Atopic Dermatitis (AD) Models

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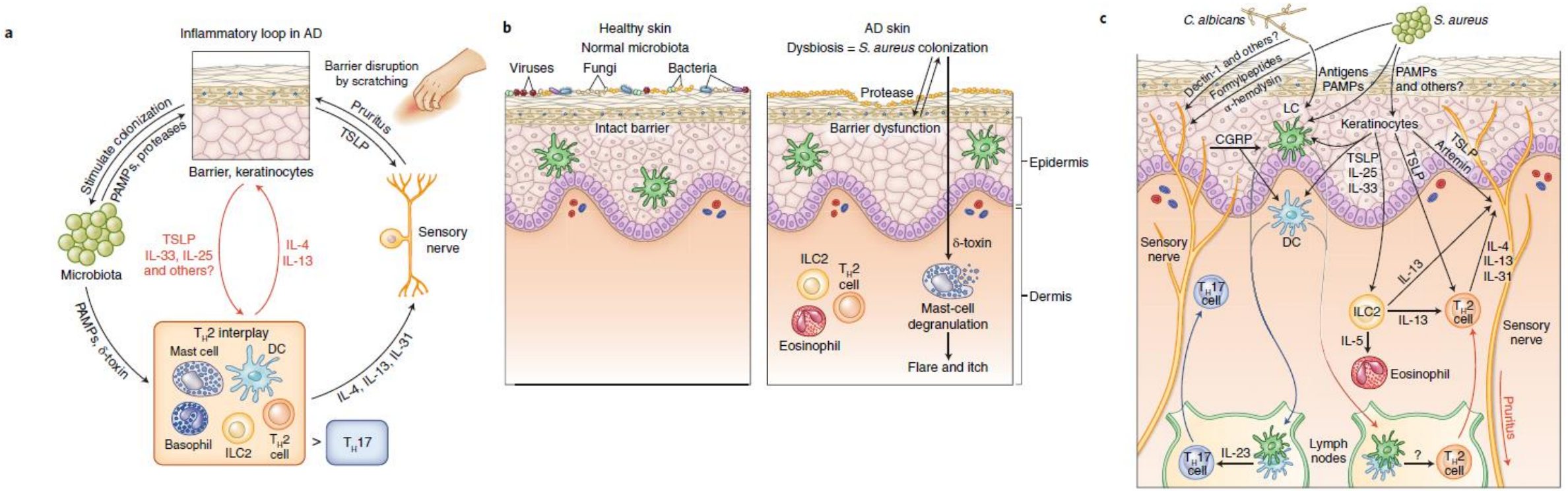
Outline

- **Background**
  - Molecular Mechanism of Atopic Dermatitis (AD)
  - Disease-Modifying Atopic Dermatitis Drugs in Clinic
- **Development of Atopic Dermatitis Model in Mice**
  - DNFB-induced Atopic Dermatitis Model in Mice
  - DNCB-induced Atopic Dermatitis Model in Mice
  - MC903-induced Atopic Dermatitis Model in Mice
- **Development of DNCB-Induced Atopic Dermatitis Model in Beagle Dogs**
  - Model summary
  - In-life results
  - Histopathology results

Molecular Mechanism of Atopic Dermatitis (AD)

