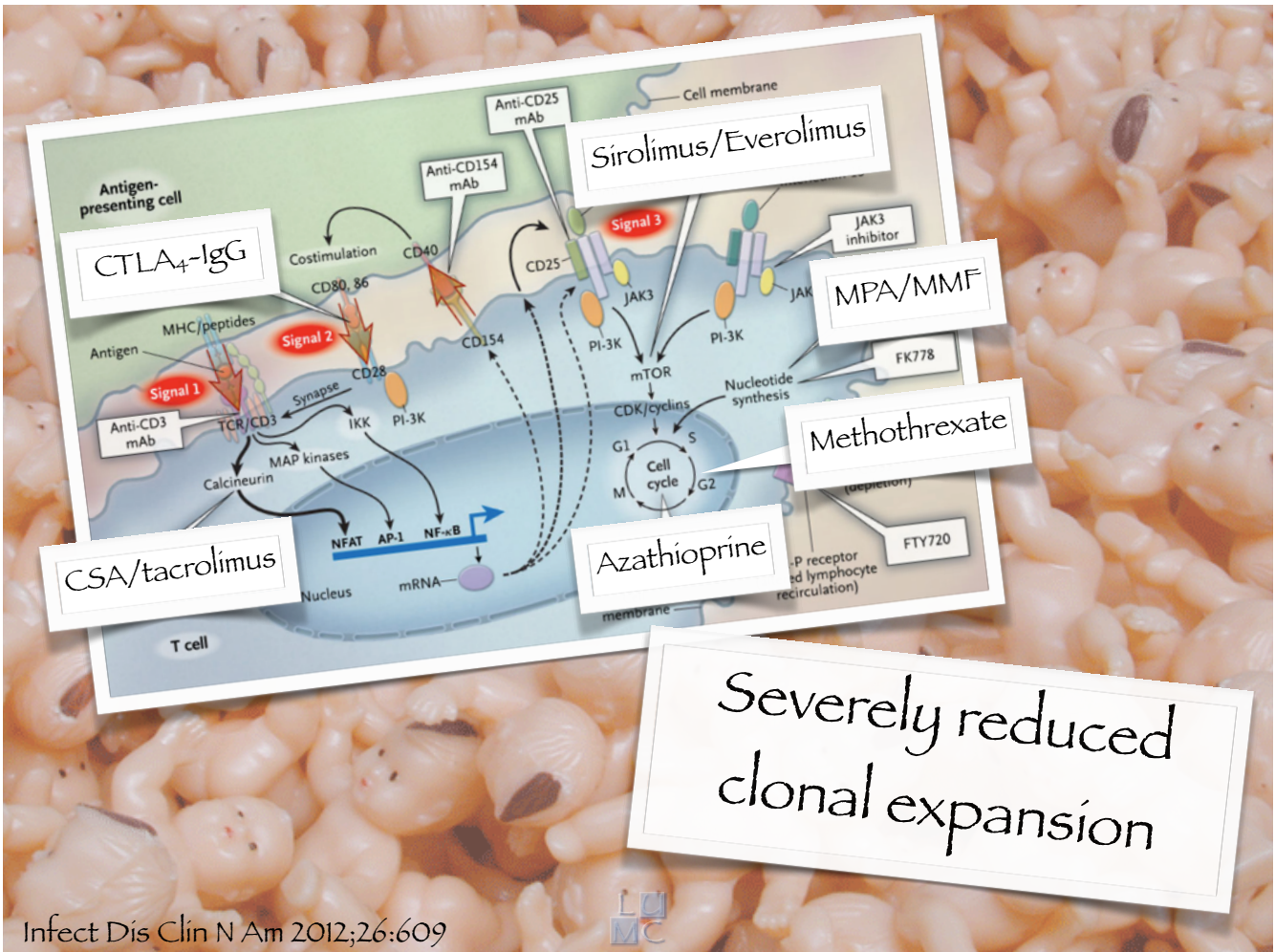




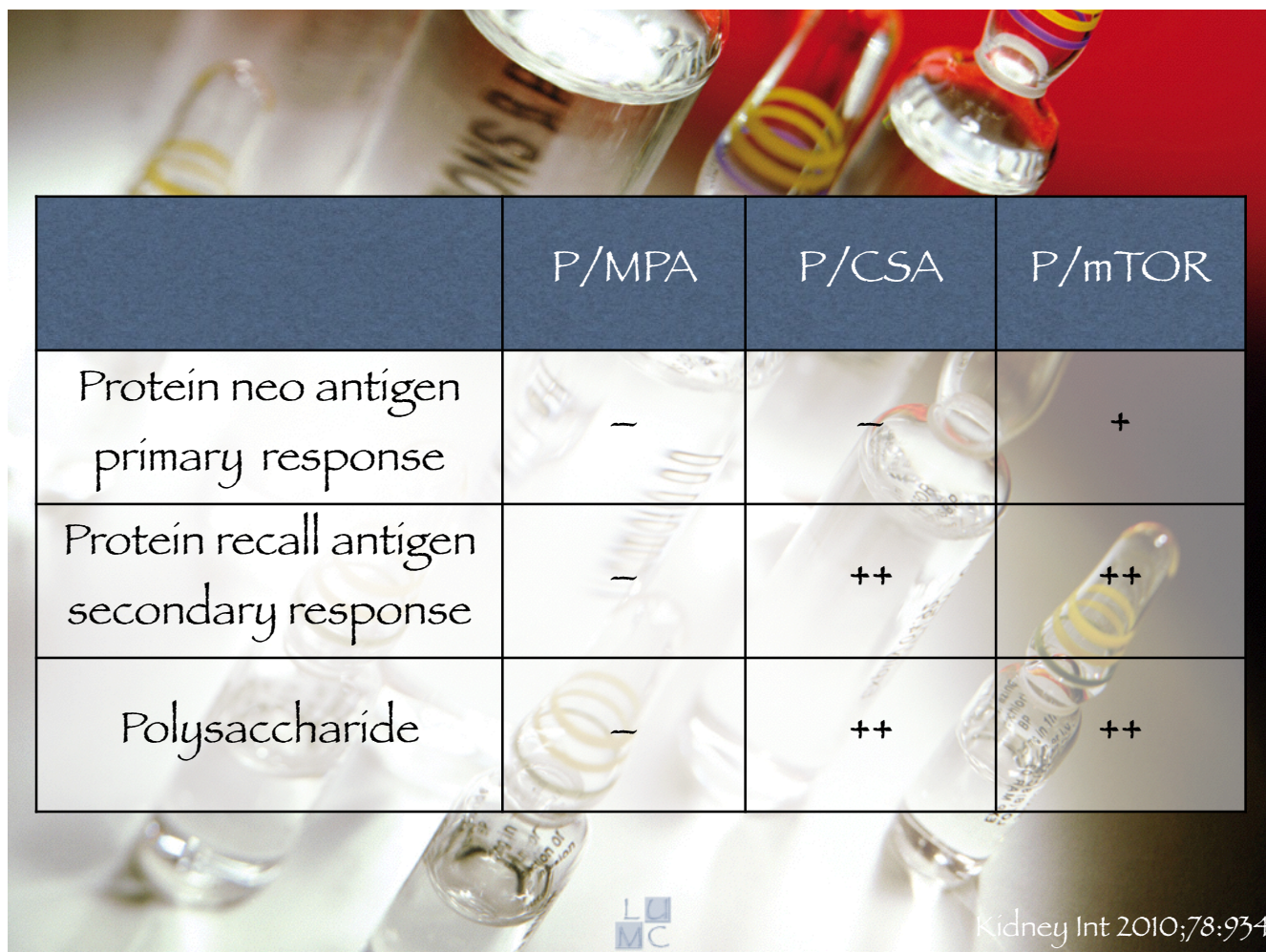




	MTX	azathioprine	mycophenolic acid
Nucleotide synthesis	purines (FH2 polyglutamates)	guanosine purines	guanosine activated T/B
duration effect	1 mo	2 mo	5 d
drug-drug interactions	antifolates	1:300 TPMT-deficient	glucuronyl transferase



Severely reduced
clonal expansion



	P/MPA	P/CSA	P/mTOR
Protein neo antigen primary response	–	–	+
Protein recall antigen secondary response	–	++	++
Polysaccharide	–	++	++

Kidney Int 2010;78:934

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Serologic Vaccination Response after Solid Organ Transplantation: A Systematic Review

Isabella Eckerle^{1,2*}, Kerstin Daniela Rosenberger¹, Marcel Zwahlen³, Thomas Junghanss¹

¹ Section of Clinical Tropical Medicine, Department of Infectious Diseases, University Hospital Heidelberg, Heidelberg, Germany, ² Institute of Virology, University of Bonn Medical Centre, Bonn, Germany, ³ Institute of Social and Preventive Medicine, University Bern, Bern, Switzerland

