TOPICAL ATORVASTATIN FOR DRY EYE AND BLEPHARITIS ADDITIONAL INFORMATION

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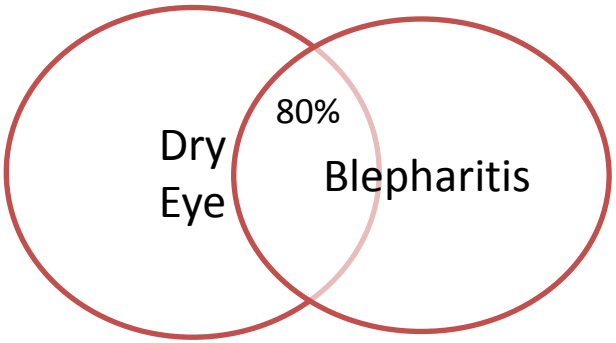
No financial or proprietary interest in any material discussed

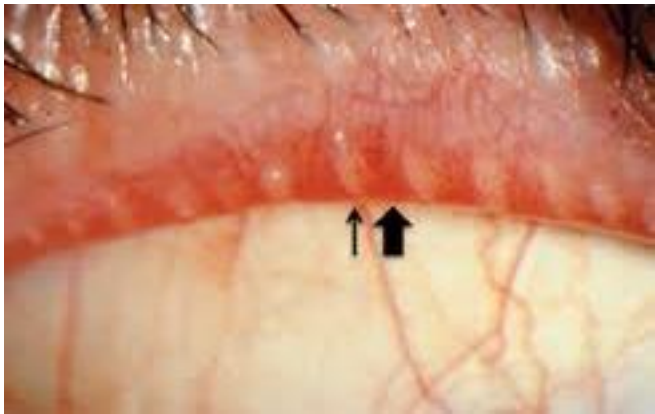
URGENT NEED FOR DRY EYE PRODUCTS

- Increasing dry eye prevalence
  - Aging population
  - Lifestyle changes
  - Improved diagnosis
  - Increased physician and patient awareness
- New markets
- Novel mechanisms
- Current dearth of treatment options
  - Still room for pipeline therapies

BLEPHARITIS

- Inflammation of the lid margin
- Common - up to 15% of the population
- Troublesome - discomfort & blurred vision
- Caused by Meibomian gland disease





TRENDS IN OPHTHALMOLOGY

- Repurposing of existing medication
  - Shorten drug approval pathway
  - Existing safety data
  - Reduced costs of drug development
- Examples
  - Cyclosporin
  - Mucocosta
  - BCG for multiple sclerosis

Colligris et al, Expert Opin Pharmacother 2014, 15:1371-1390

GLOBAL OPHTHALMIC PIPELINE

Indication	PC	Phase I	Phase II	Phase III	Pending approval	Total
DRY EYE	7	4	25	6	2	44
ARMD	41	22	40	4	1	109
GLAUCOMA	24	10	28	6	4	74

MedTrack, July 2011

WHAT IS IN THE PIPELINE?

- Anti-inflammatories
  - Steroids
  - Non-steroidals
  - Other
- Antibiotics
- Tear substitutes
- Secretagogues

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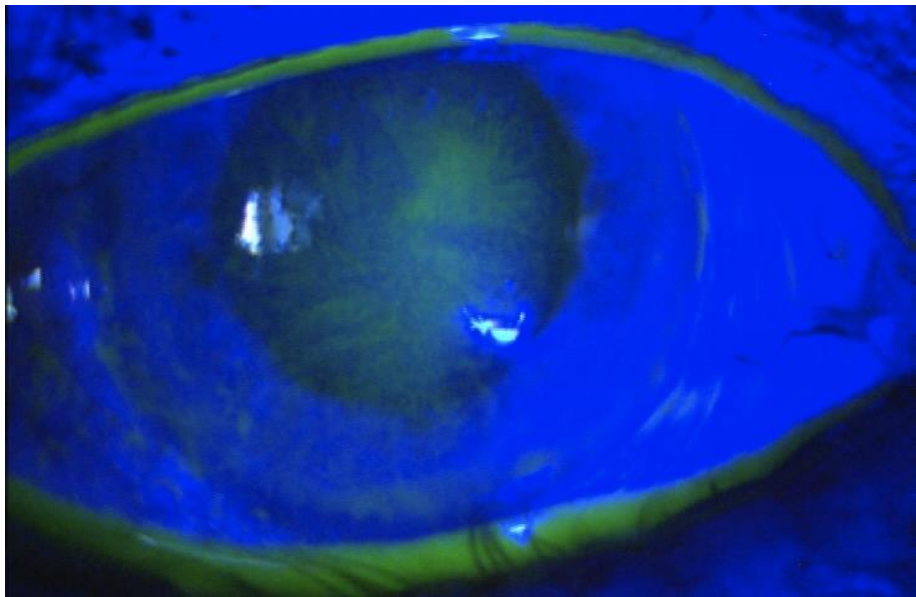
PILOT STUDY

