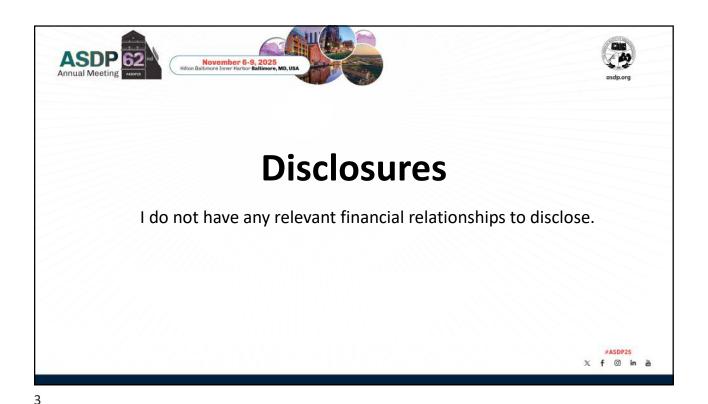


# We would like to thank all our collaborators in the Granuloma Rubella Cutaneous Research Working Group!

- Northwestern:
  - Joan Guitart, Cuong Nguyen, Pedram Gerami, Jeffrey Zhao, Shantel Olivares, Nathaniel Lampley, Anastasiya Boutko
- Yale:
  - o William Damsky, Caroline Nelson, Brian Wei
- BWH:
  - o Sotonye Imadojemu, Megan Noe
- UW Madison:
  - o Bridget Shields, Beth Drolet
- UPenn
  - Jina Chung, Misha Rosenbach, Alexandra Coromilas, Katherine Lattanzio, Juliana Berk-Krauss

- University of Iowa:
  - o Brian Swick
- OHSU:
  - o Kevin White, Gina Calco, Claire Turina
- Mayo:
  - Olayemi Sokumbi, Aaron Mangold, Meera Patel, Caitlin Brumfiel, Kevin Severson, Puneet Bhullar, Blake Boudreaux, Jacob Kechter, Angelina Hwang
- · University of Florida:
  - Kiran Motaparthi, Macartney Welborn, Emma Albrecht



#### **Background**

- Rubella Virus (RuV) declared eradicated from the United States in 2004
- Vaccine-derived rubella virus related to the vaccine strain RA27/3: immunodeficiencyrelated vaccine-derived rubella viruses (iVDRV)
- Wild-type RuV has also been reported within granulomas
- RuV cutaneous granulomatous disease (RuV-CGD) occurs in patients with inborn errors of immunity (IEI) and immunocompetent adults



#### **RuV Granulomatous Inflammation in Inborn Errors of Immunity**

**Inborn Errors of** Immunity (Defective T-cell / NK-cell cytotoxic function)

Impaired clearance of RuV → Persistent viral antigen within macrophages & neutrophils

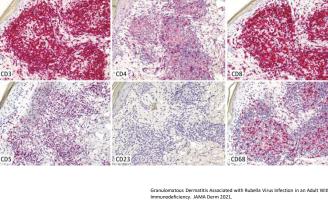
Chronic and activation of lymphocytes

Granulomatous driven)

Rubella Virus Infected Macrophages and Neutrophils Define Patterns of Granulomatous Inflammation in Inborn and Acquired Errors of Immunity. Frontiers Immunology 2021.

### Histopathologic and Immunohistochemical Features of Granulomas in Inborn Errors of Immunity

	Diagnosis	Histo- pathology	CD4+/ CD8+ ratio	CD4+ (cells/μl) in PB	+ ratio in PB
atient 1	CID	Necrotizing	1.14	160	1.33
atient 2	ALPS	Non- necrotizing	0.44	205	0.5
atient 3	AT	Necrotizing	0.28	440	1.91
atient 4	CVID	Necrotizing	0.12	_	_
atient 5	Sarcoidosis	Non- necrotizing	2.19	_	_
atient 6	Sarcoidosis	Non- necrotizing	2.71	_	_
atient 7	Sarcoidosis	Non- necrotizing	2.65	_	_
I					



Rubella Vaccine Persistence Within Cutaneous Granulomas in Common Variable Immunodeficiency. Am J Dermatopathology 2020.

