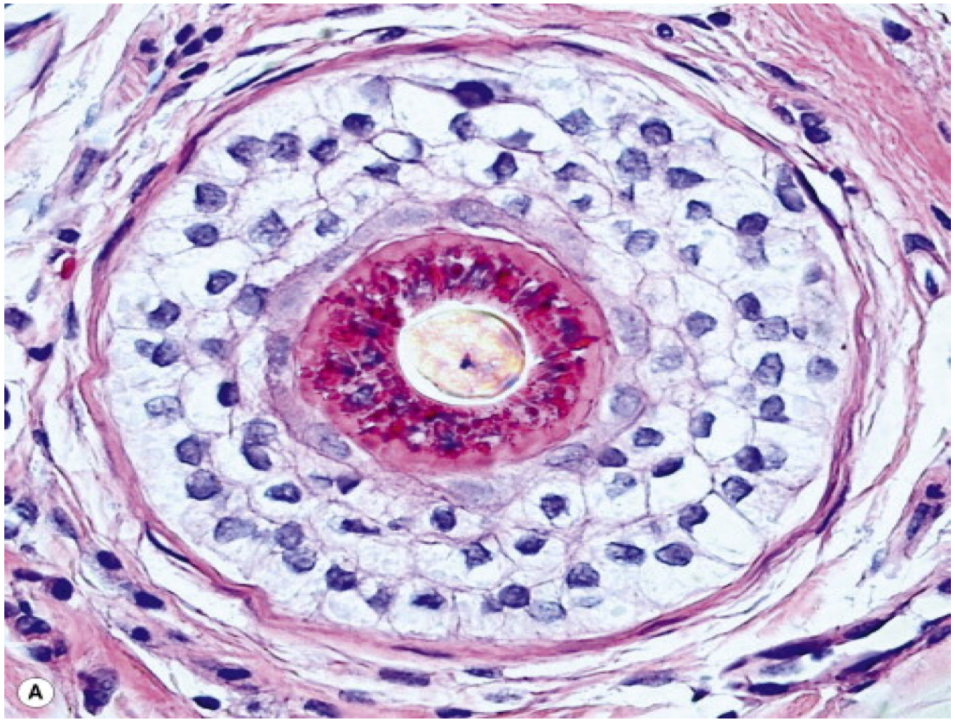
Ancient & New

An Update on Alopecia Areata & Frontal Fibrosing Alopecia



Dr Paul Farrant

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Alopecia Areata

Aim: Review advances in the understanding of Alopecia Areata

Learning objectives - Gain knowledge in:

- Presentation
- Pathogenesis
  - Pathobiology & immune privilege collapse
  - Genetics
  - Specific cells and cytokines
- Management

Alopecia Areata

- Hippocrates created the term alōpekia, which translates as fox mange (alopex= fox)
- Areata described in AD 30 by Cornelius Celsus (total loss, and ophiasis = snake pattern)

- 1800s – two thoughts – parasitic and nervous
- Later ideas were nerve irritation from defective teeth or eye strain

