Improving Immunity

in the Climacteric Years

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I declare no conflict of interest with the content of this presentation

The enormous diversity in human immune system

>10^{13} MHC class I haplotypes (IMGT-HLA)

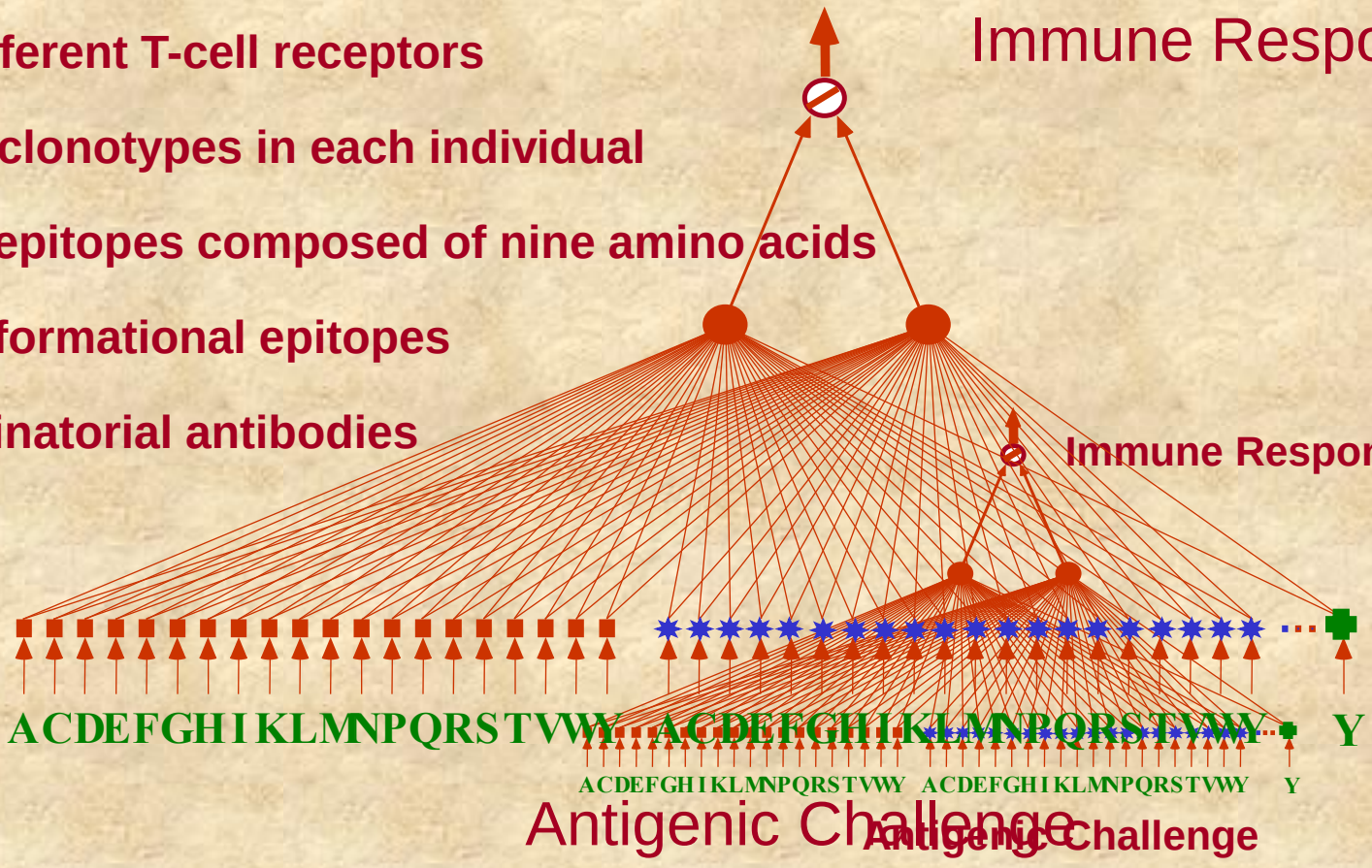
10^{7}-10^{15} different T-cell receptors

10^{12} B-cell clonotypes in each individual

10^{11} linear epitopes composed of nine amino acids

>>10^{11} conformational epitopes

>10^{9} combinatorial antibodies



Lymphocytes and myeloid cells express **ERs and AR**

Oestrogen and testosterone directly modulate the function of cells involved in the immune response

- Modulate lymphoid and myeloid cell differentiation
- Cytokine production
- Helper T-cell polarization
- Nitric oxide production
- MHC class II expression
- APC recruitment and function

Bebo et al. (1999)
***J Immunol* 162: 35**
Komi and Lassila (2000)
***Blood* 95: 2875**

