Dermatology Issues in Inborn Errors of Immunity

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Conflicts of Interest

No financial conflicts or other significant disclosures

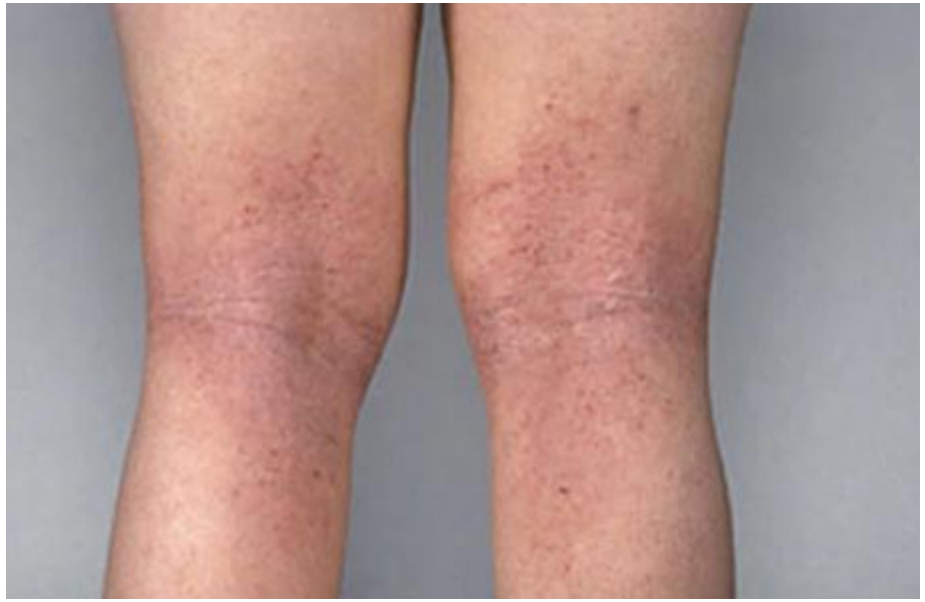
Views represented are my own and not those of the US Federal Government or the National Institutes of Health

Objectives

- Common Dermatology Conditions seen in IEI
- General approaches to therapies of skin conditions in IEI
  - *Comments are general, and your medical team may have specific treatment plans for you/your family member*
- When to see a dermatologist and how to find one with IEI experience
- General guidelines for skin health
- Some ongoing research for skin conditions in IEI

Atopic Dermatitis/Eczema

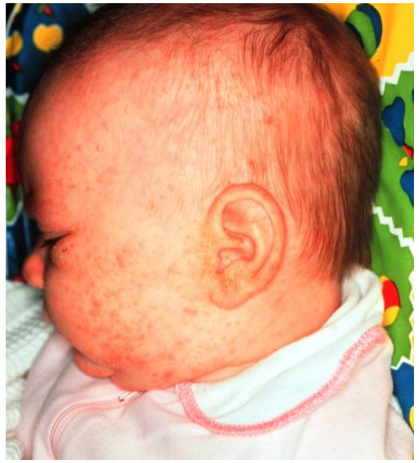
- Common! Especially in kids and adults with other allergy symptoms, such as environmental allergies and asthma
- Dry and itchy patches of skin
  - Hands, inside of elbows and knees, face (cheeks, around ears)
  - Often starts in infancy or early childhood
    - Can be triggered by exposures (nickel, food, etc)

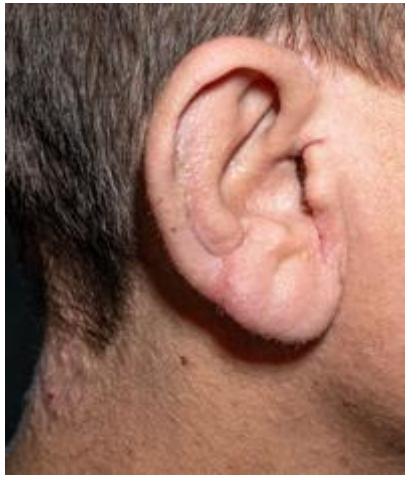


https://www.mayoclinic.org/diseases-conditions/atopic-dermatitis-eczema

Atopic Dermatitis: Which IEI?

