Advances and Opportunities in Autoimmune Skin Diseases

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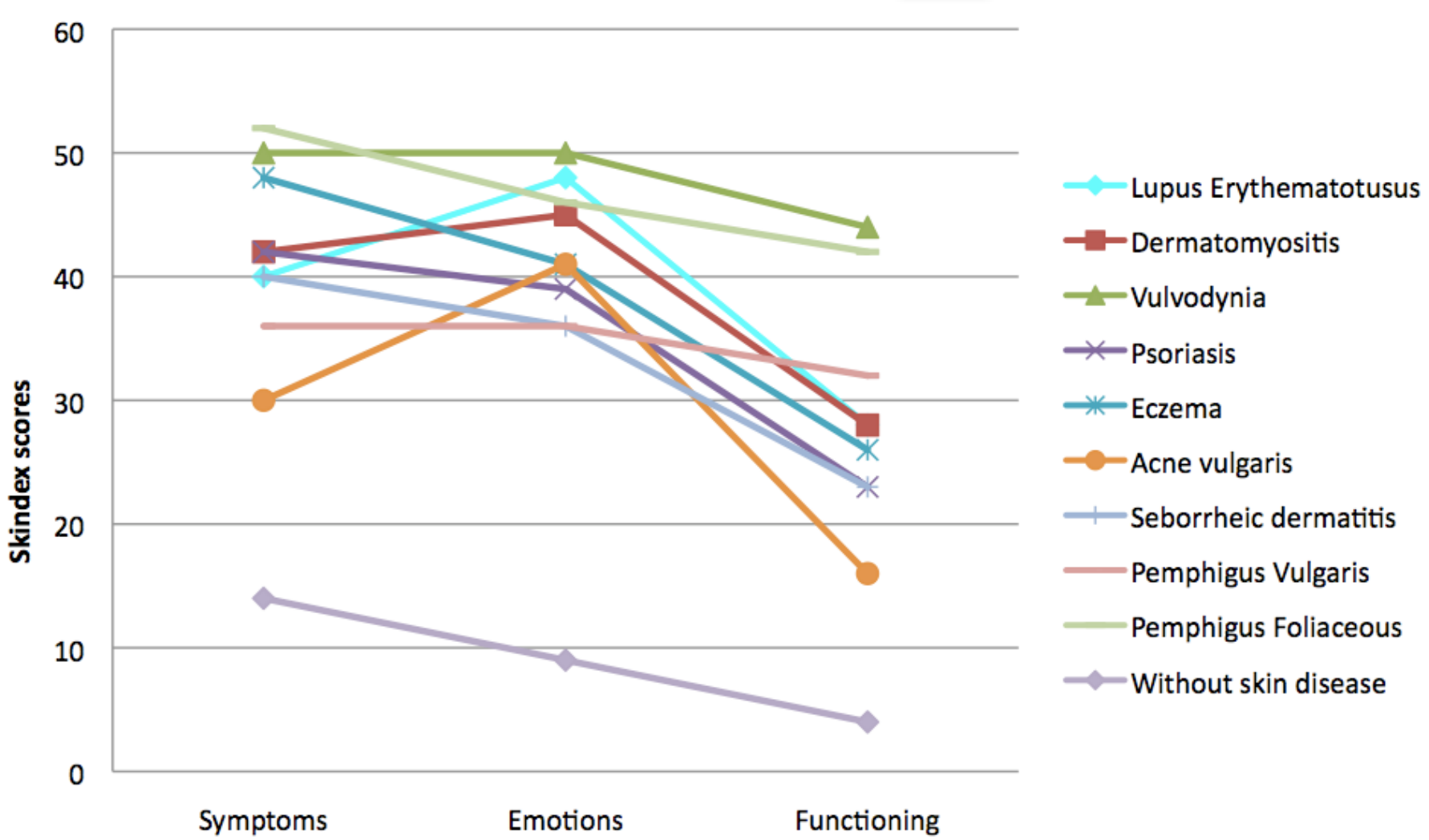
Quality of Life (QoL) in Autoimmune Skin Diseases (Skindex)



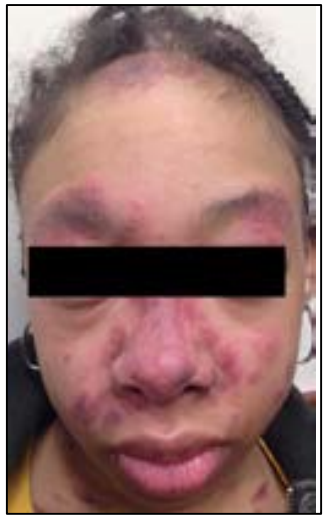
Klein R, et al, JAAD 64:649, 2012

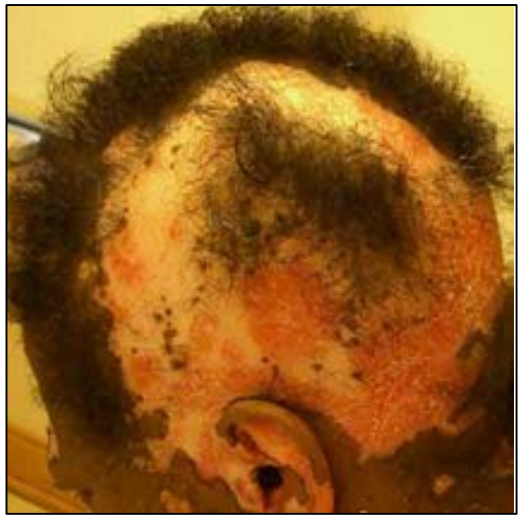
QoL in CLE (n=157) compared to common medical conditions (SF-36)

	Sample size	PF Mean (p)	Social F Mean (p)	RE Mean (p)	MH Mean (p)
CLE	156	46	44	45	45
General population	2474	51 (<0.01)	50 (<0.01)	49 (<0.01)	50 (<0.01)
HTN	2089	46 (0.76)	51 (<0.01)	48 (<0.01)	52 (<0.01)
CHF	216	35 (<0.01)	45 (0.70)	44 (0.39)	50 (<0.01)
T2DM	541	44 (<0.01)	49 (<0.01)	48 (0.01)	51 (<0.01)
Recent MI	107	44 (0.05)	50 (<0.01)	47 (0.05)	50 (<0.01)
Clinical depression	502	45 (0.26)	39 (<0.01)	36 (<0.01)	34 (<0.01)

