

Molecular mechanisms in atopic eczema - why do they matter in the clinic?

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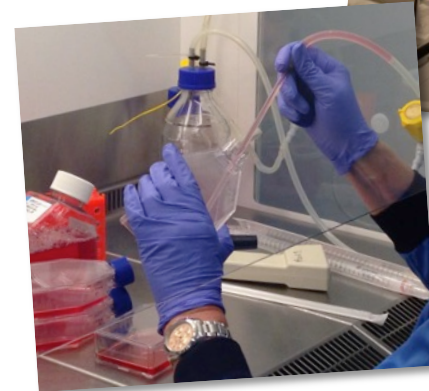


'Professor of Molecular & Genetic Dermatology'

Consultant
Dermatologist



Laboratory
researcher



Outline

- Atopic eczema (& differential diagnoses)
- Molecular mechanisms
- Increasing understanding → opportunities for better care
- Future possibilities?
- Questions / discussion 😊

Atopic eczema (atopic dermatitis)

- Itchy inflammatory skin disease
- Chronic, relapsing-remitting
- Common
- Significant impairment in quality of life

Some important differential diagnoses

Examine carefully

& think 'outside the box'

- Other types of eczema?
- Psoriasis?
- Fungal infection?
- Immunodeficiency syndromes?
- Langerhans cell histiocytosis??
- Cutaneous lymphoma???

Other types of eczema

Allergic
contact
dermatitis

Irritant
dermatitis

A diagnosis not to miss!

Monomorphic

Punched out lesions



Eczema herpeticum

A diagnosis not to miss!

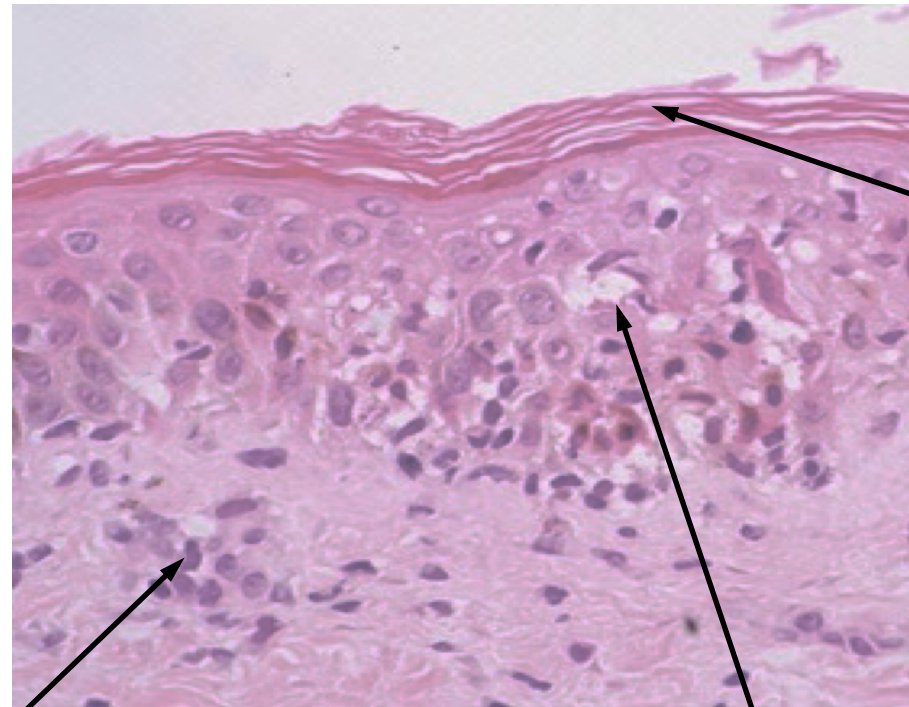
Scabies

What is (atopic) eczema?