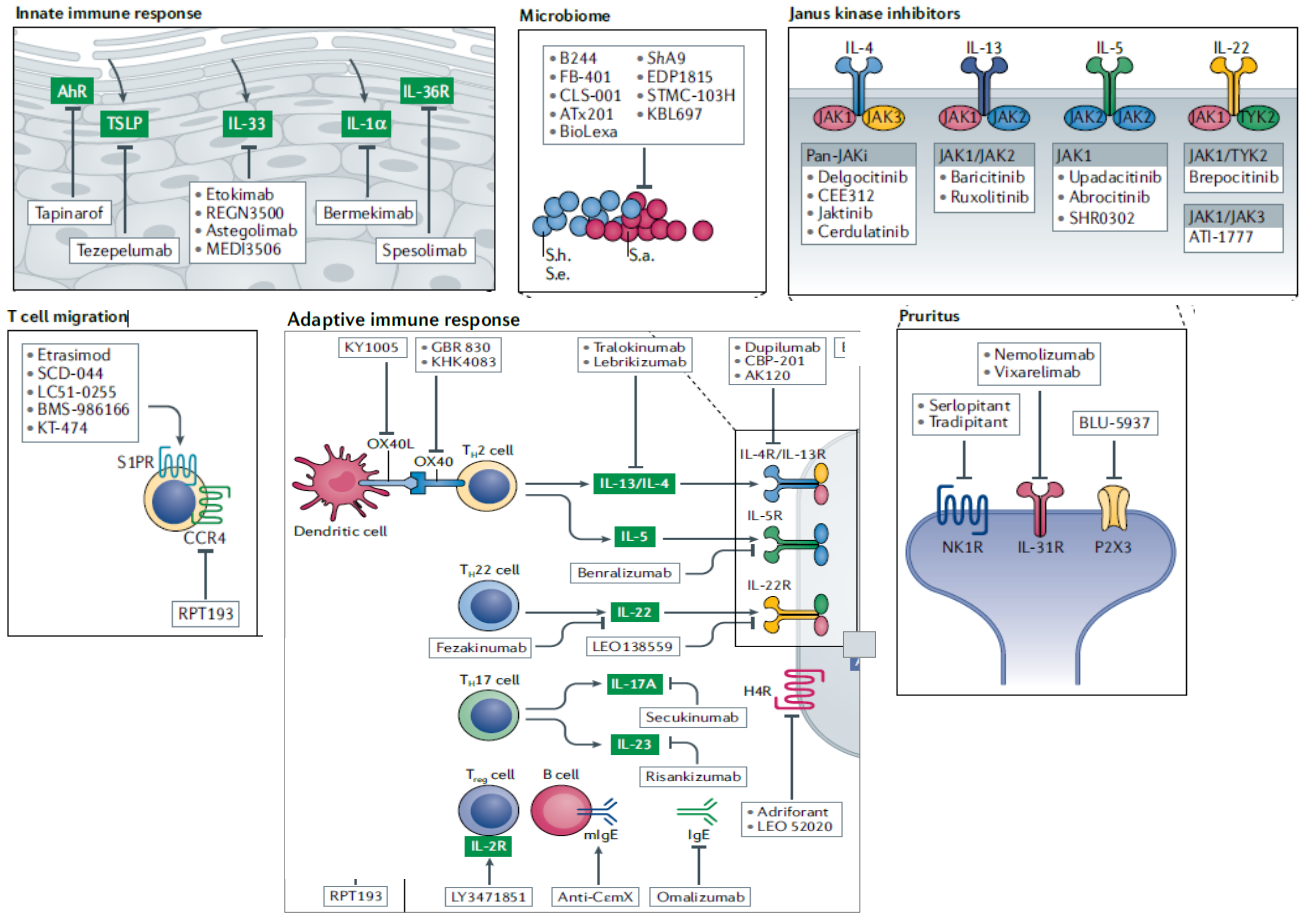
- **Atopic dermatitis (AD) is a chronic inflammatory skin disease. AD is characterized by recurrent eczematous skin lesions (red patches with blistering and crusting that can lead to scaling, cracking and thickening of the skin) and intense itch and discomfort.**



Dainichi T. et al. (2018) Atopic Dermatitis s. Nat Immunol. Primers doi:10.1038/s41590-018-0256-2

Disease-Modifying Atopic Dermatitis Drugs in Clinic

- **In addition to regulatory approval for the IL-4Ra inhibitor dupilumab, the anti-IL-13 inhibitor tralokinumab and the JAK1/2 inhibitor baricitinib in Europe, now more than 70 new compounds in development.**

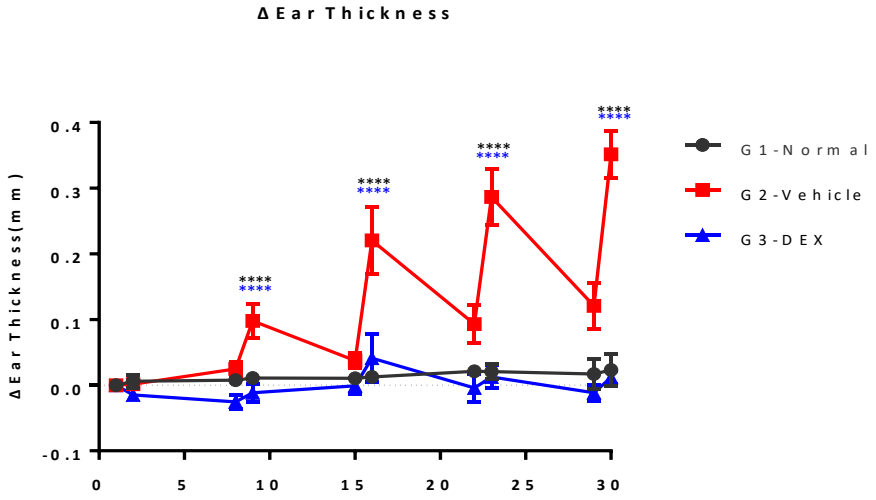


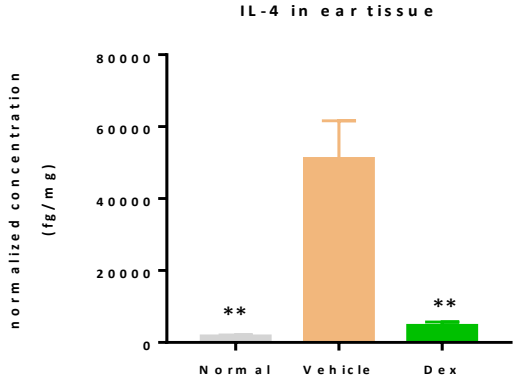
Bieber T. et al. (2022) Atopic dermatitis. Nat. Rev. Dis. Primers doi:10.1038/s41573-021-00266-6

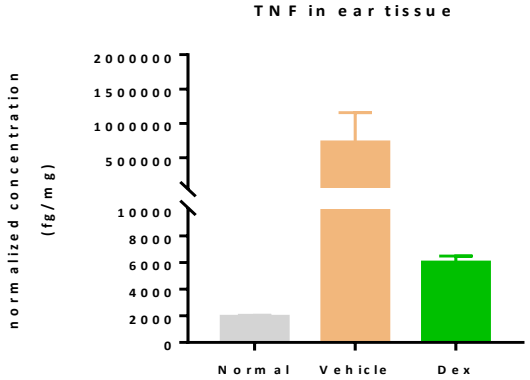
■ **Current Therapeutic Pipeline for Atopic Dermatitis**