20 century – links with endocrine disorders (thyroid), syphilis, poisons

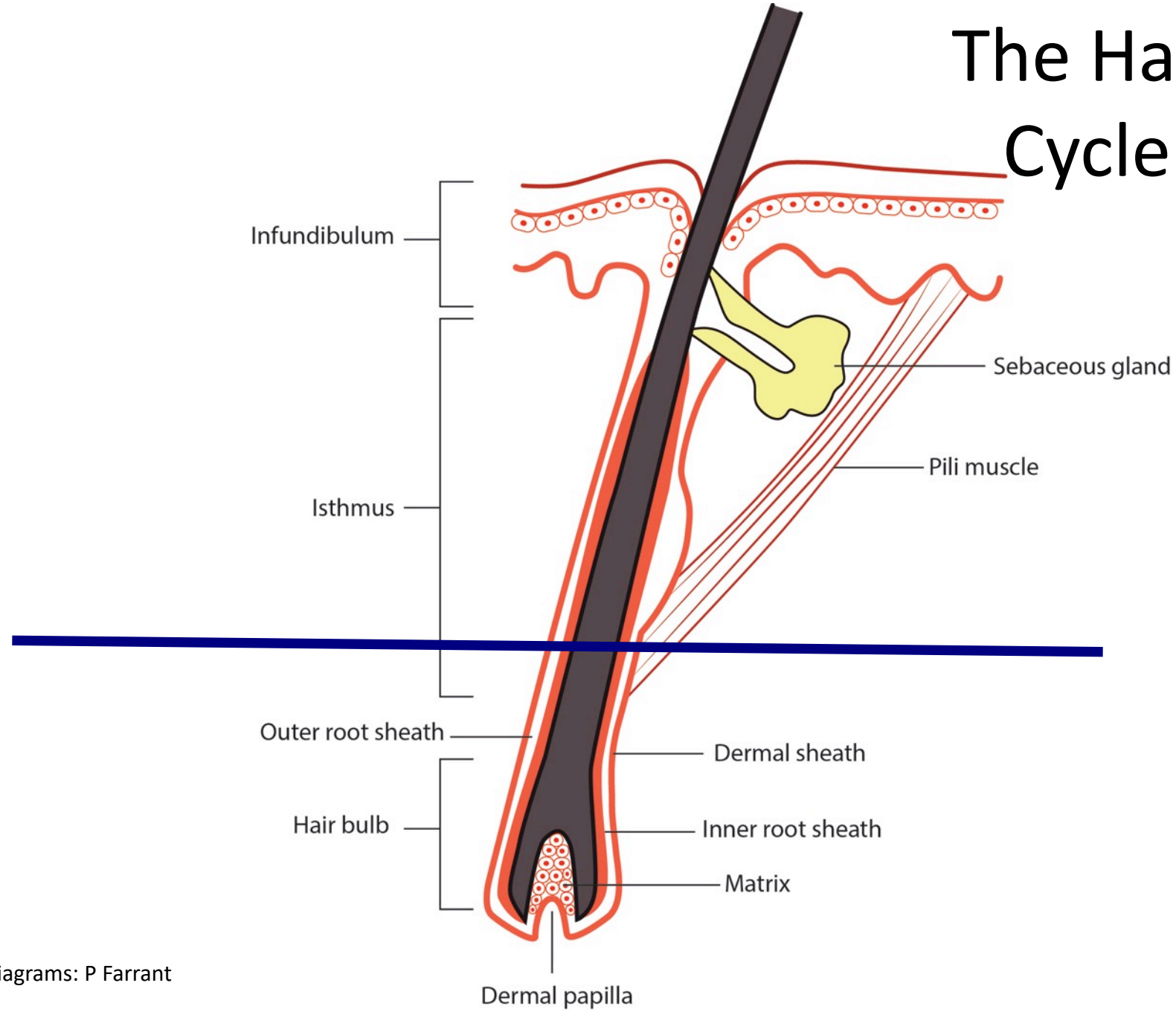
Alopecia Observations

- Small patches spread outwards
- Can stop when reach a certain size
- Attack pigmented hair and spares white > Going white overnight

Alopecia Observations

- Worse in Atopics
- Strong link with lupus
- Link with other autoimmune conditions – particularly thyroid
- Worse with time over the years
- Ophiasis, Totalis, Universalis, FHx all have worse prognosis
- Less than 10% have any obvious trigger

The Hair Cycle



Diagrams: P Farrant

Immune Privilege

- Suppression of surface molecules required for presenting autoantigens to CD8 T Cells (MHC class1a)
- Immunoinhibitory signaling
- Decreased MHC 1 puts follicle at risk of NK cells
- Down regulation of ligands for activation of NK cell receptors (NKG2D)
- + factors that inhibit NK and T cells eg TGFβ, αMSH, macrophage migration inhibitory factor

Alopecia Areata - Pathobiology

- Hair cycling disorder
- Immune attack around the bulb of Anagen VI follicles leads to exit of anagen to catagen and then telogen
- Regression of the follicle
- Dystrophy of the follicle – hair is no longer anchored and is shed

Pathobiology

- Hair follicle retains potential to regrow and continue cycling
- Like other autoimmune conditions – chronic relapsing inflammatory disorder
- Suggests cyclic recurrence of disease promoting events