- Hyper IgE syndromes
  - Can present in newborn period, often in face, scalp
- DOCK8 Deficiency
- Wiskott- Aldrich Syndrome
- IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked)
- Others!! As Atopic dermatitis/eczema is common





Atopic Derm: Treatment Approaches

- Hydration of skin: emollients (creams, lotions)
- Decreasing bacterial load on the skin (dilute bleach baths, swimming in chlorinated pools, chronic antimicrobials)
- Topical immune suppression: topical steroids (discuss strength with treating team) and steroid-sparing agents (tacrolimus, pimecrolimus, ruxolitinib)
- Systemic therapy: dupilumab, JAK inhibition
- Depending on IEI, HSCT may be considered

Dupilumab treatment for STAT3 HIES

Skin Infections: bacterial

- Atopic dermatitis predisposes to infection as the skin barrier is broken down
- Bacterial: Staph/Strep, impetigo, folliculitis, boils
- Diagnosis
  - Culture of pus (e.g. from boils) or nose to obtain Staph colonization
  - MRSA PCR: quick, but can't test which antibiotics are best
- Treatment
  - Topical: Mupirocin if small lesions
  - Incision and drainage of infection if boil
  - Systemic antibiotics: cephalexin, doxycycline, trimethoprim/sulfa, clindamycin, linezolid

Impact of Early Diagnosis in STAT3 HIES Improved Atopic Dermatitis

- Diagnosis in infancy due to family history compared to new proband diagnosis
- Antibiotic initiation in infancy as well as (typically) antiseptics suggests antibiotics do help!

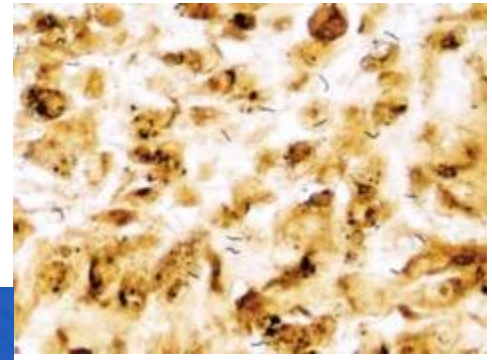
Characteristic	Family history (n = 8, 44%)	Proband (n = 10, 56%)	*P* value
Female, n (%)	6 (75)	5 (50)	.28
Current age, median (y)	9	13	.32
Age at diagnosis, median (y)	0.2	2	.001*
STAT3 mutation domain, n (%)			
DNA	5 (63)	5 (50)	.60
SH2	3 (38)	4 (40)	.91
TA	0 (0)	1 (10)	.36
Clinical features			
Serum IgE, mean (IU/mL)	6865	13,317	.31
Abs eosinophil count, mean (cells/μL)	1023	1182	.73
HIES score, median	32	60.5	.001*
Skin abscesses (>4), n (%)	1 (13)	9 (90)	.001*
Parenchymal lung abnormalities, n (%)	1 (13)	5 (50)	.09
Bronchiectasis	1 (13)	5 (50)	.09
Pneumatoceles	1 (13)	3 (30)	.37
Eczema, n (%)			
None	1 (13)	0 (0)	.25
Mild	3 (38)	0 (0)	.03*
Moderate	3 (38)	4 (40)	.91
Severe	1 (13)	6 (60)	.04*
Recurrent pneumonia, n (%)	1 (13)	9 (90)	.001*
Chronic lung infection	0 (0)	3 (30)	.04*
Pulmonary *Aspergillus*	0 (0)	2 (20)	.07
Lifetime hospitalizations, mean	0.875	6.3	.02*
Severe infections,† n (%)	0 (0)	4 (40)	.04*

An et al, JACI in practice 2023

Rare- but important to be aware in XLA

- X-linked agammaglobulinemia (Bruton's) associated *Helicobacter and Campylobacter* species infections
- Requires long-term combination antibiotics, possibly HSCT

Murray P. *et al.* Arch Dermatol 2010; 146:523-6.



