

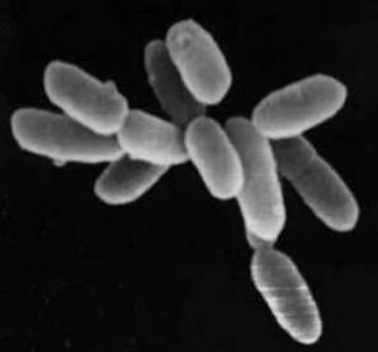
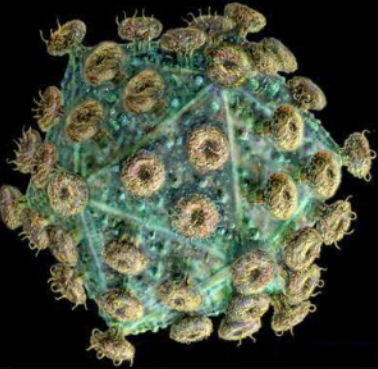
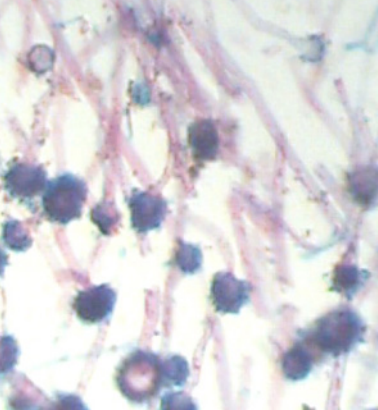
Eczema, immunity & the skin microbiome

Heidi H. Kong

Dermatology Branch, CCR, NCI

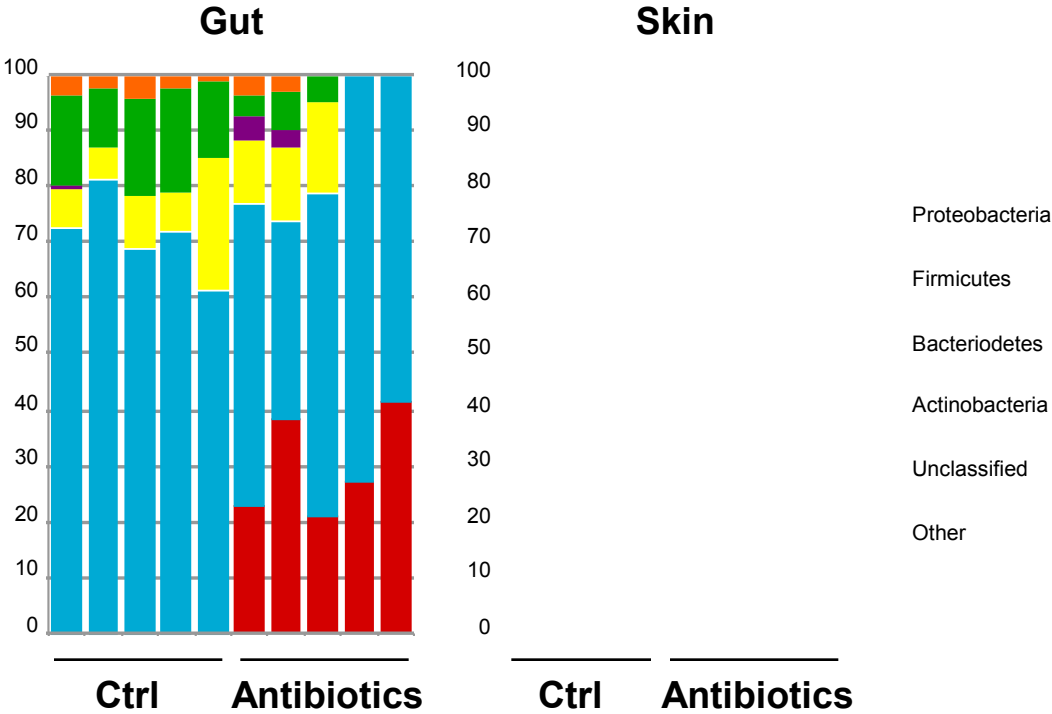


Eczema, immunity & the skin microbiome

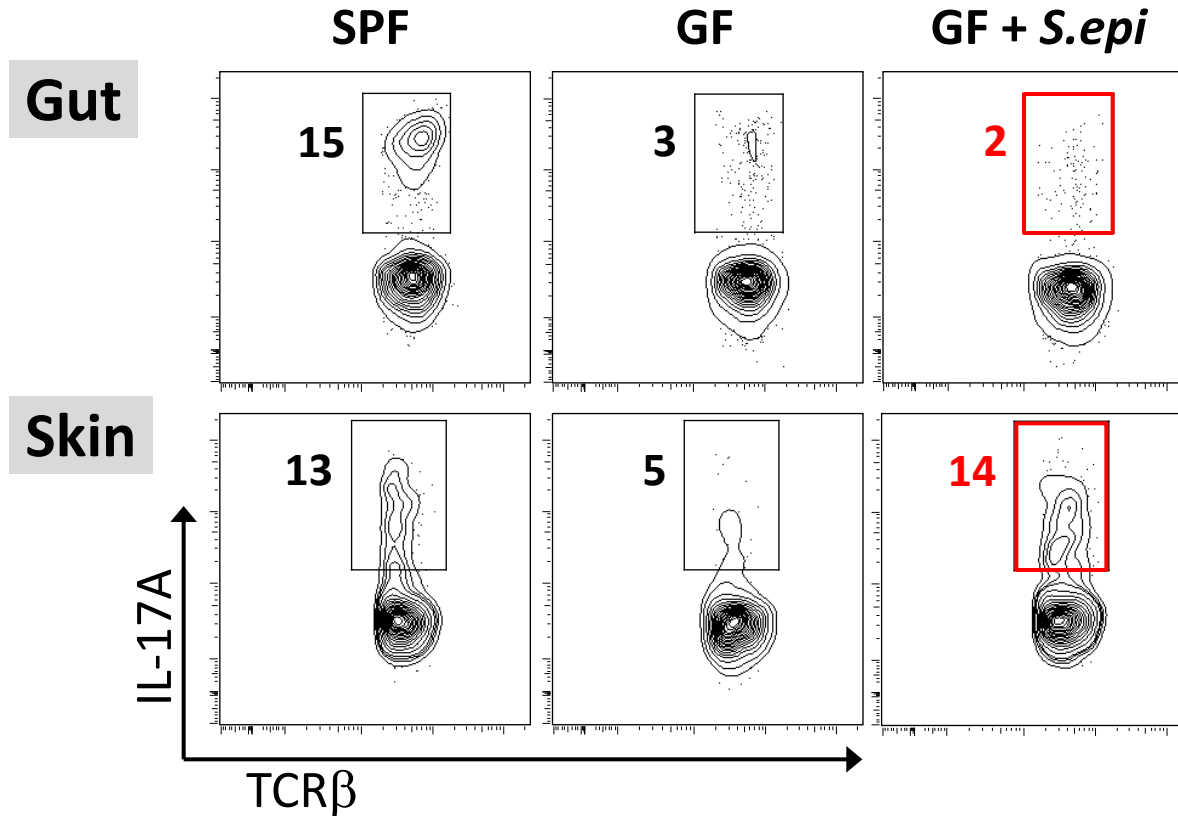


- Do skin microbes influence host skin immunity?
- Healthy human skin microbiome surveys
- The microbiome in eczematous skin
 - Atopic dermatitis
 - Primary immunodeficiency syndromes
- Gaps, needs & challenges

Commensal niches in distinct epithelia demonstrate differential responses after antibiotics



Topical *S. epidermidis* association can increase IL-17A production in the skin of germ-free mice



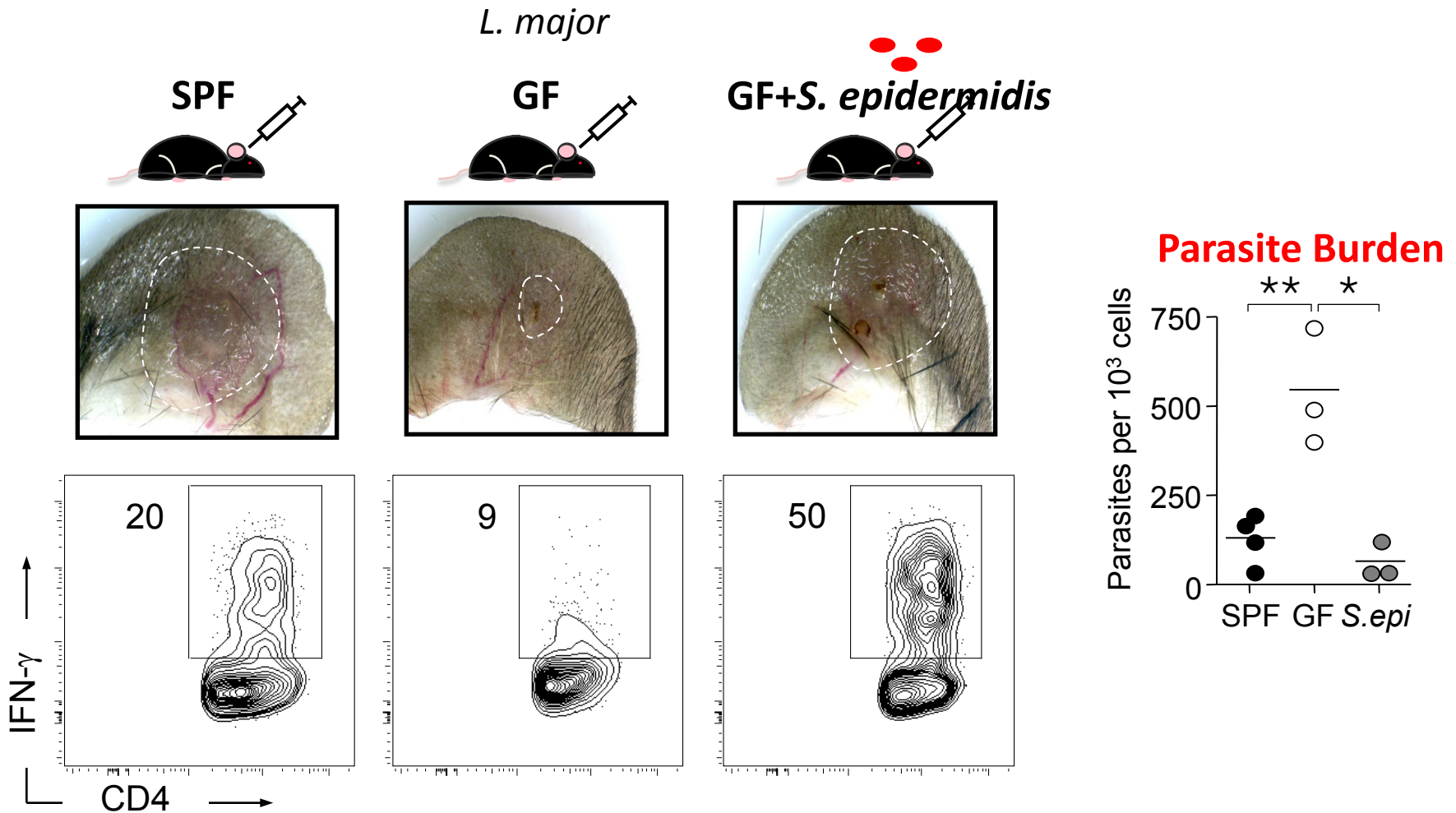
SPF – Specific Pathogen Free

GF – Germ Free

GF + *S.epi* – Germ Free associated with *S. epidermidis*

Naik S *et al.* Science 2012

Skin commensals restore immunity to *Leishmania major* in germ-free mice



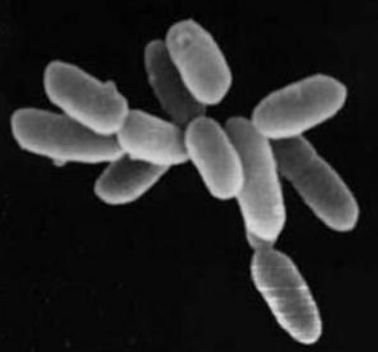
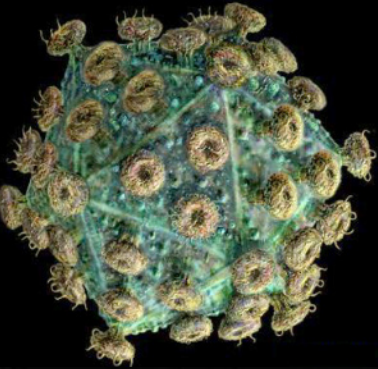
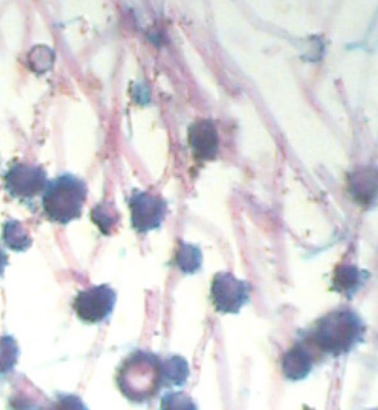
The host immunity-microbial interactions in skin are distinct.