Components of the Immune System

Complex

Gonadal Steroids Influence Immune Response

Simple

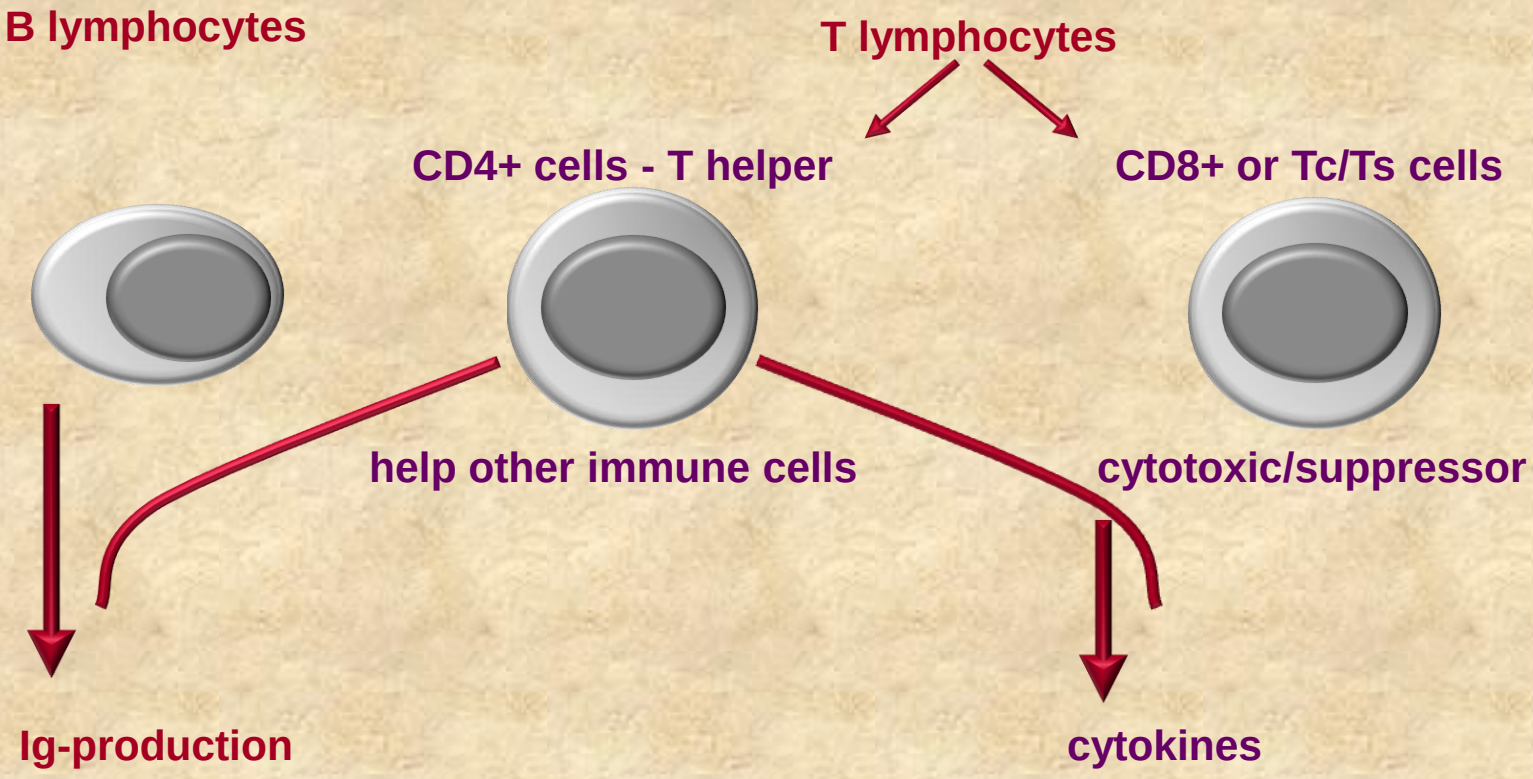
Innate or Natural Immune System

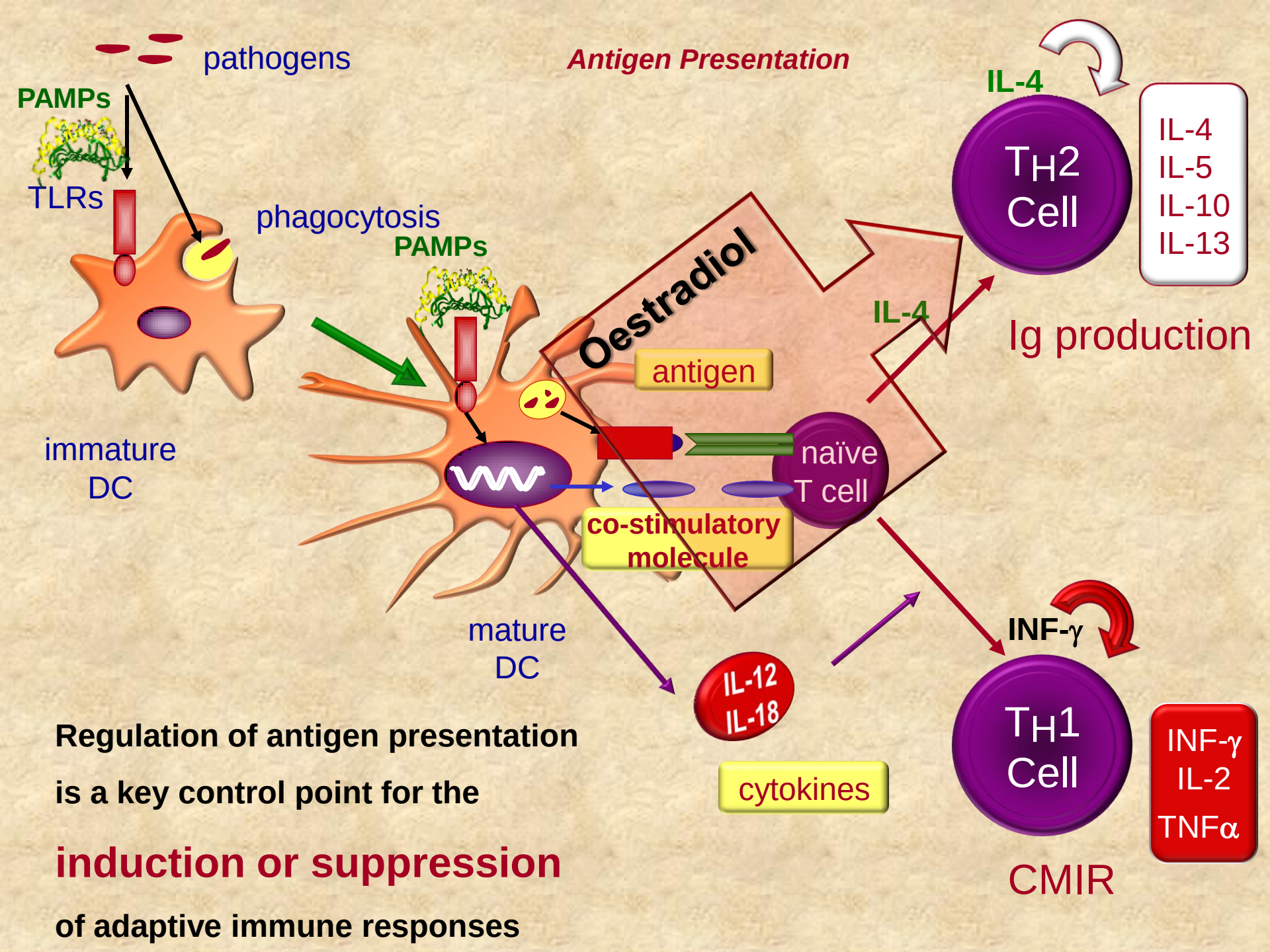
Recognises structures specific for microbes