Warthin-Starry

Skin Infections: Viral

- Common in certain IEI affecting T lymphocytes
  - Examples: DOCK8 deficiency, GATA2 deficiency, SCID (leaky), STAT1 GOF
- HPV: warts- verrucous (bumpy, classic warts) and flat
  - Treat: examples- OTC or prescription salicylic acid, freezing (dermatologist), duct tape
- Molluscum contagiosum
  - Treat: examples- cantharidin (blisters), freezing, laser
- Herpes simplex/Zoster
  - Treat: antivirals (acyclovir, valacyclovir)
  - Prophylaxis given for certain IEI

HPV- warts

Molluscum

zoster

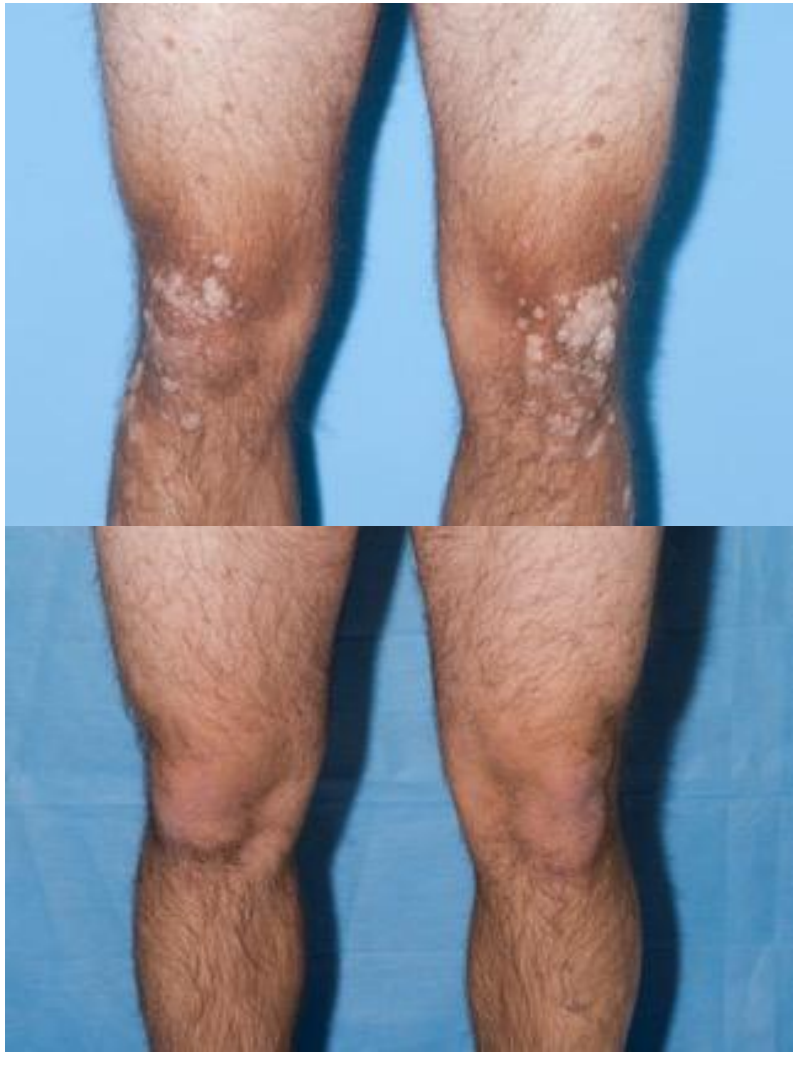
Viral Skin Infections: when to seek more care

Warts and Molluscum are common and can last a long time (years!) in healthy kids

- Dermatologist is concerned that the distribution/type/course are atypical
- Frequent recurrence after treatment
- Flat warts
- Recurrent shingles- or in multiple parts of the body
- Herpes or Varicella (chickenpox)/zoster (shingles) requiring IV therapy
- Early onset HPV related cancers

Flat warts

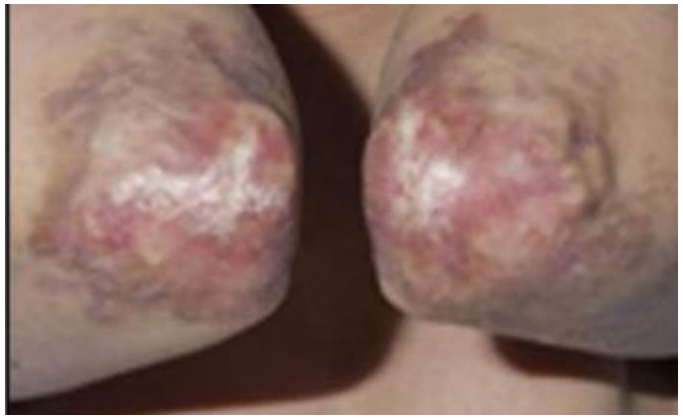
Bone marrow transplant for DOCK8 deficiency