	Short-term (%)	Long-term (%)
D/T/iP	85 – 100	~17 (D)
HepA/HepB	26 – 71/7 – 36	~42 (HepA)
<i>S. pneumoniae</i>	32 – 100	?
TBE	35	?

37-yo physical therapist

2000 Kidney transplantation

prednison, 5 mg, od
mofetil mycophenolate, 500 mg, bid

Varanasi, 12W

Pronounced inhibition of clonal
proliferation with very poor primary and
secondary immune response



Immunosuppression most pronounced first 6 mo
(alemtuzumab ≥ 9 mo) and after rejection therapy
Inhibition clonal proliferation affects
primary immune response more than secondary
Lower antibody levels, shorter protection
Immunise before transplantation if possible



33-yo pilot (I)

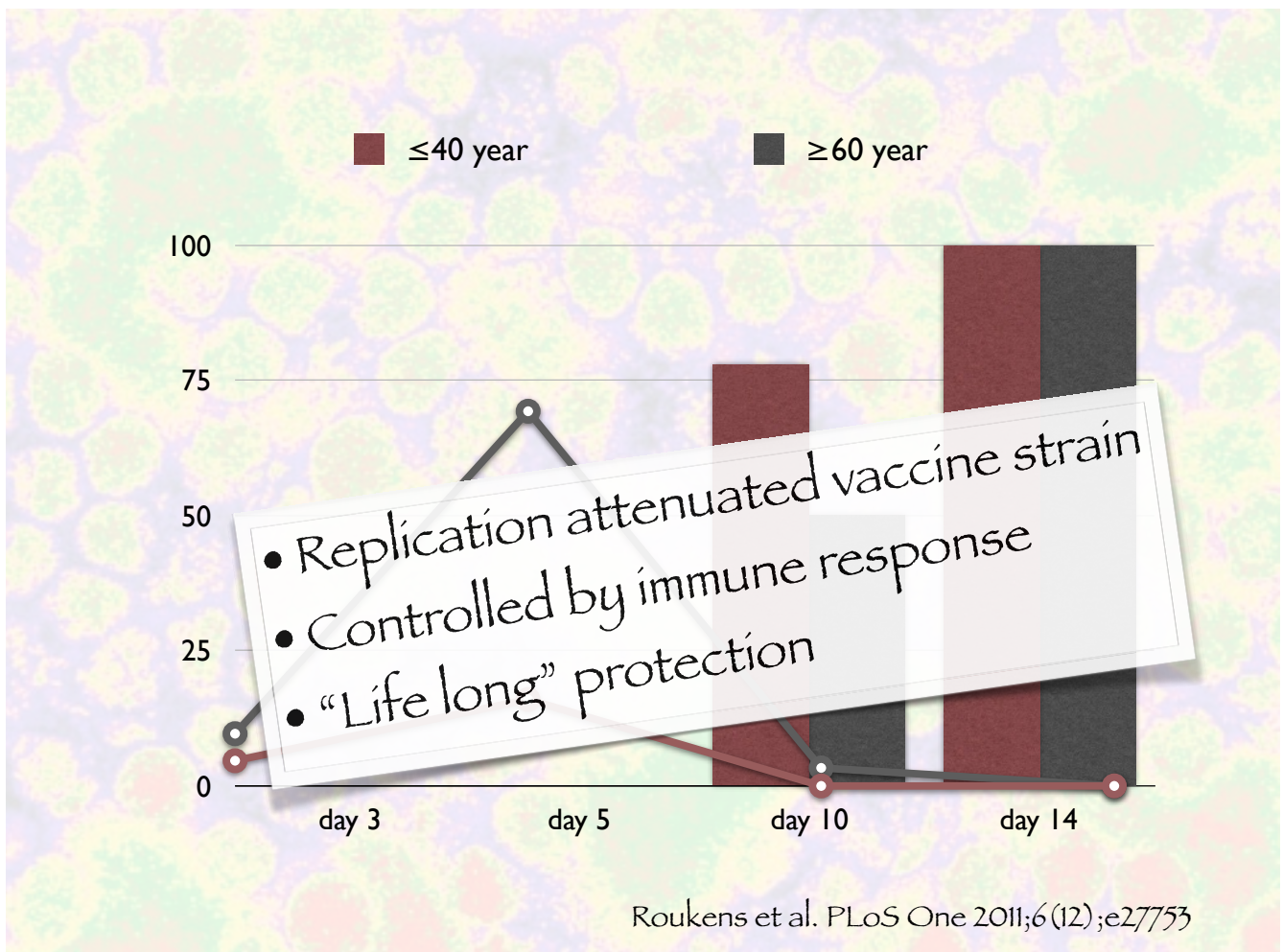
1997 Crohn's disease

2009 ileocecal resection

Azathioprine (150 mg) stopped (6W)

Budesonide (9 mg) started (2W)

When can yellow fever vaccination be given safely?