- Included
  - 10 volunteers
  - 10 patients with dry eye and blepharitis
- Topical atorvastatin
  - 8 times a day for one month
- Visits
  - Baseline, week 1, week 4
- Primary outcome
  - Corneal erosions



BACTERIAL LOAD AND BLEPHARITIS

- Cholesterol provides nutrition for lid margin bacteria
- Excess bacterial load promotes blepharitis
- Reduction in lid margin bacteria can increase ocular comfort
- Bacteria produce several lipolytic enzymes
- These enzymes change the lipid-based meibum
  - Increased fatty acids which are irritating and toxic to the ocular surface
  - Increased thickening of meibum destabilizing the tear film lipid layer
  - Thickened and inflammatory meibum atrophies the meibomian glands
- Demodex blepharitis
  - Demodex mites carry bacteria that increase matrix metalloproteinases

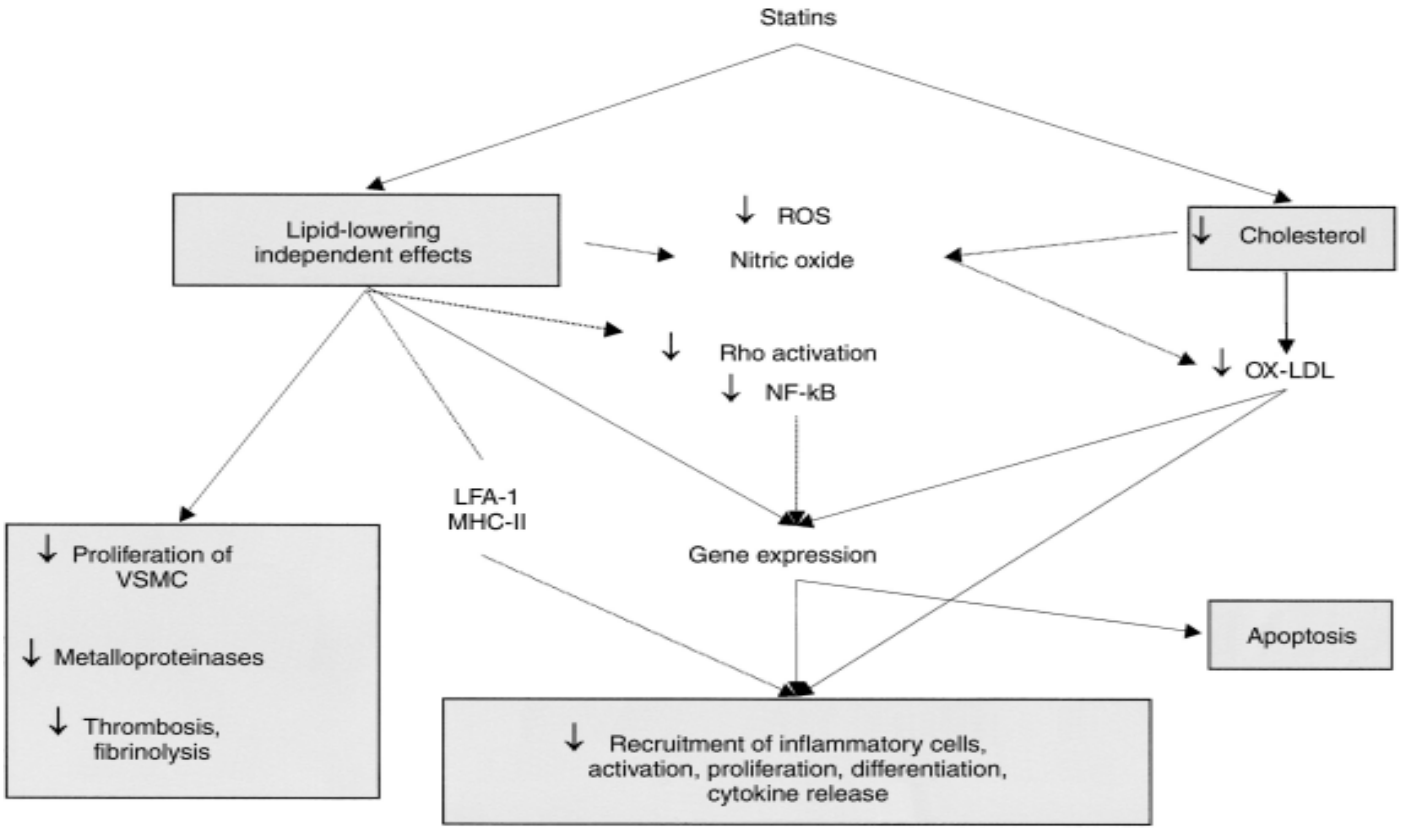
- Statins can be anti-bacterial by lowering cholesterol and reducing matrix metalloproteinases