- In mice, skin microbes can
 - Tune the level of activation & function of skin-resident T cells,
 - Promote immunity to pathogens, &
 - Drive responses locally that are distinct and independent from the gut flora.

What about *human* skin immunity-microbial interactions?



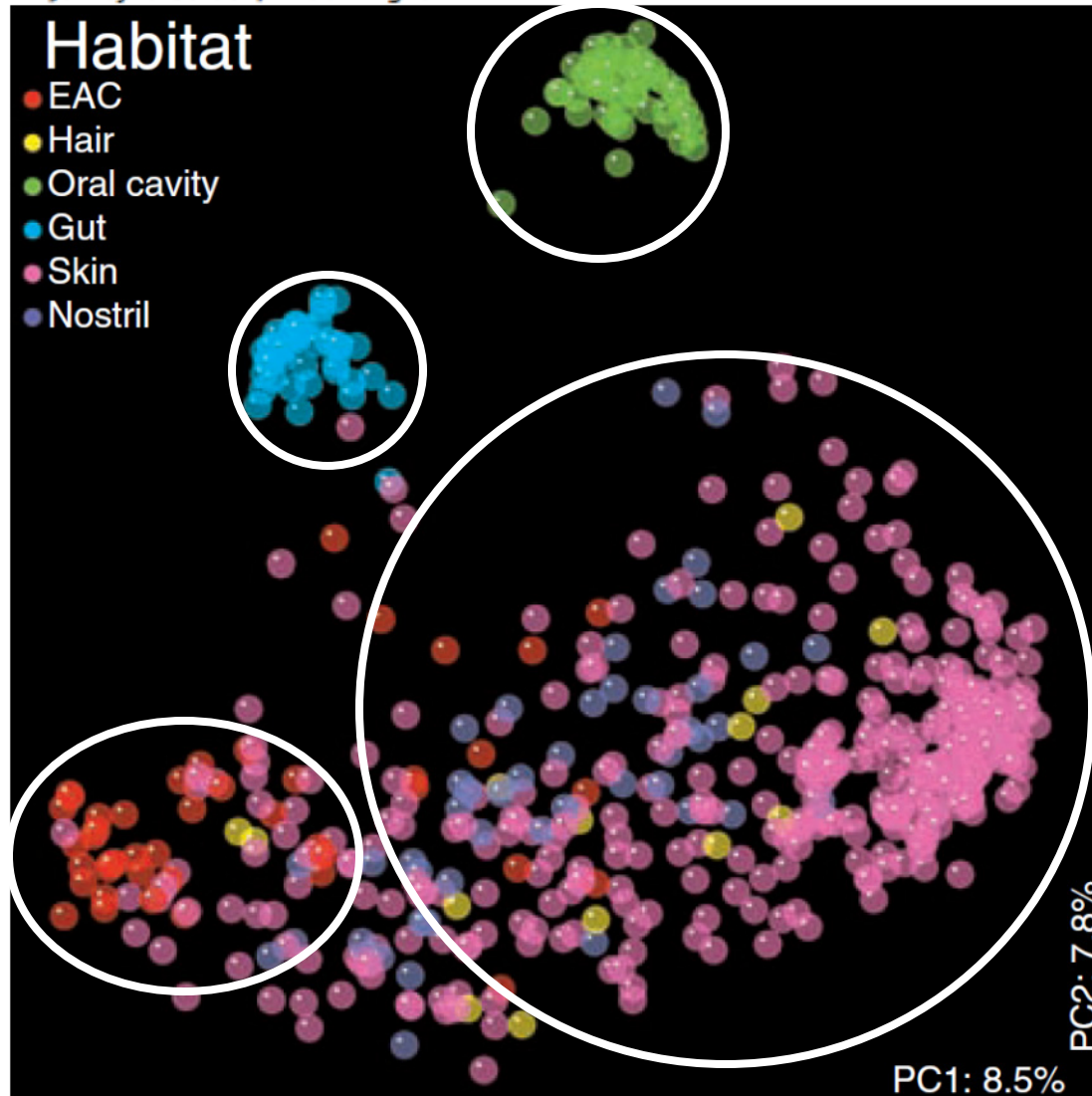
Eczema, immunity & the skin microbiome



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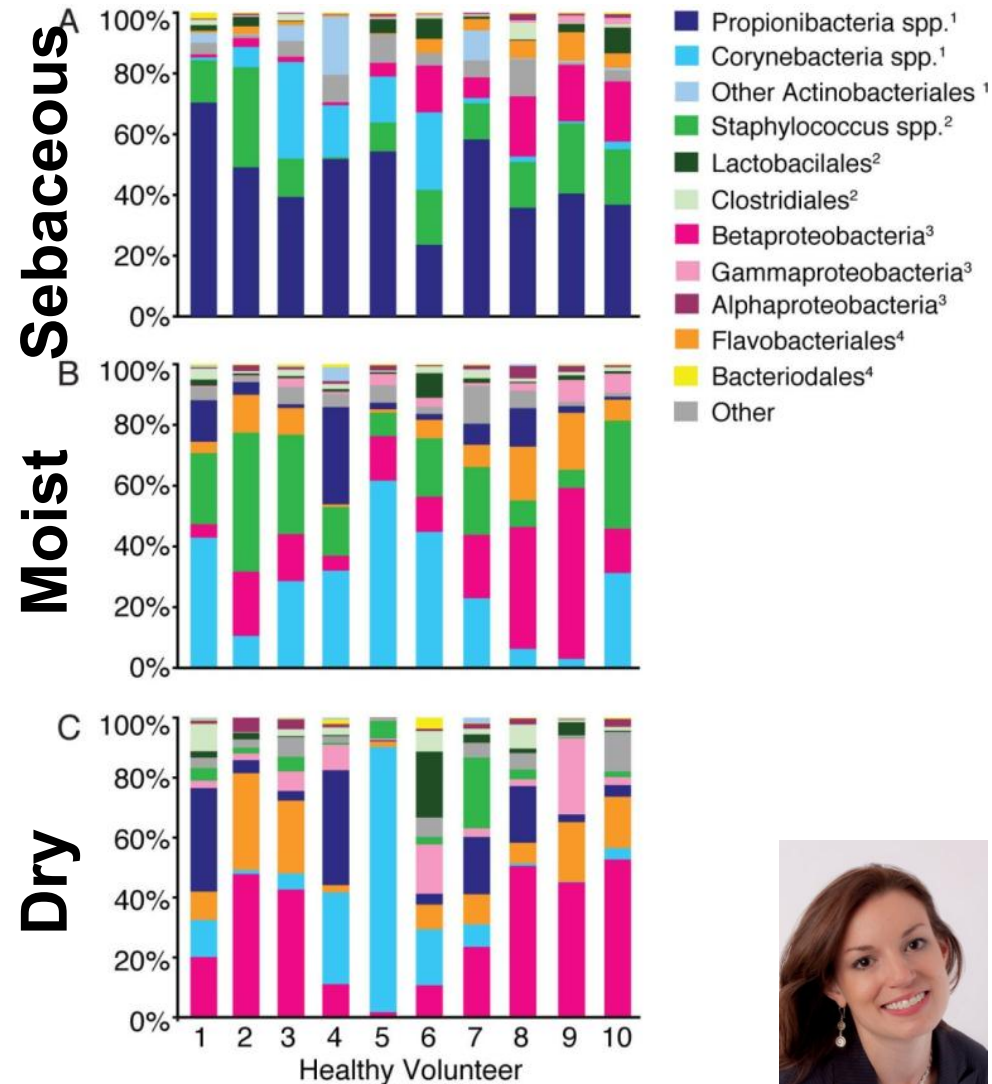
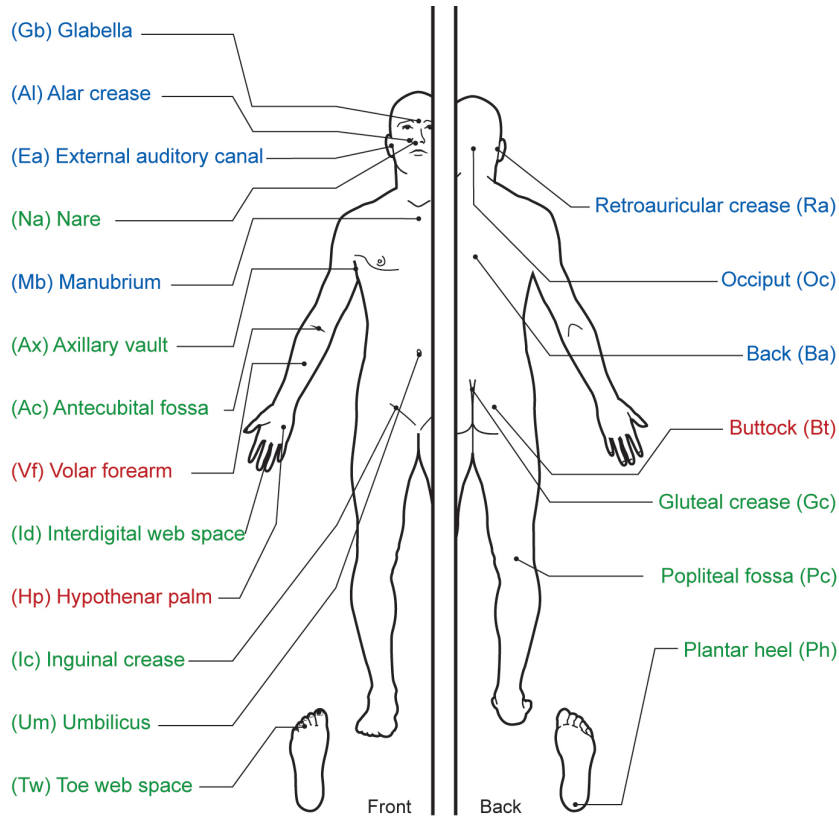
Bacterial Community Variation in Human Body Habitats Across Space and Time

Elizabeth K. Costello,¹ Christian L. Lauber,² Micah Hamady,³ Noah Fierer,^{2,4} Jeffrey I. Gordon,⁵ Rob Knight^{1,6*}