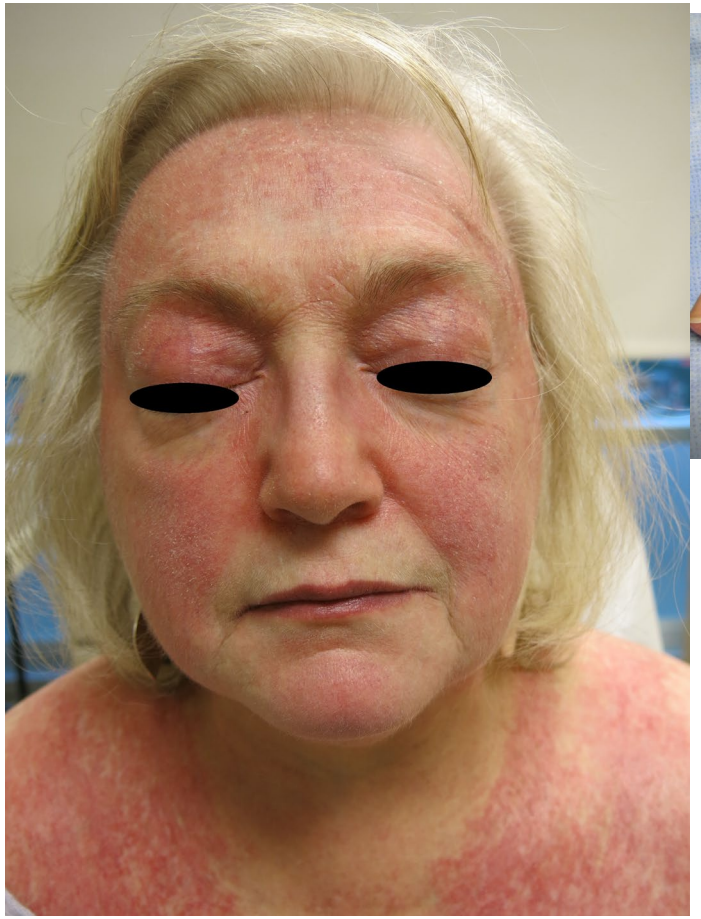
Klein R, et al, JAAD 64:649, 2012

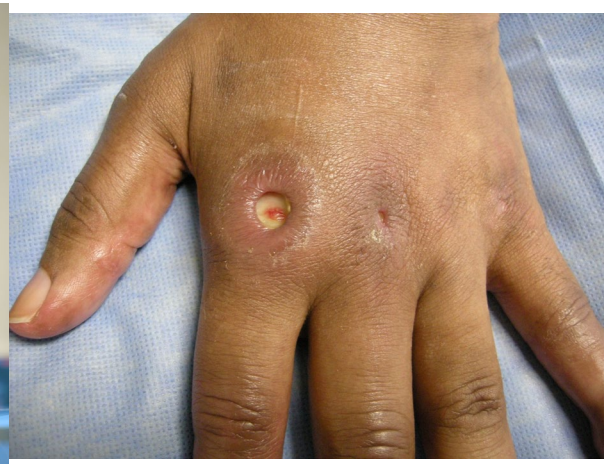
Autoimmune skin diseases Impact QoL





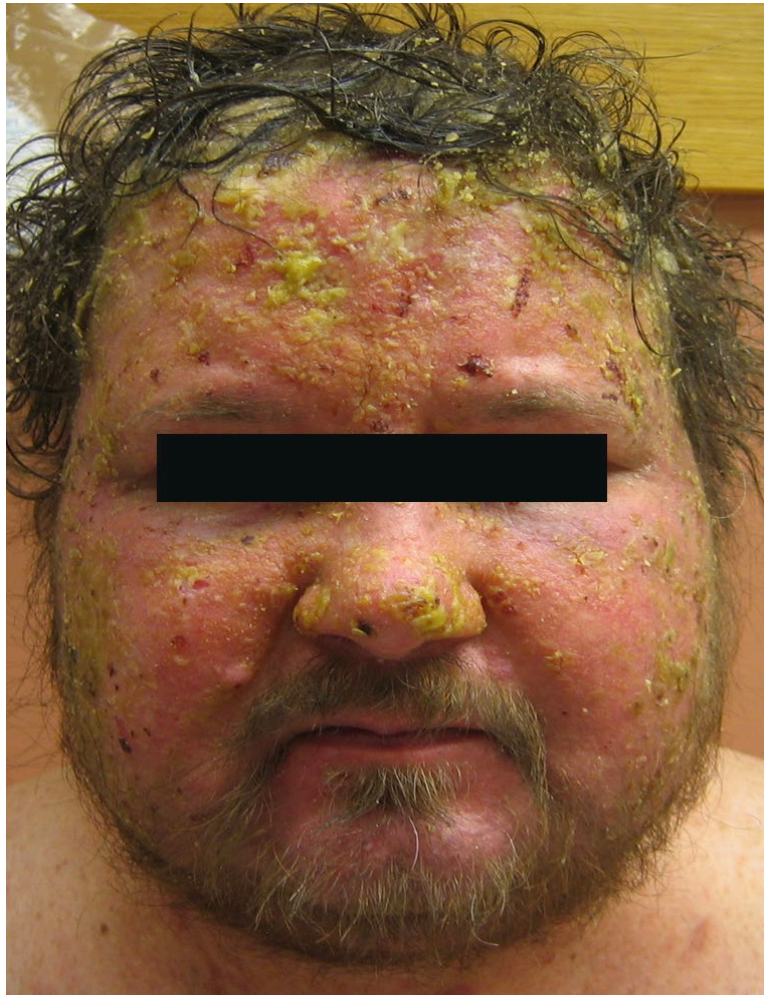
DLE



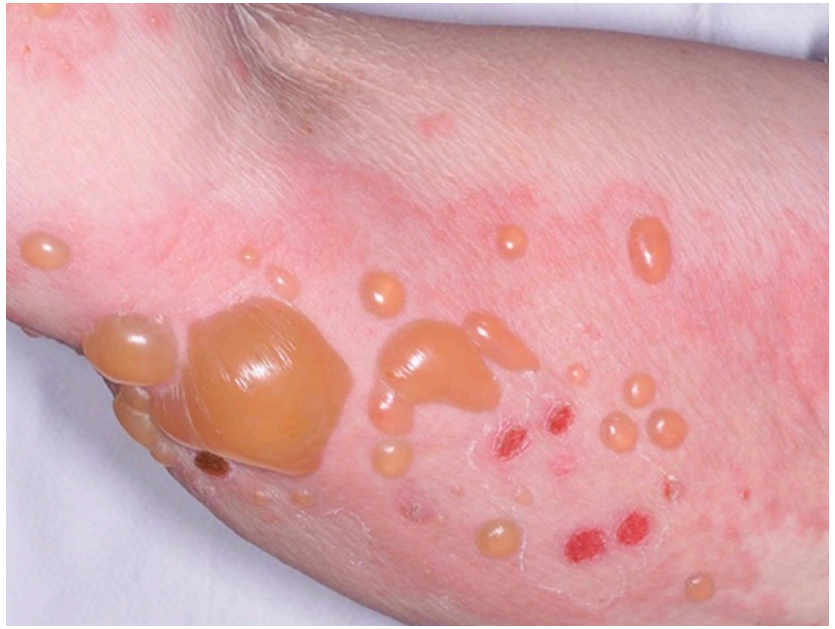


Dermatomyositis

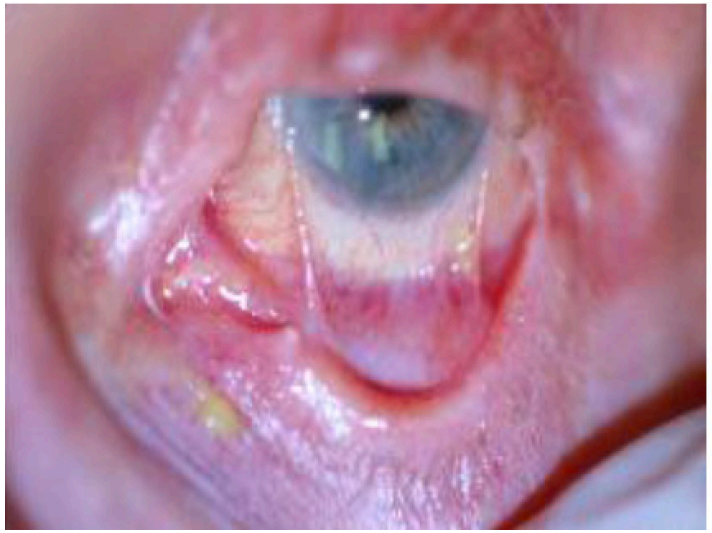
Subepidermal blistering diseases

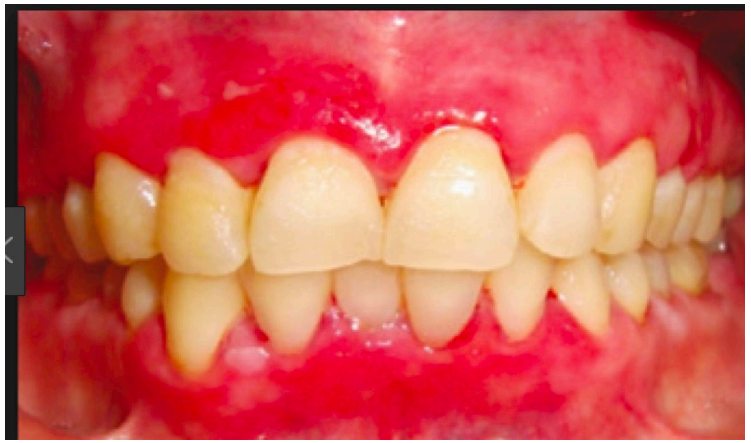


Pemphigus vulgaris

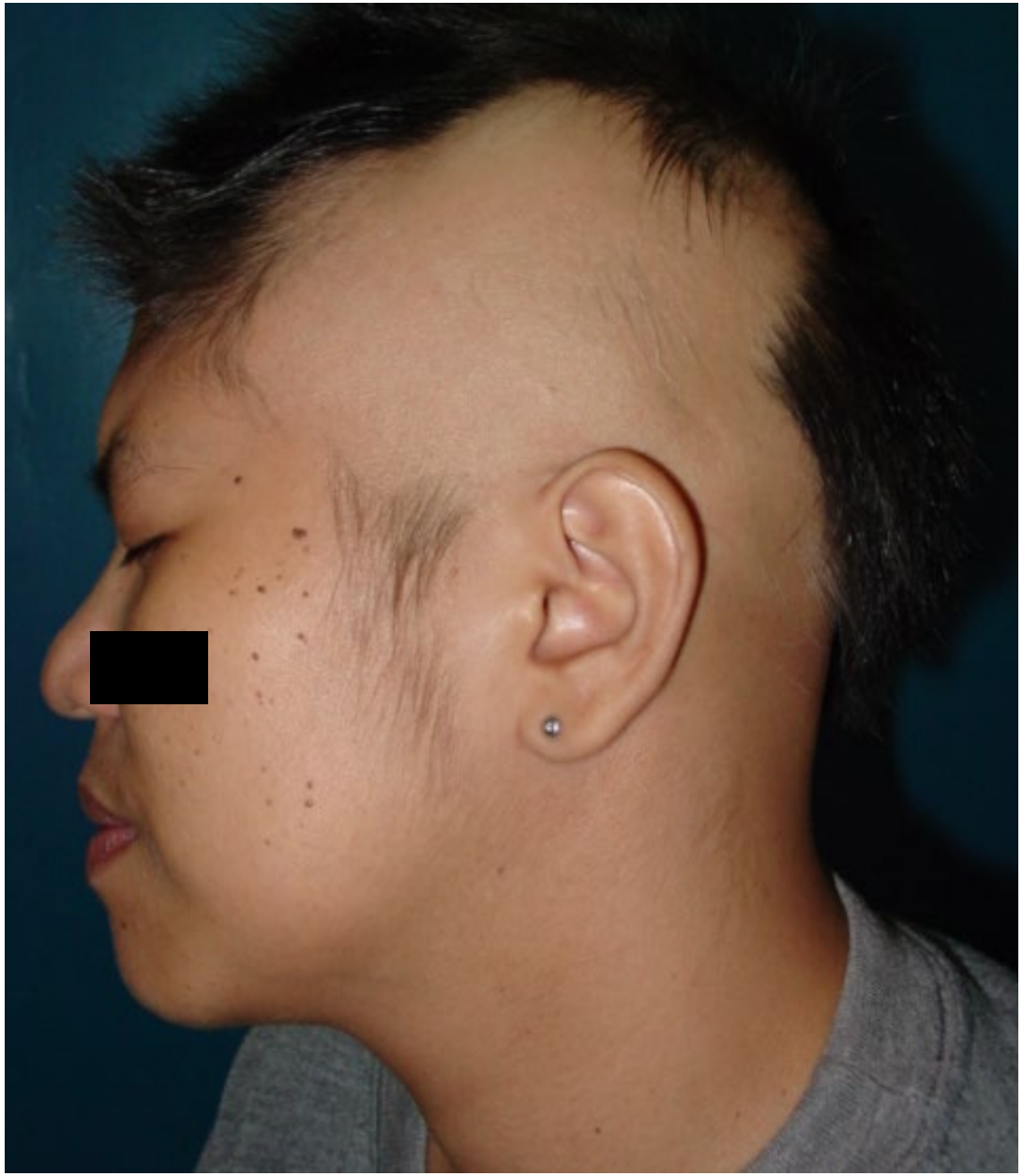


Bullous Pemphigoid

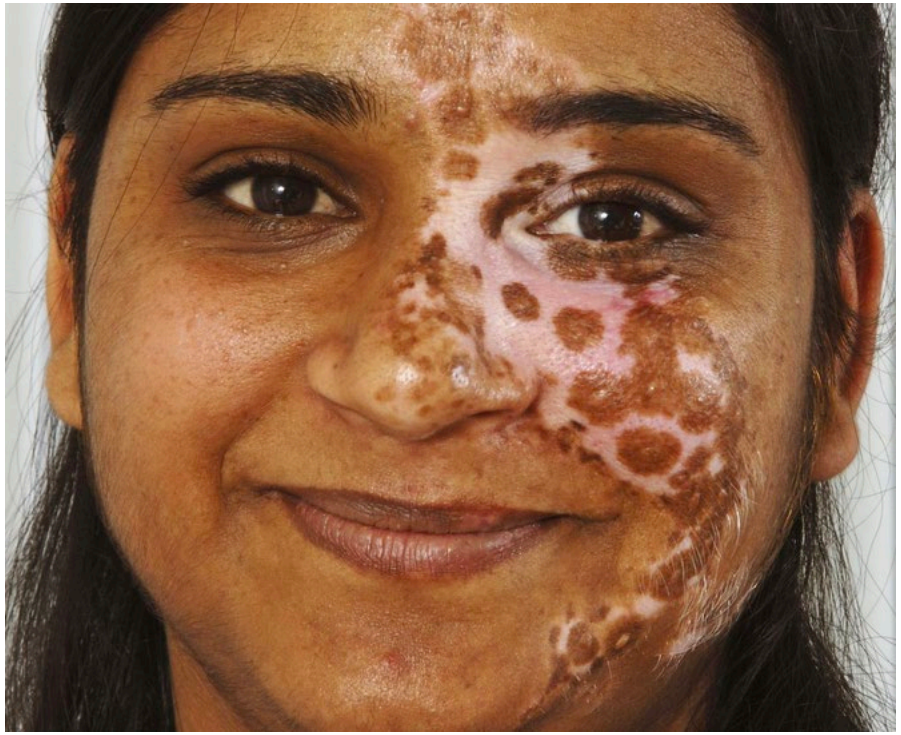




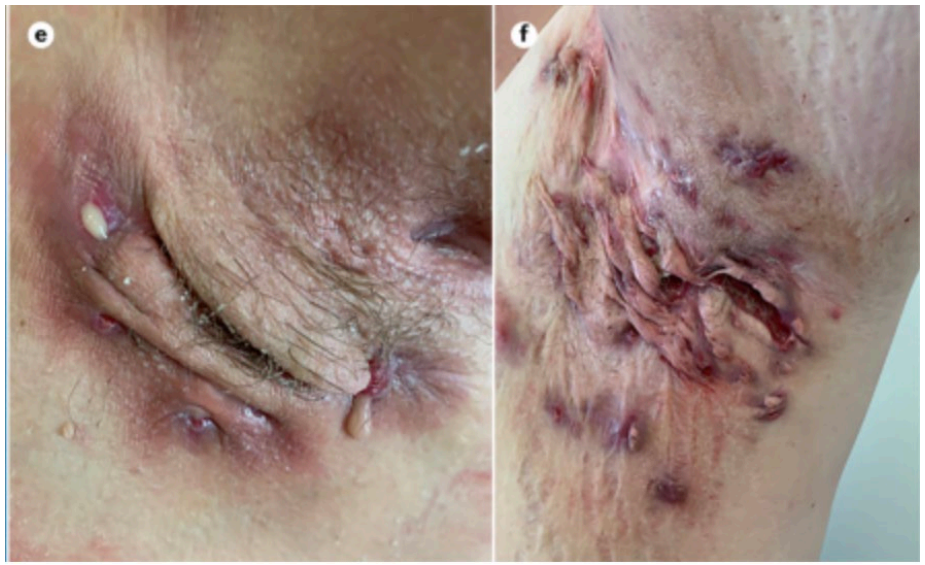
Mucous Membrane Pemphigoid



Alopecia Areata



Vitiligo



Hidradenitis Suppuritiva (axilla)

Autoimmune Diseases: Skin

- **Psoriasis** (incidence **30-321/100,000**), prevalence 1.5% (Parisi R et al, BMJ. 2020; 369: m1590. 10.1136/bmj.m1590)
- **Eczema** (prevalence 1-3% of adults)
- **Vitiligo** (prevalence 0.5-2%)
- **Alopecia areata** (2% lifetime risk)