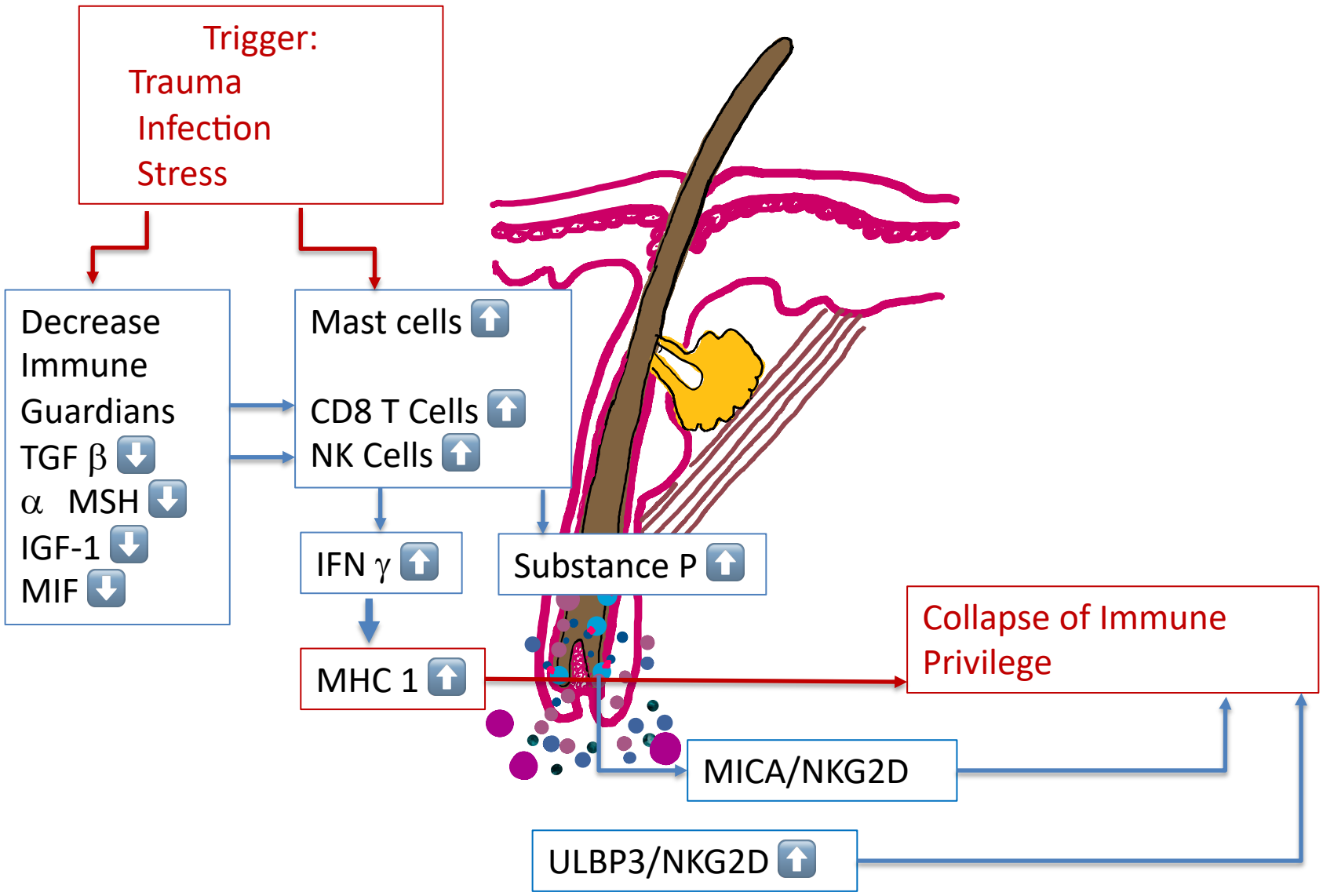
Immune Privilege collapse

- [Decrease in immune privilege guardians]
- Pro-inflammatory signals eg IFN γ, Substance P
- Upregulations of MHC 1
- Expose follicle associated autoantigens* to CD8+ T cells
- Co-stimulation from CD4 and Mast cells leads to attack on hair follicle bulb

* Autoantigens generated and/or presented only in anagen (eg melanogenesis associated peptides)

- Upregulation of MICA (intrafollicular), a NKG2D agonist > IFN γ
- Increase ULBP3 (peri-follicular), another ligand for NKG2D > IFN γ

- NKG2D mediated signalling
- Increase in CD56 and NKG2D+ NK cells


Trigger:
Trauma
Infection
Stress
Decrease Immune Guardians
TGF β
α MSH
IGF-1
MIF
Mast cells
CD8 T Cells
NK Cells
IFN γ
Substance P
MHC 1
Collapse of Immune Privilege
MICA/NKG2D
ULBP3/NKG2D

Genetic Component in Alopecia Areata

- Many patients have family history of AA
- High concordance between monozygotic twins (55%)
- Fhx of Atopy
- Down's syndrome
- Autoimmune polyendocrinpathy-candidiasis-ectodermal dyrstophy syndrome
- Other autoimmune diseases
- Ethnic variations

Genetic Component in Alopecia Areata

GWAS of 1054 patients, 3278 controls by Petukhova et al

- 139 single-nucleotide polymorphisms associated with areata
- Reconfirmed Chr 6p (HLA)
- Genes controlling T Cell activation and proliferation
  - CTLA4
  - IL2/21 and IL2 Receptor A
- Genes for ULBP which encode ligands for activating NKG2D