- 'An itchy inflammatory skin condition'
- Often starts in childhood – also affects adults
- Heterogeneous
- Associated with other atopic conditions
- **Relapsing & remitting**

What is (atopic) eczema?

- 'An itchy inflammatory skin condition'
- 'Spongiotic dermatitis'

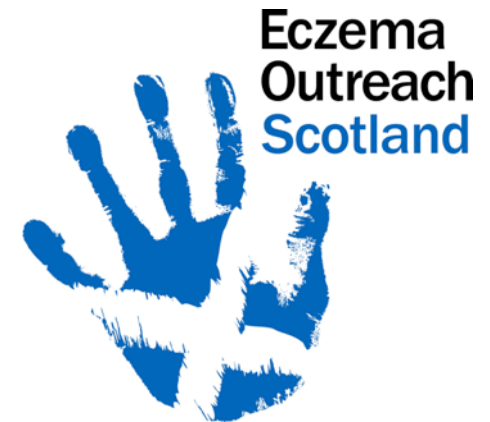


Hyperkeratosis

Inflammatory cell
infiltrate

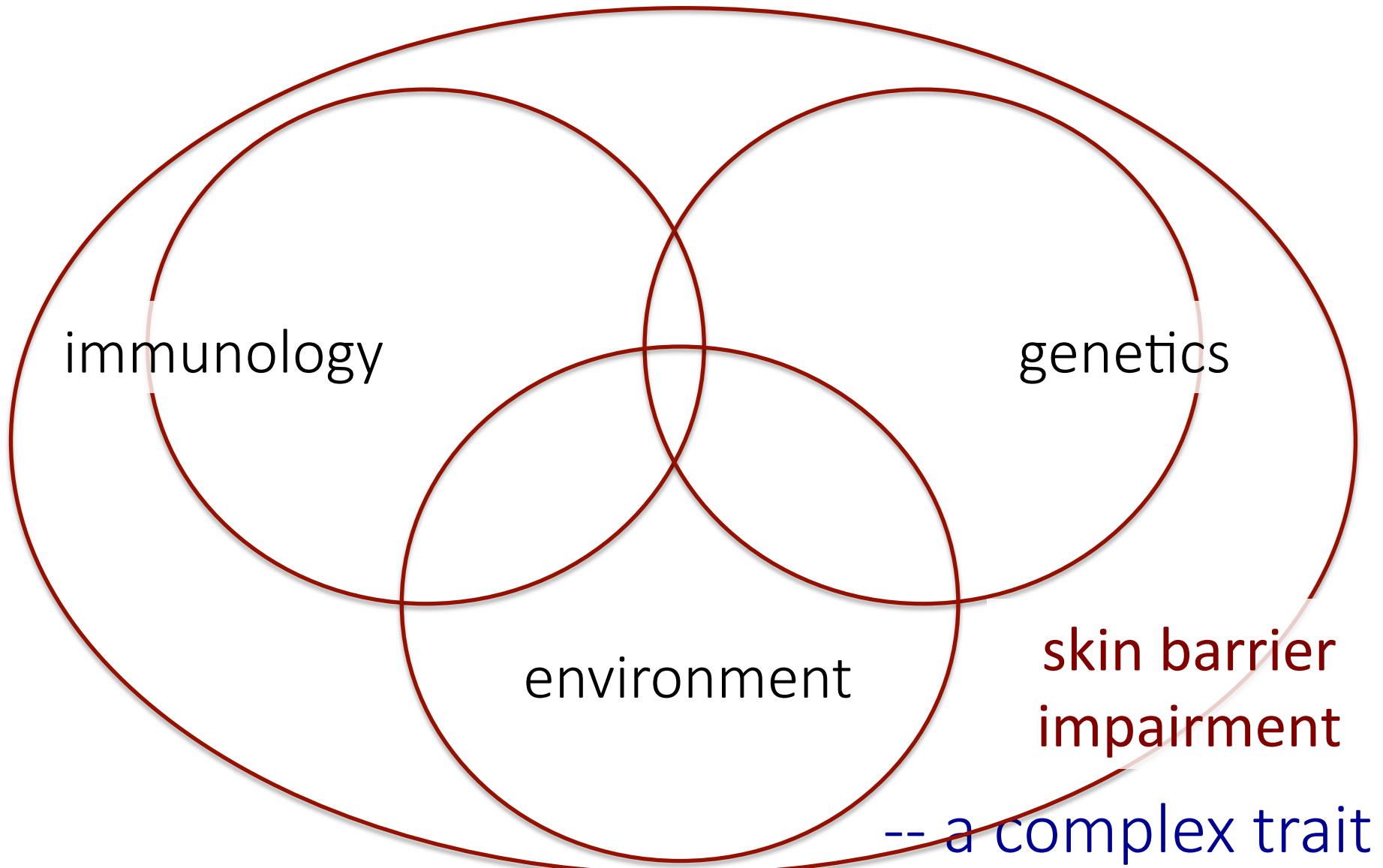
Spongiosis = intercellular
oedema

Incomplete understanding of eczema
→ limited treatment options



Understand genetic mechanisms
→ design better treatments ?

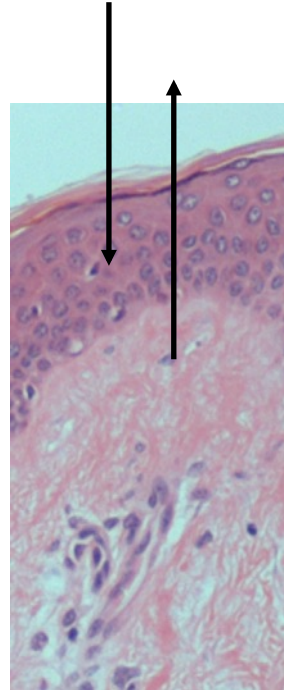
What causes atopic eczema?



What & where is the 'skin barrier'?

Barrier against:

- Water loss
- Allergen & irritant entry
- Microbial infection