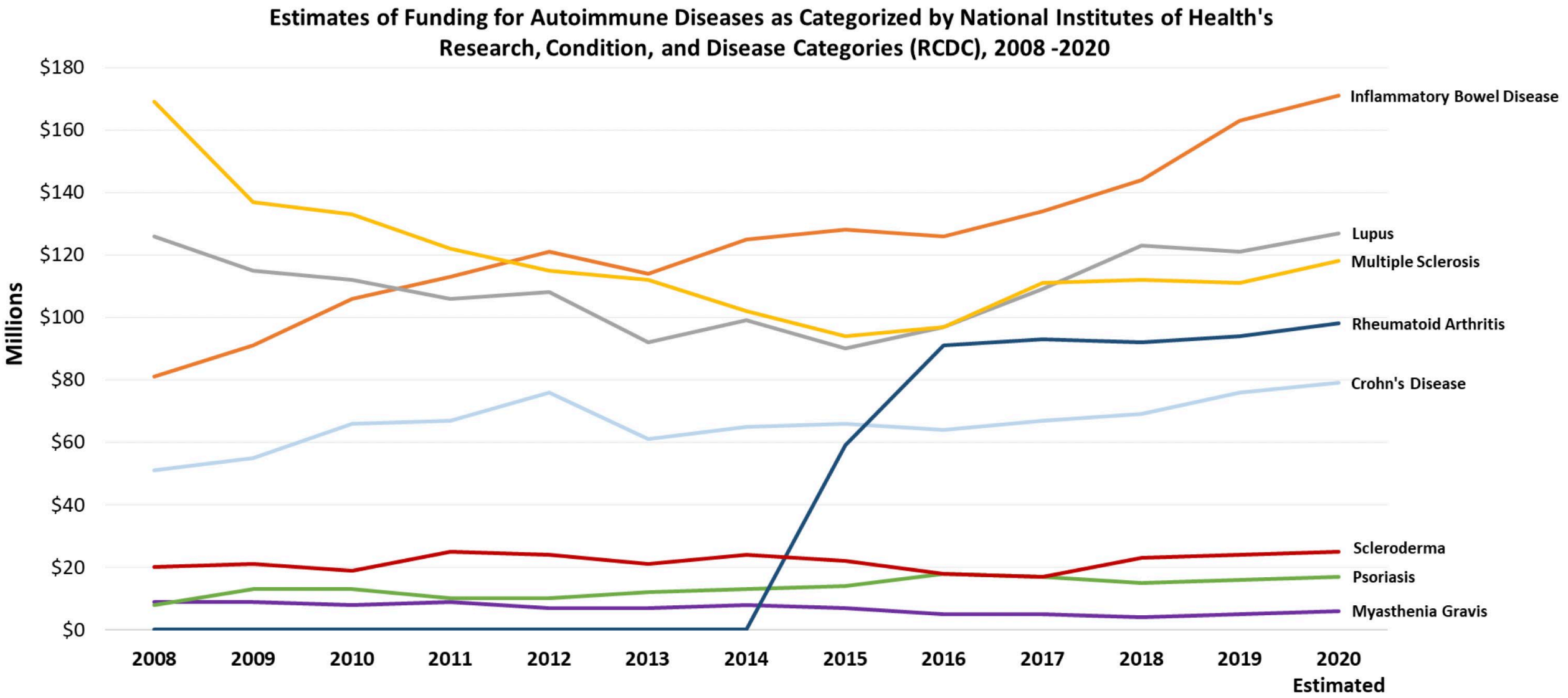
- Similar to Rheumatoid Arthritis in prevalence

Autoimmune Diseases: Skin

- Autoinflammatory diseases: **Hidradenitis suppuritiva** (Incidence: **11.4/100,000;** more in women and African Americans (>2.5x**)**
- **Autoimmune blistering diseases**
  - **Pemphigus** (incidence **0.7/100,000**; prevalence 5/100,000) (Langan SM et al, BMJ. 2008 Jul 19; 337(7662): 160–163.
  - **Bullous pemphigoid** (incidence **4.3/100,000**); increased between 1996 and 2001—about 17% for each calendar year, or a 4.8-fold increase over the 11 years.

Autoimmune Diseases in Skin ± Systemic

- **Cutaneous lupus erythematosus** (incidence **4/100,000**)
- **Dermatomyositi**s (incidence **1/100,000**), Prevalence between 1/10,000-50,000
  - True incidence unknown due to under-diagnosis
  - At least 20% amyopathic DM and likely increasing (not muscle disease) (90% women in amyopathic DM vs 60% for classic DM)
  - Understudied
  - Environmental exposures (UV, immunostimulatory herbs, etc) likely important
- Morphea (incidence **3/100,000**) and scleroderma (incidence **2/100,000**)
- Leukocytoclastic Vasculitis (**4.5/100,000**) *(Arora A et al, Mayo Clin Proc 89:1515-1524, 2014)*



- **Dermatomyositis?**
- **Cutaneous Lupus?**

Barriers to Autoimmune Skin Disease Research

- Huge effects on QoL remain underappreciated
  - QoL needs to factor into importance for funding since if can improve the disease, the QoL improves
- Investigator-initiated clinical research in autoimmune skin disease is relatively recent development

Barriers to Autoimmune Skin Disease Research

- Proportionately less research in certain autoimmune skin diseases, especially in areas where there are skin manifestations in addition to systemic features
  - Gaps in disease definitions
  - Pathogenesis of disease heterogeneity is often unclear
    - Why are different organs affected
    - Clinical research that examines biological bases for heterogeneity of disease and responses to therapy (beside to bench)
    - Vital to define research (basic, translational, clinical) that allows study of these skin predominant patients in a way that will lead to approval of new therapies

Successful NIH funding mechanisms

- Early trials for autoimmune skin diseases (NIAMS, NIAID)
  - Pemphigus (NIAID): infliximab (TNFα blocker)
  - First trial in amyopathic dermatomyositis with linked mechanistic studies (NIAMS)
  - Scientific studies linked to clinical trials (R01, R21)
- R01s: Cell therapy-proof of principle (Tregs for pemphigus; CAAR-T cells for pemphigus); IL-15 for vitiligo;
- Mechanisms that have helped systemic (but not skin) disease:
  - Vasculitis infrastructure: NIH-funded Vasculitis Clinical Research Consortium
  - Accelerating Medicine Partnership (AMP): RA, SLE

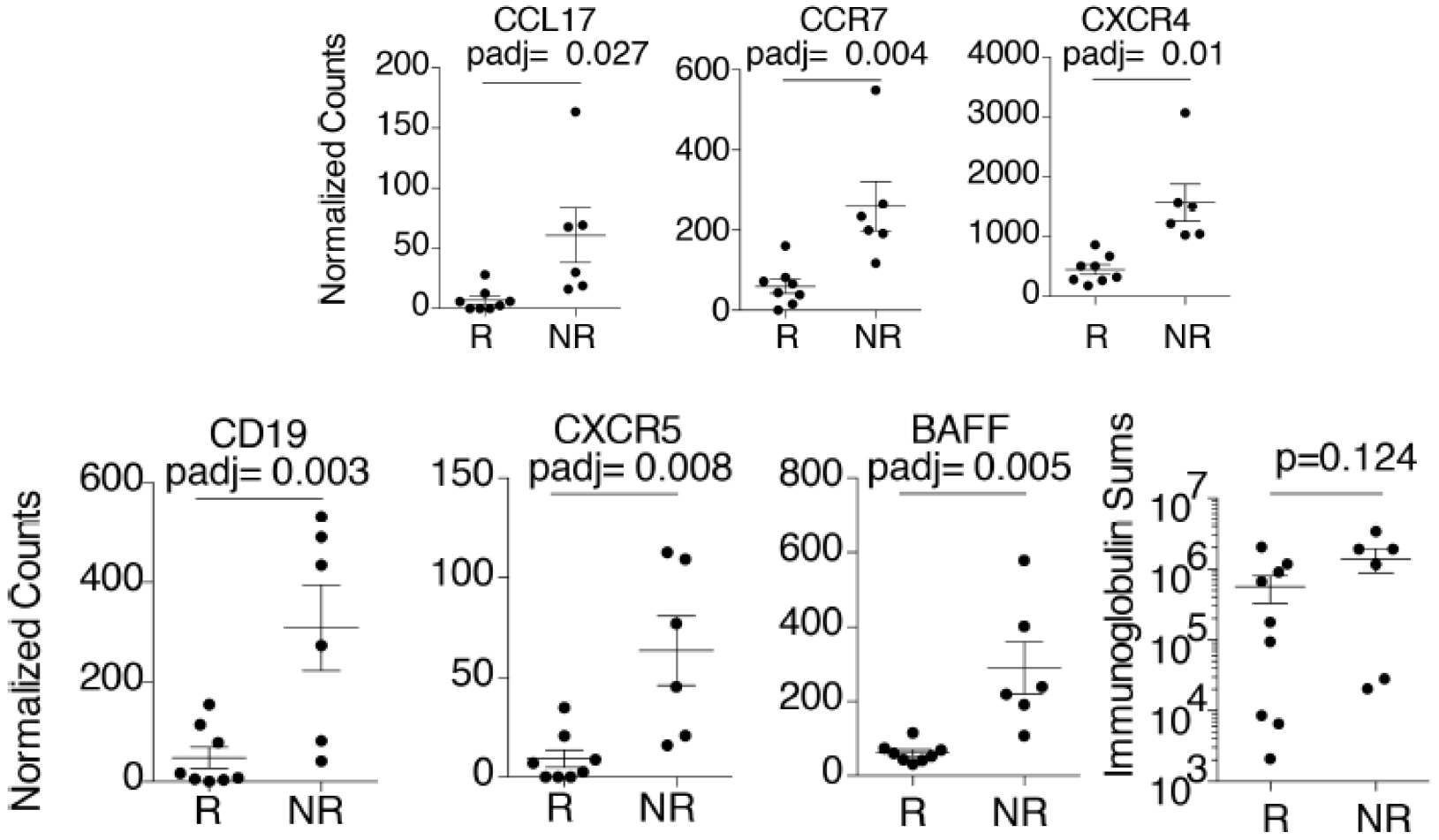
Successful early and mid-career NIH funding mechanisms

- Early career K awards for training (translational training beyond epidemiology needed to advance the fields at this point)
- Clinical Translational studies to advance therapeutics (CTSA funding and infrastructure helpful; linked funding for Masters in Translational Research)
- K24 mid-career awards: critical to sustain clinical and translational investigation

Successes in Autoimmune Skin Diseases

- Rituximab (anti-CD20) approved by FDA for pemphigus vulgaris and works!
- Huge therapeutic armamentarium for psoriasis
- Adalimumab (anti-TNF) is approved for hidradenitis suppuritiva
- *But* how to identify subsets of patients who will a priori benefit from a given therapy

Immunopathogenesis of hidradenitis suppurativa and response to anti–TNF-α therapy



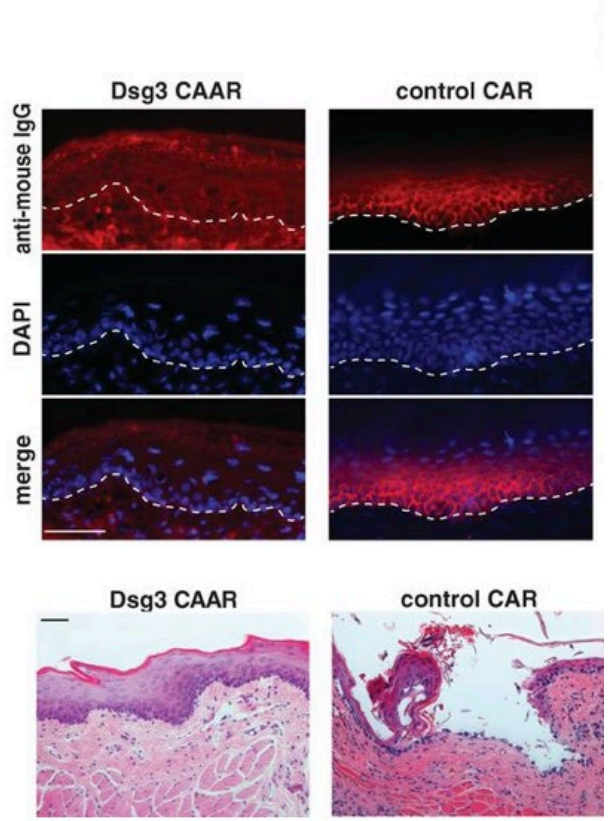
Lowe MM, et al. JCI Insight 2020;5(19):e139932.

Ongoing Investigations in Autoimmune Blistering Disease

- New potential therapeutic approaches being investigated for pemphigus (NIAMS, NIAID, bench to bedside)
  - T regulatory cells infusion
  - CAAR chimeric autoantigen receptor T cell therapy
  - Anti-IL-15 for vitiligo
  - Speculative scientific proof of principle

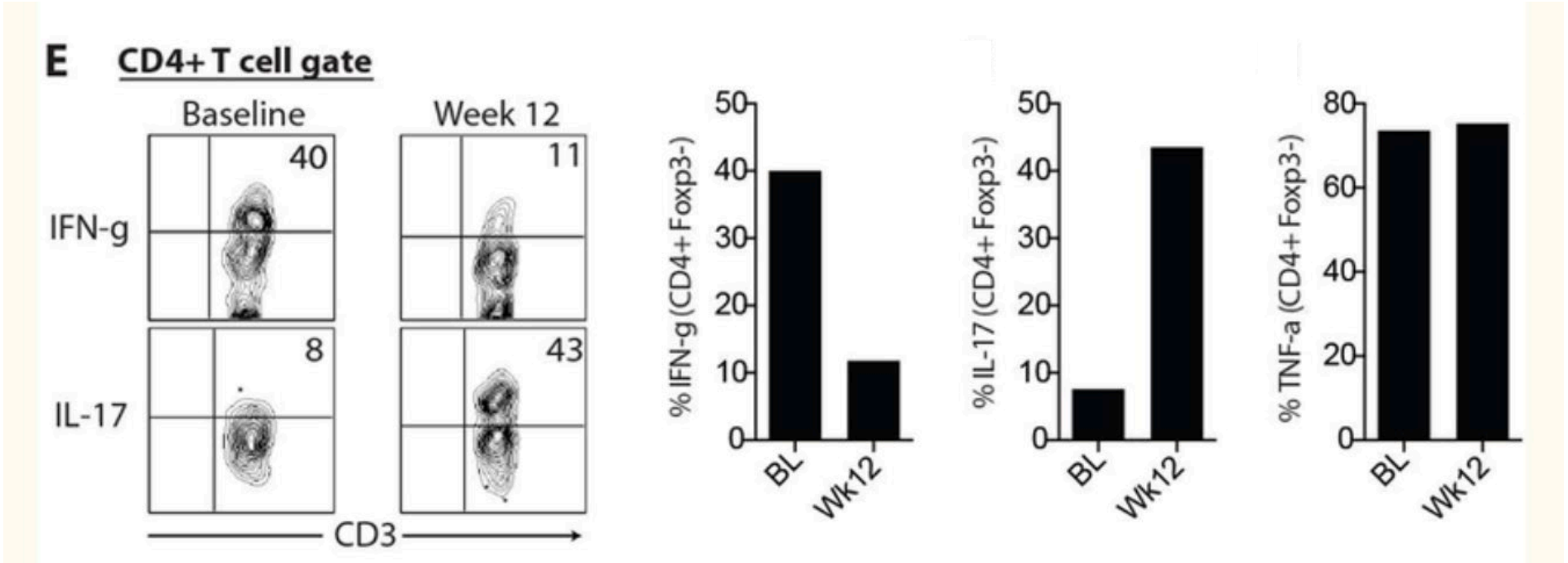
CAAR T cells

- Dsg3 CAAR-T cells exhibit specific cytotoxicity against cells expressing anti-Dsg3 BCRs in vitro and expand, persist, and specifically eliminate Dsg3-specific B cells in vivo.