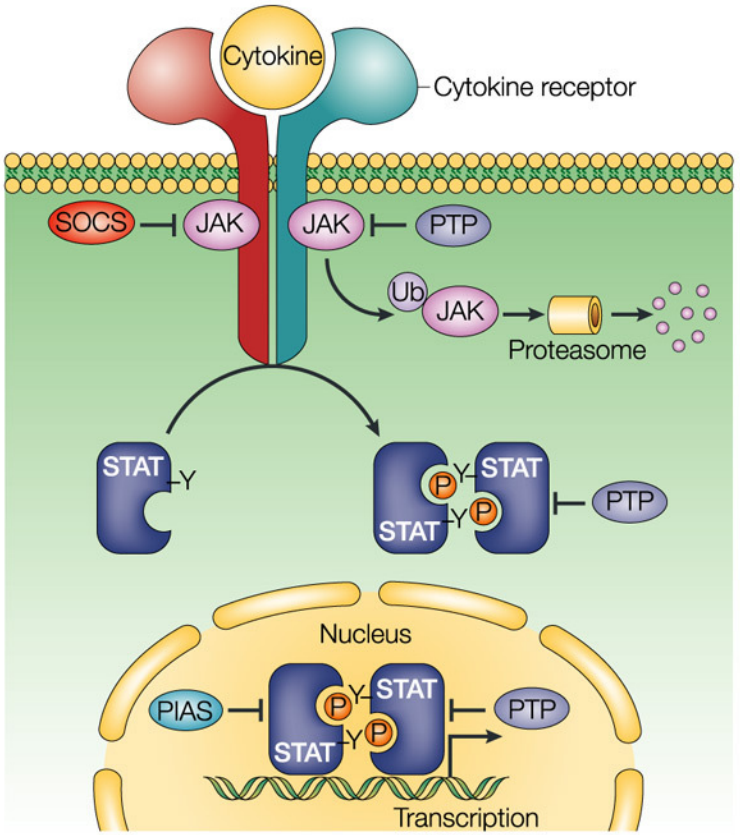
Petukhova et al 2010 Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. *Nature 466, 113–117*

Pathobiology & Genetics combined

- Decrease in immunosuppressive signaling, “immune privilege guardians”
- Loss of immune privilege, “trigger” in genetically susceptible individuals
- Increase in MHC 1a, presentation of “antigen”
- Increase MICA, ULBP3 and expression of NKG2D
- CD8, CD4, NK cells, Mast cell influx “swarm of bees”
- Immune attack leading to hair cycling from anagen to catagen