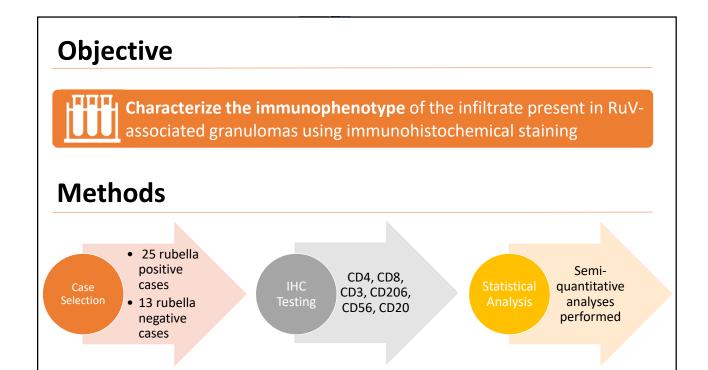
Immunohistochemical features of cutaneous granulomas in primary immunodeficiency disorders: a comparison with cutaneous sarcoidosis. JCP 2008

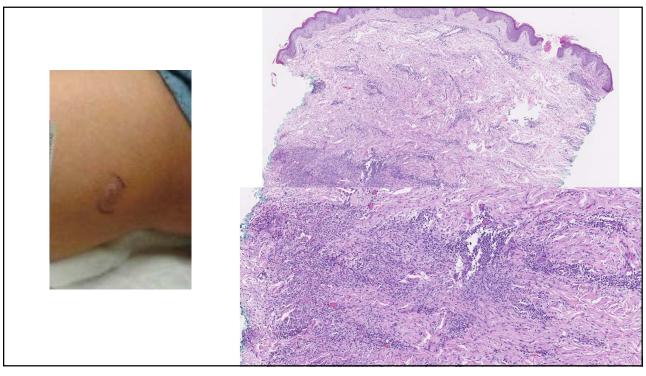
Rubella-virus cutaneous granulomas in patients with Common Variable Immune Deficiency

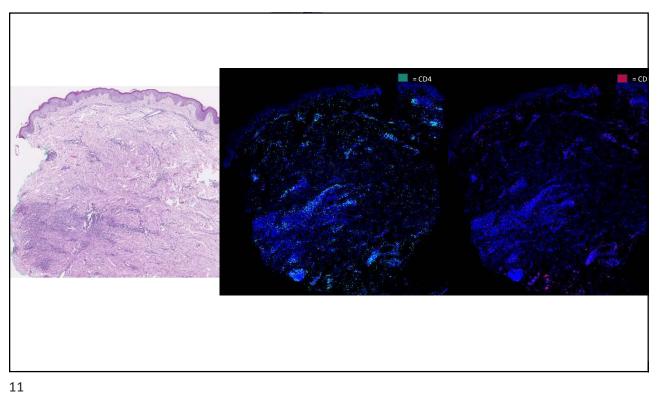
Location of granulomas	Superficial	8
Location of grandiomas	Deep	5
	Palisaded	5
Characteristics of annual areas	Sarcoidal	3
Characteristics of granulomas	Interstitial	3
	Necrobiotic	2
	Multinucleated giant cells	6
Characteristics of giant cells	Foreign body type	4
	Angulated and osteoclast-like	1
	Perigranulomatous	8
Location of associated inflammation	Perivascular	2
	Interstitial (dermal)	1
	Lymphocytes	8
Inflammatory cell	Eosinophils	2
	Plasma cells	1
Dermal fibrosis	Present	3
Deliliai librosis	Absent	5
Immunohistochomistru stoinine	Present	1
Immunohistochemistry staining	Absent	6