- UV radiation
- Mechanical damage



Complex

Multifactorial

Passive & active

- Str corneum
- Str granulosum
- Whole epidermis
- Dermis

Genetics has focused interest
on the skin barrier in eczema

Loss of function mutations in *FLG* cause dry skin:
ichthyosis vulgaris

Genetics has focused interest on the skin barrier in eczema

Loss of function mutations in *FLG* increase risk of **atopic eczema**

Palmer *et al Nat Genet* 2006 | Rodriguez *et al. J Allergy Clin Immunol* 2009 | Brown *et al. J Allergy Clin Immunol* 2011

Odds ratio from meta-analysis ~3.1

Monogenic disease → complex trait

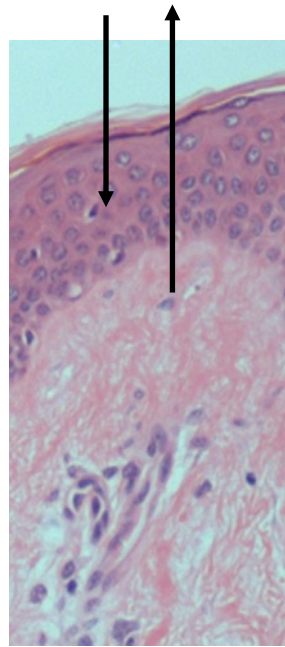
Predisposes to disease & **modifies course** of disease

How does filaggrin do this??