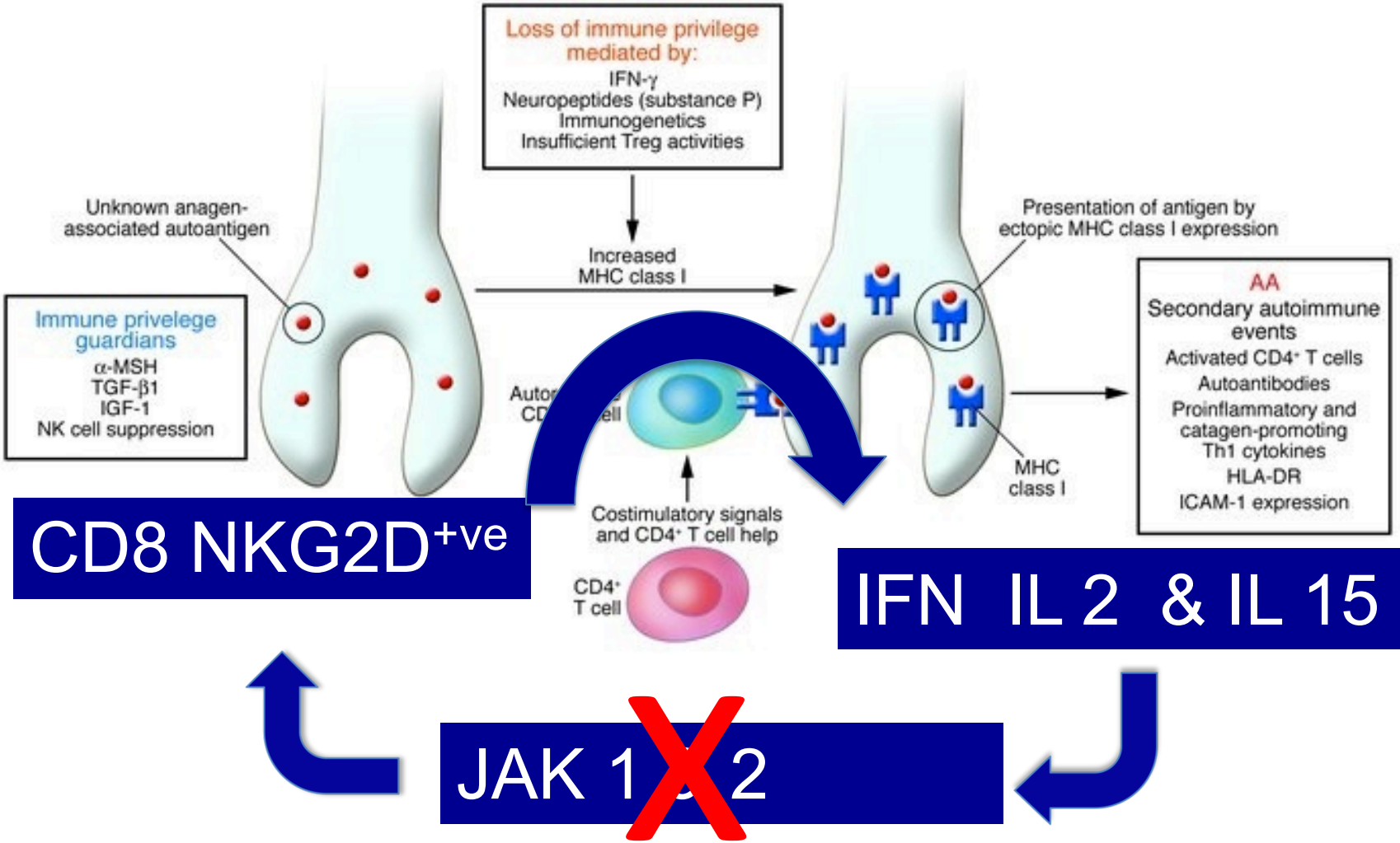
JAK Kinases

- IFN gamma receptors signal through JAK 1 / 2
- Can blocking the downstream effects of IFN –gamma achieve the same effect using inhibitors of JAK Kinases?



Nature Reviews | Immunology

Gilhar et al Lymphocytes, neuropeptides, and genes involved in alopecia areata. J Clin Invest. 2007 Aug 1; 117(8): 2019–2027



So we've got Alopecia sorted then?

- Current treatments (and majority of IPs in research) are non-specific
- Systemic and intralesional treatments have associated side effects
- High rates of relapse off treatment
- No long-term restoration of immune privilege

Management of Alopecia Areata

- Counselling, support groups
- No treatment
- Corticosteroids
- Contact Immunotherapy
- Photochemotherapy
- Minoxidil
- Dithranol

British Association of Dermatologists' guidelines for the management of alopecia areata 2012. Messenger et al.Br J Dermatol 2012; 166: 916–926

Management of Alopecia Areata

- Calcineurin Inhibitors
- Prostaglandin Analogues
- Biologic drugs
- Miscellaneous
  - Sulfasalzine
  - Methotrexate
  - Isoprinosine
  - Laser therapy
- Wigs & Prostheses

British Association of Dermatologists' guidelines for the management of alopecia areata 2012. Messenger et al.Br J Dermatol 2012; 166: 916–926

Corticosteroids

- Topical steroids
  - Super-potent 3 months
  - 6 weeks on and off for children
- Intralesional steroids
  - 2.5-10mg/ml
- Systemic corticosteroids

Immunomodulatory
Allergic vs Irritant Dermatitis

- Diphencyprone
  - Sensitisation
  - Titration
  - Maintenance
- Dithranol

Systemic Immunosuppression

- JAK inhibitors
- Biologic Therapies
- Methotrexate
- Ciclosporin

Clinical Trials.Gov

- 8 Trial presently recruiting
- JAK inhibitors
  - Tofacitinib
  - Baricitinib
  - Jaktinib
  - PF06651600/Allegro
  - CTP 543
- Dupilimumab

JAK Inhibitors – Do they work and will heath authorities pay?

- Too early to say
- 70% respond, 50% achieve SALT 50
- What is acceptable treatment?
- Need to be continued to maintain benefit
- Likely to be expensive and restricted to severe disease, reflecting trial recruitment

Methotrexate

- 63% response rate
- 36% complete response
- Works best in combination with long term prednisolone
- High doses required 20-25 mg Methotrexate weekly
- 3/12 for initial regrowth and 6-12 months for complete regrowth

J Am Acad Dermatol 2019; 80: 120-127

Ciclosporin

- Very small sample size 32 (16 drug vs 16 placebo)
- 4mg/kg
- 50% reduction in SALT score in 31% vs 6% at week 12
- P=0.07

Summary

- Common autoimmune condition
- Genetic predisposition
- Triggers poorly understood
- New understanding is leading to new treatments