TEAR FILM STABILITY AND CHOLESTEROL

- Excess cholesterol reduces TFBUT
  - Increases evaporative dry eye
  - Increases ocular surface inflammation
- Cholesterol deposits on CL ➡ discomfort
  - Increased water content and oxygen permeability lenses have higher lipid degradation
  - Thicker lipid layer would improve CL comfort

STATIN MECHANISMS

- Inhibit HMG-CoA reductase biosynthesis of triglycerides + cholesterol
- Commonly prescribed to reduce serum cholesterol and prevent coronary artery disease and stroke



Anti-inflammatory and immunomodulatory effects of statins. Blanco-Colio LM, Tuñón J, Martín-Ventura JL, Egido J. Kidney Int. 2003 Jan;63(1):12-23. Review.

STATIN MECHANISMS

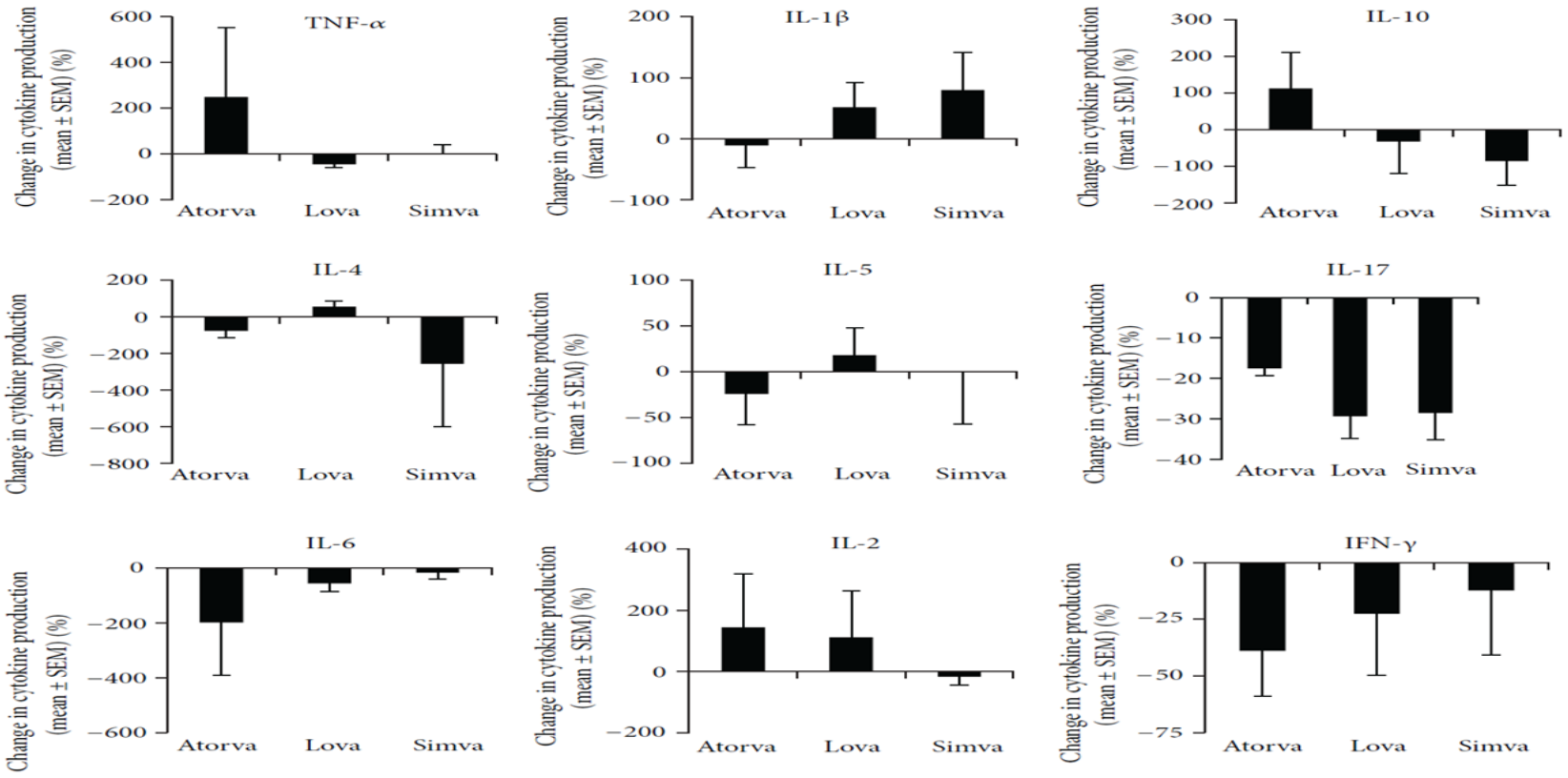


FIGURE 3: Graphs showing percentage changes in cytokine production by cells cultured with PMA/ionomycin ± statins. These studies show a multitude of varied responses indicating that the different statins have slightly different profiles of action.

Statin Modulation of Human T-Cell Proliferation, IL-1β and IL-17 Production, and IFN-γ T Cell Expression: Synergy with Conventional Immunosuppressive Agents.
Jameel A, **Ooi KG**, Jeffs NR, Galatowicz G, Lightman SL, Calder VL. Int J Inflam. 2013;2013:434586. Epub 2013 Sep 18.