Genetics has focused interest on the skin barrier in eczema

The multiple functions of filaggrin

- Water loss
- Allergen & irritant entry
- Microbial infection
- UV radiation
- Mechanical damage



- *Hygroscopic amino acids*
- *Stratum corneum; interaction with innate immunity*
- *Staph aureus binding*
- *? no evidence yet in vivo*
- *redundancy in filament aggregation; corneocyte fragility*

Loss of function mutations in *FLG* contribute to the atopic march

atopic eczema



allergic rhinitis



atopic asthma



peanut allergy



Odds
ratio:

~3.1

~2.8

~1.5

~3.8

- Skin barrier in atopic disease
- Signs of ichthyosis vulgaris predict poor prognosis

Not all skin barrier defects are associated with atopic disease

--- Atopic manifestations ---

--- Not atopic ---

SPINK5 mutation

DSP
mutation

Epidermolysis bullosa

Contact
dermatitis

Ichthyosis vulgaris &
atopic eczema

Psoriasis

DSG1
mutation

Eczema
craquelé

Not all skin barrier defects
are associated with atopic disease

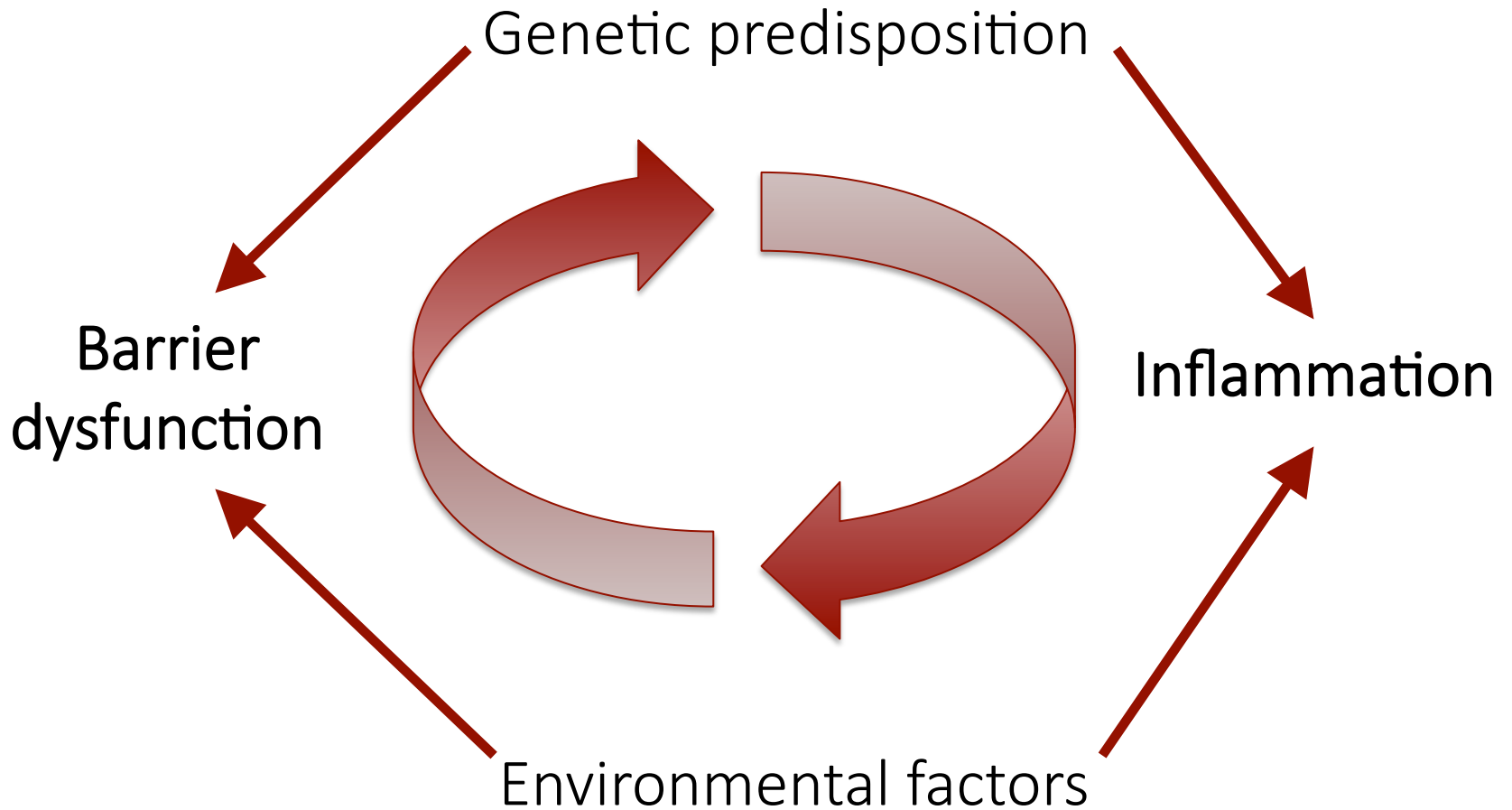
Something special about the
filaggrin-barrier defect
→ **atopic** inflammation