17D-yellow fever vaccine

- 17D-YFV by chance mutation less neurovirulent
- Severe encephalitis (YF-AND) in 50% immunosuppressed hamsters (cyclophosphamide)
- No adverse events after inadvertent administration of 17D-YFV to 18 SOT

Transplant Infect Dis 2011;14:237

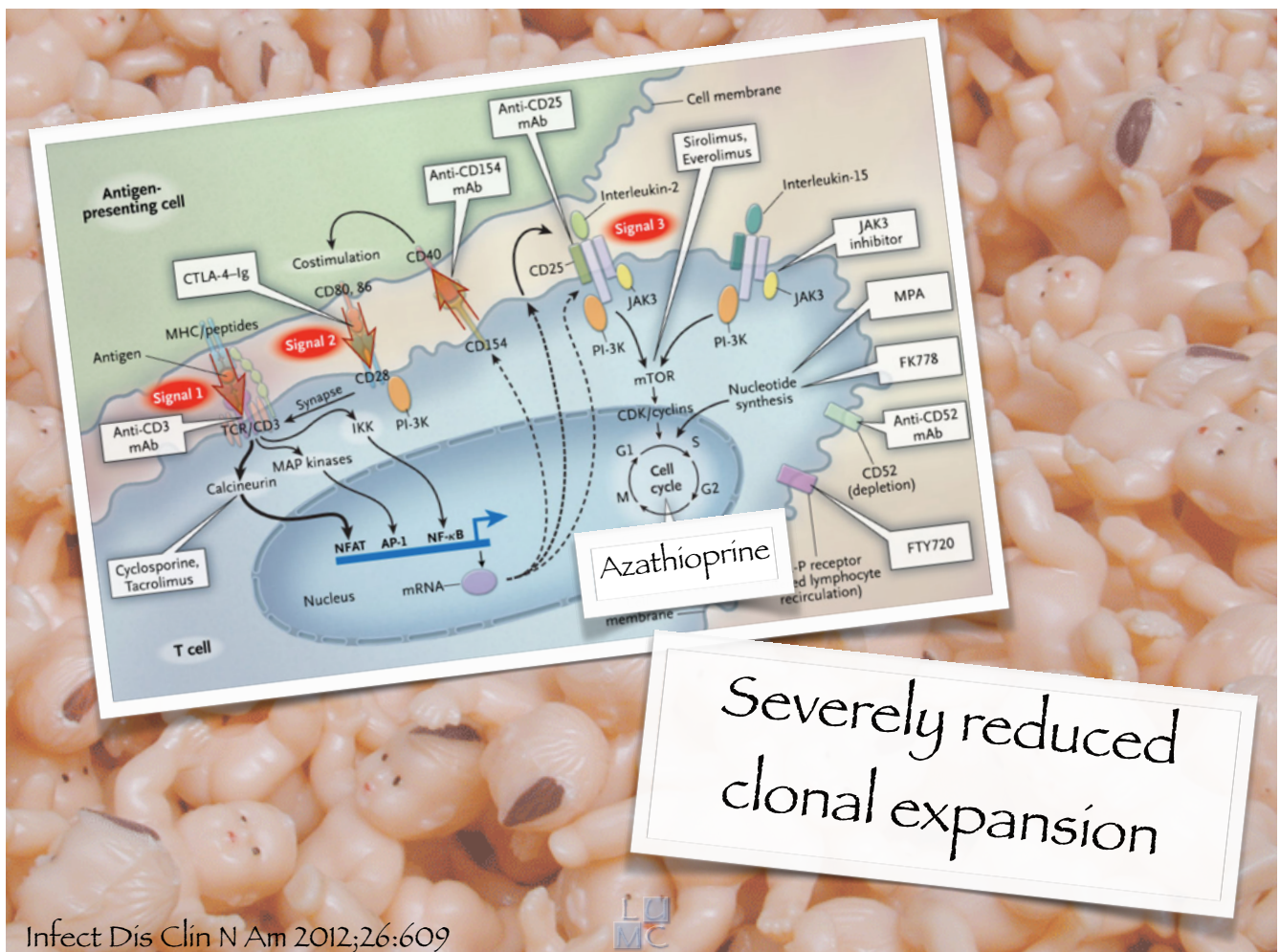


Table 2
Minimal duration of immunosuppressive activity^a

Drug	Duration
Prednisone	1 mo ^b
Cyclosporin	7 d
Tacrolimus	3 d
Sirolimus	18 d
Everolimus	9 d
Azathioprine	2 mo
Mycophenolic acid	5 d
Methotrexate	1 mo
Alemtuzumab	>1 y
Rituximab	1 y
Etanercept	1 mo
Infliximab, adalimumab, golimumab, certolizumab	3 mo

^a Old age and thymic injury may prolong time until full immune reconstitution.

^b Numbers of CD4⁺ and CD8⁺ T cells in blood should be determined to exclude lymphopenia caused by long-standing T-cell apoptosis.