STATIN MECHANISMS

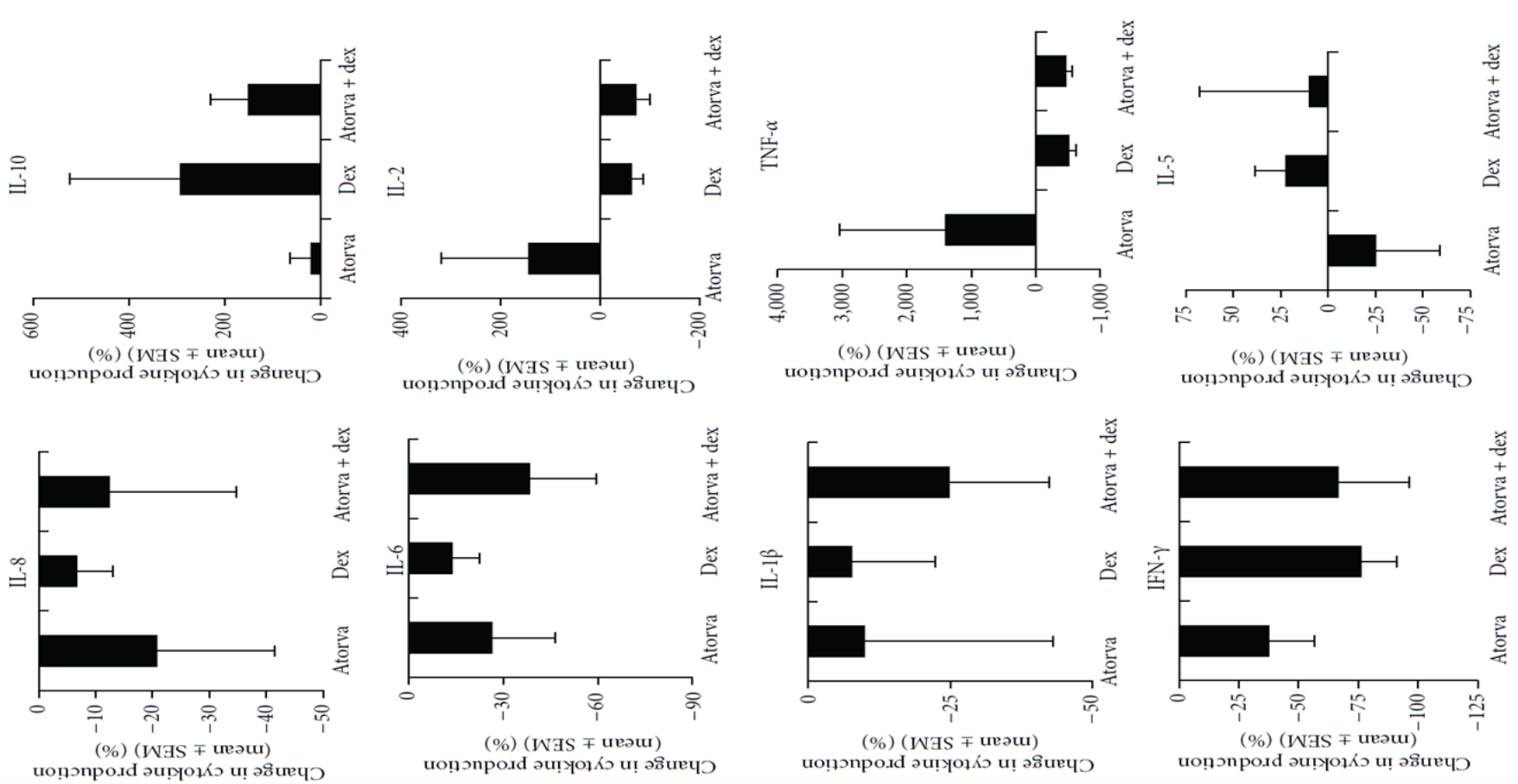


FIGURE 4: Graphs showing percentage changes in cytokine production in cells stimulated with PMA/ionomycin ± atorvastatin/dexamethasone.