Modern understanding of eczema

It's not just about *FLG* mutations

- Filaggrin is down-regulated by atopic inflammation
- Other genes affect barrier function
- Eczema itself reduces barrier function
- **Barrier dysfunction is a shared mechanism** in the diverse phenotype of 'eczema'

Modern understanding of eczema



How can we use *FLG* in the clinic?

The filaggrin story ...

- Explain to patients
- Mentioned in our national guidelines
- Barrier enhancement may be able to prevent eczema? ... and other atopic diseases?

Barrier enhancement for eczema prevention?

Atopic dermatitis and skin disease

J Allergy Clin Immunol 2014

Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention

Eric L. Simpson, MD, MCR,^a Joanne R. Chalmers, PhD,^b Jon M. Hanifin, MD,^a Kim S. Thomas, PhD,^b
Michael J. Cork, PhD, FRCP,^c W. H. Irwin McLean, FRSE, FMedSci,^d Sara J. Brown, MRCP, MD,^d Zunqiu Chen, MS,^e
Yiyi Chen, PhD,^f and Hywel C. Williams, DSc, FMedSci^b *Portland, Ore, and Nottingham, Sheffield, and Dundee, United Kingdom*

RCT: 124 high-risk neonates

Daily emollient starting from 3 weeks or younger

Feasibility

Eczema at 6 months: relative risk reduction of 50% (95% CI 0.28-0.9)



Barrier enhancement for eczema prevention?

RCT: 118 high-risk neonates

Daily emollient starting from birth

Eczema at 32 weeks:

32% fewer neonates developed eczema (p=0.012)

Allergic sensitisation (IgEs): no effect

Application of moisturizer to neonates prevents development of atopic dermatitis

Kenta Horimukai, MD,^{a*} Kumiko Morita, MD,^{a*} Masami Narita, MD, PhD,^a Mai Kondo, MD,^a Hiroshi Kitazawa, MD, PhD,^a Makoto Nozaki, MD,^b Yukiko Shigematsu, MD,^b Kazue Yoshida, MD, PhD,^b Hironori Niizeki, MD, PhD,^b Ken-ichiro Motomura, MD,^c Haruhiko Sago, MD, PhD,^c Tetsuya Takimoto, MD, PhD,^d Eisuke Inoue, PhD,^d Norio Kamemura, PhD,^e Hiroshi Kido, MD, PhD,^e Junzo Hisatsune, PhD,^f Motoyuki Sugai, DDS, PhD,^f Hiroyuki Murota, MD, PhD,^g Ichiro Katayama, MD, PhD,^g Takashi Sasaki, PhD,^h Masayuki Amagai, MD, PhD,^h Hideaki Morita, MD, PhD,ⁱ Akio Matsuda, PhD,ⁱ Kenji Matsumoto, MD, PhD,ⁱ Hirohisa Saito, MD, PhD,ⁱ and Yukihiro Ohya, MD, PhD^a

Tokyo, Tokushima, Hiroshima, and Osaka, Japan

Barrier enhancement for eczema prevention?