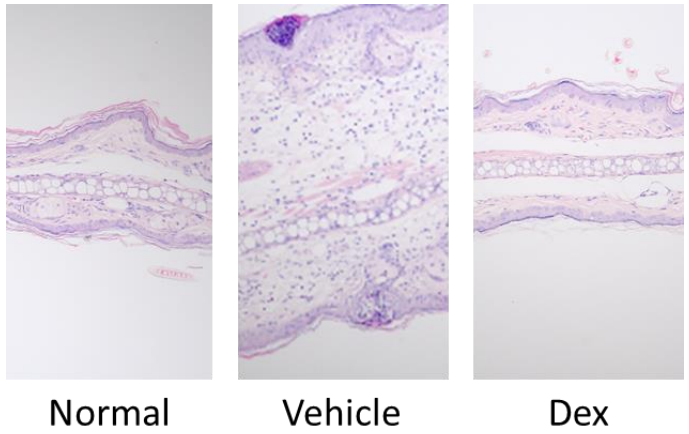
Strategy	Drug type and mode of application	Agent/company	Mode of action/target	Clinical development phase in atopic dermatitis	Clinical trial ID
Modulating the microbiome	Bacterial strains — topical	B244 (AOBiome)	Nitric oxide donor	IIb	NCT04490109
		ShA9 (NIAID)	Targeted microbiome transplant	I/IIa	NCT03151148
		FB-401 (Forte Biosciences)	Bacterial replacement, anti-inflammation via TLR5 and TNFR activation	IIb	NCT04504279
	Small molecule — topical	CLS-001/omiganan (Cutaneous Life Sciences)	Cell membrane enhancer	II	NCT02456480
		ATx201/niclosamide (Union Therapeutics)	Protonophore activity	II	NCT04339985
	Bacterial strains — oral	EDP1815 (Evelo)	Modulation of systemic inflammation	Ib	NCT03733353
		STMC-103H (Siolta therapeutics)	Immunomodulation via microbiome manipulation	Ib	NCT03819881
Targeting the innate immune response	Small molecule — topical	Tapinarof/benvitimod (Dermavant)	AhR agonist	IIb	NA
	Biologic — injection	Tezepelumab (Amgen/AstraZeneca)	TSLP	IIa	NCT02525094
		Etokimab (AnaptysBio)	IL-33	IIa	NCT03533751
		REGN3500 (Regeneron)	IL-33	IIa	NCT03738423
		Astegolimab (Genentech)	IL-33	IIa	NCT03747575
		MEDI3506 (MedImmune)	IL-33	IIa	NCT04212169
		Bermekimab (Janssen)	IL-1α	IIa	NCT03496974
		Spesolimab (Böhringer Ingelheim)	IL-36R	IIa	NCT03822832
Inhibiting Janus kinases	Small molecule — topical	Delgocitinib (Japan Tobacco/LEO)	Pan-JAK	IIb in EU, approved in Japan	NCT03725722
		Ruxolitinib (Incyte)	JAK1/JAK2	III	NCT03745638, NCT03745651
		Cerdulatinib (RVT/DMVT502) (Dermavant)	Pan-JAK/SYK	Ib	NA
		Brepocitinib (Pfizer)	JAK1/TYK2	IIb	NCT03903822
		ATI-1777 (Aclaris)	JAK1/JAK3	II	NCT04598269
		CEE321 (Novartis)	Pan-JAK	I	NCT04612062
		Jaktinib (Suzhou Zeigen Biopharma)	Pan-JAK	IIa	NCT04539639
		SHR0302 (Reistone Biopharma)	JAK1	II	NCT04717310
	Small molecule — oral	Baricitinib (Lilly)	JAK1/JAK2	Approved in EU for adults, staggered paediatric programme ongoing	NCT03952559
		Upadacitinib (AbbVie)	JAK1	III, staggered paediatric programme ongoing	NCT03646604
		Abrocitinib (Pfizer)	JAK1	III, staggered paediatric programme ongoing	NCT03627767
		SHR0302 (Reistone Biopharma)	JAK1	II	NCT04162899
Targeting itching	Biologic — injection	Nemolizumab (Galderma)	IL-31	III	NCT03989349, NCT03985943
		Vixarelimab (Kiniksa Pharma)	OSMRβ	IIa/b	NCT03816891
	Small molecule — oral	Serlopitant (Menlo)	NK1R	II	NCT02975206
		Tradipitant (Vanda)	NK1R	II	NCT03568331
		BLU-5937 (Bellus)	P2X3	II	NCT04693195

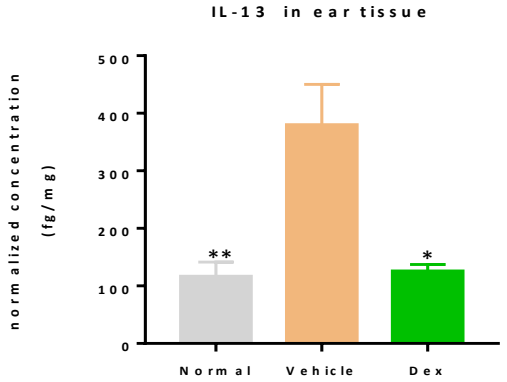
DNFB-induced Atopic Dermatitis Model in Mice