Effector cells : Monocytes, Macrophages, Granulocytes, Dendritic cells & NK cells

Produces cytokines to enhance non-specific as well as specific immune responses

Acquired or Adaptive Immune System





Regulation of antigen presentation is a key control point for the

induction or suppression

of adaptive immune responses

Oestrogen and Antigen Presentation

- Experimental Auto-immune Encephalomyelitis
- Multiple Sclerosis

Experimental Autoimmune Encephalomyelitis (EAE)

- a mouse model of multiple sclerosis (MS)
- develops by the induction of myelin basic protein (MBP)-specific T cells with a T helper 1 (Th1) cytokine profile that mediate spinal cord injury

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Pretreatment of mice with oestradiol significantly reduced

- ✓ DC numbers in the brain
- ✓ Number of DC-producing TNFα and IFNγ
- ✓ DC's ability to present antigen to MBP-specific T cells

Multiple Sclerosis

More prevalent in women

Symptoms improve during pregnancy

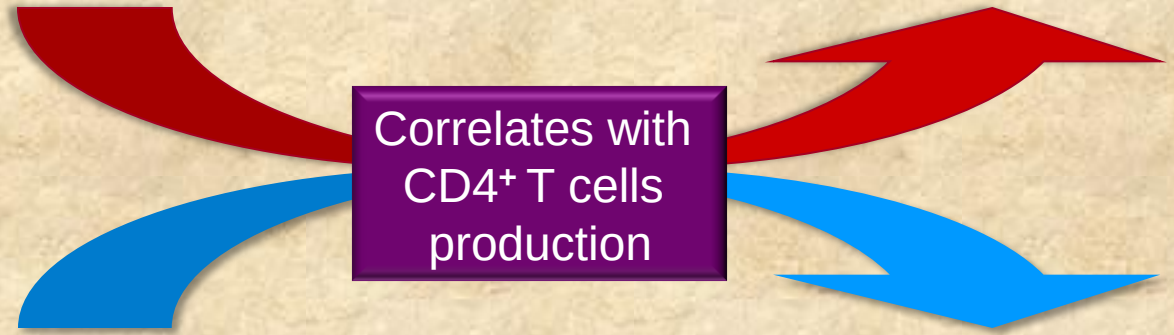
Symptoms may worsen in the post-partum period

CNS antigen-specific CD4+ TH1 cells secrete the pro-inflammatory cytokines IFNγ, TNFα and IL-12

active disease

remission

or pregnancy



pro-inflammatory cytokines TH1

anti-inflammatory cytokines TH2

↑ E_2 levels: Shift to TH2 cytokines

Correale et al. (1998) *J Immunol* 161: 3365
Gilmore et al. (1997) *J Immunol* 158: 446
Gilmore et al. (2004) *J Neurol Sci* 224: 69