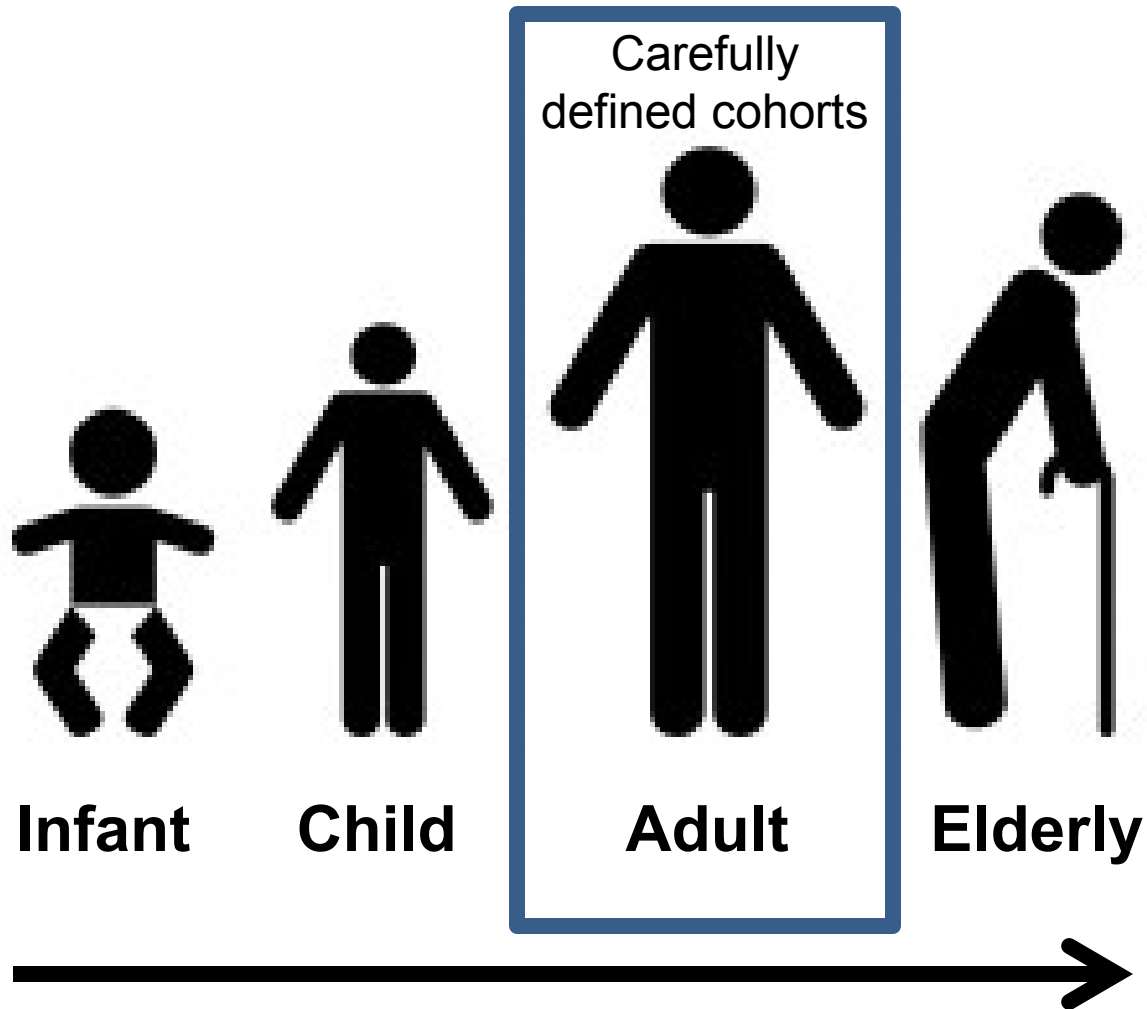


Science 2009

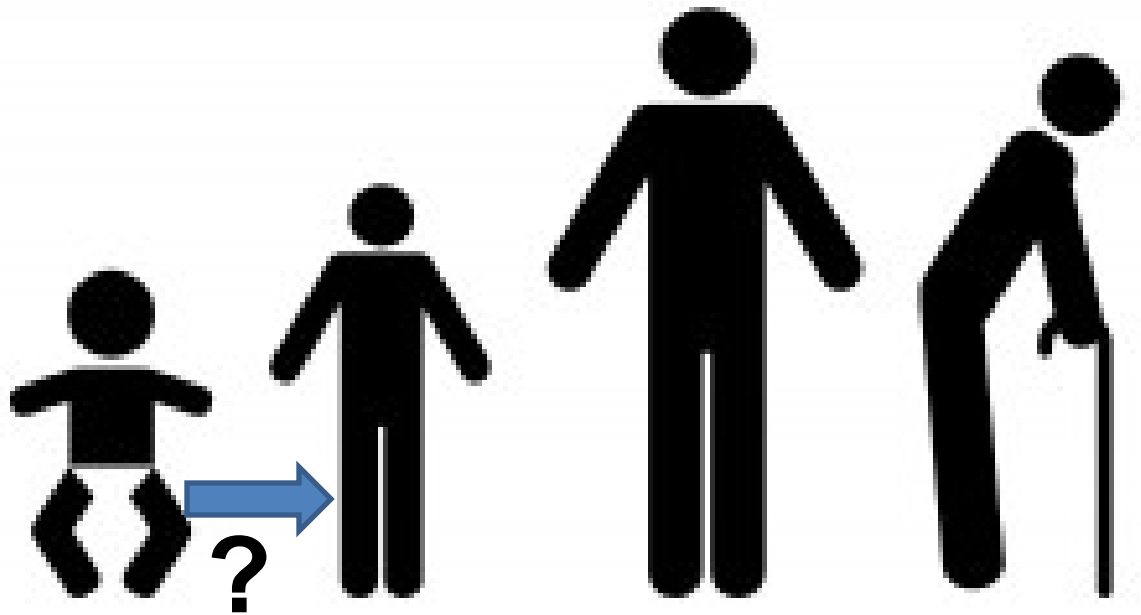
Relative abundance of predominant bacteria dependent on microenvironment



Life stages



Life Stages



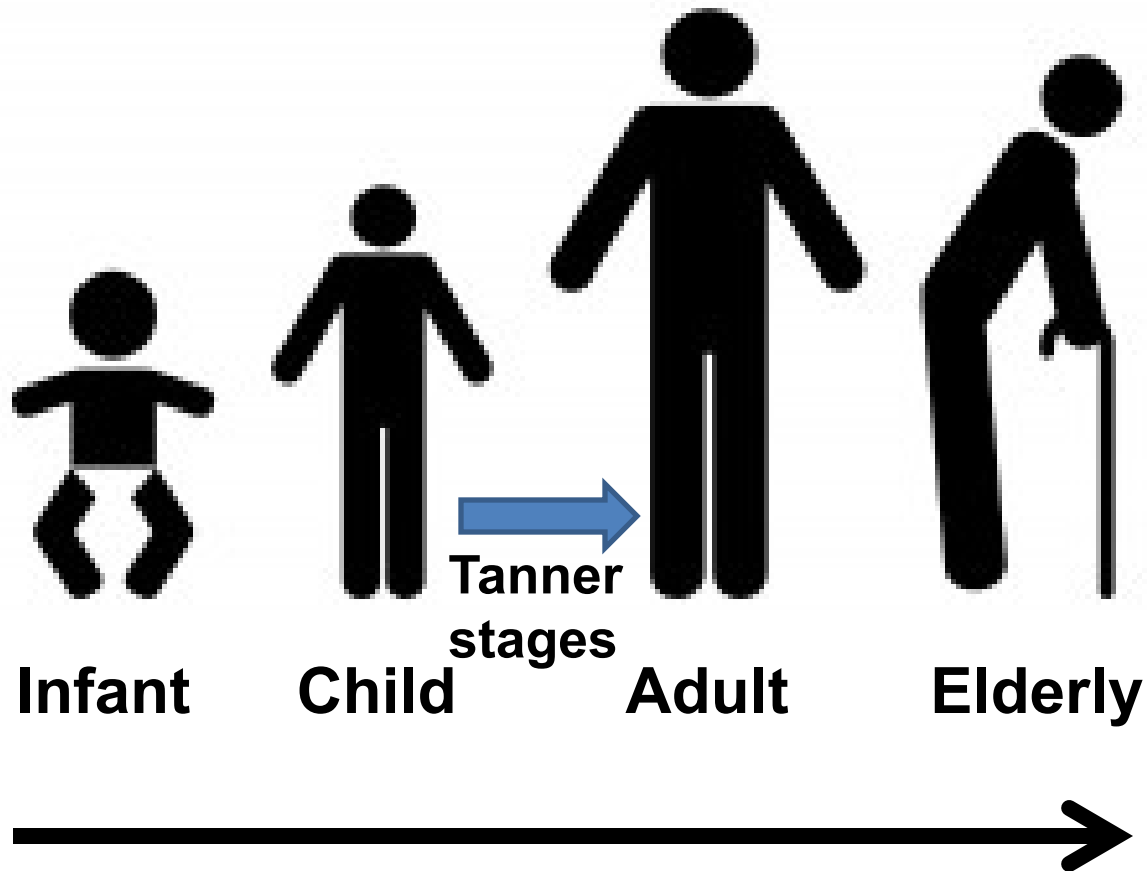
Infant

Child

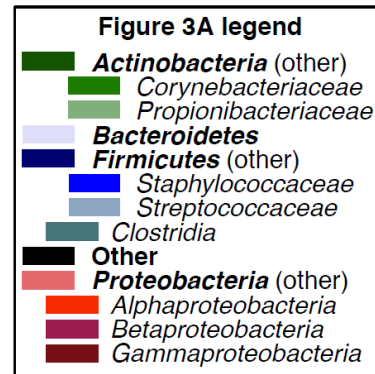
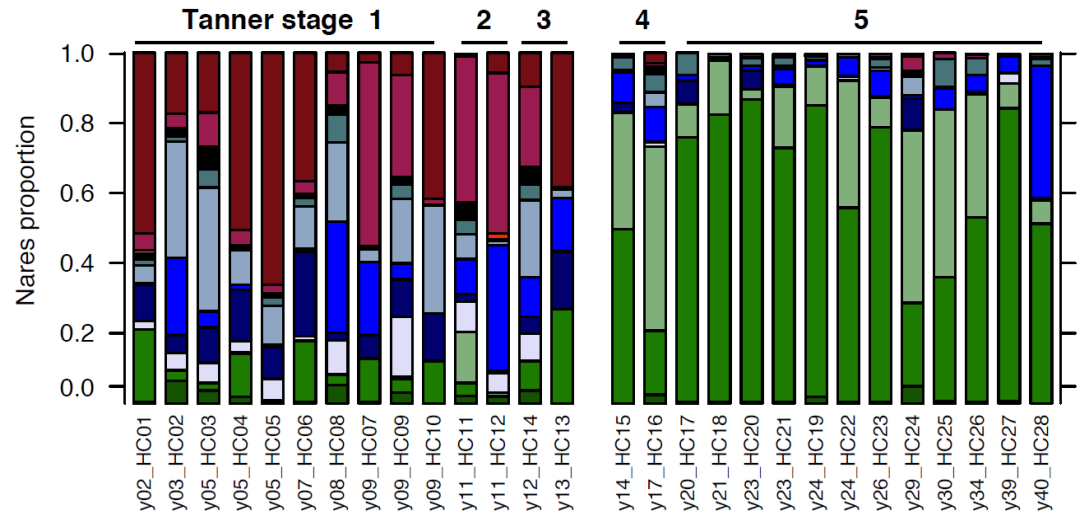
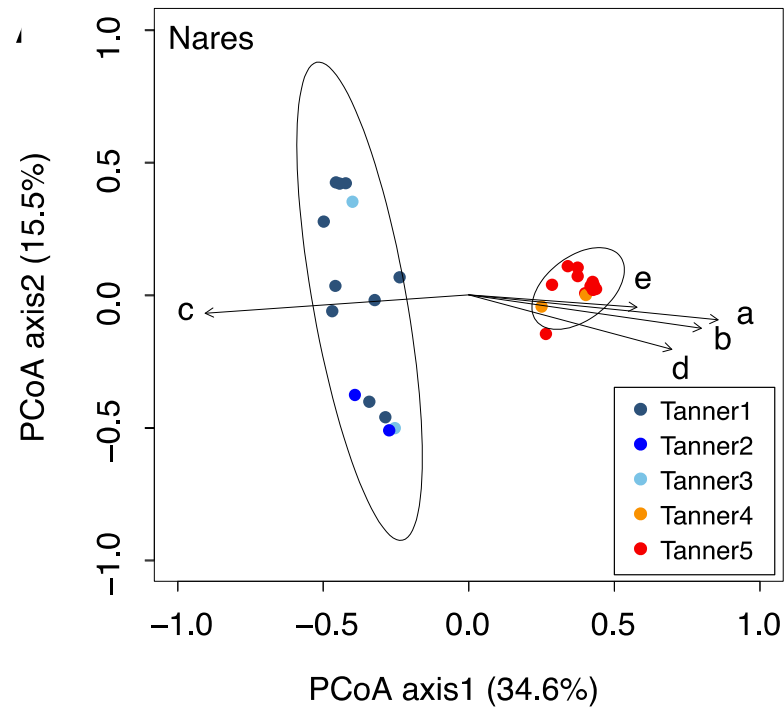
Adult