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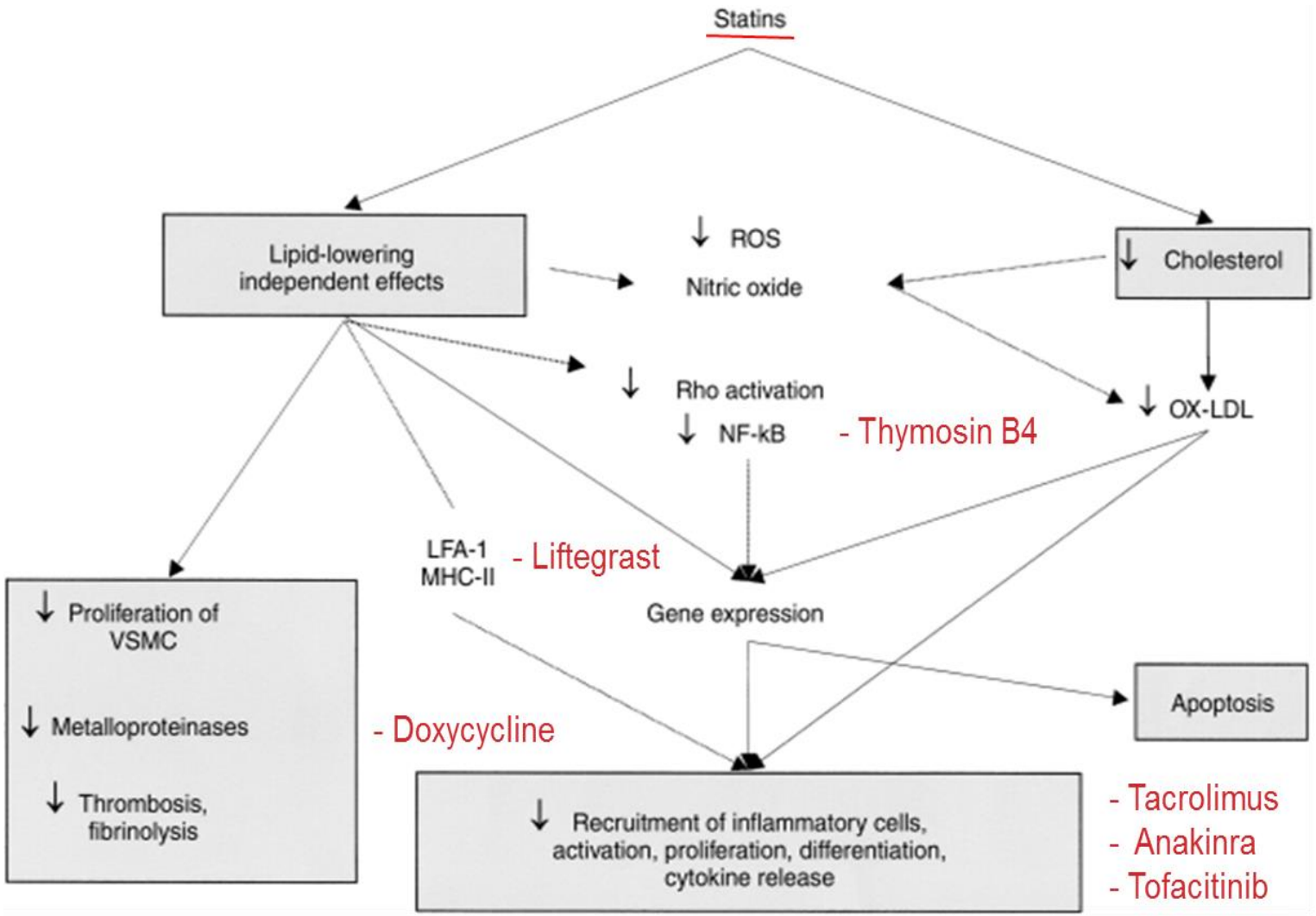