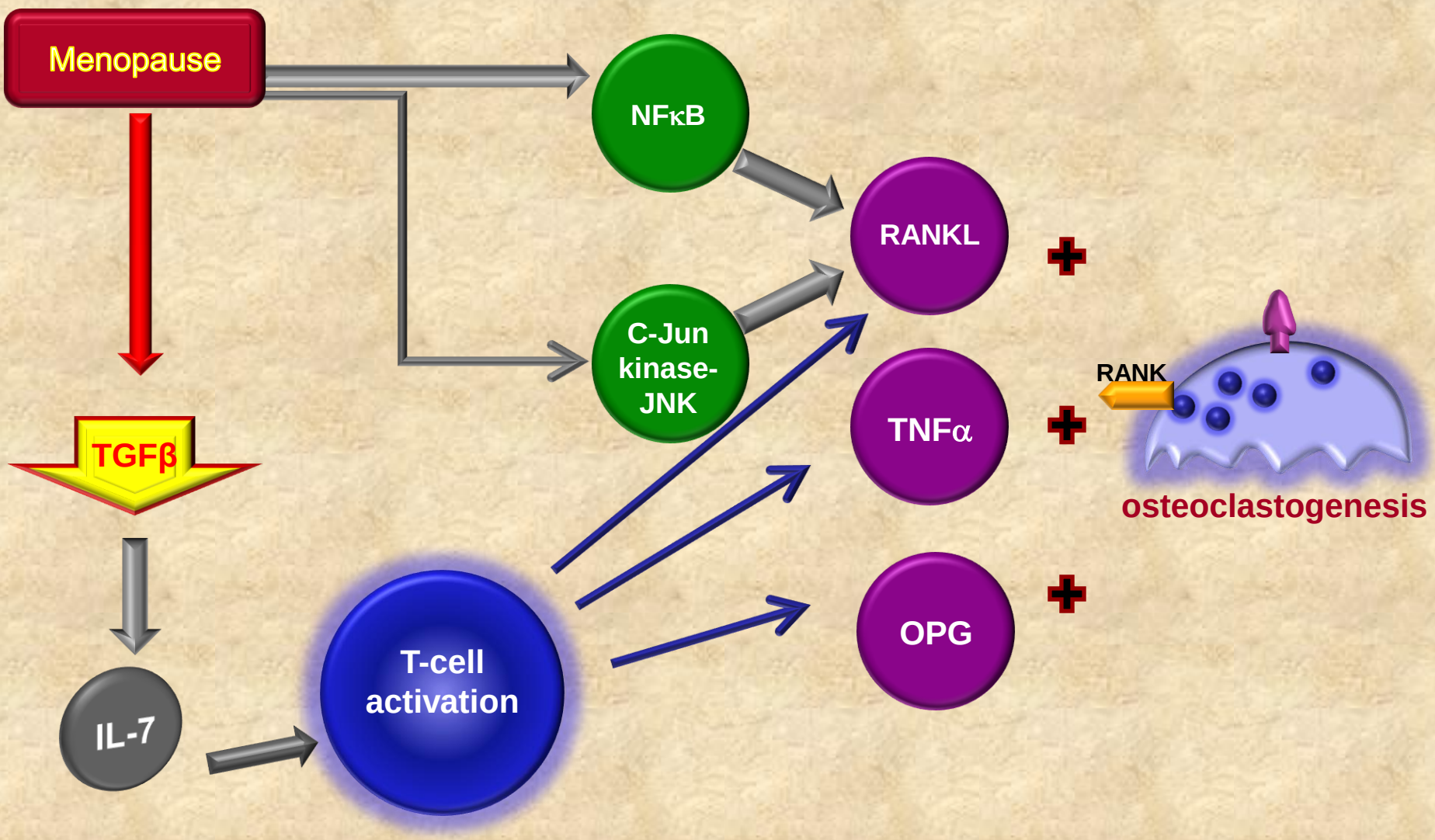
Components of the Immune System

Immune Responses and Degenerative Disorders

- Bone resorption
- Atherosclerosis and plaque instability
- Neuro-inflammatory disorders
- Effect of progestogens and progestins on immunity of the female reproductive tract (FRT)

Oestrogen deficiency augments bone loss

Activated T-cells are key regulators of osteoclast formation



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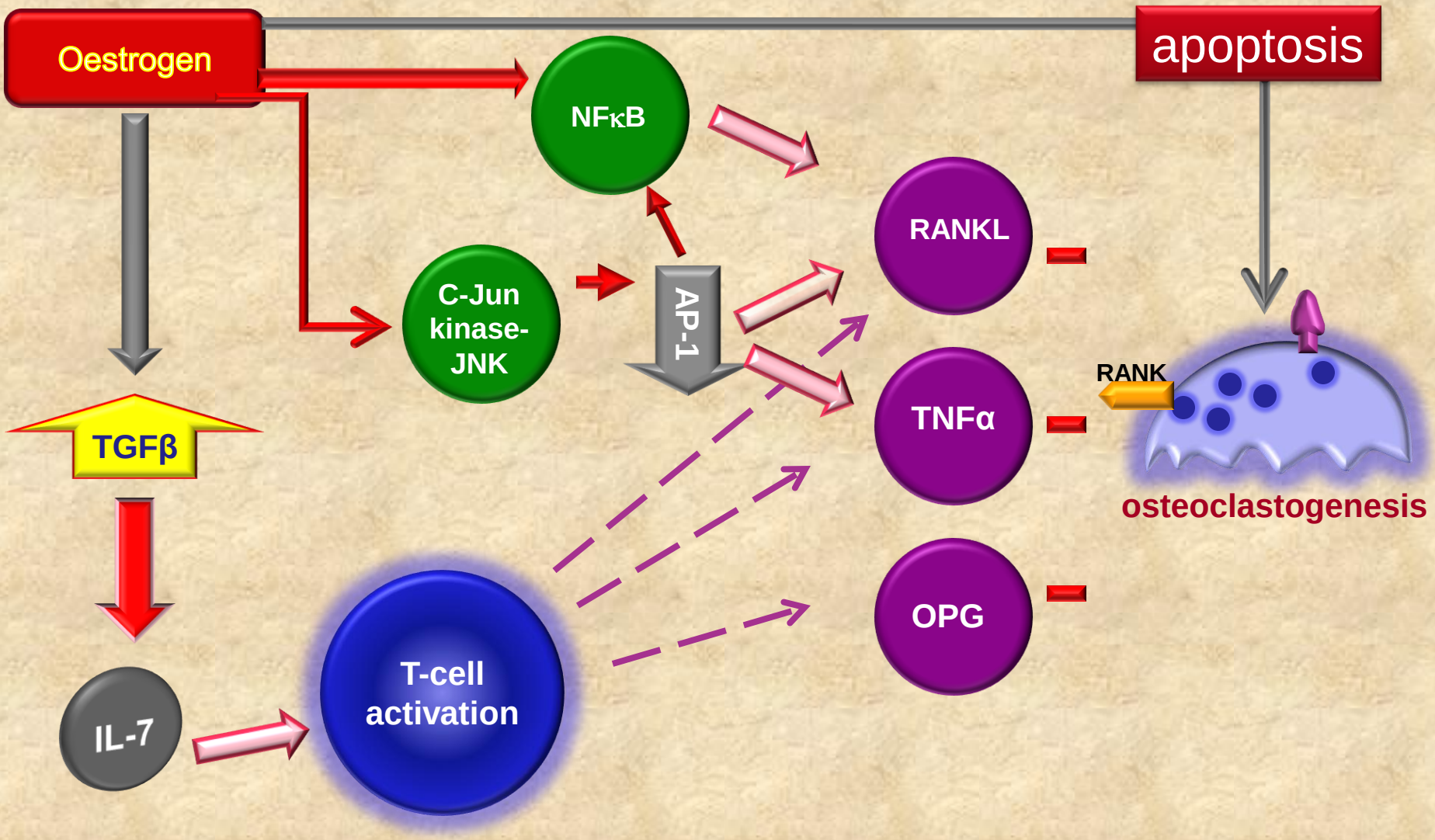