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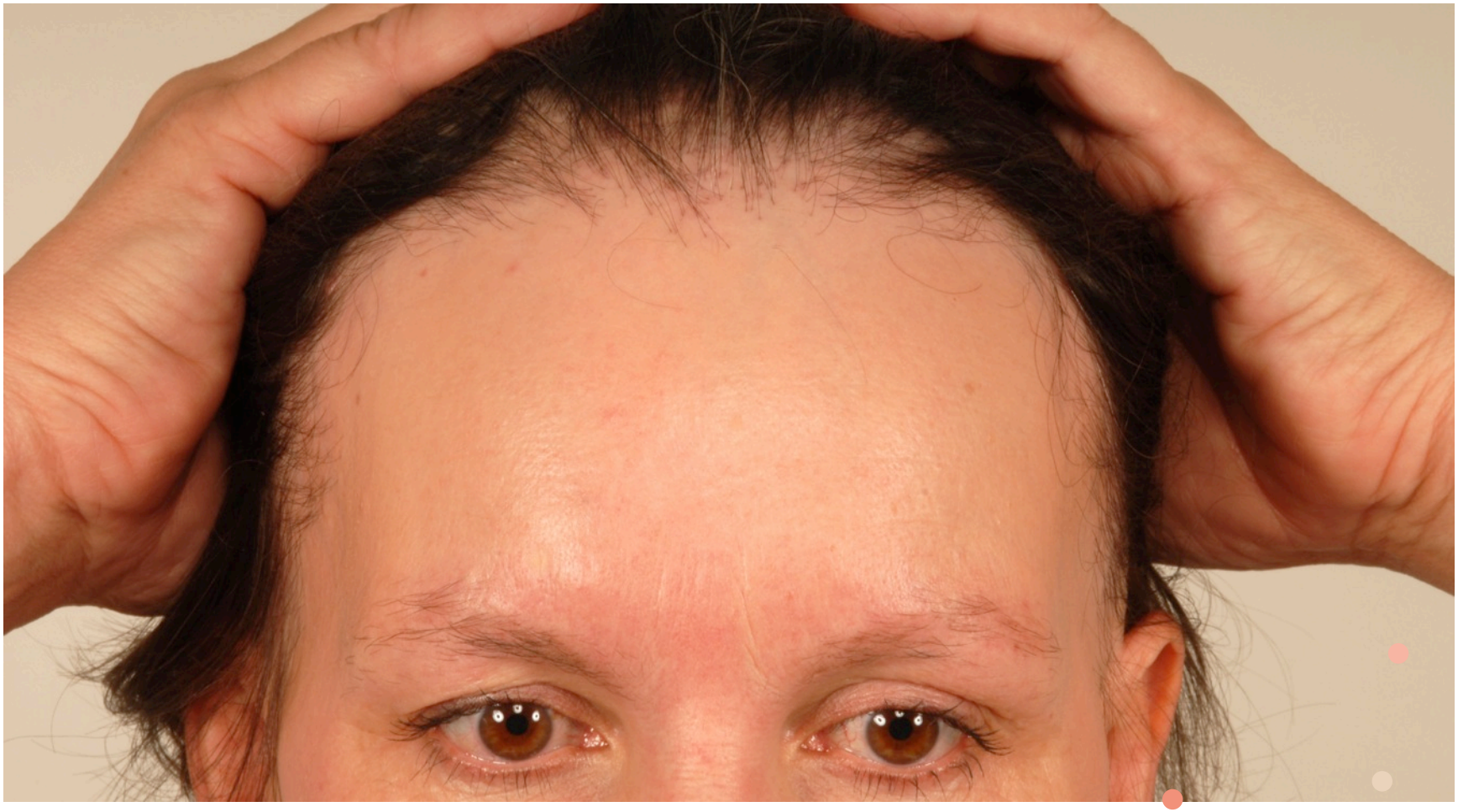
Where has Frontal Fibrosing Alopecia Come From?



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FFA

- First described by Kossard in 1994
- New entity vs previously unrecognised?
- Uncommon in 90s
- Now one of the most frequent causes of scarring alopecia
- Similar histology to LPP
- Can overlap with LPP of vertex
- Not always just frontal

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FFA

- 25 Years since First Described
- Still don't know why people get it
- Why the sudden increase?
- Why women?
- Environmental? Product related?
- Poor evidence for any treatment
- So how should we manage these cases?