Elderly

Life Stages



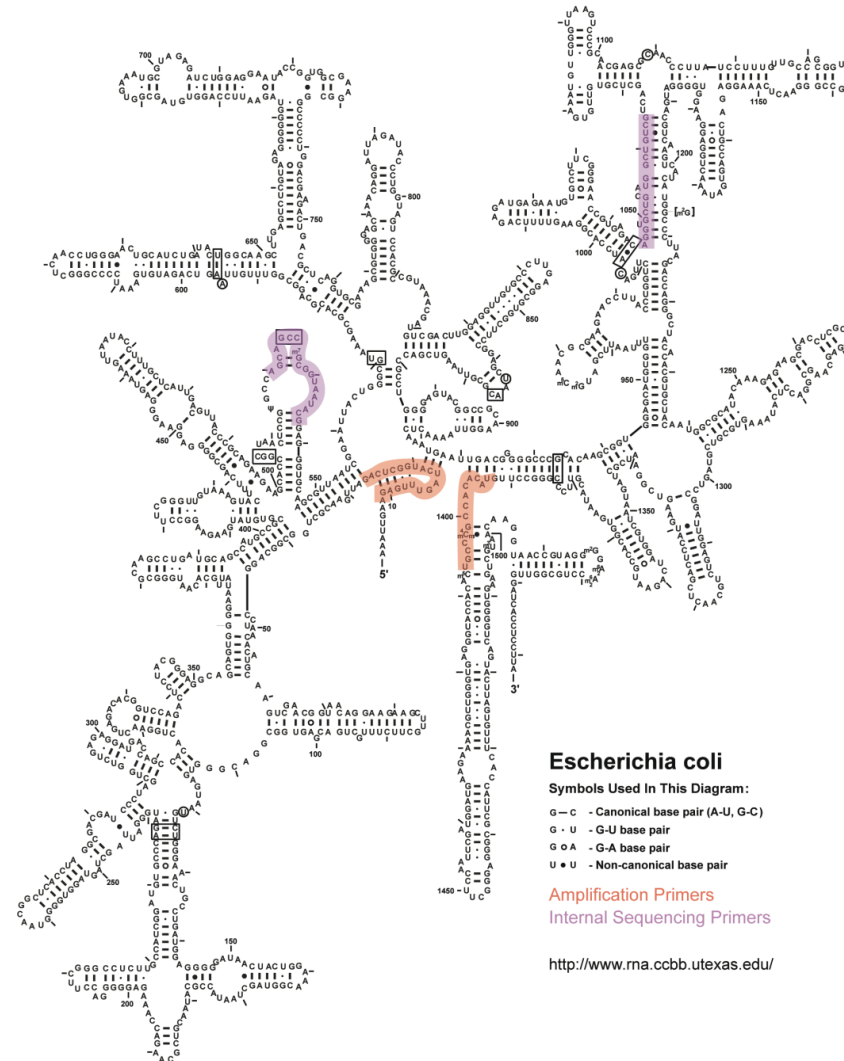
Shifts in healthy skin and nares microbiomes Tanner stages 1-3 vs. 4-5



Lipophilic bacteria

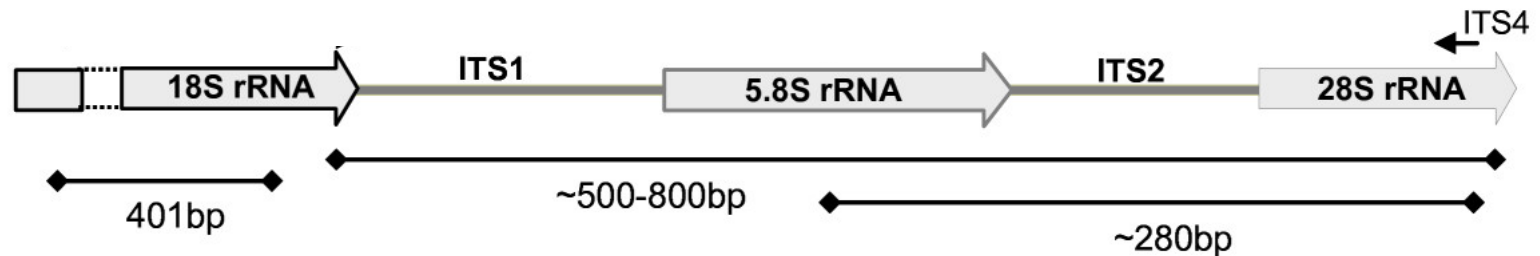


What about non-bacterial members of the skin microbiome?



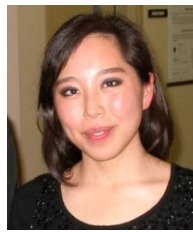
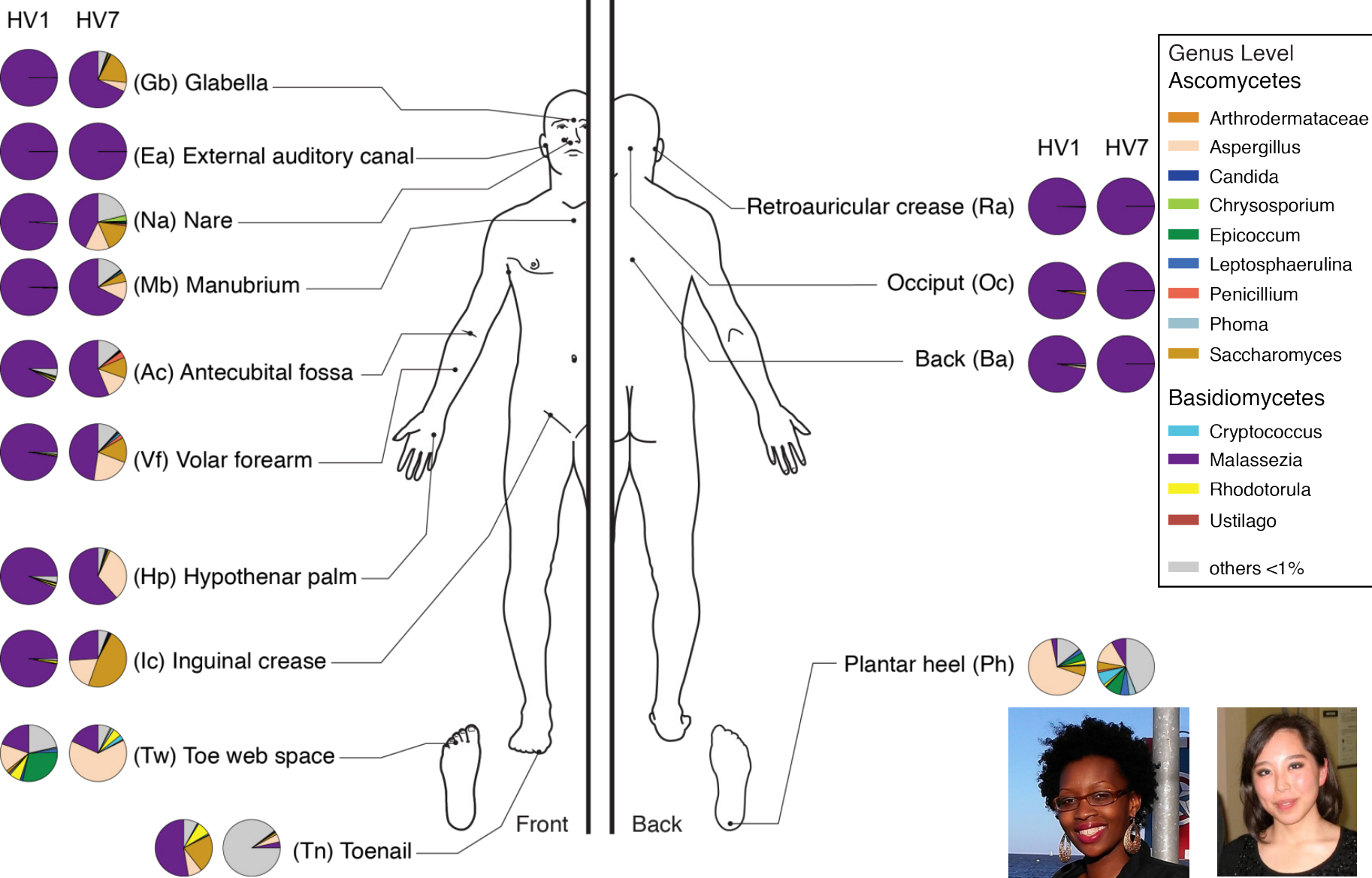
Secondary Structure: 16S small subunit ribosomal RNA

Sequencing fungal organisms

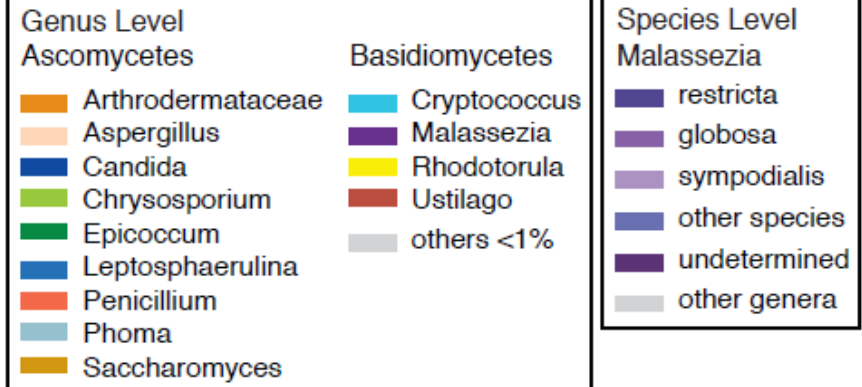
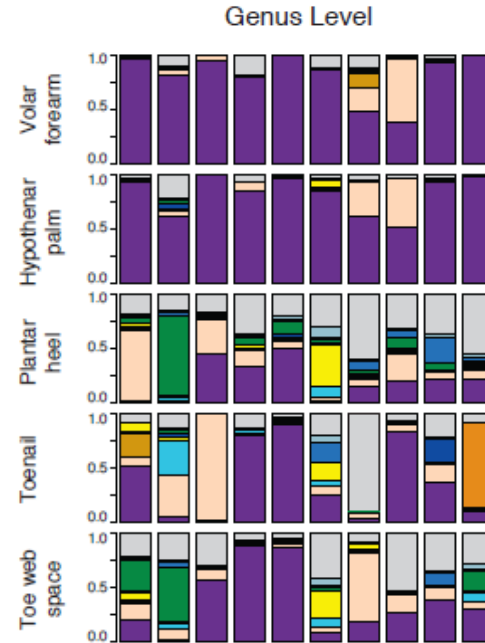
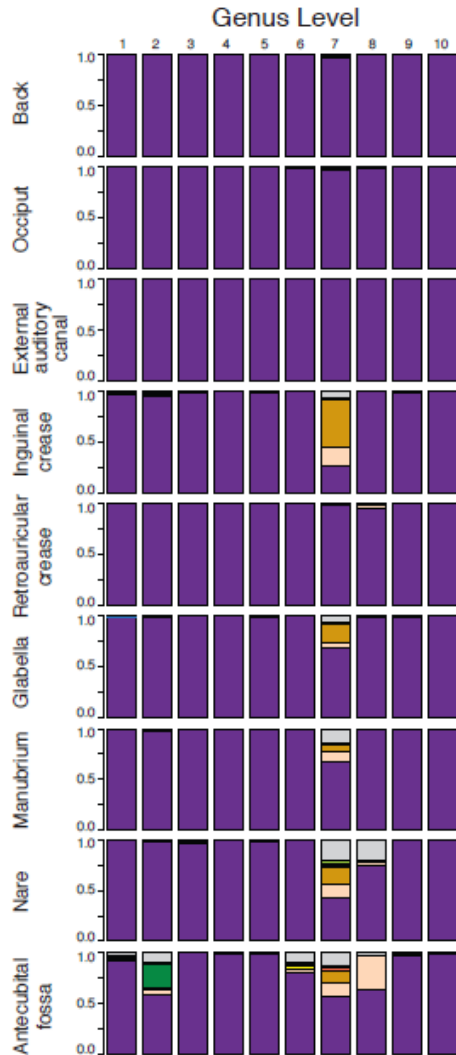