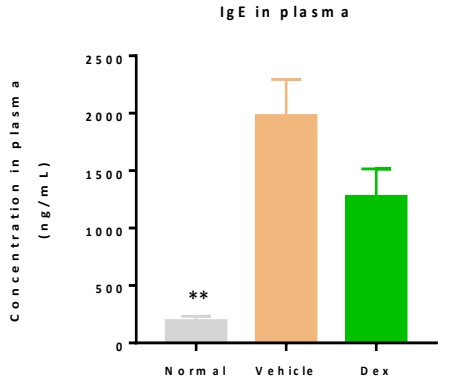




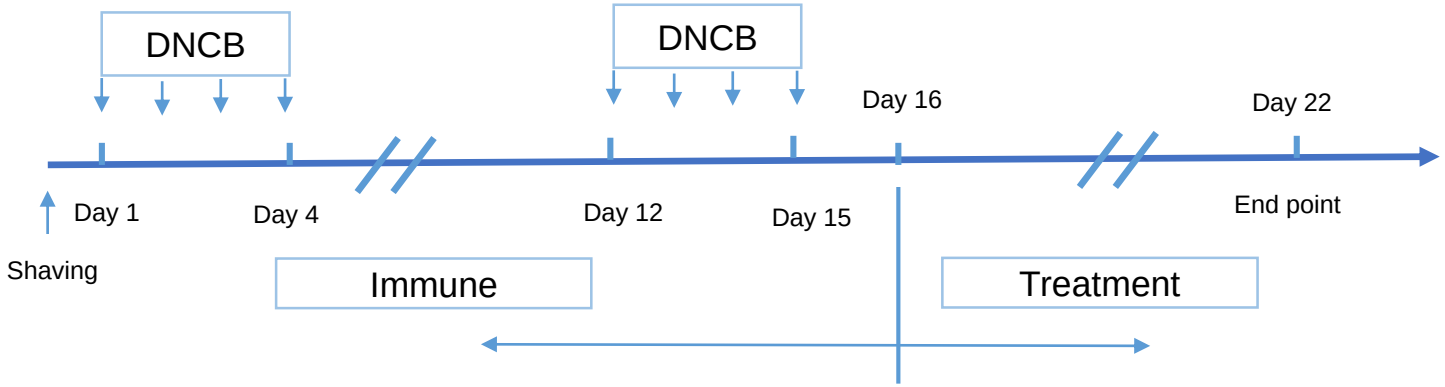


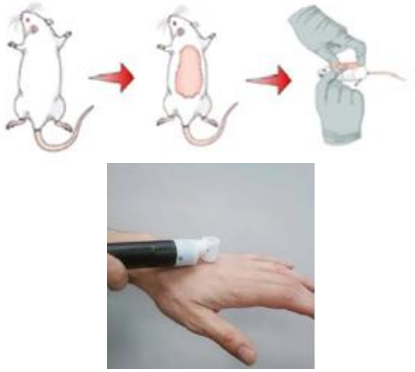




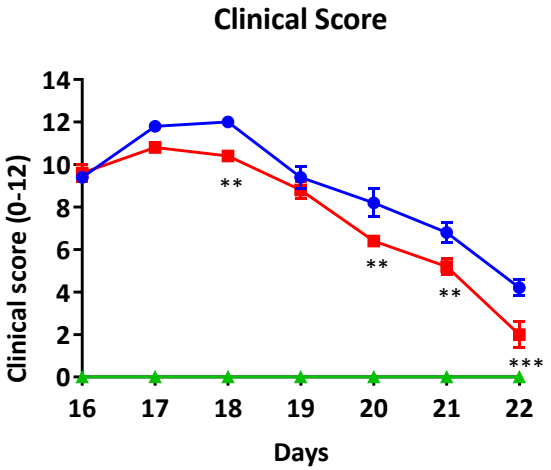


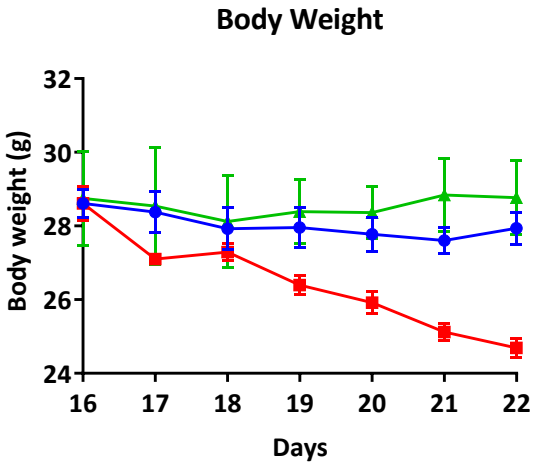
DNCB-induced Atopic Dermatitis Model in Mice