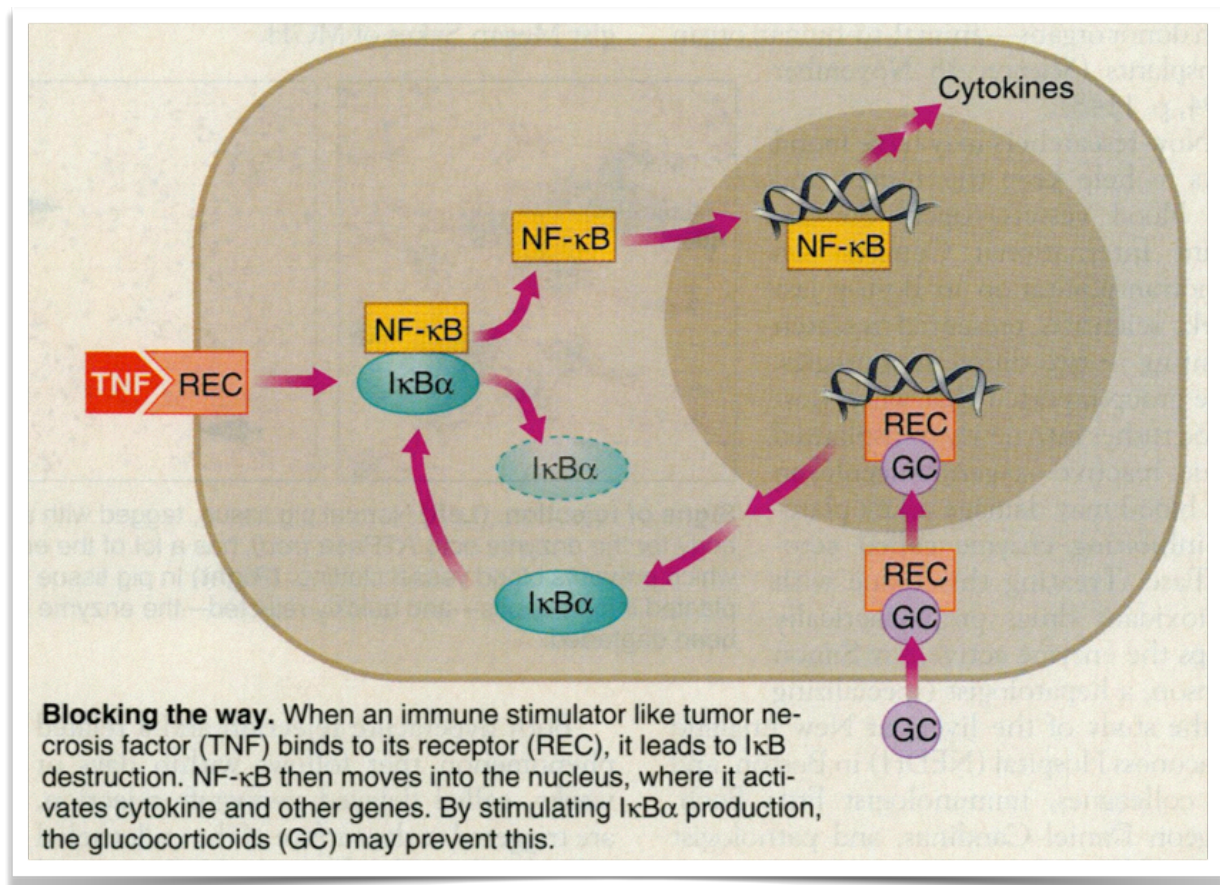
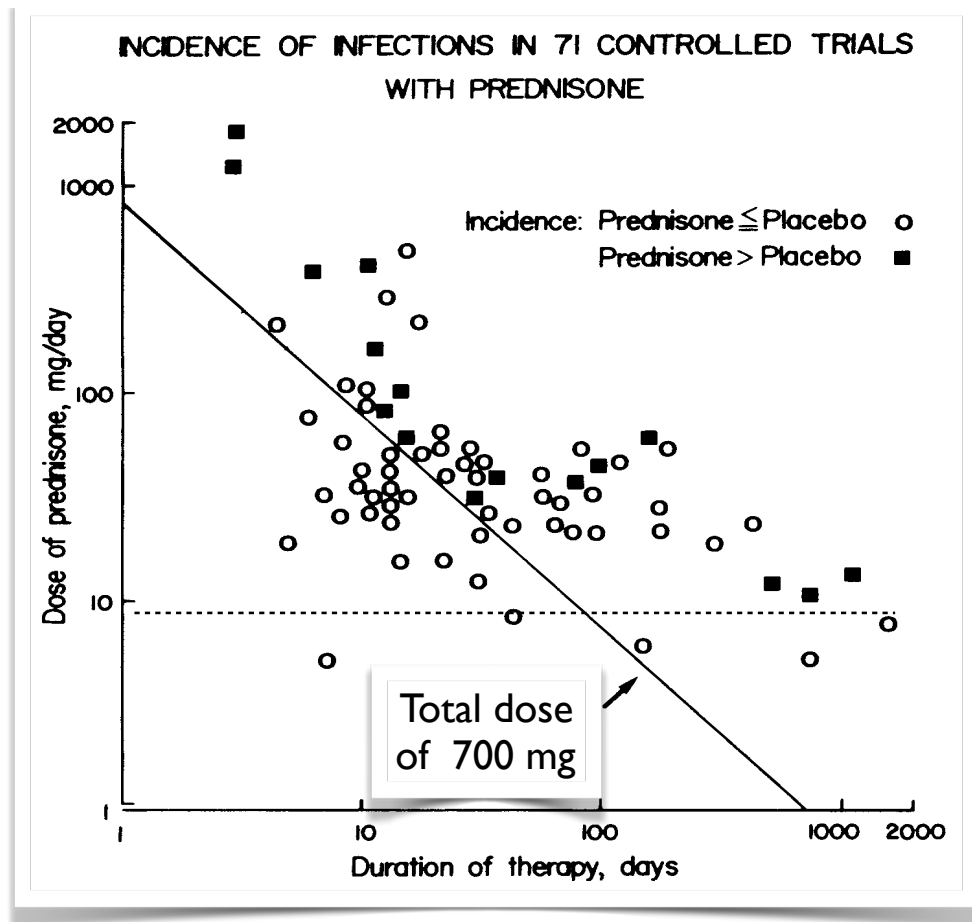


Infect Dis Clin N Am 2012;26:069

Budesonide

- Synthetic glucocorticosteroid
potency = 15 x prednisone
- Extensive first-pass effect (CYP3A4)
biological availability 10%
- Cumulative systemic dose =
 $9 \text{ mg} \times (15 \text{ mg} \times 0,10) \times 14\text{d} = 189 \text{ mg in 2W}$





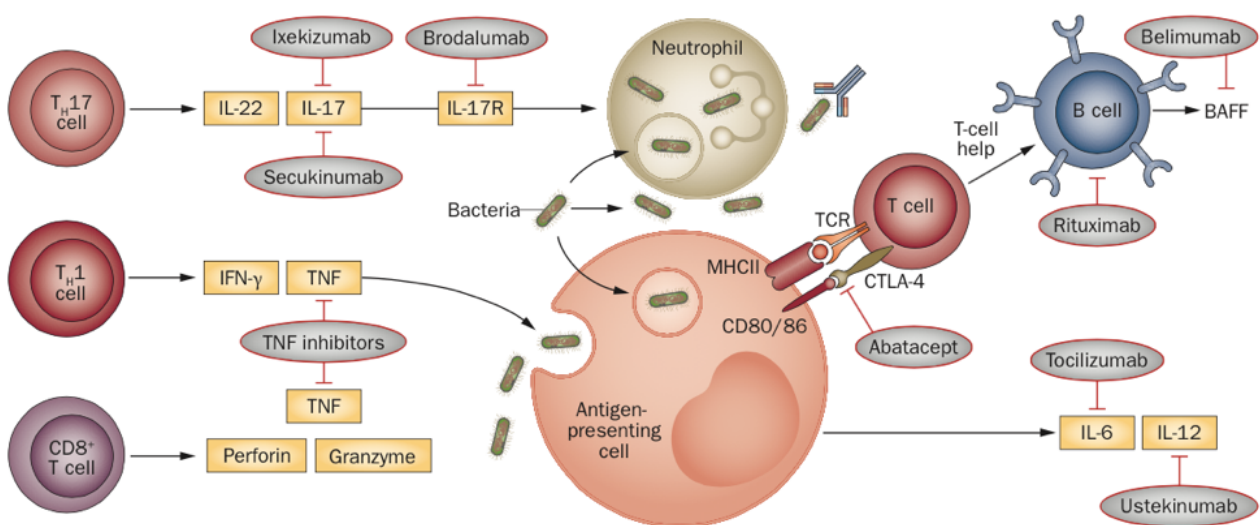
33-yo pilot (2)