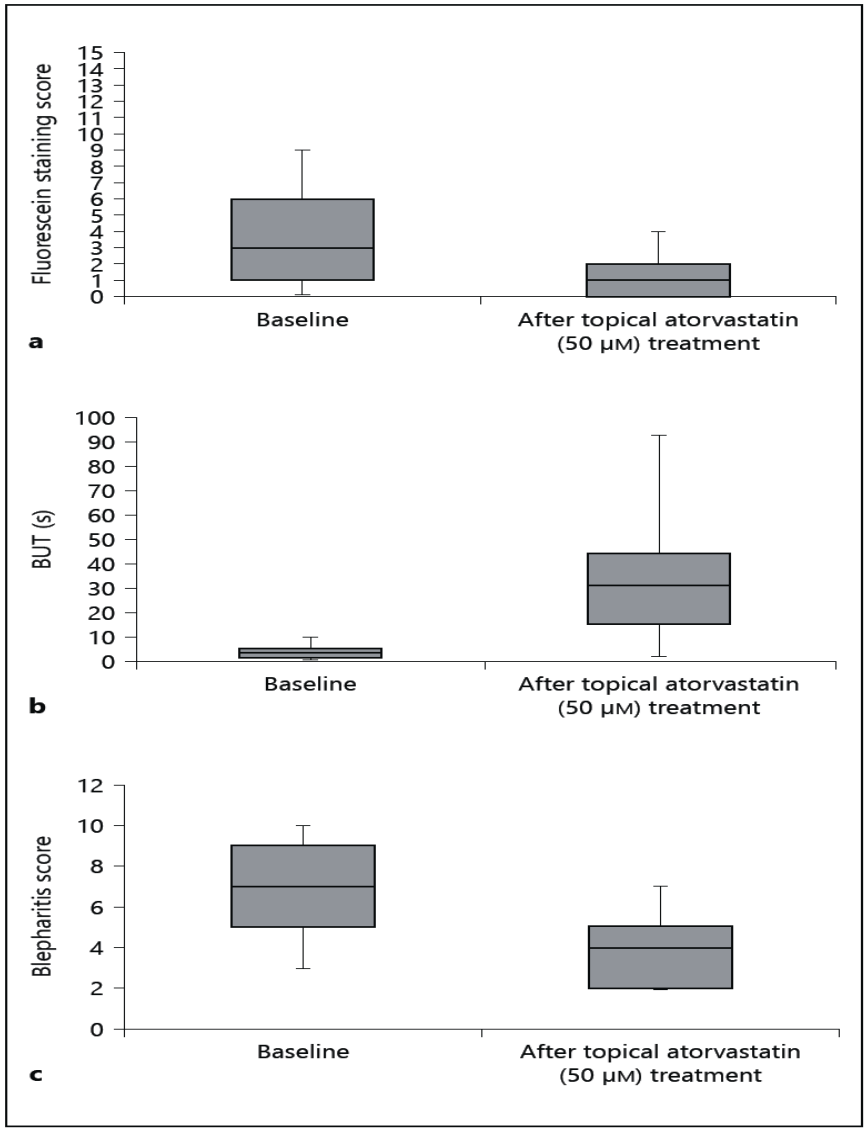
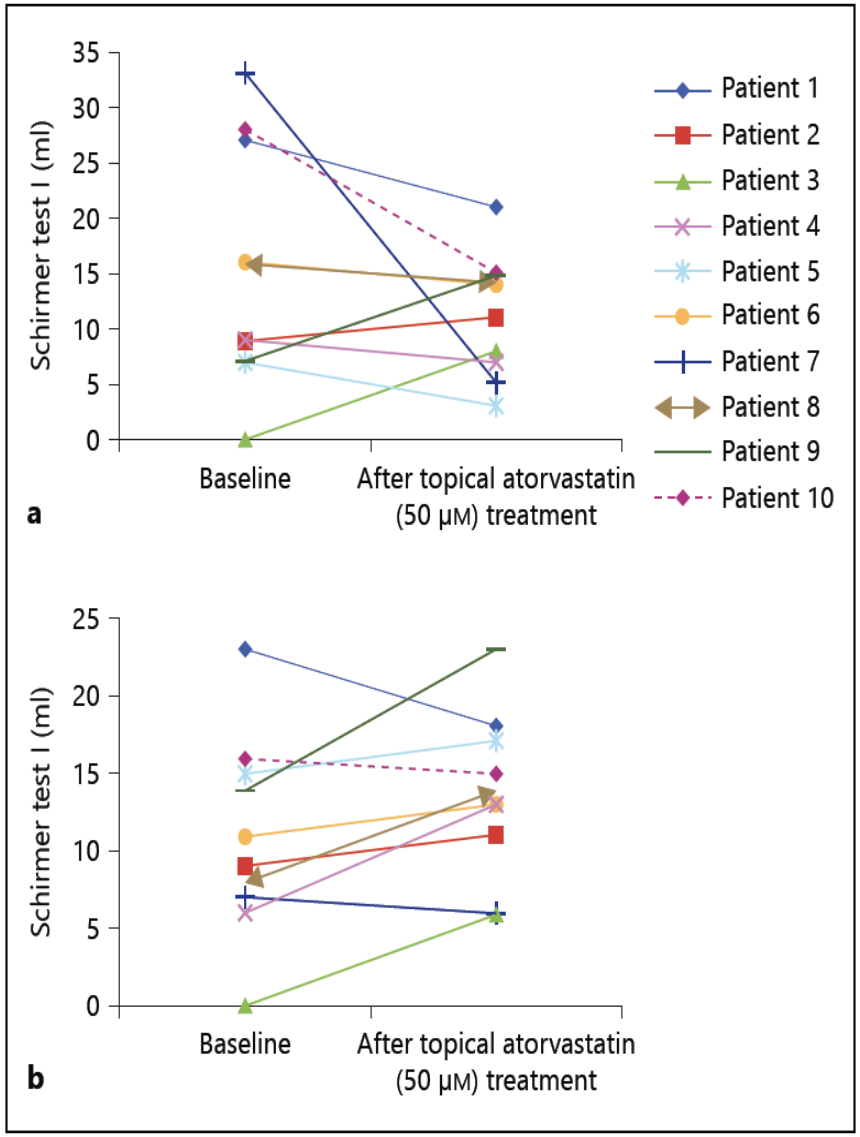
STATINS versus STATIN COMPETITIORS