Oestrogen deficiency augments bone loss

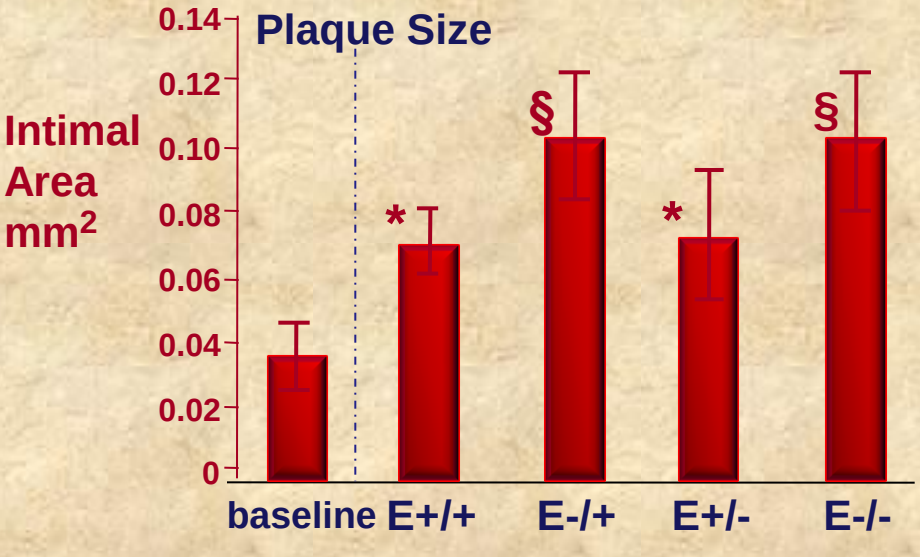
- **Increased osteoclast formation and recruitment to bone surfaces**
- **Increased erosion depth by prolonging the resorption phase of the remodeling cycle through increased osteoclast lifespan**
- **Increased production of inflammatory cytokines: IL-7 and TNFα:**
  - ✓ **limit the activity of mature osteoblasts**
  - ✓ **enhance osteoclast differentiation**

Oestrogen is the best known restorer of pre-menopausal bone homeostatic mechanisms

Immunity and Atherosclerosis

Innominate artery

- **ApoE null mice - atherogenic diet 20 weeks**
- **Baseline Group: sacrified aged 20 weeks**
- **Treatment Groups - Ovariectomy + implanted :**