- Optimizing sample collection
- Optimizing DNA extraction (bead-beating)
- Selecting primers (Internal Transcribed Spacer, ITS)
- Selecting a robust database

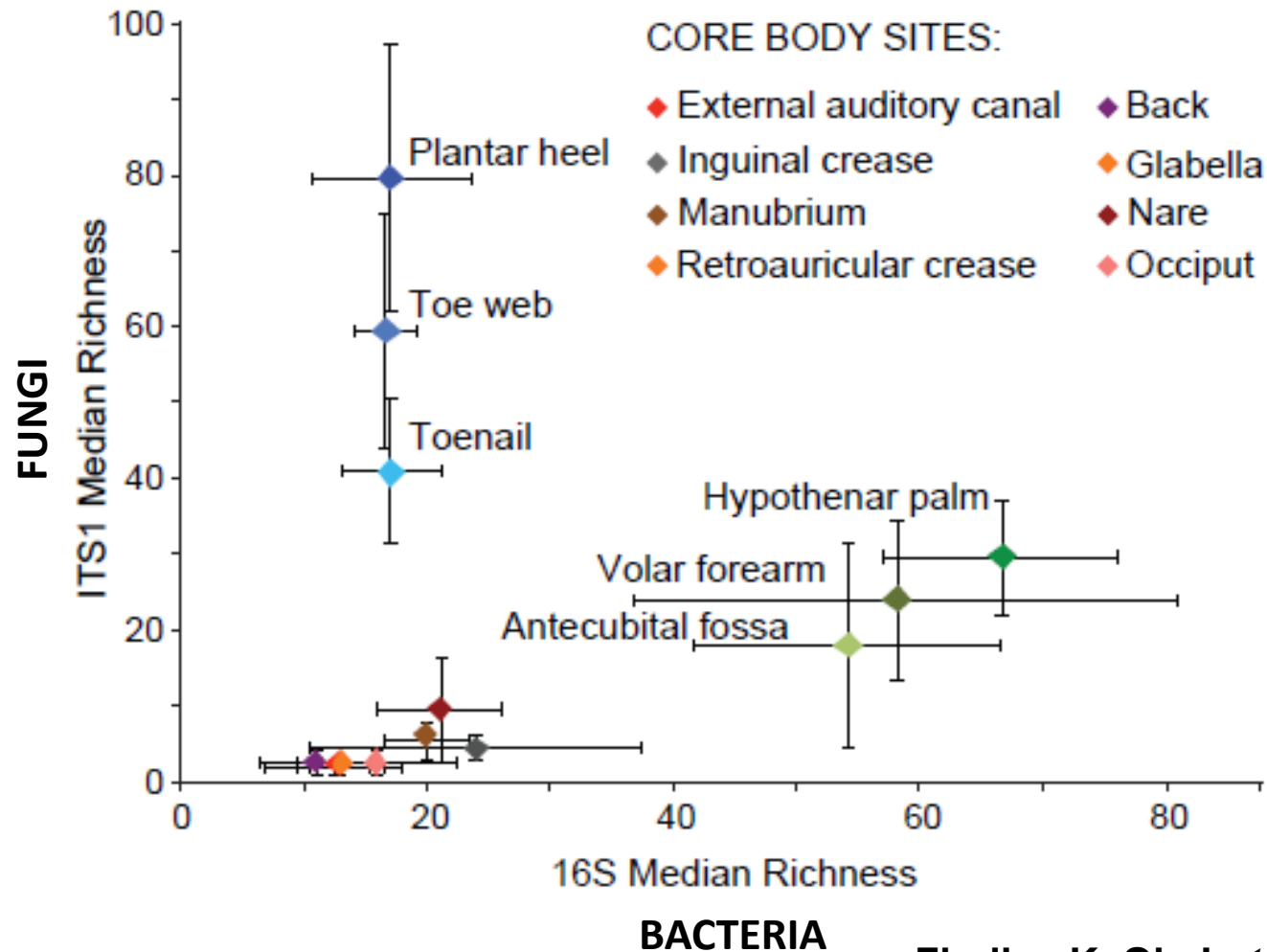
Survey of fungal diversity in human skin



Fungal diversity of human skin is site-specific



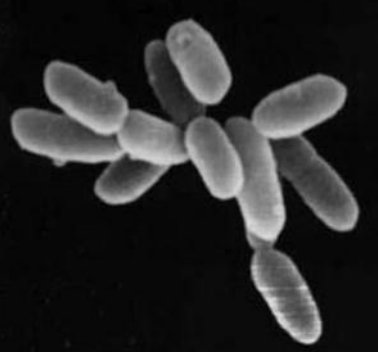
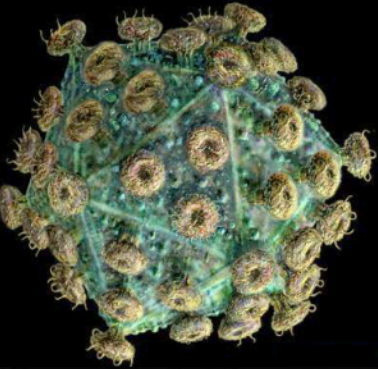
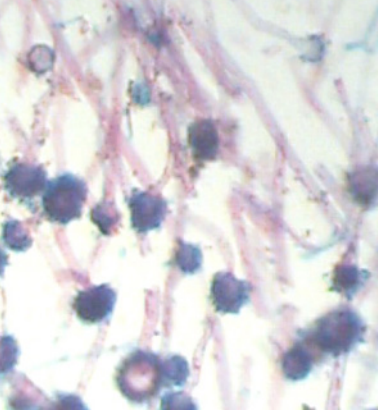
Peripheral skin sites harbor a greater number of different species



Skin microbiome in healthy individuals

- Skin bacterial microbiome is highly dependent on sampled skin site.
 - Neonatal skin bacterial microbiome varies based on mode of delivery.
 - Dramatically shifts between Tanner stages 1-3 and 4-5.
- Fungal communities over skin surface vary differentially from bacterial microbiome.

Eczema, immunity & the skin microbiome



- Do skin microbes influence host skin immunity?
- Healthy human skin microbiome surveys
- The microbiome in eczematous skin
 - Atopic dermatitis
 - Primary immunodeficiency syndromes
- Gaps, needs & challenges

Atopic Dermatitis (AD)

- Chronic itchy inflammatory skin condition
- 15% US children
- Direct costs = \$2 billion/yr
- Disease flares associated with colonization and infections with *Staphylococcus aureus*
- Common treatments include combinations of topical and systemic antimicrobials and steroids



Atopic Dermatitis (AD)

- “Atopic march”:
 - 40-70% severe AD → asthma/hay fever
 - Incidence has doubled in last three decades in industrialized countries
 - Possible external factor
 - Mice: skin exposure to antigens → mucosal sensitization
- Understanding triggers of AD may allow us to modify the development of AD/atopic diseases and develop therapeutic targets



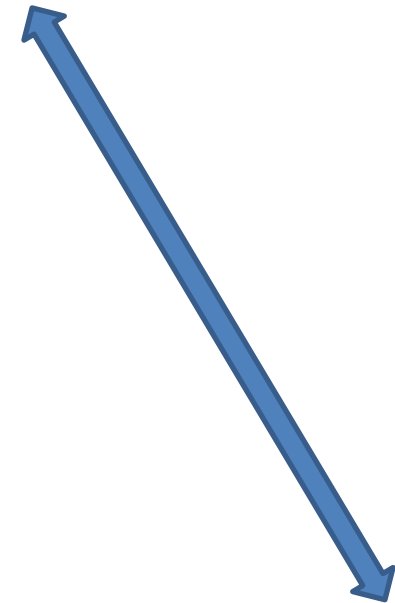
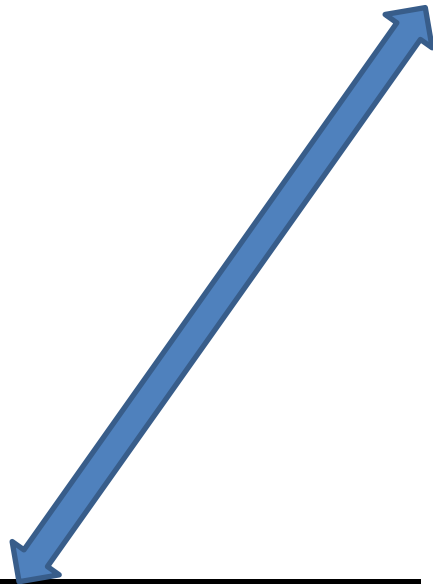
AD is a complex disease