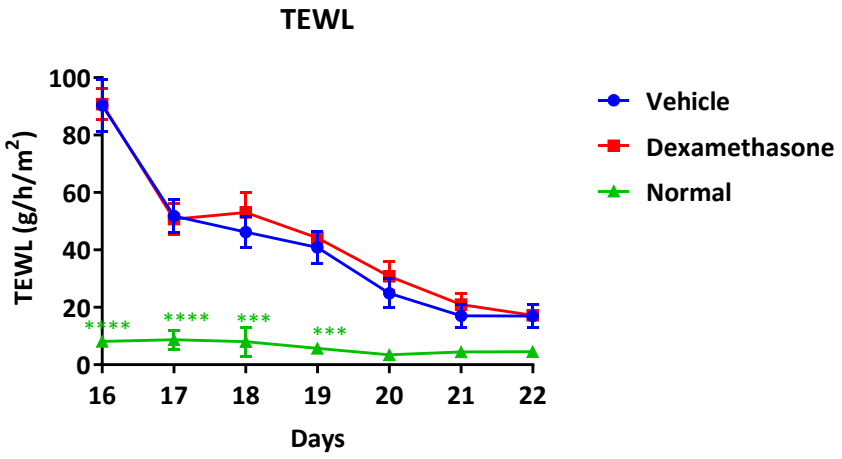




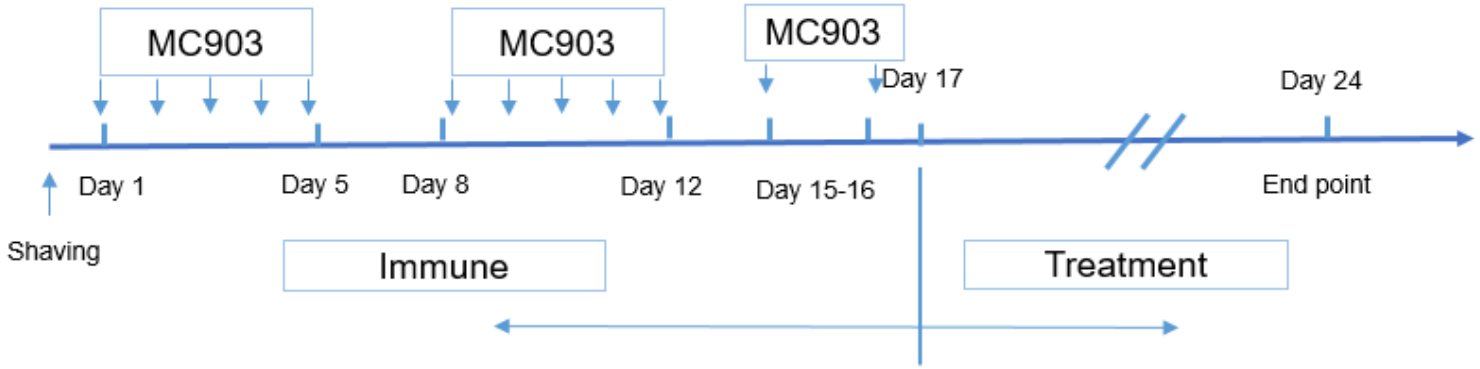
Tewameter
TM300

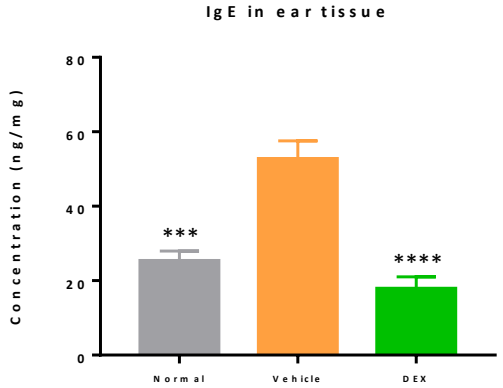


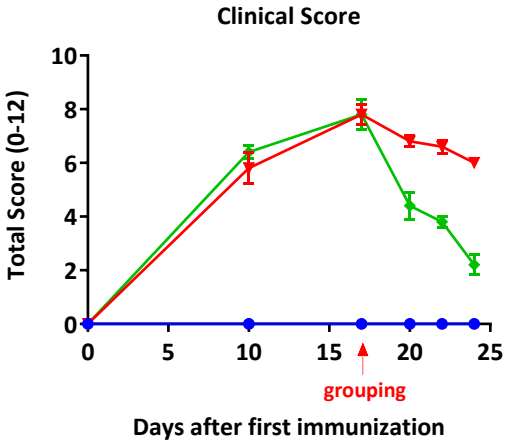


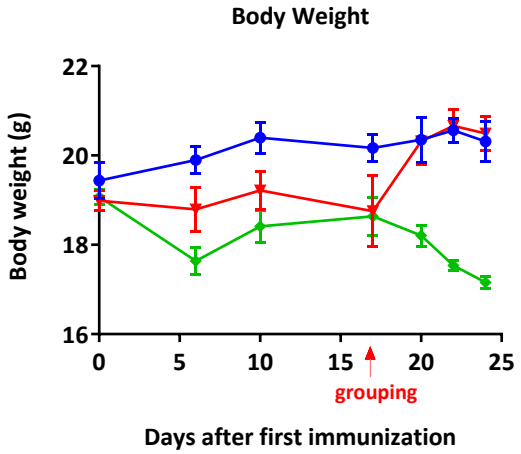


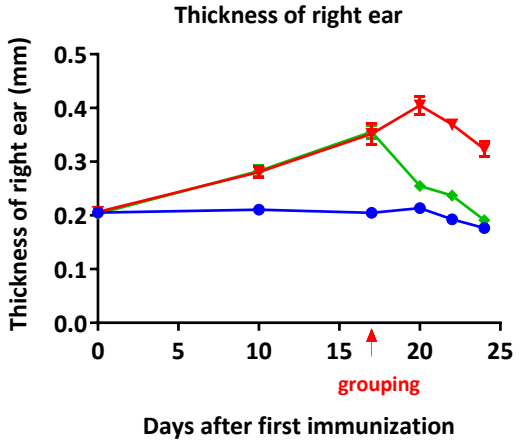
MC903-induced Atopic Dermatitis Model in Mice

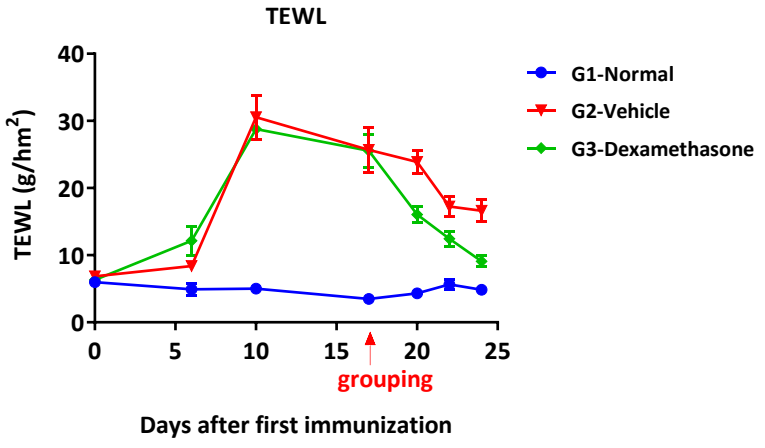












DNCB-Induced Atopic Dermatitis Model in Beagle Dogs

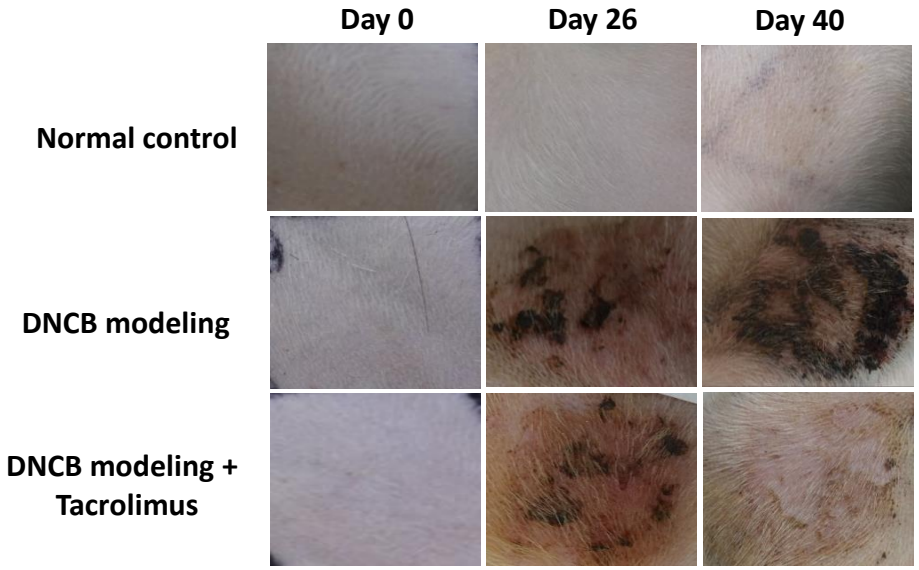
Model Summary

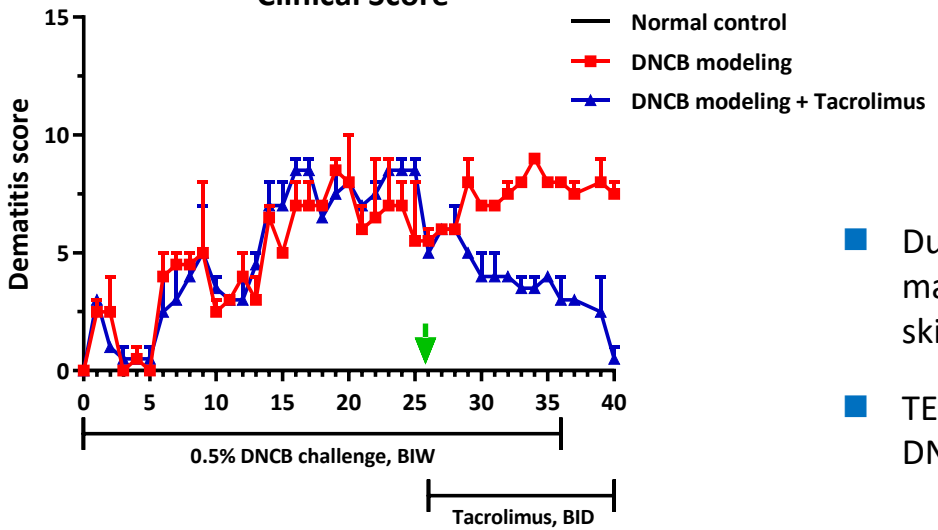
Animal species	Modeling method	Modeling time	Group	Read-outs
Beagle dog, Male	● High concentration DNCB skin application for sensitization ● Low concentration DNCB skin application to induce AD ● High safety, stable molding effect ● Validated positive control	6 weeks	● Normal control ● DNCB modeling ● DNCB modeling + positive control ● DNCB modeling + test article	● Body weight measurement and cage-side observations ● TEWL measurement ● CBC, serum IgE ● PK sampling and tissue collection ● PD marker evaluation ● Histopathology, pathology scoring ● Statistical analysis for efficacy

