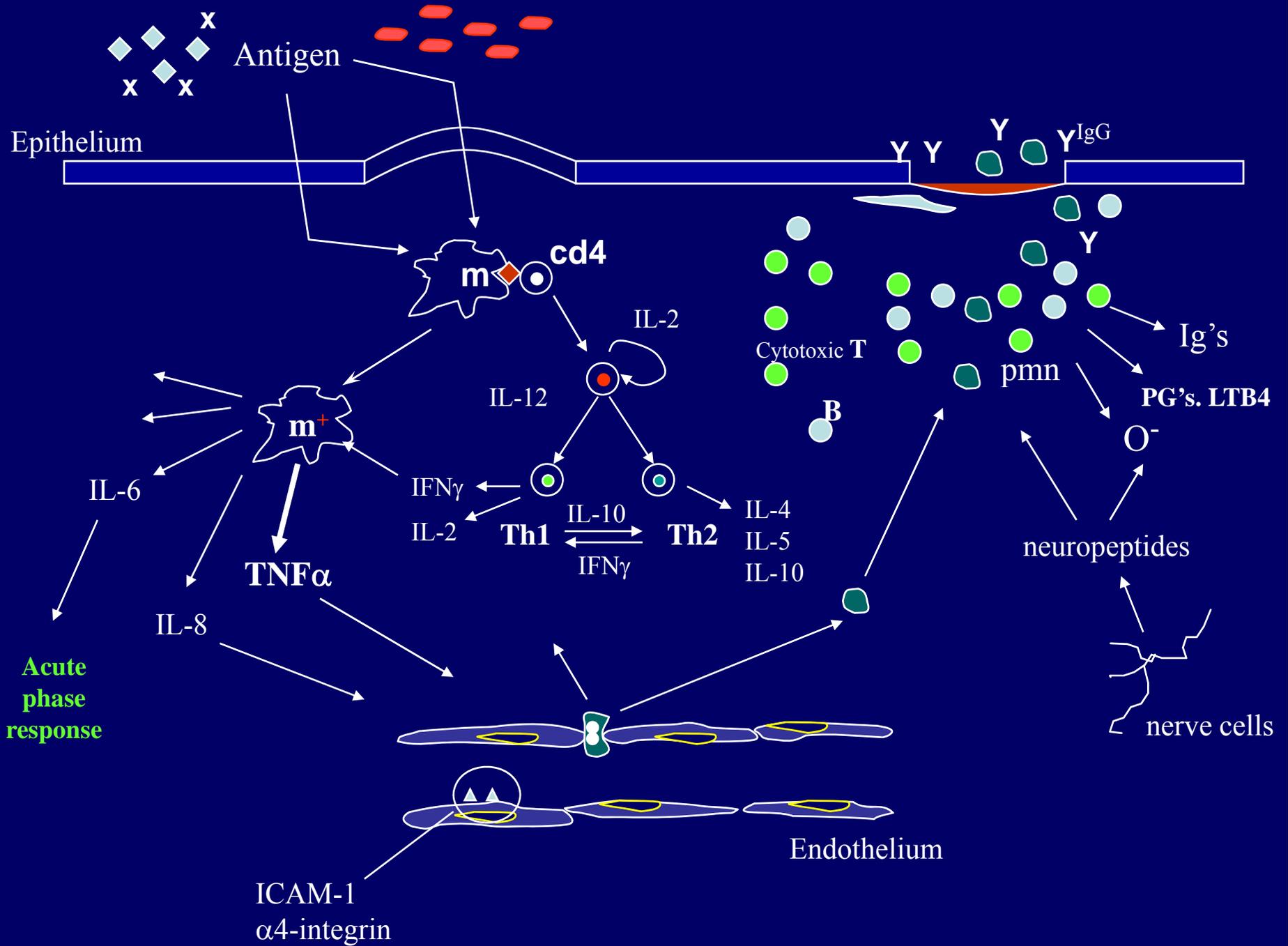


New Drugs for Uveitis

Miles Stanford

Medical Eye Unit

St Thomas' Hospital



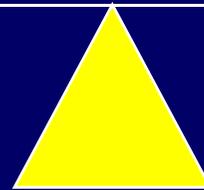
The cytokine balance

Pro-
inflammatory
cytokines

IFN γ , TNF α

Anti-
inflammatory
cytokines

IL-10, IL-4



Cytokines as drugs - Biochemotherapy

- Currently on the market or in Phase 3 trial
 - Anti TNF agents (infliximab, etanercept, etc)
 - Recombinant IL-10
 - Anti- IL 1 receptor antagonist (Anakinra)
 - recombinant IL 2
 - recombinant IL 12
 - combinations of the above

Biochemotherapy - caveats

- Very few randomised studies
- Most concentrate on salvaging eyes that have not responded to conventional immunosuppression
- Few studies concentrate specifically on CMO
- Effects are often short term and antibodies to treatment usually occur

Anti-TNF agents - Infliximab

- Monoclonal against TNF α
- Best studied for various forms of uveitic CMO
- Rapid onset of action but tends to fail long term
- Proven efficacy in Behcet's disease
- Extremely useful in JIA
- Usually used where other agents have failed