W8 Yellow fever vaccination

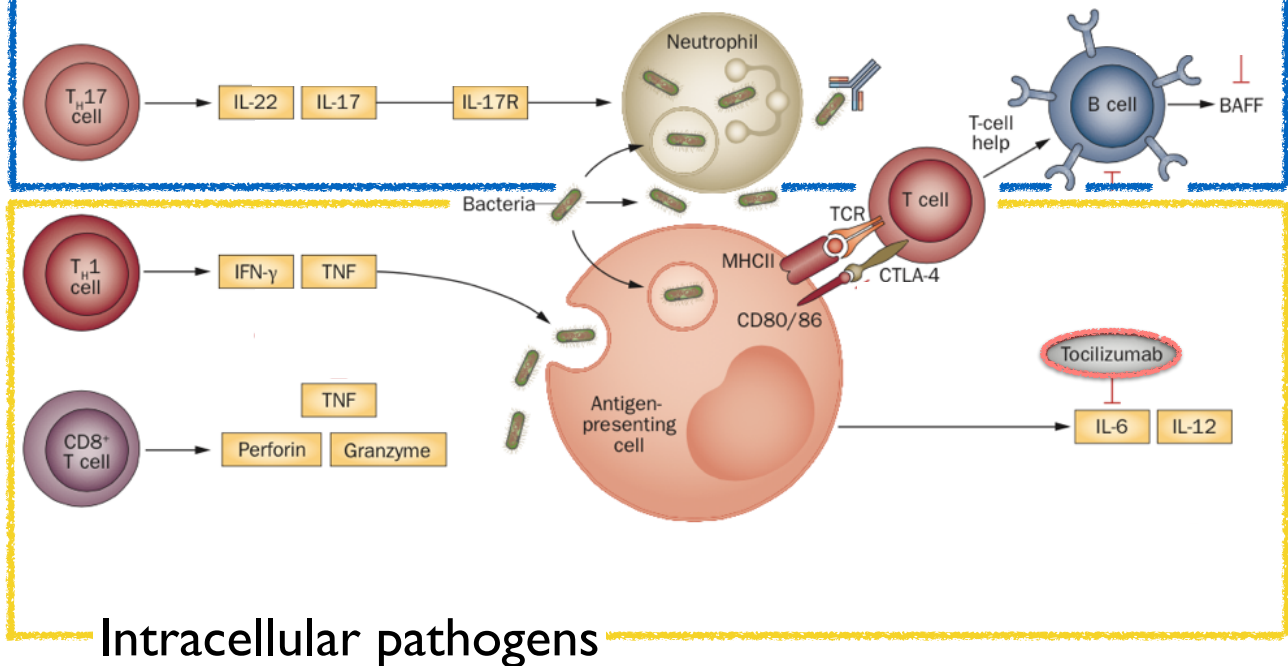
W12 Neutralising antibodies (PRNT₈₀ >1:32)