**Skin Barrier
(Filaggrin)**

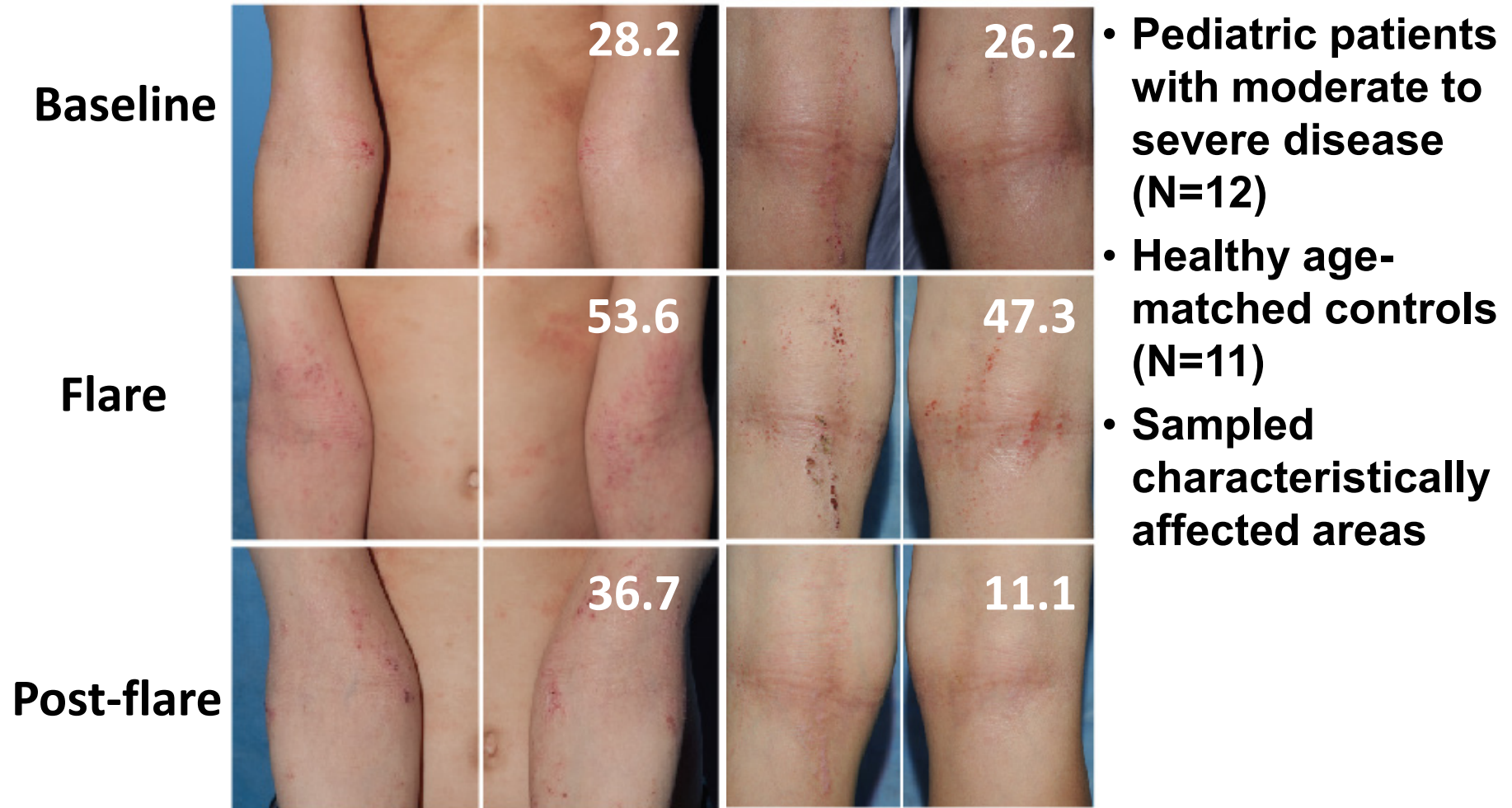


**Immune
System
(IgE, AMP)**

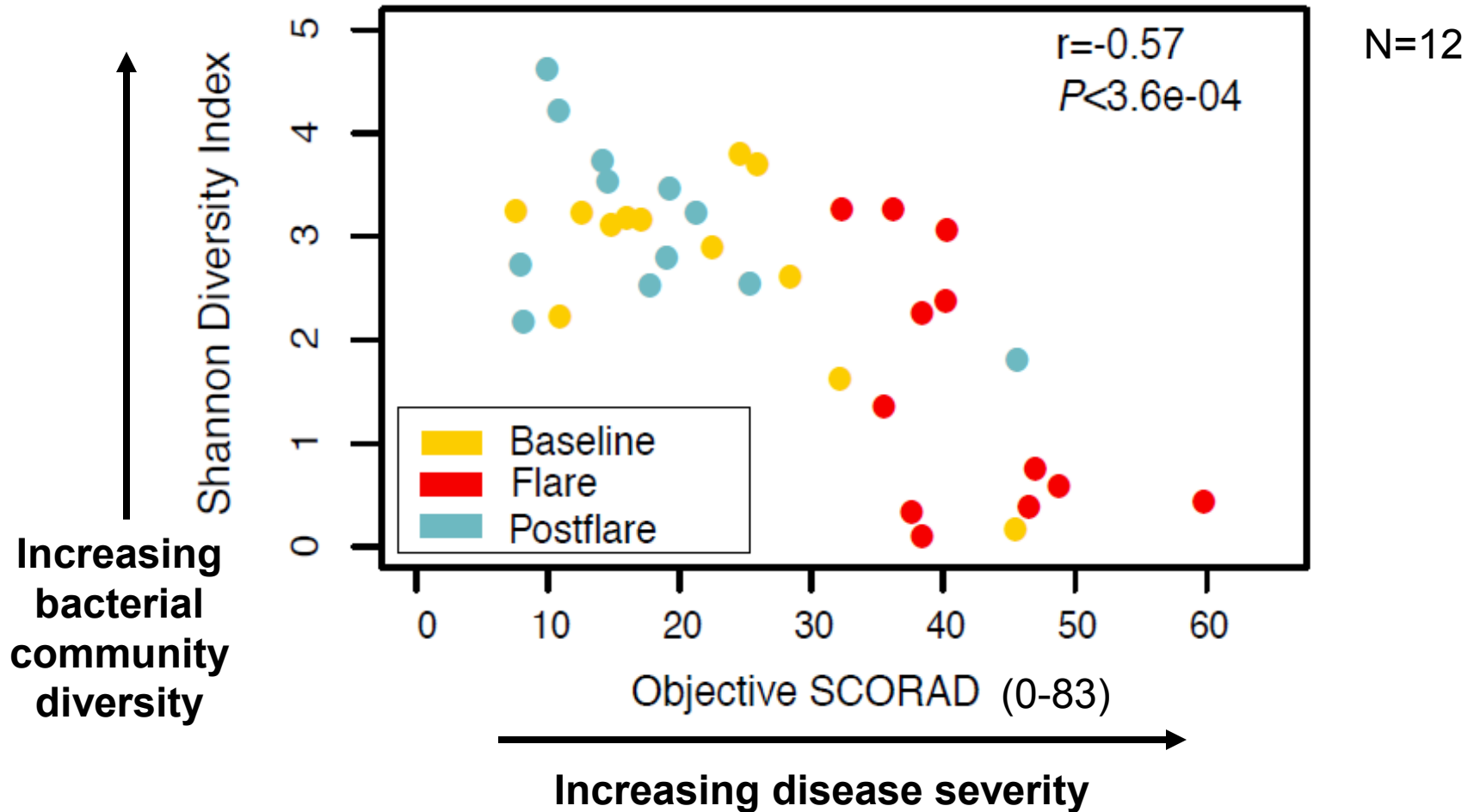
**Microbes
(*S. aureus*, viral
infections)**