DNCB-Induced Atopic Dermatitis Model in Beagle Dogs

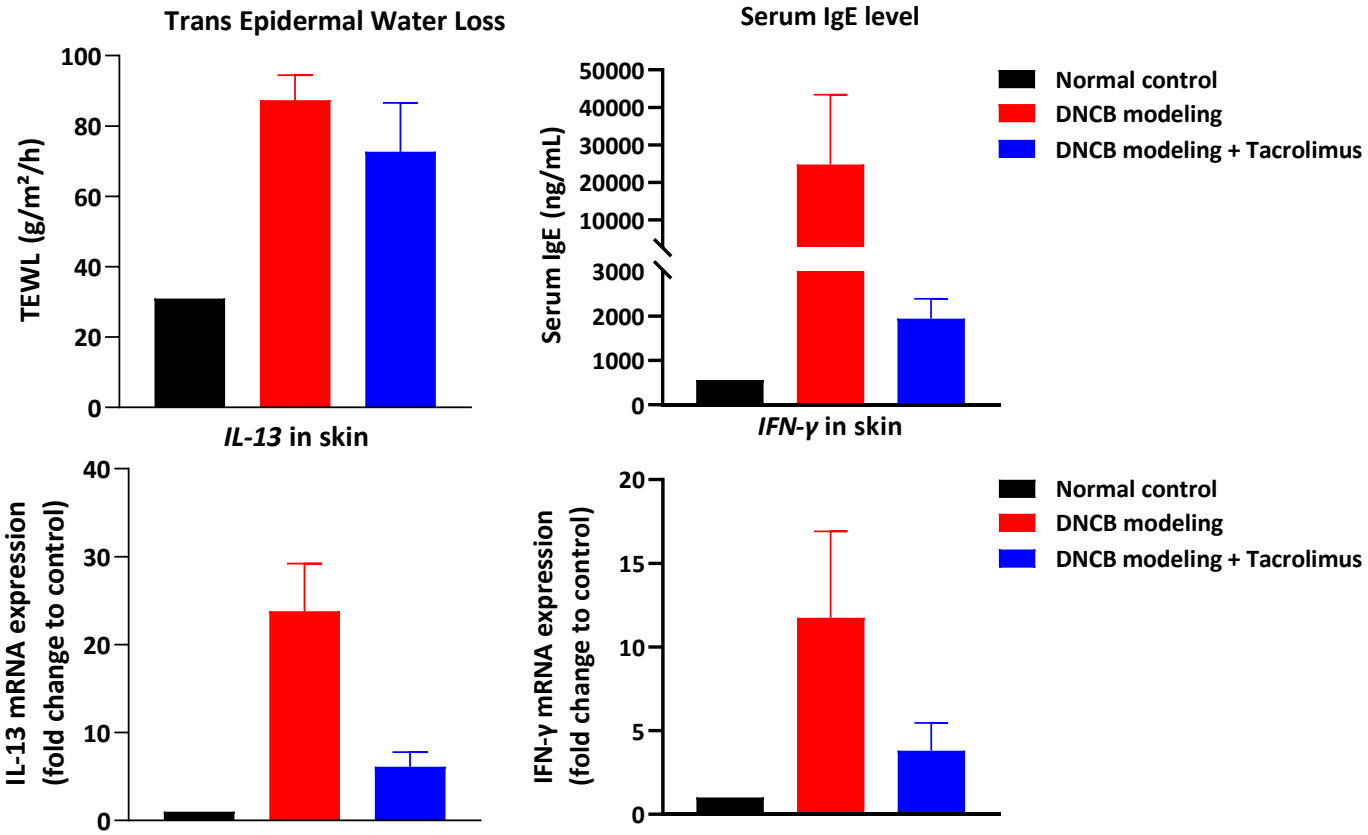
In-life results

Clinical Score Evaluation





Read-outs

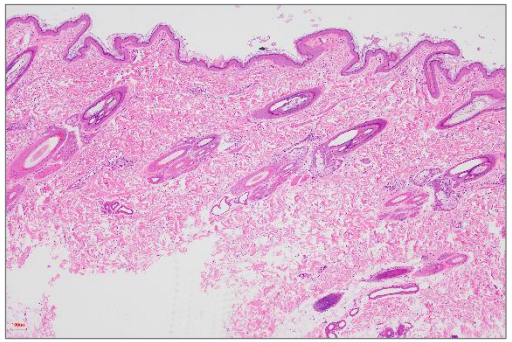


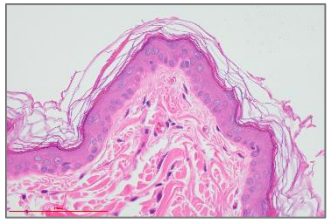
- During DNCB challenge period, dermatitis symptom including erythema, oozing, crusting and marked induration were observed, the clinical score gradually increased after repeated DNCB skin application. Tacrolimus treatment was started when a stable symptom maintained.
- TEWL, serum IgE, and mRNA levels of relative cytokines in skin were significantly increased in DNCB modeling group compared with normal control and Tacrolimus treatment groups.