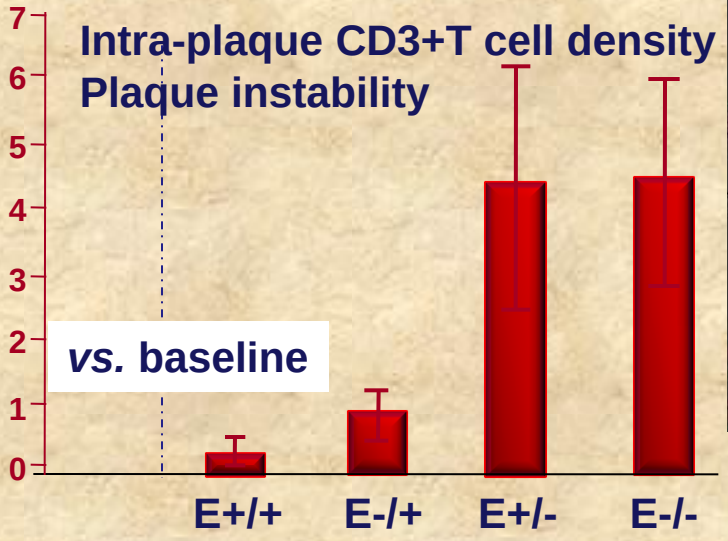


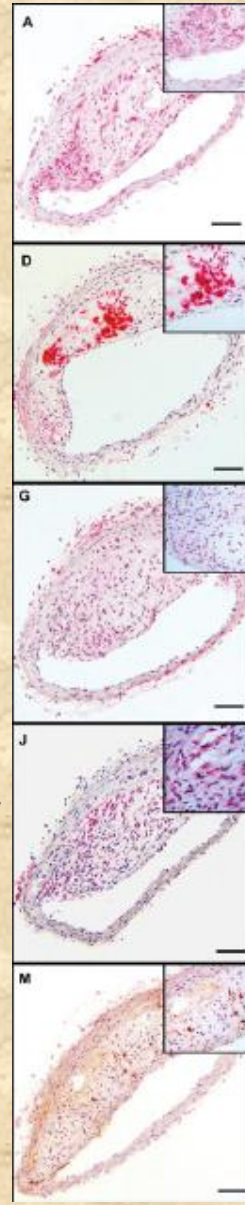
E +/+ = 90d E_2

E -/+ = 45d P + 45d E_2

E +/- = 45d E_2 + 45d P

E -/- = 90d P





Jennifer A. Cann et al. 2009
Atherosclerosis (in press)

Timely administered oestrogen promotes:

- **Pre-menopausal protection against atherosclerosis**
- **Reverses immune-mediated instability of plaques**

Animal Models of Neuro-inflammation

Microglial cells are the inflammatory cells in the brain

E_2 inhibits microglial responses to acute injuries in specific brain regions

Microglia are direct targets of E_2 action in brain

E_2 reduces the expression of inflammatory mediators

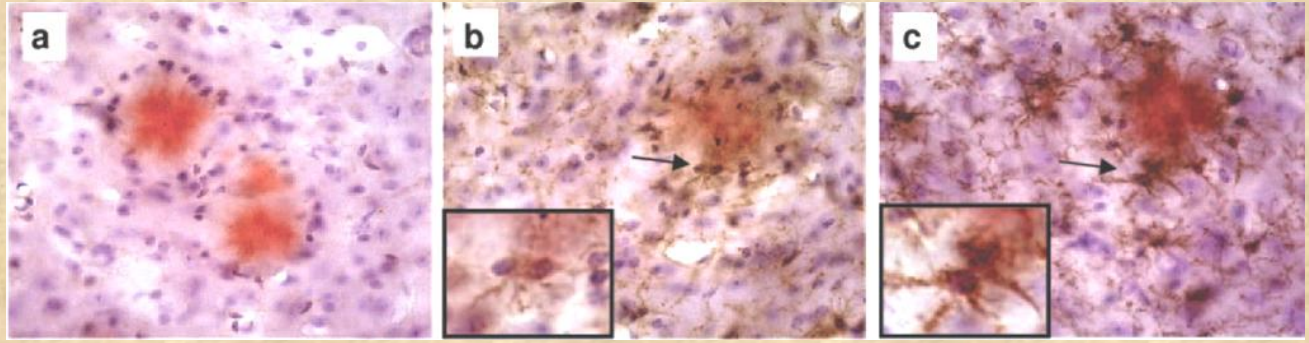
- **monocyte chemo-attractant protein-1**
- **macrophage inflammatory protein-2**
- **lipo-polysaccharide-induced TNFα**

Ovarian ablation in the animal model of Alzheimer's disease (APP23 mice)

- **increases microglial activation at β-amyloid deposits**
- **facilitates the progression of microglia toward a highly reactive state**

Vegeto, et al.(2006)
***Endocrinology* 147: 2263-72**

Neuro-inflammatory changes in AD murine model (APP23 mice)