Ellebrecht CL et al, Science 8:179-84, 2016

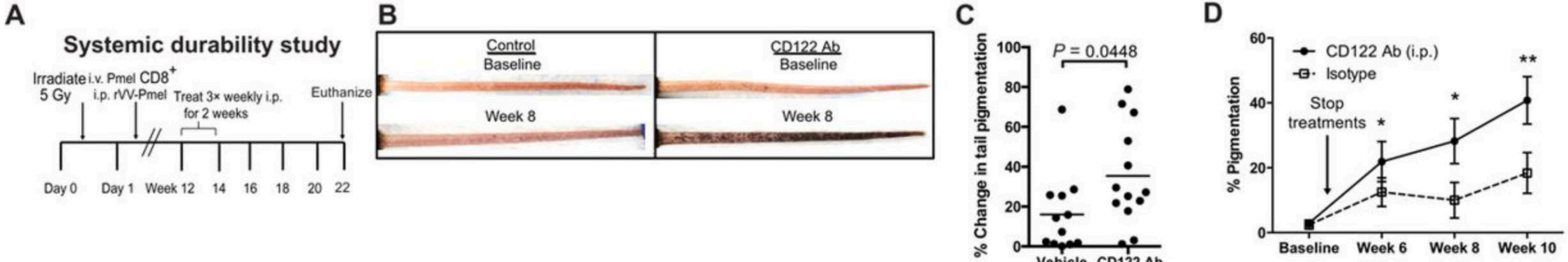
Adoptive Regulatory T Cell Therapy in SLE



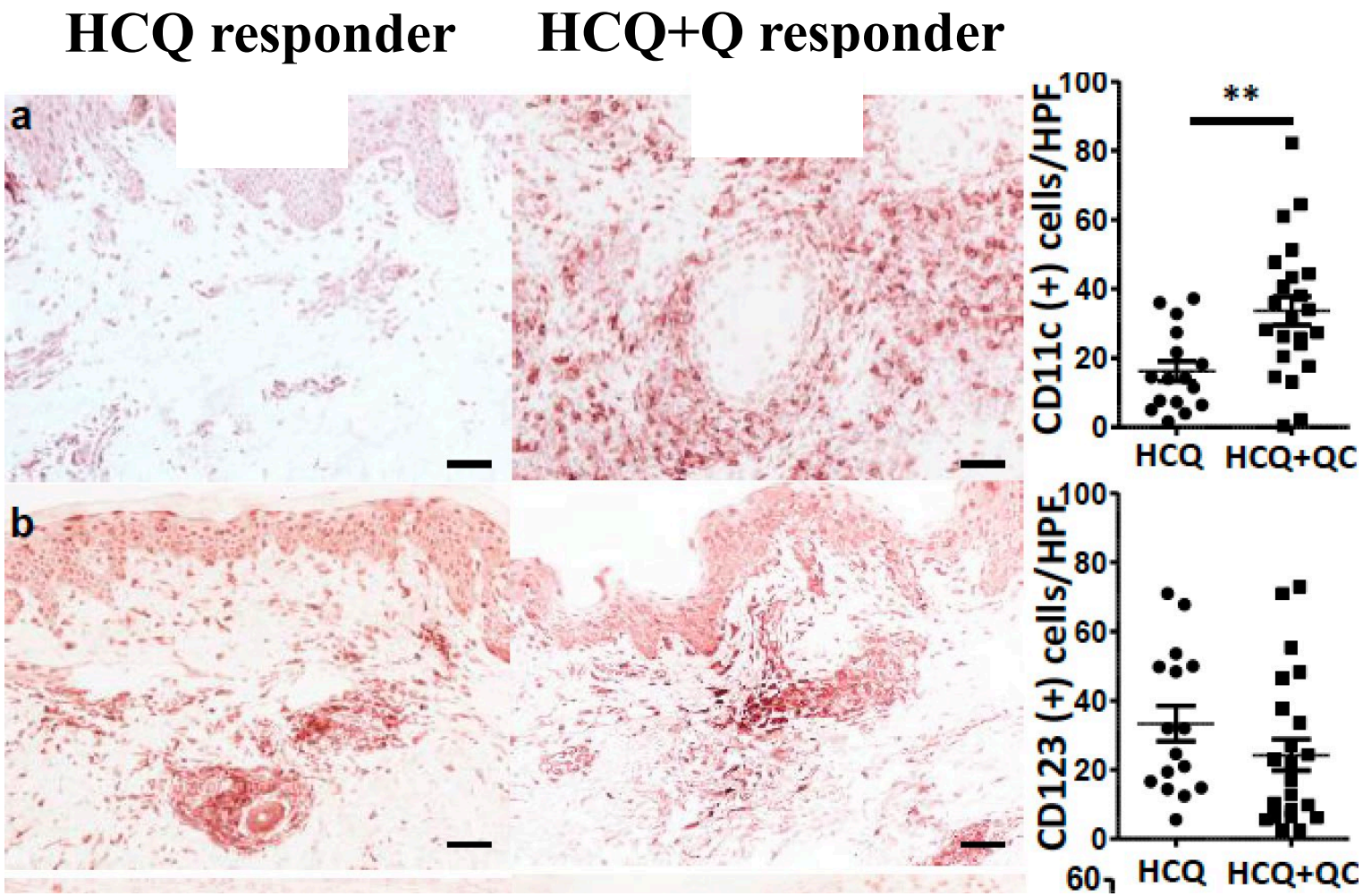
Dall'Era M, et al. Arthritis Rheumatol 71;431-440, 2019

Vitiligo

- CD8+ T cells target melanocytes
- Resident memory T cells in skin in human and mouse vitiligo model (adoptive transfer of T cell receptor (TCR) transgenic T cells recognizing the human melanocyte antigen premelanosome protein) (*J Invest Dermato.* ***132****, 1869–1876,2012)*
- IL-15, an important survival cytokine for T cells and blockade of IL-15 treated vitiligo in the mouse. (*Richmond JM et al, Science Translational Medicine 10:Issue 450, eaam7710*)
- Ongoing trial with anti-iL-15 antibody for vitiligo (NIAID, Amgen)

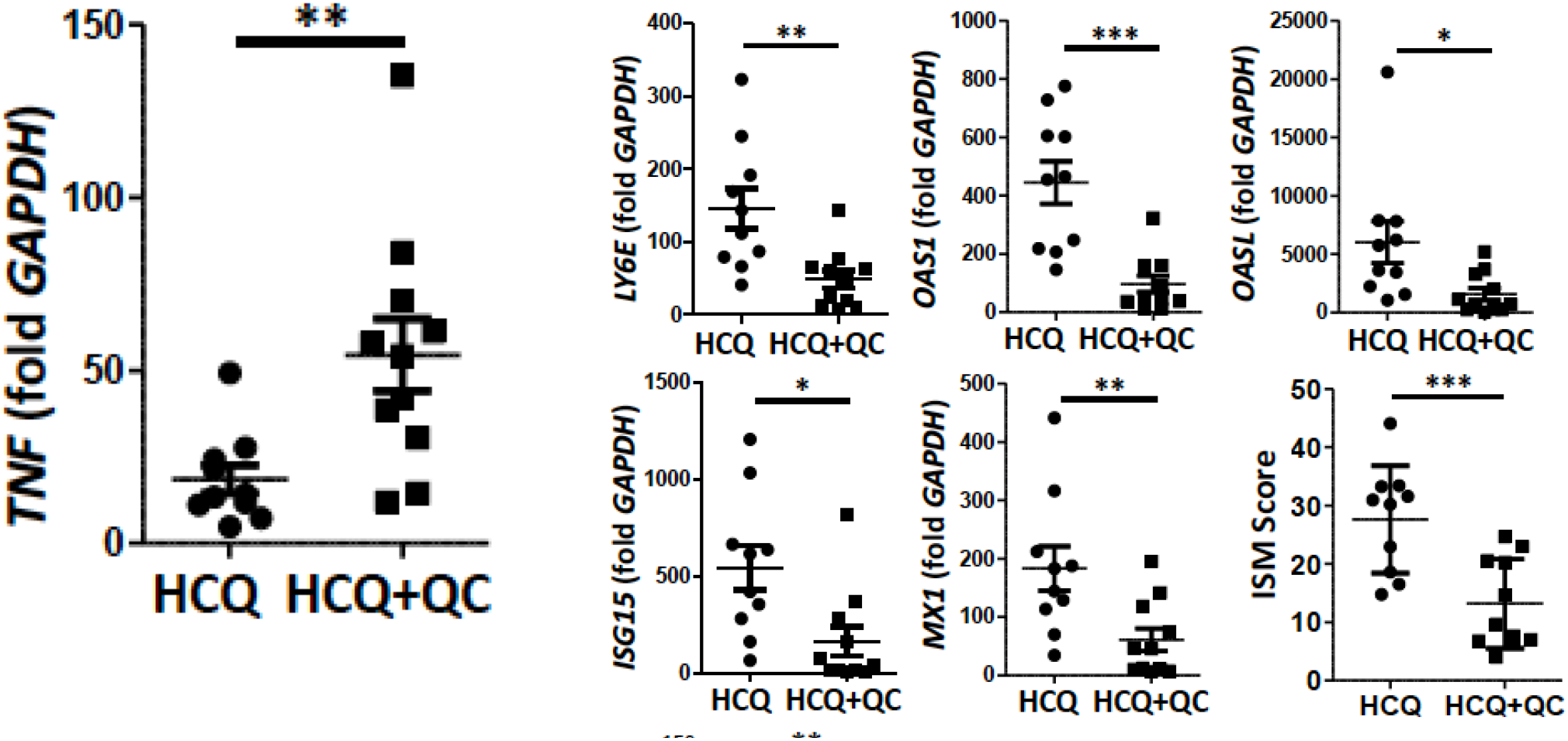


High levels of mDCs in lupus skin before therapy associate with subsequent need for quinacrine



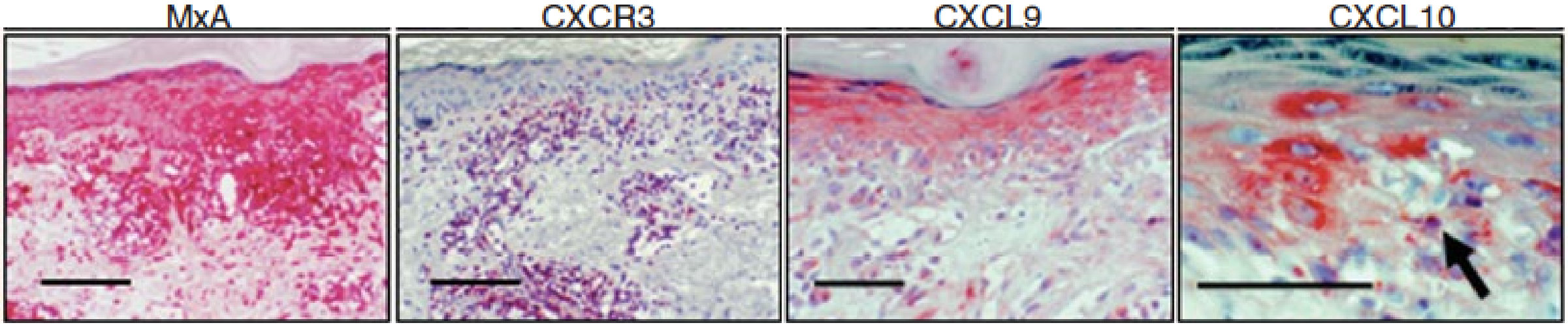
Zeidi M, Kim HJ, Werth VP. J Invest Dermatol 139:324-332, 2019