DNCB-Induced Atopic Dermatitis Model in Beagle Dogs

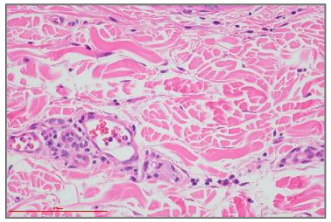
Histopathology results

Normal control



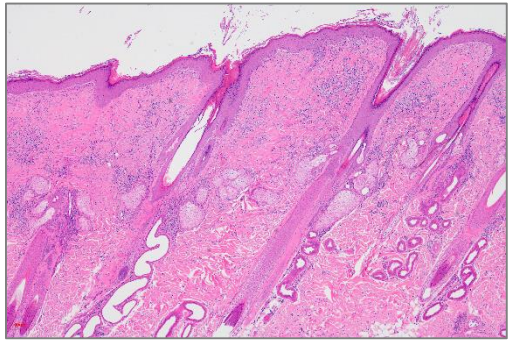


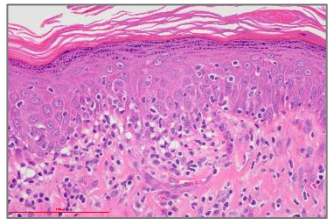
Normal



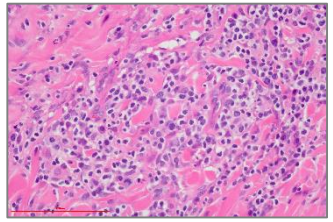
Inflammatory cell infiltration:1

DNCB modeling



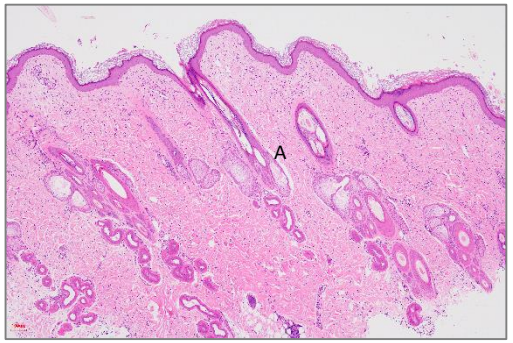


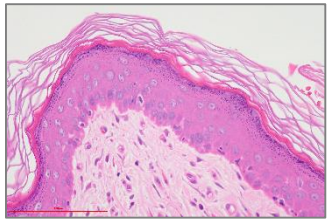
Hyperkeratosis:1
Acanthosis:2



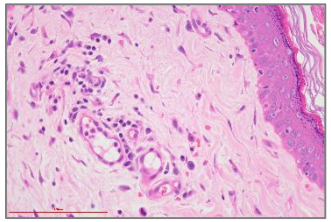
Inflammatory cell infiltration:3

DNCB modeling + Tacrolimus

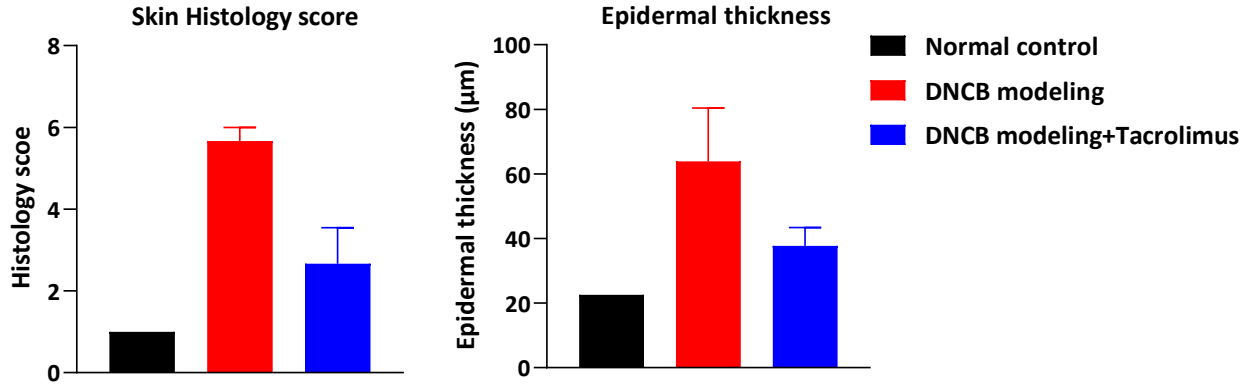




Hyperkeratosis:1
Acanthosis:1



Inflammatory cell infiltration:1



- Thickening of epidermis, and infiltration of lymphocyte into both epidermis and dermis were observed in DNCB modeling group compared with normal control and Tacrolimus treatment groups.

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