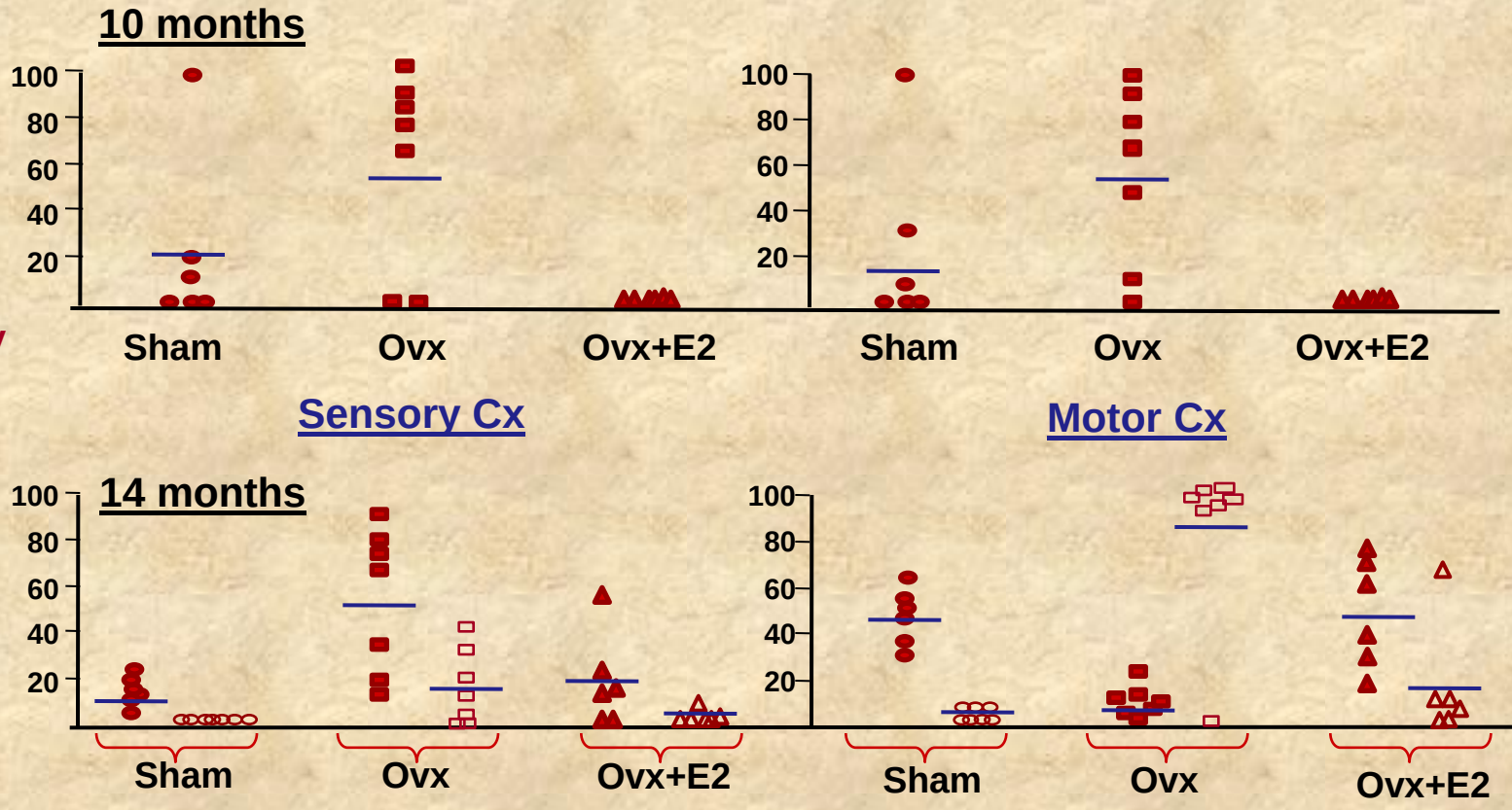
I-plaque
HI-plaque

Non-Inflam. Plaques
Mac- ve microglia cells

Inflam. Plaques
Mac+ve
reactive microglia

Highly Inflam Plaques
Mac+ve highly
reactive microglia

Inflammatory plaques (% *VS* total)



Vegeto, et al.(2006)
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Long-term administration of E_2

prevents the effects of ovariectomy

and

↓ microglial reactivity compared with control animals

Cognitive impairment in postmenopausal women is reduced when oestrogen is replaced in early menopause

Components of the Immune System

Immune Responses and Degenerative Disorders

Genital Tract Immunity and Susceptibility to Infection

Immunity and Lower Genital Tract Infections

as modulated by

Gonadal Steroids and Progestogens

- 333 million new non-HIV STD cases p.a.
- Menopausal women are at high risk of STD
- Progestogens are being liberally administered to promote amenorrhoea

Chlamydia infections

Pretreatment of mice with progesterone or MPA

- ✓**Persistent Chlamydia trachomatis infection**

Pretreatment of rats with progesterone or MPA

- ✓ **Increases susceptibility to C. trachomatis infection**
- ✓ **Oestradiol treatment reduces the susceptibility to infection**
- ✓ **Untreated rats exposed to C. trachomatis at oestrus displayed a self-limiting infection**

Kaushic et al. (2000) *Infec. Immun.* 68:4207–4216

Herpes Simplex Virus-2 (HSV-2) in mice

Progesterone or MPA + **intra-vaginal innoculation of HSV-2** = **mortality rate**; **high titers of viral shedding**

Gallichan and Rosenthal (1998) *J. Infect. Dis.* 177:1155–1161
Milligan and Bernstein (1995) *Virology* 212:481–489
Parr et al. (1994) *Lab. Investig.* 70:369–380

intra-vaginal innoculation of HSV-2

Pro-oestrus	Oestrus	Di-oestrus
Susceptible	No viral replication	High susceptibility

Gallichan and Rosenthal (1996) *Virology* 224:487–497

Progestogens and viral infection in women

Human Papilloma Virus (HPV)

Progesterone but not oestrogen stimulates the expression and oncogenic transformation of HPV, *in vitro*

Matlashewski et al. (1987) *EMBO J* 6: 1741–6

Crook et al. (1988) *Proc Natl Acad Sci USA* 85: 8820–4

Chan et al. (1989) *J Virol* 63: 3261–9

Pater et al. (1990) *Am J Obstet Gynecol* 162:1099-1103

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HPV detection increases in late pregnancy, when progesterone is elevated

Schneider et al. (1987) *Int J Cancer* 40: 198–201

Smith EM et al. (1991) *Cancer Detect Prev* 15: 397–402

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Schneider et al. (1987) *Int J Cancer* 40: 198–201
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Long term use of COC in HPV-infected women increases the risk of cervical cancer

Hildesheim et al. (1990) *Int J Cancer* 45: 860–4

Negrini et al. (1990) *Cancer Res* 50:4670–5

Brinton (1991) *Contraception* 43: 581–95

HPV detection is increased in long-term past users of combination HRT but not oestrogen-only users

Smith et al. (2002) *Eur J Cancer Prev* 11:295-305

WHO Collaborative Study of Neoplasia and Steroid Contraceptives:

Invasive cervical SCC and COC: results from a multinational study

2361 cases and 13,644 controls

Adjustment for all known confounders

31% increase in invasive cervical SCC in COC users

Berry et al. (1993) *Int J Cancer* 55:228-36

WHO Collaborative Study of Neoplasia and Steroid Contraceptives 1979-1988

Adjusted RR of cervical adeno-carcinoma & adenosquamous carcinoma

Progestin dose	Oestrogen dose: High RR	High 95% CI	Low RR	Low 95%CI
Low	0.82	0.24-2.86 (3, 27)§	1.38	0.96-2.00 (57, 317) §
High	1.26	0.89-1.79 (56, 328) §	2.61	1.27-5.36 (12, 37) §

187 cases and 1,447 controls

§ Numbers of cases and controls shown in parentheses

Thomas et al. (1996)
Am J Epidemiol 144:281-289

Explanation !