High levels of TNFα mRNA – but low levels of Type I IFN signature – in lupus skin before therapy associate with subsequent need for quinacrine



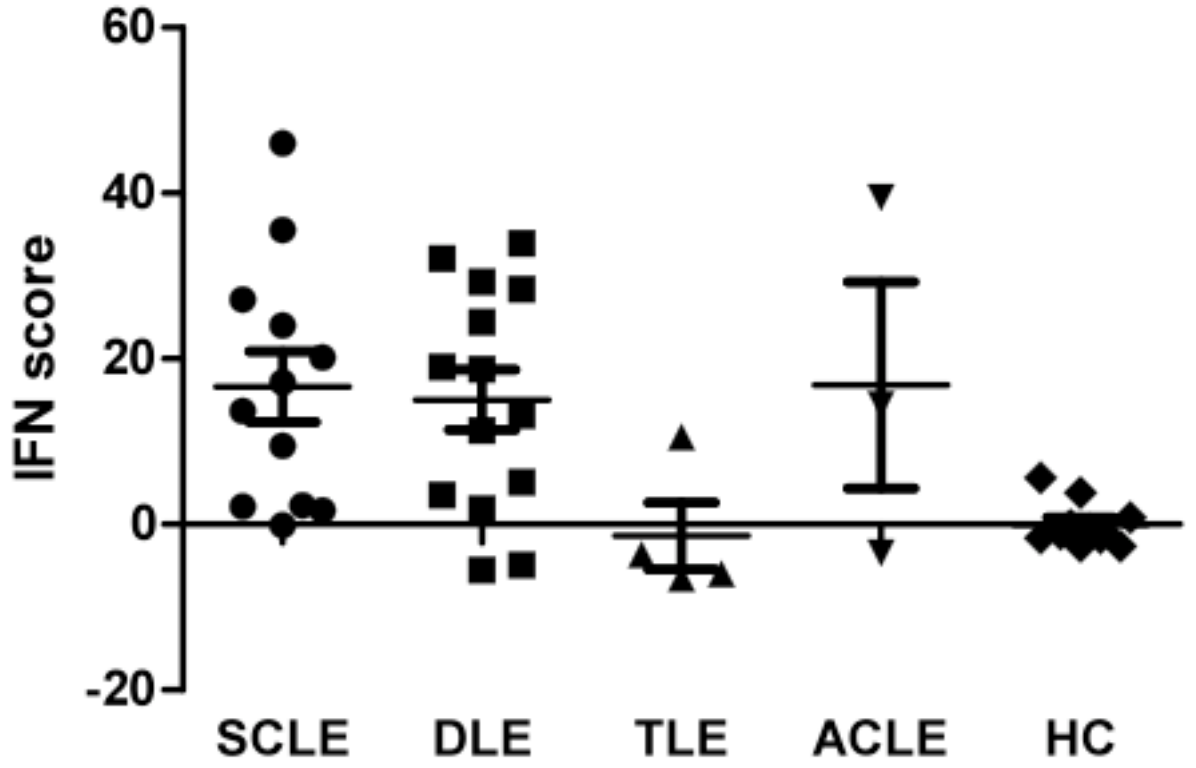
Zeidi M, Kim HJ, Werth VP. J Invest Dermatol 139:324-332, 2019

Interface Dermatitis



Wenzel, JID 128:3292, 2008

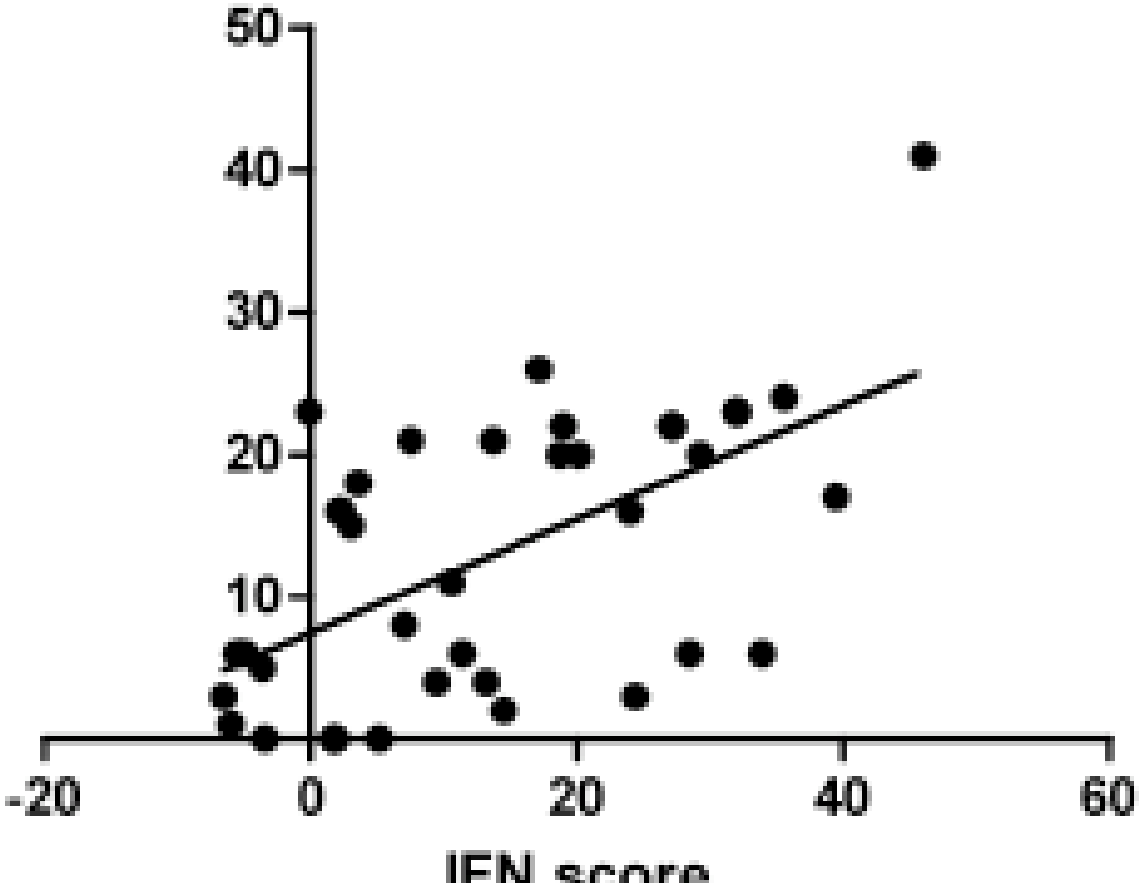
Interferon Signature in CLE PBMCs



Braunstein and Werth, Br J Dermatol 166:971-5, 2012

Correlation of IFN Signature with CLASI activity

CLASI Activity



n=36, r=0.6, p=0.0002

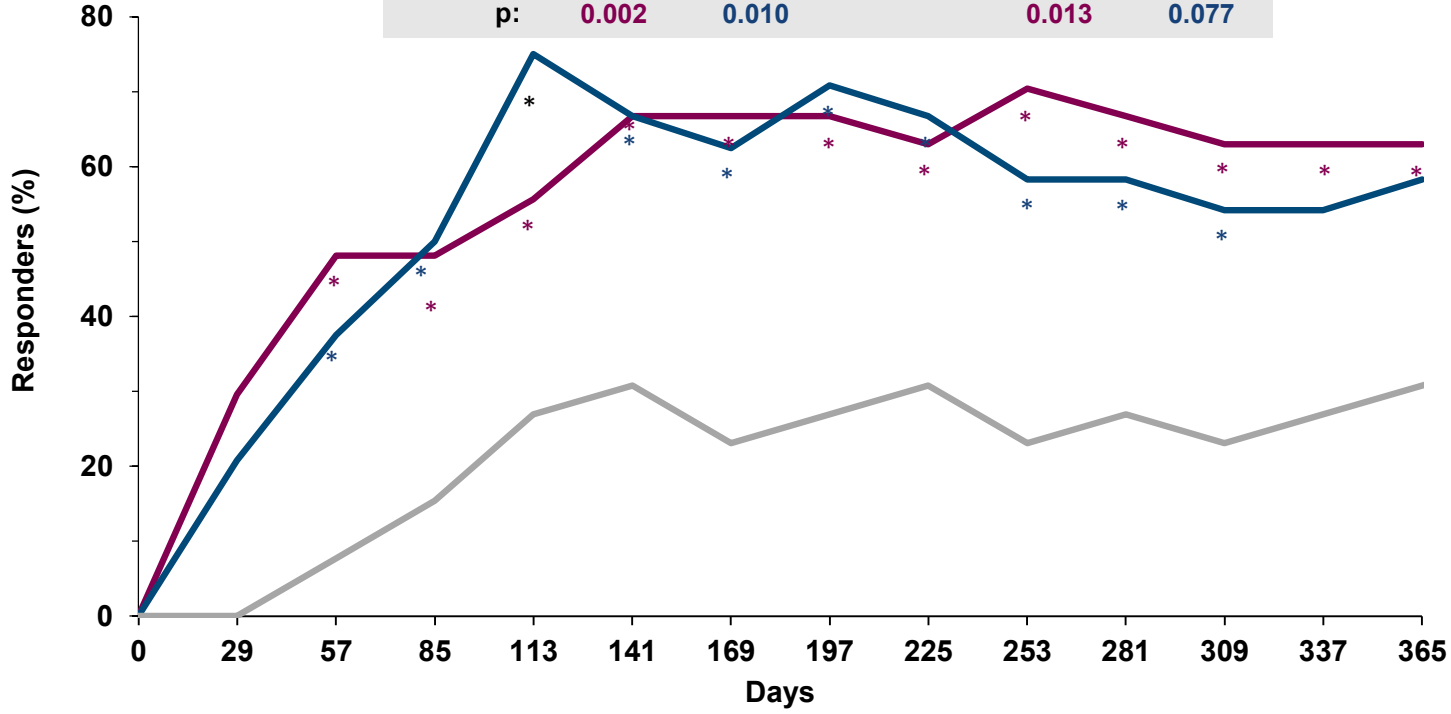
Braunstein and Werth, Br J Dermatol 166:971-5, 2012

Pathway-driven treatments for CLE

- Anti-IFN receptor monoclonal antibody (Anifrolumab)
- Anti-BDCA2
- Anti-pDC (ILT7)

At least 50% improvement in CLASI in patients with CLASI activity score ≥10 at baseline (N=77 [25%])

	Day 169		Day 365	
	300 mg	1000 mg	300 mg	1000 mg
Delta:	43.6%	39.4%	32.2%	27.5%
OR:	7.31	5.16	4.49	2.97
90% CI:	(2.56, 20.86)	(1.81, 14.73)	(1.67, 12.12)	(1.08, 8.19)
p:	0.002	0.010	0.013	0.077



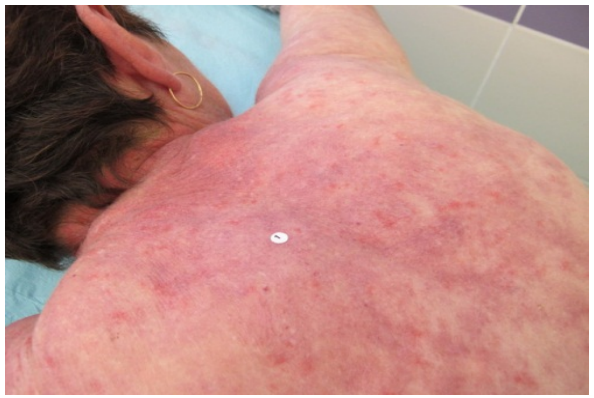
Delta = dosage vs. placebo

Placebo — Anifrolumab 300 mg Q4W — Anifrolumab 1000 mg Q4W

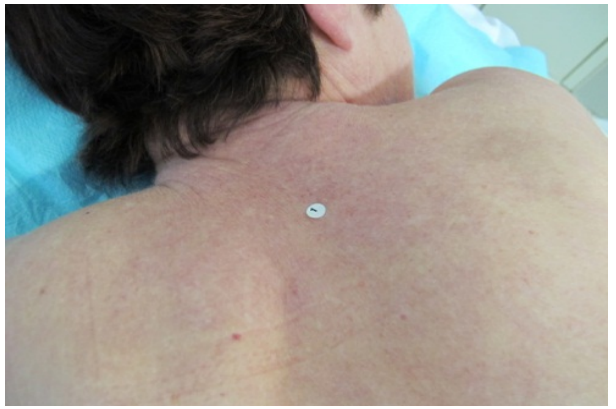
* p ≤0.05 compared with placebo

CI, confidence interval; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; mITT, modified intention-to-treat; OR, odds ratio