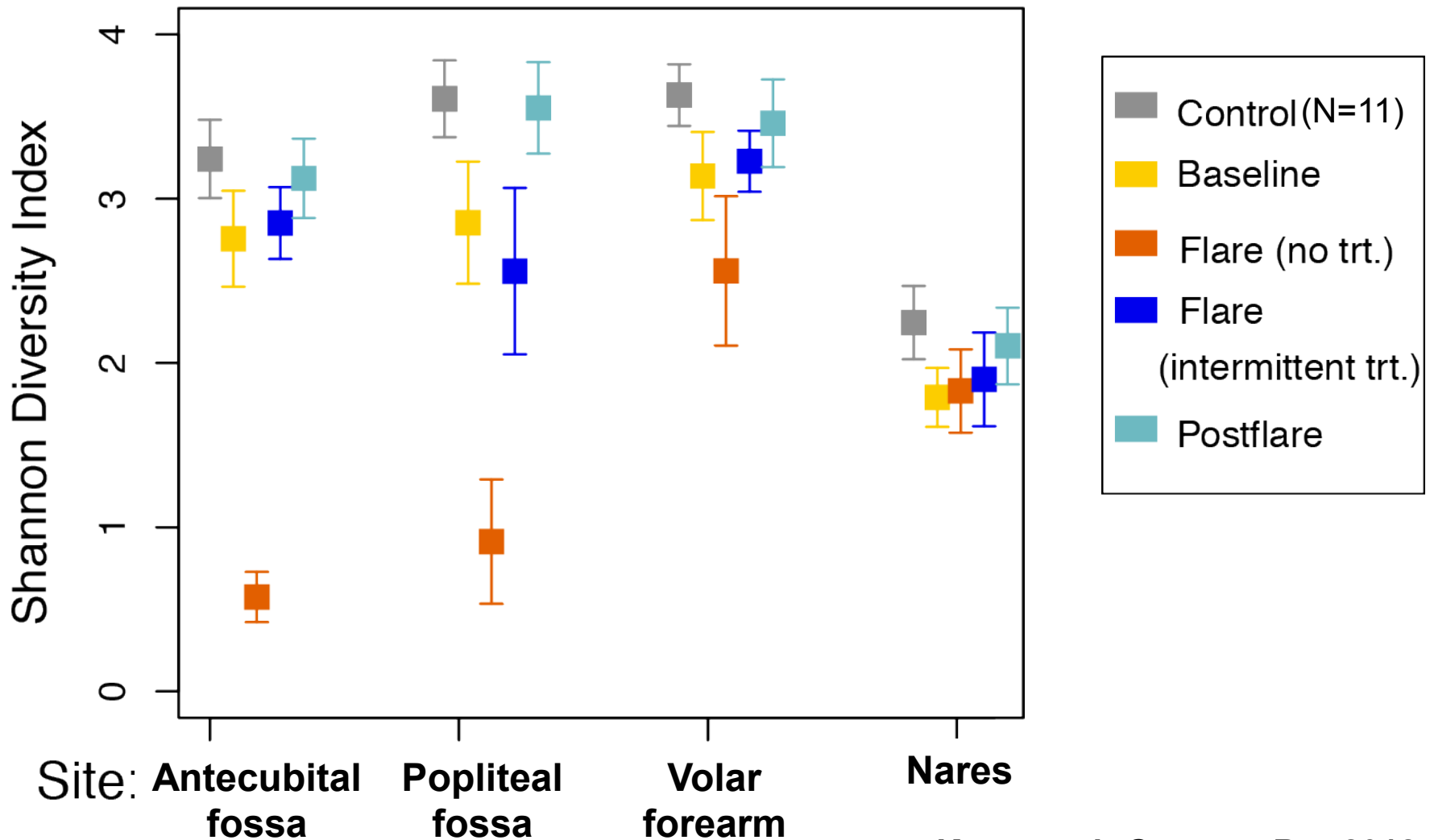
Atopic dermatitis skin microbiome



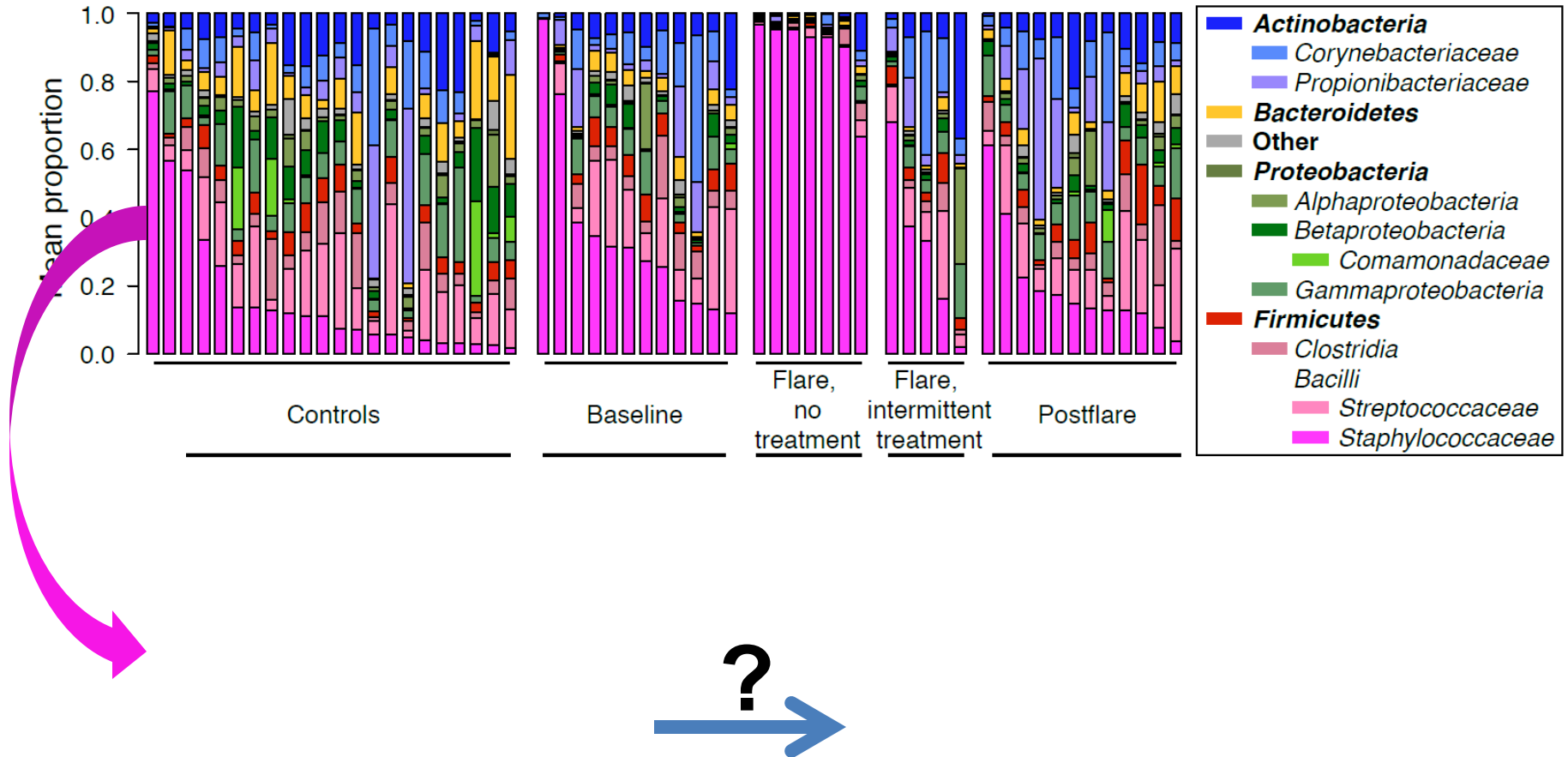
Skin bacterial diversity correlates with AD disease severity



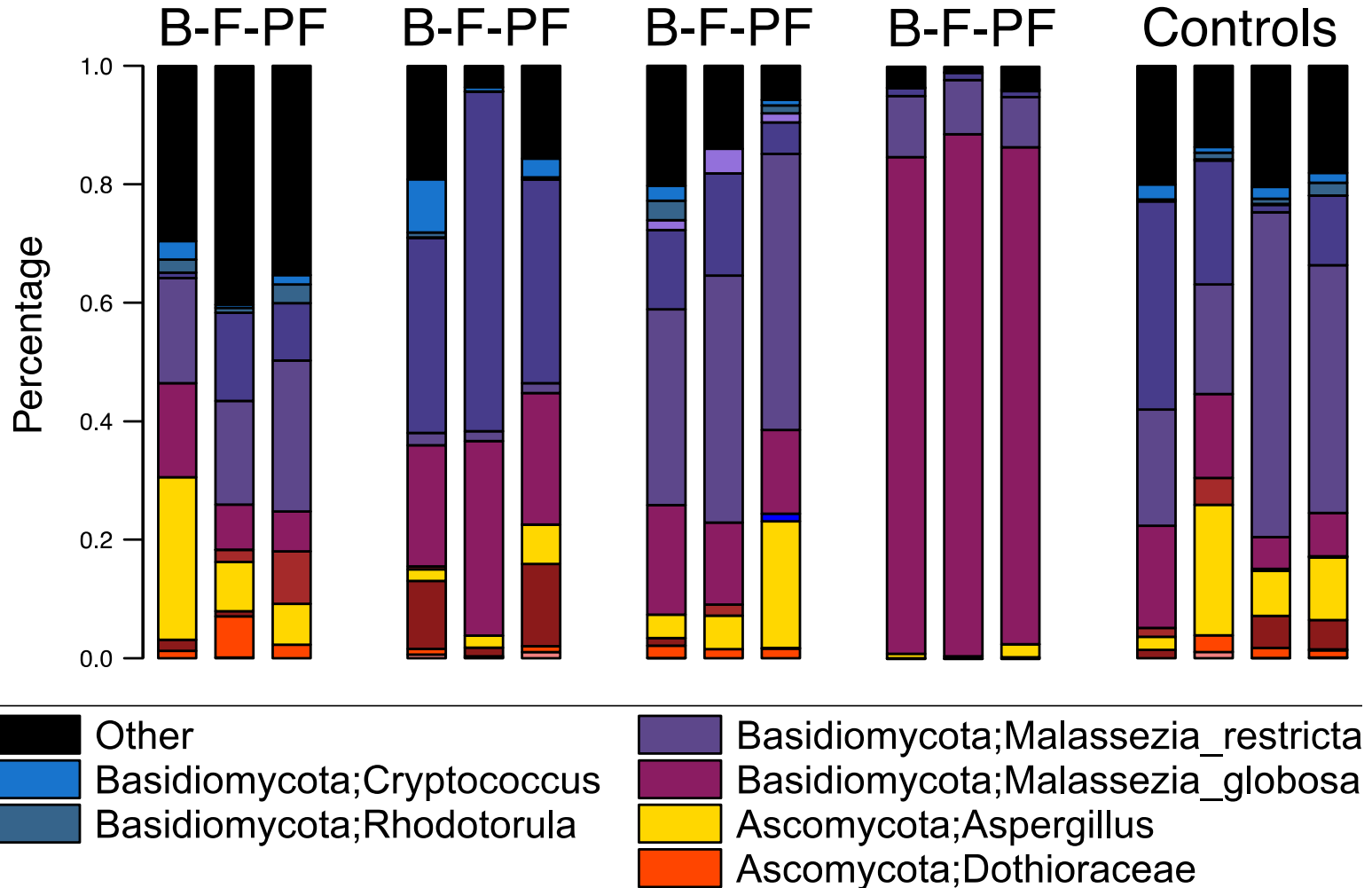
Drop in microbial diversity during AD flare specific to sites of predilection



Staphylococcus spp increase during AD flares



In contrast, fungal communities can be stable despite disease flares



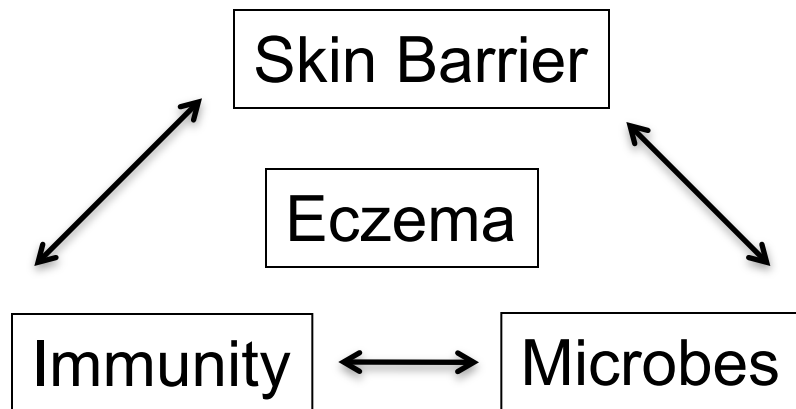
What can we learn from patients with primary immunodeficiencies with eczematous skin disease?



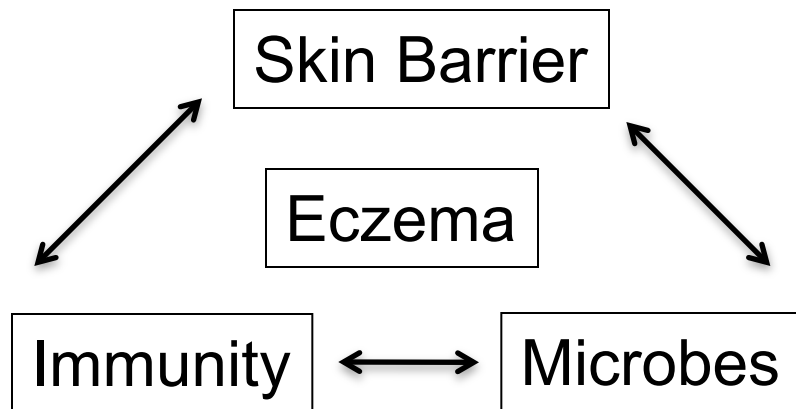
- Monogenic disorders
- AD-like dermatitis
- Antibiotic-responsive

→ Do common and rare disorders with similar phenotype share skin microbiome features?

→ How does innate and adaptive immunity shape skin microbiome?



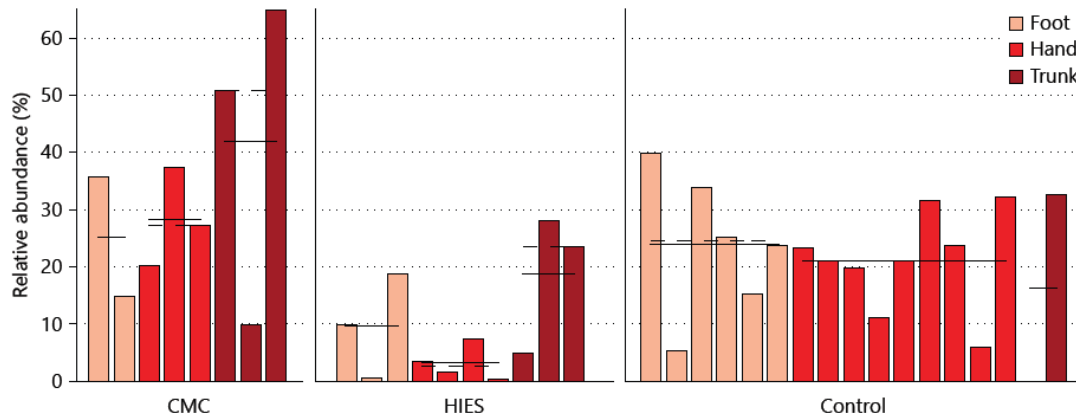
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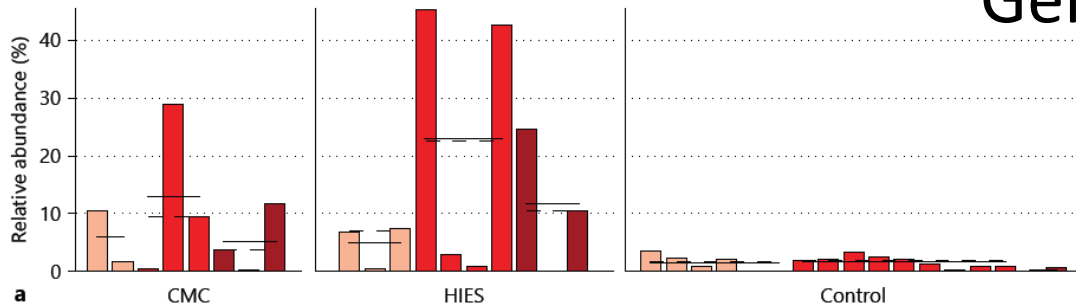
- **Hyper IgE syndrome (*STAT3* mutations)**
 - *Staphylococcal* skin & lung infections
 - *Candidal* infections
 - Secondary *Aspergillus* lung infections
- ***STAT1* mutations**
 - Chronic mucocutaneous candidal infections

Taxonomic differences in skin of patients with *STAT1* and *STAT3* mutations

Corynebacterium spp.