Azathioprine (150 mg) resumed at W12

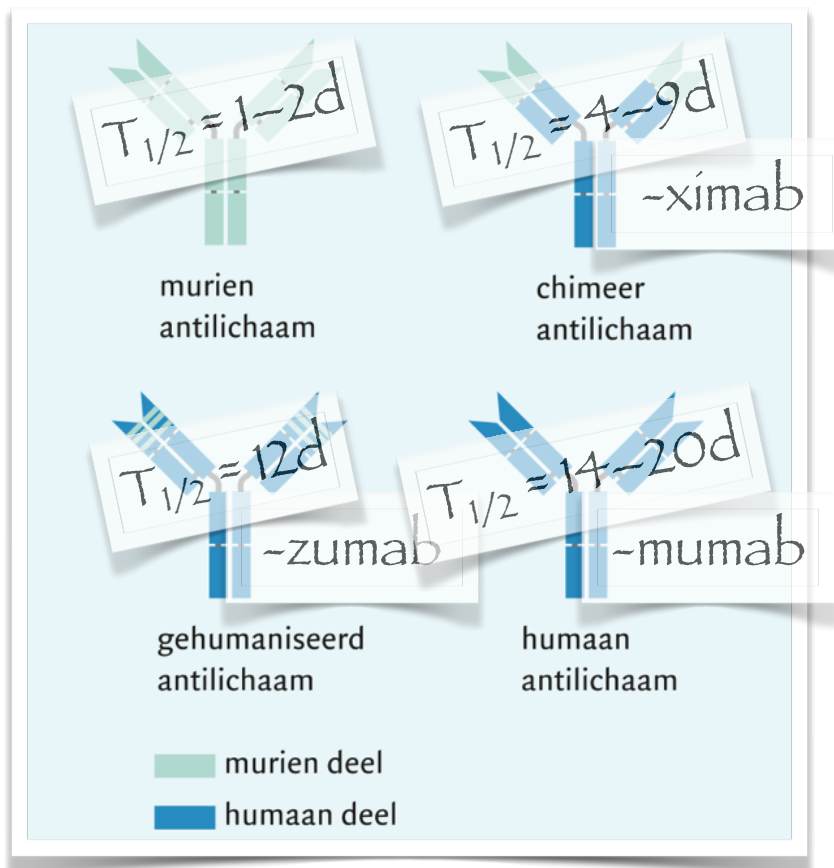
Budesonide between W8-W12



Extracellular pathogens



Nature Rev Rheumatol 2014;10:612



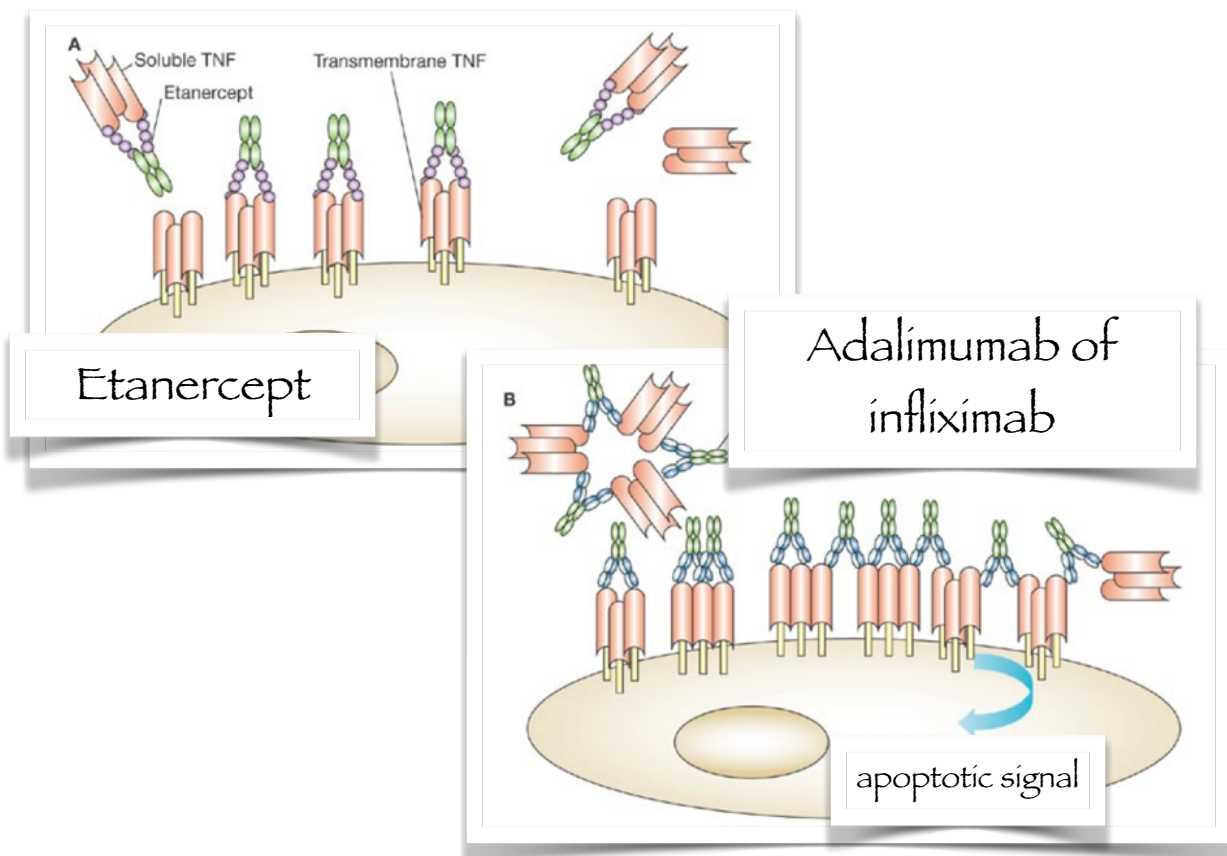
Ned Tijdschr Geneesk 2007;151:683

TNF

- TNF- α plays key role
local containment of infections
- Regulates immune cell proliferation,
differentiation and survival (or death)
- Transmembrane (tmTNF)
Soluble TNF (sTNF)



Curr Infect Dis Rep 2011;13:243



Nat Clin Pract Rheumatol 2007;3:227

Table 2
Minimal duration of immunosuppressive activity^a

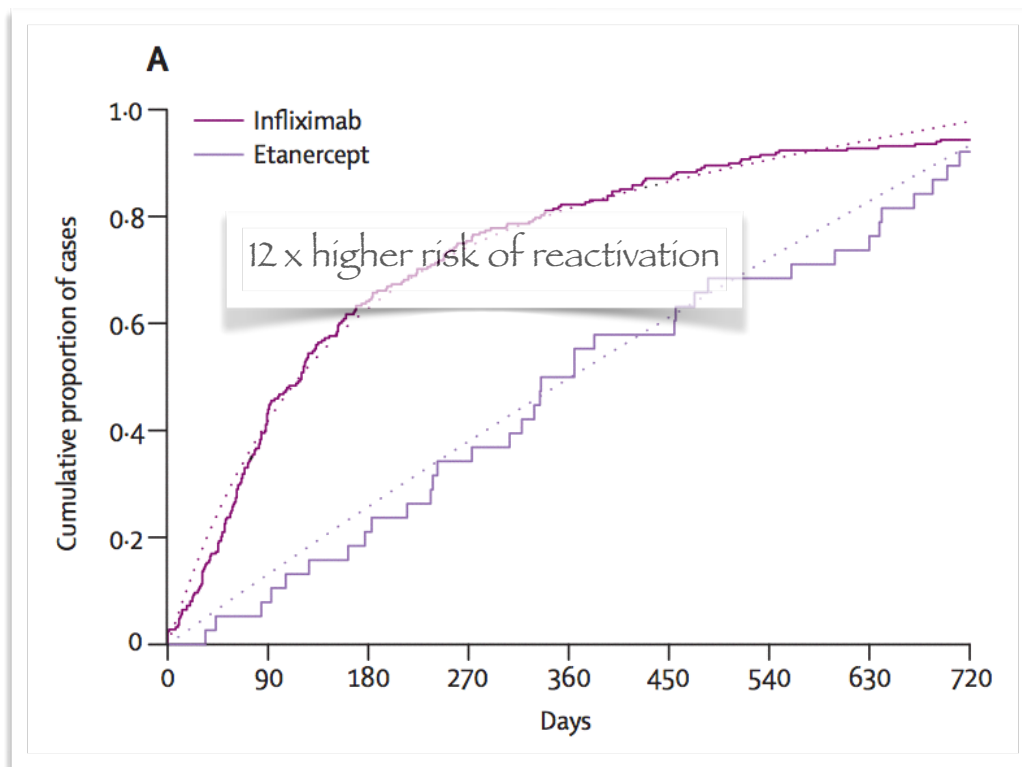
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Infect Dis Clin N Am 2012;26:069



Lancet Infect Dis 2008;8:601

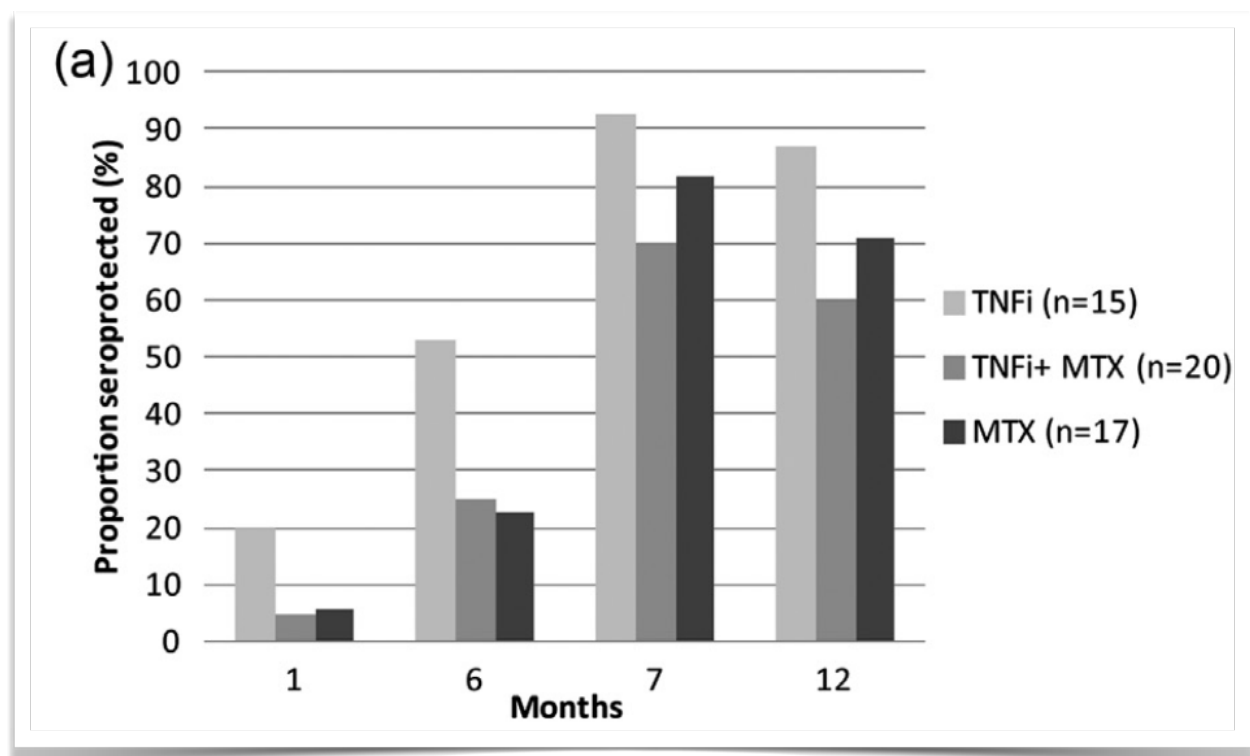
	Infliximab	Etanercept	I:E	p value*
Aspergillosis	8.63 (17)	6.19 (7)	1.39:1	0.243
Candidiasis	10.15 (20)	5.31 (6)	1.91:1	0.061
Bartonellosis	0.51 (1)	0 (0)	n/a	0.563
Coccidioidomycosis	5.58 (11)	0.88 (1)	6.34:1	0.013
Cryptococcosis	5.08 (10)	7.08 (8)	0.72:1	0.179
Histoplasmosis	18.78 (37)	2.65 (3)	7.09:1	<0.0001
Legionellosis	0.51 (1)	0 (0)	n/a	0.563
Leprosy	0.51 (1)	0 (0)	n/a	0.563
Listeriosis	8.63 (17)	0.88 (1)	9.81:1	0.0006
Non-tuberculosis mycobacterioses	11.17 (22)	6.19 (7)	1.80:1	0.066
Nocardiosis	3.55 (7)	0.88 (1)	4.03:1	0.090
Pneumocystosis	0.51 (1)	0 (0)	n/a	0.563
Salmonellosis	0 (0)	1.77 (2)	n/a	0.031
Toxoplasmosis	2.03 (4)	0 (0)	n/a	0.101
Tuberculosis	53.81 (106)	28.32 (32)	1.90:1	<0.0001