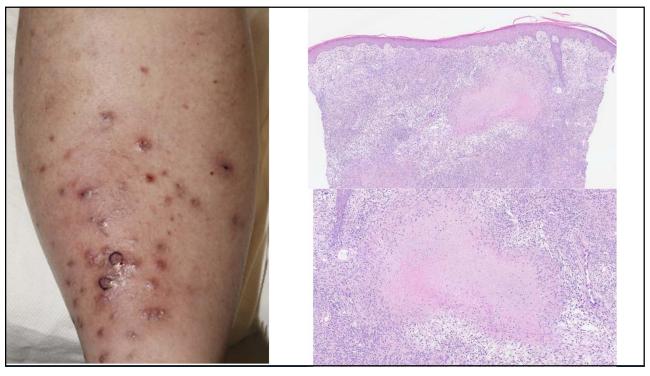
The Spectrum of Cutaneous Granulomatous Inflammation and Detection of Rubella Virus in Skin Biopsies of Patients With Common Variable Immune Deficiency, JCP 2024.

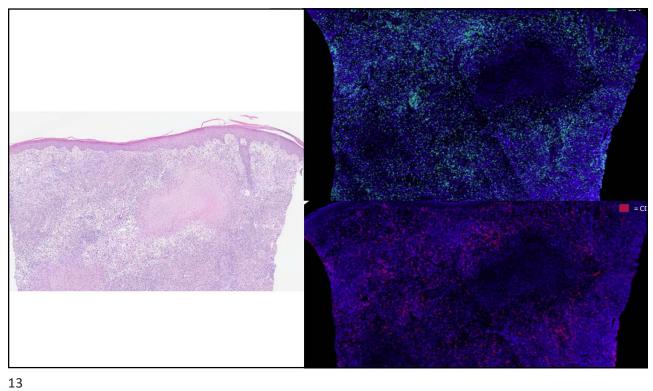
Ruv-Associated Dermatitis in Adults Without Known immunodeficiency:  Prior Findings							
	Characteristic	Rubella Positive	Rubella Negative				
Primary	Tuberculoid	19 (86%)	3 (30%)				
Granulomatous	Interstitial	6 (27%)	8 (80%)				
Patterns	Palisading	8 (36%)	3 (30%)				
	Sarcoidal	0 (0%)	2 (20%)				
-	Lymphocytes, non-brisk	5% (1/22)	50% (5/10)				
	Lymphocytes, brisk	95% (21/22)	40% (4/10)				
Histopathologic	Neutrophils	91% (20/22)	0% (0/10)				
Features	Eosinophils	41% (9/22)	20% (2/10)				
-	Plasma cells	82% (18/22)	50% (5/10)				
-	Necrosis	50% (11/22)	0% (0/10)				
Consensus Study on the Histopathological Features of Rubella Virus Associated Cutaneous Granulomas. ASDP 2024	Fibroplasia	86% (19/22)	30% (3/10)				