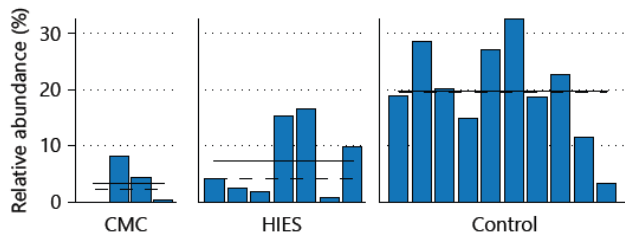
Acinetobacter spp.



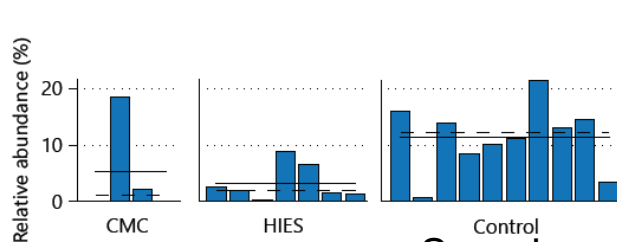
Genus-level

- ↑/↓ *Corynebacterium* spp.
- ↑ *Acinetobacter* spp. (gram-)
- ↓ *Prevotella* spp.
- ↓ *Fusobacteriales* spp.

Prevotella spp.

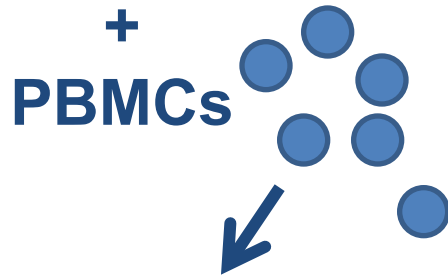


Fusobacteriales spp.



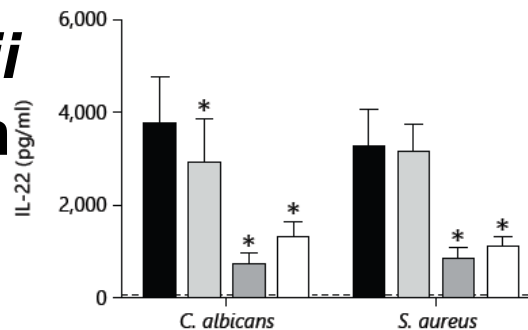
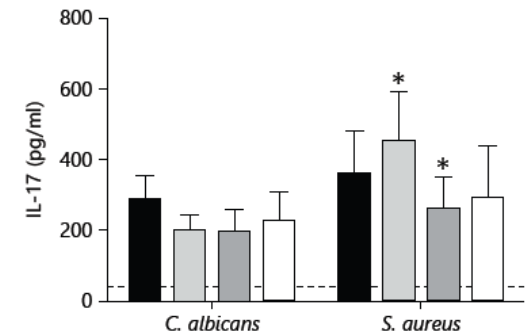
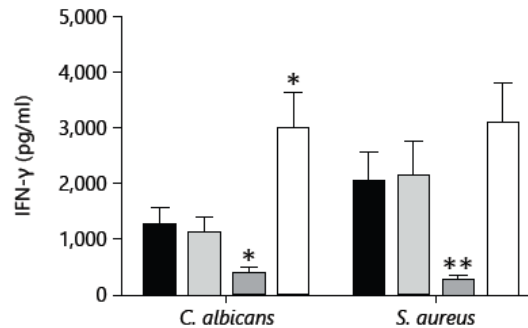
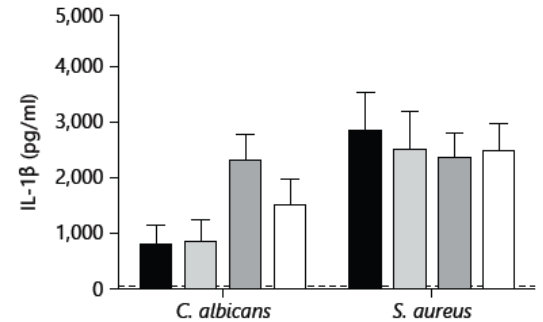
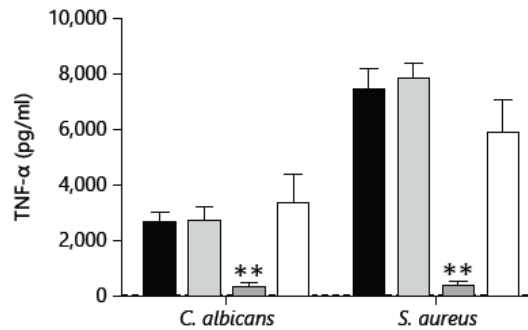
Exposure to certain skin microbes may alter PBMC cytokine response to pathogens

#1 *Corynebacterium* OR
Acinetobacter OR
Staphylococcus



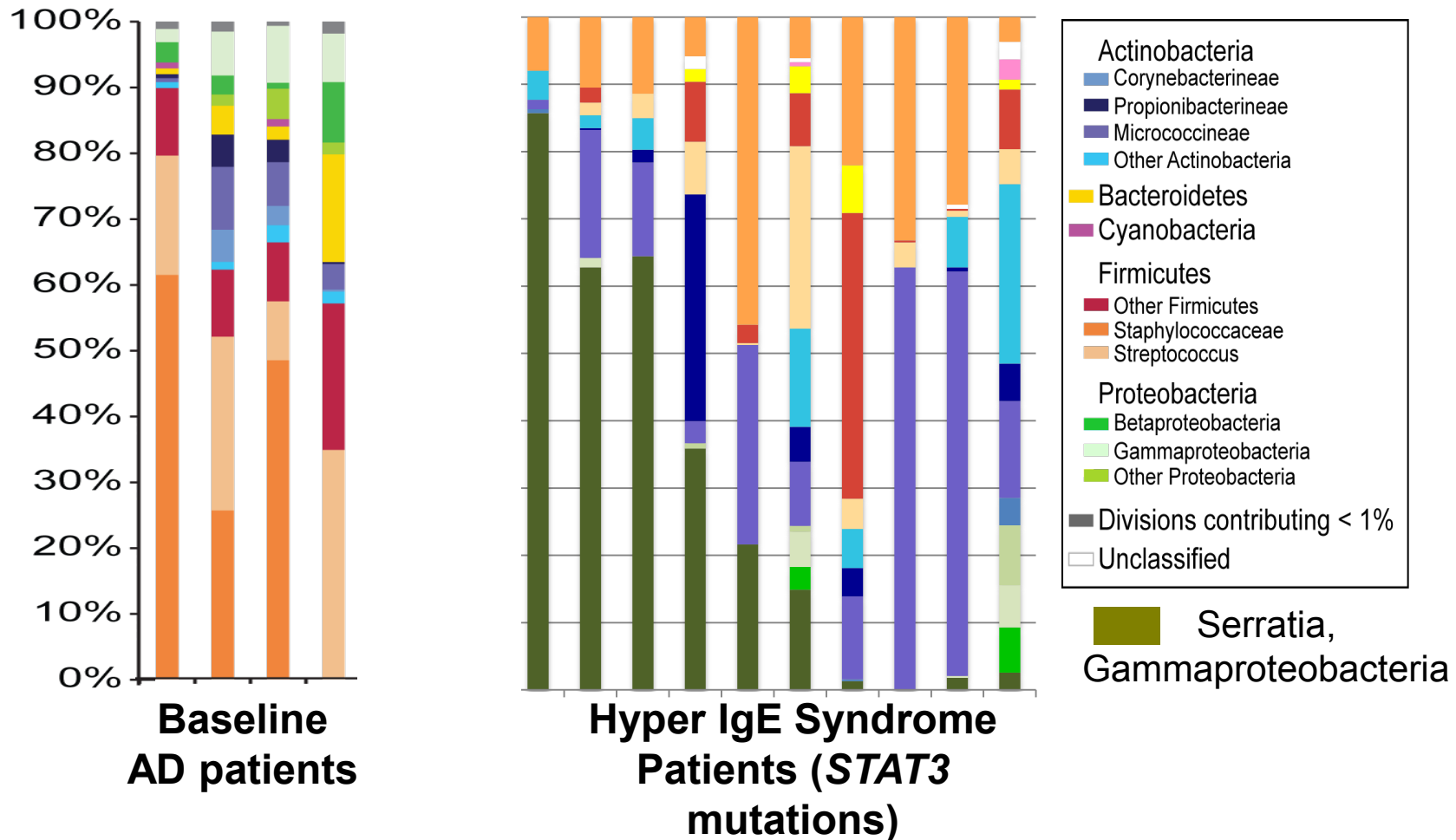
#2 *C. albicans* OR
S. aureus

Acinetobacter baumannii
↓ TNF- α , IFN- γ & IL-22 in
healthy volunteer
PBMCs



■ RPMI
□ *Corynebacterium*
■ *Acinetobacter*
□ *Staphylococcus*
--- Detection limit ELISA

Primary immunodeficiency patients are colonized with atypical skin microbiota



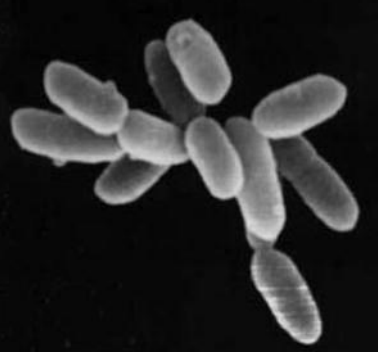
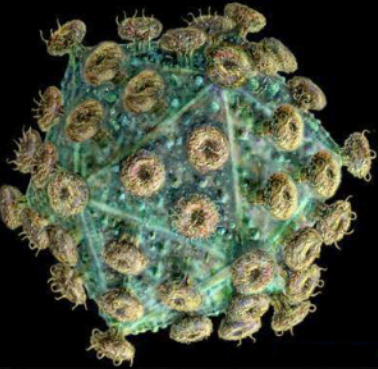
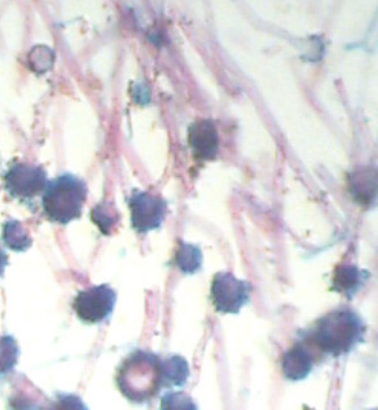
unpublished

See POSTER #31, Julia Oh

Skin microbiome in eczematous skin

- AD flares are associated with shifts in the skin bacteria.
 - *S. aureus* and *S. epidermidis*
- These specific primary immunodeficiency patients harbor bacterial skin microbiome distinct from healthy & AD skin.
 - Altering the skin microbiome may alter PBMC response to specific microbes.
- More studies needed to understand microbial role & potential for therapeutic targets.

Eczema, immunity & the skin microbiome



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- Gaps, needs & challenges

Gaps, needs, challenges

- Evolution of skin microbiome over life stages
- Physiological factors contributing to skin microbiome differences (skin barrier, hormones, etc.)
- Skin microbiome–immunity interactions (human & animal models)
- Correlation to causation
- Magnitude of interaction between fungi & bacteria and role in health & disease
- Skin metagenomics



Gaps, needs, challenges*

- Standardization of protocols
 - Clinical design
 - Phenotyping; Sampling (which skin sites, how frequent, skin prep, time since antibiotics, method); Critical metadata fields
 - DNA extraction (low biomass in skin)
 - Primers; PCR conditions
- Quantitation of microbial biomass
- More microbial characterization, incl genomes
- Metagenomics analytical tools, if low biomass
- Data submission

**These represent the opinions of the speaker and do not necessarily represent the views of, nor should be attributed to, the US government.*

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The NIH
Clinical
Center



Our patients & volunteers



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U.S. Department of Health
and Human Services



National Institute of Arthritis and
Musculoskeletal and Skin Diseases