Munger et al. (1989) *J Virol* 63: 4417–21

Progestogens and Retroviral Diseases

Progesterone enhances Simian Immunodeficiency Virus (SIV) transmission in macaque monkeys allowing more virions to move through the thinned vaginal epithelium

Marx, et al. (1996) *Nat Med* 2:1084–9

Oestrogen protects against vaginal transmission of SIV

Smith, SM et al. (2000) *JID* 182:708-15

Could this be the reason why postmenopausal women have a **4-8 fold** increase in the chance of being infected with HIV compared to pre-menopausal women ?

Aaby et al. (1996)

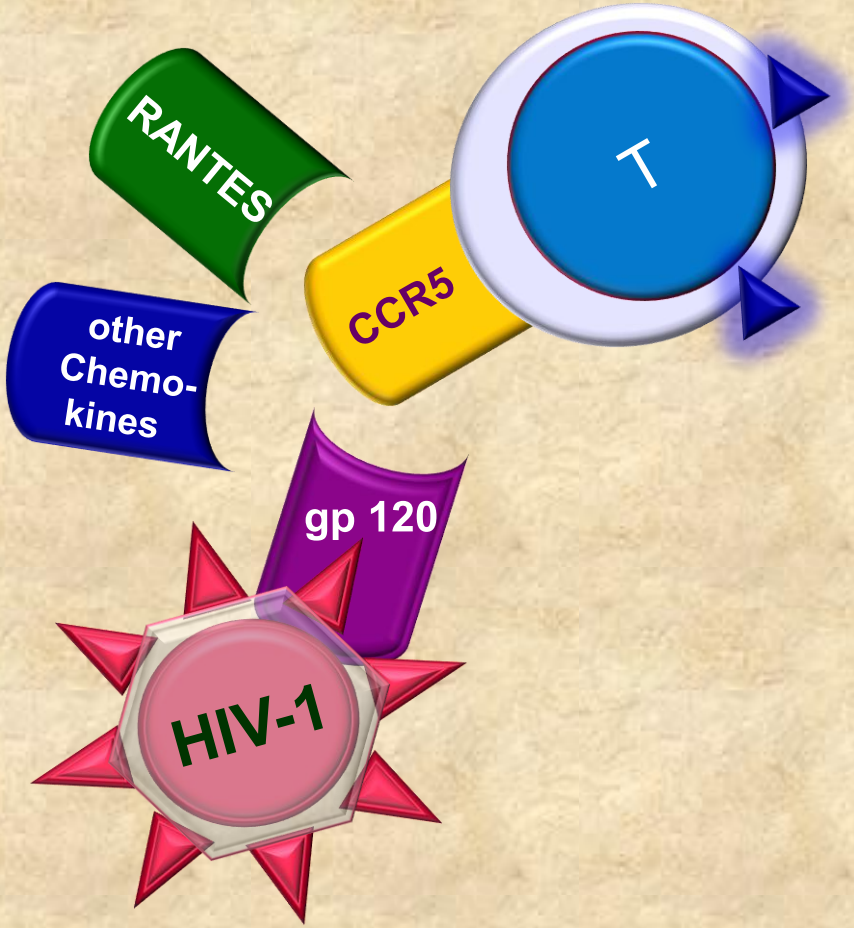
AIDS 10: 1585–1590**.**

Contraceptive method and HIV-1 seroconversion

	HR	95%CI	p
None/tubal ligation	1.0		
IUD	1.2	0.4–3.9	0.7
DMPA	**2.0**	1.3–3.1	0.003
Oral contraceptives	1.3	0.8–2.2	0.3
Low-dose	1.3	0.7–2.4	0.4
30–35 μg EE + 150 μg of LNG or desogestrel or 250 μg of norgestimate			
High-dose	**2.6**	0.8–8.5	0.1
50 μg of EE + 250 μg of LNG or 500 μg of norgestrel			

Martin et al. (1998) *J. Infect. Dis.* 178:1053–9

Individuals who are homozygous for a **non-functional** CCR5 allele (32-bp coding region deletion) are **resistant** to HIV-1 infection



Liu et al. (1996) *Cell* 86:367

Samson et al. (1996) *Nature* 382:722

Dean et al. (1996) *Science* 273:1856

- Level of expression of chemokine receptors used by the virus for cell entry – subversion of immune cells

Conclusions

Oestrogen Deficiency inflicts changes in the immune system that promote cellular and molecular mechanisms involved in

- **Osteoporosis**
- **Atherosclerosis plaque formation and instability**
- **Inflammatory and Microglial function within the CNS**

Timely administration of oestrogen reverses these processes

Hormonal milieu during the natural cycle modulates immune responses within the FRT

- **To maximise protection against infection**
- **To promote opportunities of successful conception**

Conclusions

Progestogens are not natural hormones and may use PRs, GRs and/or other pathways to exert membrane or genomic actions

Continuous administration of Progestogens :

- ✓ **Abnormal lipids handling**
- ✓ **Increased risk of breast cancer**
- ✓ **Increased susceptibility to viral infection of the FRT**

Sequential combined oestrogen-progestogen preparations offer lesser antagonism to the protective effects of oestrogen