n/a=not applicable. Data are case rate per 100 000 treated patients (number of cases). Case rates per 100 000 treated patients were calculated on the basis of 197 000 patients treated with infliximab and 113 000 treated with etanercept, as reported by the manufacturer. I:E indicates crude case rate ratio (infliximab to etanercept). *Significance was determined by Poisson analysis. Adapted from reference 53. Copyright 2004 by University of Chicago Press.

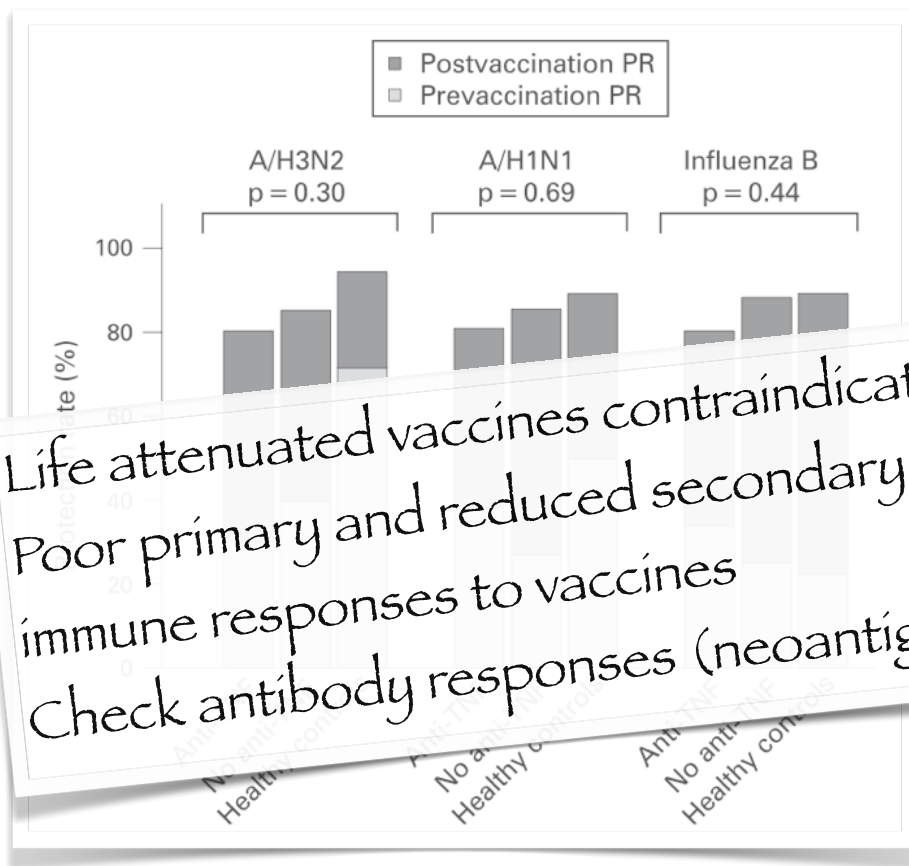
Table 1: Granulomatous infections in US patients treated with infliximab or etanercept

Lancet Infect Dis 2008;8:601

Seroprotection against hepatitis A (20 IU/ml)



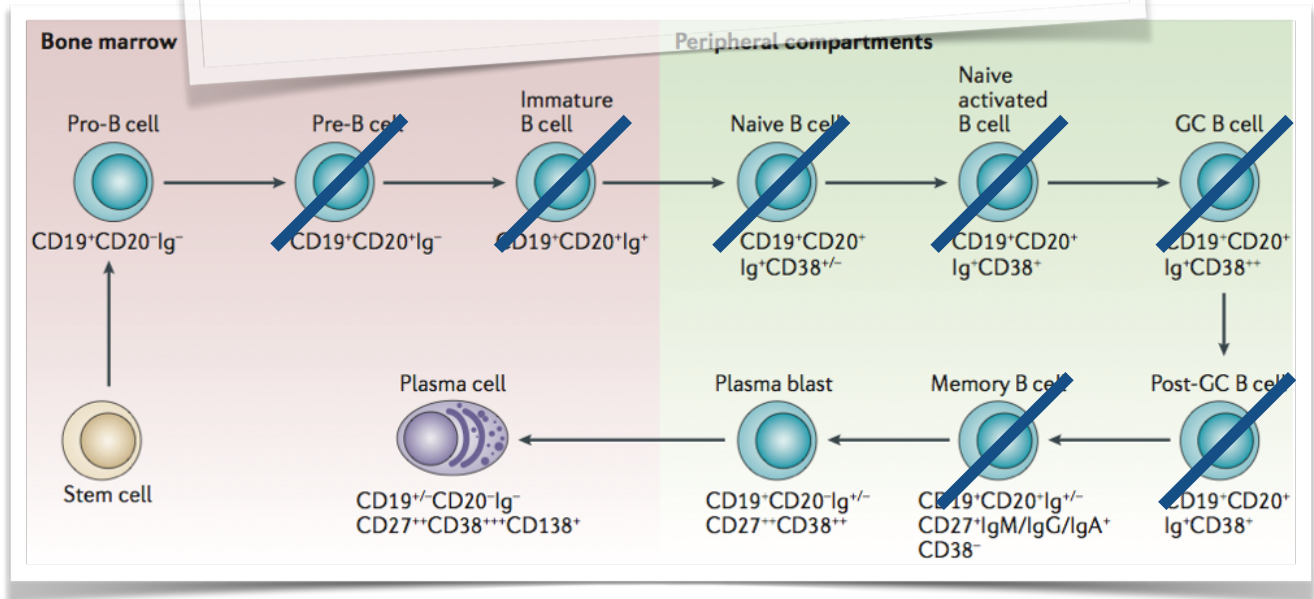
Trav Med Infect Dis 2014;12:134



Ann Rheumatol Dis 2008;67:713

**Cell depleting
monoclonal antibodies**

Chimeric anti-CD20 mIgG₁ (Rituximab)