PILOT STUDY: DRY EYE RESULTS





IN VITRO STUDIES: NON-TOXIC TO HUMAN CELLS

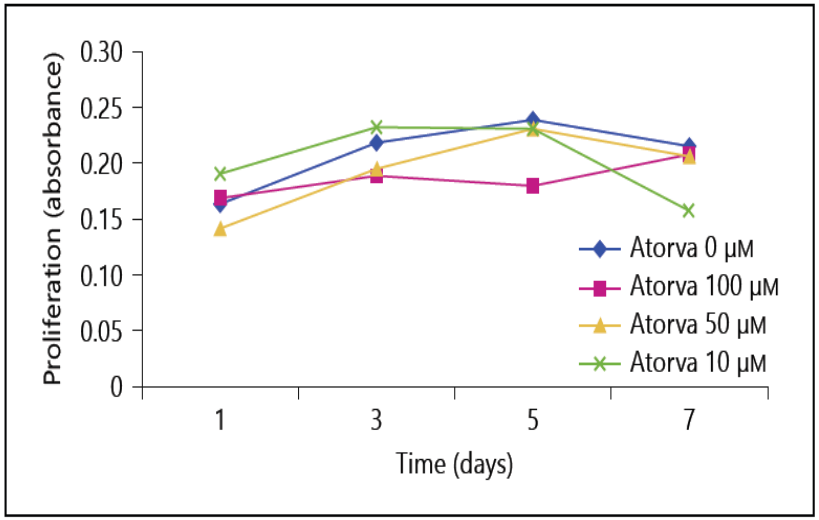


Fig. 1. Line graph showing the effects of various topical atorvastatin (atorva) concentrations on corneal epithelial cell proliferation over 7 days using a tetrazolium 3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide assay (ATCC).