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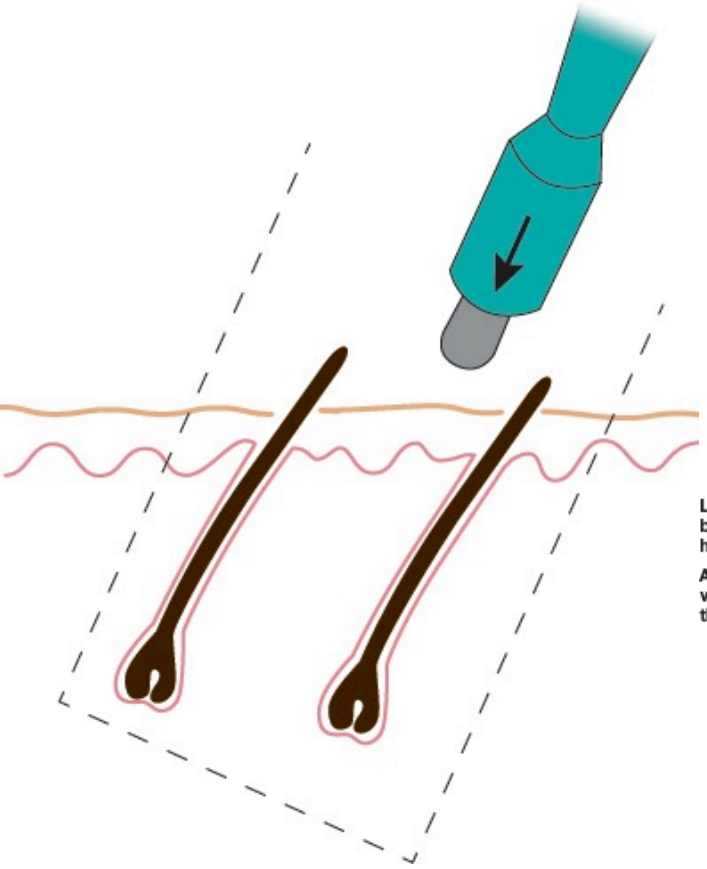
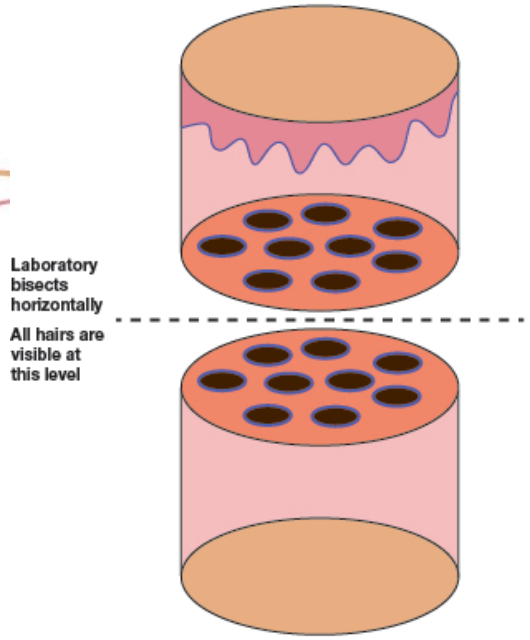


Scarring alopecia

Two 4mm punch biopsies - from peripheral "active" border

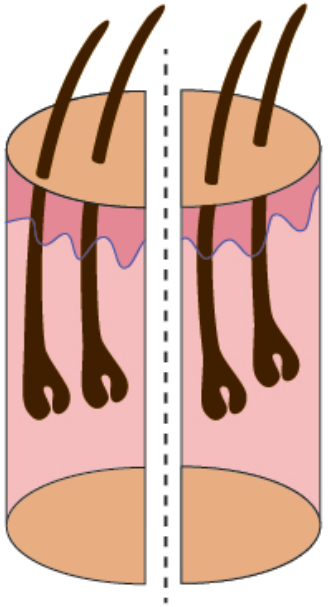
Whole specimen for laboratory sectioning

Doctor bisects vertically



Laboratory bisects horizontally

All hairs are visible at this level



Half sent for immunofluorescence

Half specimen sent for laboratory vertical sectioning
At any vertical slice only a part of a few hairs are visible

Medical therapy for frontal fibrosing alopecia: A review and clinical approach

Anthony Ho, BA, and Jerry Shapiro, MD
New York, New York

- Review of 270 papers > 23 studies
- 15 Retrospective cohort studies; 1 prospective; 7 case reports
- 622 Patients
- Treatment response based on lack of recession, improvement of signs or LPPAI improvement

Ho, Shapiro. JAAD 2019; 81: 569-580

- Intralesional Steroids (50%) better than topical steroids (25%)
- Hydroxychloroquine stabilized in 59%
- Finasteride regrowth in 47% (?) stabilized in 53%
- Isotretinoin 20mg od 12/12, 70% stabilised