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Definitive
'BEEP study'
has started
recruitment

Application of moisturizer to neonates prevents development of atopic dermatitis

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Eczema treatment in the future?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis

Lisa A. Beck, M.D., Diamant Thaçi, M.D., Jennifer D. Hamilton, Ph.D., Neil M. Graham, M.D., Thomas Bieber, M.D., Ph.D., M.D.R.A., Ross Rocklin, M.D., Jeffrey E. Ming, M.D., Ph.D., Haobo Ren, Ph.D., Richard Kao, Dr.P.H., Eric Simpson, M.D., Marius Ardeleanu, M.D., Steven P. Weinstein, M.D., Ph.D., Gianluca Pirozzi, M.D., Ph.D., Emma Guttman-Yassky, M.D., Ph.D., Mayte Suárez-Fariñas, Ph.D., Melissa D. Hager, M.A., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., and Allen R. Radin, M.D.

Phase II trial - 2014

12-week monotherapy:

‘85% of patients in the dupilumab group, as compared with 35% of those in the placebo group, had a 50% reduction in the EASI score (P<0.001)’

Articles

The Lancet



Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial

Diamant Thaçi, Eric L Simpson, Lisa A Beck, Thomas Bieber, Andrew Blauvelt, Kim Papp, Weily Soong, Margitta Worm, Jacek C Szepletowski, Howard Sofen, Makoto Kawashima, Richard Wu, Steven P Weinstein, Neil M H Graham, Gianluca Pirozzi, Ariel Teper, E Rand Sutherland, Vera Mastey, Neil Stahl, George D Yancopoulos, Marius Ardeleanu

Phase IIb trial – 2016

Dose-ranging study:

‘Clinical response in a dose-dependent manner’
‘Emphasises IL-4 and IL-13 as key drivers’

Eczema treatment in the future?



The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis

Eric L. Simpson, M.D., Thomas Bieber, M.D., Ph.D., Emma Guttman-Yassky, M.D., Ph.D., Lisa A. Beck, M.D., Andrew Blauvelt, M.D., Michael J. Cork, M.B., Ph.D., Jonathan I. Silverberg, M.D., Ph.D., M.P.H., Mette Deleuran, M.D., D.M.Sc., Yoko Kataoka, M.D., Jean-Philippe Lacour, M.D., Külli Kingo, M.D., Ph.D., Margitta Worm, M.D., Yves Poulin, M.D., Andreas Wollenberg, M.D., Yuhwen Soo, Ph.D., Neil M.H. Graham, M.B., B.S., M.D., M.P.H., Gianluca Pirozzi, M.D., Ph.D., Bolanle Akinlade, M.D., Heribert Staudinger, M.D., Ph.D., Vera Mastey, M.S., Laurent Eckert, Ph.D., Abhijit Gadkari, Ph.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., and Marius Ardeleanu, M.D., for the SOLO 1 and SOLO 2 Investigators*

N Engl J Med 2016; 375:2335-2348 | [December 15, 2016](#) | DOI: 10.1056/NEJMoa1610020