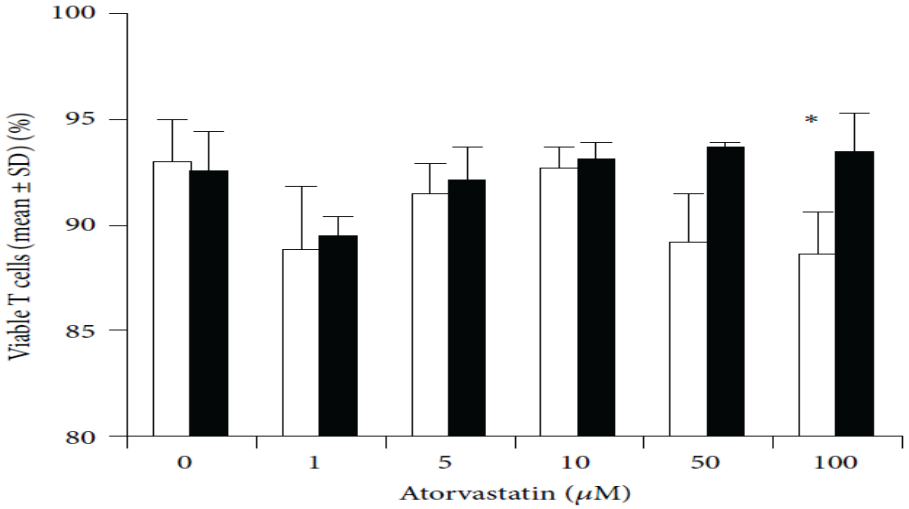


FIGURE 1: Cell viability was assessed at all concentrations of statins. The percentage viability is compared in the presence (filled bars) or absence of mevalonate (clear bars). * denotes a statistical difference between viability of cells in different concentrations of statins ($P < 0.05$), and Ø indicates a difference in viability with and without mevalonate ($P < 0.05$).

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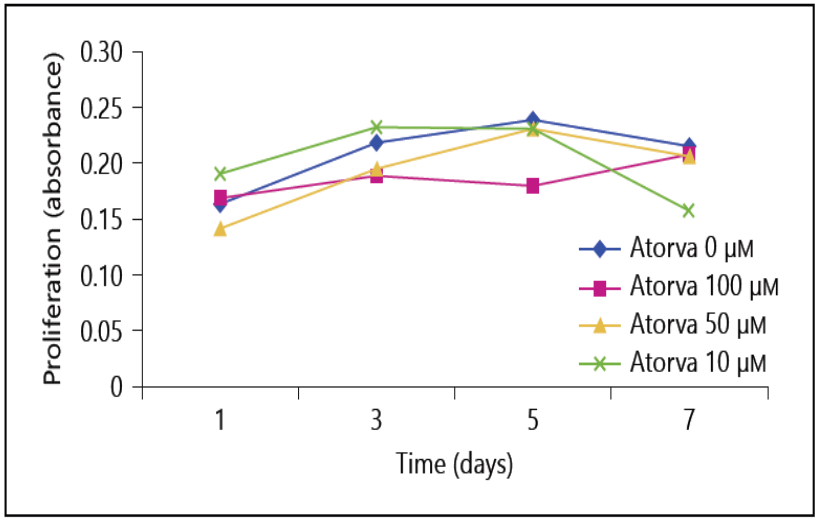

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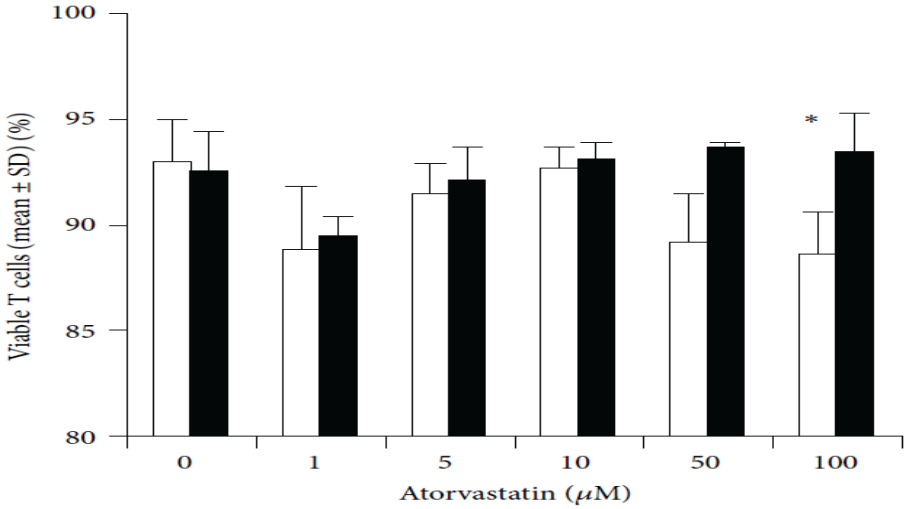

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TOPICAL versus ORAL Statin Concentrations

- Pleiotropic effects: 1-50 umol L
- Mean serum concentrations: 1-15 nmol L
- Blood protein binding high: 95-99%
- Free fraction only active: 0.01-0.5 nmol L
- Cmax 2-6x higher but present only for minutes
- Simvastatin MIC for pneumococci: 36umol L
- True Simvastatin *in vivo* >1000 fold lower

What I a relevant statin concentration I cell experiments claiming pleiotropic effects? Linda Björkhem-Bergman, Jonatan D. Lindh & Peter Bergman. British Journal of Clinical Pharmacology 72:1; 164-165 2011