Day 1



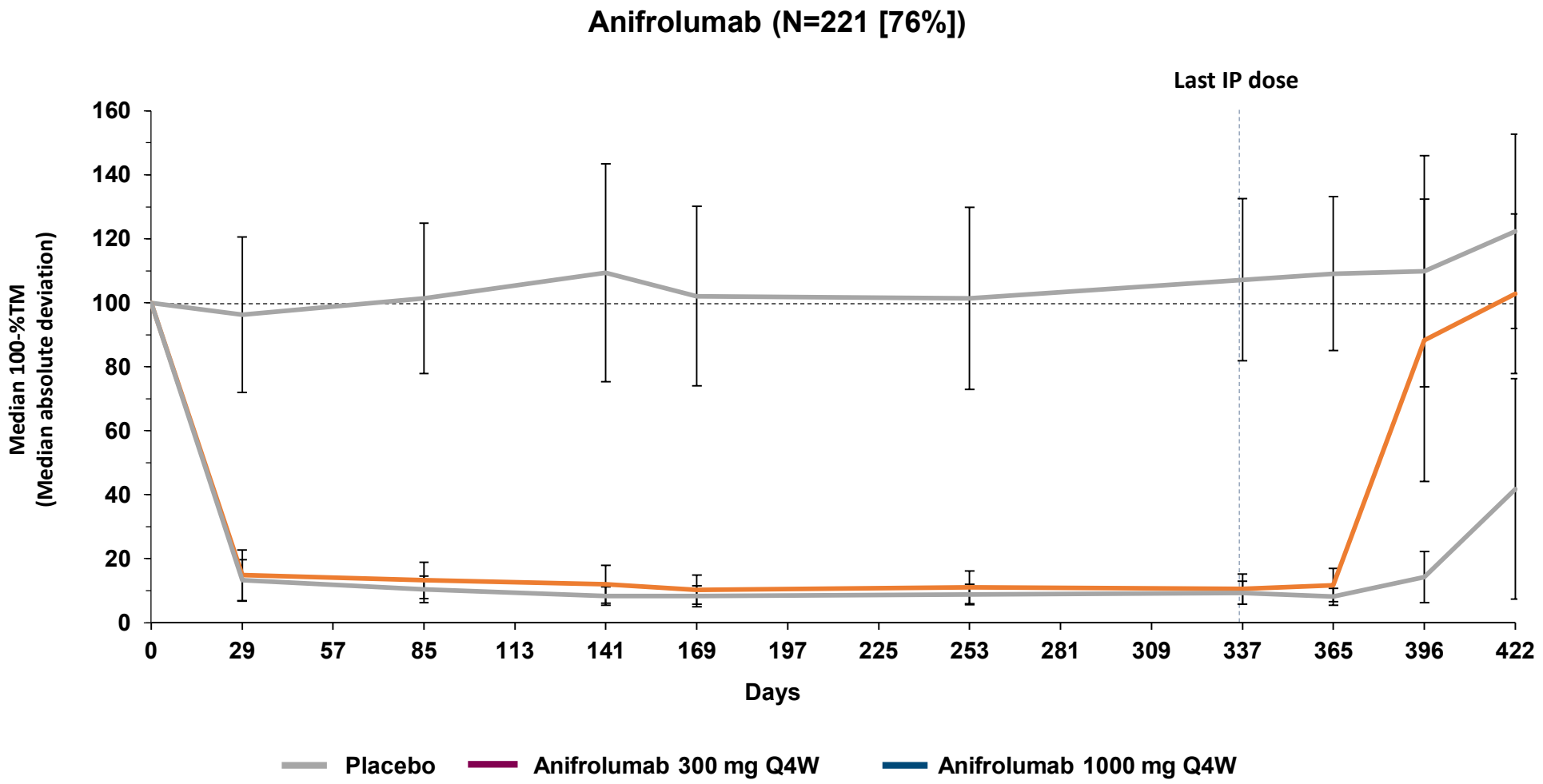
Day 281



Patient was receiving 300 mg/day anifrolumab

Furie R,et al. 69:376-386, 2017

Neutralization of 21-gene type I IFN signature

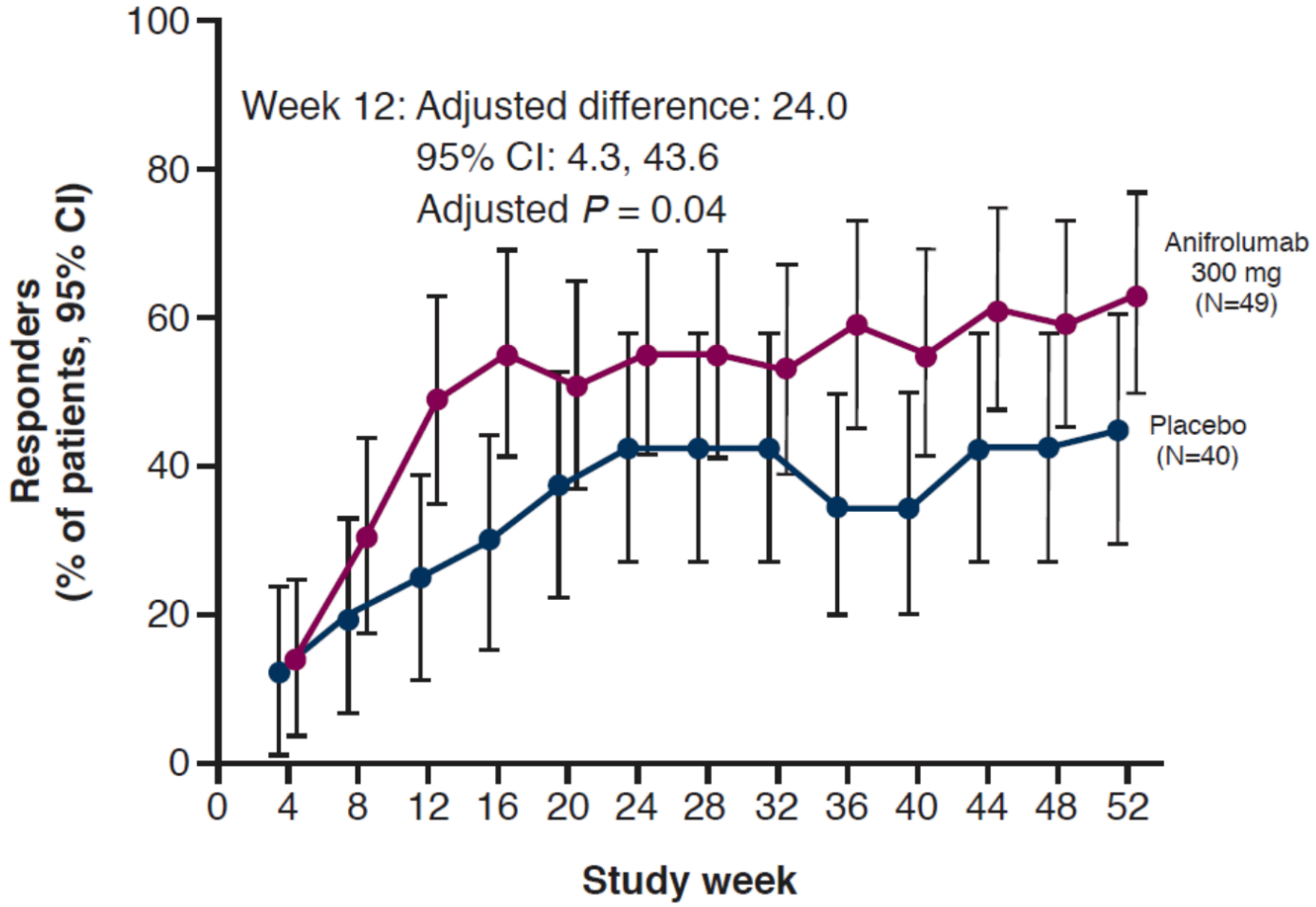


*Based on subjects with positive gene signature at baseline. Positive is defined as baseline 21-gene signature ≥2

IFN, interferon

Delta = dosage vs. placebo

Phase 3 trial: Twice as many responders in treatment arm (≥50% reduction in CLASI-A from baseline)



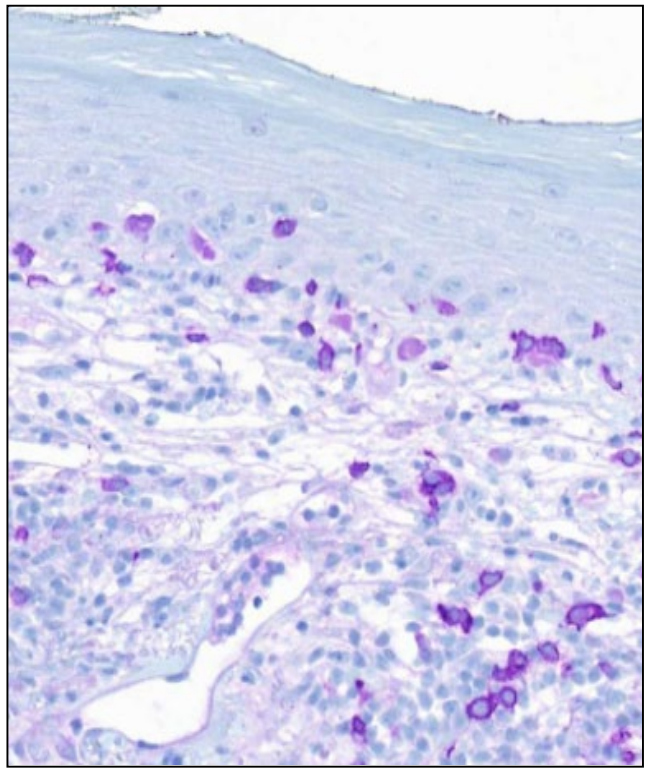
Morand E et al, NEJM 382:211-221, Jan 16, 2020.

Abbreviations: CI = confidence interval; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index.

Plasmacytoid dendritic cells (pDCs) are abundant in CLE

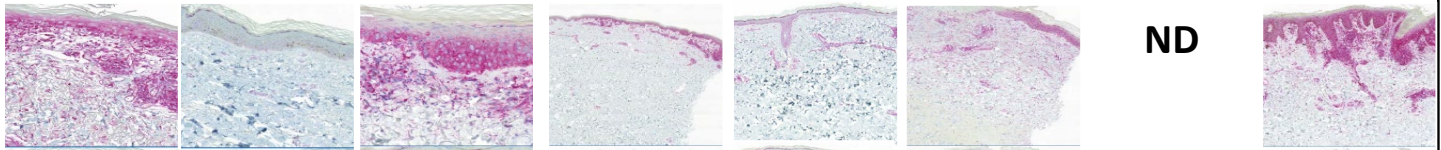
- In CLE, type I IFNs are made by pDCs, among other cell types, and amplify lesional inflammation
- pDCs activated by TLR7 and TLR9 agonists (RNA, DNA)
  - Induce IFN-inducible chemokines
  - Recruit T cells into skin

pDCs (BDCA2+)



Rheumatology.org, Grönhagen & Nyberg Indian Dermatol Online J 2014, Lee & Sinha Autoimmunity 2006, Chang & Werth Curr Rheumatol Rep 2011, Braunstein et al., Br J Dermatol. 2012;166(5):971-5; Dall'Era et al. Ann Rheum Dis. 2005;64(12):1692-7

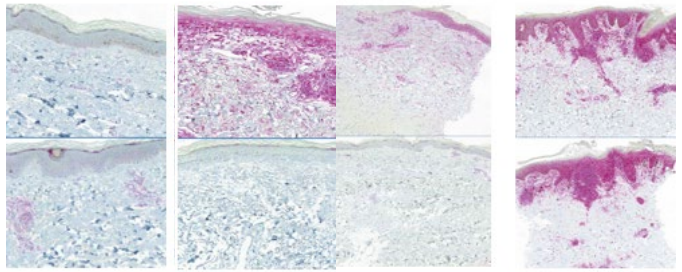
BIIB059 treated subjects have reductions in CLASI-A and skin IFN-induced MxA expression