Phase III trials – Dec 2016

RCT dupilumab vs placebo

Adults $n \approx 700 \times 2$

16-week monotherapy

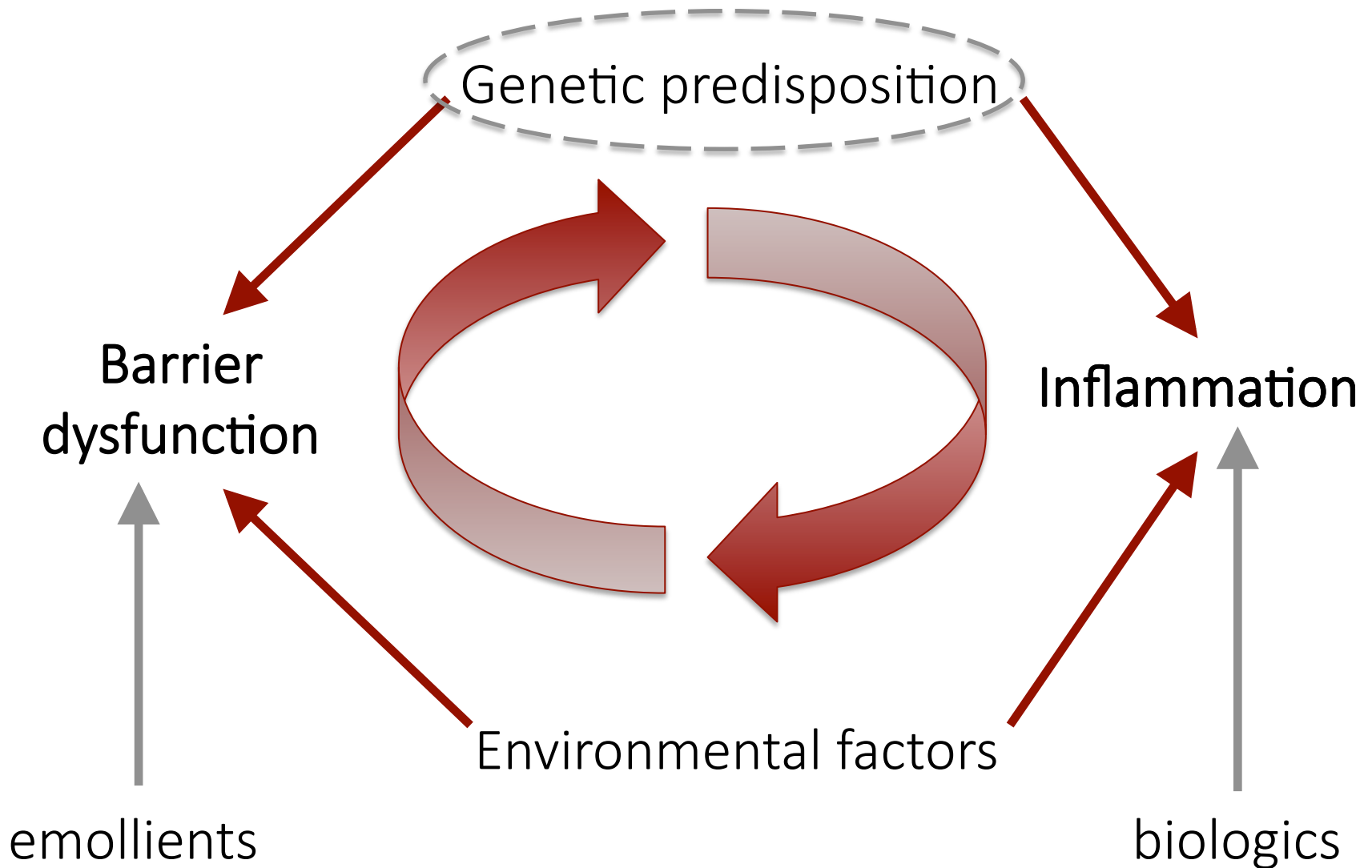
37 and 38% of patients in the dupilumab group

(compared with 10% of placebo group)

clear/almost clear on IGA (P<0.001)'