Infliximab in refractory uveitis

- 23 patients, all refractory to steroids and 1 immunosuppressant
- 18/23 clinical success at 10 weeks
- 11/23 showed FFA and OCT improvement of CMO
- 7/14 still successful at 1 year
- High rate off adverse effects (15/20 showed ANA)

Arch Ophthalmol 2005 123;903

Infliximab – adverse reactions

- Anaphylaxis during infusion
- Drug induced lupus
- Tuberculosis
- Congestive heart failure
- Worsening of MS

Etanercept

- Soluble TNF receptor
- Generally not as effective in uveitis as infliximab/ adalimumab
- Not recommended for uveitis associated with JIA.
- Little information in its possible role in CMO

Anakinra

- Recombinant non-glycosylated homologue of human IL-1 receptor antagonist
- Competitively inhibits binding of IL-1 α and IL-1 β to the IL-1 receptor type 1
- Used in refractory rheumatoid and polychondritis unresponsive to anti-TNF α
- Single case report in recalcitrant uveitis associated with CINCA syndrome
- Uveitis and disc swelling improved with lack of relapse of ocular disease but no details on use for CMO

Br J Ophthalmol 2007 91:263

Daclizumab

- Binds IL-2 receptor on activated T cells
- Case series have suggested that it may have a role in the treatment of refractory uveitis (intermediate, Behcet's and birdshot). No serious adverse events
- 1 RCT of systemic immunosuppression and daclizumab versus placebo showed no benefit in patients with Behcet's disease
- Main outcomes have been reduction in immunosuppression whilst maintaining VA
- No trials or reports have mentioned effect on CMO

Ophthalmology 2005 112;764

Rituximab

- Targets B cell antigen, CD 20
- Selective and prolonged B-cell depletion
- Single case report in patient with chronic AU and CMO, unresponsive to systemic steroids and immunosuppression (steroids, ciclosporin methotrexate, cellcept), had a 12 month remission after a single course of rituximab infusions

Ophthalmic Res 2007 39;184-6

Interferon alpha

- Cytokine belonging to type 1 interferons
- Has a number of antiviral, antiproliferative, antiangiogenic and immunomodulatory effects
- Actual mode of action on CMO not known but not all anti-inflammatory as it works in quiet eyes
- Relatively well tolerated although patients experience flu like symptoms, depression, alopecia and may develop autoantibodies (thyroiditis)

Interferon alpha-2a in Behcet's disease

- 50 patients with non-responsive ocular BD
- Relapse when $<30\text{mg}$ prednisolone
- 93% response rate
- Full remission by week 24
- 40% off treatment and disease free

Interferon alpha-2a in intermediate uveitis

- Chronic CMO (all >24 months) refractory to treatment (steroids, cellcept, methotrexate) had 6 month course of interferon alpha 2a
- 11/15 eyes had resolution of CMO
- Effect apparent within 3 days
- Recurrence requiring retreatment was common but not universal

Retina 2006 26;786-91

Interferon beta 1a in MS associated uveitis

- 13 patients, all with intermediate uveitis
- All needed >10mg prednisolone to control their disease
- 13 eyes had CMO before start of therapy
- Treated with Interferon β 1a for 24 months
- CMO resolved completely in 9 eyes
- At end of study 9 patients off steroids and the rest minimal dose
- Minimal adverse reactions

Br J Ophthalmol 2005 89;1254

VEGF Blockade

- Increased VEGF in aqueous of patients with uveitis and CMO compared to those without CMO
- 13 patients with controlled uveitis but persistent CMO (nb 9/11 no response to periocular/intravitreal steroid)
- 2.5 mg bevacizumab x1
- Cumulative probability of improved VA at 14 weeks of 1 line (81%) and 2 lines (49%)
- Effect limited as lasts only 6-8 weeks

Ophthalmology 2007 114;1574

Drugs in Ophthalmology

CAMPATH-1 H

- Anti-T cell moab are effective in EAU
- Campath-1 is a humanised moab against CD52
- 10 patients refractory to all treatment
- All showed initial improvement
- Minimal toxicity
- Remission in 8 (follow-up 8mo-6yrs)

Intravenous immunoglobulin

- 10 patients (idiopathic, birdshot, Behcet's, sarcoidosis)
- All refractory to steroids and immunosuppression
- IVIG given 3 infusions daily per month
- 5/10 patients showed sustained recovery
- Did not report effects on CMO specifically

Am J Ophthalmol 1999 127;545

Intravenous immunoglobulin – birdshot chorioretinopathy

- 18 patients
- 17/23 eyes showed FFA improvement in CMO
- 9/23 eyes showed improvement of VA

Ocul Immunol Inflamm 2000 8;49

Future therapies

- New anti TNF agents (?amazimab, gorblimeycept)
- Refinement of interferon alpha
- Biological combination therapy
- Tailoring according to cytokine gene profile
- Long acting intravitreal agents
- Enhancement of immunosuppression using homologous anti CD-25 (patient's own T regs)
- ? Tolerance