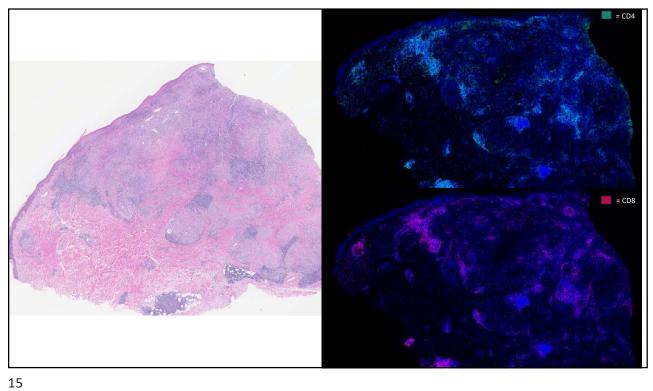


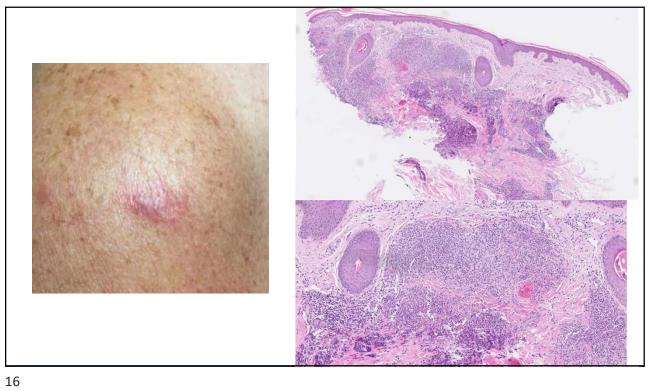


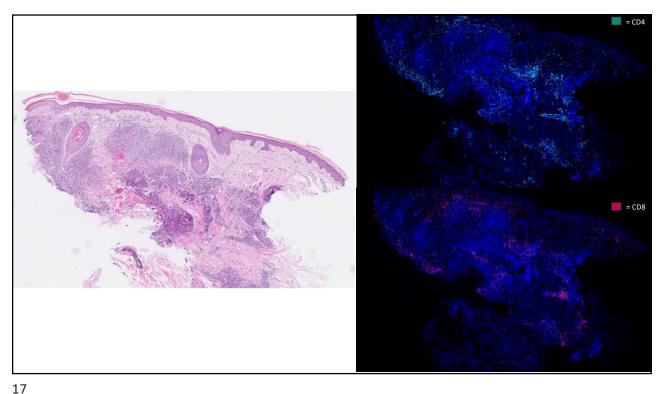


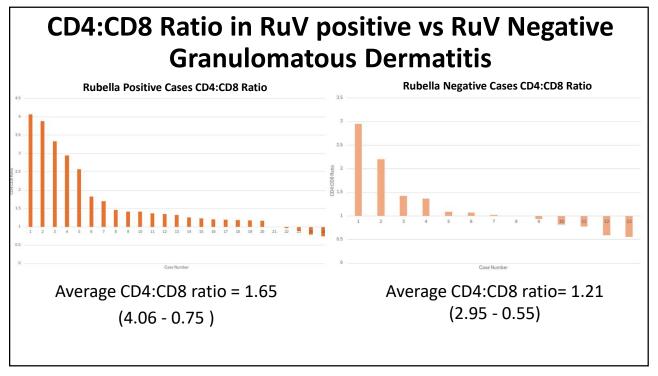






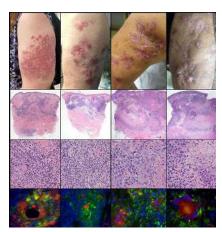






## **Conclusions and Next Steps**

- Rubella associated granulomas can have variable immunophenotype (average CD4:CD8 ratio = 1.65; range 0.75 - 4.06)
- These findings are different compared to those previously seen in patients with inborn errors of immunity, although similar in the one CVID case
- Highlights potential pathophysiology in adults without known immunodeficiency
- Evaluation of rubella associated granulomatous dermatitis should be considered in granulomas with brisk lymphocytic infiltrate, independent of immunophenotype
- Further investigation into drivers of this association are important



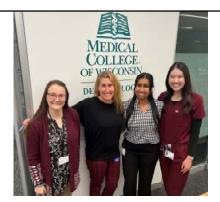
19



# Please reach out to us at <a href="mailto:grucrew@mcw.edu">grucrew@mcw.edu</a> if interested in:

- Now CLIA approved test through MCW
- Additional research testing can be done with RuV positive patients