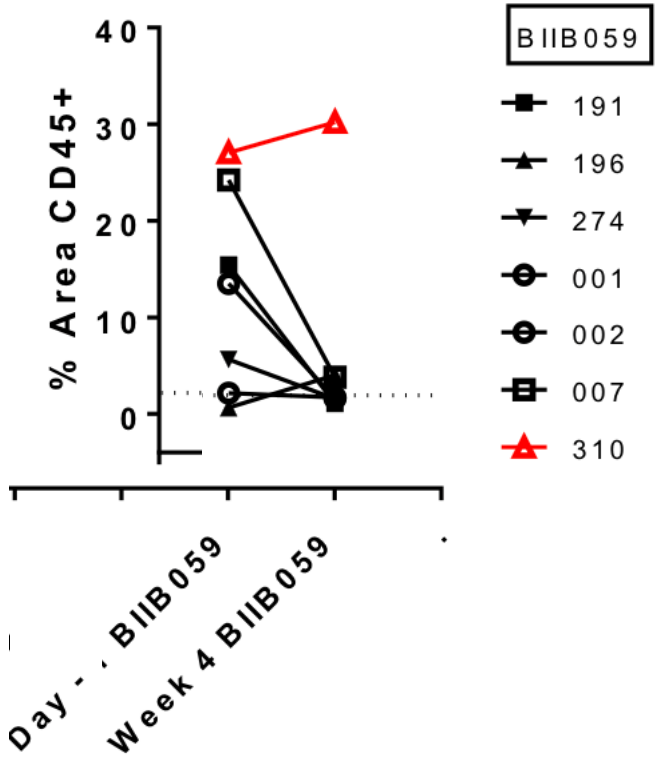
		Subject / CLE Subtype							
	Timepoint	191 SCLE	196 ACLE	274 ACLE	001 DLE	002 ACLE	007 ACLE	185 DLE	310 DLE
MxA area Epidermis	D -1 Week 4	58.4% 0.1%	1.2% 0.4%	21.0% 2.2%	34.3% 1.0%	23.1% 2.4%	26.4% 3.6%	ND ND	57.5% 78.4%
MxA histology	Day -1							ND	
	Week 4							ND	
CLASI-A score	D -1 Week 4 Week 12	9 0 0	5 0 0	6 2 4	10 6 6	14 8 2	18 8 7	4 5 4	17 15 18
CLASI response+		R	R	R	R	R	R	NR	NR

+ Response defined as a ≥4-point reduction from baseline in CLASI-A at either Week 4 or Week 12.
MxA is calculated by measuring the percent area of immunoreactivity as a ratio of total epidermal area

Furie R, et al. J Clin Invest 129:1359-1371, 2019

BIIB059 treated subjects have reductions in CLASI-A and skin IFN-induced MxA expression that correlates with decreases in skin inflammation

	Timepoint	196 ACLE	191 SCLE	007 ACLE	310 DLE
MxA area Epidermis	D -1	1.2%	58.4%	26.4%	57.5%
	Week 4	0.4%	0.1%	3.6%	78.4%
MxA histology	Day -1				
	Week 4				
CLASI-A score	D -1	5	9	18	17
	Week 4	0	0	8	15
	Week 12	0	0	7	18
CLASI response+		R	R	R	NR



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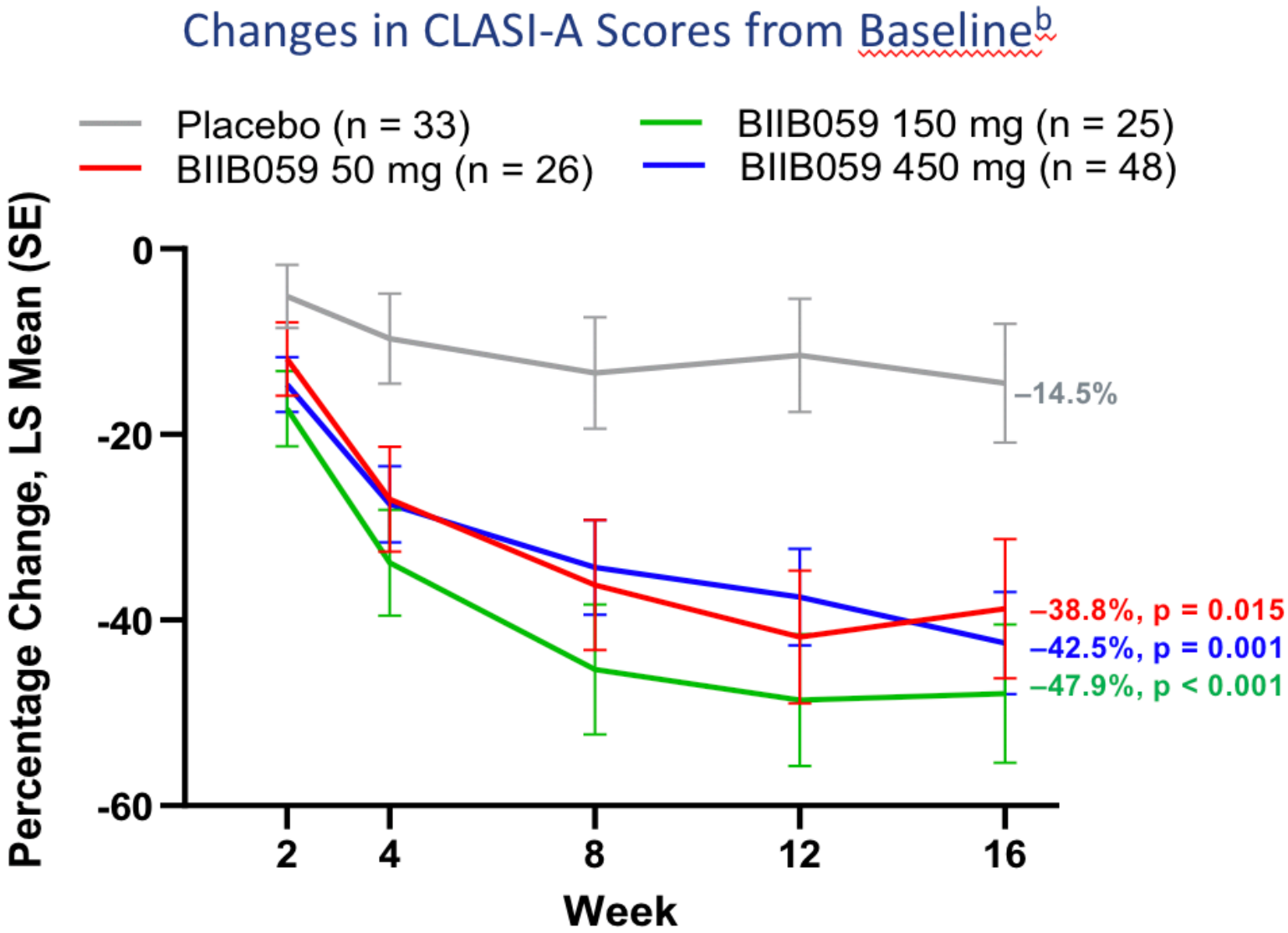
MxA is calculated by measuring the percent area of immunoreactivity as a ratio of total epidermal area

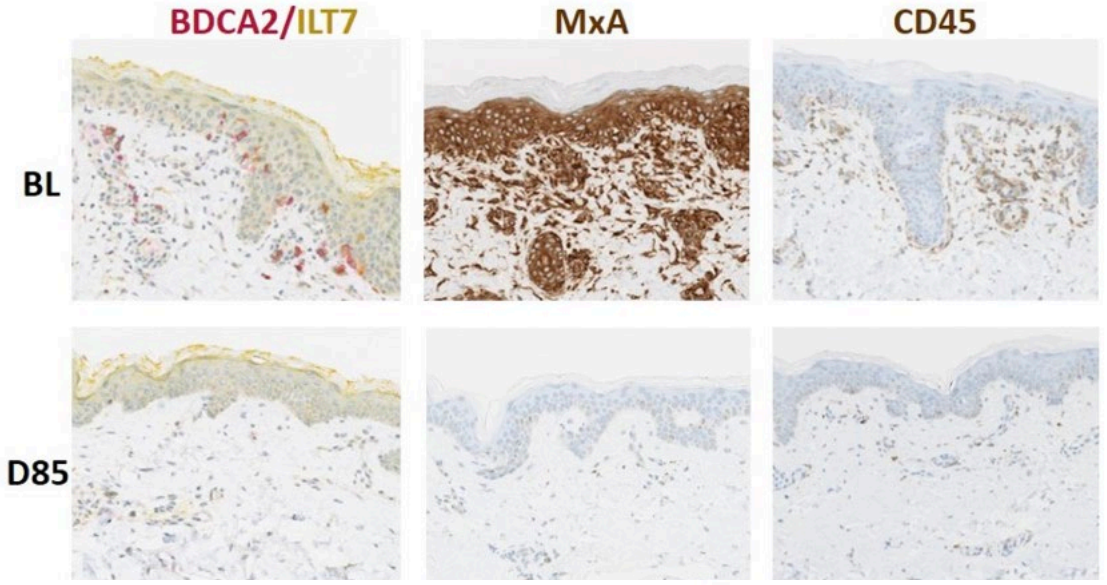
Furie R, et al. J Clin Invest 129:1359-1371, 2019

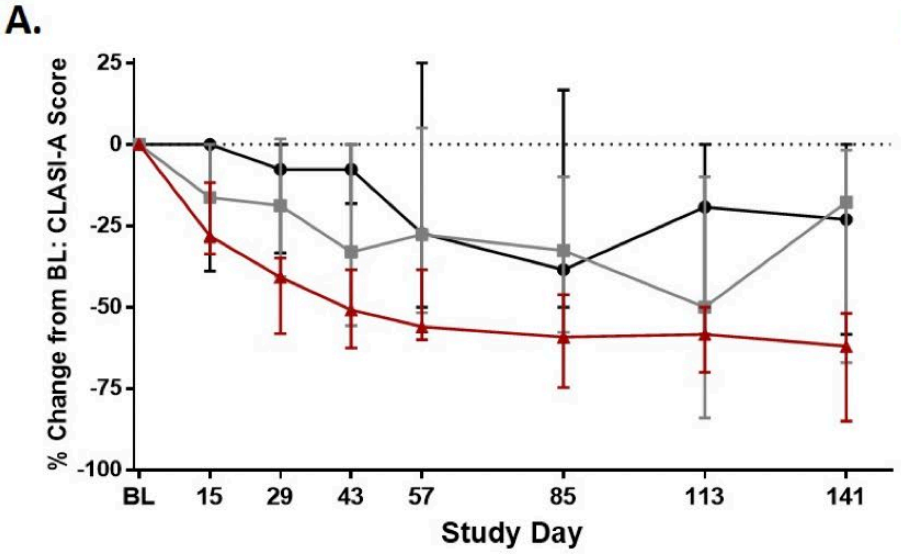
Phase 2 trial of Anti-BDCA2 (BIIB059) Antibody: Skin outcome

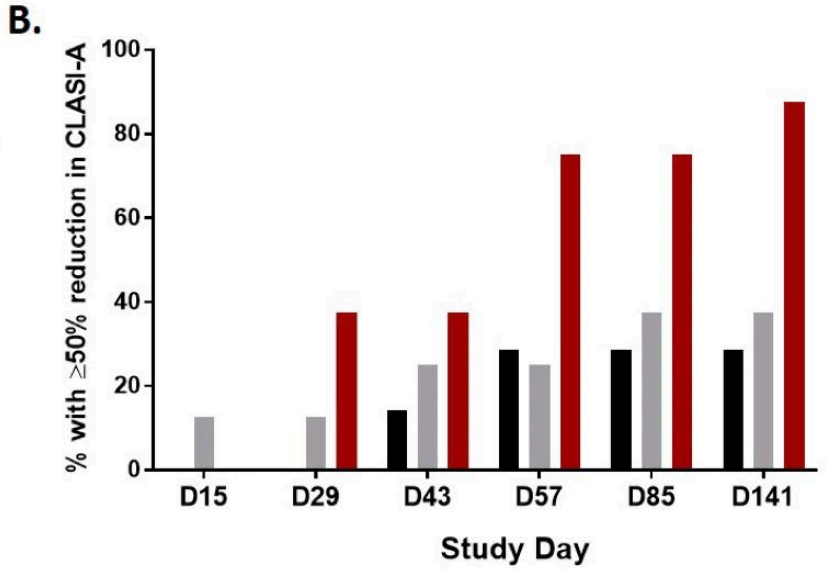


Werth VP, et al. Arthritis Rheumatol. 2020; 72 (suppl 10).