Rare: but good to be aware
Rubella Associated Granulomas

- Seen mostly in Combined immune deficiencies, DNA repair defects
- Less frequently can have non-skin granulomas as well
- Diagnosis relies on biopsy and frequently discussion with CDC
- Many treatments have been tried, but few successful outside of HSCT

TAP2 deficiency



IL2RG with reversions causing leaky SCID

Skin Infections: Fungal

- Skin:
  - Yeast (Candida) often in areas that are more moist- diaper area, under breasts
  - Dermatophytes (”ringworm”) can sometimes be worse in some IEI
  - Diagnosis: Dermatologist may scrape and look under microscope, fungal cultures
- Nails:
  - Yeast (HIES), dermatophytes
- Oral: Thrush, candida
- Vaginal: yeast
- Treatment
  - Topical : skin lesions, thrush (nystatin, azoles)
  - Systemic: Nails, widespread skin or mucosal (azoles)

Autoimmune Skin Conditions

- Immune dysregulation syndromes- infections and autoimmunity/inflammatory disease
  - Examples: CVID, “leaky” SCID, STAT1/STAT3 GOF, CTLA4, thymoma
- Lupus: discoid lupus, systemic lupus erythematosus
- Alopecia
- Vitiligo
- Cystic acne

CGD: cystic acne, lupus

RAG deficiency, Vitiligo

APECED, alopecia

Discoid lupus, HIES

Treatment of APS-1/APECED with oral ruxolitinib

Improvement:

- Alopecia areata
- Autoimmune gastritis
- Thyroiditis
- Nail dystrophy
- Oral candidiasis

Ruxolitinib: JAK inhibitor

- Immune suppressant
- Prior to use, check for TB, hepatitis
- Main infection risk is increased viral infections: e.g. shingles
- Monitor for decreased blood counts

N Engl J Med 2024;390:1873-84.

Deficiency of Adenosine Deaminase 2 (DADA2)

Table 1. Clinical and Laboratory Manifestations in Patients with Deficiency of Adenosine Deaminase 2.

Clinical Manifestation	Patients
	no./total no.
Fever	9/9
Ischemic stroke	8/9
Hemorrhagic stroke	3/9
Ophthalmologic involvement*	5/9
Livedo racemosa	8/9
Hepatosplenomegaly	6/7
Documented vasculitis†	4/9
Polyarteritis nodosa	2/9
Antinuclear antibody	3/9
Antineutrophil cytoplasmic antibody	0/9
Low serum IgM	5/5

NEJM 370;10 march 6, 2014

Antimicrobial Related Skin Changes

- Certain medications can make skin more sensitive to the sun
  - Voriconazole: Antifungal
  - Doxycycline: Antibiotic
- Allergic reactions more common with certain antibiotics
  - Penicillins
  - Sulfa

Amoxicillin-related rash

Mayoclinic.org

Doxycycline photosensitivity

Paradkar et al, Journal of Pediatrics, 2022

Photoaging and phototoxicity from long-term

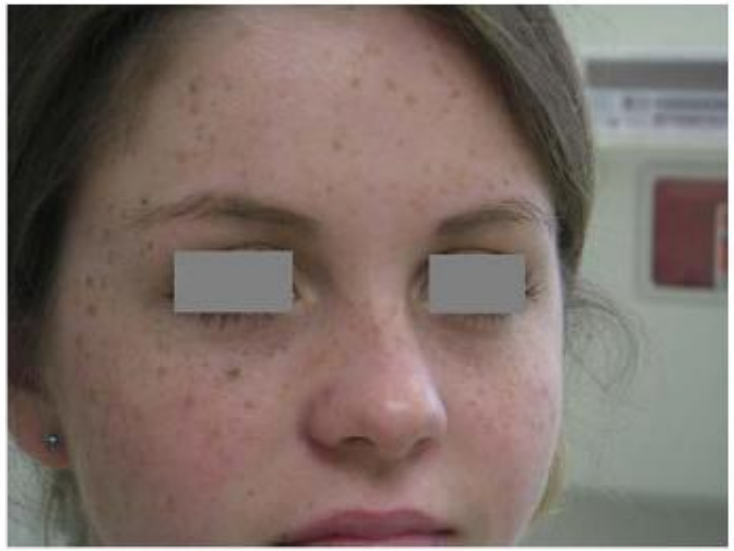


Fig 1. Numerous solar lentigines and ephelides on face 4 weeks after discontinuation of voriconazole treatment.