Ho, Shapiro. JAAD 2019; 81: 569-580

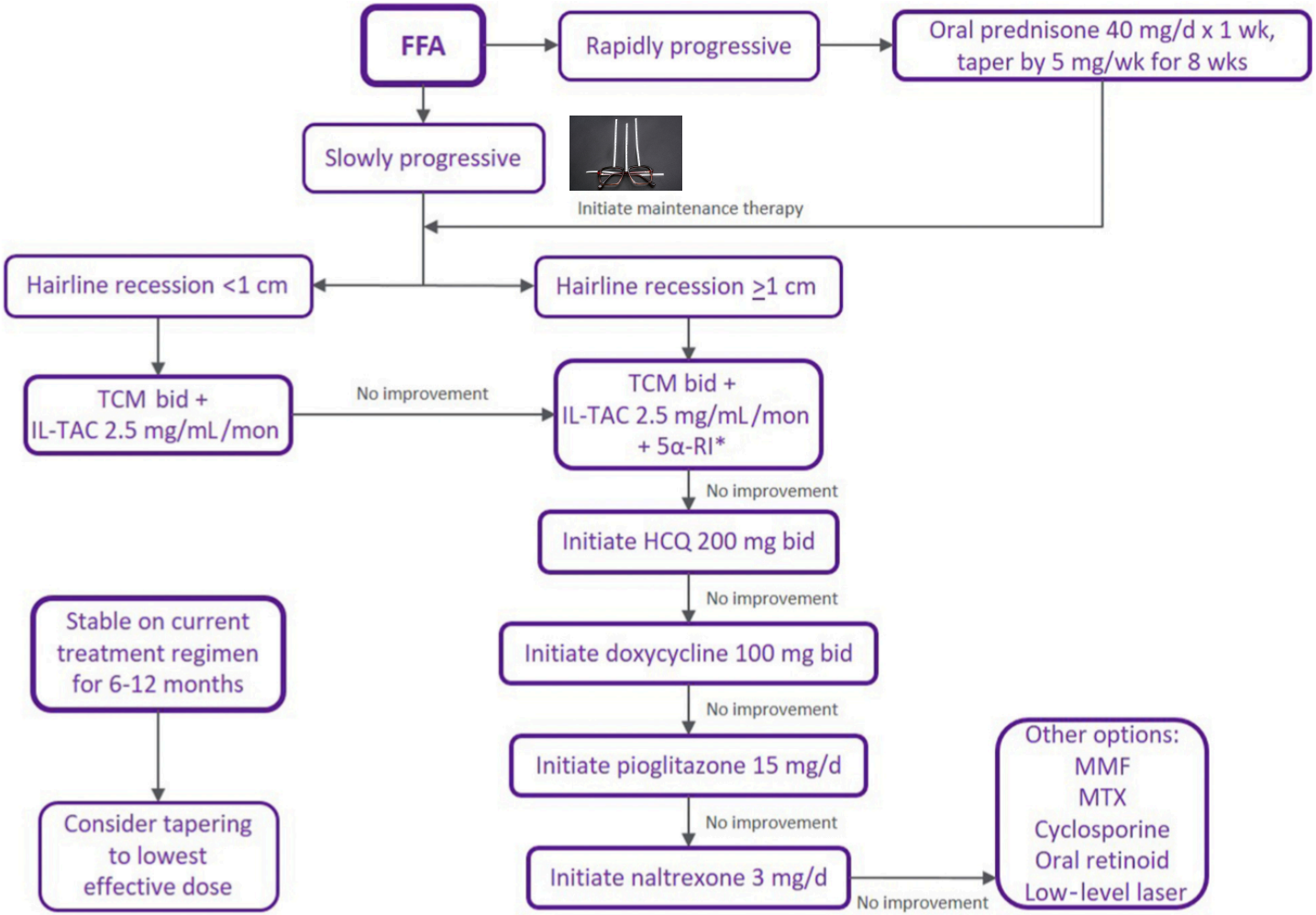


Fig 1. FFA treatment algorithm. *Finasteride 5 mg/d (premenopausal) or dutasteride 0.5 mg/d (postmenopausal). *5α-RI*, 5α-Reductase inhibitor; *bid*, twice daily; *FFA*, frontal fibrosing alopecia; *HCQ*, hydroxychloroquine; *IL-TAC*, intralesional triamcinolone acetonide; *MMF*, mycophenolate mofetil; *MTX*, methotrexate; *TCM*, tacrolimus 0.3% in Cetaphil cleanser + clobetasol solution + minoxidil 5% solution.

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Management

- Limited role for topicals
- Intralesional triamcinolone
- Hydroxychloroquine
- Tetracyclines?
- Mycophenolate Mofetil
- 5 Alpha reductase inhibitors
- Pioglitazone

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Summary

- FFA is an easy diagnosis but challenging condition to manage
- No great evidence of any treatment being beneficial
- Observation & measurements need to be standardized
- Avoid unnecessary chemicals

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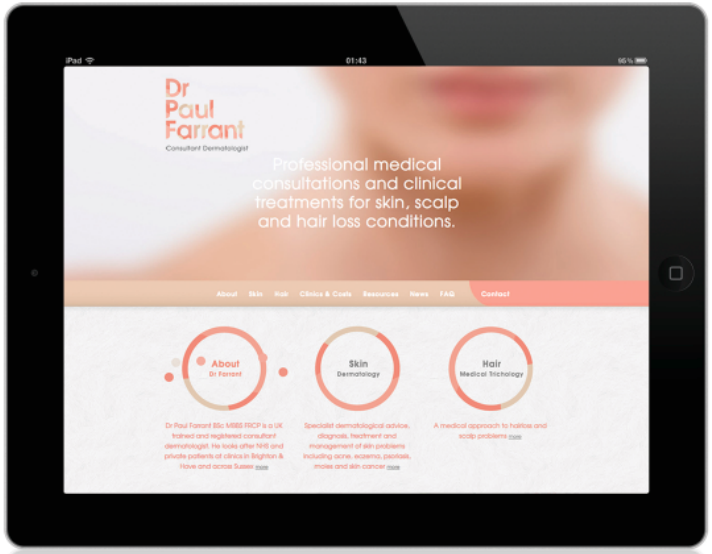

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