Phase 1 Anti-pDC (ILT7)





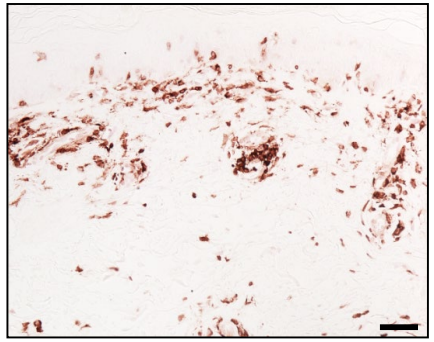


Scientific Approaches

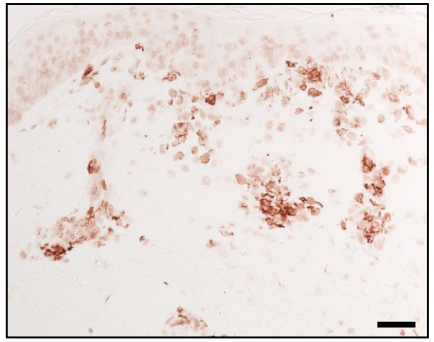
- CyTOF: Cell markers, correlate with activated pathways, cytokines
- Transcriptomics (microarray, bulk RNAseq, single cell RNAseq),
- Digital spatial profiling: gene expression in addition to protein-level expression
- Epigenomic profiling (ncRNA, miRNA, histone modifications, CpG DNA methylation)
- Lead to awareness of new cell subsets that are important drivers of disease heterogeneity and response to therapy
- Needed for personalized medicine
- Targeted animal model

Dermatomyositis

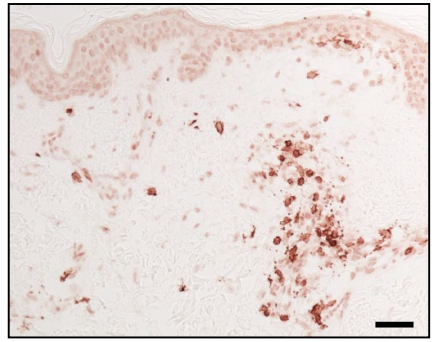
(a) CD4



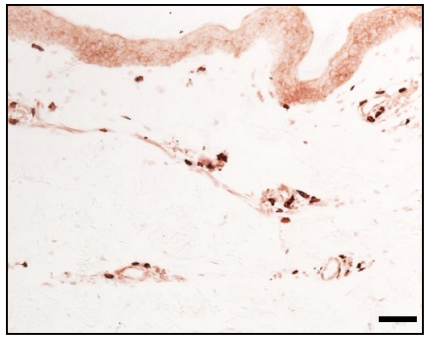
(b) CD11c



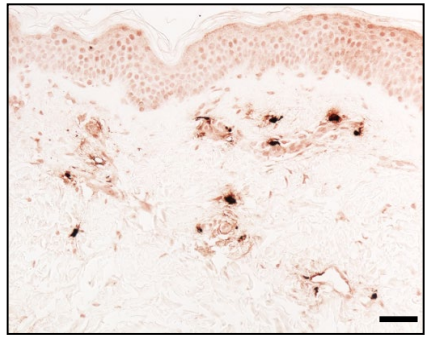
(c) CD69



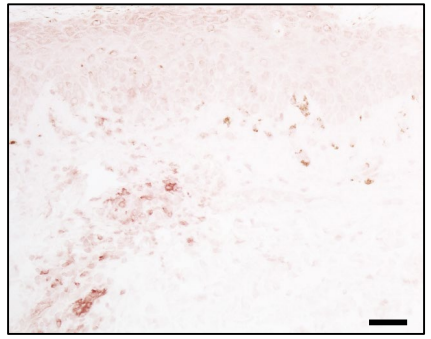
(d) CD8



(e) Tryptase



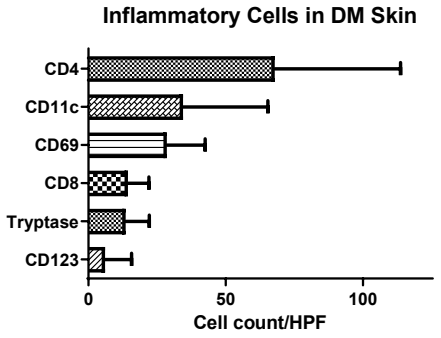
(f) CD123



(g) Mouse isotype

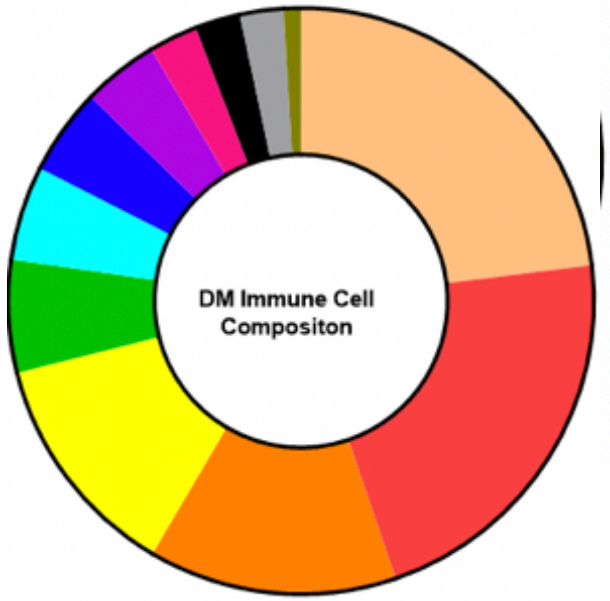
(h) Rabbit isotype

(i)

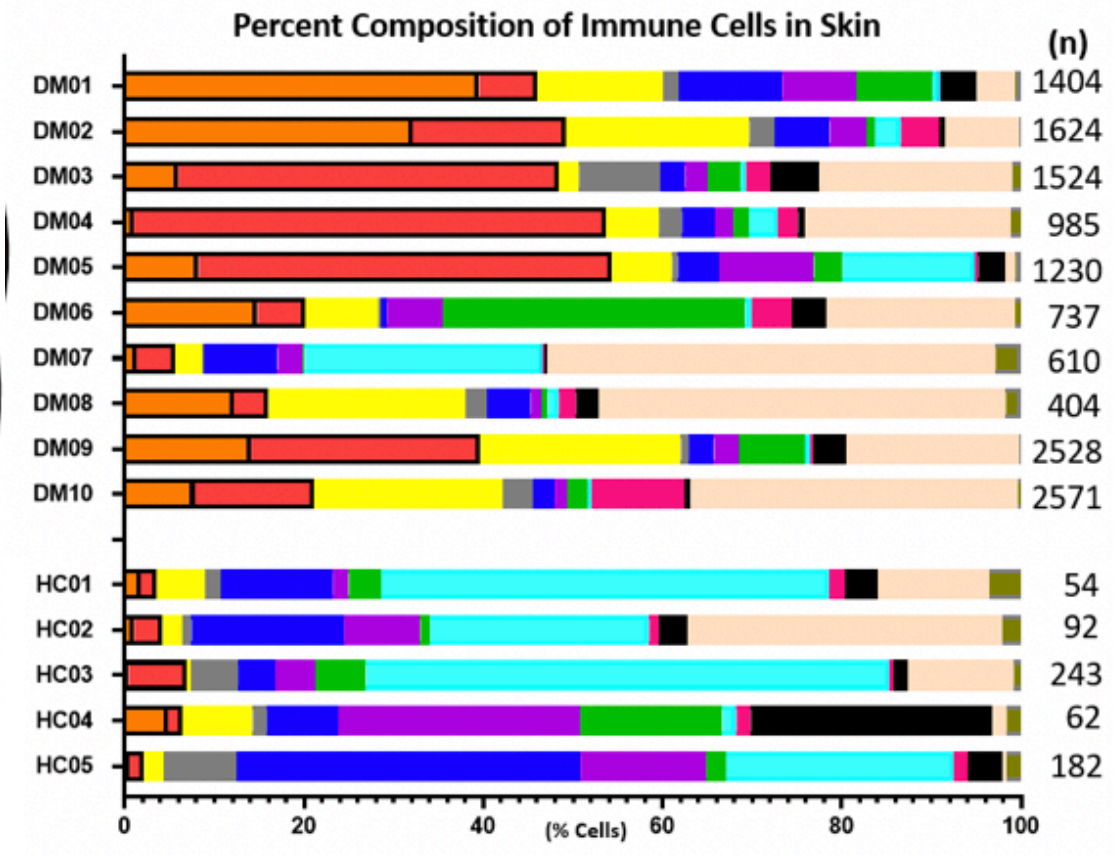


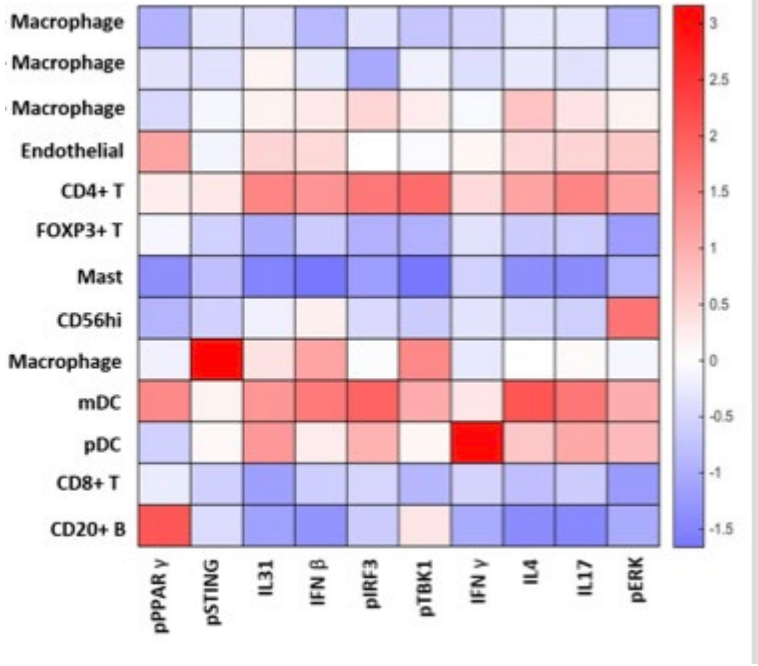
Chen K, et al. J Invest Dermatol, in press.

Dermatomyositis Immune Cell Composition



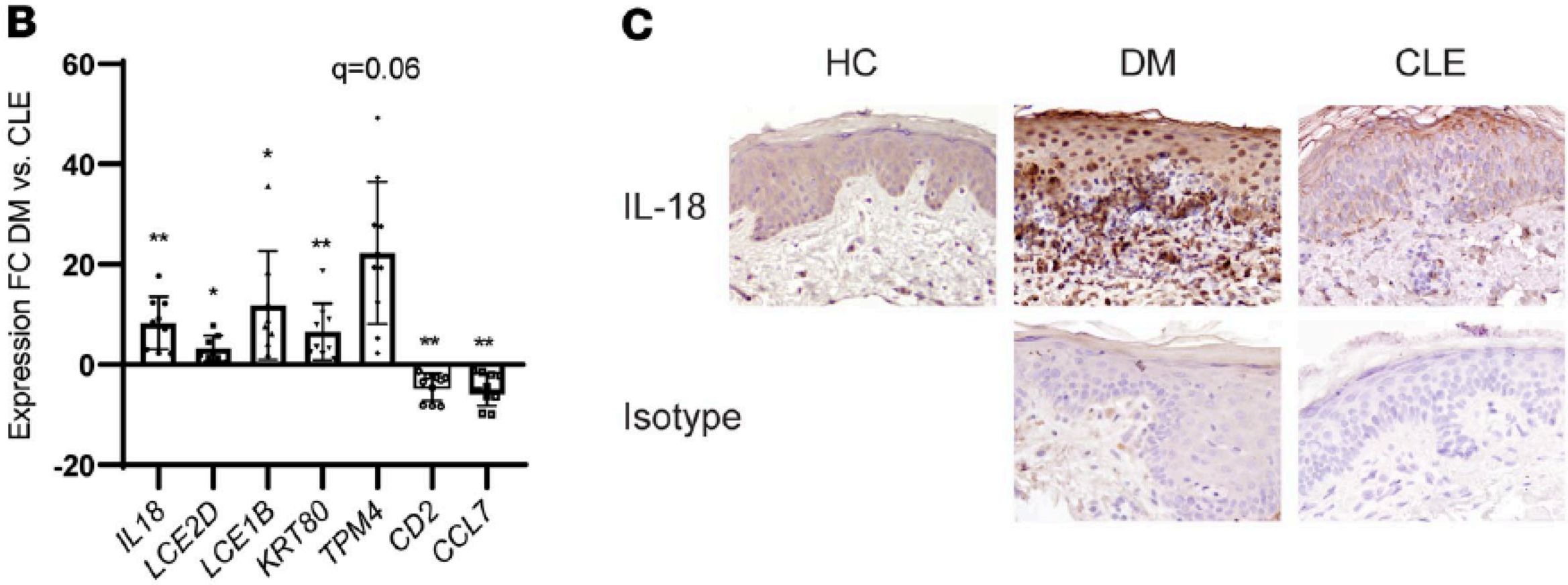
- CD14+ Macrophage
- CD11c+ mDC
- CD14+CD16+ Macrophage
- CD4 T Cell
- MAC387+ Macrophage
- Mast Cell
- CD8 T Cell
- FOXP3+ T Cell
- pSTING+ Macrophage
- BDCA2+ pDC
- CD56+ Cell
- CD20+ B Cell





Patel J et al, J Invest Dermatol, in press.

Dermatomyositis vs Cutaneous LE



Tso LC et al, JCI Insight 5:e139558, 2020

Recommendations

- Include impact on QoL as methodology for determining funding in autoimmune skin diseases
- Continue to expand focus of research funding to include skin aspects of systemic autoimmune diseases
  - Until recently quite understudied
- Apply technologic advances to study skin and blood in autoimmune skin diseases
- Consortium helpful to bring centers together to study autoimmune skin diseases
  - Possible models: Vasculitis Clinical Research Consortium; Accelerating Medicines Partnership: RA and SLE

Training and Centers

- Overall need for funding of fellowships and career development awards to develop and replenish workforce in autoimmune skin diseases.
- CTSA helpful for needed translational focus for autoimmune diseases