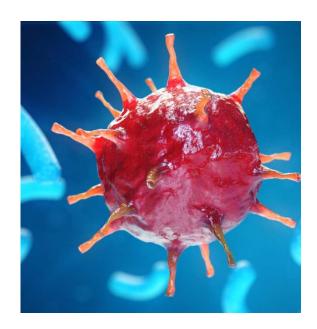


#### **Thank You!**

- Brigham & Women's Hospital
  - Megan Noe, Sotonye Imadojemu, Travis Hughes, Marjorie Archla
  - Mayo Clinic
    - Yemi Sokumbi, Aaron Mangold, Puneet Bhullar, Meera Patel, Caitlin Brumfiel, Kevin Severson, Blake Boudreaux, Jacob Kechter, Angelina Hwang
- Northwestern Medicine
  - •Joan Guitart, Cuong Nguyen, Pedram Gerami, Jeffrey W Zhao, Shantel Olivares, Nathaniel Lampley, Anastasiya Boutko, Yae Lee Kye
- Oregon Health and Science University
  - Jina Chung, Kevin White, Gina Calco, Claire Turina
- University of Pennsylvania
  - Jina Chung, Paul Haun, Alexandra Coromilas, Katherine Lattanzio, Juliana Berk-Krauss, Misha Rosenbach
- · University of Florida
  - Kiran Motaparthi, Emma Albrecht, Mary Bohannon
- University of Iowa
  - Brian Swick, John Selby, Amanda Steahr
- University of Wisconsin-Madison
- Bridget Shields, Collin Evenson, Donglin Zhang, Beth Drolet
- Yale
  - William Damsky, Caroline Nelson, Brian Wei
- CDC
- Ludmila Perelygina, Raeesa Faisthalab , Laura Yorke, Min-hsin Chen, LiJuan Hao
- MCW
  - Rachel Tao, Nathan Duncan, Alexa Ries, Jesa Landis, Karolyn Wanat

21

Questions?







#### References

- 2.
- 3.
- Bodemer C, Sauvage V, Mahlaoui N, et al. Live rubella virus vaccine long-term persistence as an antigenic trigger of cutaneous granulomas in patients with primary immunodeficiency. *Clin Microbiol Infect.* Oct 2014;20(10):0656-663. Dhossche J, Johnson L, White K, et al. Cutaneous Granulomatous Disease With Presence of Rubella Virus in Lesions. *JAMA Dermatol.* Vol 155. United States2019:859-861.

  Neven B, Pérot P, Bruneau J, et al. Cutaneous and Visceral Chronic Granulomatous Disease Triggered by a Rubella Virus Vaccine Strain in Children With Primary Immunodeficiencies. *Clin Infect Dis.* Jan 1 2017;64(1):83-86. Shields BE, Perelygina L, Samimi S, et al. Granulomatous Dermatitis Associated With Rubella Virus Infection in an Adult With Immunodeficiency. *JAMA Dermatol.* Jul 1 2021;157(7):842-847.

  Perelygina L, Plotkin S, Russo P, et al. Rubella persistence in epidermal keratinocytes and granuloma M2 macrophages in patients with primary immunodeficiencies. *J Allergy Clin Immunol.* Nov 2016;138(5):1436-1439 e1411 5. 1439.e1411.
- 6.
- Leclerc-Mercier S, Moshous D, Neven B, et al. Cutaneous granulomas with primary immunodeficiency in children: a report of 17 new patients and a review of the literature. *J Eur Acad Dermatol Venereol*. Jul 2019;33(7):1412-1420. Buchbinder D, Hauck F, Albert MH, et al. Rubella Virus-Associated Cutaneous Granulomatous Disease: a Unique Complication in Immune-Deficient Patients, Not Limited to DNA Repair Disorders. *J Clin Immunol*. Jan 2019;39(1):81-
- 8.
- Perelygina L, Faisthalab R, Abernathy E, et al. Rubella virus infected macrophages and neutrophils define patterns of granulomatous inflammation in inborn and acquired errors of immunity. Front Immunol. 2021;12:796065.

  Zhang D, Wanat KA, Perelygina L, et al. Cutaneous granulomas associated with rubella virus: A clinical review. *J Am Acad Dermatol*. 2024;90(1):111-121. doi:10.1016/j.jaad.2023.05.058

  Pronier C, Roger S, Besombes J, et al. Granuloma and persistent detection of wild-type rubella virus in an immunocompromised patient. *Microbiol Spectr*. 2025;13(7):e0234824. doi:10.1128/spectrum.02348-24