Nat Rev Immunol 2006;6:394

Rituximab

- >95% depletion CD20⁺ B cells (>6 months)
- Long-lived antibody secreting plasma cells will maintain bulk antibody production
- Repopulation with naive B cells after 6–9 mo
- Memory responses shortly after RTX (6 mo) ↓
Antibody response to neoantigens and polysaccharides (12 mo) ↓



Rituximab

- Increased infectious risk (LRTI) if sustained low IgG levels <6 g/l
- Reactivation of chronic hepatitis B?
- Active immunisation 4W before starting rituximab



Ann Rheum Dis 2011;70:414

Alemtuzumab

- Humanized anti-CD52 IgG₁ mAb
- Massive depletion T-cells (> 9 mo) and B-cells (> 6 mo). Takes years to recover
- “mAb-induced AIDS” (CD4⁺-counts ~50)
Risk infections depending on underlying illness and co-medication

Conclusions

- Immunosuppressive agents prevent clonal expansion of T- and B-cells and profoundly affect primary immune response to vaccines
- Secondary immune responses are less affected, but protection may be shorter
- Immune restoration after cell-depleting monoclonal treatment may take more than a year

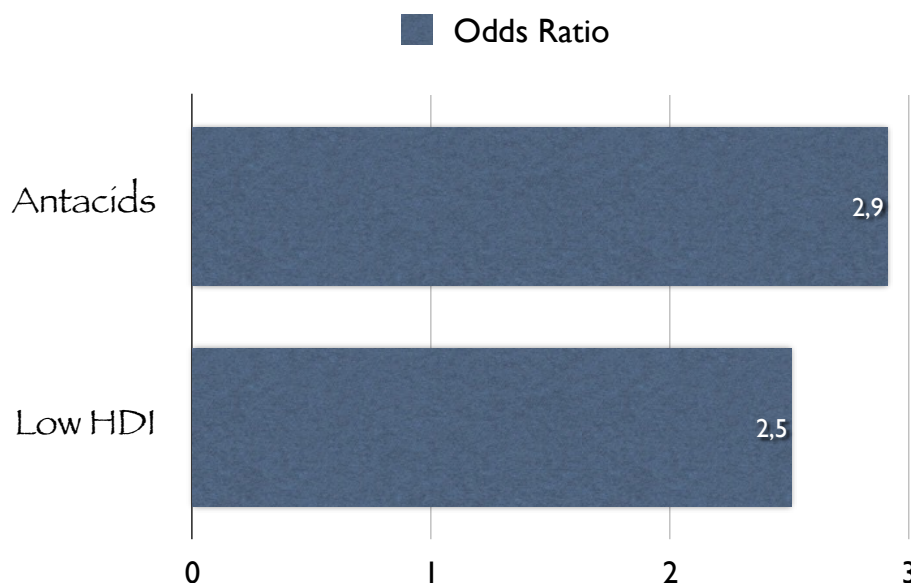


Strategies for Safe Living After Solid Organ Transplantation

- Frequent and thorough hand washing
- Avoid crowded areas, activities with increased exposure to tuberculosis, dust-laden environments, plant and soil aerosols, bird droppings and caves
- Avoid swimming in water potentially contaminated with human or animal waste
- Safe food and water consumption

Am J Transplant 2013;13:304

Risk factors diarrhoea





ESBL-producing Gram-negatives

N=370

N=136



travel



6 mo



32 (9%)

20 (5%)

7 (35%)

113 (31%)

19 (17%)



Failing cellular defence

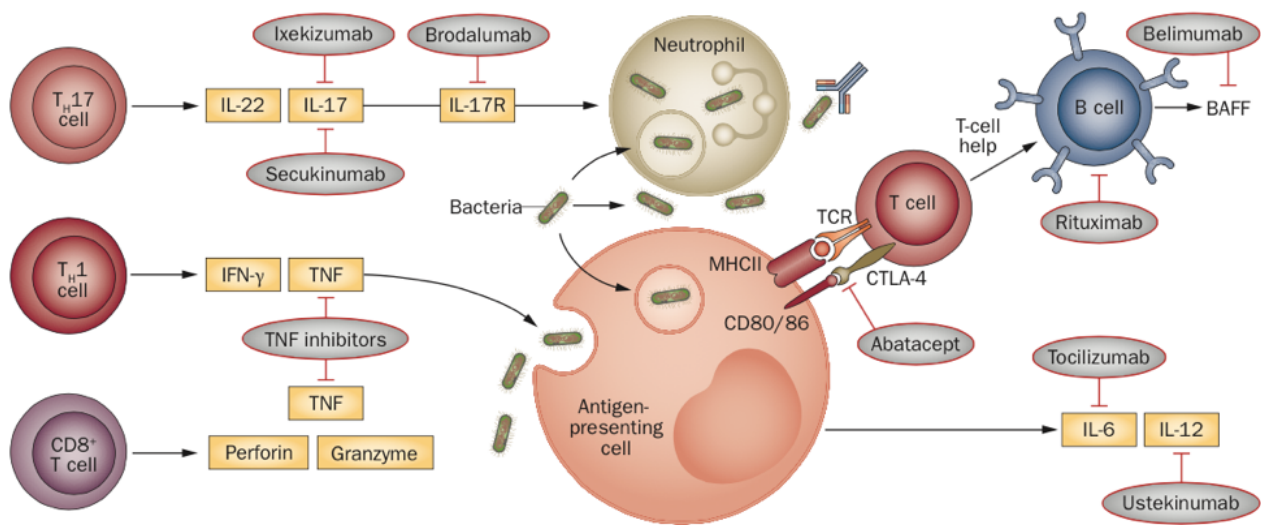
- Intracellular food-borne pathogens
Salmonella spp., *Listeria* spp., *Toxoplasma gondii*, *Cryptosporidium* spp
- Intracellular air-borne pathogens
Mycobacterium tuberculosis, *Legionella pneumophila*, *Histoplasma* spp



Failing cellular defence

- Viral infections
herpes simplex, herpes zoster, hepatitis B (EBV), human papillomavirus
- Parasitic infections
Strongyloides stercoralis, *Leishmania* spp.





Nature Rev Rheumatol 2014;10:612