Fig 2. Solar elastosis and lentigines on back of left hand immediately after discontinuation of voriconazole treatment.

Alternative Antifungals: Posaconazole, itraconazole, isavuconazole
For all azoles: drug interactions (including steroids) and can have liver toxicity

Racette AJ et al, J Am Acad Dermatol 2005

Wound Healing Concerns

- Neutrophil white blood cells are very important in wound healing
- Neutrophil disorders with skin infections/wound healing issues
  - Chronic Granulomatous Disease
    - Post-surgery can have exuberant inflammation and may need steroids paradoxically to improve healing
  - Leukocyte adhesion deficiency (LAD)
    - Umbilical cord infection, failure to fall off
    - Wound healing abnormalities
- IEI with increased *Staph aureus* infections (e.g. HIES, CGD) may benefit from increased antibiotics around large wounds, surgery

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Interleukin-12 and Interleukin-23 Blockade in Leukocyte Adhesion Deficiency Type 1

Niki M. Moutsopoulos, D.D.S., Ph.D., Christa S. Zerbe, M.D., Teresa Wild, M.S., Nicolas Dutzan, D.D.S., Laurie Brenchley, R.D.H., Giovanni DiPasquale, Ph.D., Gulbu Uzel, M.D., Karen C. Axelrod, R.N., Andrea Lisco, M.D., Lucia D. Notarangelo, M.D., George Hajishengallis, D.D.S., Ph.D., Luigi D. Notarangelo, M.D., and Steven M. Holland, M.D.

General Skin Health

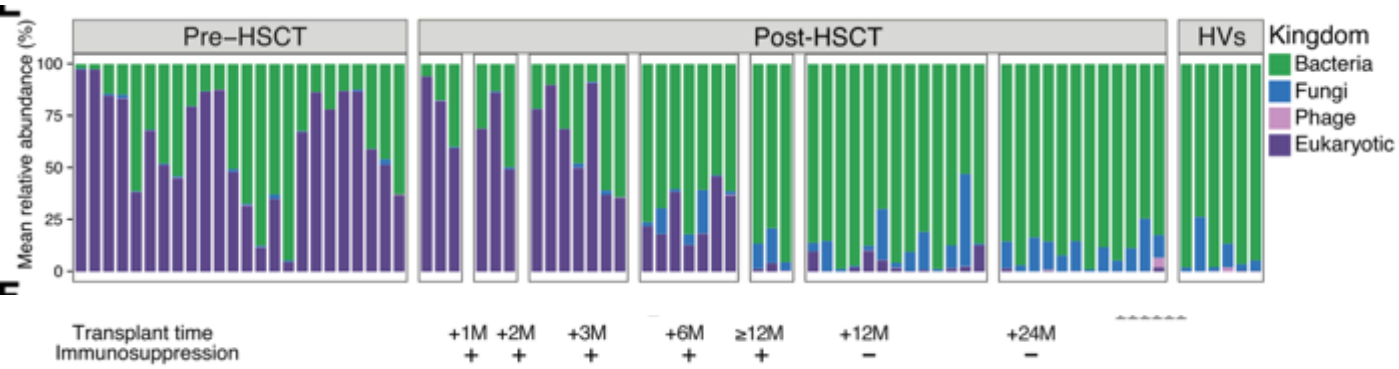
- Sun protection!
  - Sunscreen, hats, long sleeves in sun
  - Vitamin D can be obtained through food, medication
- Mild soaps and lotions
- Keeping cuts and wounds clean and dry
- Know the side effects of medications- rashes, sun sensitivity
- Keep an eye out for new spots