Next: Paediatric trials on-going
Need longer-term safety data

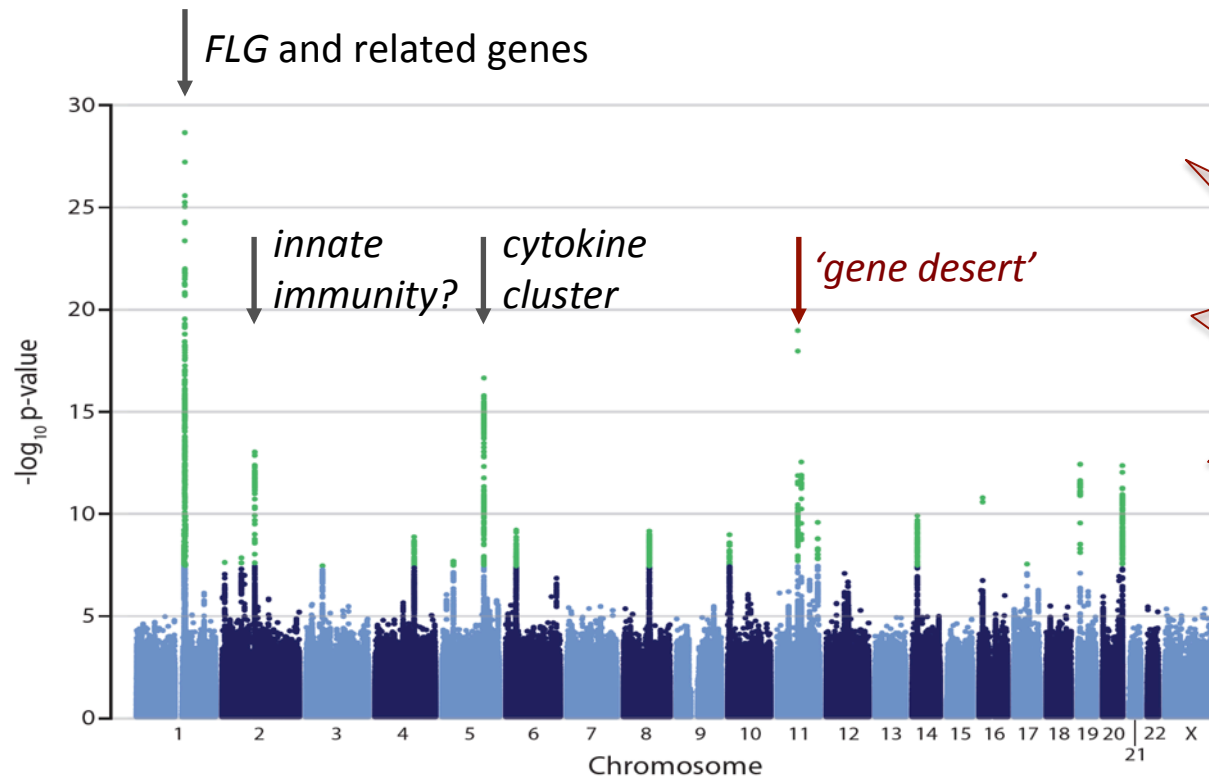
Eczema treatment in the future?



Insights from eczema genetics

Genome-wide association study (GWAS)

>50,000 cases and >250,000 controls EAGLE consortium *Nature Genetics* 2015



**Major challenge
in genetic
research**

Is there a functional effect?

→ Understanding genetic mechanisms

Eczema in the future?

Eczema
Outreach
Scotland



Patients want:

- better treatments
 - immune response **and** skin barrier
- better understanding

Unanswered questions

- Translation of genetic mechanisms to therapy ?
- Stratification for personalised medicine ?
- Key environmental effects ?
- Gene-environment interactions ?
- **Microbiome ?**
- Co-morbidity in atopic eczema (atopic & non-atopic) ?

Acknowledgements



The Brown lab group

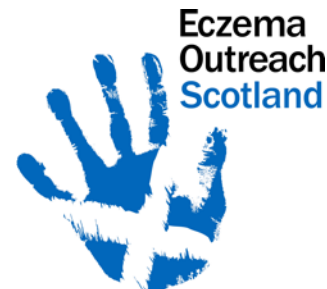
Ms Sheila Wright
Dr Saurabh Dayal

*The Manknell
Charitable Trust*



**Tayside Dermatological
Research Charity**

Data Analysis Group
> Geoff Barton
> Chris Cole



TTB
Tayside Tissue Bank

Questions ?

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