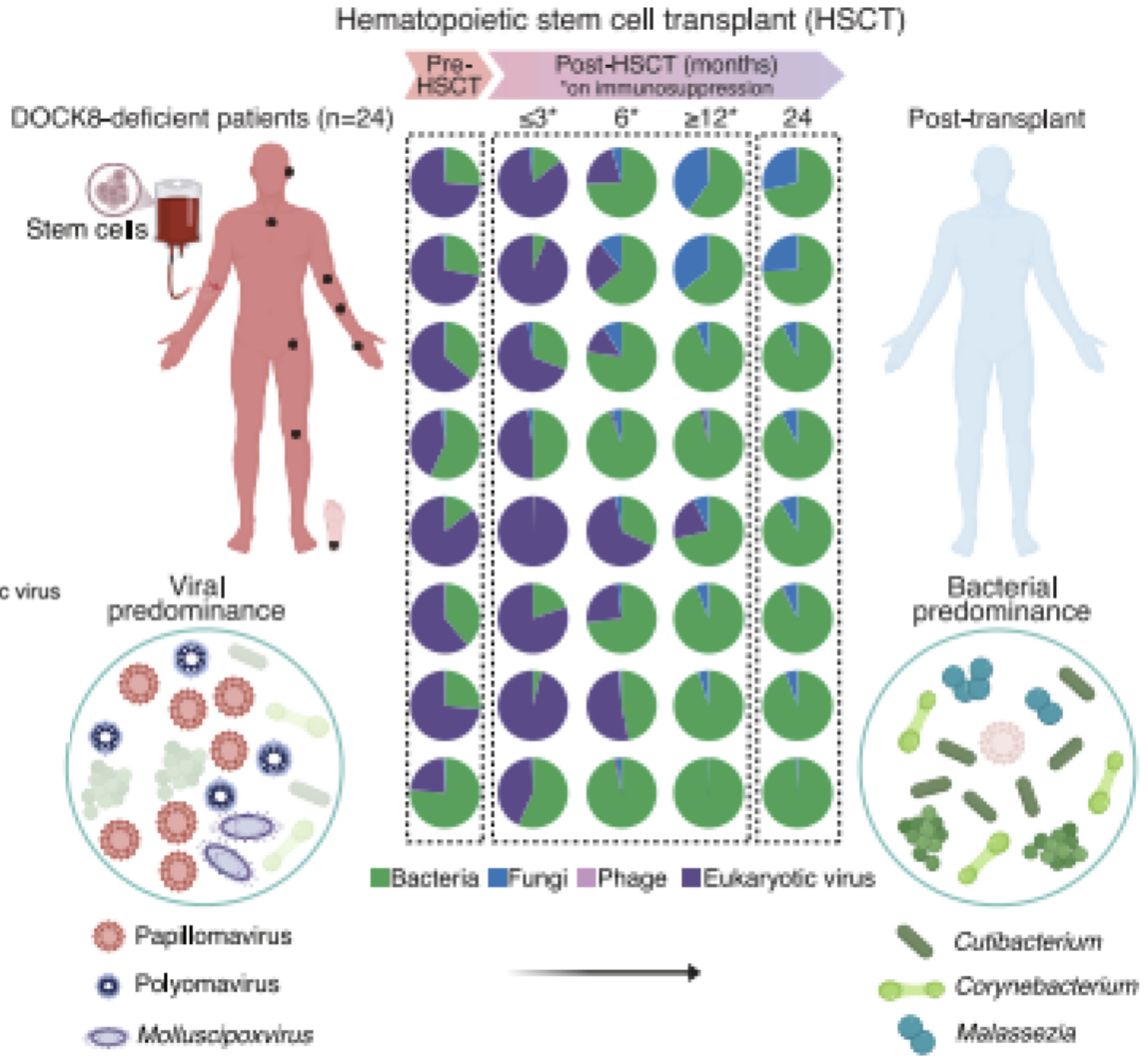
How to Find a Dermatologist

- Takes time to do a full skin exam and not just one specific spot
- Interested to hear about the underlying immune defect and willing to connect to your IEI physician
- Recommendation from your IEI treatment
- Consider an academic medical center
- Support group recommendation

Dermatology Research in IEI

Restoration of skin microbiome post-HSCT for DOCK8 deficiency





Che et al, Host Cell and microbiome, 2025

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CURRENT ISSUE SPECIALTIES TOPIC

ORIGINAL ARTICLE | BRIEF REPORT

Resolution of Squamous-Cell Carcinoma by Restoring T-Cell Receptor Signaling

Authors: Peiying Ye, Ph.D., Jenna R.E. Bergerson, M.D., M.P.H., Isaac Brownell, M.D., Ph.D., Gabriel J. Starrett, Ph.D., Roshini S. Abraham, Ph.D., Megan V. Anderson, R.N., B.A., Triscia Martin, P.A., M.S., +10 , and Andrea Lisco, M.D., Ph.D. Author Info & Affiliations

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ZAP 70 deficiency:
Impaired T cell receptor
Predisposes to viral infections

Thank you!!

Questions?

NIH Clinical Center